Reumatol Clin. 2011;**7(4)**:241–247

Reumatología Clínica

www.reumatologiaclinica.org

Original article

Economic evaluation of tramadol/paracetamol in the management of pain in patients with osteoarthritis in Spain

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ARTICLE INFO

Article history:
Received September 14, 2010
Accepted November 29, 2010

Keywords:
Cost-minimisation analysis
Tramadol/paracetamol
Non-Steroidal Anti-Inflammatory Agents
Osteoarthritis

ABSTRACT

Objective: To compare the costs of treating osteoarthritis (OA) pain using combination tramadol/paracetamol tablets, Non-Steroidal Anti-Inflammatory Agents (NSAID) alone or NSAID plus proton pump inhibitors (PPI) from the perspective of the Spanish National Health System.
Methods: A decision-analytical model was constructed to analyze the cost associated with three treatment strategies over 6 months. A cost-minimization approach was used, which considered data related to resource use, medication costs and costs for the treatment of adverse events.
Results: In the base-case analysis, costs for 6 months of treatment of OA pain using tramadol/paracetamol were €232.86, compared with €274.60 for NSAID + PPI and €133.75 for NSAID alone. This provided a savings of €41.74 per patient over 6 months for tramadol/paracetamol compared with NSAID + PPI and a cost increase of €99.11 compared with NSAID alone. When renal adverse events associated with NSAID were considered, tramadol/paracetamol was cost saving compared with all NSAID-based regimens (saving €140.02 vs NSAID alone, €280.86 vs NSAID + PPI).
Conclusion: Based on the results of a theoretical decision-analytic model, the data obtained may suggest that tramadol/paracetamol is cost saving compared with NSAID + PPI for the treatment of OA pain over a period of 6 months. Tramadol/paracetamol is also cost saving compared with treatment with NSAID alone if considering renal adverse events

Evaluación económica de tramadol/paracetamol en el manejo del dolor en pacientes con osteoartrosis en España

Palabras clave:
Análisis de minimización de costes
Tramadol/paracetamol
Antiinflamatorios no esteroideos
Osteoartrosis

RESUMEN

Objetivo: Comparar el coste del tratamiento del dolor en la osteoartrosis (OA) con tramadol/paracetamol frente a los antiinflamatorios no esteroideos (AINE) solos o en combinación con un inhibidor de la bomba de protones (IBP) desde el punto de vista del Sistema Nacional de Salud de España.
Métodos: Se realizó un modelo analítico de decisiones que evaluó los costes derivados de las tres estrategias de tratamiento durante 6 meses. Se utilizó un análisis de minimización de costes considerando datos referentes al uso de recursos, costes farmacológicos y costes derivados del tratamiento de los acontecimientos adversos (AE) de la medicación.

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1699-258X/$ - see front matter

Resultados: En el análisis del caso base, el coste del tratamiento del dolor de la OA durante 6 meses con tramadol/paracetamol fue de 232,86 €, comparado con 274,60 € con los AINE + IBP y 133,75 € con los AINE solos. Por tanto, el tratamiento con tramadol/paracetamol produce un ahorro de 41,74 € por paciente durante 6 meses respecto a AINE + IBP y un coste adicional de 99,11 € respecto a los AINE solos. Al considerar los AE renales, tramadol/paracetamol produce un ahorro comparado con los tratamientos que contienen AINE (140,02 € respecto de los AINE solos y 280,86 € respecto de los AINE + IBP).
Conclusiones: Basándose en los resultados de un modelo teórico analítico de decisiones, los datos sugieren que tramadol/paracetamol produce ahorros comparado con los AINE + IBP en el tratamiento del dolor de la OA durante 6 meses. Tramadol/paracetamol también produce ahorros comparado con los AINE solos si se consideran los AE renales.

Introduction

Rheumatic diseases affect a significant portion of the population, about 20%,[1] and have a significant economic impact in Spain. Although epidemiological studies of osteoarthritis (OA) in our country are scarce, some have shown that its prevalence ranges between 6.2% and 26.1% and affects more women than men.[2] This data is similar to that observed in Europe, where for over 75 years the prevalence of OA was doubled in women with respect to men.[3]

OA is a disease that causes pain and stiffness in the joints leading to a reduction in mobility and with a large impact on quality of life of patients as well as consumption of medical resources. Pain is usually the main symptom affecting these patients and treatment is essential to improve their quality of life. The main oral pharmacological options currently used to treat pain caused by OA include paracetamol, nonsteroidal antiinflammatory drugs (NSAIDs) and opiates.[4] Recently, the International Osteoarthritis Research Society (OARSI) has published a series of recommendations from a review of available guidelines for the management of patients with OA of the hip and knees.[5] In this consensus, it recommends the use of paracetamol as first-line therapy in the treatment of mild to moderate pain caused by OA. It also recommend taking the lowest effective dose of NSAIDs, avoiding long-term use, and the use, in patients with high risk of gastrointestinal complications, of a selective inhibitor of cyclooxygenase-2 (COX-2) or an NSAID with a proton pump inhibitor (PPIs) or misoprostol.[6] Also, NSAIDs, selective or not, should be used with caution in patients with cardiovascular risk factors.[7,8] The OARSI, the European League Against Rheumatism and the Spanish Society of Rheumatology recommends the use of opioids, with or without paracetamol, as an alternative when NSAIDs are contraindicated, ineffective and / or poorly tolerated.[9,10] Thus, the combination of the opiate tramadol with paracetamol has proven effective in patients with OA whose pain did not improve with NSAIDs or specific inhibitors of COX-2.[11,12] These studies also have shown that tramadol / paracetamol has a good safety profile, even in elderly patients.[13]

In the economic evaluation of the current therapeutic options for the treatment of pain in OA, both the drug cost and resource use associated with adverse events (AEs) should be provided for, as they can pose a significant economic burden. Liedgens et al (2005)[14] conducted a cost-minimization analysis of tramadol / paracetamol compared with NSAIDs in treating OA pain in the Netherlands. In Spain there are no economic studies that compare the economic impact of these therapeutic options, although tramadol / paracetamol has proven to be more efficient per unit of cost-effectiveness and / or cost-security than tramadol monotherapy.[15] Therefore, the aim of this study was to perform a cost minimization analysis from tramadol / paracetamol, NSAIDs and NSAID + PPI from the point of view of the Spanish National Health System.

Methods

We performed a cost-minimization analysis that assessed the costs of treating OA pain with tramadol / paracetamol compared with NSAIDs alone or in combination with a PPI. The cost-minimization analysis is especially useful in pharmacological interventions that have shown equivalent effectiveness for a single pathology, but differences in the costs associated with each of the options. In this study, it is assumed that the different pharmacological options to treat moderate pain in OA are equally effective, but with variations in the tolerability profile, and therefore show differences in the incidence of AE.[16-18] Therefore, the calculation of the costs associated with the different treatment alternatives considered on one hand the drug cost (the average cost was calculated from all the presentations available in Spain)[19] (Table 1), and on the other hand, the cost related to treatment of AE associated with each option from the Spanish cost database (e-Health)[20] (Table 1). Data was obtained from the literature and was supplemented by a panel of 6 clinical experts (rheumatologists and primary care physicians) with a specific questionnaire. The incidence of different AE was obtained, in as many cases as this was possible, from Spanish references and, when unavailable, from international reviews or meta-analysis (Table 2). In the case of NSAIDs + PPIs, the incidence of AE was calculated using the relative risk for GI AE with NSAID + PPI vs NSAID from a review,[27] and assumed the same impact for the rest of the AE. Thus, Burke et al[27] analyzed, at 6 months, the incidence and likelihood of gastrointestinal side effects of therapy with NSAIDs vs NSAID plus gastroprotective agents and celecoxib. After conducting a systematic review, we included 8 Phase III clinical trials comparing celecoxib vs NSAIDs (naproxen, ibuprofen and diclofenac). This data was compared with the systematic review of all clinical trials including gastroprotective therapy (anti-H2, PPIs and misoprostol) for the reduction of NSAID-induced GI effects. We used a meta-analysis to calculate the relative risk reduction. This risk reduction was applied to the probabilities of the NSAIDs GI AE came from Spanish sources,[23,24] thus obtaining an estimate of the risk of NSAID + IBP GI AE in Spain (Table 2).The incidence of cardiovascular AE was obtained from a metAEnalysis[8] and a review of the literature,[21] and renal AE came from a study that conducted a review of the literature.[26]

The base case analysis considered direct medical costs, including all AE with tramadol / paracetamol and gastrointestinal and cardiovascular AE with NSAIDs. Additional analysis was performed including renal AE associated with NSAIDs, because, although the incidence of AE is low, the costs associated with treatment are very high, especially in patients who are receiving dialysis. For NSAIDs, the active ingredients included ibuprofen, diclofenac and naproxen, as they are the most prescribed NSAIDs in Spain, and did not consider the specific COX-2 inhibitors, as their use in recent years has been low.[28]

Table 1
Drug costs and adverse events

Drugs (daily dose)		Cost/day: mean (minimum-maximum)[19]
Tramadol/paracetamol	75 mg/650 mg-225 mg/1,950 mg	1.23 (0.62-1.85) €
NSAID		
Diclofenac	100-150 mg	0.38 (0.16-0.61) €
Ibuprofen	1,200-1,800 mg	
Naproxen	1,000 mg	
PPI		
Omeprazole	20 mg	0.95 (0.14-1.75) €
Pantoprazole	20-40 mg	
Lansoprazole	30 mg	

AE	Cost of treating AE[20]
Vertigo	17.95 €
Somnolence	8.66 €
AE GI minor	85.24 €
AE GI severe	5,501.48 €
Symptomatic ulcer	421.20 €
Anemia with occult bleeding	3,178.94 €
Hypertension	231.91 €
Death due to CV event	4,953.90 €
Acute myocardial infarction	4,499.54 €
Stroke	5,408.30 €
Mild renal problems	96.10 €
Hospitalization due to renal problems	4,634.97 €
Home treatment due to renal problems	443.22 €
Dyalisis for patients hospitalized due to renal AE	170,604.06 €

AE indicates adverse events; CV, cardiovascular; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drugs.
Sources: Consejo General del Colegio Oficial de Farmacéuticos19, E-salud20, expert panel.

Table 2
Frequency of adverse events associated to tramadol/paracetamol, NSAID or NSAID+ PPI

Adverse event	Probability	Source
Tramadol/paracetamol		
Vertigo	0.1	Emley et al,[11] Liedgens et al,[14] expert panel
Somnolencia	0.065	Silverfield et al,[12] Liedgens et al,[14] expert panel
AE GI minor		
Constipation	0.457	Silverfield et al,[12] Liedgens et al,[14] expert panel
Nausea	0.511	Emley et al,[11] Liedgens et al,[14] expert panel
Vomit	0.032	Emley et al,[11] Liedgens et al,[14] expert panel
AE CV		
Hypertension	0.000	Morrison et al,[21] Frishman,[22] expert panel
Any CV event	0.0051	Kearney et al[8]; expert panel
Death due to CV event	0.0014	Kearney et al[8]; expert panel
Acute myocardial infarction	0.0018	Kearney et al[8]; expert panel
Stroke	0.0019	Kearney et al[8]; expert panel
NSAID		
AE GI minor	0.214	Ballina et al[23]; expert panel
Severe GI complications	0.023	Ballina et al[23]; expert panel
Death	0.0625	Lanas et al[24]; expert panel
Survival	0.9375	Lanas et al[24]; expert panel
Symptomatic ulcer	0.75	Ballina et al[23]; expert panel
Anemia with occult bleeding	0.25	Ballina et al[23]; expert panel
AE CV		
Hypertension	0.033	Morrison et al[21]; Frishman[22]; expert panel
Any CV event	0.0341	Kearney et al[8]; expert panel
Death due to CV event	0.0014	Kearney et al[8]; expert panel
Acute myocardial infarction	0.0018	Kearney et al[8]; expert panel
Stroke	0.0019	Kearney et al[8]; expert panel
AE renal	0.066	Silverstein[25]; expert panel
Renal failure	0.147*	Ahmad et al[26]; expert panel
Minor renal problems	0.853*	Ahmad et al[26]; expert panel
Hospitalization due to renal problems	0.64*	Ahmad et al[26]; expert panel
Home treatment for renal problems	0.36*	Ahmad et al[26]; expert panel
No dyalisis	0.808*	Ahmad et al[26]; expert panel
Dyalisis in patients hospitalized cue to renal AE	0.192*	Ahmad et al[26]; expert panel
NSAID+PPI	**RR of AE** (NSAID+PPI vs NSAID)	
AE GI minor	0.64	Burke et al[27]; expert panel
Severe GI complications	0.50	Burke et al[27]; expert panel
AE CV	*Same as for NSAID*	
AE renal	*Same as for NSAID*	

AE indicates adverse event; CV, cardiovascular; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; RR, relative risk. *Probabilities within the risk of a renal AE.

Table 3
Results of the cost minimization analysis

	Cost (€)	Cost difference (€)
Base case		
Tramadol/paracetamol	232.86 €	
NSAID	133.75 €	99.11 €
NSAID+PPI	274.60 €	–41.74 €
Scenario 1: including renal AE		
Tramadol/paracetamol	232.86 €	
NSAID	372.88 €	–140.02 €
NSAID+PPI	513.72 €	–280.86 €

AE indicates adverse event; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor.

univariate sensitivity analysis and extreme scenario analysis considering different probabilities and costs of AE. Additionally we performed a probabilistic sensitivity analysis (ASP) using a Monte-Carlo nonparametric simulation, following the most relevant recommendations for the analysis of uncertainty in economic evaluation studies in the health field.[29] Thus, we conducted a simulated cohort of 1,000 patients, assigning different cost variables a log-normal distribution and beta distribution to the probability model.[30] This analysis was performed under the assumption that not all patients behave like 'typical' patients and ASP explicitly intended to reflect the variability that may exist between the various subjects discussed.

The horizon of the study was 6 months (180 days) and it was assumed that, in the case severe gastrointestinal AE occurred, treatment would be reduced to 90 days, and if symptomatic ulcer or anemia manifested, treatment had lasted 150 days.

The perspective of the study was the National Health System of Spain. No discounts were applied because the time horizon of the analysis was less than one year (6 months). All costs were expressed in 2008 euros.

Figure 1 shows the basic outline of the model, which are the three therapeutic options evaluated for the treatment of pain in patients with OA: tramadol / paracetamol, NSAIDs and NSAID + PPI, and AE associated with each option are included in the model.

Results

In the base case analysis, the cost of treating OA pain (including drug costs and the costs of treatment of AE) for 6 months with tramadol / paracetamol was € 232.86, compared with 274.60 € with the NSAID + PPI and € 133.75 with NSAIDs alone (Table 3). Thus, treatment with tramadol / paracetamol produces a savings of 18% per patient for 6 months for NSAID + PPI and an extra 43% compared to NSAIDs alone. Also, when considering kidney AE, tramadol / paracetamol led to savings compared to treatments containing NSAIDs (60% compared to NSAIDs alone and 121% for NSAIDs + PPIs) (Table 3).

Deterministic sensitivity analysis confirmed the results obtained by including the extreme values of probabilities and unit costs of the model for all options. Thus, the analysis including renal AE was obtained in all cases, saving money, which ranged between €47.38 and € 790.86. And when the kidney AE were not considered, by varying the probabilities or the costs of the base case, an over charge of €179.04 by comparing tramadol/paracetamol vs NSAIDs was observed, or a maximum savings of € 102.39 in the tramadol/paracetamol vs NSAID + PPI (Table 4).

The results of the Monte-Carlo simulation used for the ASP (Figure 2) allowed us to represent the variability in the cost savings associated with tramadol /paracetamol compared to NSAIDs or NSAID + PPI. Thus, when generating the simulation of 1,000 patients, it was observed that the prescription of tramadol / paracetamol instead of NSAIDs alone would produce savings in most cases when including renal AE, and an over charge of between 50 and 162 € if kidney AE were not considered. In contrast, the comparison between tramadol /paracetamol for NSAID + PPI meant savings in almost all cases (Figure 2).

Discussion

Due to the impact of OA in our society and assuming that the analgesic efficacy of tramadol / paracetamol is equivalent to that of NSAIDs in the treatment of moderate pain,[16-18] a pharmaco-economic analysis is important to help optimize the treatment of pain in patients with OA.

Traditionally OA pain has been treated with NSAIDs, however several studies have shown that treatment with NSAIDs is often associated with the occurrence of GI AE, which can often lead to serious complications such as ulcers or bleeding.[23,24] The management of GI complications increases the total cost of the treatment of OA and may eventually account for 46% of the cost total.[31] To avoid the appearance of GI AE, NSAIDs are often prescribed with a PPI. The results of our study shows that despite the reduction in GI AE provided by the PPI, the cost of treatment with NSAIDs + PPI is superior to that of tramadol / paracetamol (this represents a saving of € 41.74 for 6 months). Also, when considering renal AE, the savings that occur when treating patients with tramadol / paracetamol instead of NSAIDs + PPI comes to 281 €, as dialysis treatment for life carries a considerable economic impact. These results are similar to those shown previously by Liedgens et al[14] in the Netherlands. These authors found that tramadol / paracetamol produce cost savings compared with NSAIDs + PPI when not considering kidney AE. In addition, there was a savings compared with NSAIDs alone or in combination with an antagonist of histamine H2 receptor in patients with a medium / high risk of GI AE or renal complications. In our study, we did not considered the therapeutic option of NSAID plus an antagonist of histamine H2 receptor, since in Spanish clinical practice this has a very limited use.

The economic impact of GI AE associated with NSAID is high in the Spanish National Health System, both because of the cost of treating GI AE themselves, as well as the cost of routine prescription of gastroprotection that in most cases is inadequate.[32] Selective inhibitors of COX-2 reduced the incidence of GI AE for NSAIDs, but also are usually prescribed with a gastroprotective agent, and their cost is also significantly higher than that of traditional NSAIDs.[33]

Unlike the Liedgens et al[14] study, our model included cardiovascular AE, since several studies have shown that patients taking NSAIDs have an increased risk of cardiovascular AE such as myocardial infarction.[8,34] However, due to the low incidence of cardiovascular AE presented by patients treated with NSAIDs, the inclusion or absence of these AEs in the analysis does not change, in a relevant way, the final results of the study. Thus, the cost differences between the compared treatment options vary only by 5% when including or not, cardiovascular AE.

Economic evaluations of treatments for the pain of OA are limited. A study similar to ours was conducted by Lizan et al,[35] who performed a cost-minimization analysis of treatment of osteoarthritis pain in Spain, noting that acetaminophen reduces costs with respect to rofecoxib, a selective inhibitor of COX-2, at 3 months and one year. However, in this study the most influential parameter on the results were drug costs and not the incidence of AE. On the other hand, Mendez et al[15] showed that the higher cost of tramadol / paracetamol with respect to tramadol is offset by the lower associated costs, such as those derived from AE, non compliance with treatment and referral to specialized care, resulting in a annual average savings of 55 € per patient.

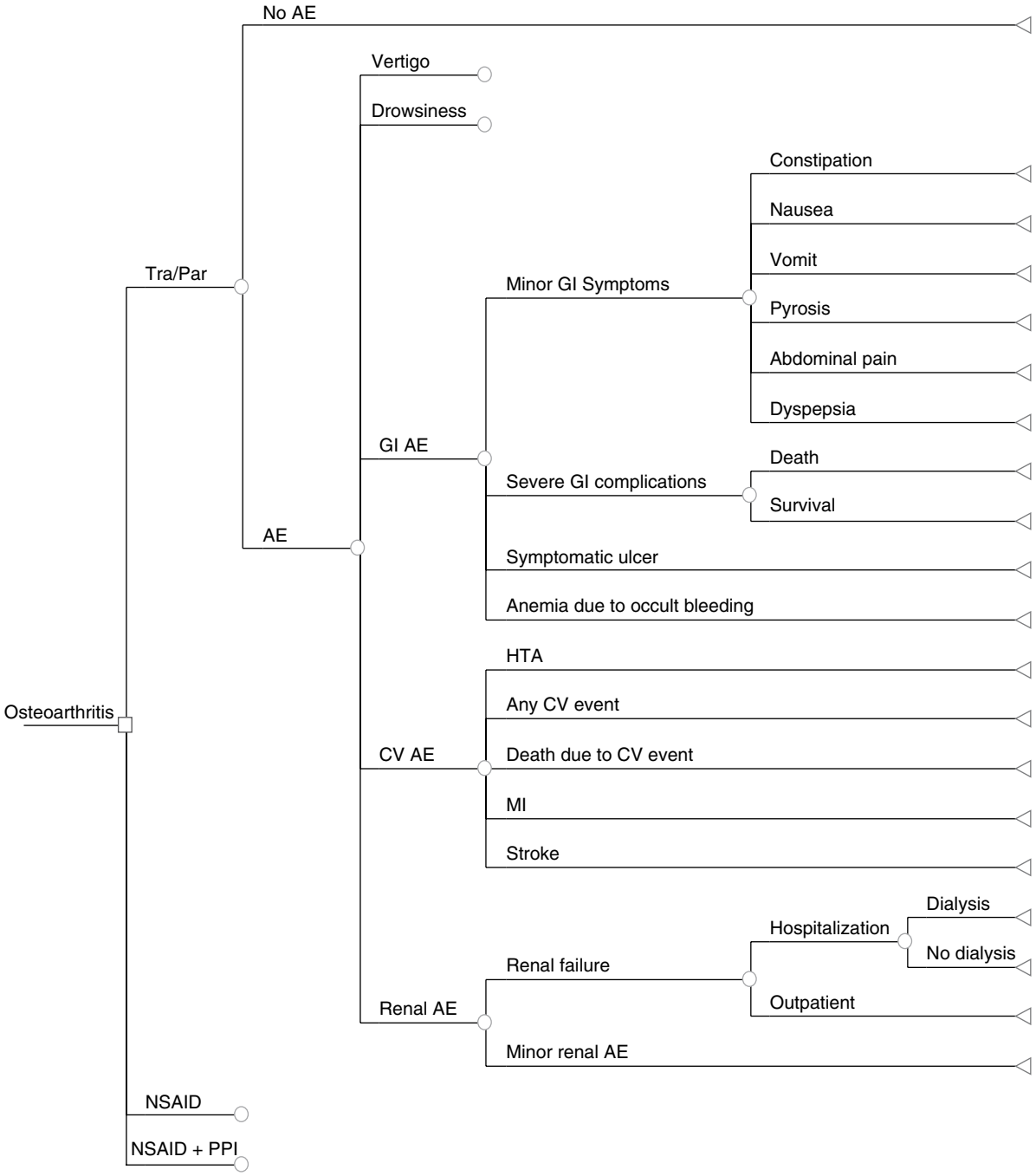

Figure 1. Decision tree. AE indicates adverse event; AMI, acute myocardial infarction; CV, cardiovascular; GI, gastrointestinal; HTA, hypertension; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; Tra/Par, tramadol/paracetamol.

Table 4
Scenario analysis

	Probabilities			Costs		
	Minimum	Medium	Maximum	Minimum	Medium	Maximum
No renal AE						
Tramadol/paracetamol vs NSAID	117.32 €	99.11 €	74.72 €	45.53 €	99.11 €	179.04 €
Tramadol/paracetamol vs NSAID+ PPI	−31.43 €	−41.74 €	−54.80 €	36.91 €	−41.74 €	−102.39 €
With renal AE						
Tramadol/paracetamol vs NSAID	−47.38 €	−140.02 €	−238.84 €	−184.80 €	−140.02 €	−509.44 €
Tramadol/paracetamol vs NSAID+ PPI	−196.13 €	−280.86 €	−368.35 €	−193.42 €	−280.86 €	−790.86 €

AE indicates adverse event; NSAID, non-steroida anti-inflammatory drugs; PPI, proton pump inhibitor.

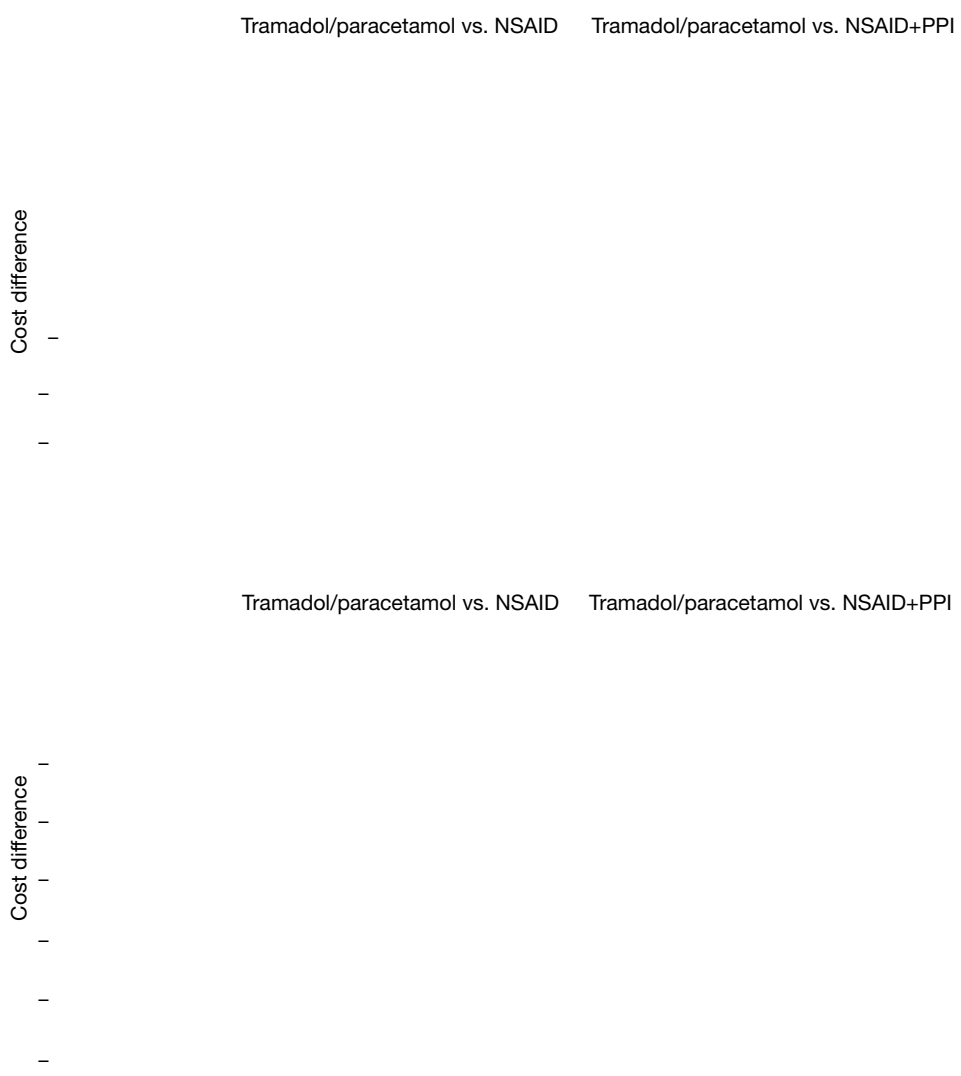

Figure 2. Probabilistic sensitivity analysis without considering the renal AE (A) and including renal AE (B).

Our cost-minimization study analysis has several limitations. First, we used a mathematical model that made different assumptions and used data from different sources. However, pharmacoeconomic models are a tool that helps decision making and seeks to represent real world complexity in a simplified and understandable manner. Thus, models allow us to simulate alternative scenarios if no evidence is available to estimate some probabilities or costs. It is therefore important to note that our study is based on a theoretical model and not based on data from actual patients.

This study evaluates the cost differences between tramadol / paracetamol, NSAIDs and NSAID + PPI based on their equivalent effectiveness, but so far there are no available clinical trial that directly compare the effectiveness of three therapeutic options. Economic analyses have assumed the equivalent effectiveness based on evidence from individual trials for each drug suggesting that the efficacy of tramadol / paracetamol, NSAIDs and NSAID + PPI may be comparable.

Another limitation of this study is that we have considered the incidence of renal AE only for specific inhibitors of COX-2, because there is no published data regarding traditional NSAIDs. This has been based on the assumption that the incidence of renal AE with COX-2 inhibitors is similar to that of NSAID.[36] Considering this limitation and that the incidence of renal AE is low, it is justified that the inclusion of renal AE has been analyzed as a separate scenario. However, it has analyzed how the inclusion of renal AE affects the final results because the cost of treating kidney disease AE is very high. Furthermore, the analysis considered only some traditional NSAIDs (ibuprofen, diclofenac and naproxen) and has not taken into account specific COX-2 inhibitors based on the statistics of use of NSAIDs in Spain.[27] Despite all the limitations of the model, the differenti sensitivity analyses confirmed the strength of the main conclusions. We must also consider that the impact of different AE included in the study comes from studies that are not Spanish (except for GI AE), although this data was validated by local clinical expert opinion.

In conclusion, our study, based on the results of a theoretical decision analytic model, suggests that tramadol / paracetamol produces savings compared with NSAIDs + PPIs in the treatment of OA pain for 6 months and compared with NSAIDs alone if AE are considered.

Conflict of interest

Javier Vidal, Enrique Batlle, Pere Benito, Francisco Blanco, Domingo Ly-Pen and Anna Manresa have participated as clinical experts in the elaboration of the study; Diana Nieves and Max Brosa have received a grant from Grünenthal for carrying out this research.

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