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Evaluation of the cost-effectiveness of buprenorphine in treatment of chronic pain using competing EQ-5D weights

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HIGHLIGHTS

- Chronic pain is a life altering condition and common among elderly persons.
- Buprenorphine could be a suitable pain treatment for elderly persons in Sweden.
- Both UK and Swedish EQ-5D weights show improved HRQoL from buprenorphine treatment.
- Buprenorphine is cost-effective for patients aged >50 with moderate chronic pain.

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ABSTRACT

Background and aims: Chronic pain is a life altering condition and common among elderly persons. The 7-day buprenorphine patch could be a suitable treatment for managing chronic pain of moderate severity in elderly patients in Sweden.

The objective of this analysis was to investigate the cost-effectiveness of the 7-day buprenorphine patch, versus no treatment, in patients >50 years old who suffer from moderate pain in a health economic perspective. An additional aim was to evaluate how the cost-effectiveness is affected by the choice of EQ-5D weights.

Methods: The annual treatment cost and the potential gains in health-related quality of life (HRQoL) of buprenorphine, compared to no treatment, were evaluated. Original EQ-5D data were collected from four clinical reference studies at baseline and at the final visit. Treatment effects on HRQoL were then assessed using both UK and Swedish EQ-5D weights. Annual treatment costs were calculated based on costs of physician visits and pharmaceuticals.

The optimal treatment dose was 10–15 μg/h and the analysis was hence performed on both a 10- and a 15 μg/h buprenorphine patch.

Results: The analysis of buprenorphine treatment resulted in improved HRQoL in all reference studies, irrespective of choice of EQ-5D weight set. The change in quality adjusted life years (QALYs) varied with a gain of 0.042–0.118 using the UK weights and 0.020–0.051 with the Swedish weights. The average annual treatment cost was SEK 14 454 for the 10 μg/h patch and SEK 17 017 for the 15 μg/h patch, while cost for the no-treatment alternative was SEK 9 960. The base case incremental cost-effectiveness ratios (ICER) with the UK weights were SEK 40 000–SEK 170 000 and SEK 90 000–SEK 350 000 when applying the Swedish weights. The corresponding ICER-span in the sensitivity analysis was SEK 15 000–SEK 400 000 when applying the UK weights and SEK 30 000–SEK 840 000 with the Swedish weights (SEK 100 is about €11).

Conclusions: The results imply that the 7-day buprenorphine patch may be a cost-effective treatment of moderate chronic pain in patients over 50 years of age. The UK and the Swedish EQ-5D weights generated vastly different HRQoL estimates but buprenorphine remains cost-effective regardless choice of weight set.

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Abbreviations: EQ-5D, EuroQoL 5-dimension quality of life instrument; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NBHW, the National Board of Health and Welfare; OA, osteoarthritis; QALY, quality adjusted life year; RCT, randomized clinical trial; TLV, the Dental and Pharmaceutical Benefits Agency (the Swedish reimbursement authority).

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Implications: Buprenorphine is a treatment alternative that could be included in the Swedish reimbursement system, although the substantial different HRQoL estimates call for clear guidelines regarding the applicability of each weight regimen.

1. Introduction

Chronic pain is a common and life-altering condition. The prevalence has been estimated to be 19 percent in the adult population in Europe, a fraction that increases with age [1]. Yet treatment of chronic pain remains complex, especially in older patients who face an ample risk of side effects [2]. Thus, the availability of an efficient analgesic therapy that minimizes side effects is essential [3].

Pain is typically divided into three levels of severity; mild, moderate, and severe [4]. The choice of analgesic treatment depends on the severity level. Paracetamol is the primary choice when treating chronic pain but is limited to a maximum dose of 3–4 grams per day due to potential side effects, primarily hepatic events [2,5]. For patients with moderate pain the maximal paracetamol dose often provides insufficient pain relief. In elderly patients the second line pain treatment is opioids [6].

Due to a severe risk of opioid side effects for patients over the age of 65 the treatment recommendations for chronic pain from the Swedish National Board of Health and Welfare (NBHW) are cautious regarding most opioids for elderly patients [2]. Both COX inhibitors and tramadol, in addition to excessive utilization of paracetamol, are related to increased risks for side effects and are therefore viewed as risky treatments for elderly. Buprenorphine can be administered in low doses, which limits the risk of side effects, and could therefore be a suitable second line pain treatment in Sweden for elderly patients when the maximal dose of paracetamol provides insufficient pain relief. The health economic analysis therefore focuses on the cost-effectiveness of buprenorphine in patients >65 years of age with moderate chronic pain.

This analysis is based on the effect of treatment on health-related quality of life (HRQoL) from published studies on buprenorphine and provides an estimation of treatment costs. In cost-effectiveness analyses both HRQoL gains and costs of a suggested treatment regimen are compared to the best available treatment alternative. As the NBHW is cautious regarding opioids apart from buprenorphine when treating patients >65 with moderate chronic pain, the comparator is no treatment. The no-treatment alternative is defined as no opioid treatment, i.e. the maximum paracetamol dose of 4 g per day.

HRQoL is often measured through the generic EuroQol instrument EQ-5D. EQ-5D weights based on interviews of the UK population [7] has been the standard application in Sweden for many years [8,9] according to recommendations by the Swedish reimbursement authority the Pharmaceutical Benefits Board (TLV) [10]. In the UK interviews, respondents were asked to rank different health states using a hypothetical health approach [7]. In 2013, a Swedish study reassigned the EQ-5D weights based on a Swedish general population health survey. Here, individuals were asked to value their current health state, using an experienced-based approach [8].

The objective of this analysis was to investigate the cost-effectiveness of a 7-day buprenorphine patch, versus no-treatment, in patients over >50 years of age with moderate chronic pain. An additional aim was to evaluate how the cost-effectiveness is affected by the choice of EQ-5D weights.

2. Materials and methods

2.1. Treatment and sample population

Buprenorphine is a synthetic opioid analgesic available in the form of transdermal patches. The patches are administered every 7th day and are available in three strengths (5, 10 and 20 μg/h) that allows for individually adjusted treatment [3,11–14].

The present analysis is based on four clinical trials that evaluated buprenorphine's efficacy and effects on HRQoL [11–14]. All studies consider patients with moderate to severe chronic osteoarthritis (OA) pain of the hip and/or knee. In three of the studies patients were randomly assigned to either buprenorphine treatment or a control group, where the control group was treated with tramadol [12], co-codamol [13] or placebo [11]. In the fourth study all patients were treated with buprenorphine [14]. The clinical studies on which this analysis is based are hereafter referred to as the reference studies. The reference studies are summarized in Table 1.

The reference studies provide evidence of significant treatment effects with favourable global impression of pain relief for buprenorphine treatment, or confirm a non-inferiority assumption, irrespective of patient age [11–14]. Other previous studies have indicated that buprenorphine has a good tolerability profile and clinical evidence of tolerance development is lacking, implying that dose escalations (and consequent escalation of side effects) are unlikely [3]. Furthermore, buprenorphine is an appropriate treatment of elderly patients as it does not require any adjustment of treatment dose for patients with impaired kidney function [13,15,16]. Buprenorphine could therefore be more attractive than other strong opioids in patients with renal failure.

Although buprenorphine is an opioid that is associated with a risk of opioid side effects, it has a reduced risk profile in comparison with other opioids that have proven to be clinically effective [5]. Some of the side effects that are traditionally associated with opioid treatment are severe and may cause health decrements, e.g. dizziness and risk of falling [5,6,17]. Yet, the unsuitability of other available opioids mainly applies to patients over 65 years of age with increased risk of side effects. Still a combined cost-effectiveness analysis for patients over 50 years of age was performed. The combined analysis could be motivated by previous studies that show similar pharmacokinetics and pharmacodynamics for buprenorphine in all patients over the age of 50 [12,18]. Two of the reference studies included patients younger than 50 years of age, but these patients were excluded from the present analysis [11,12]. The other two reference studies included patients older than 50 and 60 years of age, respectively [13,14].

2.2. Health-related quality of life

All four reference studies used the generic EuroQol instrument EQ-5D to assess HRQoL [11–14]. Although EQ-5D data was collected in all reference studies, none of them applied EQ-5D weights or presented any in-depth HRQoL results nor did they explore the treatment effect on HRQoL. Therefore, analyses of the original EQ-5D data collected in each reference study were performed, applying both the UK and the Swedish EQ-5D weights.

Table 1
Patient characteristics and background data of the reference studies.

Study descriptives	Karlsson and Berggren [12]	Breivik et al. [11]	Conaghan et al. [13]	Karlsson et al. [14]
N	134	199	220	122
Age, mean	64	63	71	55 vs. 80
Gender, female (%)	76 (57)	136 (68)	145 (66)	75 (61.5)
Type of pain	Osteoarthritis	Osteoarthritis	Osteoarthritis	Osteoarthritis
Initial pain severity	≥4 on BS-11 pain scale when using 4 g/day paracetamol	Grade II–IV osteoarthritis of the hip or knee, defined by the Kellgren and Lawrence scale, while on a NSAID or a coxib	≥5 on the BS-11 pain scale when taking the maximum tolerated dose of paracetamol	≥4 on BS-11 pain scale when using 2–4 g/day paracetamol
Treatment allocation	7-day buprenorphine patches (n = 69), Tramadol tablets (n = 65)	7-day buprenorphine patches (n = 100), Placebo patches (n = 99)	7-day buprenorphine patches (n = 110), Co-codamol tablets (n = 110)	7-day buprenorphine patches (N = 122)
Inclusion criteria	≥18 years of age with diagnosed OA of hip and/or knee	>40 years of age, at least moderate radiographic OA changes, at least moderate pain in hip and/or knee while on NSAID or a coxib	≥60 years of age with diagnosed OA of the hip and/or knee	≥50 years of age with OA, moderate to severe chronic pain
Previous treatment	Paracetamol 4 g/day	NSAID or a coxib	Maximum tolerated dose of paracetamol	Non-opioid analgesic
Rescue medication	Paracetamol	Paracetamol	Ibuprofen	Paracetamol
Follow-up	12 weeks	28 weeks	12 weeks	12 weeks
Countries	Sweden	Denmark, Finland, Norway, Sweden	UK	Sweden

EQ-5D has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and each dimension has three levels of severity corresponding to *no problems*, *some problems*, and *extreme problems*. This allows the generation of 243 (3^5) possible combinations, i.e. health states [19]. Each of the 243 EQ-5D health states are assigned a value on a scale from 1 (perfect health) to 0 (death). The more desirable the health state, the higher the ascribed value. Negative values can thus be considered to correspond to health states worse than death [19]. A change in health is then quantified by its corresponding change in EQ-5D value.

At the final visit of each reference study, patients treated with buprenorphine were assumed to have reached their individual optimal pain relief, i.e. their optimal HRQoL level. The difference in EQ-5D estimates between the baseline visit and the final visit was therefore used as a measure of the treatment effect of buprenorphine on HRQoL. These HRQoL changes were estimated for each reference study and are referred to as gains in quality adjusted life years (QALYs).

Patients were allowed paracetamol during the screening phase and as co-administered rescue medication in three of the four reference studies [11,12,14]. The forth study allowed ibuprofen instead [13]. The EQ-5D estimate at baseline is thus assumed to correspond to the HRQoL when treated with paracetamol. As it is likely that HRQoL does not change under constant treatment of a chronic disease this analysis assumes that the HRQoL of the no-treatment alternative is constant over time, i.e. the changes in HRQoL of the no-treatment alternative is set to zero.

All statistical analyses of the EQ-5D data were performed using STATA 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

2.3. Treatment costs

Treatment costs were estimated for a 12-month period, including costs for drugs and physician visits for the two evaluated alternatives; the 7-day buprenorphine patch and the no-treatment alternative.

Pharmaceutical costs were calculated based on the reported optimal treatment dose of buprenorphine in each study plus co-administration of rescue medication (paracetamol, assuming the maximum dose of 4 g per day) [11–14]. Two of the reference studies present optimal buprenorphine doses and they exclusively fall in the range 10–15 μg/h. Consequently the base case cost calculation of buprenorphine treatment considers both a 10- and a 15 μg/h dose. The no-treatment alternative was assumed to be the maximum dose of paracetamol, 4 g per day. Thereby, the assumed use of rescue medication is equivalent to the no-treatment alternative.

Since no information regarding the quantity of annual physician visits was available in any of the publications six physician visits were assumed irrespective of treatment alternative. The six-visit assumption was based on the need of individualized opioid treatment, which requires continuous physician visits [6]. The assumption was strengthened by a European study of chronic pain that stated that 60 percent of all pain patients made between 2 and 9 medical visits during 6 months, converting to 4–18 visits per year [1]. An average of six annual physician visits seems an appropriate, or even conservative, assumption. Throughout the analysis 70 percent of the physician visits were allocated to primary care while the remaining 30 percent was assumed to be specialist visits. The 70/30 allocation is according to estimates of the European study of chronic pain [1]. In the base case analysis of six annual physician visits, the 70/30 allocation correspond to four primary care visits and two specialist visits per year (4/2).

Unit costs for pharmaceuticals and physician visits were collected from official Swedish price lists [15,20]. All unit costs are expressed in 2013 SEK and presented in Table 2.

Table 2
Unit costs of physician visits and pharmaceuticals (in 2013 SEK). SEK 100 was about €11.

Resources	Unit cost
Primary care visit	1 386
Specialist visit[a]	1 434
Buprenorphine 5 μg	49
Buprenorphine 10 μg	86
Buprenorphine 15 μg[b]	135
Buprenorphine 20 μg	154
Paracetamol (lowest price), 500 mg	0.53

[a] An average cost of specialist visits at a rheumatology clinic (SEK 1 685) and an orthopaedic clinic (SEK 1 183).
[b] Combination of buprenorphine 5 μg/h and buprenorphine 10 μg/h (SEK 86 + SEK 49).

2.4. Incremental cost-effectiveness ratio

An incremental cost-effectiveness ratio (ICER) is the ratio of a change in treatment cost induced by implementation of a new treatment alternative relative to the change in treatment effect, i.e. HRQoL [21]. The ICER hence translates into the cost per gained health effect with the new treatment compared to its alternative. In the present analysis the effects are measured in gained QALYs and the costs refer to treatment costs. Thus, the ICERs are calculated as:

$$\text{ICER} = \frac{\text{Cost}_{\text{buprenorphine}} - \text{Cost}_{\text{no-treatment}}}{\text{Effect}_{\text{buprenorphine}} - \text{Effect}_{\text{no-treatment}}}$$

EQ-5D data retrieved from each reference study were evaluated and the corresponding QALY gain from buprenorphine treatment was estimated. The reference studies that generated the largest and smallest QALY gains were then used as a proxy range of the true gain in QALYs from buprenorphine treatment. The assessed QALY range was then applied in the cost-effectiveness calculations in order to establish the minimum and maximum ICER.

2.5. Sensitivity analysis

In order to evaluate the robustness of the base case results a number of sensitivity analyses were conducted by varying the uncertain parameters; physician visits, buprenorphine dosage and costs of pharmaceuticals.

The annual physician visits were varied between 4, 10 and 13 for buprenorphine treatment. Keeping the 70/30 visit allocation resulted in a primary-/specialist visit variation as 3/1, 7/3 and 9/4. The number of visits for the no-treatment alternative was fixed at six.

Additionally, a buprenorphine dose of 20 μg/h following the base case visit allocation 4/2 was included. The 20 μg/h dose, falling outside the optimal-dose range, constitutes a sensitivity analysis in itself and the physician visits were thus not varied for this treatment alternative.

A supplementary sensitivity analysis was performed on the no-treatment alternative, where both pharmaceutical cost and number of annual visits were varied.

3. Results

3.1. Health-related quality of life

Results from the analyses of HRQoL data from the reference studies, applying both the UK and the Swedish EQ-5D weights, are presented in Table 3.

At baseline the UK weights estimate HRQoL to be approximately half as good as in a state of perfect health (0.505–0.592), while the Swedish application value the baseline health at around three quarters of a perfect health state (0.757–0.782).

Furthermore, the estimation with the UK weights shows that buprenorphine treatment increases HRQoL with between 0.042 and 0.118 QALYs annually, depending on reference study. The estimation using Swedish weights is approximately half as large, between 0.020 and 0.051 QALYs.

The results indicate that buprenorphine treatment improves HRQoL, irrespectively of EQ-5D weight set.

3.2. Costs

Treatment costs, including both the cost of pharmaceuticals and of physician visits, are presented in Table 4. In the base case the annual treatment cost of the no-treatment alternative sums to SEK 9 960. The total annual cost of buprenorphine treatment varies with dosage from SEK 14 454 for the 10 μg/h patch to SEK 17 017 with the 15 μg/h patch.

3.3. Incremental cost-effectiveness

The ICER corresponds to the ratio of the additional cost of buprenorphine treatment over the improvement in HRQoL compared to the no-treatment alternative. The results of the base case analysis are presented in Table 5.

The cost of treatment, and consequently the ICER, varies with the buprenorphine dose. In the base case analyses, the maximum ICER when applying the UK weights is SEK 168 000 per QALY gained, while the corresponding number using the Swedish EQ-5D weights is SEK 353 000.

The highest cost per QALY gained, i.e. the highest ICER value, corresponds to treatment with the more costly buprenorphine dose of 15 μg/h. Conversely, the lowest ICER value is found when considering the lower treatment dose, buprenorphine 10 μg/h.

The ICERs of the Swedish EQ-5D weights are approximately twice the ICERs of the UK weights in all cases.

3.4. Sensitivity analysis

The results from the sensitivity analyses are presented in Table 5. The ICER-span is between SEK 14 000 and SEK 400 000 with the UK weights and stretch from SEK 33 000 to SEK 840 000 with the Swedish weights.

The main part of the total treatment cost corresponds to costs of physician visits. Consequently, a variation of the number of visits has the highest influence on the ICERs. Again, the ICERs based on the Swedish EQ-5D weights are approximately twice the ICERs estimates using the UK weights.

Varying the annual physician visits of the no-treatment alternative between 4 and 13, when considering the lowest available market price of paracetamol, produced annual treatment costs in the range SEK 4 368–SEK 19 758 (not presented).

4. Discussion

This health economic analysis evaluates the cost-effectiveness of buprenorphine patches compared to no-treatment in patients with moderate chronic pain over the age of 50, in a Swedish setting. HRQoL data was collected from four clinical trials and annual treatment costs were calculated based on costs of physician visits and pharmaceuticals. The base case result present ICERs up to SEK 168 000 when applying the UK weights and SEK 353 000 with the Swedish EQ-5D weights.

The ICER-values in the sensitivity analysis vary considerably, even under a given EQ-5D weight set. The variation primarily depends on the number of annual physician visits. The conservative assumption potentially causes underestimated treatment costs in absolute terms. Provided that the number of visits is kept equivalent between the evaluated alternatives they will cancel out in the comparison and are irrelevant to the ICER. In addition, patients in the no-treatment group may experience more pain and may therefore be inclined to seek additional medical care. If so, the treatment cost of the no-treatment alternative would increase and further strengthen the cost-effectiveness of buprenorphine.

Sweden presently lacks general guidelines regarding the economic worth of a QALY, although a threshold of SEK 655 000 has been discussed [22]. However, the NBHW has quantified the cost per QALY gained below SEK 100 000 as *low* and SEK 100 000–SEK 500 000 as *moderate* [23]. The results of the present analysis state that the treatment effect of buprenorphine generally falls within the moderate cost range. Thus, buprenorphine treatment could be considered cost-effective since the ICER-values correspond to

Table 3
Mean HRQoL outcomes based on EQ-5D data in patients >50 treated with buprenorphine.

Reference studies	N[a]	UK EQ-5D weights			Swedish EQ-5D weights		
		Baseline visit	Final visit	Difference[b]	Baseline visit	Final visit	Difference[b]
Karlsson and Berggren [12]	60	0.526	0.625	0.099	0.772	0.823	0.051
Breivik et al. [11]	84	0.592	0.634	0.042	0.782	0.801	0.020
Conaghan et al. [13]	102	0.516	0.632	0.116	0.757	0.785	0.028
Karlsson et al. [14]	116	0.505	0.623	0.118	0.758	0.804	0.046

[a] Patients where an EQ-5D assessment was available at both baseline and final visit.
[b] Refers to the number of QALY gained.

Table 4
Annual costs of pharmaceuticals and physician visits (in 2013 SEK). SEK 100 was about €11.

Pharmaceuticals	Drug costs			Cost of physician visits[b]	Total treatment cost
	Units	Drug cost	Rescue medication[a]		
Paracetamol 4 g/day (lowest price), tablets	2 920	1 548	–	8 412	9 960
Buprenorphine 10 μg/h, patches	52	4 494	1 548	8 412	14 454
Buprenorphine 15 μg/h[c], patches	52	7 057	1 548	8 412	17 017

[a] Equivalent to the drug cost of paracetamol 4 g/day.
[b] Cost corresponding to 2 specialist visits and 4 primary care visits.
[c] Drug costs correspond to a combination of buprenorphine 5 μg/h and buprenorphine 10 μg/h.

an accepted cost range [22,23], particularly since TLV recommends use of the UK weights which generates ICERs below SEK 400 000.

Even though the UK and the Swedish HRQoL estimates in this analysis are based on the same EQ-5D data they generate rather diverse estimates, both in absolute terms and regarding the benefit of health improvements. The variations are explained by the EQ-5D weights ascribing different HRQoL values to the same health states. Compared to the estimates using the Swedish weights, the UK weights generate considerably larger QALY gains which results in more cost-effective results.

The UK weights are based on a hypothetical health methodology while the Swedish weights were constructed using an experienced-based approach. A hypothetical health methodology asks the study participants to rank a provided set of health states without the participant necessarily having personal experience from any of the presented health states. In an experienced-based approach, as that of the Swedish study, the study participants are asked to rank their own current health in relation to a state of perfect health during a given time period. It is a known fact that individuals tend to value their own health state higher than the average population would [24], which explains the higher estimates in absolute terms when using the Swedish weights. Consequently, an impaired health state such as chronic moderate pain is penalized harder, and an improved health is rewarded more generously, with the UK weights. The variation in penalties are especially large regarding the pain dimension [7,8]. Therefore the varying HRQoL outcomes between the weight sets in the present analysis are according to expectation.

Table 5
Base case and sensitivity analyses of incremental cost-effectiveness ratios (ICERs), 2013 prices in SEK. SEK 100 was about €11.

Treatment	Treatment cost buprenorphine			Cost no treatment[b]	Cost difference	ICERs based on UK EQ-5D weights		ICERs based on Swedish EQ-5D weights	
	Drug cost[a]	Physician visits	Total			QALY gain 0.042	QALY gain 0.118	QALY gain 0.020	QALY gain 0.051
Buprenorphine 10 μg/h									
Base case, 6 visits	**6 042**	**8 412**	**14 454**	**9 960**	**4 494**	**107 000**	**38 085**	**224 700**	**88 118**
4 visits	6 042	5 592	11 634	9 960	1 674	39 857	14 186	83 700	32 824
10 visits	6 042	14 004	20 046	9 960	10 086	240 143	85 475	504 300	197 765
13 visits	6 042	18 210	24 252	9 960	14 292	340 286	121 119	714 600	280 235
Buprenorphine 15 μg/h									
Base case, 6 visits	**8 605**	**8 412**	**17 017**	**9 960**	**7 057**	**168 024**	**59 805**	**352 850**	**138 373**
4 visits	8 605	5 592	14 197	9 960	4 237	100 881	35 907	211 850	83 078
10 visits	8 605	14 004	22 609	9 960	12 649	301 167	107 195	632 450	248 020
13 visits	8 605	18 210	26 815	9 960	16 855	401 310	142 839	842 750	330 490
Buprenorphine 20 μg/h									
6 visits	9 556	8 412	17 968	9 960	8 008	190 667	67 864	400 400	157 020

[a] Including cost of rescue medication.
[b] No treatment is defined as paracetamol 4 g/day, 4 primary care visits and 2 specialist visits per year (SEK 9 960).

The estimated differences between the UK and the Swedish EQ-5D weights in this analysis may have considerable implications. Health care interventions found cost-effective using the UK weights will not necessarily be cost-effective with the Swedish regimen, or vice versa. Suppliers of health care interventions are often required to provide evidence of cost-effectiveness of their product when applying for reimbursement status, the results of which may be affected by the choice of EQ-5D weights as shown in the present analysis. This in turn implies that the assessment by the reimbursement authority, i.e. what health care intervention reaches the patients, may be determined by the choice of EQ-5D weight set.

Clinical studies show that the 7-day buprenorphine transdermal patch is an effective and well tolerated treatment alternative for patients with moderate to severe chronic pain [11–14]. These results are supported by the findings of the present analysis where buprenorphine improved HRQoL.

Opioid treatments are known to cause a high frequency of side effects [5]. In one of the reference studies about 30 percent of the patients withdrew from the study due to side effects from buprenorphine [11]. Still, buprenorphine is a more gentle treatment than other available opioids [2]. Costs for treatment of opioid side effects, e.g. nausea, constipation, dizziness and falls are not included in the analysis due to lack of information on incidence and treatment cost of complications. Including the costs of side effects would increase the cost of buprenorphine treatment compared to the no-treatment alternative. Excluding the withdrawn patients in the reference studies is also likely to effect the HRQoL results in favour of buprenorphine. In addition, this analysis also excludes additional costs of potentially insufficient pain management of the no-treatment alternative, which may lead to a need for excess utilization of other health services. These exclusions, due to lack of available data, are a weakness of the present analysis although each exclusion may reduce the effect of the other. Additionally, the effects of unrelieved pain are assumed to be incorporated in the HRQoL assessment.

The buprenorphine doses applied in the present analysis were based on the average doses found in the reference studies, varying between 11 μg/h and 14.5 μg/h [11,14]. The highest average dose was found in a patient aged 50–60 while the optimal dose were lower for patients aged 65 or older [14]. The absolute treatment cost of buprenorphine may thus be lower for the >65 than the 50–60 patient group and it is possible that buprenorphine becomes more cost-effective with age. It might therefore be a limitation that the present analysis includes patients between 50 and 65 years of age even though similar pharmacokinetics and pharmacodynamics have been reported for all patients older than 50 years of age [14,18].

It is also noteworthy that despite the implied cost-effectiveness of buprenorphine for all analyzed patients, the treatment recommendations for patients aged 50–65 differ from those for patients >65. There are additional recommended treatment alternatives available for the 50–65 age group that face lower risk of opioid side effects, and the present analysis does not rule out that there are more cost-effective alternatives than buprenorphine for these patients.

An advantage of buprenorphine, in addition to the cost-effectiveness implied in the results of this analysis, is that it does not require dose adjustment due to renal impairment in contrast to strong opioids. This is partly why buprenorphine may be a suitable opioid treatment alternative. Since many elderly suffer from renal impairment this may further strengthen the attractiveness of buprenorphine for this patient group.

Health economic analyses are performed on a group level, while treatments such as pain management need to be individually tailored for each patient. Therefore, the present analysis cannot rule out that there may be treatment alternatives that are more suitable and more cost-effective than buprenorphine for individual patients, e.g. patients who suffer from side effects of buprenorphine.

5. Conclusion

The ICERs of the 7-day buprenorphine patch fall within moderate cost per QALY according to the NHBW categorization. Buprenorphine can thus be considered a cost-effective treatment of moderate chronic pain in older patients.

The UK and the Swedish EQ-5D weights generated vastly different HRQoL estimates but buprenorphine remains cost-effective regardless choice of weight set.

6. Implications

Buprenorphine is a treatment alternative in clinical praxis that could be included in the Swedish reimbursement scheme.

The substantial differences in the HRQoL estimates show that the choice of EQ-5D weight is crucial for the results of a cost-effectiveness analysis. Thus, the comparability of studies applying separate weight sets is doubtful. Clear guidelines of the appropriateness of each weight set are thus of utter importance.

Conflict of interest

The present work was financed by Mundipharma AB. Mundipharma AB had no influence on either structure, analytical methods or the presented results of the analysis.

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