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Intrathecal drug delivery systems for the management of chronic non-cancer pain: a systematic review of economic evaluations

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Competing interests

The authors declare that they have no competing interests.

ABSTRACT

Background: Intrathecal drug delivery (ITDD) systems are one of a limited number of management options for chronic non-cancer pain, cancer pain and spasticity. Concerns over their effectiveness and high initial costs led NHS England to decommission ITDD for patients with chronic non-cancer pain. However, the extent to which this decision is in line with existing economic evidence is unclear. The aim of this systematic review is to identify and review the existing evidence on the cost-effectiveness of ITDD for chronic non-cancer pain.

Methods: Full and partial economic evaluations on ITDD were identified through systematic searches in MEDLINE, EMBASE, Web of Science and the National Health Service Centre for Reviews and Dissemination databases. Database searches were complemented by hand searching of reference lists of relevant studies and searches of grey literature. Study selection was carried out by two assessors, independently. Study quality assessment was performed to inform critical appraisal of health economics studies. Data were extracted using a data extraction form developed for this study.

Results: 4464 unique studies were identified, of which seven met the inclusion criteria. With the exception of one study, the studies found ITDD to be either cost-saving or cost-effective compared to conventional medical management. ITDD becomes cost-ineffective in one further study following price year adjustment to 2016.

Conclusions: Study findings show ITDD as not cost-effective only in extremely conservative scenarios. There is limited evidence on the effectiveness of ITDD in non-cancer pain; however, the available economic evidence controverts arguments to refute the treatment on economic grounds.

Keywords: chronic pain, cost-effectiveness, economic evaluations, intrathecal drug delivery

INTRODUCTION

Estimates of the prevalence of chronic pain range between 13% to 51%.[1-3] The variation across studies is mainly due to the employed definition of chronic pain and the populations studied. Regardless, the prevalence of chronic pain is higher than other common chronic conditions such as diabetes mellitus (Type 1 or Type 2), which has a considerably lower prevalence of 7% among men and 4.9% among women.[4] Chronic pain presents a significant health burden associated with significant reductions in health-related quality of life. The National Pain Audit 2012 observed that the mean EuroQol index score in people suffering from chronic pain was 0.4, which is lower than that reported by people with progressive neurological disorders such as Parkinson's disease (0.432).[5] Furthermore, persistent pain conditions such as neck pain, migraine, arthritis and low back pain cause more global disability than any other condition.[6]

The economic burden of chronic pain is equally significant. The UK economy incurs about £12.3 billion per year for managing back pain alone and costs associated with pain are estimated to be much higher.[7] Chronic pain sufferers are seven times more likely to quit their jobs due to ill health than the general population, and chronic pain remains the second most common reason for claiming

incapacity benefit.[7] More concretely, pain prevents 40% of people with chronic pain from working and causes an additional 12% to have reduced working hours.[5]

Pain management strategies explored first include those options with the lowest risk of complications and least invasiveness. Treatment plans with higher risks are gradually introduced as the pain becomes refractory to previous options.[8]

Spinal cord stimulation (SCS) and intrathecal drug delivery (ITDD) have been seen as 'last resort' options and are typically made available to patients who have experienced prolonged periods of pain, sometimes as long as 40 years.[9-11] ITDD is used for the management of cancer and non-cancer pain, and spasticity.[12,13] There are different levels of evidence for the use of ITDD in these different conditions.[14-16] NHS England currently commissions ITDD for the management of cancer pain [17] and spasticity [18] but not for pain of non-cancer origin as it was considered that there was insufficient evidence to support routine commissioning in this patient group.[19] Although the limitations of the effectiveness data are undeniable (randomised controlled trials [RCTs] are not available), poor quality economic evaluation studies were used to inform the commissioning decision for chronic non-cancer pain.

The overarching aim of this systematic review is therefore to investigate the cost-effectiveness of ITDD systems using opioids for the management of chronic non-cancer pain. To the authors best knowledge this is the first systematic review on the topic.

Accordingly, this work sets out to:

- Search bibliographic sources to identify relevant evidence on the cost-effectiveness of ITDD as compared to conventional medical management (CMM);

- Appraise the quality of the identified studies, and highlight their strengths and limitations;

- Use evidence reported in the studies to determine the cost-effectiveness of ITDD as compared to CMM;

- Discuss the potential policy implications of the findings, especially in relation to future policy reviews of ITDD for chronic non-cancer pain.

METHODS AND ANALYSIS

The systematic review was conducted according to a pre-specified protocol.[20] Systematic review registration number: PROSPERO CRD42016035266. The systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[21]

Search methods for identification of studies

Systematic searches were conducted to identify relevant economic evaluations of ITDD for the management of chronic non-cancer pain. The searches were carried out using the following electronic databases: MEDLINE(R) In-Process & Other Non-Indexed Citations and MEDLINE(R) (Ovid), EMBASE (Ovid), Science Citation Index (Web of Science), Conference Proceedings Citation Index (Web of Science), the National Health Service (NHS) Centre for Reviews and Dissemination databases NHS Economic Evaluation Database (EED), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) (all via Wiley). Grey literature was searched using OpenGrey, GreyNet, GreyLit. Searches in the electronic databases were complemented by hand searching of reference lists of relevant studies.

Databases were initially searched from their inception to 15th February 2016 and updated up to 5th September 2017. Economic studies filters designed by the NHS EED [22] and Scottish Intercollegiate Guidelines Network (SIGN) [23] to locate economic evaluation studies were used and a comprehensive search strategy developed (Appendix 1). No language restriction was applied in the searches. Literature search results were uploaded to and managed using EndNote X7.0.1 software.

Study selection

The selection criteria described in Table 1 were applied to the citations identified from the literature search. Two reviewers screened titles and abstracts of all retrieved citations independently. Where compliance with the selection criteria was unclear from titles and abstracts, full texts were retrieved. Full papers for studies deemed potentially relevant were retrieved and selection criteria were

applied. Disagreement was resolved by discussion and consensus between the two reviewers. A third reviewer would have been involved if dissenting opinions were observed and consensus was not reached.

Data extraction

Two reviewers extracted relevant information using an extraction form developed specifically for the purposes of this study. A third reviewer assessed the extracted data to ensure accuracy. Disagreements were resolved by discussion. Information was extracted in relation to the following factors: (1) general information including study author, year, funding source, country, setting, study design; (2) recruitment details, sample size, demographic characteristics (age, gender) and baseline health data (diagnosis, co-morbidities); (3) interventions, effectiveness data, cost data; (4) type of economic evaluation, perspective, time horizon, measure of benefit; (5) quality assessment; (6) results; (7) analysis of uncertainty; (8) conclusions. The outcomes for which data was sought were selected taking into account the data necessary to conduct an economic evaluation.

[Insert Table 1 here]

Quality assessment

Quality assessment of all included studies was performed using the Evers checklist (all economic evaluations)[25] and the Philips et al. checklist for model-based economic studies [26] as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[27] Two reviewers independently assessed the quality of the included studies. Any discrepancies were resolved by discussion and consensus between the two reviewers and if necessary consultation of a third reviewer.

Data synthesis and reporting

The results section was organised based on the good practice recommendations for narrative summary of health economic studies as outlined in the Cochrane Handbook for Systematic Reviews.[28] To facilitate the comparison of estimates reported in different studies, monetary values reported in all the identified studies were converted to UK pounds sterling (£) at 2016 price year. The year the study was published was assumed as the price year for those studies not reporting this information. Conversion of cost estimates were performed using the CCEMG – EPPI-Centre Cost Converter web-based tool v.1.5. The CCEMG – EPPI-Centre Cost Converter tool takes into consideration international exchange rates based on Purchasing Power Parities and gross domestic product deflator values as recommended in the economics evidence section of the Cochrane Handbook for Systematic Reviews.[28]

RESULTS

The search identified 4891 records from database searches and reference lists. After removal of duplicates (n = 427) and records not meeting the eligibility criteria (n = 4448), 16 full-text articles were retrieved and assessed for eligibility. Nine studies were excluded from the review following assessment of the full-text for various reasons as shown in Figure 1. One cost description study was excluded because the study population comprised patients with spasticity (14%), cancer pain (6%) and other chronic pain conditions but cost results were not presented separately for the different aetiologies.[29] Another study that compared the costs of ITDD to external infusion pumps was excluded because 60% of the patients had cancer pain and the cost comparison was not presented for each patient group.[30] Three of the nine studies were narrative reviews of other economic evaluations already included in this review, and were therefore excluded.[31-33] Staats et al [34] did not report any cost data and the conference abstract by Sawyer and Blowey [35] presented no information on how the total cost estimate (£460,000 for all the patients in the study, equivalent to £24,000 per patient) was calculated. Both records were excluded. The last two studies were excluded because an

economic evaluation of ITDD therapy was not performed; either only the cost impact of dose escalation [36] or of elimination of systemic opioid use were captured.[37]

[Insert Figure 1 here]

Seven studies were included in the final set of relevant studies (Table 2). Six of the studies were published in peer-reviewed journals [38,39,41-44] and one was a conference proceeding.[40] The study designs in the seven studies varied considerably. Two of the studies were retrospective analyses of database records [38,39] while another pair were retrospective case series.[40,41] Two model-based studies were identified.[42,43] Kumar et al. [43]developed a Markov model based on retrospective assessment of patient notes and de Lissovoy et al. [42] a Markov model based on the literature. One of the studies was an economic evaluation based on an RCT.[44]

In terms of the type of analysis, the two retrospective database studies were partial economic evaluations: one cost-analysis evaluation [38] and one cost description study.[39] The other five studies were full economic evaluations including, two cost-consequence analyses;[40,44] two cost-utility analyses;[41,43] and one cost-effectiveness analysis.[42]

[Insert Table 2 here]

Findings from economic evaluations of ITDD

The five full economic evaluations included in this systematic review found that ITDD is a cost-effective alternative to CMM (Table 3). The two cost-consequence analyses observed better patient outcomes and reduced costs following ITDD. Bensemmane et al reported an average treatment cost reduction per patient year of 26% following ITDD and improvements in pain and disability.[40] Kumar et al saw an average improvement in disability of 27% and a break-even point in comparison to CMM at 28-months post ITDD implantation.[44] The model-based cost-effectiveness analysis by de

Lissovoy et al found that only in a worst-case scenario would ITDD become more costly than CMM.[42] The cost-utility analyses by Biggs et al and Kumar et al reported that ITDD was cost-effective when compared to CMM at a willingness-to-pay (WTP) threshold of £30,000 per quality adjusted life year (QALY) gained in the UK and $20,000 per QALY gained in Canada respectively.[41,43] Biggs and colleagues also observed that there was a reduction in costs between the decision to implant a patient and the actual procedure, which could have an impact in the cost-effectiveness analysis.[41] Kumar et al estimated an 84% probability that ITDD was a cost-effective alternative to CMM at the Canadian WTP threshold and that these results were resistant to parameter uncertainty.[43] Discrepant findings were reported by the two partial economic evaluations included in this systematic review. Guillemette et al observed that non-cancer pain patients that receive an ITDD implant experienced a reduction in future medical costs when compared to CMM.[38] Thrasher and Fisher reported that the post-implantation costs were higher than the costs prior to implantation.[39] The time horizon for this study was six years which includes three years prior to implantation and three years' post-implantation. Other studies have found that ITDD breaks-even within three years following implantation.[38,44]

[Insert Table 3 here]

Currency and price year adjusted findings

For the purposes of comparison across studies, the cost estimates were converted to pounds sterling (£) for the price year 2016 (Table 4). The most important change occurred in the Biggs et al study but giving more relevance to what the authors had observed, i.e. a reduction in healthcare resource use in the period between the decision to implant a patient and the actual procedure (latent period).[41] The inclusion in the study time horizon of this latent period would lead to ITDD being considered cost-ineffective at the UK's WTP threshold of £30,000 per QALY gained. This period was found to have an average duration of 263 ± 176 days (range 3–489).[41] The incremental cost effectiveness ratio

(ICER) without and with the inclusion of a latency period were £26,080/QALY gained and £29,030/QALY gained respectively.[41] These values increased to £29,453 and £32,784 after currency and price year adjustment. No relevant alterations were observed for the remaining studies.

[Insert Table 4 here]

Methodological aspects

Perspective

Four of the studies adopted a health services perspective [40,41,43,44] and the three US studies, that of the insurer.[38,39,42] Thrasher and Fisher mention societal costs throughout the study.[39] However, only costs from medical and pharmacy claims were analysed from the perspective of health insurance. It is also clearly stated by the authors that only direct costs were included and indirect costs, such as lost time or lost productivity, were not considered. Throughout the title, abstract and text, the term 'societal' was incorrectly used as only insurance claims were considered.

Costs, currency and price year

All the included studies reported the currency, which included Canadian dollars,[43,44] US dollars,[38,39,42] UK pounds sterling [41] and Euros.[40] With the exception of the Bensemmane study, all of the studies reported the price year used.[40]

There was considerable variation amongst the included studies regarding the costs that were included in their analyses. Equipment and implantation costs were included in all of the full papers. It is not clear whether these costs were included by Bensemmane et al which appears to only have included pharmaceutical costs, number of visits and days of hospitalisation.[40] Costs of intrathecal drugs were considered by all the included studies but it is unclear if all the studies accounted for the refill procedure, which incurs a higher cost than just the intrathecal drug(s). A limitation evident in most of the studies was the non-inclusion of additional treatments and systemic medications that

patients may still require even if using an ITDD system. The exceptions were the studies by Biggs et al and Guillemette et al.[38,41]

Only one of the studies acknowledged the omission of costs that would be relevant to address the economic question as a limitation of the study. Biggs et al did not include costs due to general practitioners appointments and prescriptions related to the patients' pain but argued that the inclusion of these costs would lead to an increase of the cost-effectiveness of ITDD.[41] The rationale was that as patients gain access to pain clinicians, it would be likely that patients require fewer GP appointments for pain-related causes.

Measures of benefits used in the economic analysis

The measure of benefit was the QALY in two of the studies, derived from responses to the EQ-5D instrument.[41,43] The CCA by Kumar et al [44] used disability as measured in the Oswestry Disability Index, while de Lissovoy et al [42] defined efficacy as good to excellent pain relief. Two studies collected effectiveness data but did not employ a measure of benefit.[40,44] The studies by Guillemette et al [38] and Thrasher and Fisher [39] were partial economic evaluations where no assessment of benefits was undertaken.

Time horizons and discount rates adopted

Chronic pain is typically a life-long condition and this would be the ideal time horizon for an economic evaluation in this population.[24] The longest time horizon reported was 10-years in the economic model developed by Kumar and colleagues.[43] The effectiveness data and estimates of complications were sourced from patients' notes. The authors considered a 10-year time horizon as meaningful because robust outcome data was unavailable, and technological and pharmacological advances would have occurred within this period. All of the studies included had a time horizon longer than one-year. Guidance on the conduct of economic evaluations prescribes that costs and outcomes estimated over one year should be discounted at an appropriate rate, and reported.[24]

However, four studies either did not use or did not report a discount rate.[39-41,44] Thrasher and Fisher evaluated information from a longitudinal claims database over a 6-year period.[39] For patients with pre and post-implantation data, 12-months information before and after implant were considered in the analysis while information on just the first 12-months were considered in patients for whom only post-implantation data were available. Given that the total information content for the former patient group was 24 months, cost and benefits should have been discounted.

Kumar et al. [43] and de Lissovoy et al. [42] used an annual 5% discount rate. Kumar et al. [43] discounted both costs and benefits, but it is not clear if de Lissovoy et al. [42] applied the discount rate to the treatment outcomes and cost or only the costs. In their cost-analysis, Guillemette and colleagues only discounted costs at a 3% annual rate.[38]

Assessment of uncertainty

Two studies did not assess uncertainty.[39,40] Different approaches were observed in the remaining studies. Biggs et al. used a nonparametric bootstrapping approach to analyse the data.[41] Guillemette et al. carried out univariate sensitivity analysis to investigate the impact of changes in the ITDD battery life, the pre-implant experience period and the medical cost trend assumptions.[38] Sensitivity analyses in the form of best and worst-case scenarios were undertaken in de Lissovoy et al. [42] and Kumar et al.[44] Kumar and colleagues also investigated the impact that an increase in the cost of the pump, increase in the pump's battery life and a reduction in the costs of complications associated with ITDD surgery would have in the results.[44] The rationale for choosing these aspects and the reason for not investigating the impact on the results, for example of a reduction in the pump's battery life (the potential consequence of a higher intrathecal dose), is not clear. Kumar et al. carried out deterministic and probabilistic sensitivity analyses to identify key areas of uncertainty and determine model drivers.[43]

Generalisability of the results

Most studies attempted to address the generalisability of the observed results to other settings, either by carrying out assessments of uncertainty or by comparing the results with those from previous studies. The exceptions to this were the abstract by Bensemmane et al. [40] and the study by Thrasher and Fisher.[39] There were no indications that the results in Thrasher and Fisher were generalisable to settings outside the US. The authors discussed other studies that evaluated the cost-effectiveness of ITDD, however, they did not conduct a full economic evaluation and the perspective used was incorrectly claimed as societal. Kumar et al. attempted to address the generalisability of the results to other settings by reporting the costs and quantities separately, by carrying out sensitivity analyses and comparing the results obtained to those observed in previous studies.[44] The data that informed the Markov model in Kumar et al. was obtained from a single centre, and as acknowledged by the authors, the model represents the management of a typical patient with chronic non-cancer pain at that particular centre.[43] The authors carried out sensitivity analyses that demonstrated the robustness of the results. Kumar and colleagues compared their results with those from previous studies and to the WTP threshold adopted in the US and UK.[43]

Methodological quality and limitations

The conference proceedings abstract by Bensemmane et al. [40] does not contain sufficient information to allow quality assessment. Based on the Evers checklist, the studies addressed most items (Appendix 2).[25] Five of the six studies addressed more than half of the items on the checklist. None of the studies addressed item 19, which relates to the discussion of ethical and distributional issues. Some of the studies were partial economic evaluations; therefore, items on outcome measures would be answered negatively. Based on the Evers checklist, the study by Thrasher and Fisher [39] was considered to be of the lowest quality as only four questions were answered positively. According to the Evers checklist, the best quality study was Kumar et al.,[43] which just failed to address ethical and distributional issues.

Two of the studies were model-based economic evaluations and were therefore also assessed using the Philips checklist (Appendix 3).[26] The first model was developed in 1997,[42] before the publication of any specific checklist for economic models. Twenty-five out of 57 questions in the Philips checklist were either unclear or not addressed in de Lissovoy's et al. model,[42] and 15 questions were not applicable; 11 of 15 questions were in the 'Data' section of the checklist. The second model by Kumar et al. [43] addressed 35 questions in the checklist and only eight were answered negatively. According to the Philips criteria, the paper by Kumar et al. [43] presented a better quality economic model of ITDD for chronic non-cancer pain.

Additional methodological issues

In the abstract by Bensemmane et al the data was collected retrospectively from the medical records of five patients implanted during 2006/2007.[40] Although the authors stated that data from a period of three years after implantation was collected, the effectiveness results only covered the first 12 months and it is not clear if the remaining data collected was limited to this period as well. Although the authors did not use a measure of benefit in the economic evaluation, effectiveness outcomes included the visual analogue scale (VAS) and Oswestry disability index (ODI).

One of the economic models intended to focus on chronic intractable pain attributed to failed back surgery syndrome (FBSS).[42] However, the authors considered that the available data on the rate of occurrence of specific complications associated with ITDD was sparse and therefore also pooled data from ITDD studies on cancer pain. Patients with cancer pain usually require higher intrathecal doses, leading to a higher rate per day, which contributes to faster battery depletion and consequent replacement. It is not clear if the data provided by the manufacturer on pump failure rates and pump life (median = 48 months) refers only to those patients with FBSS or also includes other non-malignant aetiologies and cancer pain. The adverse event rates were converted into an annual rate and assumed to remain constant over the 60-month time horizon. Although this approach is acceptable, the most common complications which are catheter related occur early; the estimates

used are likely not reflective of current practices due to improvement in technology and for some adverse events, alternative time to event rates may need to be considered. The longest average follow-up in the studies included was 27.8 months. Some complications and associated co-morbidities may occur or may be identified at later stages such as granulomas,[45-47] hypogonadotrophic hypogonadism [48,49] or decrease in bone mineral density [50,51] and could have an impact on the results observed.

The only conventional management included by de Lissovoy et al in the ITDD group was supplemental medication with a base case cost of $59.[42] Although patients receiving CMM are more likely to require interventions, in the long term, it is possible that patients receiving ITDD will also require additional treatments (e.g. spinal fusion, facet injections) if their condition deteriorates. A large discrepancy in the cost of medication was used for the model, with CMM patients estimated to have an annual medication cost of $4847 compared with ITDD patients cost of $59 per month or $708 per year. Patients receiving CMM may also experience complications / side-effects which have not been accounted for.

Efficacy data used in de Lissovoy et al [42] was based on data from two studies.[52,53] Neither of these studies had a focus on patients with FBSS and the administration route in the Auld et al study was epidural rather than intrathecal. For CMM patients, it was assumed that these would only have inadequate pain relief and therefore efficacy of CMM was valued as zero (i.e. zero months of pain relief), presumably for base, best and worst-case scenarios.

It should be noted that although the data from Kumar et al [44] was based on a RCT, besides stating that the two groups were matched for age, sex and number of prior operations, the authors did not present additional details to assess the quality of the RCT design including information on power calculation, methods of randomisation or loss to follow-up. The authors collected effectiveness data using the ODI, VAS and patient satisfaction. While the results for improvement in disability using the ODI were presented for each group, the VAS and satisfaction were only reported for those patients receiving ITDD, therefore not allowing comparisons with the CMM group.

Guillemette et al extracted data over a six-year period, which covered three years prior to implant, implant month and three years following implant.[38] The data for this period of time was used as the basis for extrapolating the patient medical costs over a 30-year time horizon. The pre-implant data was used to simulate a CMM protocol to compare with the actual post-ITDD implant claim experience to determine the difference in outcomes. For the simulation of the CMM protocol, it was assumed that the patients costs would follow the patterns as experienced during the pre-implant period. Although the authors indicated that the data extracted were for a six-year period, from a sample size of 555, only 7% (n=39) of the patients prior to implant and 8.3% (n=46) of the patients post-implant provided three-year data for each of the time periods. However, when the authors present the three-year 'actuarial' cost projection for the CMM group post-implant, the number of patients is claimed to be 46, when in fact the information had been derived from the data of 39 patients (those with prior to implant data).

DISCUSSION

This systematic review investigated the cost-effectiveness of ITDD for the management of chronic non-cancer pain. Although a limited number of economic evaluations were identified, six of the seven studies indicate that ITDD is a cost-effective alternative to CMM for this population. While differences across the studies in terms of type of economic evaluation, perspective adopted and setting in which ITDD was evaluated do not allow to draw firm conclusions, this systematic review reveals important points that are relevant for future economic evaluations of ITDD for chronic non-cancer pain. An important finding of this review concerns the limitations and biases observed in current literature which should be taken into account in subsequent economic evaluations; mainly:

- No RCT evidence on the effectiveness of ITDD for chronic non-cancer pain which could inform an economic evaluation;
- CMM not standardised across the studies and unclear if standardised within studies;

- Systematic review of effectiveness and safety data not performed to inform development of existing economic models;

- Costs may have been underestimated as not all costs related to interventions for the management of the patients' pain were included in the studies;

- Costs associated with complications due to CMM not included in the studies;

- Discount rates were not used in all studies with a time horizon longer than one year;

- No economic evaluations have been conducted adopting a societal perspective.

Strengths and weaknesses of the current review

This systematic review focused on the cost-effectiveness of ITDD for chronic non-cancer pain. Comprehensive methods were employed, including searches in key electronic bibliographic databases, citation searching and discussion with experts. The search results were also not restricted for language, type of study or type of economic evaluation. Furthermore, an assessment of the quality of all of the studies was performed including an additional quality assessment of model-based economic studies where appropriate. Because there is currently no agreement as to a minimum methodological criterion to be applied to decide whether economic evaluations are included in systematic reviews, no study was excluded based on quality assessment. The implication is that the review explored the full range of costs and outcomes for ITDD. Although studies have investigated the impact of excluding studies following quality assessment on results of systematic reviews,[28] there is currently no consensus on how to generate a score or the value of these scores from the Evers et al. [25] and Philips et al. [26] checklists. A study by Thurston et al. identified six different scoring systems,[54] however, quality-scoring systems have several limitations, their use is not currently recommended and it is preferable to present a checklist or a descriptive critical assessment.[55]

Pooled estimates of costs and cost-effectiveness were not produced in this systematic review. The value of meta-analytic methods remains unexplored, and the feasibility and usefulness of this technique for economic data requires further study.[56] It has been argued that the genuine contribution that a systematic review of economic evaluations can provide is to help identify the most relevant studies considering the decision problem and setting; understanding the causal relationships in a decision problem or policy area; and informing decision model development.[56-58] Considering the decision problem (is ITDD a cost-effective alternative to CMM) and setting (hospital), the most relevant study identified was Kumar et al.[43] Only one study was conducted in the UK, although it was based on a single-centre and with a small sample size.[41] Both studies found ITDD to be a cost-effective alternative to CMM. The longest time horizon in the currently available literature is 10-years, but a model with a life-long time horizon would be the most beneficial. Other factors to contemplate when developing a model-based economic evaluation of ITDD include consideration of systemic medication and additional treatments (despite the use of an ITDD), complications that may occur following the prolonged use of ITDD, changes in practice and technology, complications following CMM, and societal costs. Societal costs are likely to assume particular importance considering the life-long nature of this condition, potential deterioration of the patient and continuous support necessary. It should be noted, that none of the studies identified included or discussed societal costs and its potential implications for the economic evaluation of ITDD.

Limitations of included studies

Limitations inherent to the studies included also contribute to the strengths and weaknesses of this review. The main limitation is the reduced number of available full economic evaluations. Five full economic evaluations were identified, one of which was merely published as a conference proceeding abstract. There were several methodological limitations in the studies included. Four of the studies did not mention the use of a discount rate, and none of the studies used a life-long time

horizon which would be appropriate for this chronic condition. Furthermore, five of the seven studies relied on cost and outcome data from either database claims data or retrospective assessment of patients notes. The data for one of the studies[44] came from an RCT, however there are not many details to appraise the quality of the RCT, and the results of the RCT were not published in a separate paper. Therefore, a quality assessment for the effectiveness study on which this economic study was based was not performed. The data to inform the remaining study [42] was derived from a literature review, although due to the limited available literature, the authors had to extract data from cancer pain papers. Although the studies included were conducted in the UK, France, Canada and the US, and considered different perspectives, the majority of the studies concluded that ITDD was less costly or cost-effective when compared to CMM. Only one of the studies considered that the costs of ITDD are superior to CMM.[39] However, this study was judged as the one with the lowest quality and the perspective was incorrectly presented; claimed to be societal when it was in fact that of the insurer. The findings from Thrasher and Fisher [39] may have occurred since there may be a reduction in health care costs once the patient is informed of suitability for ITDD. The reduction in health care costs at this stage may lead to a significant impact in the results of the economic assessment, although reliant on delay period between decision and implantation, which is practice dependent.[41]

Implications for policymakers

NHS England currently commissions the use of ITDD for the management of severe cancer pain [17] and spasticity.[18] However, NHS England does not routinely commission ITDD for severe chronic non-cancer pain as it was considered that there was insufficient evidence to support routine commissioning.[19] The economic studies used for the decision concerning ITDD for severe chronic non-cancer pain were de Lissovoy et al [42] [although Mueller-Schwefe et al. [32] was referenced], Kumar et al [44] and Bolash et al [29]. It is important to note that Bolash et al. included patients with non-cancer pain, spasticity and cancer pain, but cost results were not presented separately for the different

aetiologies. This systematic review therefore assumes particular importance, and it is thought that its findings may be taken into consideration when this policy is reviewed in 2017. Nevertheless, the main limitation in the currently available literature is the absence of an RCT on ITDD in non-cancer pain patients. Despite this lack of RCT evidence, it is unlikely that such study would obtain funding and report its findings within this timeframe. RCT evidence is difficult to produce for a fourth or fifth line therapy due to lack of a plausible comparator therapy at this stage. Alternatively, long-term observational studies may provide appropriate data to inform a model-based economic study with a longer time horizon. A de novo economic evaluation should take into account the aspects identified through this review and addressing the limitations of previous economic evaluations. Similarly to other medical technologies, ITDD has high initial costs, but according to the identified economic evaluations, the cost of ITDD breaks-even within two to three-years following implantation when compared to CMM and has reduced costs subsequently.

Future research

A limitation of currently available literature in the field of ITDD for chronic non-cancer pain is the lack of robust effectiveness studies. Systematic reviews which investigated the clinical effectiveness of ITDD for the management of chronic non-cancer pain did not identify RCTs in this area.[59-63] There has been a recently published RCT evaluating the efficacy of ITDD by randomising the patients to either a dose reduction group or a dose maintenance group.[16] Although this study supports the efficacy of ITDD, the design is not adequate for use in an economic evaluation since the same intervention (ITDD) is being compared. The lack of reliable data limits the value and interpretation of economic evaluations in this field. An adequately powered RCT comparing ITDD to CMM with a nested economic evaluation is therefore necessary to address enduring uncertainties around the clinical effectiveness and the cost-effectiveness of ITDD for chronic non-cancer pain. Alternatively, a systematic review of effectiveness, safety and cost data to inform a de novo economic evaluation comparing ITDD to CMM could be carried out. An HTA of ITDD has been

previously conducted.[59] This HTA did not develop an economic model and a plethora of additional evidence has been published since which could be valuable to inform such a model. Recently, an HTA from Health Quality Ontario identified four economic evaluations of ITDD for non-cancer pain, not considering partial economic evaluations.[64] In the HTA, quality of the economic evaluations was assessed using the Phillips checklist which should only be used for model-based economic evaluations. The authors scored the quality of the economic papers (low and very low), although the Phillips checklist was not developed or validated for this purpose. The HTA considered that current evidence does not establish (or rule out) superiority or cost-effectiveness of ITDD for managing chronic non-cancer pain. We agree with the HTA report that evidence from within-trial studies is weak. However, models are meant to address this issue. The results suggest that model ICERS are only higher than the £20,000/QALY threshold in extremely conservative scenarios, therefore suggesting that in the absence of better evidence, ITDD should be funded by the NHS. The commissioning of SCS for the management of complex regional pain syndrome (CRPS) and FBSS in the UK followed the publication of the Simpson et al. HTA.[65] The data to inform the SCS economic model was however based on RCT evidence.

In relation to methodological research a survey observed that for decision makers that require information on the quality and relevance of health economic studies, it would be of most use to have a combination of a summary or score, together with a short abstract.[54] Taking into consideration the above-mentioned difficulties to generate a single score based on quality assessment tools of economic evaluations; currently, the best alternative would be to present a checklist together with a short abstract. It may be beneficial, that such a format is requested by NHS England following a systematic review of the economic evidence to better inform the next policy review of ITDD for chronic non-cancer pain.

CONCLUSION

This systematic review identified seven economic evaluations of ITDD for chronic non-cancer pain. Six of the seven studies concluded that ITDD was less costly or cost-effective compared to CMM for a chronic non-cancer pain population. Despite the homogeneity in these findings, the main limitation of the currently available evidence is the lack of robust effectiveness data to inform economic evaluations, which also limits the robustness of the results observed. In addition to summarising the existing literature on the cost-effectiveness of ITDD, this systematic review identified factors that need to be taken into consideration in the process of model development and discusses implications for policymakers. Of particular importance is the fact that the recent NHS England policy review of ITDD for severe chronic pain did not take into account the better quality economic evidence, relying instead on lower quality studies including one which included cancer pain and spasticity patients. In some occasions, it is possible that important evidence with potential to influence decisions may not have been identified. Therefore, if there is uncertainty about the clinical effectiveness or cost-effectiveness of a treatment, a systematic review should be commissioned prior to a decision. The authors do not state that this review alone or the use of better quality economic evaluations would lead to a change in the decision, due to the limited evidence for effectiveness. However, economic models are meant to address the lack of effectiveness data. In the absence of better evidence, the results observed suggest that ITDD should be funded by the NHS based on the model ICERs observed. Even with better effectiveness data, the assessment of poor economic evaluations (when better evidence is available) could tip the decision towards non-commissioning and as a consequence, access to patients with non-cancer pain that could potentially benefit from ITDD would be denied. For the large majority of these patients, ITDD is the last option to obtain improvements in quality of life.

Figure legends

Figure 1. PRISMA flow diagram detailing the literature search

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Table 1. Inclusion criteria for identification of relevant studies

Population	Patients with chronic non-cancer pain lasting for at least three months prior to intervention
Intervention	• ITDD systems using opioids alone or in combination with other agents
Comparator	• Any comparator
Outcomes	• Effectiveness data (i.e. patient reported quality of life, pain intensity, disability, patient satisfaction) – only applicable for full economic evaluations • Direct and/or indirect costs to the health care system, patients and society • Items on resource use • Cost per unit of outcome (i.e. cost-per-QALY, incremental cost-effectiveness ratio)
Study design	• Full or partial economic evaluations as defined by Drummond et al.[24]

Type of economic evaluation	Comparison of two or more alternatives?	Costs examined?	Consequences examined?
Full economic evaluation			
Cost-minimisation analysis	Yes	Yes	No*
Cost-consequence analysis	Yes	Yes	Yes
Cost-effectiveness analysis	Yes	Yes	Yes
Cost-benefit analysis	Yes	Yes	Yes
Cost-utility analysis	Yes	Yes	Yes
Partial economic evaluation			
Cost analysis	Yes	Yes	No
Cost description	No	Yes	Yes
Cost-outcome description	No	Yes	No

* consequences assumed to be equal

ITDD, intrathecal drug delivery; QALY, quality-adjusted life years; QoL, quality of life.

Table 2: Characteristics of the included studies

Author & year	Funding	Country	Setting	Sample size	Age	Gender (%)	Diagnosis	Study design	Interventions	Effectiveness data	Cost data
Bensemmane 2011 [40]	None declared	France	Secondary care	5	NR	NR	Chronic LBP	Retrospective case series	CMM with ITDD versus CMM alone	Hospital visits and hospital days per patient per year, number of pharmaceuticals, ODI, VAS	Costs of pharmaceuticals and ITDD. All costs were in Euros (€). Unclear if the price year was 2011.
Biggs 2011 [41]	None declared	UK	Secondary care	12	54 ± 11 y (SD)	7 Female (58%)	Chronic LBP	Retrospective case series	CMM with ITDD versus CMM alone	EQ-5D	Costs of surgery and injection treatments, investigations, drugs, and consultations for pain management. All costs were in pounds sterling (£), for the price year 2009.
de Lissovoy 1997 [42]	Contract between Medtronic, Inc., and the Battelle Memorial Institute, Washington, DC	US	Secondary care	1000	N/A	N/A	Neuropathic pain (FBSS) *	Economic model based on review of the literature	CMM with ITDD versus CMM alone	Efficacy defined as good to excellent pain relief ranged from 65% (worst case) to 81% (best case). Base case was the average of the two figures (73%). Base case for duration of pain relief was calculated as 60 months x 0.73. Assumed to be 0 for CMM group.	Analysis of expenditures for alternative modalities and analysis of billing data for patients of two of the authors. Physician fees were adjusted upwards to the average private sector using a Medicare to private sector payment ratio of 0.64. Costs were in US dollars ($) for the price year 1994.
Guillemette 2013 [38]	Funded by Medtronic, Inc.	US	Secondary care	555	Median age group = 50 to 59	205 Female (37%)	Chronic non-cancer pain	Retrospective database analysis of claims data	CMM with ITDD versus CMM alone	N/A	Cost data was derived from a national claims database, comprising medical and prescription drug claims. Annual trend rates were applied to the reimbursement amounts based on each claim's date. An annual discount rate of 3% was used. Costs were in US dollars ($) for the price year 2007.

Study	Conflict of interest	Country	Setting	Sample size	Age	Sex	Condition	Study design	Intervention	Outcome measures	Cost details
Kumar 2002 [44]	None declared	Canada	Secondary care	Total - 67 ITDD group - 23 CMM group - 44	NR	ITDD group - 32 F (48%) CMM group - 21 F (48%)	FBSS	RCT	CMM with ITDD versus CMM alone	ODI, VAS, patient satisfaction	Cost references were taken from province's fee schedule where the study was conducted (Regina, Saskatchewan, Canada). Costs of the implantable devices were obtained from the manufacturer. The costs for each category were tabulated and averaged for a 5-year period. Costs were in Canadian dollars ($) for the price year 2000.
Kumar 2013 [43]	None declared	Canada	Secondary care	Total - 169 ITDD group - 125 CMM group - 44	ITDD group - 52 y CMM group - 51 y	ITDD group - 58 F (46%) CMM group - 21 F (48%)	Chronic non-cancer pain	Economic model based on retrospective assessment of patient's notes	CMM with ITDD versus CMM alone	EQ-5D	Cost references were taken from province's fee schedule where the study was conducted (Regina, Saskatchewan, Canada). Costs of the implantable devices were obtained from the manufacturer. Costs were in Canadian dollars ($) for the price year 2011.
Thrasher 2013 [39]	Funded by Pentec Health, Inc.	US	Secondary care	Before and after implantation - 1139 After implantation only - 22582	Range: 18-64 y	NR	Chronic pain	Retrospective database analysis of claims data	ITDD	N/A	Cost data were obtained from a claims database of 14 commercial health plans operating throughout the US comprising medical and pharmcy claims. Costs were in US dollars ($) for the price year 2011.

* Data from studies of ITDD on cancer pain was pooled for the rate of occurrence of specific complications

CMM, conventional medical management; FBSS, failed back surgery syndrome; ITDD, intrathecal drug delivery systems; LBP, low back pain; N/A, not applicable; NR, not reported; ODI, Oswestry disability index; RCT, randomised controlled trial; VAS, visual analogue scale; y, years

Table 3. Findings from the included studies

Author & year	Type of economic evaluation	Perspective	Time horizon	Measure of benefit	Analysis of uncertainty	Results	Conclusions
Bensemmane 2011 [40]	CCA	Health service	8 years	VAS	Not performed	Average treatment cost per patient per year decreased by 26% from €3,163 (drugs) to €2,326 (€806 drugs + €7600 pump cost amortised over 5 years). Average number of visits and hospital days per patient per year decreased by 30% (from 10 to 7 consultations) and 37% (6.2 days 3.9 days) respectively.	The use of ITDDs appears to provide better management of pain and decreased treatment costs. However, this study covers only 5 patients over a short period and does not include the cost of installation and monitoring costs. A prospective study on a larger number of patients is needed to confirm these preliminary results.
Biggs 2011 [41]	CUA	Health service	4 years plus latent period	QALY	Results presented using nonparametric bootstrapping	The estimated mean QALYs were 0.3341 before implantation and 0.6458 after implantation. When including the latent period the incremental cost per QALY gained with the ITDD versus CMM was £29,029.52. When excluding the latent period the incremental cost per QALY gained with the ITDD versus CMM was £26,079.54.	ITDD offers an economically feasible alternative solution for chronic non-malignant pain patients whose current treatment is inappropriate or ineffective. Assessments of the cost effectiveness of a health care treatment should take into consideration the existence of a latent period since this may influence not only cost efficacy evaluations but also decisions to go through with a treatment.
de Lissovoy 1997 [42]	CEA	Third party (Medicare)	5 years	Efficacy defined as good to excellent pain relief	Sensitivity analyses were conducted on all parameters of the model by varying their values across low (best case) to high (worst case) ranges to assess the effects on projected total cost. The best case value was set at 50% and the worst case value set at 200% of the base case. Elasticity values were calculated.	The incremental cost per year of pain relief for the base case was -$624, -$7,832 for the best case and $12,276 for the worst case. Based on the elasticity value, the cost of the pump/catheter implant, ongoing monthly expenses for therapy, and pump replacement were the most sensitive parameters of the model.	ITDD appears to be cost-effective when compared with alternative (medical) management for selected patients when the duration of therapy exceeds 12 to 22 months.

Guillemette 2013 [38]	Cost analysis	Third party (private commercial and Medicaid)	Data for a 6-year period was modelled over 30-years	N/A	Univariate sensitivity analysis: 1) changes in the ITDD system's battery life; 2) altering the preimplant experience period used to establish starting average cost for projection purposes; and 3) altering the medical cost trend assumptions.	ITDD was found to break-even in comparison to CMM after 27 months post-implant. Analysis of the 30-years post-implant time horizon indicates annual per patient savings of $3,111 compared with CMM. Sensitivity analyses indicated that an ITDD life expectancy increase of 50% would result in an increase of 311% in patient per year savings. If assuming a 3-year ITDD replacement cycle, ITDD would cost more than CMM over the 30-year time horizon. The other variables subjected to sensitivity analysis did not impact on the results.	Non-cancer pain patients that receive an ITDD implant may experience reduced future medical costs relative to anticipated costs under conventional therapeutic methods. The level of savings is sensitive to the duration of the implantation cycle. The longer the cycle, the greater the savings as implantation costs are amortised over the cycle period and reductions in patient utilisation begin to accumulate. Implant financial break-even point is likely to occur soon after the second year for non-cancer pain patients.
Kumar 2002 [44]	CCA	Health service	5 years	ODI	Best and worst-case scenarios. Best-case group consisted of 9 patients who experienced no complications in the 5-year follow-up period. Worst-case group consisted of 14 patients who experienced 1 or more complications during the follow-up period. Sensitivity analyses were conducted for cost of the pump, changes in the pump battery's life and complications associated with surgery for ITDD.	The cumulative costs per patient receiving ITDD for a 5-year period equalled $29,410. The cumulative costs per patient receiving CMM totalled $38,000 during the 5-year period. The cumulative costs for patients receiving ITDD in a best and worst-case scenarios were $28,264 and $31,131 respectively. ITDD was found to break-even in comparison to CMM at 28 months in the base-case scenario, 26 months best-case scenario and 30 months in the worst-case scenario. Sensitivity analyses indicated that an increase in the cost of the pump would lead to a delay in break-even point, an increase in the pump battery life would have no impact in the break-even point, while a decrease in costs associated with complications would shorten the break-even point to 26 months. Patients receiving ITDD experienced an average improvement in disability of 27% over the 5-year period compared with 12% improvement in those patients in the CMM group.	ITDD is a cost-effective method of treating chronic non-malignant pain caused by FBSS in patients who respond positively to an initial trial of ITDD. This holds true even when considering worst-case scenarios in which multiple complications may be involved. Additional benefits include increased ability to work and improved QoL with better pain control. Further cost savings will result from technological advances that will increase the life span of the pumps and improvements in catheter design that will decrease the incidence of their fracture, occlusion, and detachment. Better understanding of the long-term cost implications of ITDD compared with CPM will lead to more effective allocation of scarce health care resources.

Kumar 2013 [43]	CUA	Health service	10 years	QALY	Deterministic and probabilistic sensitivity analyses were conducted. For the cost and efficacy parameters, the extremes of ±20% from the mean were selected as reasonable upper and lower bounds.	The incremental effectiveness of ITDD was 1.1508 QALYs, at an incremental cost of $13,034, which produced an ICER of $11,326/QALY. Results from deterministic and probabilistic sensitivity analyses revealed that the cost effectiveness of ITDD was resistant to parameter uncertainty. The probability of ITDD providing a cost-effective alternative to CMM at a WTP threshold of $20,000/QALY was 84%.	Over 10 years, a patient in ITDD treatment will, on average, accrue an additional 1.15 QALYs compared with CMM. ITDD is a cost-effective treatment strategy compared with CMM, generating an ICER of $11,326/QALY, which falls below commonly accepted WTP thresholds. Significant cost savings can be attained with the use of ITDD in patients with chronic non-cancer pain.
Thrasher 2013 [39]	Cost description	Third party (medical and pharmacy claims)	6 years	N/A	Not performed	For those patients with data for before and after implantation, the costs of care pre-implant (mean ± SD) were $15,873 ± 25,273, the implantation costs were $24,413 ± 39,851 and post-implant costs were $23,541 ± 77,546. For those patients with only post-implantation data, the medical costs were $15,034 ± 63,950 and the pharmacy costs were $451 ± 2805.	The societal costs for ITDD patients are high and extremely variable. This heterogeneous population is complex and represents a heavy societal cost burden. Our data highlight the open-ended risk these patients represent for a health insurance plan and society as a whole. The opportunity exists to drastically change this pattern with a method to better identify the highest-risk individuals and develop an improved care model that is able to minimise some of the cost variability.

CCA, cost-consequence analysis; CMM, conventional medical management; CE, cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost effectiveness ratio; ITDD, intrathecal drug delivery system; ODI, Oswestry disability index; QALY, quality-adjusted life-years; QoL, quality of life; VAS, visual analogue scale; WTP, willingness-to-pay

Table 4. Findings from the included studies (currency and price year adjusted)

Author & year	Findings	Findings (currency and price year adjusted) *
Bensemmane 2011 [40]	Average treatment cost per patient per year decreased from €3,163 (drugs) to €2,326 (€806 drugs + €7,600 pump cost amortised over 5 years).	Average treatment cost per patient per year decreased from £2,804 (drugs) to £2,062 (£715 drugs + £6,738 pump cost amortised over 5 years)
Biggs 2011 [41]	With latent period included, the incremental cost per QALY gained with the ITDD versus CMM was £29,029. When excluding the latent period the incremental cost per QALY gained with the ITDD versus CMM was £26,079.	With latent period included, the incremental cost per QALY gained with the ITDD versus CMM was £32,784. When excluding the latent period the incremental cost per QALY gained with the ITDD versus CMM was £29,452.
de Lissovoy 1997 [42]	The incremental cost per year of pain relief for the base case was -$624 -$7,832 for the best case and $12,276 for the worst case.	The incremental cost per year of pain relief for the base case was -£654 -£8,213 for the best case and £12,873 for the worst case.
Guillemette 2013 [38]	Analysis of the 30-years post-implant time horizon indicates annual per patient savings of $3,111.	Analysis of the 30-years post-implant time horizon indicates annual per patient savings of £2,473.
Kumar 2002 [44]	The cumulative costs per patient receiving ITDD for a 5-year period was $29,410 and $38,000 for patients receiving CMM over the same period. The cumulative costs for patients receiving ITDD in a best and worst-case scenarios were $28,264 and $31,131 respectively.	The cumulative costs per patient receiving ITDD for a 5-year period was £22,972 and £29,682 for patients on CMM over the same period. The cumulative costs for patients receiving ITDD in a best and worst-case scenarios were £22,077 and £24,316 respectively.
Kumar 2013 [43]	The incremental effectiveness of ITDD was 1.1508 QALYs while the incremental cost was $13,034 when compared to CMM generating an ICER of $11,326/QALY.	The incremental effectiveness of ITDD was 1.1508 QALYs while the incremental cost was £7,869 when compared to CMM generating an ICER of £6,829/QALY.

| Thrasher 2013 [39] | For those patients with data for before and after implantation, the costs of care pre-implant (mean ± SD) were $15,873 ± 25,273, the implantation costs were $24,413 ± 39,851 and post-implant costs were $23,541 ± 77,546. For those patients with only post-implantation data, the medical costs were $15,034 ± 63,950 and the pharmacy costs were $451 ± 2,805. | For those patients with data for before and after implantation, the costs of care pre-implant (mean ± SD) were £11,888 ± 18,928, the implantation costs were £18,284 ± 28,846 and post-implant costs were £17,631 ± 58,077. For those patients with only post-implantation data, the medical costs were £11,260 ± 47,895 and the pharmacy costs were £338 ± 2,101. |

* Cost estimates were converted to pounds sterling (£) for the price year 2016
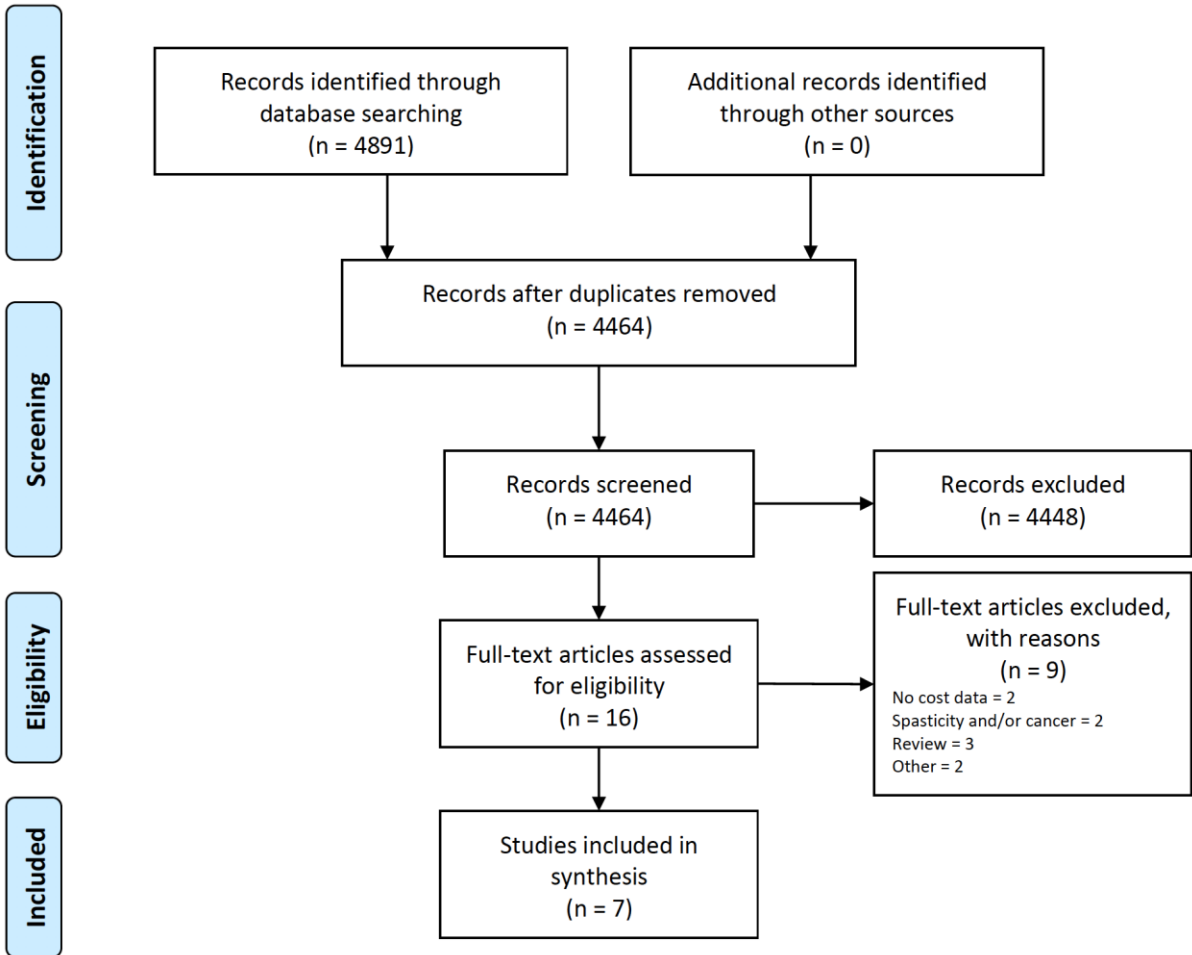
Appendix 1
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
Search strategy:
1   pain.mp. or exp Pain/
2   ((Chronic or intractable or refractory or persistent) adj3 pain$).mp.
3   or/1–2
4   infusion pumps.mp. or exp Infusion Pumps/
5   drug delivery systems.mp. or exp Drug Delivery Systems/
6   (intrathecal adj3 administration).mp.
7   it administration.mp.
8   intrathecal.mp.
9   or/4–8
10 health care costs.mp. or exp Health Care Costs/
11 direct service costs.mp. or exp Direct Service Costs/
12 drug costs.mp. or exp Drug Costs/
13 employer health costs.mp. or exp Employer Health Costs/
14 hospital costs.mp. or exp Hospital Costs/
15 health expenditures.mp. or exp Health Expenditures/
16 capital expenditures.mp. or exp Capital Expenditures/
17 health economics.mp.
18 economic evaluation$.mp.
19 economic analy$.mp.
20 costs.mp. or exp "Costs and Cost Analysis"/
21 cost-benefit analysis.mp. or exp Cost-Benefit Analysis/
22 cost effective$.mp.
23 cost benefit$.mp.
24 cost utility$.mp.
25 cost consequence.mp.
26 value of life.mp. or exp "Value of Life"/
27 economics, hospital.mp. or exp Economics, Hospital/
28 economics, medical.mp. or exp Economics, Medical/
29 economics, nursing.mp. or exp Economics, Nursing/
30 economics, pharmaceutical.mp. or exp Economics, Pharmaceutical/
31 exp "Fees and Charges"/ or fees charges.mp.
32 (fees and charges).mp.
33 budgets.mp. or exp Budgets/
34 (cost or costs or costed or costly or costing$).mp.
35 (economic$ or pharmacoeconomic$ or price$ or pricing$).mp.
36 quality-adjusted life years.mp. or exp Quality-Adjusted Life Years/
37 (qaly or qaly$).af.
38 or/10–37
39 3 and 9 and 38

Appendix 2. Quality assessment of the included studies (Evers checklist)

Item	Biggs 2011	de Lissovoy 1997	Guillemette 2013	Kumar 2002	Kumar 2013	Thrasher 2013
1. Is the study population clearly described?	Yes	Yes	Yes	Yes	Yes	No
2. Are competing alternatives clearly described?	Yes	Yes	Yes	Yes	Yes	No
3. Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	No
4. Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Yes	Yes	No
5. Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Yes	Yes
6. Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes	No
7. Are all important and relevant costs for each alternative identified?	No	No	Yes	Yes	Yes	No
8. Are all costs measured appropriately in physical units?	Yes	Yes	Yes	Yes	Yes	Yes
9. Are costs valued appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
10. Are all important and relevant outcomes for each alternative identified?	Yes	Yes	No	Yes	Yes	No
11. Are all outcomes measured appropriately?	Yes	Yes	No	Yes	Yes	No
12. Are outcomes valued appropriately?	Yes	Yes	No	Yes	Yes	No
13. Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	No	No	Yes	No
14. Are all future costs and outcomes discounted appropriately?	No	No	Yes	No	Yes	No
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Yes	Yes	No	No	Yes	No
16. Do the conclusions follow from the data reported?	Yes	Yes	Yes	Yes	Yes	No
17. Does the study discuss the generalizability of the results to other settings and patient/ client groups?	Yes	Yes	Yes	Yes	Yes	No
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	Yes	Yes	Yes	Yes
19. Are ethical and distributional issues discussed appropriately?	No	No	No	No	No	No

Appendix 3. Quality assessment of model-based studies (Philips checklist)

Item	de Lissovoy 1997	Kumar 2013
Structure		
1. Is there a clear statement of the decision problem?	Yes	Yes
2. Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes
3. Is the primary decision maker specified?	No	Yes
4. Is the perspective of the model stated clearly?	Yes	Yes
5. Are the model inputs consistent with the stated perspective?	Yes	Yes
6. Has the scope of the model been stated and justified?	Yes	Yes
7. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Unclear	Yes
8. Has the evidence regarding the model structure been described?	Yes	Yes
9. Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Unclear	Yes
10. Are the sources of data used to develop the structure of the model specified?	Yes	Yes
11. Are the causal relationships described by the model structure justified appropriately?	Unclear	Yes
12. Are the structural assumptions transparent and justified?	No	Yes
13. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Unclear	Yes
14. Is there a clear definition of the options under evaluation?	Yes	Yes
15. Have all feasible and practical options been evaluated?	No	Yes
16. Is there justification for the exclusion of feasible options?	No	Not applicable
17. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	No	Yes
18. Is the time horizon of the model sufficient to reflect all important differences between options?	No	No
19. Is the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Yes	Yes
20. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	No	Yes
21. Is the cycle length defined and justified in terms of the natural history of disease?	Not applicable	Yes
Data		
22. Are the data identification methods transparent and appropriate given the objectives of the model?	No	Yes
23. Where choices have been made between data sources, are these justified appropriately?	Unclear	Yes
24. Has particular attention been paid to identifying data for the important parameters in the model?	No	Yes
25. Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	No	Unclear
26. Has the quality of the data been assessed appropriately?	Unclear	Unclear
27. Where expert opinion has been used, are the methods described and justified?	No	Not applicable
28. Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	Unclear	Unclear
29. Is the choice of baseline data described and justified?	Yes	Yes
30. Are transition probabilities calculated appropriately?	Not applicable	Yes
31. Has a half cycle correction been applied to both cost and outcome?	Not applicable	Unclear
32. If not, has this omission been justified?	Not applicable	No
33. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Not applicable	Not applicable

34. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes	Unclear
35. Have alternative extrapolation assumptions been explored through sensitivity analysis?	Yes	Yes
36. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Not applicable	Not applicable
37. Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	Not applicable	Not applicable
38. Are the utilities incorporated into the model appropriate?	Not applicable	Yes
39. Is the source for the utility weights referenced?	Not applicable	Yes
40. Are the methods of derivation for the utility weights justified?	Not applicable	Yes
41. Have all data incorporated into the model been described and referenced in sufficient detail?	Yes	Yes
42. Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Yes	Yes
43. Is the process of data incorporation transparent?	Yes	Yes
44. If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Not applicable	Yes
45. If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Not applicable	Unclear
46. Have the four principal types of uncertainty been addressed?	No	No
47. If not, has the omission of particular forms of uncertainty been justified?	No	No
48. Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	No
49. Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	No	No
50. Has heterogeneity been dealt with by running the model separately for different sub-groups?	No	No
51. Are the methods of assessment of parameter uncertainty appropriate?	No	Yes
52. If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Yes	Not applicable
Consistency		
53. Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	No	No
54. Are the conclusions valid given the data presented?	Yes	Yes
55. Are any counterintuitive results from the model explained and justified?	Not applicable	Not applicable
56. If the model has been calibrated against independent data, have any differences been explained and justified?	Not applicable	Not applicable
57. Have the results of the model been compared with those of previous models and any differences in results explained?	Not applicable	Yes