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

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ABSTRACT

Introduction: Intrathecal drug delivery (ITDD) systems are an option for the management of patients with chronic non-cancer pain, cancer pain and spasticity. Concerns over their invasiveness and high initial costs have led National Health Service (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. To address this question, we will carry out a systematic review to identify and evaluate the existing evidence on the cost-effectiveness of ITDD for chronic non-cancer pain.

Methods and analysis: A high-sensitivity search strategy will be employed in Cochrane Library, MEDLINE, EMBASE, Web of Science, NHS EED, DARE and HTA. Database searches will be complemented by additional searching techniques. Screening of the results will be performed by 2 reviewers independently using predetermined inclusion and exclusion criteria. Full and partial economic evaluations will be included. Data extraction will be carried out using a form created for the purposes of this review. Quality assessment of all included studies will be performed using recommended checklists.

Ethics and dissemination: Ethical approval is not required as primary data will not be collected. Findings will be disseminated through peer-reviewed publications and conference presentations.

PROSPERO registration number: CRD42016035266.

INTRODUCTION

Definition of chronic pain

Chronic pain is often defined according to the duration of its symptoms, although the time to heal or repair depends on the type of the underlying injury or disease and is extremely variable. For the purposes of consistency, 3 months have been considered an appropriate point to distinguish between acute and chronic non-cancer pain, although 6 months is usually preferred for research

Strengths and limitations of this study

- First systematic review to investigate the cost-effectiveness of intrathecal drug delivery (ITDD) for chronic non-cancer pain.
- The review will consolidate the existing evidence on the cost-effectiveness of ITDD for chronic non-cancer pain.
- It may not be possible to pool estimates of costs and cost-effectiveness.
- Data synthesis will follow good practice recommendations in a narrative summary of health economic studies.

purposes.¹ Chronic pain can also be characterised as pain that persists past the time point when an injury or disease is healed or repaired has ended.¹ Healing or repair does not apply to several conditions that are treated as chronic pain, such as rheumatoid arthritis, osteoarthritis or spinal stenosis, and therefore, the concept of chronic pain should be understood as persistent pain that is not responsive to specific treatments or to typical pain relief methods including non-narcotic analgesics.¹

Prevalence of chronic pain

Estimates of the prevalence of chronic pain vary across studies, mainly due to the employed definition of chronic pain and the populations studied. A survey conducted in 15 European countries and Israel defined chronic pain as pain lasting >6 months, with pain being experienced several times during the week prior to the survey, and the last pain episode having an intensity of five or more on a 1 (no pain) to 10 (worst pain imaginable) numerical rating scale.² Based on this definition of chronic pain, Breivik *et al*² estimated the adult prevalence of chronic pain in the UK to be 13%. The UK Biobank study recruited 503 325 people aged



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between 40 and 69 years in England, Scotland and Wales.³ No specific characterisation of chronic pain was used in this case; instead, the study relied on individuals reporting their pain as acute or chronic. The study found that the overall prevalence of chronic pain was 42.9% and increased with age from 39.6% for people aged between 40 and 44 years to 45.7% for responders with an age between 65 and 69 years.³ The Health Survey for England characterised chronic pain as the experience of pain or discomfort at all of the time or on and off for >3 months.⁴ The prevalence of chronic pain was found to be higher in women (37%) than in men (31%), to increase with age from 14% of men and 18% of women aged 16–34 years to 53% of men and 59% of women aged 75 years and over, to be higher in those living in the poorest households (40% of men and 44% of women) than in the richest households (24% of men and 30% of women) and to be higher in those living in more deprived areas (36% of men and 42% of women) than in those living in the least deprived areas (31% of men and 34% of women).⁴ The prevalence of chronic pain is higher than that of other common chronic conditions such as diabetes mellitus, which has a considerably lower prevalence of 7% among men and 4.9% among women.⁵ Nevertheless, the Chief Medical Officer's Annual Report indicated service provision for pain management to be inadequate and existing services not evenly distributed across the country.⁶

Impact on health and quality of life

Chronic pain represents a significant health burden that can lead to important reductions in health-related quality of life (QoL). The National Pain Audit 2012 observed that the mean EuroQol index score in people suffering with chronic pain was 0.4, which is lower than that reported by people with progressive neurological disorders such as Parkinson's disease (0.432).⁷ It has been reported that, of 291 conditions studied, 4 of the 12 top conditions to cause global disability are persistent pain conditions including neck pain, migraine, arthritis and low back pain.⁸ The latter was found to cause more global disability than any other condition.⁸ Around 65% of people with chronic pain report difficulty sleeping and ~16% of them feel that their pain is so bad that sometimes they want to die.⁶

Economic burden of chronic pain

The economic burden of chronic pain is equally significant. It is estimated that back pain alone costs the UK economy £12.3 billion per year with the cost of pain from all causes being much higher.⁶ In the UK, people with chronic pain report up to five times more general practitioner (GP) appointments than the general population, accounting for 4.6 million GP appointments per year.^{4 9} Chronic pain sufferers are seven times more likely to quit their job due to ill health than the general population and chronic pain is the second most common reason to claim incapacity benefit.⁶ Pain was

found to have the greatest impact on ability to work as measured by the Brief Pain Inventor; it prevented 40% of people with chronic pain from working and led to 12% having to reduce their working hours.⁷

Interventions for chronic pain

A multitude of strategies are available for the management of chronic non-cancer pain. Treatment strategies for pain start with those with lowest risk and least invasiveness, and progress if the pain is refractory to the treatment selected.¹⁰ For many patients, it can take several years to identify treatments that can decrease their pain and increase their QoL. Although treatments may initially present some benefits, in the long term, those initial benefits seem to subside. For example, oral opioids, which are frequently used to alleviate postsurgery pain, lead to good short-term pain relief; however, many chronic non-cancer pain patients discontinue long-term therapy due to the need to increase the dose required to obtain similar pain relief, or due to unbearable side-effects. In addition, there is only weak evidence to support the effectiveness of oral opioids in patients who are able to continue opioid therapy in the long term.¹¹

Spinal cord stimulation (SCS) and intrathecal drug delivery (ITDD) have been seen as 'last resort' options, which are typically made available to patients who have experienced prolonged periods of pain, sometimes as much as 40 years.^{12–14} The approach to start with those strategies with lowest risk and least invasiveness can be considered as reasonable from a clinical and economic perspective because SCS and ITDD are costly, invasive and carry additional treatment risks. However, it has been observed that chronic pain may cause decrease in brain grey matter, which can be normalised if pain is adequately treated.^{15 16} Besides leading to a potential brain grey matter loss, a longer duration of pain is also associated with a decrease in perceived treatment efficacy.^{13 17} Therefore, it is important to identify effective management options for chronic non-cancer pain at an early stage. Expectations may influence a patient's perception of treatment efficacy and it is important for the patients to understand that there is no cure for chronic pain, but there may be options that can help to decrease their pain in a meaningful way, which can lead to improvements in their QoL.

Intrathecal drug delivery

ITDD has been a recognised treatment for chronic non-cancer pain since the first opioid reservoir was implanted in 1981.¹⁸ Since the administration of opioids is performed directly to a site with opioid receptors, the intrathecal dose required is much lower than that needed when using the oral or epidural route.¹⁹ The oral and epidural opioid doses are, respectively, 300²⁰ and 24²¹ times higher than the same intrathecal dose. Generally, the direct delivery to the intrathecal space

and the lower dose required lead to a reduction of side-effects and enable better analgesia.²²

An ITDD system consists of a small battery-powered pump implanted into the patients' abdominal area, which delivers medication directly to the intrathecal space through a catheter. The daily dose to be administered is programmed via an external device during refill appointments. The refill procedure and necessary dose adjustments are performed only by doctors or pain nurses with experience in programming the ITDD system.

Candidates for an ITDD undergo a multidisciplinary assessment to evaluate suitability and a trial to assess the patient's response to the intrathecal drug. ITDD trial methodologies are varied and none has proven superior.^{23–25} An ITDD trialling algorithm has been developed suggesting alternative types of trialling strategies based on the type of pain, drug to be administered and time required to evaluate patient's response among other factors. For illustrative purposes, an ITDD trial may be performed using an implanted catheter connected to an external pump, in a single-blind placebo-controlled fashion, with the intrathecal morphine and a saline solution being administered in different days and the patient's response is recorded; patients who report $\geq 50\%$ pain relief with intrathecal morphine will receive an ITDD implant.

ITDD is used for the management of cancer and non-cancer pain and spasticity.^{26–27} There are different levels of evidence for the use of ITDD in these different conditions. A randomised controlled trial (RCT) evaluating the effectiveness of ITDD in cancer pain observed improvements in pain control, QoL and significantly less drug toxicity with ITDD when compared with conventional medical management.²⁸ Although the current evidence for the use of intrathecal baclofen for the management of spasticity is limited to case series, this treatment is established in the UK.²⁹ For chronic non-cancer pain, the evidence on intrathecal delivery of opioids is currently limited to case series and a small RCT suggesting effectiveness of ITDD for pain relief in long-term patients.³⁰

National Health Service (NHS) England currently commissions ITDD for the management of cancer pain³¹ and spasticity³² but not for the pain of non-cancer origin.³³ Although the limitations of the effectiveness data are undeniable, poor-quality economic evaluations seem to have been used to inform the commissioning decision for chronic non-cancer pain.

Aim and objectives

The overarching aim of this systematic review is to investigate the cost-effectiveness of ITDD systems using opioids for the management of chronic non-cancer pain.

Towards this aim, this work sets out to

- ▶ Search many sources to identify relevant evidence on the cost-effectiveness of ITDD;

- ▶ 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 this treatment option;
- ▶ Discuss the potential policy implications of the findings, especially in relation to future policy reviews of ITDD for chronic non-cancer pain;
- ▶ Highlight gaps in the existing evidence, and suggest areas for further research.

METHODS AND ANALYSIS

This systematic review protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) reporting guidelines.³⁴ A PRISMA-P checklist can be found in online supplementary additional file 1.

Search methods for the identification of studies

Systematic searches will be conducted to identify relevant economic evaluations of ITDD for the management of chronic non-cancer pain. The searches will be carried out in the following sources:

- ▶ Databases: MEDLINE(R) In-Process and Other Non-Indexed Citations and MEDLINE(R) (Ovid), EMBASE (Ovid), Science Citation Index (Web of Science), Conference Proceedings Citation Index (Web of Science), Cochrane Library (Wiley) and the National Health Service (NHS) Centre for Reviews and Dissemination databases NHS EED, DARE and HTA (all via Wiley).
- ▶ Grey literature databases: OpenGrey, GreyNet, GreyLit.

Searches in the above bibliographic databases will be complemented by

- ▶ Hand searching of reference lists of relevant studies.
- ▶ Consultation with experts in the field for additional information on unpublished and ongoing economic evaluations.

Databases will be searched from their inception. Economic studies filters designed by the NHS EED³⁵ and SIGN³⁶ to locate economic evaluation studies will be also used. An example of the search strategy to be used in searches in MEDLINE(R) (Ovid) is presented in online supplementary additional file 2. No language restriction will be applied in the searches. Literature search results will be uploaded to and managed using the EndNote V.X7.0.1 software.

Study selection

The selection criteria described in [table 1](#) will be applied to the citations identified from the literature search. Two reviewers will screen titles and abstracts of all retrieved citations independently. Full texts where compliance with the selection criteria is unclear from title and abstracts will be retrieved. Full papers for studies deemed potentially relevant will be retrieved and selection criteria will be applied. Disagreement will be

**Table 1** Inclusion criteria for the identification of relevant studies

Population	Patients with chronic non-cancer pain lasting for at least 3 months prior to intervention
Intervention	ITDD systems using opioids alone or in combination with other agents
Comparator	Any comparator
Outcomes	Effectiveness data (ie, patient-reported QoL, pain intensity, disability, patient satisfaction) Direct and/or indirect costs to the healthcare system, patients and society Items of resource use Cost per unit of outcome (ie, cost-per-QALY, incremental cost-effectiveness ratio)
Study design	Full and partial economic evaluations as defined by Drummond <i>et al</i> ³⁷

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

resolved by discussion and consensus between the two reviewers. A third reviewer will be involved if dissenting opinions are observed and consensus is not reached. The study selection process will be summarised in a PRISMA flow diagram.

Data extraction

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

Quality assessment

Quality assessment of all included studies will be performed using the Evers checklist (all economic evaluations)³⁸ and the Philips checklist for model-based economic studies³⁹ as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.⁴⁰ Two reviewers will independently assess the quality of the included studies. Any discrepancies will be resolved by discussion and consensus between the two reviewers and if necessary consultation of a third reviewer. Quality assessment of included studies will be presented in a table format.

Data synthesis and reporting

The results section will be organised taking into consideration the good practice recommendations in a narrative summary of health economic studies from the Cochrane Handbook for Systematic Reviews.⁴¹ The recommendations advise detailed reports of methods

such as the study design; time horizon adopted; currency and price year; measures of benefits used; assessment of uncertainty; methodological quality and limitations of all studies included in the review. The actual results from the studies will be reported in a separate results subsection.

To facilitate the comparison of estimates reported in different studies, monetary values reported in all the identified studies will be converted to UK pounds sterling (£) at 2015 price year. Conversion of cost estimates will be performed using the CCEMG—EPPI-Centre Cost Converter web-based tool V.1.4. 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.⁴¹

ETHICS AND DISSEMINATION

Ethical approval is not required as primary data will not be collected. Findings will be disseminated through peer-reviewed publications and conference presentations.

DISCUSSION

Alongside clinical evidence, economic evaluations are an important tool for policymakers. Taking into consideration budget limitations, it is imperative that decisions to recommend a treatment and make it available to NHS patients are underpinned by robust evidence on its clinical effectiveness and cost-effectiveness. In some occasions, it is possible that important evidence with the 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. Recently, NHS England has decommissioned the use of ITDD for the management of chronic non-cancer pain.³³ Poor-quality economic evaluations seem to have been used to inform the commissioning 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, 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.

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Contributors RVD wrote the protocol and conceived the initial idea for the study. TL, JHR, SE and LA critically appraised the protocol and contributed to its development. All authors approved the final version and took responsibility for its content.

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