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Paper:

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Title: A systematic review of cost-effectiveness modelling in neuropathic pain: variation in practice, key challenges and recommendations for the future

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Abstract

Objectives:

Complexities in the neuropathic pain care pathway make the condition difficult to manage and difficult to capture in cost-effectiveness models. The aim of this study is to understand, through a systematic review of previous cost-effectiveness studies, some of the key strengths and limitations in data and modelling practices in neuropathic pain. Thus, we aim to guide future research and practice to improve resource allocation decisions and encourage continued investment to find novel and effective treatments for patients with neuropathic pain.

Methods:

The search strategy was designed to identify peer-reviewed cost-effectiveness evaluations of non-surgical treatments for neuropathic pain published since January 2000, accessing five key databases. All identified publications were reviewed and screened according to pre-defined eligibility criteria. Data extraction was designed to reflect key data challenges and approaches to modelling in neuropathic pain and based on published guidelines.

Results:

The search strategy identified 20 cost-effectiveness analyses meeting the inclusion criteria, of which 14 had original model structures. Cost-effectiveness modelling in neuropathic pain is established and increasing across multiple jurisdictions. However, amongst these studies, there is substantial variation in modelling approach, and there are common limitations. Capturing the effect of pain treatments upon health outcomes, particularly health-related quality of life, is challenging, and the health effects of multiple lines of ineffective treatment, common for patients with neuropathic pain, have not been consistently or robustly modelled.

Conclusions:

To improve future economic modelling in neuropathic pain, we suggest further research into the effect of multiple lines of treatment and treatment failure upon patient outcomes and subsequent treatment effectiveness; the impact of treatment-emergent adverse events upon patient outcomes; and consistent and appropriate pain measures to inform models. We further encourage transparent reporting of inputs used to inform cost-effectiveness models, with robust, comprehensive and clear uncertainty analysis, and where feasible, we encourage open-source modelling.

Introduction

Neuropathic pain causes considerable patient burden and is challenging for clinicians to treat[1]. It may be defined as pain resulting as a direct consequence of a lesion or disease that affects the somatosensory system[2], but it can have many underlying causes, leading to a categorisation of subtypes. The most common of these are post-herpetic pain and pain occurring as a result of diabetes[3, 4]. Neuropathic pain is also associated with many other diseases, including trigeminal neuralgia, multiple sclerosis, spinal cord injury, HIV, and cancer[5]. Caring for patients with neuropathic pain is complex, with considerable heterogeneity across patients in how and when the pain occurs[5], and in the effectiveness of different treatment strategies[1, 4]. Poor levels of pain relief, low duration of response to treatment and commonly reported and intolerable treatment-emergent side-effects can result in depression, poor sleep, negative moods and poor social functioning[6-8]. This means that switching between alternative therapies is common. Patient satisfaction with currently available medication is low, and patients have reported feeling helpless and anxious for their future[9, 10].

As neuropathic pain is difficult to resolve, it is associated with a substantial burden on healthcare resources, and large societal costs arise from reduced productivity and employment[7, 11]. New interventions offer the prospect of improved quality of life for sufferers as well as the possibility of reducing the direct and indirect cost of care. Assessing the net impact of a new treatment can be complex, and it is commonplace in many jurisdictions to use cost-effectiveness models to assist decision making in deciding whether proposed innovations in care provision offer good value for money[12, 13].

Complexities in the care pathway for neuropathic pain make the condition difficult to manage and are difficult to capture in cost-effectiveness models. These complexities include: patient and treatment heterogeneity; challenges in understanding how treatments affect health outcomes, in particular health-related quality of life (HRQL); and understanding the HRQL and cost implications of multiple, consecutive lines of often ineffective treatment. In 2013, the National Institute for Health and Care Excellence (NICE) in England and Wales reviewed previous economic analyses in neuropathic pain to inform guidance on pharmacological management of neuropathic pain[5], and were critical of "potentially serious limitations" in each of the 13 studies identified[4, 14-25]. However, the NICE reviewers were not specific in their criticism[5].

The aim of this study is to understand, through a systematic review of previous cost-effectiveness models in neuropathic pain, some of the key strengths and limitations in data and modelling practice. Thus, we identify key modelling challenges and recommend areas of research to prioritise. We hope that this will help to improve modelling practice, optimise healthcare allocation decisions and encourage investment in innovative strategies for the management of patients who have a great need for effective healthcare.

Methods

Study identification
A search strategy was designed to identify peer-reviewed cost-effectiveness evaluations of non-surgical treatments for neuropathic pain published since January 2000. Pre-2000 studies were excluded from the search strategy as cost-effectiveness modelling practice in healthcare has developed substantially since then, and studies published before this date are unlikely to be informative of current data limitations and for future practice guidance. Searches were conducted in MEDLINE, EMBASE, the NHS Economic Evaluation Database,

the Health Technology Assessment Database and EconLit. All searches were performed at the University of Sheffield's School of Health and Related Research (ScHARR) in April 2014 and updated in February 2015. Full details of the search strategy are available as supplementary material.

Studies were included if they were published cost-effectiveness studies (including cost-benefit and cost-utility studies) evaluating oral, nasal or transdermal pharmacological treatments for neuropathic pain in adult patients. Inclusion was restricted to studies published in English, and studies available only as conference posters or abstracts were not included.

Data extraction
Data extraction was performed using a pre-defined extraction table. A scoping exercise using International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published guidance on good practice for economic modelling in health care was performed to identify key categories of modelling practice and data important in neuropathic pain[26]. Key modelling practice categories comprised: model type, pain measurement and outcome categories, adverse events considered, cycle length, and model time horizon. Key scope and data categories comprised: setting and pain type, treatment alternatives considered, the perspective on costs, and HRQL and treatment-emergent adverse event data.

Results

Search results
Figure 1 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram describing the results of the search. The search identified 797 studies, 20 of which met the inclusion criteria. Of the 20 included studies, 14 presented original model structures[4, 5, 14-22, 25, 27, 28], and six used existing model structures populated with data and assumptions that differed from those in the original study[3, 23, 24, 29-31].

Herein, where data and scope are compared, we refer to all 20 included studies, but where model type and structural elements are compared, we compare across the 14 original model structures only.

Results in Table 1 suggest that the volume of cost-effectiveness studies in neuropathic pain is increasing; over 50% of the 20 inclusions (11 studies) were published after January 2010[3-5, 15, 17, 18, 23, 27, 29-31]. This may reflect an emergence of new treatments for neuropathic pain, and an increasing need across jurisdictions to demonstrate cost-effectiveness in order to receive reimbursement for these types of therapies.

The majority of studies identified were European[3-5, 14, 16, 22-24, 27, 29-31]. Pregabalin is the most commonly appraised analgesic across these studies, assessed in all except two European studies[16, 22]. The second most widely appraised therapy was gabapentin, used in five European studies[5, 22, 24, 28, 29].

Seven studies were conducted were in North America[15, 17, 18, 20, 21, 25, 28], where appraisal of pregabalin and gabapentin was common across cost-effectiveness analyses and over time[15, 17, 18, 20, 21, 25, 28]. Duloxetine has been appraised in two North American studies published since 2011[15, 18]. Only one identified study was set outside of Europe and North America. This study assessed treatment alternatives for Columbian patients with neuropathic pain[19].

<Insert Figure 1 here>

Table 1 reports the key elements of the model structures in the 14 original models. Table 2 summarises the scope and key data of the 20 included studies.

<Insert Table 1 here>

<Insert Table 2 here>

Overview of model types

Brennan et al. published a taxonomy of model types for economic evaluations of health technologies in 2006[32]; this serves as a useful tool for categorising cost-effectiveness models. The taxonomy subdivides model types by whether they analyse cohorts of patients or model patients individually, whether they are deterministic or stochastic, whether interactions between individual entities are allowed and how time is modelled. Decision tree and Markovian model types analyse a cohort of identical individuals, passing through different health states. Individual-level models simulate the movement of each individual with different attributes through a process[32], meaning that the attribution of individual patient characteristics or disease-related events on disease trajectory, health outcomes and costs is less cumbersome.

All but one of the models informing previous neuropathic pain cost-effectiveness analyses have a decision tree or Markov model structure, as shown in Table 1. Only one individual-level simulation model was identified. This was used to estimate the relative cost-effectiveness of pregabalin and usual care in the UK and in Sweden in different applications[4, 31]. Key assumptions were required to populate these analyses, including data surrounding long-term effectiveness[4, 31].

In relation to neuropathic pain, a decision tree structure can easily categorise patients into clear pain outcomes; however, the repetition and complexity of appropriate health states specific to neuropathic pain may result in an unmanageable number of decision tree branches. A Markov model permits repeated events and timed elements of the cohort experience to be captured more easily, which is likely to be important in reflecting key aspects of neuropathic pain such as multiple lines of treatment. Markov models can also capture important differences between patient groups by subdividing health states[32], but with the disadvantage of increased complexity. This complexity may mean that an individual-level simulation may best accurately reflect the true neuropathic pain a patient experiences in cost-effectiveness analyses, where individual patient characteristics can be accounted for however, the choice of model type cannot make up for key gaps in data.

Approaches to modelling temporal sequences of events

The number of treatment lines considered varies across models. Analyses considering multiple treatment lines may better reflect important aspects of the patient experience. However, information demands are substantial. These include information regarding the effect of prior therapy on treatment effectiveness; knowledge of the effects on HRQL of failing one treatment and moving on to another and the uncertainty around the care pathway. In modelling in multiple treatment lines, assumptions have been required which have been an important source of uncertainty. Two studies assumed that failure to respond to one medication had no effect on responses to subsequent treatment[16, 28]. In other studies capturing multiple treatment lines, assumptions made relating to how treatment failure affected subsequent treatment effectiveness and patient utility were not clear [4, 14, 15, 22].

Dose titration varies considerably in neuropathic pain care, across patients and across therapies, and it is a key aspect of overall patient experience[33]. While both duloxetine and pregabalin are common treatments for neuropathic pain, duloxetine can be titrated from a daily dose of 60mg up to a maximum of 120mg with no delay, whereas pregabalin, can be titrated from 150mg per day to 600mg per day, but only over a 3-7 day interval with each dose increase[34, 35]. Across many jurisdictions, guidelines encourage physicians to titrate treatments to achieve optimal balance between analgesic effect and adverse effects of treatment[1, 5, 8, 36]. Titration may be important in influencing health and cost outcomes, yet outcomes associated with titration were considered in only three included models[15, 22, 23]. In

studies where titration was not considered, justifications for its omission were generally lacking[16, 17, 20, 27].

Approaches to capture pain outcomes
Pain measurement is well-researched, and there are many measurement tools used in practice[6, 37]; however, this variety may have inhibited comparative effectiveness analyses. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines on core outcome measures in chronic pain have encouraged consistent use of the 11-point numeric rating scale (NRS) tool[6]. The NRS is a universal scale, where the respondent selects a number from 0 to 10 that is best reflective of the pain they experience; 0 represents no pain and 10 represents the worst pain imaginable[38, 39]. This scale was used in four of the 14 models[4, 14, 16, 25] and in a further four studies[24, 29-31]. In one further model the pain data were informed by a daily pain score, but the scale used was not explicitly reported[17]. How pain outcomes were measured was not reported for three models[15, 19, 28].

A key challenge in capturing health outcomes for cost-effectiveness modelling in neuropathic pain is overcoming the use of relative measures of pain improvement as primary outcomes in cost-effectiveness models. Table 1 illustrates how seven model structures from eight studies[3, 5, 15-17, 19, 27, 28] have used categories of relative pain relief to measure clinical effectiveness. Defining pain status in relative terms implicitly ensures that patients achieving the same proportion of pain relief are regarded the same, irrespective of their baseline pain levels. Categorising pain status in absolute terms, accounting for the pain experienced at baseline, allows severity of pain at different time-points, as well as quantifiable changes in pain levels over time, to be reflected in model outcomes. Both are important factors for HRQL. IMMPACT guidelines encourage the use of absolute reductions and relative reductions in pain as outcome measures in clinical trials[6]; however, relative reductions in pain neglect the importance of baseline pain. Perhaps as a consequence of both IMMPACT recommendations and historical precedent, the primary clinical outcomes reported in some clinical trials have not been the most useful clinical outcome to inform an economic model structure. From a health technology appraisal (HTA) perspective, absolute pain measures are more amenable than relative measures.

There are further challenges in capturing how pain outcomes relate to utility in cost-effectiveness analyses, which from the evidence presented here are problematic in analyses in neuropathic pain. Where utility data have been collected in the same patients as the key effectiveness data, the relationship between pain and utility (for these patients, at least) may be estimated with a fair degree of accuracy; such data are regarded as the gold standard[13]. However, this was not generally conducted; as illustrated in Table 1, across included studies, this approach was only taken in two applications of the same model[3, 27]. Two further applications of one model structure used mapping[40] to link utility estimates to pain data within their analyses[4, 31]. The vast majority of the studies in this review used estimates from another study to inform utility assumptions in their analyses[5, 14-25, 28, 30]. The validity of such an approach depends on the quality and relevance of the other study; inferred differences in utility across treatment comparisons could be confounded by differences in patient characteristics, treatments and overall experiences across the target patient group and the source of utility data. One study did not report the method used to elicit utility values[29].

Approaches to capture treatment-related adverse events
For many patients with neuropathic pain, treatment-emergent adverse events are difficult to manage and can result in withdrawal from treatment[9]. Commonly reported AEs for patients with neuropathic pain include dizziness, vomiting, nausea, drowsiness and gastrointestinal effects[5, 8, 15, 33]. Of the 14 model structures in the review, 12 estimated the effect of AEs on

results[4, 5, 14-22, 28]. Three of these considered adverse events only in terms of their effect on discontinuation[14, 16, 28]. Several studies did not report the precise AEs considered within the analysis; rather, they reported only the severity of the event, for example, minor/major or tolerable/intolerable[4, 17-22].

Only one study provided a comprehensive list of adverse events[15]; NICE's analysis incorporated only two adverse events (dizziness and nausea), while stating that other adverse events, considered important, could not be included within their analysis due to data limitations[5]. There is a paucity of evidence relating to adverse events of neuropathic pain treatments and, consequently, a lack of evidence in how these adverse events can impact cost and quality of life, limiting the ability of modelling studies to capture these relevant outcomes[5]. Adverse events should be collected within randomised controlled trials (RCTs) as standard; however, they are not consistently reported in findings and publications. Although the Consolidated Standards of Reporting Trials (CONSORT) table outlines the framework for reporting adverse events from clinical trials, the reporting adverse event data in neuropathic pain trials has been described as 'substandard' and 'poor'[41, 42].

Approaches to capture resource use and costs
Table 2 shows the cost perspective of each study, describing whether indirect costs were included as well as direct costs. In general, direct costs refer to costs directly attributable to the healthcare payer, such as drug costs, costs of primary and secondary care and any resource use relating to tests and procedures. Indirect costs can include those to the wider society, such as productivity costs, and the costs of carers not directly paid for by the healthcare payer.

All 20 studies in the review indicated that costs had been incorporated into their model; however, the quality of reporting varied, and the resource use considered in some of the studies was unclear[14, 30]. Ultimately costs are at the crux of the overall cost-effectiveness calculation, therefore for HTA, it is important to be transparent in both the derivation of the relevant costs and the sources of the costs used[13]. Every study identified within the systematic review included components of direct costs. The most commonly considered components were treatment costs and elements of resource use, such as physician visits, and costs of screening procedures. The approach to costing was not clear in some studies[14, 30]. Four studies considered indirect costs; three of these included costs of lost productivity[3, 27, 31], while one study interpreted indirect costs to be the costs of care workers[28]. In general, indirect costs are not considered in HTA, although some agencies do encourage such information, such as the Tandvårds- och läkemedelsförmånsverket (TLV) in Sweden.

Approaches to assess uncertainty
Attempts to quantify uncertainty around results were made in all identified analyses. Seventeen studies assessed parameter uncertainty using probabilistic sensitivity analysis (PSA)[3, 5, 14-24, 27, 28, 30, 31]. Sixteen of these tested the importance of specific parameters, methodological approaches, or aspects of model structure with deterministic scenario analyses[4, 5, 15-17, 20-25, 28-31], although these analyses were not always comprehensive. The three studies that modelled the effects of titration did not fully assess the importance of this parameter for overall cost-effectiveness results[15, 22, 23].

The sensitivity analysis conducted was generally well reported within the identified studies, and several studies provided the distributions and ranges used to inform such analysis[22, 28]. In some studies, important uncertainty assumptions were made and clearly reported; for example, one study reported the percentage of uncertainty assumed for different parameters[18]. In other studies, assumptions relating to the scale of uncertainty were unclear[19]. If such assumptions are arbitrary, inferences regarding their influence on results

will also be arbitrary and, therefore, of little use to decision makers. Recent work has highlighted the potential effect of such assumptions on health economic model results in chronic pain studies[43]. In the absence of robust data on the shape, and particularly the scale, of uncertainty around parameter estimates, existing guidance on the elicitation of such data from experts can be used to improve the robustness of uncertainty analyses [44].

Discussion

The aim of this systematic review was to guide future cost-effectiveness modelling practice and research in neuropathic pain, by understanding and illustrating the key challenges in modelling the cost-effectiveness of treatments for neuropathic pain from previous studies.

Cost-effectiveness analysis in neuropathic pain is well established; 20 studies have assessed 20 pharmacological treatments in nine countries across three continents, and the number of analyses adding to the catalogue of evidence in this field is increasing. The most commonly considered therapies were pregabalin and gabapentin[5, 15, 18, 20, 21, 24, 25, 28, 29]. Previous analyses have used sensible approaches to link pain measures to health outcomes and widely used HRQL measures. Nearly all studies have analysed the importance of uncertainty around model inputs for uncertainty around their results.

Treatment failure is endemic in neuropathic pain, and therefore the treatment pathway for patients can be very complex. Despite this, few studies have applied model structures that can capture such complexity. Whilst some studies have modelled multiple treatment lines[16, 28], none have attempted to capture the differential timing of treatment failure, the subsequent treatment effectiveness, or the effect these factors have on a patient's HRQL. Other models, such as the one developed by NICE to inform treatment guidance[5], have restricted their perspective to one treatment line, in the base case at least, to avoid reliance on arbitrary assumptions. It is standard and practical that only one line of treatment is considered within an RCT, but despite potential limitations it is feasible to conduct trials exploring several lines of therapy. Patient satisfaction with currently available medication is low[9, 10] and, due to the complicated nature of neuropathic pain, there is a clear need for data on patient outcomes spanning the entire neuropathic pain care experience. The effects of repeated treatment failure upon subsequent patient outcomes may be highly important and of great benefit to help inform future cost-effectiveness analyses in neuropathic pain.

IMMPACT guidelines, created with the intention of improving the design and interpretation of clinical trials in treatments for pain,[45] encourage the use of both absolute pain reduction and relative pain improvements as endpoints in clinical trials. It is fairly common that relative pain improvements are used as the primary endpoint within trials as they allow an easy comparison between studies, however, the use of relative pain improvement measures in cost-effectiveness model inputs is incompatible with accurately attributing HRQL/utility and costs to model health states. Although used by many modellers to be in line with trial evidence and IMMPACT guidance, relative pain measures do not reflect baseline pain, which is a determinant of HRQL. Cost-effectiveness models should make use of data on absolute pain including baseline pain, routinely collected in trials, to inform model HRQL outcomes. In addition, there is an apparent scarcity of HRQL data collected in neuropathic pain clinical trials.

The effect of adverse events is substantial in the neuropathic pain patient experience[9], and can affect both patient quality of life and healthcare costs; consequently, the incorporation of adverse events into cost-effectiveness models is crucial. The majority of models included evaluation of the effects of AEs[16-22, 28]; however, it has been acknowledged that there is a lack of evidence regarding the associated disutility of adverse events[4, 5, 31], and several studies made assumptions regarding anticipated costs of treating such events[15, 17-19]. Further

research into the impact of adverse events and their impact on HRQL and healthcare costs has been encouraged[5].

High levels of resource use associated with neuropathic pain care have been reported in previous studies[4]. Direct costs of neuropathic pain were incorporated into all studies identified, while only four considered indirect costs. Although the cost perspective is determined by HTA bodies, and many reimbursement agencies take a direct cost perspective on costs to the healthcare payer, the acceptance of indirect costs by some agencies, such as the TLV, may be particularly apt in neuropathic pain, where indirect costs and health effects are substantial, and may warrant further research and consideration.

From the findings of this review, we make five recommendations to help improve cost-effectiveness evidence to inform future resource allocation decisions in neuropathic pain. These recommendations, for both data collection to inform cost-effectiveness studies, and approaches to modelling available data, are shown in Box 1.

Box 1: Recommendations for future practice

Data collection to inform cost-effectiveness studies
1. For future modelling practice, in line with recent research in non-neuropathic chronic pain[43], we encourage research into the implications of multiple treatment sequences and treatment failure on treatment effectiveness, patient HRQL, costs and resource use. More research over multiple treatment lines, obtained where feasible through the hierarchy of evidence, can help provide a larger evidence base to not only assess the impact that multiple treatment lines have on a patients' pain and response to treatment, but also to further understand how HRQL is affected by repeated treatment failures. Such research will allow sufficiently complex model types and structures to be better populated with less reliance on poorly-informed assumptions.
2. In line with recent NICE recommendations[5], we encourage future research to discover the effect of treatment-emergent adverse events in neuropathic pain therapy. It is essential that when treatment-emergent adverse events significantly affect patient HRQL or healthcare costs, these effects are captured and inform decision-making based on cost-effectiveness models, and robust data in this area are required.

Approaches to modelling available data
3. We strongly recommend that absolute pain categories from 11-point NRS data are used to capture key pain outcomes in future economic studies. Relative methods are often presented as the primary outcome within trials and this easily permits a comparison across studies. Relative approaches are not amenable to cost-effectiveness modelling as patient HRQL is a function of baseline pain as well as pain improvement.
4. In line with other previously published guidance, we recommend that future studies should ensure that all inputs into cost-effectiveness models are transparent, well reported and referenced, with clear justification to the values and sources used[46]. In addition to this, we encourage open-source modelling; the practice of making the economic models including their underlying data and code publicly available, where possible; to improve the transparency of modelling and facilitate further research and collaboration.
5. We recommend that increased care should be taken to report robust approaches to address uncertainty surrounding the parameter inputs used to inform future cost-effectiveness models. While it is clear from long-published recommendations that

probabilistic and deterministic recommendations should be reported[46], and this has generally been the case across previous studies, the uncertainty analyses have been of limited use. The scale of uncertainty around key parameters has frequently been based on arbitrary assumptions rather than robust data; in the absence of data to inform such parameters, it is crucial that existing guidance of the elicitation of such information from experts is followed[44].

As this review identified all studies identified by the only previous systematic review of economic evaluations in neuropathic pain[5], we believe that the search strategy was comprehensive.

One limitation of this systematic review is that it does not quantitatively appraise the importance of the different assumptions and approaches to modelling that it identifies. Nevertheless, this study highlights limitations within current modelling practice and how these relate to the patient experience, and importantly, how practice can improve in future work.

Conclusions

Modelling in neuropathic pain is challenging. By identifying key areas of variation in previous models, and by determining how model structures compare to key components of the patient experience, we hope this research provides a valuable resource for future modelling. We encourage: research into the effect of multiple lines of treatment and treatment failure upon patient outcomes; further evidence on the impact of treatment-emergent adverse events and consistent and appropriate pain measures to inform models. We further encourage inputs used to inform cost-effectiveness models to be reported transparently; with robust, comprehensive and clear uncertainty analysis; and wherever feasible, we encourage open-source modelling. We hope our recommendations can drive research and practice, to assist pharmaceutical companies in identifying and developing therapies of patient-centred value, and aid HTA bodies in making correct resource allocation decisions.

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