Appendix F Full health economic report

Introduction

The National Institute for Health and Clinical Excellence (NICE) has been asked to produce a guideline on the pharmacological management of neuropathic pain.

This is the health economic analysis developed to support the guideline development group (GDG) in making recommendations. The analysis was conducted according to NICE methods outlined in the 'The guidelines manual 2012' and 'Guide to the methods of technology appraisals 2008'. It follows the NICE reference case (the framework NICE requests all cost-effectiveness analysis follow) in its methods.

Contents

1 Systematic review of published economic evaluations

A systematic review for cost-effectiveness evidence was undertaken for this guideline.

1.1 Information sources

The following databases were searched for economic evidence: NHS Economic Evaluation Database (NHS EED), and the Health Economic Evaluations Database (HEED). MEDLINE, MEDLINE (in-process) and Embase were searched using a validated economic filter to ensure any non-indexed economic studies were identified. No date filters were applied. The search strategies for health economics are included in Appendix D.

1.2 Selection criteria for included evidence

Studies that compared the costs and health consequences (cost–utility analyses) of different strategies in terms of an incremental cost effectiveness ratio, or net benefit, were included. All other study types (cost-effectiveness, cost–benefit, cost–consequence, and comparative costing studies) were excluded.

Studies conducted in OECD countries were included.

Studies that met the NICE reference case criteria (The guidelines manual, 2012) for applicability and quality were included.

The health economist sifted the literature search results by comparing the title and abstract of the study with the selection criteria and PICO question.

Posters, reviews and letters, non-English studies and unpublished studies were excluded.

Duplicates were excluded, and if identical study designs were available but from a different setting, the study closest to the NHS and PSS setting was included and the other excluded.

1.3 Assessment of applicability and quality of studies

The health economist assessed full texts of potential studies for applicability and methodological quality using the NICE methodology checklist for economic evaluations (The Guidelines manual, 2012, Appendix G). The checklist helped to assess the applicability of the economic evaluation to the clinical guideline, the current NHS situation and the context for NICE guidance as one of the following:

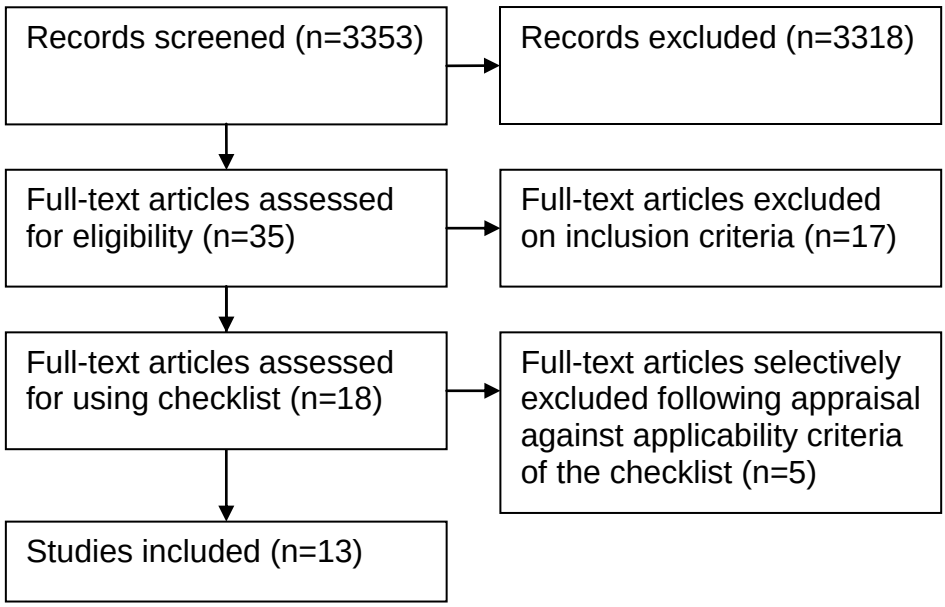
- Directly applicable – the study met all applicability criteria, or failed to meet 1 or more applicability criteria but was unlikely to change the conclusions about cost effectiveness.
- Partially applicable – the study failed to meet 1 or more applicability criteria, and this could change the conclusions about cost effectiveness.
- Not applicable – the study failed to meet 1 or more applicability criteria, and was likely to change the conclusions about cost effectiveness. Such studies were excluded from further consideration.

If the study was directly or partially applicable, the overall methodological study quality of the economic evaluation was then classified as one of the following:

- Minor limitations – the study met all quality criteria, or failed to meet 1 or more quality criteria but was unlikely to change the conclusions about cost effectiveness.
- Potentially serious limitations – the study failed to meet 1 or more quality criteria, and could change the conclusions about cost effectiveness.
- Very serious limitations – the study failed to meet 1 or more quality criteria, and this was highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration.

1.4 Results

1.4.1 Selectively excluded studies



Eighteen studies were deemed to be eligible for inclusion; these were assessed using NICE's economic checklist (The Guidelines manual, 2012, Appendix G). Five studies were selectively excluded; see Table F1.

Table F1 Reasons for selectively excluding studies

Study	Reason for exclusion
(de Salas-Cansado et al. 2012)	Did not meet NICE reference case (pooled productivity costs)
(Simpson et al. 2009)	Did not include a relevant comparator
(Smith 2007)	Did not meet NICE reference case (pooled productivity costs)
(Vissers 2011)	Did not include a relevant comparator
(Ward et al. 2007)	Did not include a relevant comparator

1.4.2 Included studies

Thirteen cost–utility studies were identified and included in the economic evidence review on peripheral neuropathic pain. They are summarised in the economic evidence profiles (Table F2, below), and described in greater detail in the Appendix F1.

No studies on central pain or trigeminal neuralgia were identified.

Table F2 Economic evidence profiles

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Annemans et al. 2008) Intvn 1: Usual care Intvn 2: pregabalin 150 mg + usual care Intvn 3: pregabalin 300 mg/d + usual care Intvn 4: pregabalin 600 mg/d + usual care Intvn 5: pregabalin mix + usual care	Potentially Serious Limitations[46]	Partially Applicable[47]	People with peripheral neuropathic pain Markov model Belgian health care public payer	Intvn 2: −€225 (−£186.01)[48] Intvn 3: −€127 (−£92.64)[48] Intvn 4: −€306 (−£223.21)[48] Intvn 5: −€216 (−£157.56)[48]	Intvn 2: 0.009 Intvn 3: 0.007 Intvn 4: 0.014 Intvn 5: 0.009	Intvn 2: dominates Intvn 3: dominates Intvn 4: dominates Intvn 4: dominates	It cannot be concluded that pregabalin is cost saving.
(Armstrong et al. 2011) Intervention 1: Capsaicin topical 8% versus: Intervention 2: TCA – Nortriptyline Intervention 3: Lidocaine topical 5%	Potentially Serious Limitations[8]	Partially Applicable[9]	People with post-herpetic neuralgia Markov state transition model US payer	Intvn 1: Capsaicin topical versus: Intvn 2: $3605 (£2444.42)[10] Intvn 3: $317 (£214.95)[10] Intvn 4: $3097	Intvn 1: Capsaicin topical versus: Intvn 2: 0.062 Intvn 3: 0.004 Intvn 4: 0.074 Intvn 5:	Intvn 1: Capsaicin topical versus: Intvn 2: $59,919 (£40,629)[11] per QALY gain Intvn 3: $554,627	- Less frequent retreatment using capsaicin patch. Retreatment every 14.5 week ICER vs all other oral less than $51,000 (£34,581) per QALY gain, retreatment every 17.7 weeks: less than $44,000 (£29,834) per QALY gain - Cost of replacement treatment (oxycodone) was a cost driver.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
Intervention 4: Gabapentin Intervention 5: Pregabalin Intervention 6: Duloxetine				(£2099.96)[10] Intvn 5: $2562 (£1737.20)[10] Intvn 6: $2898 (£1965.03)[10]	0.065 Intvn 6: 0.067	(£376,073)[11] per QALY gain Intvn 4: $42,008 (£28,484)[11] per QALY gain Intvn 5: $40,241 (£27,296)[11] per QALY gain Intvn 6: $43,908 (£29,772)[11] per QALY gain	
(Beard et al. 2008) Intvn 1: Amitriptyline → Gabapentin → Tramadol Intvn 2: Duloxetine → Amitriptyline → Gabapentin → Tramadol Intvn 3: Amitriptyline → Duloxetine → Gabapentin	Potentially Serious Limitations[25]	Partially Applicable[26]	People with painful diabetic neuropathy Decision analytic model UK NHS	versus Intvn 1 (per 1000 patients):[27] Intvn 2: -£34791 Intvn 3: -£77071 Intvn 4: £4338 Intvn 5: £3458	versus Intvn 1 (per 1000 patients): Intvn 2: 2.5 QALYs Intvn 3: 1.9 QALYs Intvn 4: 1.6 QALYs Intvn 5:	versus Intvn 1: Intvn 2: dominates Intvn 3: dominates Intvn 4: £2698 Intvn 5:	Probability Intvn 3 cost-effective: 94% (at £30,000 per QALY threshold) - Longer time horizon: Intvn 3: most cost effective. - Use of pregabalin instead of gabapentin: Intvn 2 vs Intvn 3: approx. £75,000 per QALY gain. - First line anticonvulsant (of Intvn 1): Intvn 2 dominates.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
→Tramadol Intvn 4: Amitriptyline → Gabapentin → Duloxetine → Tramadol Intvn 5: Amitriptyline → Gabapentin → Tramadol → Duloxetine					1.6 QALYs	£2109	
(Bellows et al. 2012) Duloxetine versus pregabalin	Potentially Serious Limitations[28]	Partially Applicable[29]	People with painful diabetic neuropathy Decision analytic tree US third party payer	-$187 (£126.80)[30]	0.011	Duloxetine dominates pregabalin	- Real-world (range of doses from real world, but mean from efficacy): $16,300 (£11,052)[31] per QALY gain - Real-world: Pooled efficacy of doses: $20,667 (£14,014)[31] per QALY gain - Without adherence: duloxetine dominates
(Carlos et al. 2012) Intvn 1: Generic gabapentin Intvn 2: Duloxetine Intvn 3: Pregabalin Intvn 4: Branded gabapentin	Potentially Serious Limitations[32]	Partially Applicable[33]	People with painful diabetic neuropathy Decision analytic model Mexican payer perspective	versus Intvn 1: generic gabapentin (per 1000 patients): Intvn 2: $491,676 (£40,862.40)[34] Intvn 3: $1,501,512 (£124,788.24)[34] Intvn 4:	versus Intvn 1: generic gabapentin (per 1000 patients): Intvn 2: 4.8 Intvn 3: 2.9	versus Intvn 1: generic gabapentin: Intvn 2: $102,433 (£8513.04)[35] Intvn 3: $517,763 (£43,030.45)[35]	- RR of achieving good pain relief for each active drug relative to placebo was the most sensitive parameter.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
				$2,233,647 (£185,634.79)[34]	Intvn 4: 0	Intvn 4: NA	
(Cepeda 2006) Intvn 1: Amitriptyline Intvn 2: Carbamazepine Intvn 3: Tramadol Intvn 4: Gabapentin	Potentially Serious Limitations[1]	Partially Applicable[2]	People with post-herpetic neuralgia or diabetic peripheral neuropathy Decision analytic model US third party payer	Versus Intvn 1: Amitriptyline Intvn 2: $20 (£12.65)[3] Intvn 3: $68 (£43.01)[3] Intvn 4: $241 (£152.44)[3]	Versus Intvn 1: Amitriptyline Intvn 2: 0 Intvn 3: -0.038 Intvn 4: -0.11	Versus Intvn 1: Amitriptyline Intvn 2: dominated Intvn 3: dominated Intvn 4: dominated	Multivariate sensitivity analysis adjusting doses and resources: - Tramadol and gabapentin dominated by amitriptyline - ICER of carbamazepine vs. amitriptyline $43,296 (£27,385) per QALY gain
(Dakin et al. 2007) Lidocaine 5% medicated plaster versus gabapentin	Potentially Serious Limitations[16]	Partially Applicable[17]	People with post-herpetic neuralgia Markov model UK NHS	-£16911[18]	0.0502	Lidocaine dominates	Probability cost-effective: 99.99% at £20,000 per QALY gain threshold - Lidocaine more cost-effective if more plasters per day used. - Longer time horizon: lidocaine dominates
(Gordon et al. 2012) Pregabalin versus Usual Care	Potentially Serious Limitations[43]	Partially Applicable[44]	People with refractory neuropathic pain Stochastic simulation model UK NHS	£27,483[45]	0.25	£10,803 per QALY gain	- Result was sensitive to alternative sources of utility inputs: ICER for Pregabalin rose above threshold of £20,000 per QALY gain
(O'Connor et al. 2007) Intvn 1: Desipramine Intvn 2: Pregabalin Intvn 3: Gabapentin	Potentially Serious Limitations[12]	Partially Applicable[13]	People with post-herpetic neuralgia Decision analytic model US third party payer	Versus Intvn 1: Desipramine Intvn 2: $116.90 (£73.94)[14] Intvn 3:	Versus Intvn 1: Desipramine Intvn 2: -0.0074 Intvn 3: -	Desipramine dominates gabapentin and pregabalin Gabapentin versus	- Result was sensitive to utility in severe pain, utility in mild pain, probability of pain relief with desipramine and utility of minor side effects

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
				$397.63 (£397.63)[14]	0.0061	pregabalin: $216,000 (£136,622)[15] per QALY gain	
(O'Connor et al. 2008) Intvn 1: Desipramine Intvn 2: Duloxetine Intvn 3: Pregabalin Intvn 4: Gabapentin	Potentially Serious Limitations[36]	Partially Applicable[37]	People with painful diabetic neuropathy Decision analytic model US third party payer	versus Intvn 1: Desipramine (per 1000 patients): Intvn 2: $107.24 (£67.20)[38] Intvn 3: $212.73 (£133.29) [38] Intvn 4: $439.03 (£273.21) [38]	versus Intvn 1: Desipramine (per 1000 patients): Intvn 2: 0.0022 Intvn 3: -0.0014 Intvn 4: -0.0024	versus Intvn 1: Desipramine (per 1000 patients): Intvn 2: $47,700 (£29,888)[39] per QALY gain Intvn 3: dominated Intvn 4: dominated	- Using base observation carried forward estimates of the probability of achieving 50% pain score: duloxetine become cost ineffective - Results most robust probabilities of obtaining pain relief, probabilities of intolerable adverse effects.
(Ritchie and Liedgens 2010) Lidocaine 5% medicated plaster versus pregabalin	Potentially Serious Limitations[19]	Partially Applicable[20]	People with post-herpetic neuralgia Markov model UK NHS	£19614[21]	0.067	£2925 per QALY gain	- Extending the time horizon: Lidocaine remained cost-effective at the £35,000 per QALY gain threshold - Using EQ-5D data for utility: Lidocaine cost-effective - Increasing number of plasters: Lidocaine cost-effective - higher doses of pregabalin: lidocaine cost-effective
(Rodriguez et al. 2007)	Potentially Serious	Partially Applicable[5]	People with post-herpetic neuralgia or diabetic	€98.61 (£84.01)[6]	0.0048 QALYs	€20,535 (£17,494)[7] per QALY	- Sensitive to changes to mean generic gabapentin dose

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
Pregabalin versus gabapentin	Limitations[4]		peripheral neuropathy Stochastic simulation model Spanish NHS		per patient	gain	- 23% reduction in costs of medical visits or healthy utility values, or increase in cost of spinal cord stimulation, cause ICERs to fall or become cost saving.
(Tarride et al. 2006) Pregabalin versus gabapentin	Potentially Serious Limitations[22]	Partially Applicable[23]	People with post-herpetic neuralgia Markov model Ontario Ministry of Health, Canada	−$53.54 (−£27.51)[24]	0.0086	Pregabalin dominates	- lower dose of gabapentin 1800 mg/day (daily cost for 1800 mg/day): ICER: $575 (£295) per QALY gain - lower dose of gabapentin 1800 mg/day (daily cost for 900 mg/day): ICER: $20,101 (£10,330) per QALY gain
(Tarride, Gordon, Vera-Llonch, Dukes, & Rousseau 2006) Pregabalin versus gabapentin	Potentially Serious Limitations[40]	Partially Applicable[41]	People with painful diabetic neuropathy Markov model Ontario Ministry of Health, Canada	−$19.04 (−£9.78)[42]	0.0047	Pregabalin dominates	- lower dose of gabapentin 1800 mg/day (daily cost for 1800 mg/day): ICER of pregabalin compared with gabapentin: $6502 (£3341) per QALY gain - lower dose of gabapentin 1800 mg/day (daily cost for 900 mg/day): ICER: $31,148 (£16,007) per QALY gain

[1] Short time horizon (1 month). Unclear method of weighting in the meta-analysis. Costs of management of some adverse effects were not included. PSA conducted, but on triangular distributions. Not a fully incremental analysis.

[2] Based on third-party healthcare US payer. Did not include all relevant comparators.

[3] Converted using 2004 purchasing power parities http://stats.oecd.org

[4] Short time horizon (12 weeks). Effects of efficacy not from a systematic review of evidence. Did not include costs and utilities from adverse effects of treatment.

[5] Based on Spanish healthcare system, unclear if adults only, some relevant comparators not included.

[6] Converted using 2006 purchasing power parities http://stats.oecd.org

[7] Converted using 2006 purchasing power parities from original ICER (not increments): http://stats.oecd.org. Discrepancy in ICERs may be due to rounding.

[8] Short time horizon (1 years), and does not state if HRQoL outcomes reported by patients or carer. Not a fully incremental analysis. No PSA conducted.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	

[9] US population. Unclear if adult only population considered.

[10] Converted using 2011 purchasing power parities http://stats.oecd.org.

[11] Converted using 2011 purchasing power parities http://stats.oecd.org. Discrepancy in ICERs may be due to rounding.

[12] Short time horizon (3 months). Unclear if a systematic review was used to estimate of relative effect. PSA not conducted. Source of funding not stated.

[13] Perspective of US healthcare system, other relevant comparators not included.

[14] Converted using 2006 purchasing power parities http://stats.oecd.org.

[15] Converted using 2006 purchasing power parities http://stats.oecd.org. Discrepancy in ICERs may be due to rounding.

[16] Delphi panel used and no published sources used for resource use, small size of Delphi panel (n=9).

[17] Some relevant comparators not included.

[18] 2006 UK Pounds.

[19] Short time horizon (3 months): disease may last longer, Unclear if efficacy from systematic review of literature, Small Delphi panel, unclear if literature search was conducted for resource use data.

[20] Not all relevant comparators included.

[21] 2009 UK Pounds.

[22] Short time horizon (12 weeks). No systematic review of evidence for baseline or efficacy outcomes; role of adverse effects not clear in the model. No PSA conducted.

[23] Not all relevant comparators included; Perspective of the Ontario Ministry of Health, Canada.

[24] Converted using 2004 purchasing power parities http://stats.oecd.org.

[25] Short time horizon (6 months). Unclear how the management of adverse effects were included. Pooling of studies: unclear how heterogeneity was taken into account.

[26] Some relevant comparators not included.

[27] 2005 UK pounds.

[28] Short time horizon (6 months), systematic review was based on a search of PubMed only; triangular distributions used in PSA with no clear rational.

[29] US healthcare system, not all relevant treatment comparisons included.

[30] Converted using 2011 purchasing power parities http://stats.oecd.org.

[31] Converted using 2011 purchasing power parities http://stats.oecd.org. Discrepancy in ICERs may be due to rounding.

[32] Short time horizon (12 weeks). Simple pooling of efficacy estimates: not meta-analysis studies. Irregular decision rules used in analysis. Not a fully incremental analysis.

[33] Mexican payer systems, some relevant comparators not included.

[34] Converted from Mexican dollars to GBP using 2010 purchasing power parities http://stats.oecd.org.

[35] Converted using 2010 purchasing power parities http://stats.oecd.org. Discrepancy in ICERs may be due to rounding.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	

[36] Short time horizon (12 weeks). Likely to be shorter than disease length. PubMed only search for efficacy data. Unclear method of weighting for pooling outcomes. Not a fully incremental analysis.

[37] Some relevant comparators not included US healthcare system.

[38] Converted using 2006 purchasing power parities http://stats.oecd.org.

[39] Converted using 2006 purchasing power parities http://stats.oecd.org. Discrepancy in ICERs may be due to rounding.

[40] Short time horizon (12 weeks). No systematic review of evidence for baseline or efficacy outcomes; role of adverse effects not clear in the model. No PSA conducted.

[41] Not all relevant comparators included; Perspective of the Ontario Ministry of Health, Canada.

[42] Converted using 2004 purchasing power parities http://stats.oecd.org

[43] Usual care includes various treatments (pooling these may underestimate the relative effect size to some comparators). Non randomised controlled trial (RCT) data used in efficacy results. Unclear how pooled estimate was calculated from several heterogeneous studies. Resource use estimates from Cardiff and Vale NHS Trust pain clinic, not a national average.[44] Some relevant comparators not included.

[45] 2011 UK Pounds.

[46] Short time horizon (1 year). Clinical efficacy data from obtained from 1 randomized trial, not from a systematic review. RCT 'usual care' arm was made up of SSRIs, SNRIs, non-opioid analgesics, NSAIDS, or antiepileptic drugs. Does not consider issue of side effects within the model explicitly, titration not included. Not a fully incremental analysis.

[47] Belgian perspectives. Unclear if adults. Some relevant interventions not included.

[48] Converted using 2003 purchasing power parities http://stats.oecd.org

1.5 Economic evidence review conclusion

Thirteen partially applicable studies with potentially serious limitations were identified. However, no study included the range of comparators included in the scope of the guideline. The GDG's economic considerations were therefore based on the de novo economic model developed for this guideline.

2 Original health economic model – methods

2.1 Model overview

2.1.1 Comparators

The model was designed to assess the cost effectiveness of alternative pharmaceutical treatments neuropathic pain.

In total there were 16 pharmaceutical treatments with sufficient data to be included in the model for all neuropathic pain.

For several drugs, several formulations (such as capsules and dispersible tablets) can be prescribed, sometimes with markedly different costs. Guidance was sought from the pharmacist on the GDG as to the most appropriate formulation to be used in the model and whether multiple formulations needed to be considered.

The full list of evaluated drugs and formulations is provided in Table F3 below.

Table F3 Drugs evaluated and formulations

Drug	Formulation
Amitriptyline	Tablets
Cannabis sativa extract	Nasal spray
Capsaicin 0.075%	Cream
Capsaicin 8%	Patch
Duloxetine	Capsules
Gabapentin	Tablets
Lacosamide	Tablets
Lamotrigine	Tablets
Levetiracetam	Tablets
Morphine	Tablets
Nortriptyline	Tablets
Oxcarbazepine	Tablets
Pregabalin	Capsules
Topiramate	Tablets
Tramadol	Capsules
Venlafaxine	Capsules

2.1.2 Population

The hypothetical population included in the analysis was all people with neuropathic pain. It would have been possible to perform a dedicated analysis limited to people with peripheral pain; however, since the GDG concluded that there was insufficient evidence to distinguish between the peripheral-only group and the overall population (see full guideline, section 3.2.4), a peripheral-only model was not pursued. Therefore, attention was focused on a single analysis including all types of neuropathic pain.

2.1.3 Time horizon, perspective, discount rates used

The analysis was undertaken from the perspective of the NHS and personal social services, in accordance with NICE guidelines methodology.

There were no studies identified and included in the efficacy review to suggest that there was a difference in mortality between the drugs considered in the model.

Data on efficacy and adverse effects of drugs were available for up to 20 weeks. Extrapolation beyond this point in the absence of evidence would

require making the same assumptions on temporal efficacy profiles for all drugs, and so would lead to the same conclusions as at 20 weeks.

With a 20-week time horizon there was no requirement to apply a discount rate to either costs or QALYs.

2.1.4 Approach to modelling

The de novo economic model was built based on the availability of data, together with the views of the GDG.

With different scales being used to measure pain, the GDG agreed that pain data should be modelled as a discrete variable, with pain reduction of less than 30%, 30–49%, or 50% or more. This approach to categorising pain relief is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group and commonly used in the literature (Dworkin et al. 2005).

With such a short time horizon and with no data available on the independence of effect between different drugs (that is, we do not know how failure to achieve pain relief on one drug affects the likelihood of a patient achieving pain relief on another) the model is a simple decision tree rather than a Markov transition state model.

On starting a drug treatment, patients record pain relief of either 30–49% or 50% or more. If pain relief is less than 30% then no pain relief is assumed.

Data were available on 2 minor adverse effects for all drugs: dizziness/vertigo and nausea. Data were also available on patients withdrawing due to adverse effects. On advice from the GDG, withdrawal is assumed to occur at 4 weeks, with drug costs incurred up to that point and any efficacy benefits seen included in the analysis.

Experience of an adverse event was assumed to be independent of pain reduction and individual adverse events were assumed to be independent of each other – including adverse events leading to withdrawal. The latter of these assumptions means that a single patient could experience each of the

adverse events considered and withdraw due to adverse events and the utility decrements of each of these events would be additive for that patient.

The purpose of the model was not to estimate the cost effectiveness of treatment strategies over more than 1 line. There are insufficient data on the correlation of effectiveness on 1 drug having taken another in a different or same class to model multiple line treatment strategies. The model therefore focussed on the cost effectiveness of individual drugs as monotherapies.

In the base case it was assumed that at withdrawal from a drug due to adverse effects the patient received no pain relief for the remaining 16 weeks of the model. The impact of this assumption was explored in a scenario analysis (see section 4.1, below).

A schematic of the base case model is shown in Figure F1.

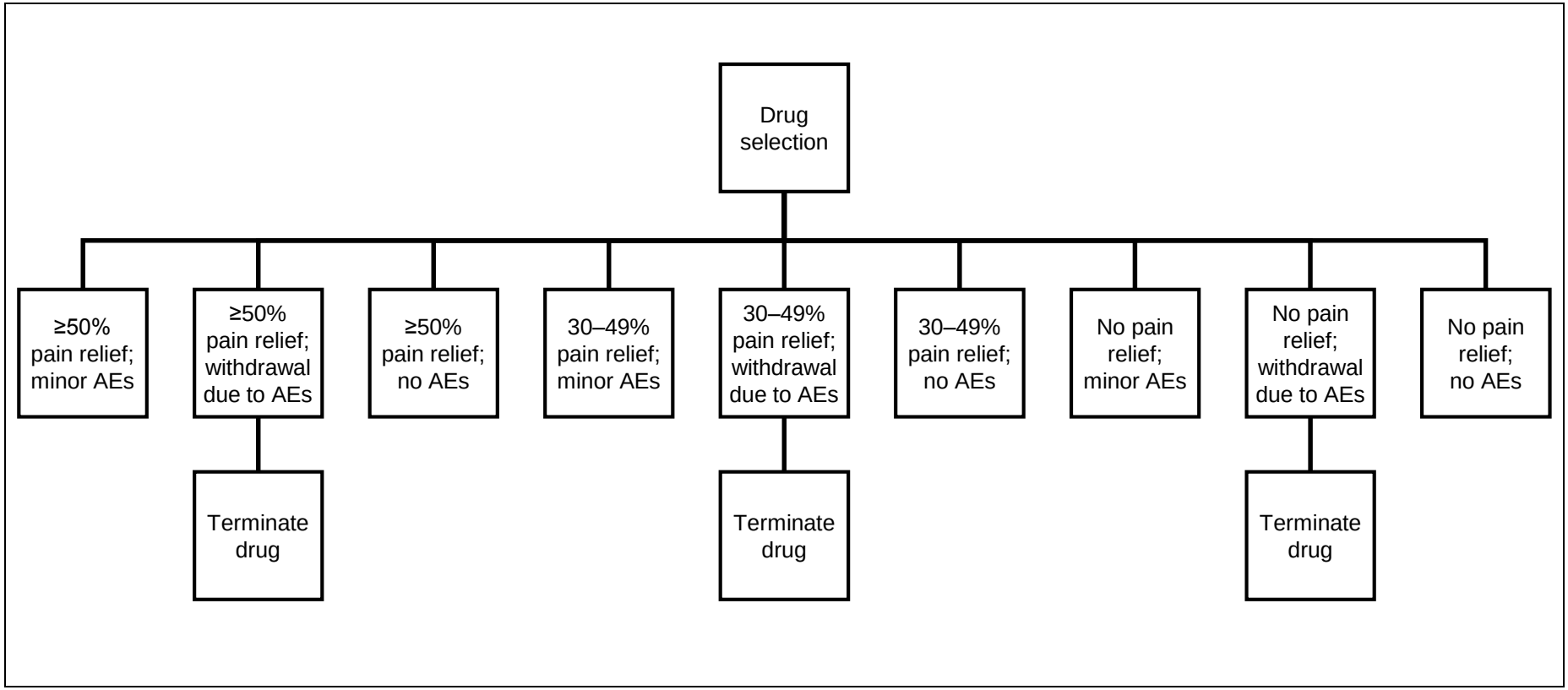


Figure F1 Neuropathic pain model schematic

2.1.5 Uncertainty

The model was built probabilistically to take account of the uncertainty surrounding each input parameter. In order to characterise uncertainty, a probability distribution was defined for utilities and the length of adverse effects and resource use associated with them. This was based on means and standard errors for utilities. For adverse effects the GDG provided a range for duration and for resource use. The distributions chosen are shown in Table F4.

A beta distribution was chosen for utilities because there was no evidence found that utility values for neuropathic pain could be less than zero.

For the adverse event costs a uniform distribution was applied to the number of GP visits required, and in the case of nausea a uniform distribution was applied to the number of days antiemetic medication was needed for.

Because of the way effectiveness data was derived from a probabilistic process (Bayesian Markov-chain Monte-Carlo sampling), when the cost-effectiveness model was run a value was chosen at random directly from the posterior distribution for the relevant parameter from the evidence synthesis model (WinBUGS CODA output). For costs and utilities, when the cost effectiveness model was run a value was randomly selected from its respective distribution. The model was run repeatedly (10,000 times) to obtain mean cost and QALY values.

Table F4 Distributions used for parameters in probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution	Parameters for the distributions
Utilities (pain relief and minor adverse effects)	Beta	Bound between 0 and 1	Alpha = mean*([mean*{1-mean}/standard error^2]-1) Beta = mean*([{1-mean}/standard error^2]-1)-alpha
Utility (adverse effects leading to withdrawal)	Uniform	All values within the specified bounds equally likely	Bound between 0.8 and 0.93
Resource use due to AEs (GP visits and days of antiemetic medication)	Uniform	All values within the specified bounds equally likely	Bound between 1 and 2 (GP visits for minor AEs) Bound between 2 and 4 (GP visits for AEs leading to withdrawal) Bound between 7 and 14 (days of antiemetic medication)
Duration of minor AEs (days)	Uniform	All values within the specified bounds equally likely	Bound between 7 and 14

2.2 Model parameters

2.2.1 Summary of model parameters

Table F5 Efficacy and safety parameters (all neuropathic pain) 20 weeks

	Pain relief after 20 weeks			Probability of event within 20 weeks		
Drug	**<30%**	**30–49%**	**≥50%**	**Withdrawal due to AEs**	**Dizziness**	**Nausea**
Placebo	0.64 (0.49,0.77)	0.13 (0.10,0.16)	0.23 (0.13,0.36)	0.09 (0.08,0.11)	0.13 (0.10,0.17)	0.10 (0.08,0.14)
Amitriptyline	0.47 (0.25,0.70)	0.15 (0.12,0.17)	0.38 (0.18,0.60)	0.24 (0.12,0.41)	0.16 (0.07,0.30)	0.09 (0.01,0.30)
Cannabis extract	0.46 (0.20,0.73)	0.15 (0.11,0.17)	0.39 (0.16,0.66)	0.48 (0.10,0.98)	0.37 (0.13,0.73)	0.21 (0.07,0.47)
Capsaicin cream	0.20 (0.03,0.48)	0.12 (0.04,0.16)	0.68 (0.36,0.92)	0.46 (0.21,0.81)	0.57 (0.02,1.00)	0.60 (0.05,1.00)
Capsaicin patch	0.53 (0.37,0.70)	0.15 (0.12,0.16)	0.32 (0.18,0.48)	0.11 (0.03,0.27)	0.12 (0.04,0.25)	0.16 (0.08,0.30)
Duloxetine	0.43 (0.27,0.60)	0.15 (0.14,0.17)	0.41 (0.26,0.58)	0.24 (0.13,0.40)	0.27 (0.13,0.48)	0.34 (0.20,0.53)
Gabapentin	0.47 (0.28,0.66)	0.15 (0.13,0.17)	0.38 (0.21,0.57)	0.18 (0.10,0.30)	0.41 (0.24,0.63)	0.13 (0.05,0.26)
Lacosamide	0.55 (0.36,0.72)	0.15 (0.12,0.16)	0.31 (0.16,0.48)	0.23 (0.12,0.38)	0.28 (0.05,0.80)	0.18 (0.09,0.33)
Lamotrigine	0.55 (0.37,0.72)	0.15 (0.12,0.16)	0.31 (0.17,0.47)	0.18 (0.10,0.29)	0.20 (0.08,0.42)	0.12 (0.06,0.21)
Levetiracetam	0.68 (0.34,0.93)	0.12 (0.04,0.16)	0.20 (0.03,0.50)	0.41 (0.13,0.87)	0.46 (0.12,0.94)	0.25 (0.06,0.67)
Morphine	0.38 (0.16,0.62)	0.15 (0.12,0.17)	0.48 (0.24,0.72)	0.52 (0.07,1.00)	0.27 (0.05,0.75)	0.45 (0.08,0.99)
Nortriptyline	0.42 (0.13,0.74)	0.14 (0.09,0.16)	0.44 (0.15,0.77)	0.28 (0.03,0.92)	0.15 (0.03,0.42)	0.07 (0.00,0.34)
Oxcarbazepine	0.45 (0.22,0.71)	0.15 (0.12,0.17)	0.40 (0.17,0.65)	0.35 (0.14,0.65)	0.67 (0.29,0.99)	0.24 (0.09,0.50)
Pregabalin	0.43 (0.28,0.59)	0.16 (0.14,0.17)	0.41 (0.26,0.58)	0.19 (0.13,0.26)	0.36 (0.24,0.51)	0.12 (0.05,0.23)
Topiramate	0.49 (0.27,0.72)	0.15 (0.12,0.17)	0.36 (0.17,0.59)	0.32 (0.16,0.55)	0.20 (0.04,0.58)	0.18 (0.09,0.34)
Tramadol	0.43 (0.22,0.65)	0.15 (0.13,0.17)	0.42 (0.21,0.64)	0.45 (0.17,0.86)	0.55 (0.21,0.94)	0.39 (0.19,0.66)
Venlafaxine	0.50 (0.27,0.73)	0.15 (0.11,0.17)	0.35 (0.16,0.58)	0.24 (0.08,0.54)	0.40 (0.02,1.00)	0.29 (0.11,0.58)
NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credible intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1						

Table F6 Efficacy and safety parameters (all neuropathic pain) 16 weeks

	Pain relief after 16 weeks			Probability of event within 16 weeks		
Drug	**<30%**	**30–49%**	**≥50%**	**Withdrawal due to AEs**	**Dizziness**	**Nausea**
Amitriptyline	0.45 (0.03,0.94)	0.12 (0.02,0.16)	0.43 (0.03,0.93)	0.20 (0.10,0.34)	0.13 (0.05,0.25)	0.07 (0.01,0.25)
NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credible intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1						

Table F7 Model cost parameters (20-week drug costs)

Drug	Daily dose	20-week costs
Amitriptyline	100 mg	£8.20
Cannabis sativa extract	11 sprays	£2138.89
Capsaicin cream	4 × 1 g applications	£177.96
Capsaicin patch	2 patches over 140 days	£420.00
Duloxetine	90 mg	£250.60
Gabapentin	2600 mg	£46.73
Lacosamide	450 mg	£828.90
Lamotrigine	350 mg	£25.50
Levetiracetam	3000 mg	£61.69
Morphine	70 mg	£51.08
Nortriptyline	125 mg	£406.00
Oxcarbazepine	1800 mg	£372.12
Pregabalin	400 mg	£322.00
Topiramate	300 mg	£23.94
Tramadol	300 mg	£26.88
Venlafaxine	150 mg	£25.30

Table F8 Model cost parameters (16-week drug costs)

Drug	Daily dose	16-week costs
Amitriptyline	100 mg	£6.56

Table F9 Model utility parameters

State / event	Mean (SE)	95% CI
No pain reduction	0.16 (0.036)	0.09–0.23
30–49% pain reduction	0.46 (0.015)	0.43–0.49
50%+ pain reduction	0.67 (0.015)	0.64–0.70
Withdrawal due to adverse effects (relative utility multiplier)	0.9	0.80–0.93 (upper and lower bounds)
Dizziness (absolute utility decrement)	−0.12 (0.0024)	
Nausea (absolute utility decrement)	−0.065 (0.0013)	

2.2.2 Efficacy and safety

Efficacy and safety data for all neuropathic pain were available for up to 20 weeks (Table F5). For full details of methods of evidence synthesis, please see Appendix K.

3 Resource use and costs

3.1 Costs of drugs

Drug prices were taken from the NHS Electronic Drug Tariff (March 2013). The cost per mg of each drug in different doses was determined. The GDG pharmacist checked and confirmed drug prices and formulations. On the advice of the GDG pharmacist no pill splitting was simulated.

In its base case, the model used a weighted average of dosages from the trials from which efficacy evidence was drawn. The dose was rounded up to the nearest whole tablet (or spray or patch). The cost of the dose was determined by the combination of tablets of different strengths that was the most cost efficient. For capsaicin cream no information was available on the number of applications in a 45 g tube. It was assumed that 1 g of cream would be applied in each application.

A full list of drugs, dosages and costs used in the modelling is shown in Table F10 and Table F11.

Table F10 Drug prices and formulations

Drug	Tab size (mg)	Number of caps	Drug tariff (March 2013) price (£)	Cost per mg/spray/patch (£)
Amitriptyline (tablets)	10	28	0.73	0.0026
	25	28	0.74	0.0011
	50	28	0.82	0.0006
Cannabis sativa extract	2.7	90	125.00	0.5144
Capsaicin cream	1 tube		143.0	
Capsaicin patch	1 patch	1	210.00	210
Duloxetine	30	28	22.40	0.0267
	60	28	27.72	0.0165
Gabapentin	100	100	2.83	0.0003
	300	100	3.87	0.0001
	400	100	4.62	0.0001
	600	100	13.00	0.0002
	800	100	38.73	0.0005
Lacosamide	50	14	10.81	0.0154
	150	56	129.74	0.0154
	200	56	144.16	0.0129
Lamotrigine (non dispersible)	25	56	1.78	0.0013
	50	56	2.14	0.0008
	100	56	3.08	0.0006
	200	56	4.98	0.0004
Levetiracetam	750	60	6.61	0.0001
Morphine (tablets)	10	56	5.31	0.0095
	20	56	10.61	0.0095
	60	60	16.20	0.0045
Nortriptyline	10	100	35.74	0.0357
	25	100	58.00	0.0232
Oxcarbazepine	600	50	44.30	0.0015
Pregabalin	25	56	64.40	0.046
	50	84	96.60	0.023
	75	56	64.40	0.0153
	100	84	96.60	0.0115
	150	56	64.40	0.0077
	200	84	96.60	0.0058
	225	56	64.40	0.0051
	300	56	64.40	0.0038
Topiramate (tablets)	25	60	2.71	0.0018
	50	60	3.67	0.0012
	100	60	3.42	0.0006

	200	60	14.60	0.0012
Tramadol (capsules)	50	30	0.96	0.0006
	50	100	3.20	0.0006
Venlafaxine	37.5	56	2.53	0.0012

Table F11 Daily dosages, dosage mix and price per dosage (trial data)

Drug	Trial dosage[a]	Rounded up to nearest whole tablet dose or 20-week dosage	Most cost efficient tab mix	140-day cost
Amitriptyline	95.0 mg	100 mg	2×50	£8.20
Cannabis sativa extract	27.7 mg of THC	29.7 mg of THC	11 sprays	£2,138.89
Capsaicin cream	3.75 applications	4 × 1 g applications	tube (assume 45×1 g applications)	£177.96
Capsaicin patch	1.0 patch	2 patches over 140 days	Patch (90 days)	£420.00
Duloxetine	78.0 mg	90 mg	1 × 60 + 1 ×30	£250.60
Gabapentin	2572.0 mg	2600 mg	6×400+2×100	£46.73
Lacosamide	422.2 mg	450 mg	2×200+1×50	£828.90
Lamotrigine	318.7 mg	350 mg	1×200+1×100+1×50	£25.50
Levetiracetam	2375.0 mg	3000 mg	4×750	£61.69
Morphine	62.0 mg	70 mg	1×60+1×10	£51.08
Nortriptyline	122.0 mg	125 mg	5×25	£406.00
Oxcarbazepine	1261.0 mg	1800 mg	3×600	£372.12
Pregabalin	397.6 mg	400 mg	2×200	£322.00
Topiramate	252.2 mg	300 mg	3×100	£23.94
Tramadol	297.5 mg	300 mg	3×100	£26.88
Venlafaxine	118.8 mg	150 mg	4×37.5	£25.30

[a] Weighted average of doses used in trials contributing evidence to efficacy synthesis (weighted according to number of participants in each relevant trial arm)

3.1.1 Administration costs

The GDG advised that administration costs of the drugs would be equal in a primary care setting, and so these were excluded from the analysis.

3.1.2 Costs of treating adverse effects

Costs of treating adverse effects could not be identified in the literature and so were estimated by the GDG. It was assumed that for minor adverse effects either 1 or 2 visits to a GP would be needed. For nausea it was assumed that a course of antiemetics would be given for between 7 and 14 days.

For other minor adverse effects no treatment costs were considered beyond the cost of the GP visit.

For adverse effects leading to withdrawal it was assumed that there would be between 2 and 4 visits to a GP before drug withdrawal. No treatment costs were assumed for the adverse effects. Table F12 summarises the costs of treating adverse effects.

Table F12 Adverse event costs

Adverse event	No of GP visits	Cost/visit (£)	Source	Drug used	Drug cost/day	Number of days	Total cost (£)
Dizziness	1–2 (uniform)	63.00	PSSRU 2012	N/A	N/A	N/A	63.00–126.00
Nausea	1–2 (uniform)	63.00	PSSRU 2012	Cyclizine hydrochloride 50 mg (3 pills a day)	44.07 (Drug Tariff)	7–14 (uniform)	66.08–132.17
Withdrawal due to adverse effects	2–4 (uniform)	63.00	PSSRU 2012	N/A	N/A	N/A	126.00–252.00

3.2 Utilities

Measures of health benefit in the model are valued in quality-adjusted life years (QALYs). A QALY is a combination measure of a person's health-related quality of life (HRQoL) over a specified time period. There are several questionnaires available to ascertain HRQoL for specific health states, such as the EQ5D, that allow linking of these health states to population-based utility indices. These utility indices allow time spent in a particular health state to be weighted against time spent in a different health state – usually perfect health.

For the cost–utility model, utility values were needed for no pain relief, 30% pain relief, 50% pain relief, minor adverse effects (nausea, dizziness) and

withdrawal due to adverse effects. The timeframe of the guideline development did not allow for a systematic review of utility values to be undertaken. A pragmatic approach was taken to review the utility values incorporated in previous economic analyses identified in the systematic review of effectiveness evidence discussed earlier in this section.

A full list of identified studies with details of measurements used and health states described is provided in Table F13.

Table F13 Utility values used in identified cost–utility studies

Study	Health state description	Utility value	Range (SD)	Comments
Lawrence	Pain relief with minor side effects	0.95		
Gordon	Severe pain (pain score ≥7)	0.2		EQ5D on Canadian patients
	Moderate pain (pain score ≥4 and <7)	0.47		
	No or mild pain (<4)	0.71		
Capeda	Persistent pain (initial titration phase and/or dropout)	0.418	0.16–0.55	
	Pain relief with minor (local) AEs (maintenance and/or additional treatment)	0.722	0.44–0.95	
Bala	Disutility from uncontrolled pain	0.47		Mean utility score for persons with severe pain from shingles using SG
	Disutility of controlled pain	0.27		
Gore	Moderate to severe pain	0.39		EQ5D on US patients using UK preference values
	Mild pain	0.7		
McCrink	Full response (≥50% improvement)	0.78	0.77–0.79	Poster abstract only. Patients with diabetic neuropathy
	Partial response 30-40% improvement	0.7	0.68–0.72	
	No response <30% improvement	0.61	0.59–0.63	
Oster	No withdrawal and no AEs	0.695	(0.016)	
	Mild to moderate AEs not leading to withdrawal	0.583	(0.007)	
Rejas	Severe pain (≥7)	0.27		HUI from Spanish perspective
	Moderate pain (≥4 – <7)	0.48		
	Without pain/mild pain (<4)	0.64		
Wilby	Intolerable adverse effects	0.9	0.80–0.93 (uniform)	Disutility. Study on patients taking antiepileptic medication
McDermott	Mild pain	0.67	(0.015)	Pan-European survey of patients with neuropathic pain using EQ5D and UK population preference values. Standard errors were not provided but were calculated from 95% confidence intervals
	Moderate pain	0.46	(0.015)	
	Severe pain	0.16	(0.035)	
Revicki	Dizziness	−0.12	(0.0024)	
Sullivan	Nausea	−0.065	(0.0013)	

From the identified studies there was no particular study that was clearly superior for inclusion over the others. Either the patients were not from the UK, the 3 health states of relevance for our model were not considered, the

study was on only 1 subgroup of neuropathic pain patients, or the health states considered were absolute rather than relative and not identical to the health states needed for the model (that is, ‘mild pain’ as opposed to ‘50% pain reduction’).

The 2 studies that appeared most favourable were McCrink (2006) and McDermott (2006). McCrink provides utility measures in the same health states as needed for the model. However, the study was reported as a conference abstract and not in a peer-reviewed journal. In addition, it was for patients with diabetic neuropathy only. The McDermott study was a pan-European survey of patients with neuropathic pain with health states valued using the UK preferences for EQ-5D measured health states. Although 3 health states were recorded (mild, moderate and severe pain), they were absolute rather than states reflecting change in pain.

The McDermott study was chosen over the McCrink study because it was available as a detailed, peer-reviewed publication, and the values were for patients with any neuropathic pain. The values for mild pain were assumed to equate to 50% pain reduction, moderate pain 30–49% reduction and severe pain <30% reduction.

For minor adverse effects individual disutilities for nausea and dizziness were identified. The disutility was assumed to last for between 7 and 14 days. For adverse effects leading to withdrawal, a disutility was assumed for withdrawal due to adverse effects rather than applying disutilities for individual adverse effects. For this value the study by Wilby (2005) was chosen for ‘intolerable adverse effects’ (the same value was used by 4 of the identified cost-effectiveness studies). It is noted that the Wilby study is of patients treated with antiepileptic drugs but the value is used due to the absence of other evidence. The model applies this disutility throughout the initial 4-week treatment period during which intolerable adverse effects are assumed to emerge.

4 Scenario analyses

Two scenario analyses were performed to explore the sensitivity of the model to critical assumptions.

4.1 Second-line treatment

The GDG wished to explore the robustness of the assumption that no further treatment would be received by people withdrawing from their assigned treatment due to intolerable adverse effects (see section 2.1.4). Therefore, a scenario analysis was undertaken in which patients were given amitriptyline (the cheapest treatment considered) after withdrawal. The purpose of the scenario was to explore the impact of assuming no further treatment over 16 weeks following withdrawal in the base case and not to model a second-line therapy. As such, in the amitriptyline second-line scenario it was assumed that after withdrawal from amitriptyline due to adverse effects, another drug of equal efficacy and cost as itself was prescribed.

4.2 Dose-adjusted efficacy and safety inputs

In recognition of heterogeneity of dosages investigated in the included trials, an alternative synthesis model was explored that sought to estimate the relationship between dose and effect in reported response rates. Using this model, estimates of response probability could be computed for any specified dose level. The GDG was asked to estimate typical maintenance dosages for each drug in the decision-set; where necessary, these amounts were rounded up to the nearest whole tablet (or spray or patch). These values were used as the expected dosage with which effects were calculated. In all cases, the dosages specified by the GDG were within the range of dosages observed in the trial evidence on which the model was based; therefore, the model was not asked to extrapolate beyond its data. For some less commonly used drugs, the GDG was unable to provide estimates of typical practice; for these, the mean value of dosages used in the trials was used instead. Drug costs were also calculated using these estimates.

Parameters for this analysis are shown in Table F14 and Table F15.

Table F14 Dose-adjusted scenario analysis: efficacy and safety parameters – 20 weeks

Drug	Assumed dose	Probability (95%CrI) of pain relief after 20wk			Probability (95%CrI) of event within 20 weeks		
		<30%	30–49%	≥50%	Withdrawal due to AEs	Dizziness[a]	Nausea[a]
Placebo	-	0.64 (0.49,0.78)	0.13 (0.10,0.16)	0.23 (0.12,0.36)	0.09 (0.08,0.11)	0.13 (0.10,0.17)	0.10 (0.08,0.14)
Amitriptyline	50 mg/d[b]	0.54 (0.30,0.77)	0.14 (0.10,0.16)	0.31 (0.13,0.54)	0.24 (0.14,0.39)	0.16 (0.07,0.30)	0.09 (0.01,0.30)
Cannabis extract	4 sprays/d[b]	0.46 (0.17,0.78)	0.14 (0.10,0.16)	0.39 (0.12,0.71)	0.46 (0.12,0.96)	0.37 (0.13,0.73)	0.21 (0.07,0.47)
Capsaicin cream	4 apps/d[b]	0.20 (0.03,0.48)	0.12 (0.04,0.16)	0.68 (0.36,0.93)	0.43 (0.23,0.70)	0.57 (0.02,1.00)	0.60 (0.05,1.00)
Capsaicin patch	1 × 60-min	0.53 (0.36,0.70)	0.15 (0.12,0.16)	0.32 (0.18,0.48)	0.11 (0.03,0.24)	0.12 (0.04,0.25)	0.16 (0.08,0.30)
Duloxetine	60 mg/d[b]	0.44 (0.28,0.61)	0.15 (0.14,0.17)	0.41 (0.25,0.58)	0.22 (0.14,0.33)	0.27 (0.13,0.48)	0.34 (0.20,0.53)
Gabapentin	1800 mg/d[b]	0.39 (0.19,0.62)	0.15 (0.12,0.17)	0.46 (0.24,0.68)	0.19 (0.09,0.35)	0.41 (0.24,0.63)	0.13 (0.05,0.26)
Lacosamide	400 mg/d[Error! Reference source not found.]	0.55 (0.37,0.73)	0.15 (0.11,0.16)	0.30 (0.16,0.47)	0.20 (0.13,0.31)	0.28 (0.05,0.80)	0.18 (0.09,0.33)
Lamotrigine	400 mg/d[b]	0.54 (0.37,0.72)	0.15 (0.12,0.16)	0.31 (0.17,0.48)	0.19 (0.11,0.29)	0.20 (0.08,0.42)	0.12 (0.06,0.21)
Levetiracetam	3000 mg/d[c]	0.68 (0.34,0.93)	0.12 (0.04,0.16)	0.21 (0.03,0.51)	0.42 (0.14,0.87)	0.46 (0.12,0.94)	0.25 (0.06,0.67)
Morphine	120 mg/d[b]	0.39 (0.17,0.65)	0.15 (0.11,0.17)	0.46 (0.22,0.72)	0.52 (0.09,1.00)	0.27 (0.05,0.75)	0.45 (0.08,0.99)
Nortriptyline	50 mg/d[b]	0.44 (0.13,0.79)	0.14 (0.08,0.16)	0.42 (0.11,0.77)	0.27 (0.02,0.92)	0.15 (0.03,0.42)	0.07 (0.00,0.34)
Oxcarbazepine	1800 mg/d[c]	0.46 (0.22,0.70)	0.15 (0.12,0.17)	0.39 (0.18,0.65)	0.31 (0.17,0.53)	0.67 (0.29,0.99)	0.24 (0.09,0.50)
Pregabalin	300 mg/d[b]	0.47 (0.31,0.64)	0.15 (0.13,0.17)	0.37 (0.22,0.54)	0.14 (0.10,0.19)	0.36 (0.24,0.51)	0.12 (0.05,0.23)
Topiramate	100 mg/d[b]	0.49 (0.09,0.90)	0.13 (0.05,0.16)	0.38 (0.05,0.83)	0.22 (0.14,0.34)	0.20 (0.04,0.58)	0.18 (0.09,0.34)
Tramadol	400 mg/d[b]	0.43 (0.22,0.66)	0.15 (0.13,0.17)	0.42 (0.21,0.65)	0.43 (0.20,0.78)	0.55 (0.21,0.94)	0.39 (0.19,0.66)
Venlafaxine	75 mg/d[b]	0.55 (0.31,0.77)	0.14 (0.10,0.16)	0.30 (0.13,0.53)	0.22 (0.09,0.46)	0.40 (0.02,1.00)	0.29 (0.11,0.58)

[a] Not dose-adjusted

[b] Estimate provided by GDG

Error! Reference source not found. GDG felt unable to comment based on own experience; weighted mean of doses in trials contributing to evidence-base used instead

NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credible intervals for mutually exclusive outcomes can only be

considered separately, and cannot be expected to sum to 1

Table F15 Dose-adjusted scenario analysis: daily dosages, dosage mix and price per dosage (GDG-advised)

Drug	GDG-advised dosage	Rounded up to nearest whole tablet dose or 20-week dosage	Most cost-efficient tab mix	140-day cost
Amitriptyline	50 mg od	50 mg	1×50	£4.10
Cannabis extract	4 sprays/d	4 sprays/d	4 sprays	£777.78
Capsaicin cream	1 g qds	4×1 g applications	tube (assume 45×1 g applications)	£177.96
Capsaicin patch	2 patches	4 patches over 140 days	Patch (90 days)	£840.00
Duloxetine	60 mg od	60 mg	1×60	£138.60
Gabapentin	600 mg tds	1800 mg	4×400+2×100	£33.80
Lacosamide	200 mg bd	400 mg	2×200	£720.80
Lamotrigine	200 mg bd	400 mg	2×200	£24.90
Levetiracetam[a]	750 mg qds	3000 mg	4×750	£61.69
Morphine	60 mg bd	120 mg	2 ×60	£75.60
Nortriptyline	25 mg bd	50 mg	2×25	£162.40
Oxcarbazepine[a]	600 mg tds	1800 mg	3×600	£372.12
Pregabalin	150 mg bd	300 mg	2×150	£322.00
Topiramate	50 mg bd	100 mg	2×50	£17.13
Tramadol	100 mg qds	400 mg	4×100	£35.84
Venlafaxine	37.5 mg bd	75 mg	2×37.5	£12.65

[a] GDG feel unable to comment based on own experience; weighted mean of dosages in trials contributing to evidence-base used instead

Abbreviations: bd, twice daily; d, day; od, once daily; qds, 4 times a day; tds, 3 times a day.

5 Interpreting results

5.1 Incremental cost effectiveness ratios

The results of cost-effectiveness analysis are presented as incremental cost-effectiveness ratios (ICERs). ICERs are calculated by dividing the difference in costs associated with 2 alternative treatments by the difference in QALYs:

$$ICER = \frac{Cost\ of\ B - Cost\ of\ A}{QALY\ of\ B - QALY\ of\ A}$$

Where more than 2 interventions are being compared, the ICER is calculated according to the following process:

- The interventions are ranked in terms of cost, from least to most expensive.
- If an intervention is more expensive and less effective than the preceding intervention, it is said to be 'dominated' and is excluded from further analysis.
- ICERs are then calculated for each drug compared with the next most expensive non-dominated option. If the ICER for a drug is higher than that of the next most effective strategy, then it is ruled out by 'extended dominance'
- ICERs are recalculated excluding any drugs subject to dominance or extended dominance.
- When there are multiple comparators, the option with the greatest average net benefit (see below) may also be used to rank comparators.

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In general, an intervention is considered to be cost-effective if either of the following criteria applies:

- The intervention dominates other relevant strategies (that is, is both less costly in terms of resource use and more clinically effective than all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per QALY gained than the next best strategy.

5.2 Net benefit framework

The net benefit (NB) framework allows us to rearrange the decision rule using the threshold value.

NB = Threshold value × total QALYs − total costs

The decision rule then becomes a simple question of maximising net benefit; the strategy with the greatest average NB is also the most cost-effective option. This framework also eliminates the need to consider dominance and calculate ICERs with respect to the most appropriate comparator. As such, it allows us to rank order interventions according to cost effectiveness.

Using the net benefit framework in probabilistic modelling, we are able to calculate the probability that a strategy will be cost effective (have the greatest NB) over a number of simulations. However, because this method does not take into account the magnitude of the NB in each of the simulations, the optimal treatment is not always the one with the greatest proportion of simulations in its favour. In order to calculate the optimal treatment when there are a large number of strategies, it is most useful to consider the cost-effectiveness frontier.

6 Results

6.1 Base-case results

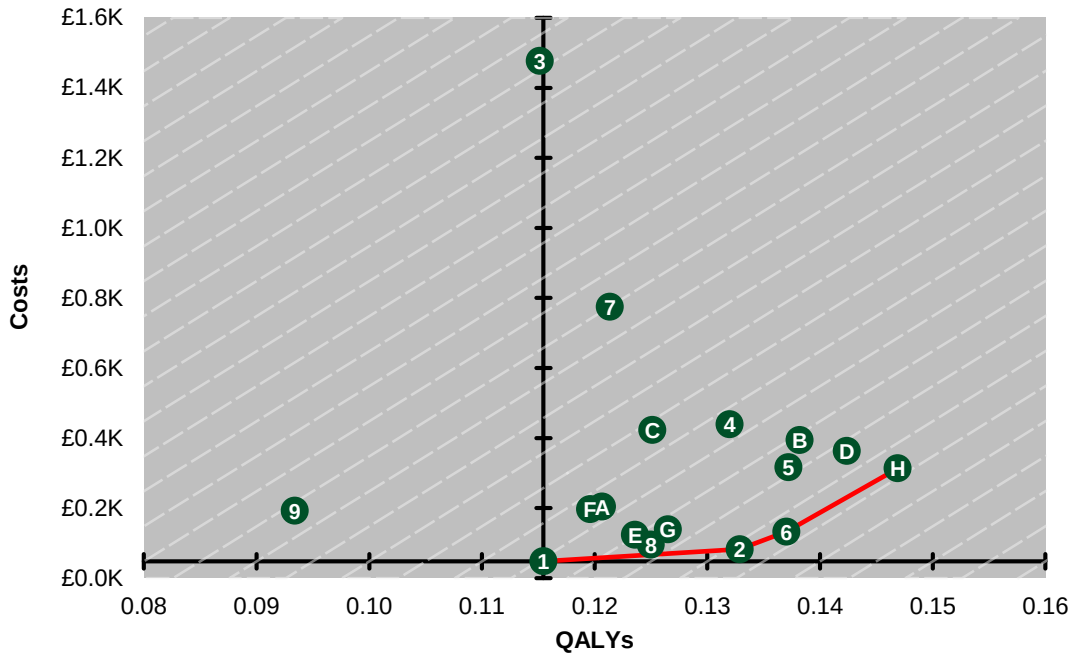
6.1.1 Incremental analysis

The incremental analyses of the average costs and QALYs generated from 10000 simulations of the model for treatments for all neuropathic pain are presented in Table F16, with the efficiency frontier shown in Figure F2.

Table F16 Incremental mean cost–utility results

Cohort	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Placebo	£48.01	0.115			
Amitriptyline	£82.50	0.133	£34.49	0.017	£1,980
Lamotrigine	£95.31	0.125	£12.81	−0.008	dominated
Topiramate	£123.80	0.124	£41.30	−0.009	dominated
Gabapentin	£132.73	0.137	£50.24	0.004	£12,091
Venlafaxine	£139.20	0.126	£6.47	−0.011	dominated
Levetiracetam	£192.65	0.093	£59.92	−0.044	dominated
Tramadol	£196.81	0.120	£64.08	−0.017	dominated
Morphine	£204.54	0.121	£71.81	−0.016	dominated
Capsaicin cream	£313.34	0.147	£180.60	0.010	£18,297
Duloxetine	£316.20	0.137	£2.86	−0.010	dominated
Pregabalin	£363.31	0.142	£49.97	−0.005	dominated
Nortriptyline	£394.41	0.138	£81.07	−0.009	dominated
Oxcarbazepine	£423.35	0.125	£110.01	−0.022	dominated
Capsaicin patch	£439.56	0.132	£126.22	−0.015	dominated
Lacosamide	£774.90	0.121	£461.56	−0.026	dominated
Cannabis extract	£1,476.69	0.115	£1,163.35	−0.032	dominated

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.



1=placebo; 2=amitriptyline; 3=cannabis sativa extract; 4=capsaicin patch; 5=duloxetine; 6=gabapentin; 7=lacosamide; 8=lamotrigine; 9=levetiracetam; A=morphine; B=nortriptyline; C=oxcarbazepine; D=pregabalin; E=topiramate; F=tramadol; G=venlafaxine; H=capsaicin cream

Figure F2 Efficiency frontier

The base-case incremental analysis suggests that amitriptyline, gabapentin and capsaicin cream all sit on the efficiency frontier all with ICERs below £20,000.

In addition, a cluster of drugs sits either well above the frontier or in the top left quadrant (costing more and being less effective than placebo): cannabis sativa, oxcarbazepine, levetiracetam, lacosamide and capsaicin patch.

The GDG wished to explore the impact of removing capsaicin cream from the analysis. In this scenario, at the base case pregabalin will sit on the frontier with amitriptyline and gabapentin in the base case analysis at an ICER of £43,009 compared with gabapentin. If gabapentin and amitriptyline were removed from the analysis the ICER for pregabalin compared with placebo would be £11,707. Duloxetine would sit close to the frontier in both instances.

6.1.2 PSA and net benefit analysis

This analysis is based on the average cost and QALY values generated from the 10000 simulations of each model. This masks the significant variation in cost and QALYs generated for individual drugs across the simulations that reflects the uncertainty around effectiveness in the data. This variation is shown in a scatter plot of the cost and QALYs generated for each drug across the first 1000 simulations in Figure F3.

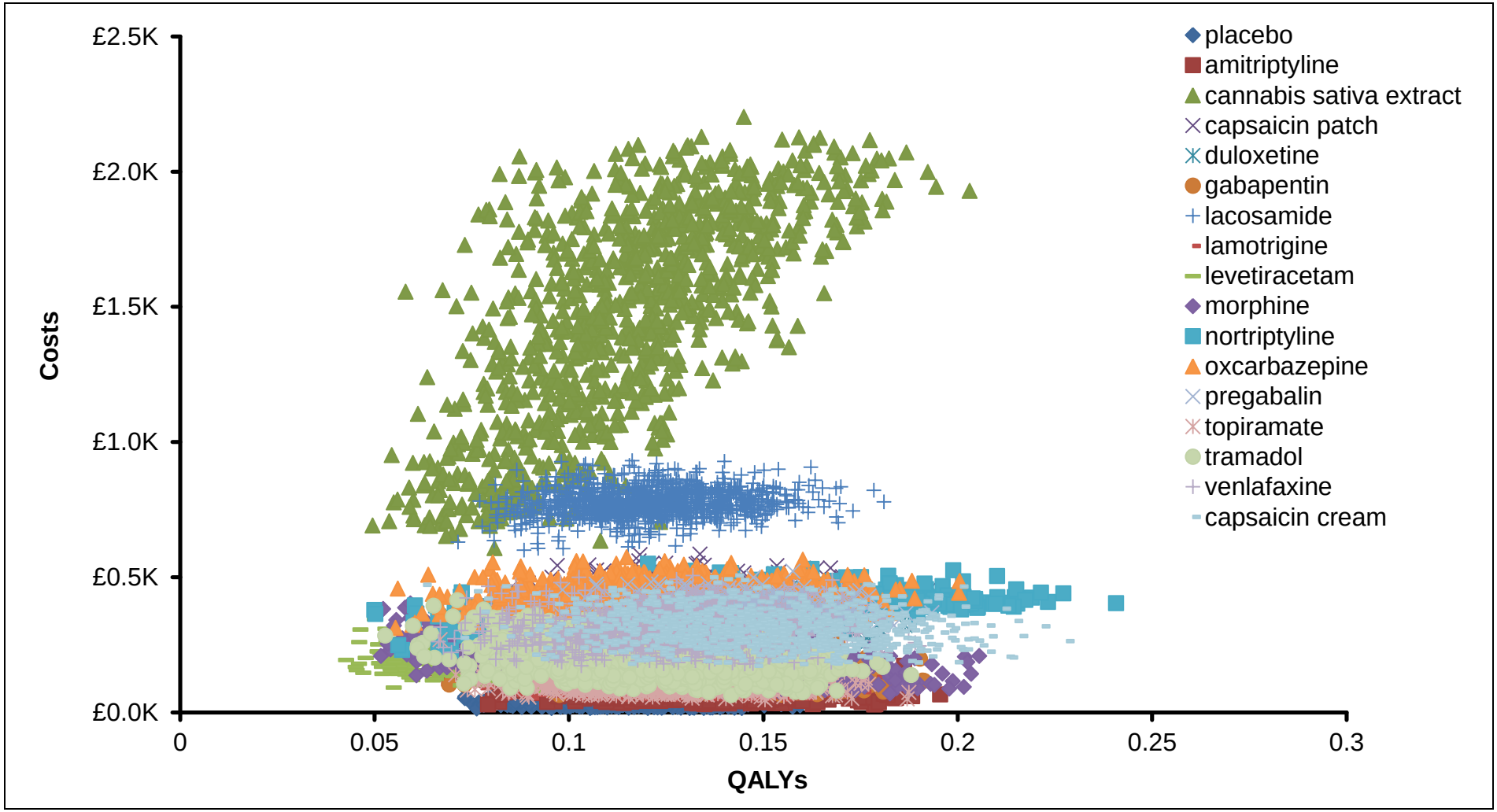


Figure F3 Scatter plot of first 1000 probabilistic simulations

The lack of clarity in the scatter plot is in part is due to the number of drugs in the analysis, but also reflects the similarity in cost and outcome across the majority of drugs considered.

A net benefit analysis at £20,000 a QALY provides further detail of this uncertainty. The probability of each drug having the highest net benefit when QALYs are valued at £20,000 and £30,000 is shown in Table F17. The cost effectiveness acceptability curve (CEAC) is shown in Figure F4.

Table F17 Net benefit analysis

	QALYs valued at £20,000			QALYs valued at £30,000		
Treatment	**Mean NMB**	**Prob. of highest NMB**	**Prob. NMB > placebo**	**Mean NMB**	**Prob. of highest NMB**	**Prob. NMB > placebo**
Capsaicin cream	£2624.67	28.1%	75.4%	£4093.67	30.0%	80.4%
Gabapentin	£2607.86	9.5%	94.3%	£3978.16	7.6%	95.8%
Amitriptyline	£2575.01	13.3%	84.7%	£3908.42	10.7%	86.0%
Pregabalin	£2484.51	1.0%	98.3%	£3903.76	2.0%	100.0%
Duloxetine	£2427.91	1.3%	84.8%	£3799.97	2.1%	94.3%
Lamotrigine	£2404.57	1.2%	80.9%	£3751.60	0.8%	83.7%
Venlafaxine	£2390.80	6.5%	64.9%	£3655.80	5.6%	68.4%
Nortriptyline	£2369.60	16.9%	56.6%	£3654.51	20.1%	63.1%
Topiramate	£2348.01	4.1%	61.1%	£3583.92	3.5%	64.5%
Placebo	£2261.15	0.0%	–	£3519.76	0.0%	–
Morphine	£2208.58	12.4%	49.1%	£3415.72	11.6%	51.8%
Capsaicin patch	£2199.99	0.0%	33.3%	£3415.13	0.1%	68.5%
Tramadol	£2195.03	3.4%	44.2%	£3390.96	3.1%	48.9%
Oxcarbazepine	£2079.31	1.5%	30.3%	£3330.64	2.3%	43.0%
Levetiracetam	£1675.06	0.8%	10.0%	£2865.86	0.7%	11.2%
Lacosamide	£1652.27	0.0%	0.2%	£2608.91	0.0%	2.5%
Cannabis extract	£826.13	0.0%	0.0%	£1977.54	0.0%	0.6%
Abbreviations: NMB, net monetary benefit; QALY, quality-adjusted life year; prob., probability.						

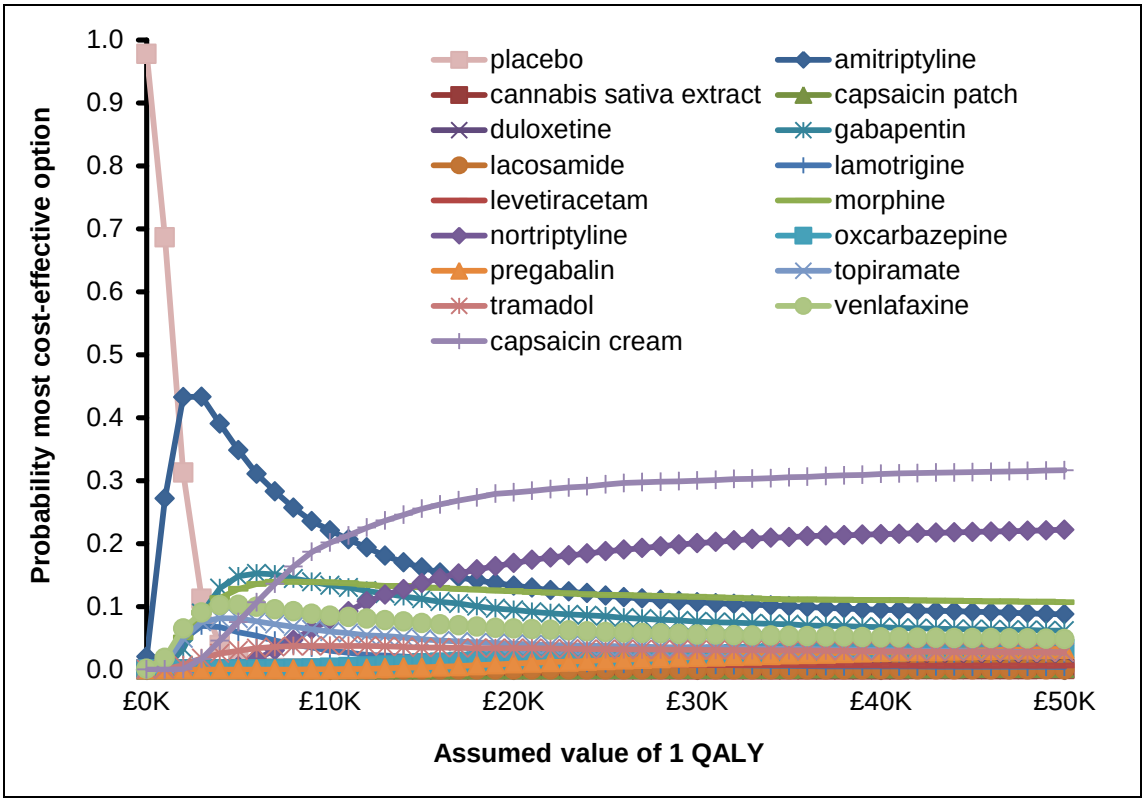


Figure F4 Cost-effectiveness acceptability curve

The drugs with the highest probability of maximal net benefit are those that are also clustered around the efficiency frontier, with the exception of nortriptyline. The evidence available on nortriptyline generates a wide credible interval for its potential effectiveness, meaning that whilst there is a significant probability that it is the most cost effective option there is also a nonzero probability that it is less effective than placebo. Our analysis suggested that in 43% of the 10,000 simulations of the model nortriptyline had a lower net benefit than placebo at £20,000 a QALY.

The drugs with zero or very low probability of being the most cost effective options at £20,000 per QALY were the ones that were the furthest away from the efficiency frontier.

6.2 Scenario analyses

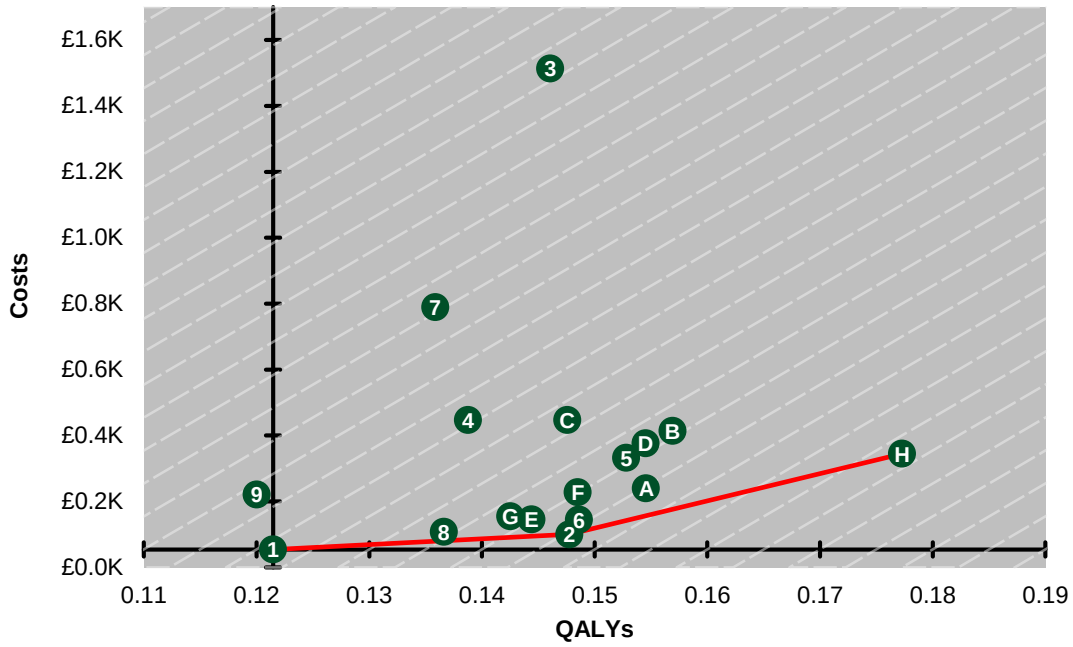
6.2.1 Second-line treatment

This scenario analysis explored the impact of second-line treatment following withdrawal due to adverse effects by assuming people who are unable to tolerate their assigned treatment will receive amitriptyline (instead of nothing) for the remainder of the 20-week modelled period. Incremental results are shown in Table F18, with the efficiency frontier depicted in Figure F5 and the probabilistic net benefit analysis shown in Table F19.

Table F18 Incremental analysis (amitriptyline second line)

	Absolute		Incremental		
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Placebo	£54.40	0.121			
Amitriptyline	£100.17	0.148	£45.77	0.026	£1,740
Lamotrigine	£107.66	0.137	£7.49	−0.011	dominated
Gabapentin	£144.71	0.149	£44.54	0.001	ext. dom.
Topiramate	£145.44	0.144	£45.27	−0.003	dominated
Venlafaxine	£154.89	0.143	£54.72	−0.005	dominated
Levetiracetam	£221.07	0.120	£120.90	−0.028	dominated
Tramadol	£227.73	0.149	£127.56	0.001	dominated
Morphine	£240.04	0.155	£139.87	0.007	ext. dom.
Duloxetine	£332.80	0.153	£232.63	0.005	dominated
Capsaicin cream	£344.86	0.177	£244.69	0.030	£8,291
Pregabalin	£376.14	0.155	£31.28	−0.023	dominated
Nortriptyline	£414.32	0.157	£69.46	−0.020	dominated
Oxcarbazepine	£447.07	0.148	£102.21	−0.030	dominated
Capsaicin patch	£447.13	0.139	£102.27	−0.039	dominated
Lacosamide	£789.67	0.136	£444.81	−0.041	dominated
Cannabis extract	£1,513.67	0.146	£1,168.81	−0.031	dominated

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.



1=placebo; 2=amitriptyline; 3=cannabis sativa extract; 4=capsaicin patch; 5=duloxetine; 6=gabapentin; 7=lacosamide; 8=lamotrigine; 9=levetiracetam; A=morphine; B=nortriptyline; C=oxcarbazepine; D=pregabalin; E=topiramate; F=tramadol; G=venlafaxine; H=capsaicin cream

Figure F5 Efficiency frontier (amitriptyline second line)

Table F19 Net benefit analysis (amitriptyline second line)

Treatment	QALYs valued at £20,000			QALYs valued at £30,000		
	Mean NMB	Prob. of highest NMB	Prob. NMB > placebo	Mean NMB	Prob. of highest NMB	Prob. NMB > placebo
Capsaicin cream	£3200.59	48.7%	94.9%	£4973.32	52.4%	96.8%
Amitriptyline	£2855.02	7.9%	93.0%	£4396.40	5.5%	93.7%
Morphine	£2850.92	12.9%	83.3%	£4332.62	11.7%	86.1%
Gabapentin	£2827.61	4.4%	98.0%	£4313.78	3.4%	98.6%
Topiramate	£2742.54	3.4%	88.1%	£4293.11	2.5%	90.1%
Tramadol	£2742.36	3.9%	83.3%	£4259.39	3.4%	86.3%
Nortriptyline	£2723.96	12.3%	73.9%	£4251.48	14.4%	80.9%
Duloxetine	£2723.39	0.6%	97.1%	£4227.40	0.8%	99.2%
Pregabalin	£2714.22	0.2%	99.8%	£4186.53	0.4%	100.0%
Venlafaxine	£2695.48	3.9%	84.9%	£4120.66	3.1%	87.4%
Lamotrigine	£2624.94	0.3%	94.7%	£3991.23	0.2%	96.0%
Oxcarbazepine	£2504.24	1.2%	62.9%	£3979.90	1.6%	75.5%
Placebo	£2374.86	0.0%	–	£3715.71	0.0%	–
Capsaicin patch	£2328.10	0.0%	35.2%	£3589.49	0.1%	73.2%
Levetiracetam	£2179.35	0.6%	32.0%	£3379.57	0.5%	36.1%
Lacosamide	£1927.55	0.0%	1.9%	£3286.16	0.0%	15.1%
Cannabis extract	£1407.66	0.0%	5.2%	£2868.33	0.0%	15.2%

Abbreviations: NMB, net monetary benefit; QALY, quality-adjusted life year; prob., probability.

The scenario analysis of amitriptyline second line suggests that lowering the impact of withdrawal due to adverse events from capsaicin cream means that capsaicin cream extendedly dominates gabapentin.

However, the drugs that cluster around the frontier are the same in both the base case and amitriptyline second line analysis. As well as gabapentin and amitriptyline, topiramate, venlafaxine and lamotrigine sit close to the frontier using either dataset. Two options appear to benefit in this scenario – morphine and tramadol, both of which are subject to high dropout rates.

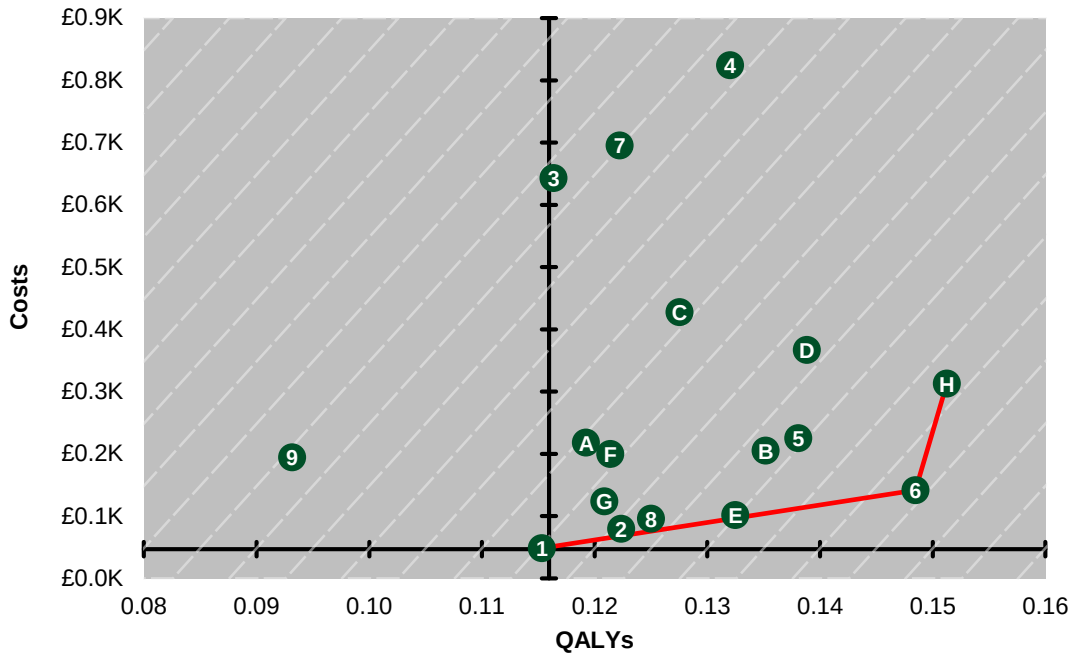
6.2.2 Dose-adjusted inputs

This scenario analysis explored the impact of relying on efficacy and safety data derived from models that sought to account for dose–response effects in the assembled evidence (methods and results of the dose-adjusted syntheses are provided in appendices D and G, respectively). Incremental results are shown in Table F20, with the efficiency frontier depicted in Figure F6 and the probabilistic net benefit analysis shown in Table F21.

Table F20 Incremental analysis (dose-adjusted inputs)

Cohort	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Placebo	£48.40	0.115			
Amitriptyline	£79.65	0.122	£31.25	0.007	ext. dom.
Lamotrigine	£95.80	0.125	£47.41	0.010	ext. dom.
Topiramate	£101.75	0.132	£53.35	0.017	ext. dom.
Venlafaxine	£123.58	0.121	£75.19	0.006	dominated
Gabapentin	£141.55	0.148	£93.15	0.033	£2,810
Levetiracetam	£194.16	0.093	£52.61	−0.055	dominated
Tramadol	£199.79	0.121	£58.24	−0.027	dominated
Nortriptyline	£205.11	0.135	£63.56	−0.013	dominated
Morphine	£217.87	0.119	£76.33	−0.029	dominated
Duloxetine	£225.03	0.138	£83.48	−0.010	dominated
Capsaicin cream	£312.58	0.151	£171.03	0.003	£61,582
Pregabalin	£366.84	0.139	£54.26	−0.012	dominated
Oxcarbazepine	£427.39	0.128	£114.82	−0.024	dominated
Cannabis extract	£642.66	0.116	£330.09	−0.035	dominated
Lacosamide	£695.23	0.122	£382.65	−0.029	dominated
Capsaicin patch	£824.04	0.132	£511.46	−0.019	dominated

Abbreviations: ext. dom., extendedly dominated; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.



1=placebo; 2=amitriptyline; 3=cannabis sativa extract; 4=capsaicin patch; 5=duloxetine; 6=gabapentin; 7=lacosamide; 8=lamotrigine; 9=levetiracetam; A=morphine; B=nortriptyline; C=oxcarbazepine; D=pregabalin; E=topiramate; F=tramadol; G=venlafaxine; H=capsaicin cream

Figure F6 Efficiency frontier (dose-adjusted inputs)

Table F21 Net benefit analysis (dose-adjusted inputs)

Treatment	QALYs valued at £20,000			QALYs valued at £30,000		
	Mean NMB	Prob. of highest NMB	Prob. NMB > placebo	Mean NMB	Prob. of highest NMB	Prob. NMB > placebo
Gabapentin	£2,827.90	24.1%	97.3%	£4,312.62	22.1%	98.1%
Capsaicin cream	£2,712.42	21.3%	84.3%	£4,224.91	24.0%	88.8%
Topiramate	£2,547.94	22.6%	63.0%	£3,917.62	21.3%	64.0%
Duloxetine	£2,536.74	0.9%	97.4%	£3,872.78	1.1%	99.2%
Nortriptyline	£2,498.68	18.5%	62.5%	£3,850.57	18.9%	65.3%
Pregabalin	£2,410.03	0.2%	91.4%	£3,798.46	0.3%	99.3%
Lamotrigine	£2,404.45	0.6%	80.8%	£3,654.57	0.4%	83.6%
Amitriptyline	£2,367.47	2.1%	62.8%	£3,591.03	1.7%	64.3%
Venlafaxine	£2,293.72	1.9%	52.9%	£3,502.37	1.5%	56.2%
Placebo	£2,258.15	0.0%	–	£3,441.84	0.0%	–
Tramadol	£2,227.97	1.4%	47.5%	£3,411.42	1.3%	53.3%
Morphine	£2,166.60	5.2%	46.3%	£3,398.44	5.0%	49.1%
Oxcarbazepine	£2,123.17	0.5%	32.8%	£3,358.84	0.8%	47.4%
Capsaicin patch	£1,816.57	0.0%	0.2%	£3,136.87	0.0%	9.7%
Lacosamide	£1,749.49	0.0%	0.2%	£2,971.84	0.0%	4.8%
Cannabis extract	£1,684.61	0.4%	11.4%	£2,848.25	1.1%	20.9%
Levetiracetam	£1,669.27	0.4%	9.4%	£2,600.98	0.4%	10.8%

Abbreviations: NMB, net monetary benefit; QALY, quality-adjusted life year; prob., probability.

Once more, results from this scenario analysis are broadly in line with those generated in the base case, with similar options clustering around the cost-effectiveness frontier. Gabapentin moves ahead of capsaicin cream as the option with greatest expected net benefit. Nortriptyline looks somewhat more cost effective than in the base case (though it was still inferior to placebo in over a third of simulations). Conversely, amitriptyline becomes a less attractive option, although it is probably a superior option to placebo, and it was associated with lower net costs than gabapentin in 99.2% of simulations. Pregabalin and duloxetine – which are closely matched in the base case – move somewhat further apart, with duloxetine being associated with greater net benefit in the majority of cases.

7 Discussion

7.1 Summary of results

Due to the large credible intervals around effectiveness estimates for most of the drugs considered, identification of the most cost-effective drugs is problematic. However, the analysis presented here suggests a number of drugs that appear to be cost effective as they:

- sit on or close to the efficiency frontier,
- have a positive net benefit compared with placebo at £20,000 per QALY **and**
- have a greater than 5% chance of being the most cost-effective option at £20,000 per QALY.

For all neuropathic pain the drugs that met these criteria were:

- gabapentin
- amitriptyline
- capsaicin cream
- venflaxine

If gabapentin, amitriptyline and capsaicin cream are removed from the analysis, then pregabalin sits on the frontier and duloxetine very close to the frontier with both having an ICER less than £20,000 compared to placebo.

There was strong and consistent evidence that the following drugs are not cost effective, with:

- a less than 1% probability of being the most cost-effective option at £20,000 per QALY
- a mean net benefit less than placebo at £20,000 per QALY.

The drugs meeting these criteria were:

- cannabis sativa extract
- capsaicin patch
- lacosamide
- levetiracetam
- oxcarbazepine.

7.2 Strengths and limitations of findings

The model allowed comparison for the maximum number of drugs for which data are available in a transparent way. The modelling was probabilistic in nature that allowed the uncertainty in the data to be reflected in the model. Assumptions that had to be taken were the minimum required for a tractable model to generate results.

The model was able to synthesise disparate datasets for drugs in terms of quality and availability of data across efficacy time scales and identify those drugs where the evidence was consistent for potential cost effectiveness or lack of cost effectiveness.

The model itself was a simple decision tree over 20 weeks of treatment. Efficacy data were generated for 4-week cycles up to 20 weeks. An alternative model of 5 4-week cycles could have been produced using this data. Such a model would be advantageous for drugs that reach maximum efficacy more rapidly than other drugs.

However, from 8 to 20 weeks there is relatively little change in efficacy seen in the data. All drugs at 4 weeks show a reduction in efficacy compared to 8 weeks that is proportionally almost identical. As such a decision tree was chosen favouring parsimony over the complexity of a 5-cycle model that would have had little or no impact on conclusions.

The model also dealt with efficacy as a discrete rather than a continuous variable. This meant, for example, that utility derived from 100% pain relief was assumed to be the same as if 50% pain relief. This assumption will be to the disadvantage of those drugs that deliver substantially greater reductions in pain than 50%. This assumption was required however as the available utility data is discrete and it also allowed easier synthesis of the efficacy evidence available. In addition there is considerable literature that is critical of the use of continuous scales in the measurement of pain within trials (see, for example, Moore et al., 2005).

Ideally multiple-line treatment strategies should be modelled but, in the absence of any evidence about how these treatments work in sequence, this could not be undertaken. In the base-case analysis it was assumed that if a patient withdraws from treatment due to adverse effects then there is no further treatment for the remainder of the 20 weeks. This would be to the detriment of drugs that have high withdrawal rates that may be very effective for patients for whom the drug is well tolerated. Whilst this assumption is a simplification of a more complex reality, the scenario analysis that moved patients onto amitriptyline after withdrawal did not produce qualitatively different findings on the drugs that were found to be cost effective or cost ineffective. As such the assumption whilst an abstraction from reality does not impact on findings.

A similar limitation is the lack of modelling of combination therapies but again due to a lack of efficacy evidence on combination therapy such treatment could not be modelled.

The findings – as with all models – are also limited by the robustness of the data populating the model. The lack of evidence on effectiveness and side

effects beyond 20 weeks may be particularly important for the development of adverse effects or addiction to some of these drugs, and a subsequent longer term reduction in quality of life. Without evidence it is impossible to say which drugs this might have had the greatest impact on.

Alternative robust utility estimates would have been beneficial to assess the impact of the utility estimates chosen. This applies for both utility from pain relief and disutility from adverse effects. Similarly, efficacy data on adverse effects was limited to withdrawal due to adverse effects, nausea and dizziness because these data were available for all drugs considered. It may be that incorporation of other side-effects, were data available, such as headache, may have influenced the findings. For topiramate especially, the GDG felt that there are unusual adverse effects. These were not captured by the model. However, the driver of the difference in QALYs generated is pain relief achieved. Unless the minor side effects of one of the drugs found to be cost effective had a very high incidence rate compared with other drugs, it is unlikely that exclusion of such minor events will have an important impact on findings.

7.3 Comparison with other economic models

Given the potentially serious limitations found in previous economic models of pharmaceutical treatment for neuropathic pain, the fact that the models did not look at all neuropathic pain as a homogeneous patient cohort, the different modelling approaches chosen (notably the number of drugs modelled) and the breadth of the data incorporated into the de novo model, there is no reason to suppose that the results found elsewhere should match those produced here.

However, putting these concerns to the side the major apparent difference would appear to be around pregabalin, which in the identified models frequently comes out as being cost effective whereas this was not the case in our analysis.

This can be explained in part by the methods of analysis undertaken in these models and utility values chosen, with three studies reporting that the cost

effectiveness of pregabalin was sensitive to utility values chosen and in 2 studies the dosage of gabapentin chosen had a significant influence on the relative cost effectiveness of pregabalin over gabapentin.

7.4 Final conclusions

The de novo economic modelling found that there are a number of drugs for the treatment of neuropathic pain (either all or peripheral), where the evidence is consistent that they are likely to be cost effective.

The modelling was also consistent in the evidence it produced on the drugs that are likely to be not cost effective.

The model was able to explore the uncertainty in the data and the probabilistic results reflect both this uncertainty and the similar levels of efficacy that many of these drugs exhibit. Indeed, it is this similarity in efficacy (and the low cost of most drugs) that means that there are a cluster of drugs that sit around the efficiency frontier and in a probabilistic analysis have a non-trivial probability of being the most cost effective at £20,000 a QALY.

The same probabilistic analysis shows that the findings are robust across the range of potential values for efficacy, adverse effects and utilities for pain and effects that could be incorporated in the model.

Assumptions were made that may limit the findings, most notably the adoption of a 20-week time horizon and the assumption, in the base case scenario, that no treatment would occur following withdrawal due to adverse effects. A scenario analysis with amitriptyline second line revealed the latter assumption to have no significant influence on results. The former assumption is an artefact of data limitations and may be important for drugs that have significant long-term adverse effects.

Appendix F1 Economic evidence tables

Annemans L, Caekelbergh K, Morlion B et al. (2008) A cost–utility analysis of pregabalin in the management of peripheral neuropathic pain. Acta Clinica Belgica 63: 170-78.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Markov state transition model Perspective: Belgian health care public payer Time horizon: 1 year Cycle length: 1 month Discounting: Costs = NA; Outcomes = NA	Population: Patients with peripheral neuropathic pain Intervention 1: Usual care Intervention 2: 150 mg/day pregabalin Intervention 3: 300 mg/day pregabalin Intervention 4: 600 mg/day pregabalin Intervention 5: Mix pregabalin	Total costs (mean per patient): Intvn 1: €6200 (£4522.62) Intvn 2: €5945 (£4336.61) Intvn 3: €6073 (£4429.98) Intvn 4: €5894 (£4299.41) Intvn 5: €5984 (£4365.06) Currency & cost year: 2003 Euros (presented here as 2003 UK pounds‡) Cost components incorporated: Drug acquisition costs, cost per day for Belgian insurance	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.510 Intvn 2: 0.519 Intvn 3: 0.517 Intvn 4: 0.525 Intvn 5: 0.520	Primary ICER: All interventions dominant when compared with usual care Uncertainty: It cannot be concluded that pregabalin is cost saving
Data sources				
Health outcomes: van Seventer et al 2006. Quality-of-life weights: SF-6D from Annemans et al 2004. 2003 costs from Annemans et al, 2004				
Comments				
Source of funding: Unclear; Limitations: Unclear if adults only, likely Belgian population, Pregabalin and usual care. Some comparators not examined, Does not consider issue of side effects within the model explicitly, titration not included. Short Time horizon. Clinical efficacy data from obtained from 1 randomised trial, not from a systematic review. RCT 'usual care' arm was made up of SSRIs, SNRIs, non-opioid analgesics, NSAIDS, or antiepileptic drugs. Not a fully incremental analysis.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years ‡ Converted using 2003 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Armstrong EP, Malone DC, McCarberg B et al. (2011) Cost-effectiveness analysis of a new 8% capsaicin patch compared to existing therapies for post-herpetic neuralgia. [Review]. Current Medical Research & Opinion 27: 939-50.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Markov model Perspective: USA payer (manager-care organization) Time horizon: 1 year Cycle length: 1 month Discounting: Costs = NA ; Outcomes = NA	Population: US patients with post-herpetic neuralgia Intervention 1: Capsaicin topical 8% 280 cm2 1.87 patches per treatment Intervention 2: TCA – Nortriptyline 50 mg/day, (titration doses of 100 mg/day and 150 mg/day) 100 mg/day, 150 mg/day Intervention 3: Lidocaine topical 5% 140 cm2 t.d.s. Intervention 4: Gabapentin 1800, 2400 mg/day Intervention 5: Pregabalin 150, 300, 600 mg/day Intervention 6: Duloxetine 60, 120 mg/day	Total costs (mean per patient): Intvn 1: $5305 (£3597) Intvn 2: $1700 (£1153) Intvn 3: $4988 (£3382) Intvn 4: $2208 (£1497) Intvn 5: $2743 (£1960) Intvn 6: $2407 (£1632) Currency & cost year: 2011 US dollars (presented here as 2011 UK pounds‡) Cost components incorporated: Drug and prescribing costs, costs of physician applying patch management of side-effects (drug and physician costs), cost of replacement treatment (oxycodone)	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.606 Intvn 2: 0.544 Intvn 3: 0.602 Intvn 4: 0.532 Intvn 5: 0.541 Intvn 6: 0.539	Primary ICER (compared with capsaicin patch): Intvn 2: $59,919 (£40,629) per QALY Intvn 3: $554,627 (£376,073) per QALY Intvn 4: $42,008 (£28,484) per QALY Intvn 5: $40,241 (£27,296) per QALY Intvn 6: $43,908 (£29,772) per QALY Analysis of uncertainty: - Less frequent retreatment using capsaicin patch. Retreatment every 14.5 week ICER vs all other oral less than $51,000 (£34,581) per QALY, retreatment every 17.7 weeks: less than $44,000 (£29,834) per QALY - Cost of replacement treatment (oxycodone) was a cost driver.
Data sources				
Health outcomes: Variety of sources (systematic review on MEDLINE and EMBASE). Quality-of-life weights: Variety of sources. Cost sources: drugstore.com				
Comments				
Source of funding: NeurogesX Limitations: US population. Unclear if adult only population considered (likely), unclear if population is in specialist services, US health system: costs of treatment likely to vary, short time horizon, and does not state if HRQOL outcomes reported by patients or carer. Not a fully incremental analysis. No PSA conducted.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER				

= incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years

‡ Converted using 2011 purchasing power parities http://stats.oecd.org

* Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations

Beard SM, McCrink L, Le TK et al. (2008) Cost effectiveness of duloxetine in the treatment of diabetic peripheral neuropathic pain in the UK. Current Medical Research & Opinion 24: 385-99.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Decision analytic model Perspective: UK NHS Time horizon: 6 months Discounting: Costs = NA; Outcomes = NA	Population: Adults with diagnoses symmetric PDN, suffering from painful symptoms Intervention 1: 1st line: Tricyclic antidepressant (TCA) Amitriptyline 75 mg/day 2nd line: Gabapentin (GBN) 1800 mg/day 3rd line: Opioid-related treatment (OPD) Tramadol 300 mg/day Intervention 2: 1st line: Duloxetine (DUL) 60 mg/day 2nd line: Tricyclic antidepressant (TCA) 3rd line: Gabapentin (GBN) 4th line: Opioid-related treatment (OPD) Intervention 3: 1st line: Tricyclic antidepressant (TCA) 2nd line: Duloxetine (DUL) 3rd line: Gabapentin (GBN) 4th line: Opioid-related treatment (OPD) Intervention 4: 1st line: Tricyclic antidepressant (TCA)	Total costs (mean per 1000 patients): Intvn 1: £306,148 Intvn 2: £271,358 Intvn 3: £229,077 Intvn 4: £310,487 Intvn 5: £309,607 Currency & cost year: 2005 UK pounds Cost components incorporated: Drug acquisition costs, administration costs and cost of treatment switching (cost of outpatient and GP attendance).	Primary outcome measure: QALYs (mean per 1000 patients) Intvn 1: 363.9 Intvn 2: 366.3 Intvn 3: 365.7 Intvn 4: 365.5 Intvn 5: 365.5	Primary ICER (compared with intervention 1): Intvn 2: Intervention 2 Dominant Intvn 3:Intervention 3 Dominant Intvn 4: £2,698 per QALY gained Intvn 5: £2,109 per QALY gained Intvn 2 vs Intvn 3: £75,036 per QALY gained Probability Intvn 3 cost-effective: 94% (at £30,000 per QALY threshold) Analysis of uncertainty: - Longer time horizon: Intvn 3: most cost effective. - Use of Pregabalin instead of gabapentin: Intvn 2 vs Intvn 3: approx. £75,000 per QALY gained. - First line anticonvulsant (of Intvn 1): Intvn 2 dominates.

	2nd line: Gabapentin (GBN) 3rd line: Duloxetine (DUL) 4th line: Opioid-related treatment (OPD) Intervention 5: 1st line: Tricyclic antidepressant (TCA) 2nd line: Gabapentin (GBN) 3rd line: Opioid-related treatment (OPD) 4th line: Duloxetine (DUL)			
Data sources				
Health outcomes: Medline database structured literature review: pooling of multiple studies. Quality-of-life weights: EQ5D UK tariff. Cost sources: PSSRU, BNF 2005				
Comments				
Source of funding: Funding by Eli Lilly and Boehringer Ingelheim; Limitations: Some relevant comparators not included, Time horizon of 6 months may be too short to fully reflect the costs and benefits associated with the treatments for the disease. Unclear how the management of adverse events were included. Pooling of studies: unclear how heterogeneity was taken into account.				
Overall applicability*: Partially applicable . Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; PDN = painful diabetic neuropathy; QALYs =quality-adjusted life years * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Bellows BK, Dahal A, Jiao T et al. (2012) A cost–utility analysis of pregabalin versus duloxetine for the treatment of painful diabetic neuropathy. Journal of Pain & Palliative Care Pharmacotherapy 26: 153-64.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Decision tree Approach to analysis: Perspective: US third-party payer Time horizon: 6 months Discounting: Costs = NA; Outcomes = NA	Population: US population with painful diabetic neuropathy Intervention 1: Pregabalin 300 mg/day (100 mg TID) Intervention 2: Duloxetine 60 mg/day (60 mg QD)	Total costs (mean per patient from PSA): Intvn 1: $967 (£656) Intvn 2: $758 (£514) Incremental (2-1): $209 (£142) Currency & cost year: (e.g. 2011 US dollars (presented here as 2011 UK pounds‡) Cost components incorporated: Drug costs, inpatient and outpatients costs, emergency costs, and adverse event management costs	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.189 Intvn 2: 0.199	Primary ICER (duloxetine vs pregabalin): ICER: Duloxetine dominates Probability cost-effective: NS for base case Analysis of uncertainty: Real-world (range of doses from real world, but mean from efficacy): $16,300 (£11,052) per QALY Real-world: Pooled efficacy of doses: $20,667 (£14,014) per QALY Without adherence: Duloxetine dominates
Data sources				
Health outcomes: Literature search PUBMED and references (included English studies of adults (18 or older) from North America or Europe with PDN for 5 weeks or longer, pooled estimates used. Quality-of-life weights: EQ5D (O'Connor et al). Cost sources: Variety of sources: commercial insurance claims database, average wholesale price for medication costs.				
Comments				
Source of funding: NS; Limitations: US healthcare system, not all relevant treatment comparisons included. Costs of treatment likely to vary; time horizon of 6 months likely to be insufficient, given the disease can last longer; systematic review was based on a search of PUBMED only; triangular distributions used in PSA with no clear rational.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; PSA = probabilistic sensitivity analysis; QALYs =quality-adjusted life years ‡ Converted using 2011 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Carlos F, Ramirez-Gamez J, Duenas H et al. (2012) Economic evaluation of duloxetine as a first-line treatment for painful diabetic peripheral neuropathy in Mexico. Journal of Medical Economics 15: 233-44.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA/CUA Study design: Decision tree Perspective: Payer perspective in Mexico Time horizon: 12 weeks Treatment effect : 12 weeks Discounting: Costs = NA; Outcomes = NA	Population: Adult diabetic patients with diagnosis of painful diabetic peripheral neuropathy with moderate to severe pain Intervention 1: Duloxetine 60 mg/day Intervention 2: Pregabalin 300 mg/day Intervention 3: Gabapentin (generic) 600 mg/day Intervention 4: Gabapentin (branded) 600 mg/day	Total costs (per 1000 patients) Intvn 1: $3,561,411 (£295,983) Intvn 2: $4,574,247 (£379,909) Intvn 3: $3,069,735 (£255,121) Intvn 4: $5,303,382 (£440,756) Currency & cost year: Mexican peso (presented here as 2010 UK pounds‡) Cost components incorporated: Drug costs, management of AE's, other additional costs due to poor pain relief	Primary outcome measure: QALYs (per 1000 patients) Intvn 1:125.7 Intvn 2: 123.8 Intvn 3: 120.9 Intvn 4: 120.9 Other outcome measures: Patients with 'Good pain relief' (per 1000 patients) Intvn 1:534 Intvn 2: 511 Intvn 3: 470 Intvn 4: 470	Primary ICER (compared with generic gabapentin): Intvn 1: $102,433 (£8,513) per QALY Intvn 2: $517,763 (£43,030) per QALY Intvn 4: gabapentin (branded) dominated Other: Cost per addition patient with 'good pain relief': Intvn 1: $7,647 (£636) per patient Intvn 2: $36,712 (£3,051) per patient Intvn 4: Dominated Analysis of uncertainty: 10 parameters influencing NMB presented. RR of achieving good pain relief for each active drug relative to placebo was the most sensitive parameter.
Data sources				
Health outcomes: PubMED/MEDLINE search for RCTs and placebo controlled trials: 14 trials included from Saini et al, 2009. Quality-of-life weights: Multiply sources mainly; O'Connor et al and Doth et al. Cost sources: average whole sales prices for medication from government sources, unit costs from reference list by the Mexican Institute of Social security				
Comments				
Source of funding: Eli Lilly; Limitations: Mexican payer system, short time horizon, simple pooling use: not a meta-analysis studies; costs likely to vary; irregular decision rule used. Not a fully incremental analysis.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years ‡ Converted using 2010 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Cepeda SM and Farrar JT (2006) Economic evaluation of oral treatments for neuropathic pain. Journal of Pain 7: 119-28.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Decision tree Perspective: Us third party payer Time horizon: 1 month Discounting: Costs = NA; Outcomes = NA	Population: Patients with pain from post-herpetic neuralgia or diabetic neuropathy who were free of cardiovascular, hepatic, and renal disease Intervention 1: Amitriptyline, 75 mg/day Intervention 2: Carbamazepine 800 mg/day Intervention 3: Gabapentin 2400 mg/day Intervention 4: Tramadol 200 mg/day	Total costs (mean per patient per month): Intvn 1: $29 (£18) Intvn 2: $50 (£32) Intvn 3: $98 (£62) Intvn 4: $270 (£171) Currency & cost year: (e.g. 2004 US dollars (presented here as 2004 UK pounds‡) Cost components incorporated: Drug acquisition costs, medical office visits, inpatient and outpatient care for adverse events, and lab tests.	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.807 Intvn 2: 0.807 Intvn 3: 0.769 Intvn 4: 0.697	Primary ICER: ICER: Dominated by amitriptyline Analysis of uncertainty: Multivariate sensitivity analysis adjusting doses and resources: - Tramadol and gabapentin dominated by amitriptyline - ICER of carbamazepine vs. amitriptyline $43,296 (£27,385) per QALY gained
Data sources				
Health outcomes: MEDLINE and Cochrane library search: pooled data from 10 studies for amitriptyline, 2 studies for carbamazepine, 6 for gabapentin, 3 for tramadol. Quality-of-life weights: HUI3 Cost sources: Drug costs from the Red Book for average wholesale prices in the USA (2004), GP visit costs from 2004 American Medicare Fee Schedule, and other costs from medication diagnosis-related groups. Lab test costs form American Medical Association.				
Comments				
Source of funding: Funded by the Columbian Chapter of International Association for the Study of Pain.; Limitations: Comparators were amitriptyline, carbamazepine, gabapentin, tramadol. Did not include all relevant comparators. Third-party healthcare US payer. Dose titration not included into model, very short time horizon. Conducted a systematic review and included meta-analyses. Medline and Cochrane only. Unclear method of weighting. Costs of management of some adverse events were not included. PSA conducted, but on triangular distributions. Not a fully incremental analysis.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years ‡ Converted using 2004 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

O'Connor AB, Noyes K, Holloway RG (2007) A cost-effectiveness comparison of desipramine, gabapentin, and pregabalin for treating post-herpetic neuralgia. Journal of the American Geriatrics Society 55: 1176-84.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Decision analytic model Perspective: US third party payer Time horizon: 3 months Discounting: Costs = NA; Outcomes = NA	Population: Patients aged 60 to 80 with PHN Intervention 1: Desipramine 100 mg/day Intervention 2: Pregabalin 450 mg/day Intervention 3: Gabapentin 1800 mg/day	Total costs (mean per patient): Intvn 1: $310.76 (£169.56) Intvn 2:$427.66 (£270.50) Intvn 3: $708.39 (£448.06) Currency & cost year: (e.g. 2006 US dollars (presented here as 2006 UK pounds‡) Cost components incorporated: Drug acquisition costs, management of serious side effect (MI)	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.1371 Intvn 2: 0.1297 Intvn 3: 0.1310	Primary ICER: Despiramine dominates both gabapentin and pregabalin ICER between gabapentin and pregabalin: $216,000 (£136,622) per QALY gain Analysis of uncertainty: - Time horizon: 1 month: Despiramine dominates. ICER of gabapentin vs pregabalin increases 6 months: Despiramine dominates. ICER of gabapentin vs pregabalin decreases - Result was sensitive to utility in severe pain, utility in mild pain, probability of pain relief with despiramine and utility of minor side effects.
Data sources				
Health outcomes: Several sources from pooled RCT data. Quality-of-life weights: EQ5D tariff – Oster et al 2005. Cost sources: Average wholesale price of medications were derived from 2006 Red Book.				
Comments				
Source of funding: Not stated; Limitations: Other relevant comparators not included, Perspective of US healthcare system, Time horizon used was 3 months, disease is likely to be longer, Unclear if a systematic review was used to estimate of relative effect, PSA not conducted ; Other: author has been supported by an intuitional career development board.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years ‡ Converted using 2006 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

O'Connor AB, Noyes K, Holloway RG (2008) A cost-utility comparison of four first-line medications in painful diabetic neuropathy. Pharmacoeconomics 26: 1045-64.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Decision analytic model Perspective: US third party payer Time horizon: 3 months Discounting: Costs = NA; Outcomes = NA	Population: Patients with painful diabetic neuropathy that is causing moderate to severe pain, but without cardiac conduction disorders or recent myocardial infarctions Intervention 1: Despiramine 100 mg/day Intervention 2: Duloxetine 60 mg/day Intervention 3: Pregabalin 300 mg/day Intervention 4: Gabapentin 2400 mg/day	Total costs (mean per patient): Intvn 1: $312.35 (£195.72) Intvn 2: $419.60 (£262.92) Intvn 3: $525.08 (£329.01) Intvn 4: $748.39 (£468.94) Currency & cost year: 2006 US dollars (presented here as 2006 UK pounds‡) Cost components incorporated: Drug acquisition costs, costs of management of adverse effects, cost of non-adherence	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.1200 Intvn 2: 0.1222 Intvn 3: 0.1186 Intvn 4: 0.1176	Primary ICER (duloxetine vs despiramine): ICER: $47,700 (£29,888) per QALY gained (pa) Intvn 3: Dominated by duloxetine Intvn 4: Dominated by duloxetine Analysis of uncertainty: - Using base observation carried forward estimates of the probability of achieving 50% pain score: duloxetine become cost ineffective - results most robust probabilities of obtaining pain relief, probabilities of intolerable adverse effects.
Data sources				
Health outcomes: Pubmed search: several RCTs pooled. Quality-of-life weights: US patients using EQ5D UK tariff. Cost sources: 2006 US Red Book.				
Comments				
Source of funding: NIH: Limitations: Some relevant comparators not included, US healthcare system. Dose titration not included. 3 month time horizon: likely to be shorter than disease length. Pubmed only search for efficacy data. Unclear method of weighting for pooling outcomes. Not a fully incremental analysis.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years ‡ Converted using 2006 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Dakin H, Nuijten M, Liedgens H. et al, (2007) Cost-effectiveness of a lidocaine 5% medicated plaster relative to gabapentin for post-herpetic neuralgia in the United Kingdom. Clinical Therapeutics 29: 1491-5007.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Markov model Perspective: UK NHS Time horizon: 6 months (base case) Cycle length: 30 days Discounting: Costs = 3.5%; Outcomes = 3.5%	Population: Predominantly elderly population of patients with post-herpetic neuralgia who had insufficient pain relief with standard analgesics and could not tolerate or had contraindications to tricyclic antidepressants. Intervention 1: Lidocaine 5% medicated plaster Intervention 2: Gabapentin ≤1800 mg/day	Total costs (mean per patient) PSA values: Intvn 1: £549 (95% CI 436-758) Intvn 2 :£718 (95% CI 531-1002) Currency & cost year: 2006 UK Pounds Cost components incorporated: Drug and plaster cost, changing costs due to titration, cost of add-in and switch therapies, cost of adverse events.	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.3000 (95% CI 0.2785-0.3158) Intvn 2: 0.2496 (95% CI 0.2324-0.2650)	Primary ICER (gabapentin vs. lidocaine): Lidocaine dominates Probability cost-effective: 99.99% at £20,000 per QALY threshold Analysis of uncertainty: Lidocaine more cost-effective if more plasters per day used. Longer time horizon: lidocaine dominates
Data sources				
Health outcomes: systematic literature review of EMABSE and MEDLINE (min 50 patients): 1 trial predominantly used Katz et al. 2002. Quality-of-life weights: HUI3 scores from Cepeda and Ferrar. Cost sources: Variety of sources: BNF, SCHIN, resource use by Delphi panel, Lidocaine use by IMS prescription data.				
Comments				
Source of funding: Grunenthal Limitations: Some relevant comparators could be included. Delphi panel, and no published sources used for resource use, small size of Delphi panel (n=9).				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Gordon J, Lister S, Prettyjohns M et al. (2012) A cost-utility study of the use of pregabalin in treatment-refractory neuropathic pain. Journal of Medical Economics 15: 207-18.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: stochastic simulation model Perspective: UK NHS Time horizon: 5 year time horizon Discounting: Costs = 3.5% ; Outcomes = 3.5%	Population: Patients with refractory Neuropathic pain Intervention 1: Usual care (1 or more weak opioids, strong opioids, NSAIDS, analgesics) Intervention 2: Pregabalin 150 – 600 mg/day combined with usual care (1 or more weak opioids, strong opioids, NSAIDS, analgesics)	Total costs (mean per patient): Intvn 1: £16,624 Intvn 2: £18,372 Incremental (2-1): £2,748 Currency & cost year: 2011 UK Pounds Cost components incorporated: Drug acquisition costs, inpatient and outpatient costs, cost of managing an adverse event	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.43 Intvn 2: 0.68	Primary ICER (Pregabalin compared with usual care): ICER: £10,803 per QALY gained (pa) Analysis of uncertainty: Result was sensitive to alternative sources of utility inputs: ICER for Pregabalin rose above threshold of £20,000 per QALY gained Result was robust for costs for drug acquisition costs, frequency and withdrawal rate, utility decrement from adverse events, probability of withdrawal for non AE-reason, cost of AEs, shorter time horizons.
Data sources				
Health outcomes: From non-randomised studies identified in a PubMED and Google search; using a pain scale from 0-10 (Stacey et al., Douglas et al., Allen, Freynhagen et al.); longer term data from Stacey et al. Quality-of-life weights: QoL pain data from Cardiff and Vale local health board NHS trust pain clinic, then mapped mean pain scores to EQ-5D. Cost sources: for resource use: survey of NEP patients attending Cardiff and Vale NHS Trust pain clinic (n=144); drug costs: BNF 2009, and NHS reference cost. Cost of AEs: PSSRU				
Comments				
Source of funding: Pfizer Ltd; Limitations: Some relevant comparators not included. Pains scores were mapped to EQ-5D utility decrements. Lit search: insufficient details about search strategy, VAS pain scale used as main outcome measure. Usual care includes various treatments (pooling these may underestimate the relative effect size to some comparators). Non RCT data used. Unclear how pooled estimate was calculated from several heterogeneous studies. Resource use estimates from Cardiff and Vale NHS Trust pain clinic, not a national average.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Ritchie M, Liedgens H, Nuijte M (2010 Cost effectiveness of a lidocaine 5% medicated plaster compared with pregabalin for the treatment of post-herpetic neuralgia in the UK: a Markov model analysis. Clinical Drug Investigation 30: 71-87.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: Markov model Approach to analysis: Perspective: UK NHS Time horizon: 6 months Cycle length: 30 days Discounting: Costs=3.5%; Outcomes=3.5%	Population: Patients with post-herpetic neuralgia who were intolerant to tricyclic antidepressants and in whom analgesics were ineffective or contraindicated Intervention 1: Pregabalin 300 mg/day followed by 600 mg/day (mean approx. 488 mg/day) Intervention 2: Lidocaine plaster 140 cm2 1.71 plasters/day	Total costs (mean per patient): Intvn 1: £784 Intvn 2: £980 Currency & cost year: 2009 UK pounds Cost components incorporated: Drug acquisition costs, costs associated with outpatients treatment	Primary outcome measure: QALYs (mean per patient) Intvn 1: 0.254 Intvn 2: 0.321 Other outcome measures (mean): Time without pain or intolerable AEs (mo) Intvn 1: 2.737 Intvn 2: 4.287	Primary ICER (lidocaine vs. pregabalin): ICER: £2925 per QALY gained (pa) Probability cost-effective: 100% (at threshold of £35,000 per QALY gained) Other: Cost/month without pain or intolerable AEs relative to pregabalin £126 addition cost/month of lidocaine vs pregabalin. Analysis of uncertainty: - Extending the time horizon: Lidocaine remained cost-effective at the £35,000 per QALY gained threshold - Using EQ-5D data for utility: lidocaine cost-effective - Increasing number of plasters: lidocaine cost-effective - higher doses of pregabalin: lidocaine cost-effective
Data sources				
Health outcomes: Mainly 1 open-level, head-to-head, trial. Quality-of-life weights: Mainly from Cepeda et al (2006); for SA used data from Baron et al (2009). Cost sources: resource use by Delphi consensus, PSSRU 2008, NHS Ref costs 06-07.				
Comments				
Source of funding: Grunenthal GmbH; Limitations: Not all relevant comparators included, Time horizon limited to 3 months: disease may last longer, Unclear if efficacy from systematic review of literature, Small Delphi panel, unclear if literature was searched for resource use				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years * Directly applicable/Partially applicable/Not applicable; ** Minor limitation /Potentially serious limitations/Very serious limitations				

Rodriguez MJ, Diaz S, Vera-Llonch M et al. (2007) Cost-effectiveness analysis of pregabalin versus gabapentin in the management of neuropathic pain due to diabetic polyneuropathy or post-herpetic neuralgia. Current Medical Research & Opinion 23: 2585-96.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA Study design: stochastic simulation model Perspective: Spanish NHS Time horizon: 12 weeks Discounting: Costs=NA; Outcomes=NA	Population: Patients with post-herpetic neuralgia or painful diabetic polyneuropathy. Intervention 1: Pregabalin 457 mg/day Intervention 2: Gabapentin 2400 mg/day	Total costs (mean per patient): Intvn 1: €1049.42 (£894.01) Intvn 2: €950.82 (£810.01) Currency & cost year: (e.g. 2006 Spanish Euros (presented here as 2006 UK pounds‡) Cost components incorporated: Drug acquisition costs, outpatient visits, diagnostic tests, non-pharmacological treatments.	Primary outcome measure: QALYs (mean per patient gained) Intvn 1: 0.1186 Intvn 2: 0.1138	Primary ICER (pregabalin compared with gabapentin): ICER: €20,535 (£17,494) per QALY gained (pa) Analysis of uncertainty: - Sensitive to changes to mean generic gabapentin dose, when 1200 mg/day ICER: €33,498 (£28537) per QALY gained. - 23% reduction in costs of medical visits or healthy utility values, or increase in cost of spinal cord stimulation, cause ICERs to fall or become cost saving.
Data sources				
Health outcomes: Freyhagen et al 2005, Backonja et al 1998, Rowbotham et al 1998. Quality-of-life weights: HUI3. Cost sources: resource use of non-pharmacological resources by group of experts. Costs from Soikos Institute, Catalogue of Medicinal Product (2006)				
Comments				
Source of funding: Funded by Pfizer Espana; Limitations: Pregabalin and gabapentin: other comparators were not included, Spanish health care system, did not include costs and utilities from adverse events of treatment, 12 week time horizon: disease can last for longer, efficacy not based on a systematic review of data.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER = incremental cost-effectiveness ratio; NA = not applicable; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years; ‡ Converted using 2006 purchasing power parities http://stats.oecd.org * Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations				

Tarride JE, Gordon A, Vera-Llonch M et al. (2006) Cost-effectiveness of pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia: A Canadian perspective. Clinical Therapeutics.28: 1922-34.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA/CEA Study design: Markov model Perspective: Ontario Ministry of Health, Canada Time horizon: 3 months Cycle length: 1 day Discounting: Costs=NA; Outcomes=NA	Population: Patients with diabetic peripheral neuropathy or post-herpetic neuralgia Cohort settings: M = 53-57% Intervention 1: Gabapentin 2400 mg (900-3600 mg/day) Intervention 2: Pregabalin 372 mg (150-600 mg/day)	Total costs (mean per patient): DPN: Intvn 1: $837.53 (£430.40) Intvn 2: $818.49 (£420.62) PHN: Intvn 1: $720.61 (£370.32) Intvn 2: $667.07 (£342.80) Currency & cost year: (e.g. 2004 Canadian dollars (presented here as 2004 UK pounds‡) Cost components incorporated: Drug acquisition costs, costs of diagnostic tests, costs of non-pharmacological treatments	Primary outcome measure: QALYs (mean per patient) DPN: Intvn 1: 0.1150 Intvn 2: 0.1197 PHN: Intvn 1: 0.1125 Intvn 2: 0.1211 Other outcome measures (mean): No. of days with no or mild pain DPN: Intvn 1: 30 Intvn 2: 36 PHN: Intvn 1: 27 Intvn 2: 36	Primary ICER: DPN: pregabalin dominates PHN: pregabalin dominates Other: Cost per no. of days with no or mild pain DPN: pregabalin dominates PHN: pregabalin dominates Analysis of uncertainty: Result was sensitive to: DPN: - lower dose of gabapentin 1800 mg/day (daily cost for 1800 mg/day): ICER of pregabalin compared with gabapentin: $6,502 (£3,341) per QALY - lower dose of gabapentin 1800 mg/day (daily cost for 900 mg/day): ICER: $31,148 (£16,007) per QALY PHN: - lower dose of gabapentin 1800 mg/day (daily cost for 1800 mg/day): ICER: $575 (£295) per QALY - lower dose of gabapentin 1800 mg/day (daily cost for 900 mg/day): ICER: $20,101 (£10,330) per QALY
Data sources				
Health outcomes: 3 RCTs: Freyhagen et al. (2005), Rowbotham et al. (2008), Backonja et al. (1998). Quality-of-life weights: EQ5D Canadian tariff based on patients, Gordon et al. (2011); Cost sources: resource used on internet based survey of 80 Canadian physicians in 2003, unit costs from Ontario Health Insurance plan schedule of benefits and fees.				
Comments				
Source of funding: Pfizer Canada, Inc; Limitations: Pregabalin and gabapentin only, not all relevant comparators included; Perspective of the Ontario Ministry of Health, Canada; Model does not clearly specify the structure: unclear how patients with adverse events are managed in this model; 12 week time horizon may be too short for this disease; No systematic review of evidence for baseline or efficacy outcomes; role of adverse events not clear in the model. ; No PSA conducted.				
Overall applicability*: Partially applicable. Overall quality**: Potentially serious limitations				
Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = confidence interval; CUA = cost-utility analysis; d/a deterministic analysis; ICER				

= incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs =quality-adjusted life years

‡ Converted using 2004 purchasing power parities http://stats.oecd.org

* Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations