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.

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Posters, reviews and letters, non-English studies and unpublished studies were excluded.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

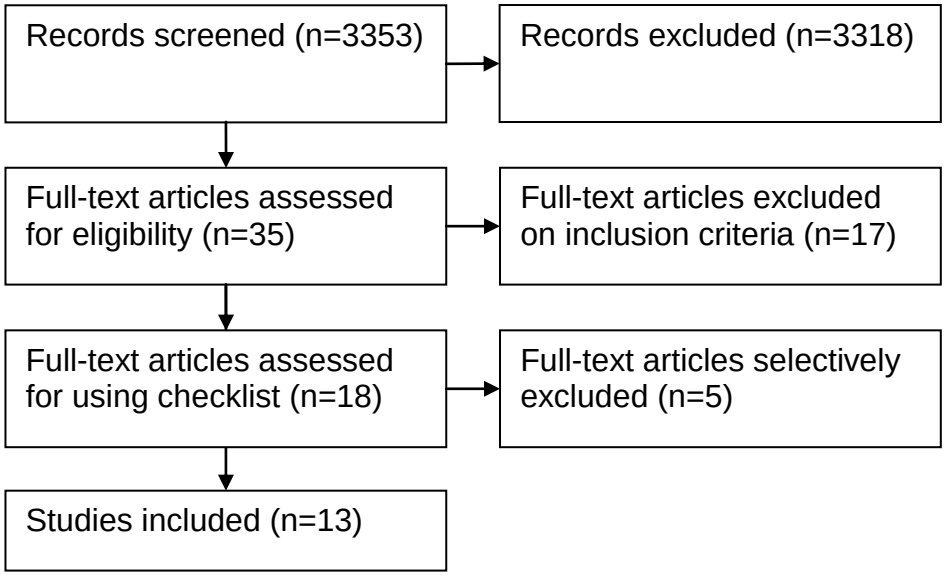
- Directly applicable – the study met all applicability criteria, or failed to meet 1 or more applicability criteria but was unlikely to change the conclusions about cost effectiveness.
- Partially applicable – the study failed to meet 1 or more applicability criteria, and this could change the conclusions 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–Table F6, below), and described in greater detail in the Appendix F1.

No studies on central pain or trigeminal neuralgia were identified.

1 **Table F2 Economic evidence profile: people with post-herpetic neuralgia or painful diabetic neuropathy**

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Cepeda 2006) Intvn 1: Amitriptyline Intvn 2: Carbamazepine Intvn 3: Tramadol Intvn 4: Gabapentin	Potentially Serious Limitations1	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
(Rodriguez et al. 2007) Pregabalin versus gabapentin	Potentially Serious Limitations[4]	Partially Applicable[5]	People with post-herpetic neuralgia or diabetic peripheral neuropathy Stochastic simulation model Spanish NHS	€98.61 (£84.01)[6]	0.0048 QALYs per patient	€20,535 (£17,494)[7] per QALY gain	- Sensitive to changes to mean generic gabapentin dose - 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.

[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 ICER's may be due to rounding.

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1 **Table F3 Economic evidence profile: people with post-herpetic neuralgia**

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Armstrong et al. 2011) Intervention 1: Capsaicin topical 8% versus: Intervention 2: TCA – Nortriptyline Intervention 3: Lidocaine topical 5% Intervention 4: Gabapentin Intervention 5: Pregabalin Intervention 6: Duloxetine	Potentially Serious Limitations[1]	Partially Applicable[2]	People with post-herpetic neuralgia Markov state transition model US payer	Intvn 1: Capsaicin topical versus: Intvn 2: $3605 (£2444.42)[3] Intvn 3: $317 (£214.95)[3] Intvn 4: $3097 (£2099.96)[3] Intvn 5: $2562 (£1737.20)[3] Intvn 6: $2898 (£1965.03)[3]	Intvn 1: Capsaicin topical versus: Intvn 2: 0.062 Intvn 3: 0.004 Intvn 4: 0.074 Intvn 5: 0.065 Intvn 6: 0.067	Intvn 1: Capsaicin topical versus: Intvn 2: $59,919 (£40,629)[4] per QALY gain Intvn 3: $554,627 (£376,073)[4] per QALY gain Intvn 4: $42,008 (£28,484)[4] per QALY gain Intvn 5: $40,241 (£27,296)[4] per QALY gain Intvn 6: $43,908 (£29,772)[4] per QALY gain	- 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	
(O'Connor et al. 2007) Intvn 1: Desipramine Intvn 2: Pregabalin Intvn 3: Gabapentin	Potentially Serious Limitations[5]	Partially Applicable[6]	People with post-herpetic neuralgia Decision analytic model US third party payer	Versus Intvn 1: Desipramine Intvn 2: $116.90 (£73.94)[7] Intvn 3: $397.63 (£397.63)[7]	Versus Intvn 1: Desipramine Intvn 2: -0.0074 Intvn 3: -0.0061	Desipramine dominates gabapentin and pregabalin Gabapentin versus pregabalin: $216,000 (£136,622)[8] per QALY gain	- Result was sensitive to utility in severe pain, utility in mild pain, probability of pain relief with desipramine and utility of minor side effects
(Dakin et al. 2007) Lidocaine 5% medicated plaster versus gabapentin	Potentially Serious Limitations[9]	Partially Applicable[10]	People with post-herpetic neuralgia Markov model UK NHS	-£16911	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
(Ritchie and Liedgens 2010) Lidocaine 5% medicated plaster versus pregabalin	Potentially Serious Limitations[12]	Partially Applicable[13]	People with post-herpetic neuralgia Markov model UK NHS	£19614	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

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Tarride et al. 2006) Pregabalin versus gabapentin	Potentially Serious Limitations[15]	Partially Applicable[16]	People with post-herpetic neuralgia Markov model Ontario Ministry of Health, Canada	−$53.54 (−£27.51)[17]	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

[1] 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.
[2] US population. Unclear if adult only population considered.
[3] Converted using 2011 purchasing power parities http://stats.oecd.org.
[4] Converted using 2011 purchasing power parities http://stats.oecd.org. Discrepancy in ICER's may be due to rounding.
[5] 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.
[6] Perspective of US healthcare system, other relevant comparators not included.
[7] Converted using 2006 purchasing power parities http://stats.oecd.org.
[8] Converted using 2006 purchasing power parities http://stats.oecd.org. Discrepancy in ICER's may be due to rounding.
[9] Delphi panel used and no published sources used for resource use, small size of Delphi panel (n=9).
[10] Some relevant comparators not included.
[11] 2006 UK Pounds.
[12] 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.
[13] Not all relevant comparators included.
[14] 2009 UK Pounds.
[15] 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.
[16] Not all relevant comparators included; Perspective of the Ontario Ministry of Health, Canada.
[17] Converted using 2004 purchasing power parities http://stats.oecd.org.

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1 **Table F4 Economic evidence profile: people with painful diabetic neuropathy (PDN)**

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Beard et al. 2008) Intvn 1: Amitriptyline → Gabapentin → Tramadol Intvn 2: Duloxetine → Amitriptyline → Gabapentin → Tramadol Intvn 3: Amitriptyline → Duloxetine → Gabapentin →Tramadol Intvn 4: Amitriptyline → Gabapentin → Duloxetine → Tramadol Intvn 5: Amitriptyline → Gabapentin → Tramadol → Duloxetine	Potentially Serious Limitations[1]	Partially Applicable[2]	People with painful diabetic neuropathy Decision analytic model UK NHS	versus Intvn 1 (per 1000 patients):[3] 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: 1.6 QALYs	versus Intvn 1: Intvn 2: dominates Intvn 3: dominates Intvn 4: £2698 Intvn 5: £2109	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.
(Bellows et al. 2012) Duloxetine versus pregabalin	Potentially Serious Limitations[4]	Partially Applicable[5]	People with painful diabetic neuropathy Decision analytic tree US third party payer	-$187 (£126.80)[6]	0.011	Duloxetine dominates pregabalin	- Real-world (range of doses from real world, but mean from efficacy): $16,300 (£11,052)[7] per QALY gain - Real-world: Pooled efficacy of doses: $20,667 (£14,014)[7] per QALY gain - Without adherence: duloxetine dominates

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Carlos et al. 2012) Intvn 1: Generic gabapentin Intvn 2: Duloxetine Intvn 3: Pregabalin Intvn 4: Branded gabapentin	Potentially Serious Limitations[8]	Partially Applicable[9]	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)[10] Intvn 3: $1,501,512 (£124,788.24)[10] Intvn 4: $2,233,647 (£185,634.79)[10]	versus Intvn 1: generic gabapentin (per 1000 patients): Intvn 2: 4.8 Intvn 3: 2.9 Intvn 4: 0	versus Intvn 1: generic gabapentin: Intvn 2: $102,433 (£8513.04)[11] Intvn 3: $517,763 (£43,030.45)[11] Intvn 4: NA	- RR of achieving good pain relief for each active drug relative to placebo was the most sensitive parameter.
(O'Connor et al. 2008) Intvn 1: Desipramine Intvn 2: Duloxetine Intvn 3: Pregabalin Intvn 4: Gabapentin	Potentially Serious Limitations[12]	Partially Applicable[13]	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)[14] Intvn 3: $212.73 (£133.29) [14] Intvn 4: $439.03 (£273.21) [14]	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)[14] 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.

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Tarride, Gordon, Vera-Llonch, Dukes, & Rousseau 2006) Pregabalin versus gabapentin	Potentially Serious Limitations[16]	Partially Applicable[17]	People with painful diabetic neuropathy Markov model Ontario Ministry of Health, Canada	−$19.04 (−£9.78)[18]	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 (6 months). Unclear how the management of adverse effects were included. Pooling of studies: unclear how heterogeneity was taken into account.
[2] Some relevant comparators not included.
[3] 2005 UK pounds.
[4] Short time horizon (6 months), systematic review was based on a search of PubMed only; triangular distributions used in PSA with no clear rational.
[5] US healthcare system, not all relevant treatment comparisons included.
[6] Converted using 2011 purchasing power parities http://stats.oecd.org.
[7] Converted using 2011 purchasing power parities http://stats.oecd.org. Discrepancy in ICER's may be due to rounding.
[8] 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.
[9] Mexican payer systems, some relevant comparators not included.
[10] Converted from Mexican dollars to GBP using 2010 purchasing power parities http://stats.oecd.org.
[11] Converted using 2010 purchasing power parities http://stats.oecd.org. Discrepancy in ICER's may be due to rounding.
[12] 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.
[13] Some relevant comparators not included US healthcare system.
[14] Converted using 2006 purchasing power parities http://stats.oecd.org.
[15] Converted using 2006 purchasing power parities http://stats.oecd.org. Discrepancy in ICER's may be due to rounding.
[16] 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.
[17] Not all relevant comparators included; Perspective of the Ontario Ministry of Health, Canada.
[18] Converted using 2004 purchasing power parities http://stats.oecd.org

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Table F5 Economic evidence profile: People with refractory neuropathic pain

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effects (QALY)	ICER	
(Gordon et al. 2012) Pregabalin versus Usual Care	Potentially Serious Limitations[1]	Partially Applicable[2]	People with refractory neuropathic pain Stochastic simulation model UK NHS	£27,483	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

[1] 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.

[2] Some relevant comparators not included.

[3] 2011 UK Pounds.

1 **Table F6 Economic evidence profile: people with peripheral neuropathic pain**

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[1]	Partially Applicable[2]	People with peripheral neuropathic pain Markov model Belgian health care public payer	Intvn 2: −€225 (−£186.01)[3] Intvn 3: −€127 (−£92.64)[3] Intvn 4: −€306 (−£223.21)[3] Intvn 5: −€216 (−£157.56)[3]	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.

[1] 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.

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

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

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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 for either all neuropathic pain or peripheral pain only.

In total there were 16 pharmaceutical treatments with sufficient data to be included in the model for all neuropathic pain, and 14 for peripheral pain only.

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 F7 below.

Table F7 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[a]	Tablets
Morphine[a]	Tablets
Nortriptyline	Tablets
Oxcarbazepine	Tablets
Pregabalin	Capsules
Topiramate	Tablets
Tramadol	Capsules
Venlafaxine	Capsules
[a] Excluded from peripheral pain analysis due to insufficient data	

2.1.2 Population

The hypothetical population included in the analysis was all people with neuropathic pain. A separate analysis was undertaken for peripheral pain.

The GDG recognised the potential limitations on the model of assuming that efficacy data in a trial of one drug for one type of neuropathic pain is equally valid for all types of neuropathic pain. However, the GDG felt the efficacy networks were too sparse for any individual conditions or subgroups apart from peripheral pain to be able to produce informative models.

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.

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 GDG wished to explore the robustness of this assumption by undertaking a scenario analysis 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.

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

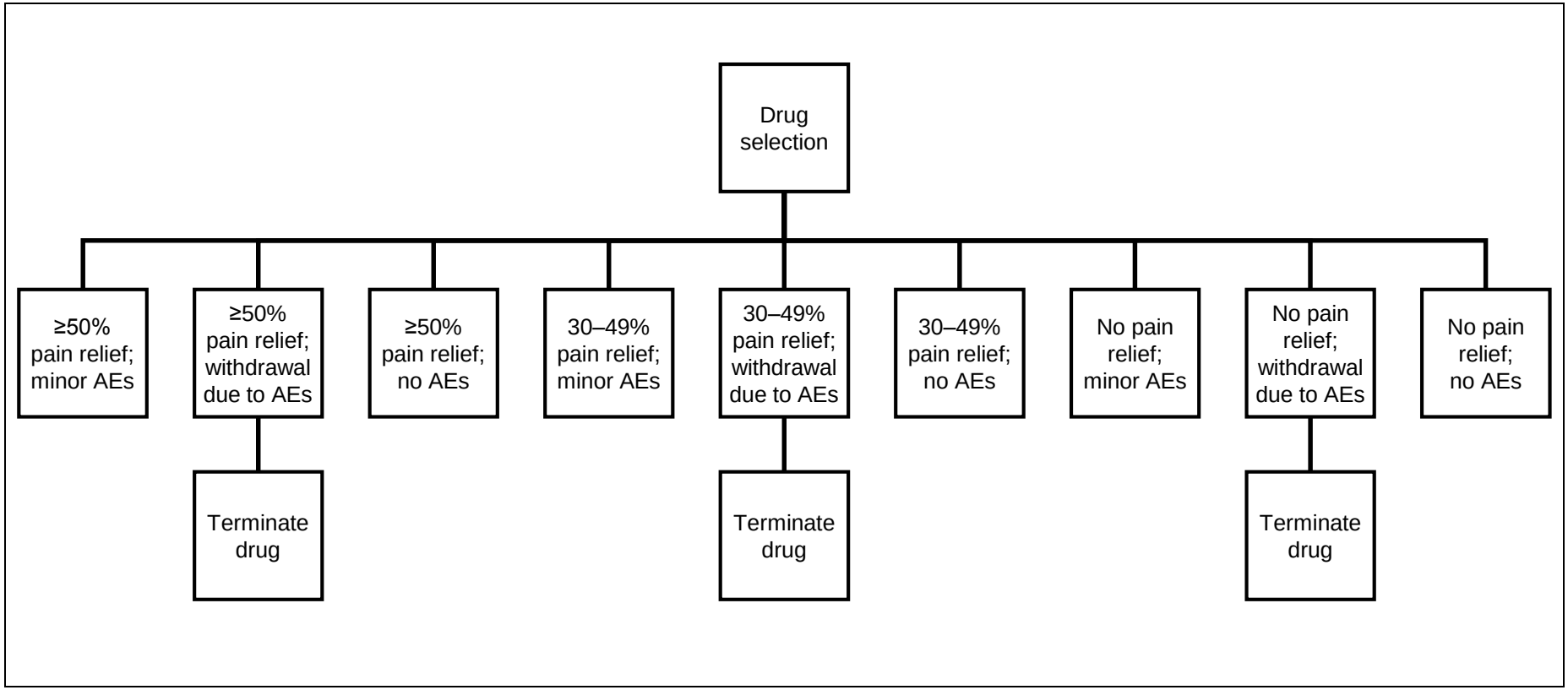

Figure F1 Neuropathic pain model schematic

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 F8.

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 (5000 times) to obtain mean cost and QALY values.

Table F8 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	Bound between 0 and 1	Min = minimum value Max = maximum value
Resource use due to AEs (GP visits and days of antiemetic medication)	Uniform	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)	Min = minimum value Max = maximum value
Duration of minor AEs (days)	Uniform	Bound between 7 and 14	Min = minimum value Max = maximum value

2.2 Model parameters

2.2.1 Summary of model parameters

1 **Table F9 Efficacy and safety parameters (all neuropathic pain – dose-adjusted) 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 (0.48,0.77)	0.14 (0.10,0.16)	0.22 (0.12,0.36)	0.09 (0.08,0.11)	0.12 (0.09,0.16)	0.10 (0.08,0.14)
Amitriptyline	50 mg/d[b]	0.54 (0.31,0.78)	0.15 (0.10,0.17)	0.30 (0.12,0.54)	0.23 (0.13,0.35)	0.12 (0.05,0.25)	0.09 (0.01,0.31)
Cannabis extract	4 sprays/d[b]	0.46 (0.18,0.76)	0.16 (0.10,0.17)	0.38 (0.13,0.70)	0.49 (0.14,0.98)	0.37 (0.13,0.75)	0.20 (0.08,0.41)
Capsaicin cream	4 apps/d[b]	0.19 (0.04,0.49)	0.13 (0.05,0.16)	0.68 (0.35,0.91)	0.43 (0.22,0.69)	0.58 (0.02,1.00)	0.47 (0.03,1.00)
Capsaicin patch	1 × 60-min	0.55 (0.37,0.74)	0.15 (0.11,0.17)	0.30 (0.15,0.47)	0.11 (0.04,0.25)	0.09 (0.03,0.21)	0.14 (0.07,0.23)
Duloxetine	60 mg/d[b]	0.44 (0.27,0.62)	0.16 (0.14,0.17)	0.40 (0.24,0.58)	0.21 (0.14,0.32)	0.26 (0.13,0.47)	0.28 (0.16,0.48)
Gabapentin	1800 mg/d[b]	0.41 (0.15,0.66)	0.16 (0.11,0.17)	0.43 (0.20,0.74)	0.18 (0.08,0.35)	0.40 (0.23,0.61)	0.11 (0.04,0.25)
Lacosamide	400 mg/d[b]	0.55 (0.36,0.71)	0.15 (0.12,0.17)	0.30 (0.17,0.48)	0.21 (0.13,0.32)	0.38 (0.18,0.66)	0.14 (0.06,0.27)
Lamotrigine	400 mg/d[b]	0.54 (0.36,0.72)	0.15 (0.12,0.17)	0.30 (0.16,0.48)	0.17 (0.11,0.27)	0.17 (0.06,0.35)	0.09 (0.05,0.16)
Levetiracetam	3000 mg/d[c]	0.70 (0.33,0.93)	0.12 (0.04,0.16)	0.18 (0.03,0.52)	0.44 (0.15,0.92)	0.57 (0.20,0.97)	0.25 (0.02,0.86)
Morphine	120 mg/d[b]	0.38 (0.15,0.60)	0.16 (0.11,0.17)	0.46 (0.25,0.74)	0.52 (0.09,1.00)	0.27 (0.05,0.74)	0.47 (0.11,0.99)
Nortriptyline	50 mg/d[b]	0.44 (0.13,0.80)	0.16 (0.08,0.17)	0.39 (0.10,0.77)	0.27 (0.03,0.83)	0.14 (0.03,0.40)	0.07 (0.00,0.34)
Oxcarbazepine	1800 mg/d[c]	0.45 (0.23,0.70)	0.16 (0.12,0.17)	0.39 (0.18,0.64)	0.30 (0.16,0.50)	0.65 (0.27,0.97)	0.18 (0.06,0.38)
Pregabalin	300 mg/d[b]	0.47 (0.34,0.68)	0.16 (0.13,0.17)	0.37 (0.19,0.50)	0.12 (0.08,0.17)	0.36 (0.24,0.50)	0.10 (0.04,0.17)
Topiramate	100 mg/d[b]	0.48 (0.09,0.89)	0.16 (0.05,0.17)	0.36 (0.05,0.82)	0.23 (0.15,0.34)	0.21 (0.04,0.59)	0.15 (0.07,0.25)
Tramadol	400 mg/d[b]	0.42 (0.23,0.69)	0.16 (0.12,0.17)	0.42 (0.19,0.63)	0.44 (0.20,0.81)	0.52 (0.18,0.93)	0.37 (0.20,0.65)
Venlafaxine	75 mg/d[b]	0.55 (0.32,0.77)	0.15 (0.10,0.17)	0.30 (0.13,0.52)	0.23 (0.09,0.48)	0.39 (0.01,1.00)	0.24 (0.11,0.45)

[a] Not dose-adjusted

[b] Estimate provided by GDG

[c] 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, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

Table F10 Efficacy and safety parameters (all neuropathic pain – dose-adjusted) 16 weeks

Drug	Assumed dose	Probability (95%CrI) of pain relief after 16wk			Probability (95%CrI) of event within 16 weeks		
		<30%	30–49%	≥50%	Withdrawal due to AEs	Dizziness[a]	Nausea[a]
Amitriptyline	50 mg/da	0.50 (0.05,0.95)	0.12 (0.03,0.17)	0.38 (0.02,0.89)	0.33 (0.13,0.35)	0.12 (0.05,0.25)	0.09 (0.01,0.31)

a Estimate provided by GDG

NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

Table F11 Efficacy and safety parameters (all neuropathic pain – no dose adjustment) 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)	0.14 (0.10,0.16)	0.22 (0.13,0.35)	0.09 (0.08,0.11)	0.12 (0.09,0.16)	0.10 (0.08,0.14)
Amitriptyline	0.48 (0.25,0.70)	0.16 (0.12,0.17)	0.37 (0.18,0.60)	0.24 (0.12,0.41)	0.12 (0.05,0.25)	0.09 (0.01,0.31)
Cannabis extract	0.44 (0.20,0.73)	0.16 (0.11,0.17)	0.40 (0.15,0.67)	0.48 (0.11,0.98)	0.37 (0.13,0.75)	0.20 (0.08,0.41)
Capsaicin cream	0.17 (0.04,0.43)	0.12 (0.05,0.16)	0.71 (0.41,0.92)	0.45 (0.22,0.78)	0.58 (0.02,1.00)	0.47 (0.03,1.00)
Capsaicin patch	0.54 (0.37,0.70)	0.15 (0.12,0.16)	0.30 (0.17,0.46)	0.11 (0.03,0.25)	0.09 (0.03,0.21)	0.14 (0.07,0.23)
Duloxetine	0.43 (0.27,0.60)	0.16 (0.14,0.17)	0.41 (0.25,0.58)	0.23 (0.13,0.37)	0.26 (0.13,0.47)	0.28 (0.16,0.48)
Gabapentin	0.49 (0.28,0.71)	0.16 (0.12,0.17)	0.35 (0.17,0.56)	0.17 (0.09,0.26)	0.40 (0.23,0.61)	0.11 (0.04,0.25)
Lacosamide	0.55 (0.36,0.71)	0.15 (0.12,0.17)	0.30 (0.17,0.49)	0.21 (0.11,0.36)	0.38 (0.18,0.66)	0.14 (0.06,0.27)
Lamotrigine	0.55 (0.37,0.72)	0.15 (0.12,0.17)	0.30 (0.17,0.47)	0.18 (0.10,0.29)	0.17 (0.06,0.35)	0.09 (0.05,0.16)
Levetiracetam	0.70 (0.32,0.94)	0.12 (0.04,0.16)	0.18 (0.03,0.53)	0.40 (0.12,0.84)	0.57 (0.20,0.97)	0.25 (0.02,0.86)
Morphine	0.36 (0.16,0.61)	0.16 (0.12,0.17)	0.48 (0.24,0.71)	0.58 (0.08,1.00)	0.27 (0.05,0.74)	0.47 (0.11,0.99)
Nortriptyline	0.44 (0.14,0.78)	0.16 (0.09,0.17)	0.40 (0.12,0.74)	0.33 (0.03,0.97)	0.14 (0.03,0.40)	0.07 (0.00,0.34)
Oxcarbazepine	0.45 (0.21,0.71)	0.16 (0.12,0.17)	0.39 (0.17,0.66)	0.34 (0.14,0.66)	0.65 (0.27,0.97)	0.18 (0.06,0.38)
Pregabalin	0.43 (0.27,0.59)	0.16 (0.14,0.17)	0.41 (0.27,0.58)	0.19 (0.12,0.26)	0.36 (0.24,0.50)	0.10 (0.04,0.17)
Topiramate	0.48 (0.26,0.71)	0.16 (0.12,0.17)	0.36 (0.17,0.59)	0.32 (0.16,0.53)	0.21 (0.04,0.59)	0.15 (0.07,0.25)
Tramadol	0.42 (0.22,0.64)	0.16 (0.13,0.17)	0.42 (0.22,0.65)	0.45 (0.17,0.88)	0.52 (0.18,0.93)	0.37 (0.20,0.65)
Venlafaxine	0.51 (0.27,0.73)	0.16 (0.11,0.17)	0.34 (0.15,0.59)	0.24 (0.08,0.55)	0.39 (0.01,1.00)	0.24 (0.11,0.45)
NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1						

Table F12 Efficacy and safety parameters (all neuropathic pain – no dose adjustment) 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 (0.03,0.91)	0.12 (0.03,0.17)	0.43 (0.04,0.92)	0.17 (0.12,0.41)	0.12 (0.05,0.25)	0.09 (0.01,0.31)
NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1						

Table F13 Efficacy parameters (peripheral neuropathic pain) 20 weeks

Drug	Assumed dose	Probability (95%CrI) of pain relief after 20 weeks					
		dose-adjusted			non-dose-adjusted		
		<30%	30–49%	≥50%	<30%	30–49%	≥50%
Placebo	-	0.64 (0.51,0.76)	0.14 (0.11,0.16)	0.22 (0.14,0.33)	0.64 (0.51,0.76)	0.14 (0.11,0.16)	0.22 (0.13,0.34)
Amitriptyline	50 mg/d[a]	0.61 (0.32,0.85)	0.14 (0.07,0.16)	0.24 (0.07,0.53)	0.56 (0.26,0.81)	0.15 (0.09,0.16)	0.29 (0.10,0.59)
Cannabis extract	4 sprays/d[a]	0.46 (0.18,0.77)	0.16 (0.10,0.17)	0.38 (0.12,0.69)	0.46 (0.22,0.72)	0.16 (0.11,0.17)	0.39 (0.16,0.64)
Capsaicin cream	4 apps/d[a]	0.18 (0.01,0.78)	0.12 (0.01,0.16)	0.70 (0.12,0.98)	0.18 (0.04,0.46)	0.12 (0.05,0.16)	0.69 (0.38,0.91)
Capsaicin patch	1 × 60-min	0.55 (0.39,0.71)	0.15 (0.12,0.16)	0.30 (0.17,0.46)	0.55 (0.39,0.69)	0.15 (0.12,0.16)	0.30 (0.18,0.44)
Duloxetine	60 mg/d[a]	0.44 (0.29,0.60)	0.16 (0.14,0.17)	0.40 (0.26,0.56)	0.43 (0.29,0.59)	0.16 (0.14,0.17)	0.41 (0.27,0.56)
Gabapentin	1800 mg/d[a]	0.42 (0.20,0.67)	0.16 (0.12,0.17)	0.42 (0.20,0.67)	0.42 (0.23,0.64)	0.16 (0.13,0.17)	0.42 (0.23,0.64)
Lacosamide	400 mg/d[a]	0.55 (0.37,0.70)	0.15 (0.12,0.17)	0.30 (0.18,0.47)	0.55 (0.38,0.71)	0.15 (0.12,0.16)	0.30 (0.17,0.46)
Lamotrigine	400 mg/d[a]	0.56 (0.39,0.72)	0.15 (0.12,0.16)	0.29 (0.16,0.45)	0.56 (0.40,0.72)	0.15 (0.12,0.17)	0.29 (0.16,0.44)
Nortriptyline	50 mg/d[a]	0.33 (0.00,1.00)	0.16 (0.00,0.16)	0.52 (0.00,1.00)	0.36 (0.10,0.71)	0.16 (0.09,0.17)	0.48 (0.17,0.81)
Oxcarbazepine	1800 mg/d[b]	0.45 (0.23,0.69)	0.16 (0.12,0.17)	0.39 (0.18,0.63)	0.45 (0.23,0.71)	0.16 (0.12,0.17)	0.39 (0.17,0.64)
Pregabalin	300 mg/d[a]	0.45 (0.31,0.58)	0.16 (0.14,0.17)	0.39 (0.27,0.53)	0.44 (0.30,0.59)	0.16 (0.14,0.17)	0.40 (0.27,0.55)
Topiramate	100 mg/d[a]	0.46 (0.00,1.00)	0.16 (0.00,0.16)	0.38 (0.00,1.00)	0.49 (0.28,0.72)	0.16 (0.12,0.17)	0.35 (0.16,0.57)
Tramadol	400 mg/d[a]	0.46 (0.23,0.71)	0.16 (0.12,0.17)	0.39 (0.17,0.64)	0.42 (0.23,0.65)	0.16 (0.13,0.17)	0.42 (0.22,0.63)
Venlafaxine	75 mg/d[a]	0.72 (0.38,0.94)	0.12 (0.03,0.16)	0.16 (0.02,0.46)	0.50 (0.29,0.71)	0.16 (0.12,0.17)	0.34 (0.17,0.56)

[a] Estimate provided by GDG

[b] 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, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

1 **Table F14 Efficacy parameters (peripheral neuropathic pain) 16 weeks**

Drug	Assumed dose	Probability (95%CrI) of pain relief after 16 weeks					
		dose-adjusted			non-dose-adjusted		
		<30%	30–49%	≥50%	<30%	30–49%	≥50%
Amitriptyline	50 mg/da	0.58 (0.07,0.97)	0.15 (0.02,0.16)	0.27 (0.01,0.85)	0.52 (0.05,0.96)	0.15 (0.02,0.16)	0.32 (0.02,0.90)

[a] Estimate provided by GDG

NB data shown do not reflect correlations between response probabilities as sampled in the model; therefore, credibility intervals for mutually exclusive outcomes can only be considered separately, and cannot be expected to sum to 1

Table F15 Model cost parameters (20-week drug costs)

Drug	Daily dose (dose-adjusted)	20-week costs (dose-adjusted)	Daily dose (no dose-adjustment)	20-week costs (no dose adjustment)
Amitriptyline	50 mg	£4.10	100 mg	£8.20
Cannabis sativa extract	4 sprays	£777.78	11 sprays	£2138.89
Capsaicin cream	4 × 1 g applications	£177.96	4 × 1 g applications	£177.96
Capsaicin patch	4 patches over 140 days	£840.00	2 patches over 140 days	£420.00
Duloxetine	60 mg	£138.60	90 mg	£250.60
Gabapentin	1800 mg	£33.80	2600 mg	£46.73
Lacosamide	400 mg	£720.80	450 mg	£828.90
Lamotrigine	400 mg	£24.90	350 mg	£25.50
Levetiracetam	3000 mg	£61.69	3000 mg	£61.69
Morphine	120 mg	£75.60	70 mg	£51.08
Nortriptyline	50 mg	£162.40	125 mg	£406.00
Oxcarbazepine	1800 mg	£372.12	1800 mg	£372.12
Pregabalin	300 mg	£322.00	400 mg	£322.00
Topiramate	100 mg	£17.13	300 mg	£23.94
Tramadol	400 mg	£35.84	300 mg	£26.88
Venlafaxine	75 mg	£12.65	150 mg	£25.30

Table F16 Model cost parameters (16-week drug costs)

Drug	Daily dose (dose-adjusted)	16-week costs (dose-adjusted)	Daily dose (no dose-adjustment)	16-week costs (no dose-adjustment)
Amitriptyline	50 mg	£3.28	100 mg	£6.56

Table F17 Model utility parameters

Drug	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 (disutility)	0.9	0.80–0.93 (upper and lower bounds)
Dizziness	−0.12 (0.0024)	
Nausea	−0.065 (0.0013)	

2.2.2 Efficacy and safety

Efficacy data for all neuropathic pain that was both dose-adjusted (Table F9) and non-dose-adjusted (Table F11) were available for up to 20 weeks, as were efficacy data for peripheral pain only (Table F13). It was assumed that the incidence of adverse effects would not vary according to the type of neuropathic pain; therefore, dose-adjusted and non-dose-adjusted safety data (Table F9 and Table F11) derived from the whole evidence-base were used for the peripheral-only model as well as the all neuropathic pain model. 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.

The GDG was asked to provide estimates of what it believed were the most common doses of each drug used to treat neuropathic pain. These estimates were used in the dose-adjusted models to determine both drug cost and efficacy.

For the non-dose adjusted models data on dose to estimate costs were taken as a simple average across trials.

In both models 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 based on the frequency of dose as advised by the GDG. 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 F18, Table F19 and Table F20.

1 **Table F18 Drug prices and formulations**

Drug	Tab size (mg)	Number of caps	Drug tariff (March 2013) price (in pence)	Cost per mg/spray/patch (in pence)
Amitriptyline (tablets)	10	28	73	0.26
	25	28	74	0.11
	50	28	82	0.06
Cannabis sativa extract	2.7	90	12,500	51.44
Capsaicin cream	1 tube		1,430	
Capsaicin patch	1 patch	1	21,000	21000
Duloxetine	30	28	2,240	2.67
	60	28	2,772	1.65
Gabapentin	100	100	283	0.03
	300	100	387	0.01
	400	100	462	0.01
	600	100	1,300	0.02
	800	100	3,873	0.05
Lacosamide	50	14	1,081	1.54
	150	56	12,974	1.54
	200	56	14,416	1.29
Lamotrigine (non dispersible)	25	56	178	0.13
	50	56	214	0.08
	100	56	308	0.06
	200	56	498	0.04
Levetiracetam	750	60	661	0.01
Morphine (tablets)	10	56	531	0.95
	20	56	1,061	0.95
	60	60	1,620	0.45
Nortriptyline	10	100	3,574	3.57
	25	100	5,800	2.32
Oxcarbazepine	600	50	4,430	0.15
Pregabalin	25	56	6,440	4.60
	50	84	9,660	2.30
	75	56	6,440	1.53
	100	84	9,660	1.15
	150	56	6,440	0.77
	200	84	9,660	0.58
	225	56	6,440	0.51
	300	56	6,440	0.38
Topiramate (tablets)	25	60	271	0.18
	50	60	367	0.12
	100	60	342	0.06

	200	60	1,460	0.12
Tramadol (capsules)	50	30	96	0.06
	50	100	320	0.06
Venlafaxine	37.5	56	253	0.12

Table F19 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	37.5 mg	50 mg	1×50	£4.10
Cannabis sativa extract	10.8 mg	10.8 mg	4 sprays	£777.78
Capsaicin cream	3.7 applications	4×1 g applications	tube (assume 45×1 g applications)	£177.96
Capsaicin patch	2 patches every 90 days	4 patches over 140 days	Patch (90 days)	£840.00
Duloxetine	52.5 mg	60 mg	1×60	£138.60
Gabapentin	1800 mg	1800 mg	4×400+2×100	£33.80
Lacosamide	400 mg	400 mg	2×200	£720.80
Lamotrigine	360 mg	400 mg	2×200	£24.90
Levetiracetam	3000 mg	3000 mg	4×750	£61.69
Morphine	120 mg	120 mg	2 ×60	£75.60
Nortriptyline	41.7 mg	50 mg	2×25	£162.40
Oxcarbazepine	1800 mg	1800 mg	3×600	£372.12
Pregabalin	300 mg	300 mg	2×150	£322.00
Topiramate	100 mg	100 mg	2×50	£17.13
Tramadol	333 mg	400 mg	4×100	£35.84
Venlafaxine	75 mg	75 mg	2×37.5	£12.65

Table F20 Daily dosages, dosage mix and price per dosage (trial data)

Drug	GDG or trial dosage	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	29.7 mg	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

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 F21 summarises the costs of treating adverse effects.

Table F21 Adverse event costs

Adverse event	No of GP visits	Cost/visit (pence)	Source	Drug used	Drug cost/day	Number of days	Total cost (pence)
Dizziness	1–2 (uniform)	6,300	PSSRU 2012	N/A	N/A	N/A	6,300–12,600
Nausea	1–2 (uniform)	6,300	PSSRU 2012	Cyclizine hydrochloride 50 mg (3 pills a day)	44.07 (Drug Tariff)	7–14 (uniform)	6,608–13,217
Withdrawal due to adverse effects	2–4 (uniform)	6,300	PSSRU 2012	N/A	N/A	N/A	12,600–25,200

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 (headache, 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 F22.

Table F22 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, headache 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.

3.3 Interpreting results

3.3.1 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.

3.3.2 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.

4 Results

4.1 All neuropathic pain

4.1.1 Incremental analysis

The incremental analyses of the average costs and QALYs generated from 5000 simulations of the model for treatments for all neuropathic pain are

presented in Table F23 and Table F24, with efficiency frontiers shown in Figure F2 and Figure F3.

Table F23 Incremental analysis for all neuropathic pain (dose unadjusted data)

	Absolute		Incremental			Net monetary benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£46.80	0.117				£2284.40	£3450.00
Amitriptyline	£78.15	0.133	£31.35	0.017	£1887	£2585.30	£3917.02
Lamotrigine	£88.65	0.125	£10.50	−0.008	dominated	£2415.70	£3667.87
Topiramate	£118.81	0.126	£40.66	−0.008	dominated	£2391.97	£3647.36
Gabapentin	£128.32	0.134	£50.18	0.001	ext. dom.	£2556.95	£3899.59
Venlafaxine	£132.35	0.127	£54.20	−0.006	dominated	£2401.33	£3668.17
Tramadol	£193.51	0.121	£115.37	−0.013	dominated	£2217.55	£3423.09
Levetiracetam	£200.78	0.093	£122.63	−0.040	dominated	£1665.62	£2598.82
Morphine	£211.11	0.118	£132.96	−0.015	dominated	£2145.18	£3323.33
Capsaicin cream	£301.84	0.150	£223.69	0.016	£13,568	£2691.35	£4187.94
Duloxetine	£309.54	0.138	£7.70	−0.011	dominated	£2458.38	£3842.35
Pregabalin	£360.99	0.144	£59.15	−0.006	dominated	£2519.92	£3960.38
Nortriptyline	£388.84	0.131	£87.00	−0.018	dominated	£2234.49	£3546.16
Oxcarbazepine	£417.00	0.126	£115.16	−0.023	dominated	£2108.14	£3370.71
Capsaicin patch	£433.38	0.131	£131.55	−0.019	dominated	£2185.51	£3494.95
Lacosamide	£783.40	0.123	£481.56	−0.027	dominated	£1667.53	£2893.00
Cannabis extract	£1493.12	0.118	£1,191.28	−0.032	dominated	£865.29	£2044.49

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

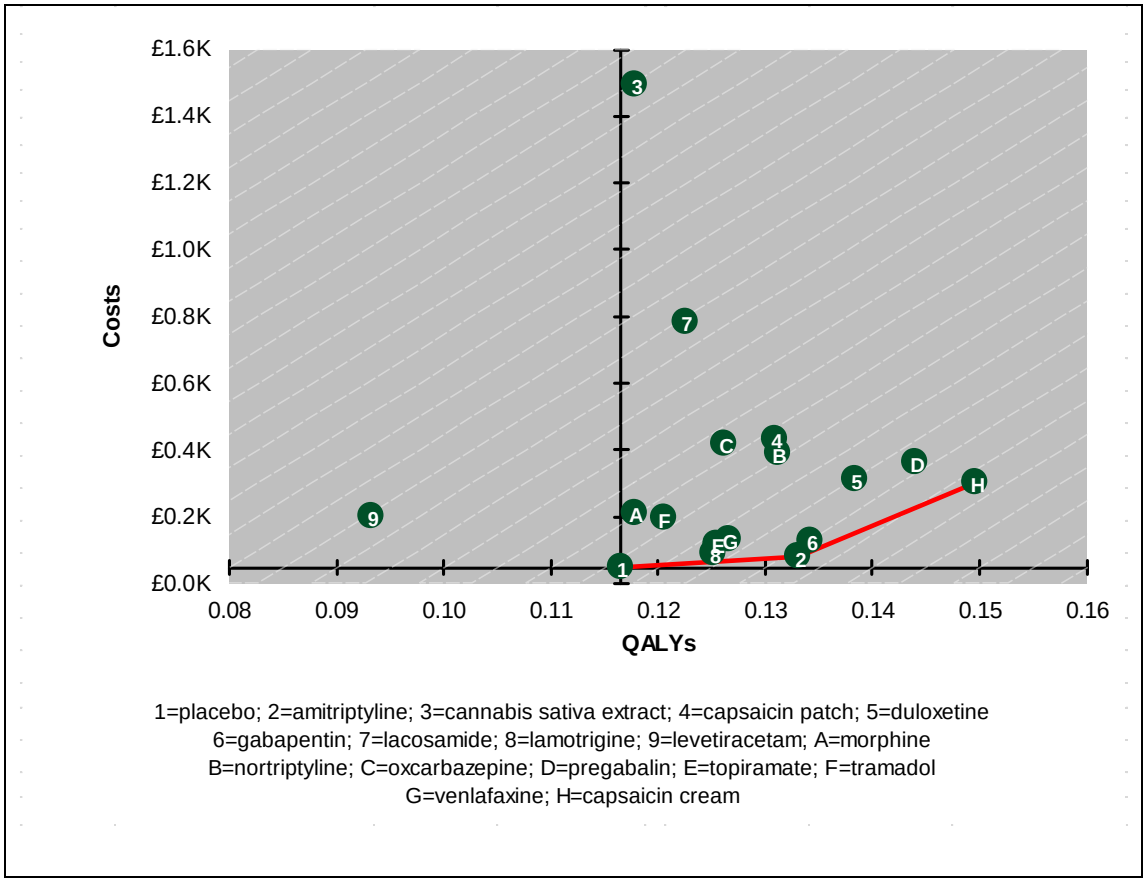

Figure F2 Efficiency frontier for all neuropathic pain (dose unadjusted data)

Table F24 Incremental analysis for all neuropathic pain (dose-adjusted data)

	Absolute		Incremental			Net monetary benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£47.36	0.116	-	-	-	£2268.28	£3426.10
Amitriptyline	£73.75	0.123	£26.39	0.007	ext. dom.	£2381.32	£3608.86
Lamotrigine	£89.70	0.125	£42.34	0.010	ext. dom.	£2416.61	£3669.76
Topiramate	£99.01	0.132	£51.66	0.016	ext. dom.	£2531.79	£3847.20
Venlafaxine	£118.15	0.121	£70.79	0.005	dominated	£2302.38	£3512.64
Gabapentin	£136.66	0.146	£89.30	0.030	£2962	£2782.02	£4241.36
Tramadol	£197.54	0.121	£60.88	−0.025	dominated	£2230.98	£3445.24
Levetiracetam	£201.89	0.093	£65.23	−0.053	dominated	£1649.49	£2575.18
Nortriptyline	£205.51	0.133	£68.85	−0.013	dominated	£2453.71	£3783.32
Duloxetine	£218.37	0.139	£81.71	−0.007	dominated	£2557.61	£3945.61
Morphine	£222.17	0.118	£85.50	−0.028	dominated	£2139.52	£3320.37
Capsaicin cream	£300.19	0.150	£163.53	0.004	£43,304	£2694.02	£4191.12
Pregabalin	£363.97	0.139	£63.77	−0.011	dominated	£2407.72	£3793.56
Oxcarbazepine	£400.78	0.113	£100.59	−0.037	dominated	£1852.88	£2979.71
Cannabis extract	£631.59	0.115	£331.40	−0.035	dominated	£1661.47	£2807.99
Lacosamide	£703.05	0.123	£402.85	−0.027	dominated	£1753.75	£2982.15
Capsaicin patch	£818.09	0.130	£517.90	−0.019	dominated	£1786.74	£3089.16

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

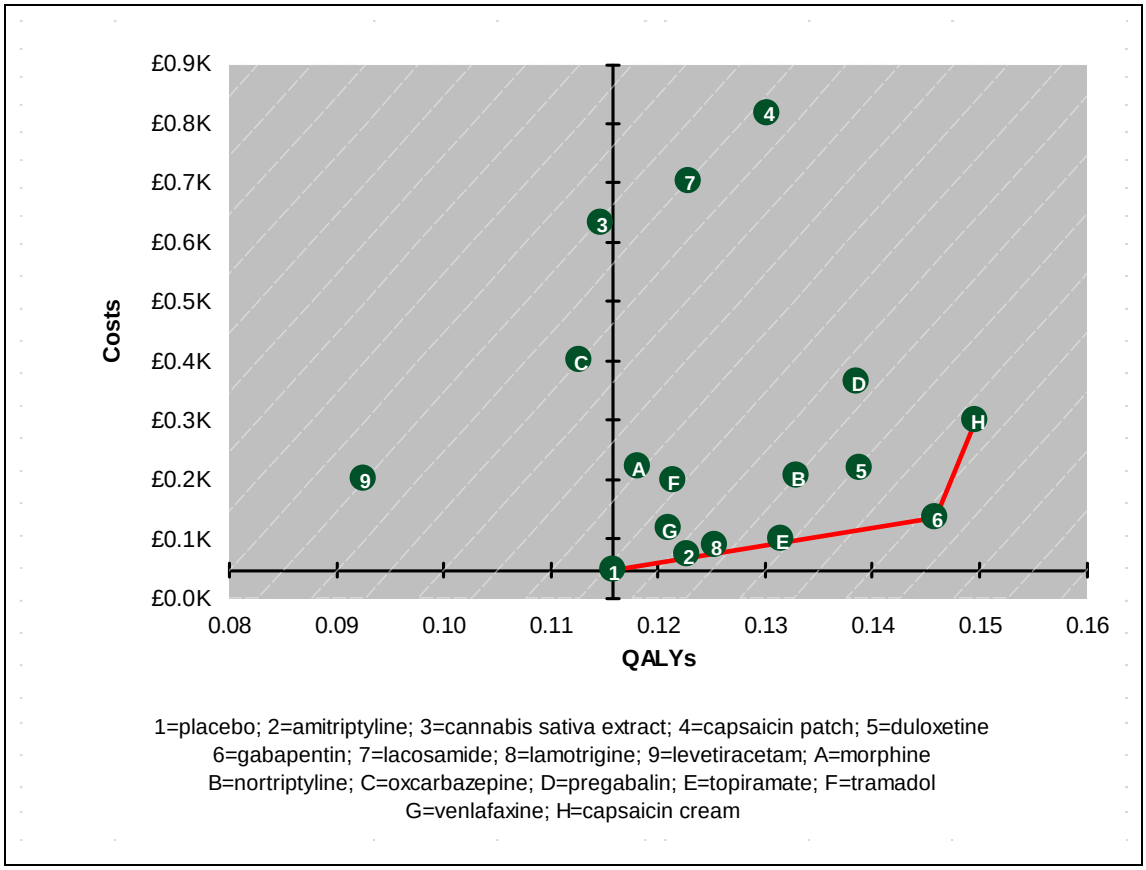

Figure F3 Efficiency frontier for all neuropathic pain (dose adjusted data)

The incremental analysis of dose adjusted and dose unadjusted data suggests some difference in the efficiency frontier. Although capsaicin cream sits on both frontiers, amitriptyline is on the dose unadjusted frontier and gabapentin sits on the dose adjusted frontier. In addition, capsaicin cream on the dose adjusted frontier has an ICER of £43,304, compared with an ICER of £13,568 on the dose unadjusted frontier.

However, the drugs that cluster around the frontier are the same using both dose adjusted and unadjusted data. As well as gabapentin and amitriptyline, topiramate, venlafaxine and lamotrigine sit close to the frontier using either data set.

In addition, a similar 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.

If capsaicin cream were to be removed from the analysis, then pregabalin would be on the efficiency frontier for the dose unadjusted data at an ICER of £26,013. For dose adjusted data only, gabapentin would be on the frontier dominating or extendedly dominating all other drugs.

The scenario analysis with amitriptyline as second-line therapy following withdrawal showed no difference in the drugs sitting on or near the efficiency frontier in either the dose unadjusted or adjusted models.

4.1.2 PSA and net benefit analysis

This analysis is based on the average cost and QALY values generated from the 5000 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 scatter plots of the cost and QALYs generated for each drug across the first 1000 simulations in Figure F4 and Figure F5.

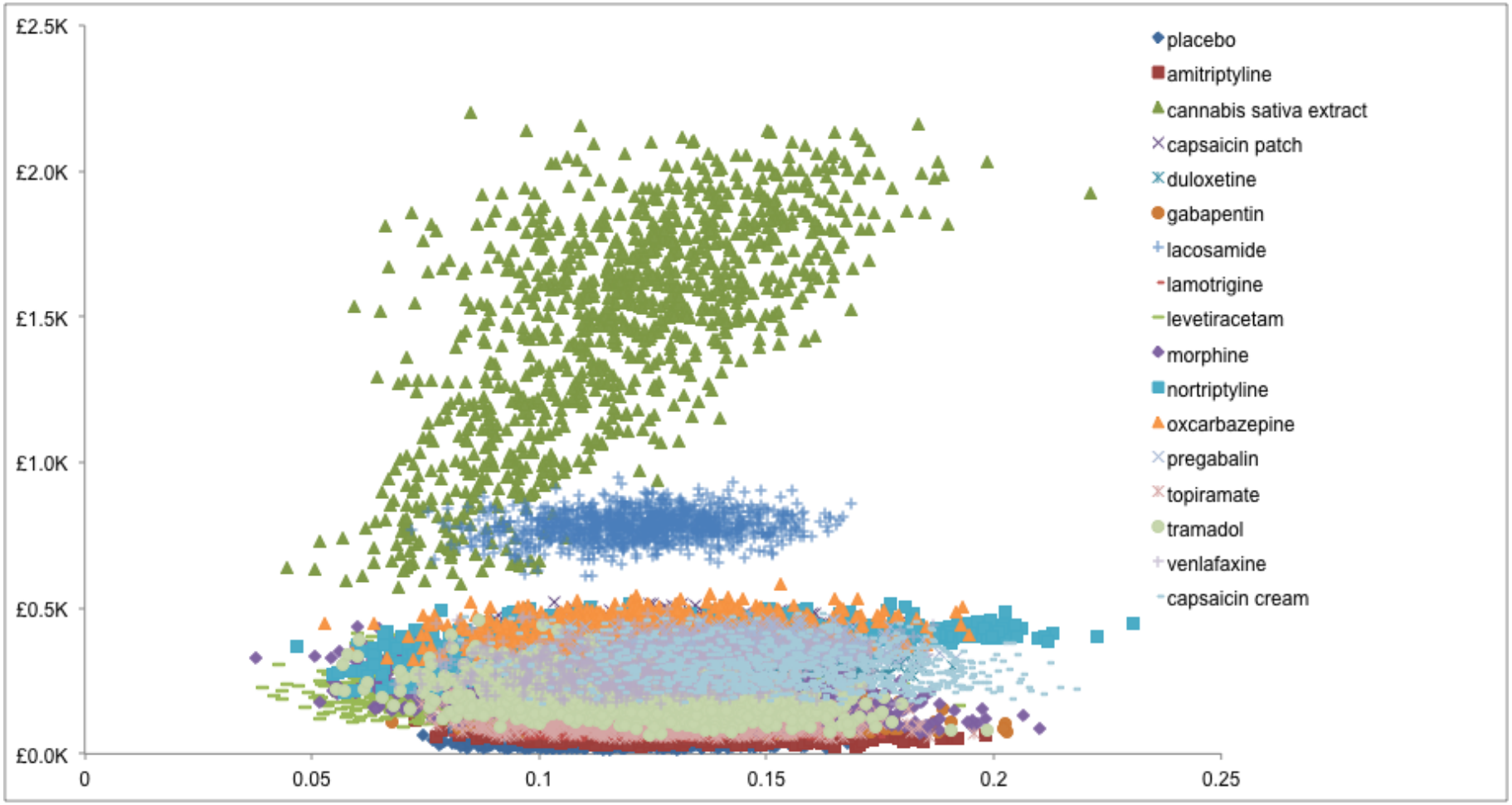

Figure F4 Scatter plot of first 1000 simulations for all neuropathic pain (dose unadjusted data)

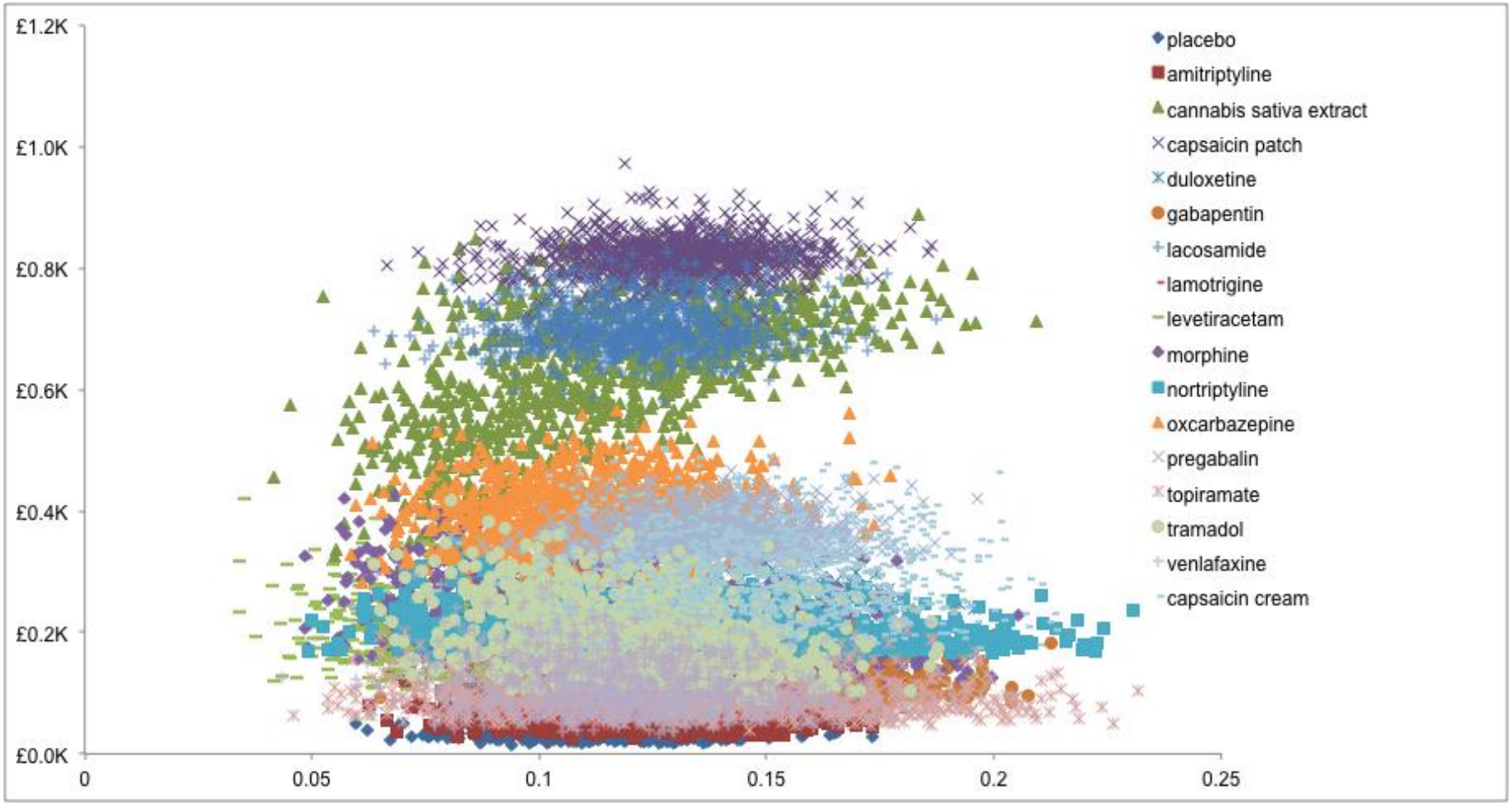

Figure F5 Scatter plot of first 1000 simulations for all neuropathic pain (dose adjusted data)

The lack of clarity in the scatter plots 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 a drug having the highest net benefit at £20,000 for dose variant and dose invariant data is shown in Table F25 and Table F26. The cost effectiveness acceptability curves (CEACs) are shown in Figure F6 and Figure F7.

Table F25 Net benefit analysis at £20,000 a QALY for all neuropathic pain (dose unadjusted data)

Drug	Probability highest net benefit at £20,000/QALY
Capsaicin cream	33.4%
Amitriptyline	14.4%
Morphine	10.9%
Nortriptyline	10.3%
Gabapentin	8.0%
Venlafaxine	7.1%
Topiramate	5.2%
Tramadol	3.7%
Duloxetine	2.1%
Pregabalin	1.6%
Oxcarbazepine	1.5%
Lamotrigine	1.3%
Levetiracetam	0.5%
Placebo	0.0%
Cannabis sativa extract	0.0%
Capsaicin patch	0.0%
Lacosamide	0.0%

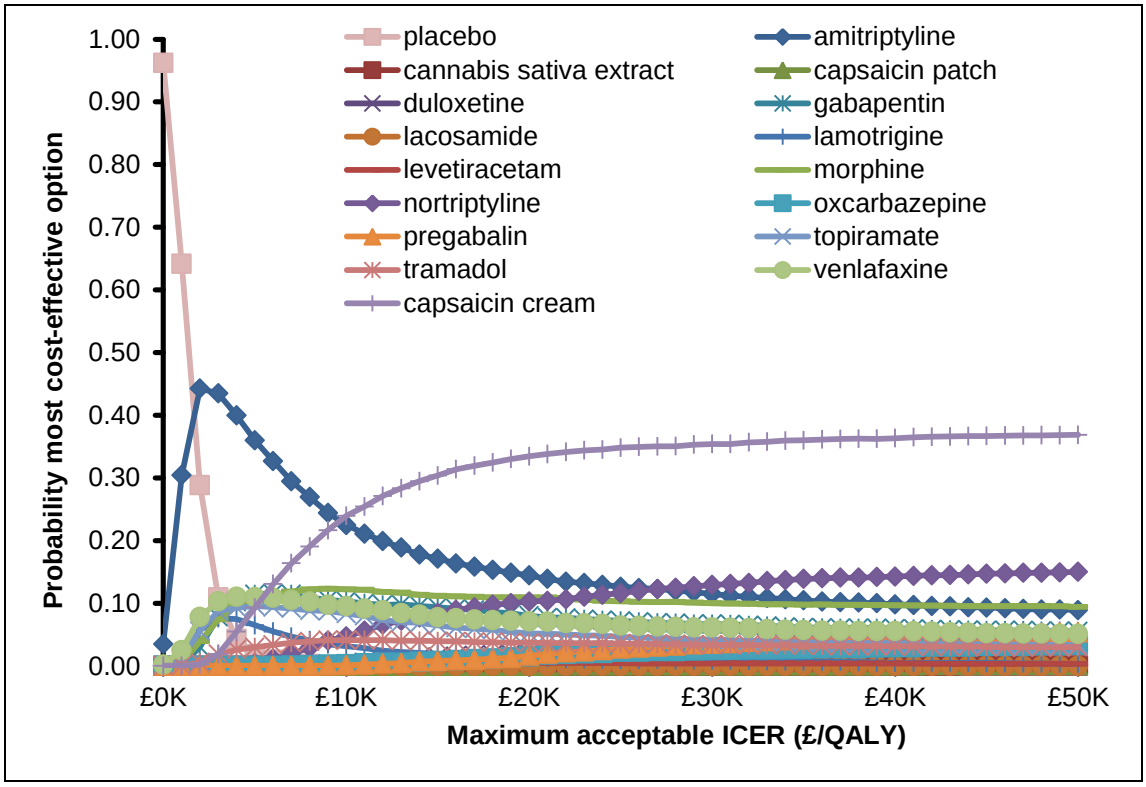

Figure F6 CEAC for all neuropathic pain (Dose unadjusted data)

Table F26 Net benefit analysis at £20,000 a QALY for all neuropathic pain (dose adjusted data)

Drug	Probability highest net benefit at £20,000/QALY
Topiramate	23.6%
Capsaicin cream	22.8%
Gabapentin	21.2%
Nortriptyline	16.3%
Morphine	5.6%
Amitriptyline	2.8%
Duloxetine	2.5%
Venlafaxine	2.2%
Tramadol	1.7%
Lamotrigine	0.7%
Cannabis sativa extract	0.4%
Levetiracetam	0.3%
Pregabalin	0.1%
Placebo	0.0%
Capsaicin patch	0.0%
Lacosamide	0.0%
Oxcarbazepine	0.0%

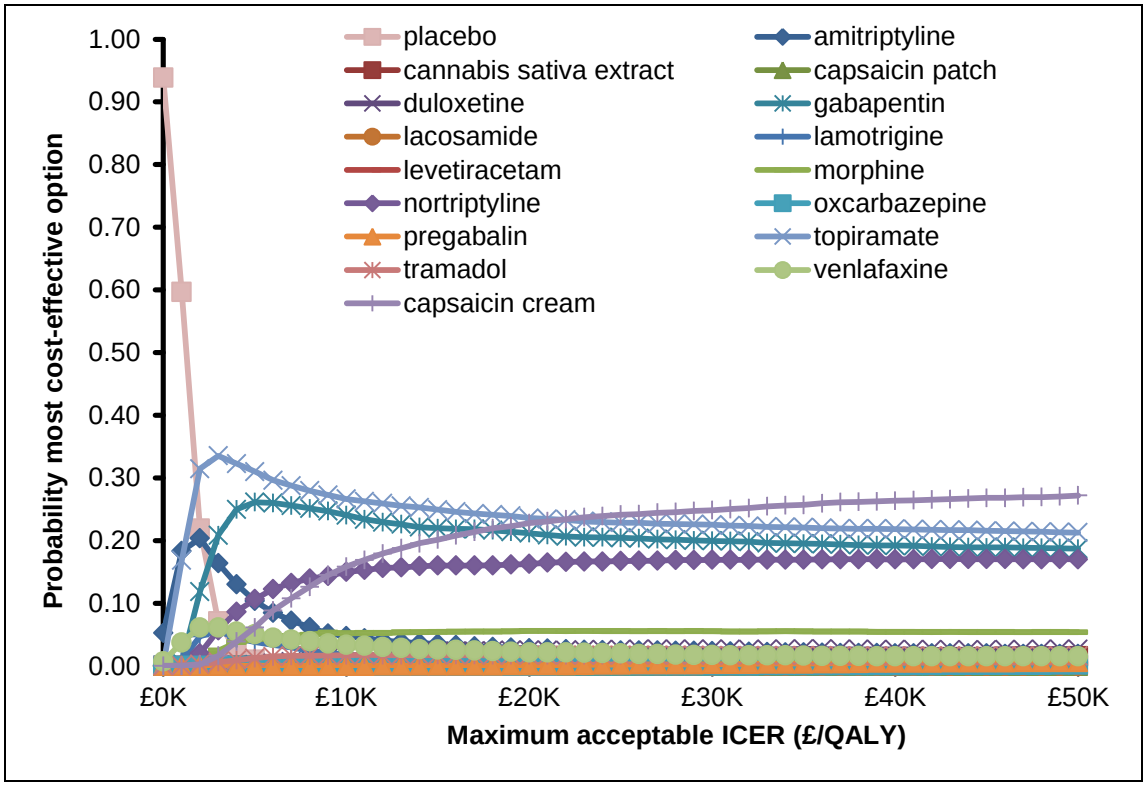

Figure F7 CEAC for all neuropathic pain (dose adjusted data)

The net benefit analysis for both dose unadjusted and dose adjusted data is similar, with 4 of the 5 drugs most likely to be the most cost effective being the same in the dose unadjusted and unadjusted data, and the drugs with a less than 2% chance of being the most cost effective also being almost identical.

The drugs that sit at the top of the net benefit tables are those that are also clustered around the efficiency frontier, with the exception of morphine. The data suggest morphine is an effective pain killer but has a high rate of withdrawal due to adverse effects. In a simulation in which an individual has a low chance of withdrawal then the potential utility gains from morphine make it a cost effective option 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.

Scenario analysis of amitriptyline as second-line therapy made no substantive difference to the ordering of the drugs in terms of the probability of cost

effectiveness at £20,000 per QALY, although capsaicin cream had a greater than 50% chance of being the most cost-effective treatment with dose unadjusted data and became the drug with the highest probability of being the most cost effective with dose adjusted data.

4.2 Peripheral pain only

4.2.1 Incremental analysis

The incremental analyses of the average costs and QALYs generated from 5000 simulations of the model for treatments for peripheral pain are presented in Table F27 and Table F28, with efficiency frontiers shown in Figure F8 and Figure F9.

Table F27 Incremental analysis for peripheral pain (dose unadjusted data)

	Absolute		Incremental			Net Monetary Benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£46.77	0.116				£2266.03	£3422.43
Amitriptyline	£77.69	0.121	£30.91	0.005	ext. dom.	£2333.27	£3538.74
Lamotrigine	£88.63	0.124	£41.86	0.009	ext. dom.	£2394.34	£3635.83
Topiramate	£119.18	0.124	£72.41	0.009	ext. dom.	£2366.33	£3609.09
Gabapentin	£128.05	0.146	£81.27	0.030	£2684	£2790.34	£4249.54
Venlafaxine	£132.79	0.127	£4.74	−0.019	dominated	£2403.57	£3671.76
Tramadol	£193.34	0.120	£65.29	−0.026	dominated	£2201.95	£3399.59
Capsaicin cream	£300.85	0.148	£172.80	0.002	£71,291	£2666.02	£4149.45
Duloxetine	£309.69	0.138	£8.84	−0.011	dominated	£2447.04	£3825.40
Pregabalin	£360.91	0.142	£60.06	−0.007	dominated	£2474.07	£3891.55
Nortriptyline	£388.69	0.142	£87.85	−0.006	dominated	£2448.86	£3867.63
Oxcarbazepine	£418.14	0.126	£117.29	−0.022	dominated	£2106.63	£3369.02
Capsaicin patch	£433.08	0.130	£132.23	−0.019	dominated	£2162.92	£3460.91
Lacosamide	£784.06	0.122	£483.21	−0.026	dominated	£1656.16	£2876.27
Cannabis extract	£1501.00	0.117	£1200.15	−0.032	dominated	£834.71	£2002.56

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

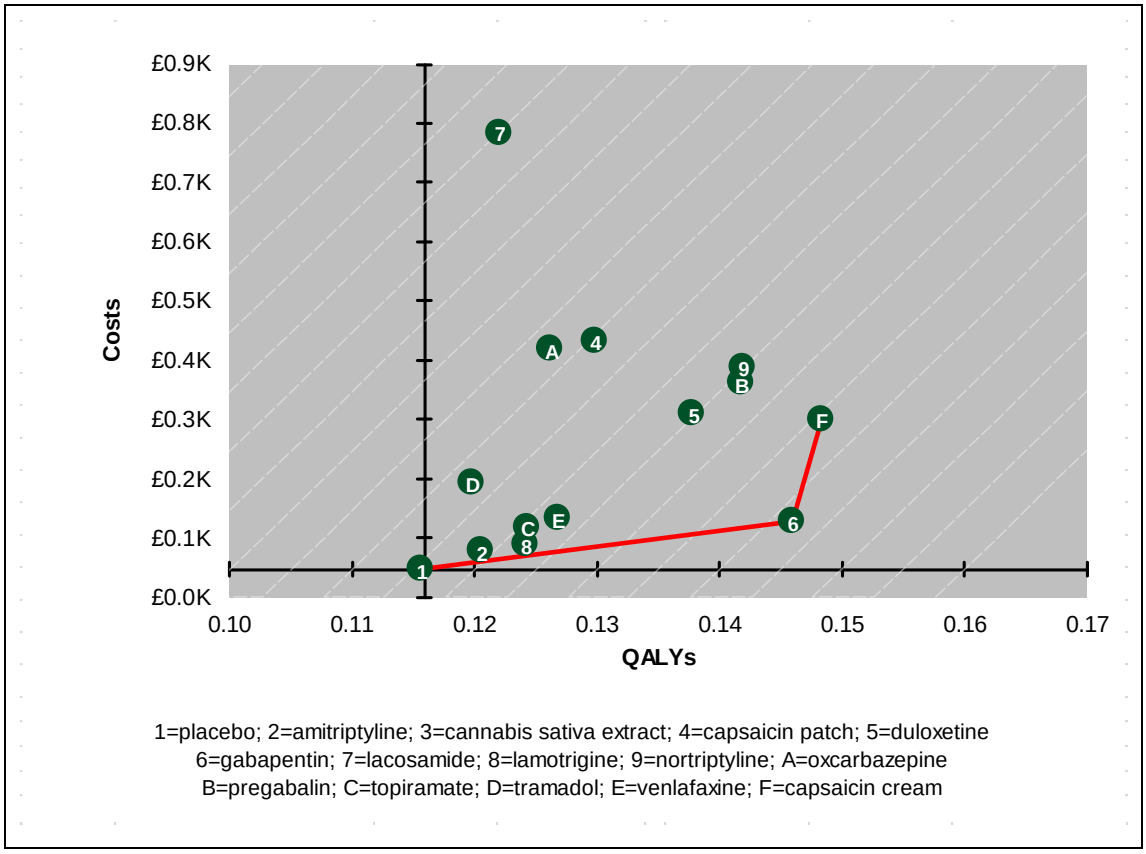

Figure F8 Efficiency frontier for peripheral pain (dose unadjusted data)

Table F28 Incremental analysis for peripheral pain (dose-adjusted data)

	Absolute		Incremental			Net monetary benefit	
Cohort	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**	**@£20K/QALY**	**@£30K/QALY**
Placebo	£46.95	0.116				£2271.05	£3430.05
Amitriptyline	£72.98	0.114	£26.02	−0.002	dominated	£2198.16	£3333.73
Lamotrigine	£89.01	0.124	£42.05	0.008	ext. dom.	£2388.26	£3626.90
Topiramate	£98.76	0.133	£51.81	0.018	£2948	£2570.71	£3905.44
Venlafaxine	£118.37	0.120	£19.60	−0.013	dominated	£2287.68	£3490.71
Gabapentin	£136.01	0.144	£37.24	0.010	£3641	£2738.02	£4175.03
Tramadol	£196.34	0.118	£60.33	−0.026	dominated	£2165.93	£3347.06
Nortriptyline	£204.91	0.147	£68.90	0.004	ext. dom.	£2744.20	£4218.75
Duloxetine	£218.13	0.139	£82.12	−0.005	dominated	£2556.04	£3943.13
Capsaicin cream	£299.00	0.153	£162.99	0.009	£17,907	£2757.07	£4285.11
Pregabalin	£363.23	0.138	£64.23	−0.015	dominated	£2388.14	£3763.83
Oxcarbazepine	£399.74	0.113	£100.74	−0.040	dominated	£1855.60	£2983.27
Cannabis extract	£630.58	0.115	£331.59	−0.038	dominated	£1660.42	£2805.93
Lacosamide	£702.16	0.123	£403.16	−0.030	dominated	£1757.40	£2987.18
Capsaicin patch	£817.88	0.130	£518.89	−0.022	dominated	£1791.01	£3095.46

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

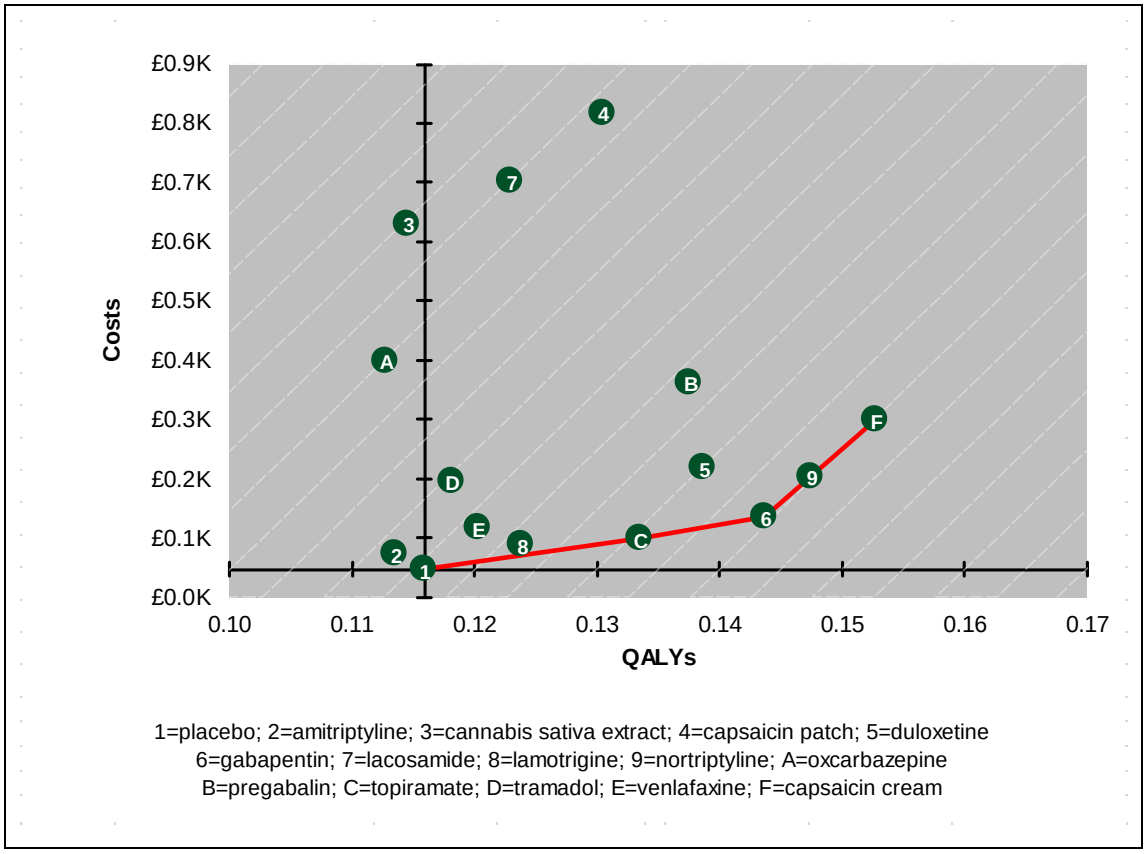

Figure F9 Efficiency frontier for all peripheral pain (dose adjusted data)

The incremental analyses of dose adjusted and dose unadjusted data suggest no difference in the drugs that sit on the efficiency frontier, with gabapentin and capsaicin cream constituting the frontier in both dose unadjusted and adjusted data sets. The ICER for capsaicin cream was higher than £20,000 a QALY in both instances.

A cluster of drugs sit close to the frontier in both data sets: topiramate, duloxetine, venlafaxine and nortriptyline.

Similarly the same drugs sit either well above the frontier or in the top left quadrant (costing more and being less effective than placebo): cannabis sativa, oxcarbazepine, lacosamide and capsaicin patch.

If capsaicin cream were to be removed from the analysis, then only in the non-adjusted analysis would another drug replace it on the frontier. In this case nortriptyline would be on the frontier but at over £400,000 a QALY.

The scenario analysis with amitriptyline as second-line therapy following withdrawal showed no difference in the drugs sitting on or near the efficiency frontier in either the dose unadjusted or adjusted models. However, in both instances the ICER for capsaicin cream was lower than £20,000 a QALY.

4.2.2 PSA and net benefit analysis

This analysis is based on the average cost and QALY values generated from the 5000 simulations of each model. This masks the significant variation in cost and QALYs generated for individual drugs across the simulations, which reflects the uncertainty around effectiveness in the data. This variation is shown in scatter plots of the cost and QALYs generated for each drug across the 1000 simulations in Figure F10 and Figure F11.

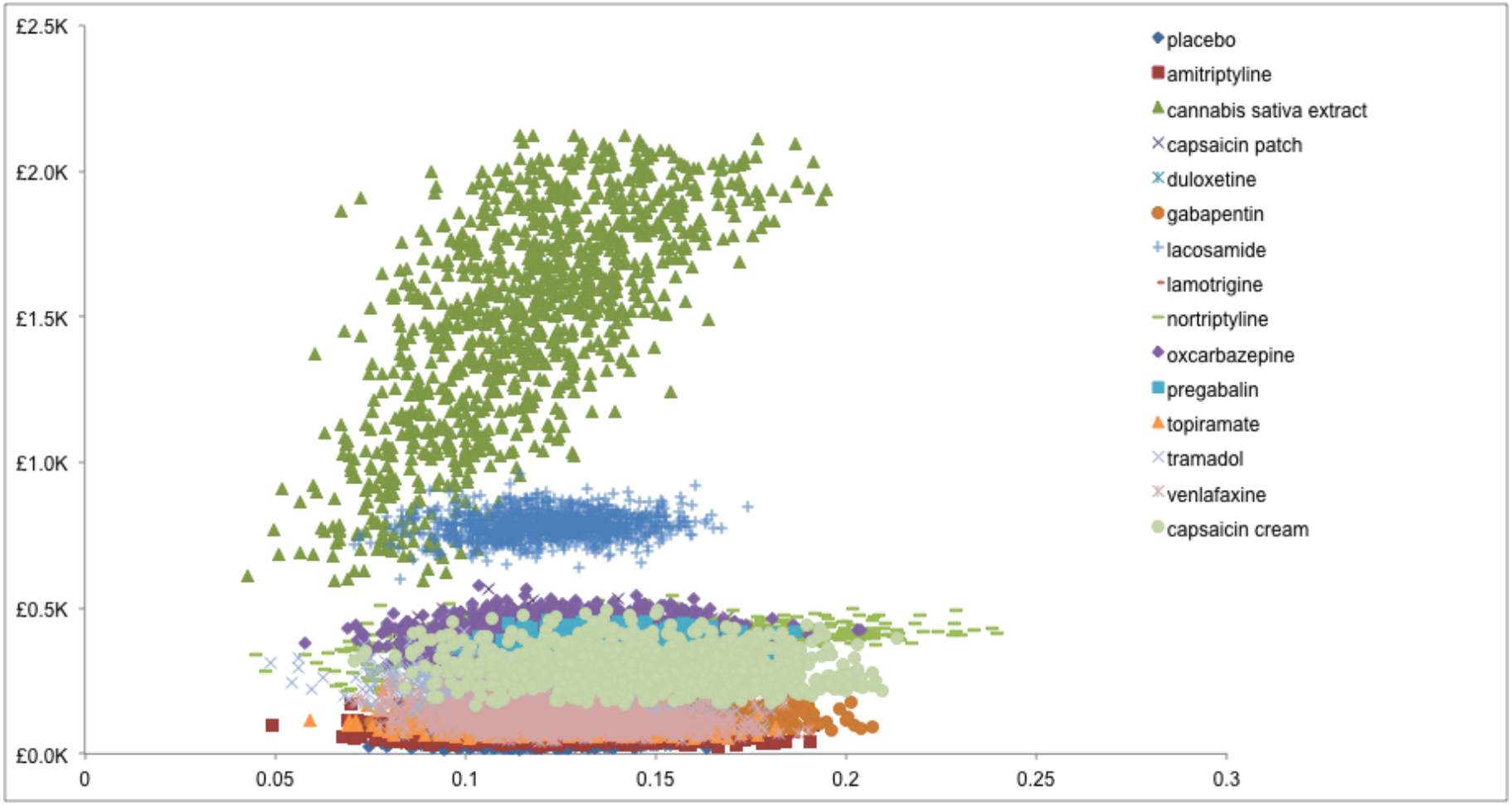

Figure F10 Scatter plot of 1000 simulations for all peripheral pain (dose unadjusted data)

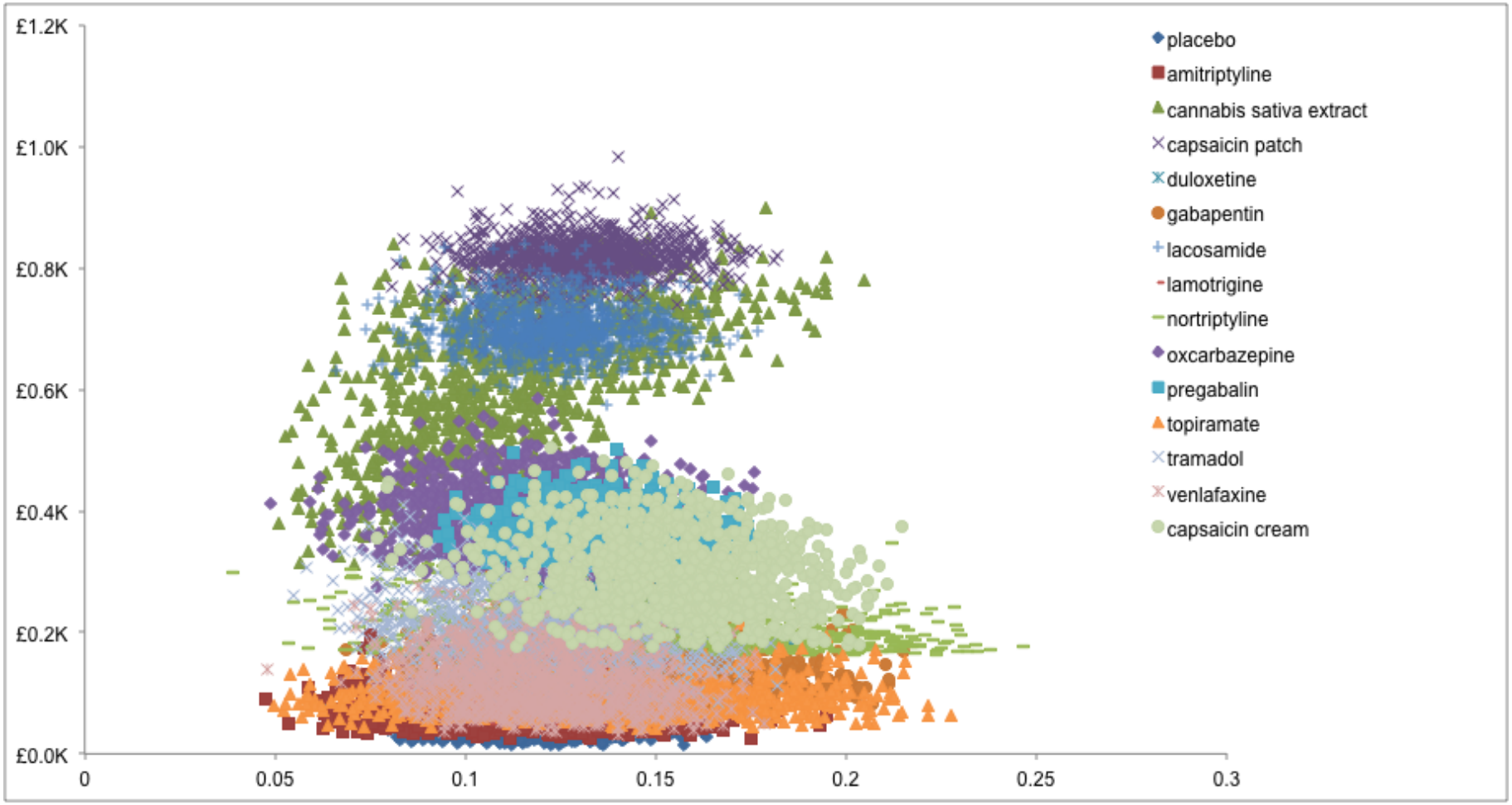

Figure F11 Scatter plot of 1000 simulations for all peripheral pain (dose adjusted data)

As with the data on all neuropathic pain, the lack of clarity in the scatter plots is partly 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 a drug having the highest net benefit at £20,000 for dose variant and dose invariant data is shown in Table F29 and Table F30. The cost effectiveness acceptability curves (CEACs) are shown in Figure F12 and Figure F13.

Table F29 Net benefit analysis at £20,000 a QALY for peripheral pain (dose unadjusted data)

Drug	Probability highest net benefit at £20,000/QALY
Capsaicin cream	28.5%
Gabapentin	28.0%
Nortriptyline	19.9%
Venlafaxine	6.1%
Amitriptyline	5.9%
Topiramate	3.9%
Tramadol	2.9%
Oxcarbazepine	1.5%
Duloxetine	1.3%
Lamotrigine	1.2%
Pregabalin	0.9%
Placebo	0.0%
Cannabis sativa extract	0.0%
Capsaicin patch	0.0%
Lacosamide	0.0%

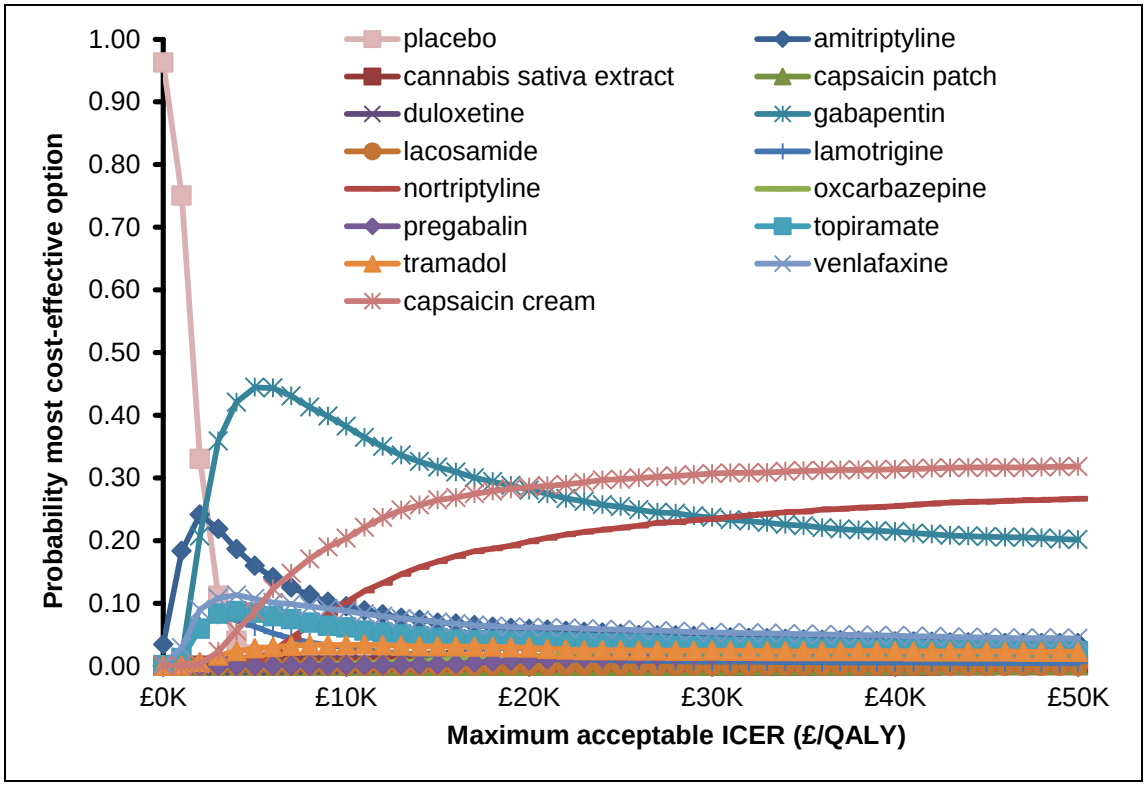

Figure F12 CEAC for peripheral pain (dose unadjusted data)

Table F30 Net benefit analysis at £20,000 a QALY for peripheral pain (dose adjusted data)

Drug	Probability highest net benefit at £20,000/QALY
Nortriptyline	31.7%
Capsaicin cream	22.4%
Topiramate	19.7%
Gabapentin	18.9%
Duloxetine	2.1%
Amitriptyline	1.6%
Venlafaxine	1.5%
Tramadol	1.2%
Lamotrigine	0.5%
Cannabis sativa extract	0.2%
Pregabalin	0.1%
Oxcarbazepine	0.0%
Placebo	0.0%
Capsaicin patch	0.0%
Lacosamide	0.0%

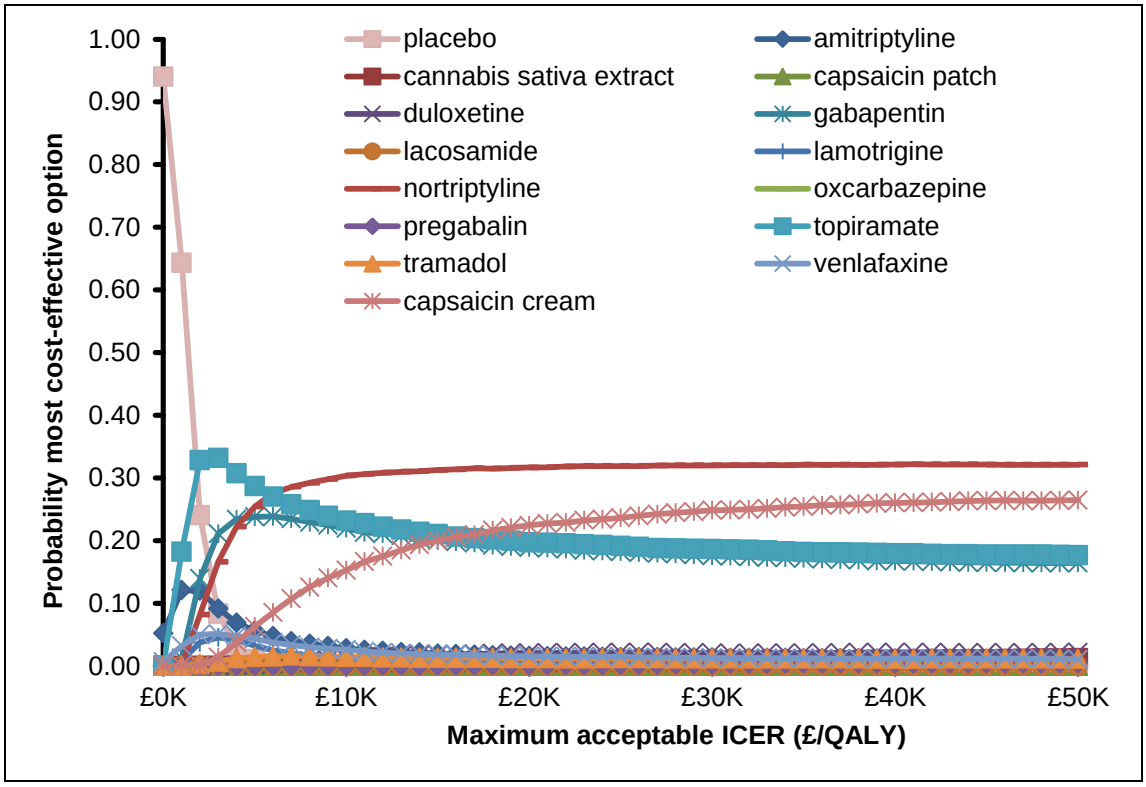

Figure F13 CEAC for peripheral pain (dose adjusted data)

The net benefit analysis for both dose unadjusted and dose adjusted data is similar, with capsaicin cream having a greater than 30% chance of being a cost effective option at £20,000 a QALY. Nortriptyline has the highest likelihood of being the most cost effective option in dose adjusted data but the third most likely in unadjusted data. However, the drugs that sit at the top of the net benefit table are those that constitute or are clustered around the efficiency frontier.

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

Scenario analysis of amitriptyline as second-line therapy made no substantive difference to the ordering of the drugs in terms of the probability of cost effectiveness at £20,000 a QALY, although capsaicin cream increased in likelihood of being the most cost effective option to around 50% at the expense of lower probabilities for gabapentin and nortriptyline for both dose unadjusted and adjusted data.

5 Discussion

5.1 Summary of results

Due to the large confidence intervals around effectiveness estimates for most of the drugs considered, identification of the most cost-effective drugs is problematic. At times the evidence was conflicting between the PSA compared to the mean net benefit analysis.

However, for several drugs there is consistency across the analyses whether dose-adjusted or unadjusted data was chosen. These drugs:

- sat on or close to the efficiency frontier,
- had a positive net benefit compared to placebo at £20,000 per QALY **and**
- had 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:

- topiramate
- gabapentin
- amitriptyline
- capsaicin cream.

Nortriptyline had a greater than 10% chance of being the most cost-effective option with either dose-adjusted or unadjusted data, but only had a mean net benefit greater than placebo at £20,000 per QALY when dose-adjusted data were used.

Venlafaxine met all 3 criteria, with the exception of having a probability of being the most cost-effective option at £20,000 per QALY greater than 5% with dose-adjusted data.

Duloxetine had a positive mean net benefit compared with placebo (and indeed compared with amitriptyline and topiramate) whether dose-adjusted or unadjusted data were used and sat close to the frontier in both cases.

However, it had a less than 5% chance of being the most cost-effective option at £20,000 QALY with both datasets.

For peripheral pain only, the drugs that met the 3 criteria above were:

- nortriptyline
- gabapentin
- capsaicin cream.

Topiramate and venlafaxine met all 3 criteria with the exception of having a probability of being the most cost-effective option at £20,000 per QALY greater than 5% with dose adjusted data.

There was strong and consistent evidence that the following drugs are not cost effective for either all or peripheral neuropathic pain. These drugs, regardless of whether dose-adjusted or unadjusted data were used, had:

- 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.

For both all and peripheral pain only the drugs meeting these criteria were:

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

Levetiracetam also met these criteria for all neuropathic pain. (It was not analysed for peripheral pain only.) Tramadol also had a negative mean net benefit compared with placebo at £20,000 per QALY for dose-adjusted and unadjusted data and for all and peripheral-only pain. However, the probability that it had the greatest net benefit at £20,000 a QALY was consistently above 1%.

5.2 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 mix of continuous and discrete 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 not a reflection of reality, the scenario analysis that moved patients onto amitriptyline after withdrawal did not produce 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.

5.3 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.

The apparent difference can also be explained by the scope of drugs considered in our model. If comparing only gabapentin with pregabalin, then the ICER for all neuropathic data using dose unadjusted data would be £23,200 for pregabalin. If capsaicin cream was not available using the same data set then pregabalin would sit on the efficiency frontier, albeit at an ICER of £26,013. These values are not dissimilar to the majority of ICERs reported in the literature for pregabalin that in some case were higher.

For dose-adjusted data and for peripheral pain we find that gabapentin dominates pregabalin which is contradiction to the literature. On the whole it would appear that the economic models would seem to overestimate the difference in efficacy seen for pregabalin over gabapentin which coupled with

the failure to look at other options makes the published findings that would strongly suggest pregabalin is cost effective to differ from ours.

5.4 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				

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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				

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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				

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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				

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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				

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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				

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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				

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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				

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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				

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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				

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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