National Institute for Health and Care Excellence

Neuropathic pain - pharmacological management
Guideline Consultation Comments Table
19 June - 17 July 2013

Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
British Society of Rehabilitation Medicine & Royal College of Physicians	1	General			BSRM fully endorses the recommendations of Neuropathic pain - pharmacological management	Thank you for your comment.
British Pain Society	1	General			We welcome the opportunity to comment on this guideline	Thank you for your comment.
Department of Health		General			I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
UK Clinical Pharmacy Association	1	General			The UK Clinical Pharmacy Association welcomes the revision of this guideline, particularly given that many of our previous concerns seem to have been taken into account.	Thank you for your comment.
Royal College of Nursing	1	General	General		The Royal College of Nursing welcomes proposals to update this guideline. It is timely.	Thank you for your comment.
Association of British Neurologists & Royal College of Physicians	1	General			I agree these are very sensible guidelines. I have one comment about trigeminal neuralgia. The guidelines group TN into the peripheral neuropathic pain category, although this isn't supported by the literature and pathophysiology remains largely 'idiopathic' and unknown. The vascular loop cases are generally considered to be secondary cases of TN , although even this is presumptive and based upon the response to decompression. There are also consistent reports of secondary TN associated with central lesions.	Trigeminal neuralgia was not considered in the peripheral pain category. It was considered separately from all other analyses as it was deemed to be unique from other types of pain. Recommendations have been made specifically for people with trigeminal neuralgia.
Association of British Neurologists & Royal College of	2	general			I think that in general the neuropathic pain guidelines are very sensible. In terms of Giles' well made comments as to whether the evidence base reflects the current IASP definition of neuropathic pain- a number of trials	This guideline development group acknowledged the difficulty with the variability in the assessment of neuropathic pain in general and in how it was defined in the studies. However, the GDG examined these

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Physicians					were conducted prior to the adoption of this definition and it's unclear if all patients enrolled did have 'definite' neuropathic pain. At the end of the day its worth being pragmatic and getting on and treating the pain appropriately if clinically it appears neuropathic especially in primary care. So I agree some qualification of the definition would be helpful. Finally topical lidocaine has been used in a number of trials of postherpetic neuralgia and is licensed for this indication yet the document refers to focal nerve lesions. 'Lidocaine (topical) - there was only 1 small crossover study on topical lidocaine, which showed no effect on pain reduction; however, the GDG felt that a research recommendation should be made to further investigate the use of this treatment for localised peripheral pain because it could be a potential alternative treatment for people who do not wish to, or are unable to, take oral medications.' I wasn't sure why post herpetic neuralgia had not been mentioned in this paragraph.	studies closely and felt that they did represent neuropathic pain. Further, the second paragraph of the guideline introduction now highlights the uncertainty regarding the nature of lesions. The GDG felt that there was not enough evidence on lidocaine that met the review protocol inclusion criteria to warrant a specific recommendation about this pharmacological agent. Using their expertise, the GDG considered 'localised peripheral pain' to cover peripheral pain and include post-herpetic neuralgia, where the pain was localised. It would not be appropriate to use patches for some patients with post-herpetic neuralgia where the pain is over a very large area.
King's College London Dental Institute	1	general			I am lead for Orofacial pain services for KCHFT and GSTTFT. I see and treat over 300 patients a year with chronic orofacial pain (COFP) There are no specific guidelines for the management of chronic orofacial pain with the exception Trigeminal Neuralgia The majority of patients presenting with COFP on my clinics have neuropathic pain We follow the NICE 2010 NePain guidelines using Amitriptyline, gabapentin, nortriptyline first line alongside psychological interventions Second level regime includes pregabalin and other antidepressant drugs Concern re these Gudielines (where is topical lidocaine patch?) I am concerned that a first line strategy often prescribed in our department for patients suffering from interrupted	There is no clinical agreement on whether chronic orofacial pain is of neuropathic origin and therefore no specific recommendations were made for this group of patients. The two studies which you have highlighted are not randomised controlled trials. Therefore, they did not meet the inclusion criteria agreed with the guideline development group (GDG) for this guideline.

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					sleep due to facial mechanical and thermal allodynia due to NePain is omitted from these guidelines Recent research supports the use of Lidocaine patches in this patient cohort Paper 1 J Pain Res. 2013 Apr 5;6:261-80. doi: **Can treatment success with 5% lidocaine medicated plaster be predicted in cancer pain with neuropathic components or trigeminal neuropathic pain?** Kern KU, Nalamachu S, Brasseur L, Zakrzewska JM. Paper 2 **British Journal of Pain April 11, 2013**2049463713483459 **Case studies illustrating the management of trigeminal neuropathic pain using topical 5% lidocaine plasters** Nadine Khawaja, Zehra Yilmaz, Tara Renton	
Napp Pharmaceuticals Ltd	1	General			In the production process to develop this draft SCG it is clear that NICE has carried out a detailed literature search for evidence to support the treatment of neuropathic pain. However it is apparent that there are many inconsistencies in the way in which the evidence has been used or interpreted. Many of the comments suggest that the "opinion of the GDG" was used on more than one occasion to supplement the evidence. For the purpose of developing the guideline it has been assumed that in some cases that the evidence can be generalised to the other types of neuropathic pain; again this may not be the case.	A structured approach was undertaken to identify, select, and analyse the evidence. Furthermore, the evidence base used to develop this guideline was complex and required the guideline development group to use their clinical expertise and judgment. Further explanation has now been added to the 'evidence to recommendations' section to further clarify the decision making rationale. The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on

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						diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings.
Napp Pharmaceuticals Ltd	2	General			The EFNS guidelines are an important source of information on the management of neuropathic pain. This type of international guideline could be a useful start point when developing guidelines for NHS England. What is apparent is that the same evidence presented to EFNS and reviewed by NICE is treated in different ways and when used for health economic purposes for which the studies were not planned different interpretations are made. There appears to be a great degree of variation in the way that the evidence has been used and interpreted in this guideline. It seems that where suited small patient number trials of short duration may provide evidence for one drug but trials of similar duration with more patients are deemed not to be suitable. This is un-scientific and clinically questionable.	NICE is mandated to produce guidance for NHS and social care services provided in England and Wales. To produce clinical guidelines NICE must also consider health economic evidence to enable development of robust recommendations and guidance. It is possible for NICE to consider published guidance if this is highlighted at the scoping stage of a guideline. Published guidance is then subject to a rigorous quality assessment process. For more information on this please see page 103 of the NICE Guidelines Manual 2012. We do not accept that development methods were unscientific. A systematic approach was undertaken to identify, select, and analyse the evidence, according to a pre-specified review protocol. The GDG also took a priori decisions based on their clinical expertise and judgement on how the results of the clinical and health economic evidence should be presented and interpreted – for example, selecting study outcomes that would be critical to their decision making. It certainly would have been unscientific to disregard pre-specified eligibility criteria in order to accommodate evidence on a wider range of options.
British Pain Society	2	General			You may state that there is insufficient evidence for point	The review protocol specifies inclusion and exclusion

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					4 above, but this is also true of your recommendation for Carbamazepine as first line therapy for Trigeminal Neuralgia when you state "No evidence was found that met the inclusion criteria specified in the review" (Section 3.4.1 pg 112). The level of evidence set by the inclusion criteria of the search strategy does exclude a reasonably sound body of evidence. It would be more logical and consistent to allow reasonable research evidence, good clinical practice and consensus to fill in these "evidence gaps". This should be done in an even-handed manner throughout the document, rather than just for older treatments which are entrenched in clinical practice, like Carbamazepine (which we would agree with).	criteria which aim to reduce bias in the evidence considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process. In the absence of good quality evidence, the GDG used their clinical experience and expertise to reach a consensus that carbamazepine should be recommended as first line therapy for trigeminal neuralgia. This decision was based on the fact that carbamazepine is currently the only drug licensed for this condition and is widely used in current practice. The GDG were aware of other very poor quality studies of different off-label drugs for trigeminal neuralgia but these studies did not meet the criteria specified in the protocol. They did not feel it was appropriate to make no recommendations about the treatment of these patients since this is such a disabling condition, so they were eager to emphasise the need to provide pharmacological pain relief from the outset, while encouraging early referral to specialists in the event that this proves unsatisfactory.
Royal College of Anaesthetists - Faculty of Pain Medicine	1	General			The Faculty warmly welcome the guidance. This was a rigorous process, as always with NICE, and they have addressed a complex condition, producing a guideline that is accessible and helpful for non-specialists. The Health Economic analysis is particularly detailed, in contrast with the previous version, however we are still concerned that this is based on several unjustified assumptions. We have not referenced all our comments. References to support our statement can be forwarded on request.	A structured approach was undertaken to identify, select, and analyse the evidence. Furthermore, the evidence base used to develop this guideline was complex and required the guideline development group to use their clinical expertise and judgment. Further explanation has now been added to the 'evidence to recommendations' section to further clarify the decision making rationale. All health economic analyses rely on assumptions that are justified by published evidence and/or clinical and patient expertise. We have attempted to address

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						particular criticisms below.
Royal College of Anaesthetists - Faculty of Pain Medicine	2	General			The whole guideline, including clinical and health economic evaluation, is notable for the repeated statements to the effect that evidence is generally poor or very poor and therefore that possible conclusions must be limited. Many of the conclusions therefore rely on the consensus of the GDG, rather than on high quality evidence. In relation to forming this consensus we also note that only one GDG member and a co-opted expert have significant specific expertise in neuropathic pain and a publication record in the field to support that. This should be reflected in the weight attached to all recommendations, and the importance with which clinicians should interpret them.	A structured approach was undertaken to identify, select, and analyse the evidence. Furthermore, the evidence base used to develop this guideline was complex and required the guideline development group to use their clinical expertise and judgment. Further explanation has now been added to the 'evidence to recommendations' section to further clarify the decision making rationale. To develop this guideline, NICE recruited individuals from a variety of clinical backgrounds and patient/ carer members, all of which are fundamental in their experience of and care for people with neuropathic pain. Members on every guideline development group (GDG) are equal and no greater weight in terms of decision-making is placed on any member of the group. Each person brings forward their own knowledge and expertise to contribute to the development of an evidence-based, robust and patient-focussed guideline. The constituency for the guideline development group was discussed at the scoping workshop for this guideline. All GDG members were selected by open advertisement against set criteria, including expertise in the area of neuropathic pain. For information of the recruitment and selection process for GDG members please see the NICE Guidelines Manual 2012.
Royal College of Anaesthetists - Faculty of Pain Medicine	3	General			The guidance acknowledges the lack of strong evidence in terms of efficacy and cost-effectiveness for recommendations but this could be made clearer in the introduction and drug recommendations	A structured approach was undertaken to identify, select, and analyse the evidence. Furthermore, the evidence base used to develop this guideline was complex and required the guideline development group to use their clinical expertise and judgment. Further explanation has now been added to the 'evidence to recommendations' section to further clarify the decision

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						making rationale. The strength of the evidence is commented on throughout the guideline and the rationale for the recommendations is clearly explained in the 'evidence to recommendations' section (section 3.1.4). In the recommendations, the GDG used wording that reflected their uncertainty in the evidence. They were unable to strongly recommend one drug over another but felt confident enough in the effectiveness and health economic evidence provided regarding the specific recommendations they made. However, the recommendations do allow some flexibility (ie. if treatment is not effective or not tolerated, try another).
Royal College of Anaesthetists - Faculty of Pain Medicine	4	General	General (&64)		The American Geriatrics Society specifically recommends against amitriptyline because of poor tolerability, especially sedation and increased falls in older individuals. These issues should be better highlighted in these guidelines. Similarly for non-specialist use there should be clear guidance on advice regarding driving etc with all the drugs recommended. This should certainly be more coherent than the vague statement made on page 64.	The guideline development group (GDG) had considerable discussion about the side effects with amitriptyline and that they may be considered intolerable by some patients. This has now been noted in the evidence to recommendations section (section 3.1.4 of the guideline). The GDG felt that driving is covered by 'daily activities' referred in the recommendations. The GDG discussion around driving and the side effects of drugs has also been noted in the evidence to recommendations section of the guideline. Furthermore, the SPC, where available, should provide information on driving.
Grünenthal Ltd	1	Full			From the summary it appears that GDG considerations for individual pharmacological agents were inconsistent, with particular benefits or limitations identified for some treatments but not others.	A structured approach was undertaken to identify, select, and analyse the evidence. Furthermore, the evidence base used to develop this guideline was complex and required the guideline development group to use their clinical expertise and judgment. Further explanation has now been added to the 'evidence to recommendations' section to further clarify the decision making rationale.

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NHS England		Full	General		Summary guidance on the likely drawbacks to each treatment will help to inform patient choice.	This information can be found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug. Appendix J of the guideline also provides information about a large number of adverse events and in which drugs they are mostly likely.
Pain UK	1	General			This draft CG is too reductive for its target audience of non-specialists. As a result it has become a simple 'list' of drugs, already widely used in primary care without adding any value to the management of NeP. The previous CG included useful dosages to help non-specialists treat patients as well as explaining first line/second line, etc. All this information should be reinstated. Since the aim of the guideline is to help non-specialists, it needs to be more detailed if it is to do its job.	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis.
British Pain Society	3	General			It would be useful to include recommendations as to how long drugs should be tried for before determining if they are beneficial or should be abandoned	The guideline development group (GDG) felt it was inappropriate to make generic recommendations about the suitable length of time which treatments should be attempted. They felt this would be different for each patient and should be part of an individual's treatment plan.
British Pain Society	4	General			Why have dose recommendations been removed from this version – they were particularly useful in the previous edition especially when considering potential referral points in Primary Care – plus this was an ideal factor to audit	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis.
Cambridge University Hospitals NHS	2	General			We cannot understand why the document fails to provide information about drug dosages or guidance for non-specialist practitioners on drug titration regimes. We	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs.

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Foundation Trust					like, very much, the recommendations for key principles of care (3.5.2 page 117), but feel that active management of drug titration and knowledge of therapeutic doses is essential in achieving compliance with the medications and increasing the likelihood of reaching a therapeutic response. Without this information, we feel that the guidelines lack direct clinical relevance for non-specialist practitioners and may be largely ignored as a resource.	Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis.
Royal College of Nursing	2	General			Why have dosages been removed from this version – they were particularly useful in the previous edition especially when considering potential referral points in Primary Care – plus this was an ideal factor to audit.	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis.
Royal College of General Practitioners	1	General			Why have dosages been removed from this version – they were particularly useful in the previous edition especially when considering potential referral points in Primary Care – plus this was an ideal factor to audit **(MJ)**	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis.
Shingles Support Society	1	General			From the original guideline – full version - sections about First Line Treatment through Other Treatments which offer full dosage details should be reinstated: Page 14, section 1.1.10 through to page 17 section 1.1.17. The introduction to the new version states how different the dosing regimen is when using e.g. TCAs for pain, the Guideline needs to help the prescriber to get dosage	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the

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					right. The Guideline needs to fully guide the clinician about how to treat neuropathic pain, particularly as the two first line drugs are being used off license.	recommendations as the dosages required for each patient will be assessed on an individual patient basis.
NHS England	2	General			Why have dosages been removed from this version – they were particularly useful in the previous edition especially when considering potential referral points in Primary Care – plus this was an ideal factor to audit	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis.
Royal College of Nursing	3	General			Should all central neuropathic pain be initially assessed in a specialised setting?	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Royal College of General Practitioners	2	General			Should all central neuropathic pain be initially assessed in a specialised setting? **(MJ)**	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Vulval Pain Society	3	General			Thank you for this important document which will benefit patients. We have one request, that in the list of neuropathic pain syndromes you include unprovoked vulvodynia. There is a large volume of literature that support the use of chronic pain strategies for this condition. The British Society for the Study of Vulval Disease (a medical professional society) acknowledge in their national guidance that unprovoked vulvodynia should be treated as a neuropathic pain problem and	Clinical agreement as to whether unprovoked vulvodynia is a type of neuropathic pain has not been reached. For this reason it is not included within the guideline as a neuropathic pain syndrome.

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					recently published clinical standards point to the role of pain management specialists for selected patients Inclusion of unprovoked vulvodynia will enable more women to access more appropriate treatment. Vulvodynia guidance http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.2010.09684.x/abstract;jsessionid=AC0C6309179E44FABB62913A1788A96D.d01t02?systemMessage=Wiley+Online+Library+will+be+disrupted+5+Nov+from+10-12+GMT+for+monthly+maintenance National Clinical Standards which support the role of pain management in the referral of patients with chronic vulval pain http://www.pcc-cic.org.uk/article/standards-care-women-vulval-conditions	
Pancreatic Cancer UK	1	General			Within the treatment of pancreatic cancer neuropathic pain often remains undiagnosed and is often not thought of until people are nearing the end of life. Which means the patient can have been experiencing considerable pain for some time before they received adequate treatment. This type of pain is largely unresponsive to opiate treatment, so should be considered very early on in pancreatic cancer. Through our Support Line we have heard that patients have been told things like "you should not have pain now as you have had X drug or Y drug". We do not fee this is acceptable practice. We therefore feel that if these guidelines are successfully implemented into the care of people with pancreatic cancer they could make a significant impact on improving the quality of life of this patient group.	Thank you for your comment. We recognise that this is an important issue but we are unable to consider diagnosis as this is outside the remit of this guideline. NICE does have a dedicated implementation and communications team which will promote the guideline when it publishes in November 2013. These teams work to ensure the key messages and recommendations from the guideline are promoted.

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Astellas Pharma Ltd	1	Full	22 - 34	Table 4	**HIV-AN** Astellas consider that it is inappropriate to include patients with HIV associated neuropathy in an analysis for neuropathic pain in a non-specialist setting. HIV patients are routinely treated for symptom management (including pain control) in a specialist setting, and would be unlikely to receive this treatment in a non-specialist setting.	People with HIV associated neuropathy are not excluded from this guideline as it is possible that a person with HIV could present with neuropathic pain in non-specialist settings. However, we anticipate that a large proportion of people with HIV are likely to be treated in specialist settings and following discussion between the specialist clinician and the patient this is likely to be the most appropriate plan. The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. In light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, this is why specific recommendations were not made by underlying cause of the pain. When breaking down the evidence to individual conditions, there were also conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence.
Napp Pharmaceuticals Ltd	3	General			For first-line use not one but two un-licensed products have been suggested. Although custom and practice has led to the accepted use of amitriptyline for first line use in a range of neuropathic pain conditions the published evidence is still weak. It must be appreciated that the quality of scientific data required for regulatory approval is high and in particular one of the concerns about using drugs that are not licensed for neuropathic pain is that the quality of the data are limited. In particular the GDG may wish to consider adherence to current ICHGCP requirements and also how missing	A structured approach was undertaken to identify, select, and analyse the evidence. Furthermore, the evidence base used to develop this guideline was complex and required the guideline development group to use their clinical expertise and judgment. Further explanation has now been added to the 'evidence to recommendations' section to further clarify the decision making rationale. Final approval prior to publication is required from NICE.

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					data should be handled in pain clinical studies and whether appropriate statistical analyses were carried out. Furthermore the guideline then suggests that a second un-licensed product, nortriptyline, could also be used as an alternative. Information about this however is limited to footnotes; this should be more prominent within the guideline. Although the health economic evidence pointed to poor value for money for amitriptyline in PNP, the GDG dismissed this as the evidence is based on a single trial. Yet in other cases medicines have been excluded on the basis of weak evidence from single trials. Where necessary it seems that a class- effect rule has been applied –e.g. interchangeability of tricyclic anti-depressants. It should be appreciated that the clinical trials conducted in pain almost always permit a background usage of pain medications. The GDG should consider how to ensure that this issue is addressed within the guideline.	NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings.

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						Each drug was considered on an individual basis and no class-effect has been applied. It is standard in NICE guidelines to include details about drugs recommended off-label in footnotes of recommendations (see section 9.3.6.3 of The guidelines manual 2012). Appendix D now discusses issues with missing data in clinical trials in chronic pain and how this was addressed in this guideline. While the individual analyses highlight the use of concomitant medications in the trials, commentary about this issue has been added in the 'evidence to recommendations' section. The GDG had considerable discussion about the use of concomitant pain medication in the trials. The 'evidence to recommendations' section (section 3.1.4 under 'quality of evidence') now reflects this discussion.
Royal College of General Practitioners	3	General			I think there is a specific concern about recommending Duloxetine which is NOT licenced for non-diabetic neuropathy. **(MJ)**	The guideline development group (GDG) felt that just because the bulk of the literature for duloxetine is in diabetic neuropathy, it does not preclude this is an effective treatment for other types of peripheral pain. The GDG considered it would be reasonable to expect that they would respond similarly.
Royal College of Anaesthetists - Faculty of Pain Medicine	5	General			There are several important differences in Recommendations from the 1st version of the Guideline, which will be confusing to non-specialists. It would be worth highlighting these differences early on, and explaining the reasons for the main changes	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. A new guideline development group (GDG) was appointed for this full update and through interpretation of the evidence and GDG expertise, the GDG have arrived at new recommendations. For this

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						reason update marking has not been applied to the guideline.
Royal College of Anaesthetists - Faculty of Pain Medicine	6	General			The analysis appears to be based upon the assumption that placebo response size is fixed and consistent across trials. Scrutiny of the trials clearly demonstrate that this is not the case. Therefore, we are concerned by the use of this flawed assumption and the impact on the analysis.	The placebo response is synthesised from the response across all trials. The model is run stochastically and so the placebo response is not fixed but varies.
Royal College of Anaesthetists - Faculty of Pain Medicine	7	General			On the other hand, the decision was made to search and recommend on the basis of a distinction between peripheral and central neuropathic pain. In retrospect, judging by the evidence available and its reporting, this was an unhelpful distinction.	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings.
Royal College of Anaesthetists - Faculty of Pain Medicine	8	General			It is important to note (Moore et al, BMJ 2013) that, while RCTs and meta-analyses are based on average response to analgesics, yet the variation between individual patient responses is important – while the majority do not respond sufficiently to any one particular drug, those that do respond will respond quickly and well, and most will respond to at least one drug or combination of drugs. The importance for this Guideline is to be quick in switching between drugs in the event of apparent non-response, even if trial-based evidence is in	The GDG acknowledged that it was important to expedite switching between drugs when one does not work. However, they did not feel they could make a recommendation about a restricted timeframe for when this should happen as it will be different for each patient. This should be discussed at an individual's clinical review.

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					favour of the drug overall and to make clear research recommendations regarding measurement and reporting of responses at patient level.	
Royal College of Anaesthetists - Faculty of Pain Medicine	9	General			We are concerned that in the various places that cannabis sativa is mentioned (although we recognise that the guideline does not recommend use of this drug) that no mention is made of the well-recognised and appreciable risk association of precipitating psychosis, schizophrenia and other mental illness with cannabis use. We would be happy to supply a summary of this mainly epidemiological evidence if required.	The guideline development group felt it was not necessary to comment on side effects as the syntheses showed that it was not efficacious at reducing pain compared to placebo.
Royal College of Anaesthetists - Faculty of Pain Medicine	10	General			The risks of imputing missing data from trials using different techniques (ie LOCF vs BOCF) should be discussed and taken into account.	Appendix D now discusses issues with missing data in clinical trials in chronic pain and how this was addressed in this guideline.
Royal College of General Practitioners	7	General			Doctors working with substance misusers are encountering widespread inappropriate use of pregabalin and gabapentin, both illicit and prescribed. Many patients have informed us that they deliberately take excessive doses for psychotropic effects. We are aware that obliging GP practices are being targeted by some service users in pursuit of prescriptions. Deaths and other adverse drug reactions related to Pregabalin and Gabapentin have been reported in the literature[1 2 3 4 5 6 7]. We are concerned that Pregabalin or Gabapentin abuse may be a risk factor for overdose particularly if used in combination with alcohol and other CNS depressant drugs. In addition we have observed cases of physical dependency, with an associated distressing withdrawal syndrome which is again well described in the literature [8 9 10 11 12 13 14 15 16].	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis. The references provided do not meet the inclusion criteria specified in the review protocol for this guideline. Following the Guidelines Manual 2012 and in discussion with the guideline development group (GDG), examples of criteria which were listed in the

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					We therefore respectfully request that the final guideline will include the potential for abuse and the need for particular caution when prescribing this class of drugs to anyone with a history of dependence. It is our opinion that in substance dependant patients, Gabapentin and Pregabalin should be reserved as 2nd/3rd line treatment only in those with confirmed neuropathic pain – and who are stable on opioid substitute medication and abstinent from illicit drugs and not abusing alcohol. References: [1] Adverse drug reactions to gabapentin and pregabalin: a review of the French pharmacovigilance database. Fuzier R et al. Drug Saf. 2013 Jan;36(1):55-62.) [2] Two Fatalities Involving Pregabalin. Jennifer Button1 David Berry and David W Holt, Analytical Unit1, St George's - University of London, London, UK & Medical Toxicology Laboratory2, St Thomas' Hospital, London, UK [3] Self-poisoning with lamotrigine and pregabalin Author(s): Braga, A. J.; Chidley, K.Source: ANAESTHESIA Volume: 62 Issue: 5 Pages: 524-527 DOI: 10.1111/j.1365-2044.2006.04913.x Published: MAY 2007 [4] Complete atrioventricular block due to overdose of pregabalin. Author(s): Aksakal, Enbiya; Bakirci, Eftal Murat; Emet, Mucahit; et al.Source: AMERICAN JOURNAL OF EMERGENCY MEDICINE Volume: 30 Issue: 9 Article Number:	review protocol were: English language studies only Adults only Randomised controlled trials or systematic reviews, Must have had at least a 4 week study period Be head to head comparisons of drugs listed in the scope or compared with placebo/ active placebo Crossover trials must have had at least a 1 week washout period or undertaken carry-over analysis

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					2101.e1DOI:10.1016/j.ajem.2012.02.008 Published: NOV 2012 [5] A Case Series of Recreational Pregabalin Overdose Resulting in Generalized Seizures Author(s): Reedy, S. J. D.; Schwartz, M. D.Source: CLINICAL TOXICOLOGY Volume: 48 Issue: 6 Pages: 616-617 Meeting Abstract: 60 Published: JUL 2010 [6] Pregabalin Overdose in Adults and Adolescents - Experience in Sweden Author(s): Sjoberg, G.; Feychting, K.Source: CLINICAL TOXICOLOGY Volume: 48 Issue: 3 Pages: 282-282 Meeting Abstract: 177 Published: MAR 2010 [7] Abuse and Misuse Potential of Pregabalin: A Review of the Clinical Evidence, 24 April 2012, Canadian Agency for Drugs and Technologies in Health http://dpic.org/sites/default/files/PregabalinAbuse_CADTH_24Apr2012.pdf [8]Potential for Pregabalin Abuse or Diversion After Past Drug-Seeking Behavior, Frank A. Filipetto, DO; Christopher P.Zipp, DO; Joshua S.Coren, DO, MBA J Am Osteopath Assoc October 1, 2010 vol. 110 no. 10 605-607. http://www.jaoa.org/content/110/10/605.full [9] Gabapentin and pregabalin: abuse and addiction. Prescriber Int. 2012 Jun;21(128):152-4. http://www.ncbi.nlm.nih.gov/pubmed/22822593 [10] Pregabalin should be moved to the prescription group B AA Westin JG Bramness F Chalabianloo T Rygnestad L Slørdal **http://translate.google.co.uk/translate?hl=en&sl=no**	

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					&u=http://tidsskriftet.no/article/2985527/&prev=/search%3Fq%3Dbmj%2Bpregabalin%2Babuse%26start%3D10%26sa%3DN%26biw%3D1280%26bih%3D738 [11] **Earlier discovery of pregabalin's dependence potential might have been possible. Caster O, Edwards IR, Norén GN et al. Eur J Clin Pharmacol 2011; 67: 319 - 20 [PubMed] [CrossRef]** [12] Pregabalin abuse and dependence in Germany: results from a database query. Maximilian Gahr, Roland. W. Freudenmann, Christoph Hiemke, Makus A. Kölle, Carlos Schönfeldt-Lecuona . European Journal of Clinical Pharmacology June 2013, Volume 69, Issue 6, pp 1335-1342 http://rd.springer.com/article/10.1007/s00228-012-1464-6 [13] Martin Grosshans, M.D.; Jochen Mutschler, M.D.; Derik Hermann, M.D.; Oliver Klein, M.D.; Harald Dressing, M.D.; Falk Kiefer, M.D.; Karl Mann, M.D. Pregabalin Abuse, Dependence, and Withdrawal: A Case Report *Am J Psychiatry 2010;167:869-869.* 10.1176/appi.ajp.2010.09091269 http://ajp.psychiatryonline.org/article.aspx?articleID=102360 [14] Pregabalin Abuse: A Case Report Ilhan Yargic, Filiz Alyanak Ozdemiroglu [Istanbul] 2010 [15] "Gabapentin Abuse Gabapentin – another drug of misuse?" Janet Webb, BSc(Pharm), MSc 2008 British Columbia Drug & Poison Information Centre [16] Adverse Drug Reactions to Gabapentin and Pregabalin, Drug Safety January 2013, Volume 36,	

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					Issue 1, pp 55-62 Régis Fuzier, Isabelle Serres, Emmanuelle Guitton, Maryse Lapeyre-Mestre, Jean-Louis Montastruc http://link.springer.com/article/10.1007%2Fs40264-012-0006-6 **(SMAH)**	
Royal College of General Practitioners	4	General			We strongly suggest that a clear statement advising caution with gabapentin and pregabalin in patients with substance misuse history is included in the Quick Reference Guide when this is published. Community GPs are very much guided by the recommendations in the Quick Reference Guides and one of the main problems nationwide in the abuse of gabapentin and pregabalin is that the current NICE CG96 recommends them both without any mention of these increasingly recognised problems. **(SEG)**	NICE no longer produce quick reference guides alongside clinical guidelines. Guideline recommendations and important accompanying information are set out on the online NICE Pathways tool. For more information on NICE Pathways and example of how these work, please see the NICE website. The guideline development group also considered dependency issues when making recommendations. This information can be found in the 'evidence to recommendations' section of the guideline.
Royal College of General Practitioners	5	General			The RCGP Secure Environments Group welcomes the review of NICE CG96 and is committed to providing the best possible, equivalent care to those vulnerable patients, who are in the custody of the State. According to the 2012 National Crime Statistics, 1.5% of adults have used a Class A substance in the last month[1]. This is thought to represent approximately half a million people. The current prison population in February 2013 was 83,687[2]. Complaints of "nerve pain" are extremely common among both groups and specific requests for pregabalin (and to a lesser extent, gabapentin) have become increasingly common over the past five years. The RCGP Secure Environments Group strongly suggests that this vulnerable population deserves particular attention in the new NICE guideline for the	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis. GDG discussion around this can be found in the 'evidence to recommendations' sections of the guideline.

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					management of neuropathic pain. <u>Experience</u> GPs who work in prisons and community drug treatment services report increasing numbers of patients insisting that they should be prescribed gabapentin and pregabalin for conditions ranging from cartilage tears, old fractures and leg ulcers. Whilst it is recognised that all these conditions may be painful and potentially require pharmacological management, the SEG does not believe that these necessarily represent neuropathy. We endorse the draft guideline 1.1.1 - 1.1.7 suggesting the need for accurate diagnosis and regular review of any prescribed treatment. It is our experience that patients regularly use "trigger terms" such as "shooting pains" or "electric shocks" to push clinicians towards considering neuropathic pain. However, descriptions are often non-anatomical and should throw doubt on such a diagnosis. Patients in treatment for substance misuse issues have reported acquiring pregabalin and gabapentin from genuine patients who have collected their prescriptions from pharmacies. Such patients also compare the effects of pregabalin and gabapentin with other abusable drugs, with statements such as: a. *"If you get the dosing right then you only need to be conscious for a few hours every day"* b. *"They are better than crack!"* When treating people who misuse drugs, it is good practice to be careful when agreeing to prescribe drugs which have been requested by name. It is also important to consider the reaction of a patient, when discussing reducing or stopping inappropriate medication.	

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					Prescribers working in secure environments and community drug treatment services report experiencing considerable hostility from patients when pregabalin and gabapentin are reviewed. Indeed, there are multiple reports of staff being threatened, taken hostage and assaulted over this issue. <u>Pharmacology</u> Pregabalin and gabapentin are known to have several effects in the drug therapy of pain: I. Both drugs potentiate the effects of opiate drugs through their actions on the μ-opioid receptor II. Both influence the secretion of gamma-aminobutyric acid (GABA), which consequently mimics the effects of benzodiazepines III. Both drugs have euphoriant effects in certain individuals. It is self-evident that these pharmacological effects would prove desirable to drug users. Indeed, in combination with opiate substitution, mental health medications and alcohol, pregabalin may be particularly dangerous as it lacks a ceiling of absorption from the gut, unlike gabapentin. Several deaths in custody have been reported to involve the prescription of pregabalin, although post-mortem toxicological examination does not yet routinely include the drug. <u>Evidence Base for the Abuse of Gabapentin and Pregabalin</u> Gabapentin and pregabalin have been thought to have a low potential for addiction or abuse. However, in 2004, reports were published in the literature of inmates with a	

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					history of cocaine use abusing and diverting gabapentin[3]. Since its introduction into clinical practice in 2004, pregabalin has become a widespread drug in UK practice with 1.7 million prescriptions issued by General Practitioners in 2011. Special mention of the risks of abuse associated with it seems imperative, based on our experience that a number of these prescriptions are diverted. Concerns about pregabalin and gabapentin abuse are not confined to the UK and USA. There have been similar reports in the published literature from Norway, Germany, Turkey[5] and the World Health Organisation[6]. Consensus guidance on the Management of Persistent Pain in Secure Environments is due to be published in the near future. This guideline is to be endorsed by the British Pain Society, RCGP, RCN, Department of Health and the Secure Environments Pharmacist Group of the Royal Pharmaceutical Society[7]. Special mention is made of gabapentin and pregabalin and the need for particular care when prescribing to patients with a history of illicit drug use. The RCGP SEG has also made specific mention of the dangers of gabapentin and pregabalin use in secure environments in its guidance *Safer Prescribing in Prisons.*[8] <u>Conclusion</u> Whilst the RCGP SEG endorse the majority of the draft NICE guidance on neuropathic pain, we believe that there is a significant case to be made for special mention of patients with a history of addiction. Recovery from addiction in this already hard-to-reach group is hampered by the indiscriminate use of pregabalin and gabapentin. These drugs should only be used in exceptional circumstances in such patients.	

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					References 1. Drug misuse declared: findings from the 2011 to 2012 Crime Survey for England and Wales (CSEW) (second edition) 2. https://www.gov.uk/government/publications/prison-population-figures [accessed 24/6/13] 3. Reccoppa L, Malcolm R, Ware M. Gabapentin abuse in inmates with prior history of cocaine dependence. Am J Addict. 2004;13:321-3. 4. Webb J. Gabapentin Abuse: Gabapentin – another drug of misuse? British Columbia Drug & Poison Information Centre. 2008 5. Yargic, I., Ozdemiroglu, I.Y. Pregabalin Abuse: A Case Report [Istanbul] 2010 6. Caster, Edwards, Norén & Lindquist. Earlier discovery of pregabalin's dependence potential might have been possible. Eur J Clin Pharmacol (2011) 67:319–320 7. http://www.rcn.org.uk/__data/assets/pdf_file/0010/465841/Final_draft_-_Management_of_persistent_pain_in_secure_environments_01.07.2012.pdf [accessed 24/6/13] 8. RCGP. *Safer Prescribing in Prisons.* 2011:16-17. http://www.rcgp.org.uk/news/2011/november/~/	

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					media/Files/News/Safer_Prescribing_in_Prison.ashx **(SEG)**	
Faculty of Pharmaceutical Medicine	1	General		-	We are concerned that currently the guidance concentrates on frequentist, clinical trial treatment group-led, statistical assessment. We believe that neuropathic pain is a condition that lends itself to more of an individualised, or 'personalised medicine' approach and that this document, although acknowledging this approach, does not fully recognise its potential and explore the possibilities.	NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain. However, the current recommendations take into consideration these factors by stating that alternative drugs should be tried if the ones provided initially are not effective, not tolerated or are contraindicated. The 'evidence to recommendations' section also highlights the importance of considering the impact of adverse events of different drugs on different patients when deciding on treatment.
Faculty of Pharmaceutical Medicine	2	General		-	The draft does not make clear where the boundary lies between product assessment and the guidance of medical practice. We do not agree that a central organisation can create a blanket policy that denies the possibility of offering the best personalised medicine by the prescriber in an indication where this is the paramount therapeutic tactic. The drugs in question are mostly generic and inexpensive, so there is not even a major financial issue at stake here.	NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain. However, the current recommendations take into consideration these factors by stating that alternative drugs should be tried if the ones provided initially are not effective, not tolerated or are contraindicated. The 'evidence to recommendations' section also highlights the importance of considering the impact of adverse events of different drugs on different patients when deciding on treatment.
Pfizer	1	General		General	Pfizer welcome, in principle, the comprehensive review of CG96 - clinical guidelines for the pharmacological management of neuropathic pain. Whilst Pfizer welcomes the inclusion of additional medications to choose from in non-specialist settings, such as gabapentin, Pfizer is also concerned about the	The key principles of care recommendations have now been amended to address issues related to patients. We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs.

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					interpretation of evidence, the consequent recommendations and the impact these will have on the delivery of high quality NeP management. In addition, there are potential fundamental inconsistencies and errors in the modelling and the dose-adjusted analysis, in particular for gabapentin, which could undermine the recommendations. Pfizer therefore makes the following suggested amendments, which are discussed in more detail below: • Re-inclusion of the more patient-focussed recommendations within the principles of care section that are mentioned in the original CG96 (2010) and greater emphasis for the importance of giving non-specialists practical advice on diagnosis, ongoing assessment, dosing and titration. • Removal of the inappropriate recommendation to use nortriptyline as a first or second-line option in its own right, including in patients who have not responded to amitriptyline, prior to use of licensed and potentially more cost-effective options, such as pregabalin. • Of the treatments recommended in this draft, only pregabalin is licensed, with a strong evidence base in central NeP and therefore should be considered as the first-line choice in these patients. • Pfizer questions the recommendation for duloxetine in 'all neuropathic pain' and suggests that it would be more appropriate to recommend duloxetine only as an option in DPN patients, in line with its license, particularly given that licensed alternatives are available for the broad	Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis. It is standard in NICE guidelines to include details about drugs recommended off-label in footnotes of recommendations (see section 9.3.6.3 of The guidelines manual). The dose-adjusted model and costs and outcomes for gabapentin are made alongside the more detailed comments from your organisation below. Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong

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					NeP population. • Greater justification and transparency of decision-making in recommending off-label treatments ahead of licensed, evidence-based and cost-effective alternatives, particularly with regards to the differences between the differential dose analyses. • Explanation of inconsistencies and correction of potential errors in the costs and outcomes for gabapentin and the plausibility of the dose-adjusted analysis.	clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings.
Pfizer	2	General		General	There is a lack of clarity around the specific level of evidence pertaining to each intervention in the full guideline and it is difficult to gain a sense of the evidence available for each intervention. For example, by listing the trials alphabetically it is not possible to understand the level of evidence (e.g. sample size) available for a given intervention. Furthermore, the GRADE summary table is also misleading because the GRADE summary per outcome is presented as an average over all interventions for which evidence was available on that outcome. As such, on page 83, Table 15, for the outcome of PGCI where pregabalin is the only drug contributing to the outcome, the quality is rated as 'moderate' based on Lesser et al.	Whilst your concerns with the lack of clarity around the specific level of evidence pertaining to each intervention are noted, this was an unavoidable consequence of the size and volume of the evidence included. Having considered alternative approaches, the tables remain listed alphabetically as this is believed to be most helpful to the majority of stakeholders. GRADE is used to assess the quality of evidence for an outcome, not the quality of each individual study. When considering a network meta-analysis, it is not appropriate to only assess the quality of evidence for each link the in the network. It should be assessed across the whole network, including the other drugs in the network.

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					(2004). However, for all other outcomes where pregabalin is one of a number of drugs contributing evidence to that outcome, the rating is generally 'very low'- despite incorporating the same trial. Additionally, Pfizer suggests that repetition of same studies for 'All NeP' and 'Peripheral NeP', given that the final recommendations do not differ between them is unnecessary and adds confusion to what is supposed to be a short clinical guideline. Instead, Pfizer asks NICE whether it would be preferable to provide more detail around the evidence and approach to synthesis for the all NeP analysis and provide full details of the additional analyses in an appendix. Pfizer requests that more detail is provided on the evidence and the approach to evidence synthesis used to inform the recommendations in the guideline, rather than repeating high-level detail across multiple, similar analyses.	The fact that there is repetition of the same studies in 'all neuropathic pain' and 'peripheral neuropathic pain' is largely due to the fact that the majority of evidence on neuropathic pain is on peripheral pain and, so, dominates the evidence for 'all neuropathic pain'. However, in order to determine if the overall results were the same between 'all' and 'peripheral', it was necessary to compare the results of each network. The detail for the evidence is provided within appendices G and H.
Pfizer	3	General		General	Given the comments noted above about the irregularity of the results produced in the dose-adjusted economic model, particularly for nortriptyline, the recommendation to use nortriptyline at 1st line does not appear to be evidence-based. In the non-adjusted dose analysis, pregabalin actually dominates nortriptyline. Furthermore, pregabalin has an ICER of only £11,637 versus placebo, and is generally cost-effective versus the other comparators in the trial-based analysis: • Placebo £11,637 • Amitriptyline £25,713	This recommendation has now changed and amitriptyline,gabapentin, pregabalin and Duloxitine are now recommended as initial treatment options. Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best

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					• Nortriptyline Dominated • Gabapentin £23,267 • Duloxetine £8,575 Even in the dose-adjusted analysis, pregabalin still has an ICER of £13,766 over placebo. As noted, by the GDG on page 66, these values are well within what would be considered a good use of NHS resources according to current thresholds used by NICE. As such, the recommendation to use nortriptyline prior to pregabalin appears neither clinically nor economically appropriate and Pfizer reiterates the request for re-consideration of this recommendation as noted in comment above.	available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings. NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.

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Pfizer	4	General		General	Given the considerable uncertainty in clinical effectiveness and parameters included in the model, Pfizer is surprised at the limited exploration of uncertainty using scenario and sensitivity analyses. A scenario analysis was undertaken looking at amitriptyline after the withdrawal of the first drug (Appendix F, pg 18 ln11-18), but this was the only scenario analysis considered. Pfizer suggests that that there are a number of structural assumptions and inputs that warrant further exploration and may have an impact on model results. Pfizer suggests the following elements are explored further: Initial clinical effectiveness data from the clinical NMAs for pain relief, a longer time horizon with the exploration of long term effectiveness and withdrawal of therapies, sequential use of treatments, utilities used in the model for pain and adverse events, and resource use implications for adverse events. Pfizer suggests that further exploration and use of scenario and sensitivity analyses would improve the robustness of the model and help determine the level of uncertainty in the current recommendations that stem from the simplistic approach to economic modelling.	Uncertainty around resource use and utilities are explored within the guideline using probabilistic sensitivity analysis (PSA). The data did not support the use of a longer time horizon, particularly in the absence of evidence on adverse events and withdrawal. With no information on contingent probabilities of effectiveness of one drug after treatment failure, sequential treatment was not considered to be appropriate to be modelled.
Primary Care Neurology Society	1	General	Title page		On reading the new guideline it is clear that the first limiting factor is its title. By only addressing pharmacological management it leaves all the non-pharmacological options out and so does not really promote a bio-psyco-social approach to management. The title assumes that a diagnosis of neuropathic pain has correctly been made and so gives no advice on how such a diagnosis should be made. Nor does it suggest any screening tools that could be helpful. **If the**	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.

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					diagnosis is incorrect then the guidance will be incorrectly used. With this in mind it seems to be rather important that guidance be included on assessment of neuropathic pain.	
Royal College of Anaesthetists - Faculty of Pain Medicine	11	full	3		Whilst allodynia and hyperalgesia do indeed sometimes occur in association with neuropathic pain, the more frequent presentation, especially with polyneuropathies, is pain in the context of sensory loss, sometimes called anaesthesia dolorosa. Also sensory /gain loss presents to a range of different sensory modalities and this needs to be highlighted.	Allodynia, hyperalgesia, and sensory/gain loss have now been added to this section.
Association of British Neurologists & Royal College of Physicians	3	General			This is largely excellent. A couple of comments: Firstly the definition … *neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system'. Central neuropathic pain is defined as 'pain caused by a lesion or disease of the central somatosensory nervous system', and peripheral neuropathic pain is defined as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system* is accepted; however it appears in much routine pain practice that most patients have no evidence of such a lesion, beyond the assumption that the presence of otherwise unexplained pain implies a lesion, for which there is no evidence beyond the presence of pain. It is unclear therefore whether the evidence base applies to patients who have a lesion manifest by clinical data other tan pain, and those with pain with no such lesion; I suggest that in routine practice the latter is the larger group. I think the guideline should acknowledge and discuss this matter. Secondly there is the matter of drug combinations; in particular analgesics and centrally active non-analgesic drugs. I think in general that nociceptive pain responds to analgesics and neuropathic or non-nociceptive pain responds to centrally active non-analgesic drugs. Furthermore the	This definition of neuropathic pain is from IASP 2011 which includes pain caused by either a lesion or disease. The guideline applies to pain that fits this definition and so patients with either a lesion or disease causing the pain are the target of this guideline. There was not enough evidence for the guideline development group (GDG) to make specific recommendations or comment on analgesics versus centrally active non-analgesics in general.

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					response of neuropathic pain to centrally active non-analgesics is enhanced by cessation of analgesics especially opiates. Medication overuse headache provides a good example of this. The evidence outside headache practice for this opinion is essentially lacking but this should not prevent discussion of this important matter and recommendation for further research.	
British Pain Society	5	Full	3	11 - 25	The document contains some guidance on assessment and diagnosis of neuropathic pain as per British Pain Society guidelines and The Map of Medicine. 1 Would it not be advantages to include here simple screening tools (LANSS or DN4), which can aid the diagnosis for the non specialist? 2 1. British Pain Society. Initial Assessment and Early Management of Pain. London: Map of Medicine, 2012. The Map of Medicine and the British Pain Society. Neuropathic Pain. England View. London: Map of Medicine, 2013 2. Bennett MI et al. Using screening tools to identify neuropathic pain. Pain 2007; 127: 199–203. These diagnostic tools can be added to the appendix and will not significantly lengthen the Guideline.	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Royal College of Anaesthetists - Faculty of Pain Medicine	12	Full	3 and general	16	Neuropathic cancer pain can also be caused by direct also direct invasion/compression of neural structures. This is probably more frequent than chemotherapy induced an antigen induced neuropathies. Distinction should be made between acute and chronic neuropathies associated with chemotherapy use (including in the analysis of trials)	This cause of neuropathic cancer pain has now been added to this section.
Royal College of Anaesthetists -	13	Full	3	28	The term "inconsistency" is misleading. The Smith 2012 reference does not support this statement – do the	The reference to inconsistency has been removed.

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Faculty of Pain Medicine					guidelines mean the Smith 2010 reference that is cited in the reference list. And, actually, a prevalence difference between 6% and 8% is small, suggesting consistent rather than inconsistent findings. The Smith 2010 reference quotes studies with a much larger range of prevalence estimates (1% to 17%)	
Napp Pharmaceuticals Ltd	4	Full	4	28	"Commonly used pharmacological treatments include ....and opioid analgesics". The guideline recognises that many options are available to manage this difficult type of pain. However the guideline appears to be very selective about the way in which the evidence has been applied for each class of medicine.	A full explanation to how the guideline development group (GDG) considered the included evidence for each intervention is available in the evidence to recommendations sections within the guideline.
Eli Lilly and Company	1	Full	5	16 - 20	We agree with the general recommendation that prescriber's should use a drug's summary of product characteristics and British National Formulary to inform decisions made with individual patients and should include consideration of special warnings, precautions for use, contraindications and adverse effects. However, these sources of data may be less reliable for off-label medications. We believe the guideline would benefit prescribers and patients if specific warnings related to the use of tricyclic antidepressants in patients with cardiovascular disease were mentioned in the guideline either alongside the recommendations or as a footnote.	The introduction of the guideline highlights that the summary of product characteristics (SPC) and British National Formulary (BNF) should be used to inform treatment decisions with individual patients. However, under each recommendation where a drug has been recommended off-label, there is a statement acknowledging this and highlighting that the prescriber should follow relevant professional guidance. NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
Grünenthal Ltd	2	Full	5	16 - 20	Given that prescribers referring to capsaicin cream's SPC and the BNF will note that '- Patients using Axsain for the treatment of painful diabetic peripheral polyneuropathy should only do so under the direct supervision of a hospital consultant who has access to specialist resources', is it appropriate to recommend this product for 'broad' use by non-specialist prescribers? The BNF states 'capsaicin is licensed for neuropathic	A footnote has been added to clarify the licensing for capsaicin cream.

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					pain (but the intense burning sensation during initial treatment may limit use). Given the likelihood of considerable impact on treatment adherence, we question the recommendation to consider this product in preference to the 5% lidocaine plaster which is not subject to this side effect and produces only a few administration site reactions.	
Grünenthal Ltd	3	Full	5	21 - 23	The NICE methods guide (section 6.3.6.3) reflects the General Medical Council (GMC) guidance on Good practice in prescribing and managing medicines and devices which states that 'Prescribing unlicensed medicines may be necessary where there is no suitably licensed medicine that will meet the patient's need'. The recommendation of two treatments (amitriptyline and nortriptyline) unlicensed for the management of pain, whilst failing to consider and recommend licensed treatments (e.g, lidocaine 5% medicated plaster or tapentadol) is clearly in breach of both NICE methods and GMC guidance on prescribing. **Grünenthal request that the recommendations be reconsidered in accordance with NICE methods to avoid exposing prescribers to the additional burden (obtaining informed consent) and responsibilities associated with off-label prescribing.**	Thank you for your comment. This recommendation has now changed and amitriptyline, pregabalin, duloxetine or gabapentin are now recommended as initial treatment options. Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin.

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						Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings. NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
British Pain Society	6	Full	5	24 - 26	The draft document suggests informed consent should be documented for off-label use of medicines. For the drugs mentioned it is accepted practice, so whilst the patient should be informed of the "off-label" use, we do not believe that it is feasible and realistic for consent to be documented.	This is standard wording in NICE guidelines derived from the General Medical Council's Good practice in prescribing medicines – guidance for doctors. For further information also see section 9.3.6.3 of the NICE Guidelines Manual 2012.
Napp Pharmaceuticals Ltd	5	Full	5	6	Further information should be made about when to refer to specialist treatment. The current guidance from NHS England is for the improved management of patients in primary care. This guideline does not seem to be in-line with this sentiment and treatment options that could be used by GPs and non-specialists are being reserved or restricted. The choice of treatments is being restricted on the one-hand based on the evidence, and on the other-hand treatments are being recommended based on poor or weak evidence.	The guideline development group (GDG) have specified the situations when it is appropriate to refer to specialist pain services and/or a condition-specific service. The GDG felt that there was enough evidence to support the drugs that are recommended in the guidance. They felt that there was not enough evidence on other drugs to recommend their use in non-specialist settings.
British Medical	1	Full	5	21	This section refers to the GMC guidance and rightly	All NICE guidelines recommend that prescribers

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Association					points out that the prescriber takes responsibility for the off label use of medications. However, it simply copies that guidance saying that documented informed consent needs to be obtained, and it is not helpful for prescribers (who are supposed to follow NICE guidance) to be referred to external guidance without any commentary. When referring to the best decisions for individual patient, it mirrors the GMC guidance again without considering the fact that NICE is looking at costs as well.	should follow professional guidance and also refer to the GMC's guidance on good practice in prescribing.
Royal College of Anaesthetists - Faculty of Pain Medicine	14	Full	5	27	British Pain Society guidance for the use of unlicensed medicines could be mentioned	It is not accepted practice within NICE guidance to discuss existing guidance or copy over sections verbatim from other pieces of guidance. Please see section 9.3.6.3 of the NICE Guidelines Manual 2012.
Royal College of Anaesthetists - Faculty of Pain Medicine	15	Full	6		Table 1 – seems out of place here, having a list of drugs not licensed for neuropathic pain before any specific drugs are mentioned in the text. What about the other drugs mentioned in Table 3, for example, and their licenses?	Thank you for pointing this out. Table 1 has now been deleted from the guideline.
British Pain Society	7	Full	6	15 - 17	Do specialist pain services include community based pain services (if they otherwise fall within the definition of specialist pain services)	Community-based pain services would be included in specialist pain services if they provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.
Royal College of General Practitioners	6	Full	6	15 - 17	Do specialist pain services include community based pain services (if they otherwise fall within the definition of specialist pain services) **(MJ)**	Community-based pain services would be included in specialist pain services if they provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.
Royal College of Nursing	4	Full	6	15 - 17	Specialist pain services include community based pain services	Community-based pain services would be included in specialist pain services if they provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.
Royal College of Nursing	5	Full	6	15-17	Do specialist pain services include community based pain services (if they otherwise fall within the definition of specialist pain services)	Community-based pain services would be included in specialist pain services if they provide comprehensive assessment and multi-modal management of all types of pain, including neuropathic pain.
Royal College of General	7	Full	6	9-10	The guidelines are right to recognise the different care pathways appropriate in different settings. We suggest	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for

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Practitioners					this might be an appropriate point to include a paragraph on taking particular care with using gabapentin and pregabalin in patients with known substance abuse issues. **(SEG)**	dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Grünenthal Ltd	4	Full	8	10-13	Given the stated desire to take patient preference into account, and the fact that all drugs only work in the minority of patients, the guideline should seek to make more treatment choices available.	The guideline development group (GDG) did not feel there was enough evidence to support recommendations on a number of the drugs. Drugs for which the GDG felt enough evidence existed to suggest they were better than placebo and represented value for money have been recommended.
Grünenthal Ltd	5	Full	8	5-7	Given the favourable attributes of the 5% lidocaine plaster discussed above, Grünenthal request that the GDG reconsider whether they would be confident that most patients would choose capsaicin cream and to consider recommending the 5% lidocaine plaster as a non-systemic treatment option for the treatment of neuropathic pain.	The guideline development group (GDG) did not feel that there was sufficient evidence to make recommendations about lidocaine. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
Pancreatic Cancer UK	2	Full	10	4-11	Through the Pancreatic Cancer UK Support Line we hear from many patients who have never been referred to a pain specialist or only after the have experience considerable pain for some time. We believe if this recommendation is implemented successfully it could considerably improve the quality of life of people with pancreatic cancer. However, we have concerns about how this will be adequately resourced on the ground to ensure that	NICE recognise that this is an important issue. However, NICE is only able to make recommendations on where referral to a pain specialist may be appropriate. These recommendations will be incorporated into implementation tools produced by NICE to support NHS organisations in implementation of this guidance but NICE is unable to provide guidance on resourcing arrangements.

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					pancreatic cancer patients have access to this level of care.	
Royal College of Anaesthetists - Faculty of Pain Medicine	16	full	10	Footnote 1	HIV services to list of condition-specific services	Condition-specific services encompass HIV-specific services. It is not possible to list all conditions that have specialist services.
Action on Pain	1	General			In considering the complete document we could not fail to notice the lack of awareness on how neuropathic pain can impact on individuals in many different ways. From our experience gained over the past fifteen years it is clear that the treating healthcare professional needs to have the best possible range of medications available to them. Yet the evidence presented in some cases as to why they should not be recommended is at best sketchy being unable to stand up to rigorous challenge. The document states that due to potential adverse effects decisions should be taken at individual patient level which on the surface is totally reasonable. Yet a patient could well be put in a position where the list of medications recommended all produce adverse effects. The doctor is then put in a difficult position with such restriction having the potential to cost the patient his/her job. We therefore conclude and strongly recommend that this document needs to be drafted to better reflect the individual needs of patients	The guideline development group (GDG) strongly felt that neuropathic pain has a significant impact on individual patients. Consequently, they prioritised the global impact that neuropathic pain has on the patient as well as patient-reported functioning as outcomes critical to their decision-making about which drugs to recommend. The key principles of care recommendations have now been amended to address issues related to patients.
Action on Pain	2	Full	10	1.1.2	We are deeply concerned that 1.1.2 appears to completely replace 1.4 to 1.9 from the previous document. We believe that the Panel has demonstrated a worrying lack of insight with regard to the social issues that can influence the impact of neuropathic pain on an individual. That the sparse and inadequate patient representation on the panel has failed to address this point only adds to our concern. Additionally the problems that lack of sleep due to neuropathic pain have largely been omitted. For this document to have any real credibility or impact we would urge the panel to give due weight to these issues by including 1.4 to 1.9 in the	The guideline development group (GDG) strongly felt that neuropathic pain has a significant impact on individual patients. Consequently, they prioritised the global impact that neuropathic pain has on the patient as well as patient-reported functioning as outcomes critical to their decision-making about which drugs to recommend. The guideline development group (GDG) have amended the recommendations to emphasise that these factors should be taken into account (for example, by including that impact on daily activities

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					finalised advice document	and other lifestyle factors should be taken into account when selecting treatment). The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. NICE considers patients representation on the GDG to be vital to the development of clinical guidelines. Following the NICE Guidelines Manual 2012, at least two patient/ carer members are appointed to each guideline. The Public Involvement Programme (PIP) at NICE works hard to promote patient/ carer involvement and support those who are appointed to our committees. All GDG members are equal and all recommendations are generated through consensus amongst the full group.
Royal College of General Practitioners	8	Full	117	3	We suggest that under recommendation 1.12 "take into account" should also include the wording "take into account whether the patient misuses drugs in making a decision about prescribing," **(SMAH)**	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Royal College of General Practitioners	9	Full	117	3 (table)	We strongly suggest that mention is made of considering substance abuse issues in recommendation 1.1.2 (bullet point 3). **(SEG)**	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for

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						a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Royal College of General Practitioners	10	Full	115	8 (table)	The guidance is right to highlight 'different lifestyle factors' in considering a treatment pathway. It also rightly mentions comorbidities and vulnerability to specific adverse effects. This would be another good place to highlight substance misuse as a specific factor to consider in the choice of treatment. **(SEG)**	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
NHS England		Full	General		It is recognized that assessment of all relevant biopsychosocial factors, and appropriate support, is of paramount importance in chronic pain. Whilst the scope of this guidance is clearly pharmacological treatment, we should be pleased to see encouragement towards a holistic approach.	The key principles of care recommendations have now been amended to address issues related to patients.
NHS England		Full	General		Patient choice and experience should be given more emphasis.	The key principles of care recommendations have now been amended to address issues related to patients.

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NHS England		Full	General		Guidance on the length of time for which treatments should be tried may be helpful.	The GDG considered this issue but concluded that they could not make helpful recommendations about length of treatment based on the available evidence (included RCTs had a median follow-up of 8wk and a maximum of 35wk) and also recognising that length of treatment will be influenced by the individual circumstances of each patient. In light of this, they decided to emphasise the importance of regular review (including assessing the continued need for treatment) as part of each individual's treatment plan.
Pfizer	5	Full	10	3	In the original CG96 (2010), under the 'Principles of Care', the following recommendation was included: *1.1.2 Continue existing treatments for people whose neuropathic pain is already effectively managed.* We are concerned that this statement has been removed from the updated, draft guideline. We support the previous recommendation and are concerned that removal of this recommendation will lead to inappropriate switching of medication in patients whose neuropathic pain is effectively managed and who have attained a good quality of life on their current treatment. The suitability of switching pain medications, particularly in a non-specialist setting, requires careful consideration and no guidance is provided. Switching may be associated with a significant risk of losing pain control and as previously noted the titration and dosing for neuropathic pain medications can be complex, particularly if factoring in switching from one medication to another. As such, switching is likely to have a negative impact on patients and is in direct contrast to the current agenda of patient-centric care in the NHS.	The guideline development group (GDG) have now inserted a recommendation about continuing existing treatments for people whose neuropathic pain is already effectively managed. The important issue of switching medications was also considered by the GDG when developing the Key Principles of Care.

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					Pfizer requests that NICE re-instate and emphasise the recommendation to continue existing treatments for people whose neuropathic pain is already effectively managed.	
Pain UK	2	FULL	11	7	***"Continue existing treatments for people whose neuropathic pain is already effectively managed"*** has been dropped from this version of the Guideline. It needs to be re-instated.	The guideline development group (GDG) have now inserted a recommendation about continuing existing treatments for people whose neuropathic pain is already effectively managed.
Pain UK	3	General			Put back sections 1.1.4 through to 1.1.9 (page 13 onwards) from the original guideline – full version. These, from the original, are more clearly written than the new version.	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. A new guideline development group (GDG) was appointed for this full update and through interpretation of the evidence and GDG expertise, the GDG have arrived at new recommendations. The only sections that were missing from the previous sections 1.1.4 and 1.1.9 are various factors to take into account when selecting pharmacological treatments performing regular clinical reviews. These have now been added back in.
Shingles Support Society	4	General			RESTORE from the original guideline – full version - (starting on page 13) sections 1.1.4 through to 1.1.9 the information is much better detailed in the original Guideline.	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. The only sections that were missing from the previous sections 1.1.4 and 1.1.9 are various factors to take into account when selecting pharmacological treatments performing regular clinical reviews. These have now been added back in.
Pfizer	6	Full	10	3	In the original CG96 (2010), under the 'Principles of Care', the following recommendation was included:	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the

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					1.1.4 When selecting pharmacological treatments, take into account: • *the person's vulnerability to specific adverse effects because of co-morbidities* • *safety considerations and contraindications as detailed in the SPC* • *patient preference lifestyle factors (such as occupation)* • *any mental health problems (such as depression and/or anxiety)* • *any other medication the person is taking* We are concerned that this recommendation has been removed from the updated, draft guideline. Given that this guideline is focussed on pharmacological prescribing by non-specialists, we feel that it is important to give additional guidance around factors to consider when choosing treatment. We are particularly concerned with the absence of the wording "any mental health problems (such as depression and/ or anxiety)" in section 1.1.4 (CG96, 2010) because some neuropathic agents are also licensed for depressive symptoms and generalised anxiety disorder. At present in the guideline, there is no clear guidance to help a clinician select the appropriate initial treatment or subsequent treatments. The absence of section 1.1.4 (CG96, 2010) reflects the lack of patient focus in these guidelines, which in turn may translate into clinical practice. Pfizer requests that NICE re-instate section 1.1.4 (CG96, 2010) recommendation, giving due recognition to the fact that the pharmacological options	new guidance should be considered as updating those in CG96. The only sections that were missing from the previous sections 1.1.4 and 1.1.9 are various factors to take into account when selecting pharmacological treatments performing regular clinical reviews. These have now been added back in.

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					recommended in this guideline can have a significant positive or negative impact on the patient and their quality of life beyond the objective of pain control.	
British Medical Association	2	Full	10	4	This recommendation does not offer any guidance or support for primary care treatment and allowing time for this to work. Given that the majority of studies looked at the effects and tolerability after 20 weeks or more, and that pain management does not typically have quick responses, this seems a rather simplistic statement.	The GDG considered this issue but concluded that they could not make helpful recommendations about length of treatment based on the available evidence (included RCTs had a median follow-up of 8wk and a maximum of 35wk) and also recognising that length of treatment will be influenced by the individual circumstances of each patient. In light of this, they decided to emphasise the importance of regular review (including assessing the continued need for treatment) as part of each individual's treatment plan.
Pain UK	4	FULL	10	4	If is necessary to have the suggestion to the non-specialist reader that the patient needs to be referred, could it be PRECEDED by a statement that "There are many treatments that can be used outside specialist centres". And something about treating patients EVEN WHEN you have decided to refer them on. Without such encouragement, the Guideline seems to suggest that patients who need to be referred should not be treated whilst waiting for the specialist appointment! Not a good idea…	The recommendation on referral has now been moved to 1.1.2. The recommendation about things to take into account when agreeing a treatment plan (which includes the statement about non-pharmacological treatments) has now been moved to recommendation 1.1.1. NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
Shingles Support Society	5	FULL	10	4	It is inappropriate to START the 'management guidelines' by suggesting to the reader that the patient needs to be referred. This paragraph needs to be well down the document AFTER the usual management has been described.	The recommendations have been reordered.
NHS England		Full	6	4	We recognize the scope of this document and welcome the statements on page 6; we suggest a strong recommendation for discussion/advice or referral to a specialist centre, for consideration of treatment beyond	The guideline development group (GDG) felt it was most appropriate for clinicians to 'consider referring' as it would not always be appropriate to refer patients to a specialist setting if their treatment was being

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					these guidelines, in refractory cases. Pain interventions exist (e.g. neuromodulation) and this may not be understood or known by professionals working outside of a specialist centres.	successfully managed outside of specialist pain services.
Pain UK	5	FULL	10	15	It is important that it is fully explained to the patient when a drug is being used off licence. Patients frequently report that they have been 'fobbed off' with an anti-depressant – or that there has been as mistake as they do not have epilepsy.	In the introduction of the guideline there is a section called 'Drug recommendations' which states that patients should provide informed consent if drugs are used for indications for which they do not have a market authorisation. Furthermore, the footnotes on each drug that is recommended off-label emphasise the importance of obtaining and documenting informed consent.
Shingles Support Society	6	FULL	10	15	Extend this bullet point slightly, to mention that this is particularly relevant where a drug is being used off licence. Too many patients tell our helpliners that they think they have been given the wrong drug as it is an antidepressant or an anti-epileptic.	In the introduction of the guideline there is a section called 'Drug recommendations' which states that patients should provide informed consent if drugs are used for indications for which they do not have a market authorisation. Furthermore, the footnotes on each drug that is recommended off-label emphasise the importance of obtaining and documenting informed consent.
Pain UK	6	FULL	10	21	Separate this into two bullet points. The first to say 'Self-management techniques including for coping with pain." The second to say "treatments that may be needed for coping with adverse effects." And include a mention of OTC treatment for adverse effects.	The guideline development group (GDG) felt this was not necessary to split these into two bullet points.
Shingles Support Society	7	FULL	10	21	Separate this into two bullet points. The first to say 'Self-management techniques including for coping with pain." The second to say "treatments that may be needed for coping with adverse effects." NB these may be prescribed or bought OTC e.g. laxatives	The guideline development group (GDG) felt this was not necessary to split these into two bullet points.
Pain UK	7	FULL	11	3	'Surgery' should be replaced with 'specialist services' in order to cover a wider choice of treatments.	Surgery was listed as an example so it is implicit that there are other choices of non-pharmacological treatments. This section has now been amended to be clearer.
Shingles Support Society	8	FULL	11	3	Change 'surgery' to 'specialist services' so that it covers a wider range of possibilities.	Surgery was listed as an example so it is implicit that there are other choices of non-pharmacological treatments. This section has now been amended to be

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						clearer.
Pancreatic Cancer UK	3	Full	11	7	If some receives a nerve block, they are usually instructed to stop opiate analgesia for example, as this would negate the effect of whether the nerve block has worked or not. How would this be considered in the overlap described in this statement?	The guideline development group (GDG) considered this to be an issue for specialist care services.
Shingles Support Society	9	FULL	11	7	This might be the point to re-introduce the statement from the original guidelines which has been removed. "Continue existing treatments for people whose neuropathic pain is already effectively managed""	The guideline development group (GDG) have now inserted a recommendation about continuing existing treatments for people whose neuropathic pain is already effectively managed.
UK Clinical Pharmacy Association	2	Full	11	12	It would be useful to include recommendations as to how long drugs should be tried for before determining if beneficial or should be abandoned, defining what is meant by 'regular'.	The guideline development group (GDG) felt it was inappropriate to make generic recommendations about the suitable length of time which treatments should be attempted. They felt this would be different for each patient and should be part of an individual's treatment plan.
Napp Pharmaceuticals Ltd	6	Full	115/116	Other considerations	We agree with the GDG that both early and regular clinical reviews are important. Recording of symptom control and treatment is essential. More clinical training, better use of pain assessment and recording of pain signs and symptoms is needed.	Thank you for your comment
British Pain Society	8	Full	11	12-18	Section 1.1.5 – the review section does not now include reviewing the mood (most commonly anxiety and/or depression) of the patient or their sleep pattern. Many of these patients have psychological symptoms and sleep disturbance so this is a vital part of the review. These specific secondary parameters may also determine the sequence of order of some monotherapies, or the most appropriate combination therapies ie:	The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological illness' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).

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					- co-existent depression may prioritise use of an anti-depressant - co-existent anxiety may prioritise use of a gabapentinoid - co-existent sleep disturbance may prioritise use of a night time sedating anti-depressant like amitriptyline or nortriptyline rather than duloxetine.	
Napp Pharmaceuticals Ltd	7	Full	11	12-18	This short section would be better before section 1.1.3 More guidance should be given to the assessment of pain, suggestions on pain scales, recording pain scores, e.g. use the BPI scale, 0-10 scale etc. . Consider those patients who may have communication issues and those with co-morbidities	It was felt that this recommendation about introducing a new treatment (previously 1.1.3 but now 1.1.4) should occur before the recommendation about clinical review (previously 1.1.5 but now 1.1.6). NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis. NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
Pfizer	7	Full	11	12-18	In the original CG96 (2010), under the 'Principles of Care', the following recommendation was included: *1.1.9 Perform regular clinical reviews to assess and monitor the effectiveness of the chosen treatment. Each review should include assessment of:* • *pain reduction* • *adverse effects* • *daily activities and participation (such as ability*	The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6). The guideline development group (GDG) felt that sleep would be covered in daily activities and participation

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					to work and drive) • *mood (in particular, whether the person may have depression and/or anxiety)* • *quality of sleep* • *overall improvement as reported by the person* In the updated, draft guideline (CG96, 2013), this has been replaced with the following recommendation: *1.1.5 Carry out regular clinical reviews to assess and monitor the effectiveness of the treatment. Each review should include an assessment of:* • *pain control* • *impact on daily activities and participation* • *adverse effects and* • *continued need for treatment* We are concerned that once-again patient-oriented outcomes have been removed from the review recommendations. Mood, quality of sleep and overall improvement as reported by the person are all components that are particularly important to the patient and should routinely be assessed by the physician. Furthermore, NICE have neglected to provide guidance on what 'regular' means in the context of clinical review or what level of 'effectiveness' should prompt a physician to consider a new treatment or indeed a referral to a specialist. It is also worth noting that the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends that function and mood should be included as core patient-reported outcomes (Dworkin,	but have added 'including sleep' after this to be clear.

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					2005) as the presence and increased severity of pain often results in reduced function and increased mood disturbance (Geisser, 2000, cited in van Seventer, 2011). Equally, sleep is another outcome that is affected adversely by pain (Smith, 2004, cited in van Seventer, 2011). Pfizer requests that NICE include the additional outcomes that are important to and reported by patients, as described in the previous version of CG96, as part of the clinical review. We request that NICE, in consultation with clinical experts for NeP and patients, provide more clarity around when clinicians should aim to have clinical reviews, how often and when it would be appropriate to change treatment or refer a patient.	
Primary Care Neurology Society	2	Full	11	12-18	Regular review is advised but reference to mood and quality of life indicators are excluded.	The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).
Pain UK	8	FULL	11	15	"Sleeping" and "Mood" bullet points are needed. This will help the clinician to ask about these issues which are really important for the patient.	The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).
Shingles Support Society	10	FULL	11	15	More bullet points are needed in this section re "sleeping" and re "mood" – the clinician may need to be prompted to ask about these issues are they are really important for the patient.	The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. The guideline development group (GDG) changed

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						'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).
NHS England		Full	11	15	Psychological state, including at least mood and sleep should also be assessed.	The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).
Royal College of General Practitioners	11	Full	11	12-18	Section 1.1.5 – the review section does not now include reviewing the mood of the patient or their sleep pattern. Many of these patients have psychological symptoms and sleep disturbance so this is a vital part of the review. **(MJ)**	The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).
Royal College of Nursing	6	Full	11	12-18	Section 1.1.5 need to include mood and sleep assessment. Many patients have psychological symptoms and sleep disturbance so assessment is vital.	The guideline development group (GDG) felt that sleep would be covered in daily activities and participation but have added 'including sleep' after this to be clear. The guideline development group (GDG) changed 'comorbidities' to 'physical and psychological wellbeing' in the recommendation about considerations when determining treatment to be clear this is about both types of comorbidities (recommendation 1.1.6).
Grünenthal Ltd	6	Full	11	24-25	It should be made clear that guideline recommends two first line treatments which aren't licensed for the management of pain • one (amitriptyline) with no evidence in any of the	There is a footnote on each recommendation where drugs are recommended for an indication that they are not licensed for.

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					critical efficacy outcomes and inconclusive evidence on its effectiveness and a low probability of its cost-effectiveness in reducing peripheral neuropathic pain • the other (nortriptyline) based on 3 RCTs in a total of 187 patients	
Pfizer	8	Full	11 12	24-25 1-5	There is increasing evidence to demonstrate that pregabalin is effective in patients who are refractory to TCAs (Freynhagen, 2007; Stacey, 2008, ; Lampl, 2010) and gabapentin, including one randomised, controlled study (Tanenberg 2011) and 9 prospective, non-randomised studies (Stacey 2008, Toth 2010, Freynhagen 2007, Douglas 2008, Allen 2005, Hanu-Cernat 2005, Lampl 2010, Morera-Dominguez, 2010, Solaro 2009). As such, Pfizer supports the recommendation for pregabalin to be considered in patients who have previously tried and failed prior TCA or gabapentin treatment. However, there is very little evidence to demonstrate that switching between amitriptyline and nortriptyline results in positive outcomes (Saarto, 2007). Such an approach would delay appropriate treatment. The original CG96 (2010) suggests nortriptyline (or imipramine) only as an alternative to amitriptyline in the event of lack of tolerability, thus recognising the lack of efficacy for first-line or refractory use: *"If amitriptyline* as first-line treatment results in satisfactory pain reduction but the person cannot tolerate the adverse effects, consider oral imipramine* or nortriptyline* as an alternative."*	This recommendation has now changed and amitriptyline, pregabalin, duloxetine or gabapentin are now recommended as initial treatment options. Nortriptyline is no longer recommended in the guideline. The references provided did not meet the inclusion criteria specified in the review protocol.

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					On page 66 of the draft guideline (CG96, 2010), under 'evidence to recommendations', it states that: *"The GDG also commented that it is an alternative drug for people who cannot tolerate some of the adverse effects associated with amitriptyline."* Furthermore, Pfizer is particularly concerned about the recommendation of nortriptyline as a first-line and refractory treatment option in its own right because there is a lack of evidence (Saarto 2007), lack of clinical experience in this indication and it is not licensed in this indication. Pfizer notes that the evidence for nortriptyline in the economic model appears to come from a single, small trial in which nortriptyline was compared to gabapentin in only 70 patients. In this trial, the efficacy was found to be similar between nortriptyline and gabapentin, but gabapentin was better tolerated. Comparatively, the evidence-base on which the pregabalin inputs in the economic model are based is much more substantial. A total of 14 placebo-controlled RCTs were included for pregabalin, involving 5,816 patients. According to the meta-analysis performed to inform the economic analysis, pregabalin is both more effective and better tolerated than nortriptyline. It is also worth noting that the first-line recommendation for nortriptyline is also not supported by the health economic evidence (please see comment**.** below). Indeed in the non-dose adjusted analysis, nortriptyline is	

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					dominated by pregabalin and yet pregabalin is only recommended after nortriptyline has been tried. The evidence to support the use of nortriptyline as an effective treatment for all neuropathic pain is weak (Saarto, 2007). In addition, there is no data to support the use of nortriptyline in patients refractory to either amitriptyline or gabapentin. Furthermore, nortriptyline is not licensed for either peripheral or central neuropathic pain, let alone all neuropathic pain. Therefore, Pfizer requests that nortriptyline is only considered as an option after licensed, evidence-based and more cost-effective (according to the non dose-adjusted analysis) options, such as pregabalin have failed. Indeed, Pfizer questions whether nortriptyline should be specifically recommended in the guideline, but left to clinical discretion for those patients where the clinicians has strong reason to believe a second TCA would be appropriate (for example in patients who have previously experienced a good response to amitriptyline, but are unable to tolerate it).	
British Pain Society	9	Full	11	23	The separation of the diabetic population into a separate group in the previous guidance was very distinct. What new evidence has made this no longer the case? This should be clearly stated.	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. A new guideline development group (GDG) was appointed for this full update and through interpretation of the evidence and GDG expertise, the GDG have arrived at new recommendations. The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be

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						presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings.
GW Pharmaceuticals plc	1	Full	11	23	The guidelines suggest that e.g. Duloxetine should be offered as treatment for all forms of neuropathic pain (except trigeminal neuralgia) despite a more or less complete absence of evidence of its effectiveness in central neuropathic pain, especially that of multiple sclerosis. There is a good level of high quality clinical trials and long-term data confirming the efficacy and safety of Sativex in this setting. This lack of an evidence base for such a key recommendation is disappointing.	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings. There was an overall lack of evidence on most drugs for central pain which is why the GDG felt it was

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						appropriate to make recommendations based on the evidence for all neuropathic pain to apply to central pain. The guideline includes all trials on cannabis sativa extract which met the inclusion criteria specified in the review protocol. The GDG's views on the quality of this evidence and the inferences that can be drawn from it are detailed in the guideline.
GW Pharmaceuticals plc	2	Full	11	23	As a general point, the guidelines implicitly determine that all forms of neuropathic pain are essentially similar. This is not in line with international regulatory guidelines or practice, nor with a reasonable approach to the neuropathology of neuropathic pain. This stakeholder would strongly make the point that the evidence supporting the use of Sativex in the treatment of central neuropathic pain due to multiple sclerosis, in a setting where other treatments have failed, can be described by the recent conclusion of Tanaescu et al. (Exp Opin Drug Metab Toxicol. 2013. (DOI: 1517/174255.2013.795542) who stated following their review of the evidence in central neuropathic pain due to MS "nabiximols is an appropriate therapy for pain patients who tend to be particularly resistant to pharmacological interventions".	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings. Tanaescu et al. (Exp Opin Drug Metab Toxicol. 2013) was not included as it is an opinion paper and did not meet our inclusion criteria.
Pfizer	9	Full	11 12	23 3-5	The draft guideline recommends duloxetine as a refractory option in patients with all types of neuropathic pain, with only a footnote acknowledging that duloxetine is licensed for diabetic peripheral neuropathic pain	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. Final approval prior to publication is required from

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					(DPN). This is a departure from the original CG96 (2010), which separated DPN and made a recommendation for duloxetine exclusively within this subgroup of NeP. Duloxetine does not have a licence for any peripheral neuropathic pain (apart from DPN) or any central neuropathic pain. In addition, there is very limited evidence outside the licensed sub-group (Lunn 2009). It is therefore inappropriate to recommend duloxetine as a treatment option for all neuropathic pain when it is unlicensed for every type of neuropathic pain apart from DPN, and pregabalin is a licensed alternative with a licence in all peripheral neuropathic pain and all central neuropathic pain. <u>Pfizer suggests that it would be more appropriate therefore to recommend duloxetine only as an option in DPN patients.</u>	NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings. It is standard in

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						NICE guidelines to include details about drugs recommended off-label in footnotes of recommendations (see section 9.3.6.3 of The guidelines manual 2012). The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings.
Primary Care Neurology Society	3	Full	11	23	The lumping together of diabetic neuropathic pain has led to potentially complicating management of diabetic neuropathic pain.	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example,

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						may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings.
Royal College of General Practitioners	12	Full	11	23	I preferred the separation of the diabetic population into a separate group in the previous guidance because their potential for risk from side effects from medication was high **(MJ)**	When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings. This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96.. The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone.
Royal College of Nursing	7	Full	11	23	Those patients with diabetes have a higher risk of medication side effects from medication so should be separated.	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on

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						diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings. There are risks related to many underlying causes of neuropathic pain. These should be considered on an individual patient basis for all patients, including those risks for specific patients with painful diabetic neuropathy.
British Medical Association	3	Full	11	24	The treatment recommendations are brief and succinct, but could, as per our first comment, contain more information, i.e. about costs. For example, amitrip is unlicensed, effective, and low cost; gabapentin is more effective, still cost effective and licensed; nortriptyline is unlicensed, slightly better tolerated than amitrip, but incredibly expensive (more than pregabalin). The suggestion to try all three of these seems wrong - as amitrip and nortrip are so similar. The guidance does deal with this issue in various points throughout the document however it would seem sensible to gather it all as a summary. The guidance on second line therapy does not seem to take into account that there is evidence that moving from gabapentin to pregabalin is not likely to be therapeutically significant. The choice of drugs appears to be totally different to other pain management guidance from NICE which came out in favour of pregabalin first. There is no comment on this.	The recommendation for initial treatment no longer includes nortriptyline. The recommendations are intended to be short and provide a set of active statements for health care professionals. Information on costs, clinical effectiveness and other factors the guideline development group (GDG) took into consideration can be found in the evidence to recommendations sections within the guideline and the evidence tables in the appendix. This guideline is a full update of CG96. For this reason, in conjunction with new GDG which was appointed to this guideline, a new approach to reviewing and interpreting the clinical and cost effectiveness evidence was taken. The guideline development group (GDG) did not feel there was sufficient evidence to consider the effect of

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						switching from one specific drug to another.
Eli Lilly and Company	2	Full	11	24	The wording of the recommendations for amitriptyline and nortriptyline use the word "offer", implying a very high level of confidence in the evidence base for these treatments. We do not believe the evidence base for these agents is robust and supportive of their first-line position overall and in particular within various subpopulations such as patients with diabetic neuropathic pain: The evidence used in the cost-effectiveness analysis for both of these treatments is very limited: - For amitriptyline the data comes from 2 crossover trials involving a total of 89 patients. In one of these trials the patients also suffered from significant depression and amitriptyline was only reported to be significantly better than placebo in the most depressed patients. - For nortriptyline the evidence is from a single trial of 70 patients. By comparison the evidence base for duloxetine, gabapentin and pregabalin involved approximately 9,000 patients in trials based predominantly on a parallel group design.	This recommendation has now changed and amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. The guideline reviewed a significant amount of evidence assessing the efficacy and safety of amitriptyline. In total, 15 RCTs were included, providing good evidence that amitriptyline is effective in reducing pain. However, it is correct that only 2 of these trials reported results in a format that could be incorporated in the efficacy syntheses used to estimate treatment effect in the health economic model. The GDG was mindful of this, but it also noted that excellent agreement had been demonstrated between the dichotomous evidence on which the model relies and the broader evidence-base analysing continuous data on pain relief with amitriptyline (see appendix L). Therefore, the GDG concluded that the efficacy of amitriptyline is unlikely to be overestimated in the subset of trials on which the health economic model relies. Moreover, the GDG was aware that, being based on a smaller number of trials, the effect estimate for amitriptyline was more uncertain than those for some other drugs. However, it understood that this parameter uncertainty was appropriately propagated throughout the health economic analysis, with the consequence that model results reflected decision uncertainty in a comprehensive way. Being aware of this, it would not be appropriate to apply an additional, arbitrary, qualitative judgement about the adequacy or otherwise of the amount of data on which the model relied. The recommendation to use nortriptyline has been

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						removed from the guideline.
Pain UK	9	FULL	11	24	Amitriptyline and nortriptyline are both TCAs and are not used at the same time, however either of these of these may be used together with gabapentin. This will follow the routine practice, where clinicians use a TCA with an anti-epileptic if one treatment alone is not giving the patient relief.	The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy.
Primary Care Neurology Society	4	Full	11	24	There are three initial treatments suggested namely amitriptyline, nortriptyline and gabapentin. The second stage then suggests that either Duloxetine or Pregabalin be used. A starting preference is not stated. It suggests that all three should be tried before moving to the second stage. No indication of what should be considered as a success or failure with a given drug is stated and so no clear advice is given as when to change from one to the next. No titration advice is included or any indication as to how long one drug should be tried before moving to the next. Clinically guidance on starting doses and titration is very important and so it would seem to be essential that this be included. As no guidance is given on when to stop a drug, or add one in or change to a new one, There is a good chance that sub-optimal levels of these three may be used leading to sub-optimal treatment and higher costs as patients are perambulated up the ladder of treatments. Titration is paramount to appropriate use of medications like Gabapentin and in inexperienced hands inappropriate titration can thus lead to unnecessary failure of its use and so lead on to a more expensive	This recommendation has now changed and amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. . NICE guidelines do not normally include dosages for recommended drugs. This level of detail is found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug. The dosages required for each patient will be assessed on an individual patient basis. The guideline development group (GDG) felt it was inappropriate to make generic recommendations about the suitable length of time which treatments should be attempted. They felt this would be different for each patient and should be part of an individual's treatment plan. The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy. The GDG felt there was not enough evidence that met the inclusion criteria specified in the review protocol to support recommendations about either lidocaine or tapentadol.

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					option at an inappropriate time. No advice is given on combining tricyclics and gabapentin. The use of two tricylics at stage one is not usually clinically appropriate . If one fails the other will usually fail as well. The exception is if somnolence occurs with amitriptyline, less may occur with nortriptyline. Combination therapy is always a problem as few trials are available but tricyclics and gabapentin work on different pain pathways and so, not considering combination therapy before moving to stage two seems to be a poor option. Lidocaine and Tapentadol are exclude in this guidance, with no explanation. Advice on appropriate use of medications like Lidocaine plasters and Tapentadol would be very useful and prevent inappropriate use thereof.	The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
Shingles Support Society	11	FULL	11	24	Put amitriptyline and nortriptyline together as these are either/or (not both). One of these may be used together with gabapentin. This will follow the routine practice, where clinicians use a TCA with an anti-epileptic if one treatment alone is not giving the patient relief.	This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy.
Royal College of Anaesthetists - Faculty of Pain Medicine	17	Full	70	3	Recommendation 1.1.7 needs to exclude HIV-SN as well as trigeminal neuralgia (see above)	People with HIV associated neuropathy are not excluded from this guideline as it is possible that a person with HIV could present with neuropathic pain in non-specialist settings. However, we anticipate that a large proportion of people with HIV are likely to be treated in specialist settings and following discussion between the specialist clinician and the patient this is likely to be the most appropriate plan.

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Cambridge University Hospitals NHS Foundation Trust	3	Full	70	4	Recommendation 1.1.7 The choice of nortriptyline, amitriptyline and gabapentin might suggest that these three drugs act on separate physiological targets. We feel that this may cause confusion. For example, if amitriptyline was used as the first drug but was tolerated, but ineffective, at a therapeutic dose, changing to a drug with a similar mode of action such as nortriptyline would be unlikely to produce benefit. We would suggest it would be more logical to offer a choice of either amitriptyline or gabapentin as first line drugs, with nortriptyline/duloxetine or pregabalin respectively as second line choices, depending upon whether the first-line drug was discontinued due to adverse effects or lack of efficacy.	This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Napp Pharmaceuticals Ltd	8	Full	11	25 Reference 4	The footnote to this reference appears on the following page and as this is a reference to un-licensed use and hence an important issue relating to consent then the warning needs to be clearer and on the same page.	Thank you for bringing this to our attention. We will ensure that the recommendation and footnote appear on the same page in the final version of the document.
Eli Lilly and Company	3	Full	12	Footnote	We agree with the inclusion of the footnotes highlighting where treatments are not licensed for specific conditions.	Thank you for your comment
British Pain Society	10	Full	12	3-5	We agree with the recommendation of the alternative drugs duloxetine and pregabalin. It would be more appropriate to adopt a scientific rationale, and organise these options within pharmacological mechanisms rather than in random order. For example, if first-line antidepressant does not work – try duloxetine, and if gabapentin does not work - try another gabapentinoid such as pregabalin. The sequence should take into account the parameters mentioned in point 4 above (anxiety, depression and sleep disorder)	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. The guideline development group (GDG) felt that there was not enough evidence to organise the options into pharmacological mechanisms and recommend which drugs work after another has not been effective.

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UK Clinical Pharmacy Association	3	Full	12	3-5	If a first tricyclic antidepressant (TCA) is not effective, is there a rationale for trying a second? We can see the sense in using where tolerability is an issue but after use of both a TCA and gabapentin, perhaps referral into a specialist service is more sensible than continuing to persevere with pharmacological options.	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
UK Clinical Pharmacy Association	4	Full	12	3-5	Given the street value and abuse potential of the gabapentinoids (gabapentin and pregabalin), consideration should be given to avoiding these agents in patients with a history of recreational drug abuse and those prescribed opioid substitution therapy. A useful reference (relating to management of pain in secure settings) can be found via: http://www.nta.nhs.uk/uploads/persistentpain.pdf	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Eli Lilly and Company	4	Full	12	1-2	We question the benefit of using another tricyclic antidepressant in patients who have failed on either nortriptyline or amitriptyline. The interpretation of the evidence by the GDG suggests that amitriptyline is more efficacious yet less well tolerated than nortriptyline. On this basis: - It is not logical to prescribe a less effective agent (nortriptyline) where a more effective agent (amitriptyline) has proved ineffective. - It is not logical to trial a less well tolerated agent (amitriptyline) in patients who have not tolerated nortriptyline We consider that if patients fail on a tricyclic antidepressant then the next treatment option should be from a new class with a new mechanism of action and	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.

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					side effect profile rather than another treatment from the same class.	
Royal College of General Practitioners	13	Full	12	3-4	Is there any evidence to show the efficacy of amitriptyline or nortriptyline is different? (I can understand swapping on basis of side effects only) **(MJ)**	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. .
Royal College of Nursing	8	Full	12	3-4	What is the evidence for a difference in efficacy of amitriptyline or nortriptyline? Is this switch because of side-effect profile only rather than efficacy?	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Grünenthal Ltd	7	Full	12	8-9	The proposed recommendation should be justified in light of the fact that, despite no change in the evidence base, in CG96 the GDG agreed that there is limited, moderate-quality evidence indicating that topical capsaicin has no efficacy for pain reduction or global improvement for neuropathic pain overall.	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. Accordingly, this guideline presents a complete reappraisal of the available evidence on pharmacological treatment of neuropathic pain. Unlike CG96, this guideline used network meta-analysis, where it was appropriate, which combines all the evidence for multiple treatments into one synthesis and can be particularly helpful where there are few head-to-head trials, as is the case for neuropathic pain. Furthermore, unlike the CG96, a dedicated de novo economic model was developed to assist the GDG's decision making.
Napp Pharmaceuticals Ltd	9	Full	12	3	The recommendation states switching to duloxetine or pregabalin. Combination therapy has also been shown to be effective at this stage. In some patients introducing a small amount of oxycodone (SR) with gabapentin has shown an improvement in pain control compared to gabapentin alone. (http://www.ncbi.nlm.nih.gov/pubmed/18262450) No mention is made of combination therapy in any of the treatment recommendations. There are opportunities for	The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy.

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					better pain management and better tolerability when lower doses are used in the combination setting. This seems a little at odds with the statements on page 15 which clearly mention combination therapy.	
Pain UK	10	FULL	12	3	It is not clear in the current wording that amitriptyline and nortriptyline can be tried alone or with gabapentin. That is routine practice: a TCA with an anti-epileptic if one treatment alone is not giving the patient relief. And change the 'all 3' to 'any of the 3' as that is what should be said here.	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy.
Royal College of Anaesthetists - Faculty of Pain Medicine	18	full	12	3	Recommendation 1.1.8. we are concerned that this requires "all three" drugs (amitriptyline, gabapentin, nortriptyline) to be tried before a switch to duloxetine or pregabalin. This could take 6 months or so, with ongoing severe distress, before reaching these latter two drugs (which are said on Page 43 line 22 to be the best at providing pain relief). It does not seem logical to switch from nortriptyline to amitriptyline in the event of absent benefit or side effects before moving on to second line drugs. Can 2nd line drugs be tried after unsuccessful trial of two of the first line drugs (one of which should be gabapentin, if not contra-indicated)?	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Royal College of General Practitioners	14	Full	12	3	We are very glad to see pregabalin relegated to second line, based on the considerations of abuse potential. **(SEG)**	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Shingles Support Society	12	FULL	12	3	Rewrite this bullet point to express the fact that either/or amitriptyline and nortriptyline can be tried alone or with gabapentin. This will follow the routine practice, where clinicians use a TCA with an anti-epileptic if one treatment alone is not giving the patient relief. Change the 'all 3' to 'any of the 3' as that is what should be said here.	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. . The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy.
NHS England		Full	12	3	Substitution of amitriptyline for nortriptyline is only likely	This recommendation has now changed. amitriptyline,

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					to be beneficial if the goal is to avoid limiting side effects.	duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Cambridge University Hospitals NHS Foundation Trust	4	Full	70	8	Recommendation 1.1.8 The economic argument fails to take into account changes in drug costs. More widespread use of nortriptyline may encourage the development of alternative cheaper generic preparations. We question the logic of favouring gabapentin over pregabalin when the latter drug is due to go off-patent and, presumably, become less-expensive in the near future, although we understand there may be reluctance to include pregabalin as a first-line drug, given the controversial cost-effectiveness data published in the previous guidelines. Should both these drugs have been included as first-line alternatives in view of favourable side-effect and pharmacokinetic profiles over amitriptyline/gabapentin respectively?	This recommendation has now changed. amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Faculty of Pharmaceutical Medicine	3	full	12	4	We believe that the recommendations and assessment of some of some treatments for off-label use is confusing and could potentially be at odds with the assessment of efficacy which occurs in a National Competent Authority (in the case of the UK the MHRA). For instance, although both nortriptyline (nortr) and amitriptyline (ami) are off-label, several drugs with labelled indications for NP and more robustly demonstrated efficacy (pregabalin especially) have not been suggested as initial treatment, which seems inappropriate. Since side effect profiles (and presumably efficacy) of ami and nortr are very similar, it is not logical to recommend that both of these drugs be used as initial treatments and others only when all 3 of the initial treatments have failed; at maximum it could be either/or ami or nortr. before progressing to 2nd line treatments.	It is standard in NICE guidelines to include details about drugs recommended off-label in footnotes of recommendations (see section 9.3.6.3 of The guidelines manual 2012). This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all

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						types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings.
Eli Lilly and Company	5	Full	12	5	We believe the evidence supports that duloxetine should be offered prior to pregabalin for the following reasons: 1) Duloxetine 60 mg demonstrated greater efficacy and comparable tolerability versus pregabalin 300 mg in the COMBO-DN trial[1]. 2) Duloxetine is simpler to use as it does not require dose titration to achieve the typical	This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. This study by Tesfaye S et al was published after the literature search so it was not possible to include in the analyses, as per the NICE Guidelines Manual 2012.

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					maintenance dose. 3) At typical maintenance doses duloxetine is cheaper than pregabalin 1.Tesfaye S et al. Duloxetine and pregabalin: High-dose monotherapy or their combination? The "COMBO-DN study" - a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013 May 31. [Epub ahead of print]	
Napp Pharmaceuticals Ltd	10	Full	12	6	Clinician's have been given no options to treat acute pain other than with tramadol. Several opioids *are* licensed for the management of pain, which includes acute pain, chronic pain, breakthrough pain, neuropathic pain, and cancer pain etc. Inclusion of opioids would allow the clinician to make a choice within primary care potentially avoiding unnecessary referral to secondary care or specialist centres early on in the management of the patient. It should be borne in mind that for many neuropathic pain patients a proportion does not respond to a particular medicine and therefore alternative rescue options should be proposed. The reasons given for not including opioids in the non-specialist setting are weak and are contradictory to the statement that opioids are commonly used (4 line 28). Tramadol is not without its issues and withdrawal and addiction may be problems here also. In fact there is currently a suggestion that tramadol should be re-scheduled as a Schedule 3 medicine. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/144116/advice-tramadol.pdf We suggest that this statement should be modified and that the evidence should be reassessed to give patients greater choice.	The guideline development group (GDG felt it was inappropriate to recommend tramadol for long-term use in non-specialist settings due to the potential for dependency. They have now clarified this position in the recommendations. The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services. The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.

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					Oxycodone should be included as an option at the same point as tramadol. The recent publication of the European Federation of Neurological Societies EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision (Attal, N. et al, European journal of Neurology 2010 17 1113-1123) discusses the available evidence for the range of medicines assessed by NICE. The article cites grade evidence published since 2005 for a number of medicines, including opioids, for the management of NP. Oxycodone and tramadol have been shown to reduce pain in diabetic PPN. The article also suggests that tramadol should be used with caution in the elderly. Doses of tramadol quoted in the NICE guideline are equivalent to approximately 40mg oxycodone per day or 80 mg of morphine. Including morphine and oxycodone would allow clinicians the opportunity to choose the most appropriate medicine and dose for elderly patients and those not suitable for tramadol. In table 1 of the same publication oxycodone is rated A grade evidence for diabetic NP For PHN both morphine and oxycodone are rated A grade and for Central pain opioids are listed as b grade along with tramadol. The EFNS guideline recommends that opioids and tramadol are 2nd or 3rd line treatment in diabetic NP and opioids are listed as second line for PHN however tramadol is not recommended for PHN. In diabetic neuropathy (and in PHN in 2 studies) combination therapy of opioids (morphine and oxycodone) was shown to be more effective than single agents (class 1 studies). It should also be borne in mind that the clinical trials conducted in pain almost always permit a background usage of pain medications. The GDG need to consider	The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy. The 'evidence to recommendations' section has been amended to reflect the difficulty the GDG had in assessing the evidence with the variation in levels of concomitant medications permitted in the studies.

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					how to ensure that this issue is covered within the guideline.	
Pain UK	11	FULL	12	6	Rewrite this as "Consider Tramadol or other pain relief while waiting for amitriptyline/nortriptyline and/or gabapentin to take effect." Patients must not be left in pain whilst waiting for the slowly building up effect of TCAs and gabapentin to start working.	The recommendation has been changed to reflect this comment. It is now recommended if acute rescue therapy is needed in general.
Shingles Support Society	13	FULL	12	6	Rewrite this as "Consider Tramadol or other pain relief while waiting for amitriptyline/nortriptyline and/or gabapentin to take effect." Patients must not be left in pain whilst waiting for the slowly building up effect of TCAs and gabapentin to start working.	The recommendation has been changed to reflect this comment. It is now recommended if acute rescue therapy is needed in general.
NHS England		Full	12	6	We would question the recommendation of only using tramadol for rescue whilst waiting for referral? Often patients can get control with tramadol (safe, if monitored and the recommendation should be amended to reflect the need for monitoring).	The guideline development group (GDG) felt it was inappropriate to recommend tramadol for long-term use in non-specialist settings due to the potential for dependency. They have now clarified this position in the recommendations.
British Pain Society	11	Full	12	6 – 7	Why only use Tramadol for rescue whilst waiting for referral – often patients can get control with Tramadol (which is safe as long as monitored). The use of opioids in a "PRN" fashion for chronic pain, is against established consensus. The accepted protocol, is that if opioids are used for moderate/severe pain, that they be given as a regular background dose (with or without extra opioid for breakthrough pain)	The guideline development group (GDG) felt it was inappropriate to recommend tramadol for long-term use in non-specialist settings due to the potential for dependency. They have now clarified this position in the recommendations.
Royal College of General Practitioners	15	Full	12	6 – 7	Why only use Tramadol for rescue whilst waiting for referral – often patients can get control with Tramadol (which is safe as long as monitored) **(MJ)**	The guideline development group (GDG) felt it was inappropriate to recommend tramadol for long-term use in non-specialist settings due to the potential for dependency. They have now clarified this position in the recommendations.
Royal College of Nursing	9	Full	12	6 – 7	Tramadol can be an effective analgesic for patients who have been referred. Why limit to provide breakthrough	The guideline development group (GDG) felt it was inappropriate to recommend tramadol for long-term

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					analgesia?	use in non-specialist settings due to the potential for dependency. They have now clarified this position in the recommendations.
UK Clinical Pharmacy Association	5	General			Unlike the previous version there is no definitive recommendation about considering strong opioids prior to referral to a specialist service. Given increased prescribing of opioids and our increased understanding of the long-term harms, a definitive position would be helpful.	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services. The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
British Pain Society	12	General			Unlike in the previous version, there is no definitive recommendation about considering strong opioids prior to referral to a specialist service. This is especially relevant for patients with cancer-induced neuropathic pain, where it may be important to add an opioid drug at an earlier stage. Given the increased prescribing of opioids and	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services.

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					increased understanding of long-term harms, a definitive position would be helpful. As a consequence, there is no guidance on which opioids have some evidence for neuropathic pain (cancer or not). Again, there should be a statement to say that it is ok to continue prescribing medications outside of these guidelines IF they have been initiated in Specialist care	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis. The guideline development group (GDG) have now inserted a recommendation about continuing existing treatments for people whose neuropathic pain is already effectively managed. However, this implicitly suggests that these should be continued if they have been initiated in specialist care if they effectively treating the pain so the GDG did not feel this needed to be specified here.
Royal College of Nursing	10	General			Why are opioids not included in the list of medications not to start (especially before referral) – as before? Very useful for intolerance of oral medications or very focal neuropathy – especially in the elderly or drivers.	The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services. They felt that there were specific safety concerns about these drugs, including the potential for dependency, so felt that they should not be started outside of these settings. The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for

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						a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Royal College of General Practitioners	16	General			Why are opioids not included in the list of medications not to start (especially before referral) – as before? Very useful for intolerance of oral medications or very focal neuropathy – especially in the elderly or drivers. **(MJ)**	The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services. The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
NHS England		General			The increasing use of opioids in primary care is a matter of serious concern and we deprecate the loss of advice to avoid their use in neuropathic pain unless recommended by a specialist service. We would ask for strong guidance against the use of opioids in this setting.	The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services. The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along

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						with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Royal College of Anaesthetists - Faculty of Pain Medicine	19	Full	70		Section 3.1.5. Morphine (or other strong opioids, apart from Tramadol) is not mentioned in these recommendations, despite having been reviewed and discussed in the previous section. It would be helpful for non-specialists to have a clear recommendation on the use of these drugs (which would presumably to the effect that they should not be used, without specialist involvement)	The guideline development group (GDG) have now added morphine and its long-term use to the list of drugs not to be started outside of specialist pain services. They felt that there was not enough evidence to make explicit recommendations about other opioids.
British Pain Society	13	Full	12	8	Section 1.1.10 Topical therapies for focal painful neuropathic pain are very useful for frail or elderly patients and those intolerant of oral medications. They are also attractive options for those patients who require full alertness and cognitive function (for example teachers or drivers). Why delay until seen by specialist pain services? There is reasonable evidence (though not Double-blind RCT) for topical lidocaine plasters and Qutenza. The former is easily administered in the community, Lidocaine plaster was included in the previous guideline. What evidence has changed the situation?	Section 1.1.10 recommends capsaicin cream outside of specialist pain services in these situations. The GDG did not feel there was enough evidence on the use of lidocaine and so did not feel it was appropriate to make recommendations about its use. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
The Walton Centre for Neurology and Neurosurgery NHS Foundation Trust	1	Full	12	8	Poor evidence for this, poor patient compliance with this treatment. Quite painful to apply 3 to 4 times a day on an allodynic area. Mechanism of action considered to be counter irritation effect. My experience was quite	The guideline development group (GDG) acknowledged the difficulties with capsaicin cream. However, they felt it was appropriate to make a recommendation about a topical treatment for localised

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					disappointing.	pain or those who could not tolerate or wished to avoid oral pain (ie. some elderly patients). Capsaicin cream came out as the most cost effective topical treatment. More details about this GDG discussion has been added to the 'evidence to recommendations' section.
UK Clinical Pharmacy Association	6	Full	12	8	Should the strength of capsacin cream (0.075%) be included given that 0.025% is commercially available?	The literature was on Axsain, the 0.075% concentration of the cream as specified in the scope and review protocol. However, it was not felt appropriate to include the concentration of cream within the recommendation as dosages have not been mentioned for other drugs.
Pain UK	12	FULL	12	9	Add new bullet with information about lidocaine plasters. There is data (e.g. the 5% lidocaine plaster vs pregabalin in PHN and DPN) which needs to be taken into account. Whilst the 5% lidocaine plaster is used pre-dominantly outside of PHN the NICE guideline could line up with many other international and national guidelines and recommend the 5% lidocaine plaster as first line for local neuropathic pain management (e.g. EFNS, IASP, and RCGP guidelines). The cost is good compared to other treatments. This is supported by the only independent published health technology appraisal (from the Scottish Medicines Consortium) which cites the 5% lidocaine plaster as being pharmaco-economically equivalent to pregabalin. The 5% lidocaine plaster meets many of the general criteria set out in this NICE guidance document to treat local neuropathic pain, including low adverse events and a **lack of drug interactions.** So limiting its initial use to specialist pain care initiation adds to waiting lists and slows patient access to a product currently used effectively in both primary and secondary care settings.	The GDG did not feel that there was enough research that met the inclusion criteria specified in the review protocol to include recommendations about the use of lidocaine. No inferences should be made from this guideline about what should and what should not be used in specialist care settings. The GDG considered the evidence on lidocaine which met the inclusion criteria but felt that there was not enough evidence to make any recommendations about lidocaine. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.

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					For these reasons, the 5% lidocaine plaster is ideally suited to non-specialist prescribing for local neuro-pathic pain and this NICE guideline should reflect this.	
Shingles Support Society	14	FULL	12	9	Add new bullet with information about lidocaine plasters. There is data (e.g. the 5% lidocaine plaster vs pregabalin in PHN and DPN) which needs to be taken into account. The 5% lidocaine plaster meets many of the general criteria set out in this NICE guidance document to treat local neuropathic pain, including low adverse events and a **lack of drug interactions.** So limiting its initial use to specialist pain care initiation adds to waiting lists and slows patient access to a product currently used effectively in both primary and secondary care settings. The cost is good compared to other treatments. This is supported by the only independent published health technology appraisal (from the Scottish Medicines Consortium) which cites the 5% lidocaine plaster as being pharmaco-economically equivalent to pregabalin. Whilst the 5% lidocaine plaster is used pre-dominantly outside of PHN the NICE guideline could line up with many other international and national guidelines and recommend the 5% lidocaine plaster as first line for local neuropathic pain management (e.g. EFNS, IASP, and RCGP guidelines). For these reasons, the 5% lidocaine plaster is ideally suited to non-specialist prescribing for local neuro-pathic pain and this NICE guideline should reflect this.	The GDG did not feel that there was enough research that met the inclusion criteria specified in the review protocol to include recommendations about the use of lidocaine. No inferences should be made from this guideline about what should and what should not be used in specialist care settings. The GDG considered the evidence on lidocaine which met the inclusion criteria but felt that there was not enough evidence to make any recommendations about lidocaine. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
Royal College of Anaesthetists - Faculty of Pain Medicine	20	Full	113	3	We recommend that the word "consider" be deleted from this Recommendation: it is essential to offer alternative treatments in the event of a failure of carbamazepine in trigeminal neuralgia, and these should follow the other main Recommendations. As currently worded, this	The wording for this recommendation has been changed. The guideline development group (GDG) now recommend that those in non-specialist settings should consider seeking expert advice or consider early referral. This should address the issues of the

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					suggests that it is reasonable to offer no further treatment until a specialist is seen	issue you raise about patients not receiving treatment until a specialist is seen.
Pain UK	13	FULL	12	17	Is it necessary to be so prescriptive in this heading? Could the heading be '***Treatments that are not normally used"*** We have heard that some of these drugs, used in primary care have been helpful. Capsaicin patches have very useful characteristics, most especially for patients on many drugs. When more clinicians are trained in their use, the lack of adverse effects will make them very suitable for neuropathic pain. New clinical guidelines by the European Federation of Neurological Societies and recommendations by the Scottish Medicines Consortium and All Wales Medicines Strategy Group state a place for capsaicin patches having, in some cases, assessed the cost-effectiveness	The guideline development group (GDG) felt that there were specific reasons why each of these drugs should not be started in non-specialist settings, including difficulties with establishing correct dosages, issues related to potential dependency of these drugs, or related to the risk of side effects which could be alleviated if these drugs are administered in specialist settings where clinicians are more familiar with these issues. However, the GDG have now clarified in the recommendation that these treatments should not be started in non-specialist settings.
Shingles Support Society	15	FULL	12	17	Is it necessary to be so prescriptive in this heading? Could the heading be '***Treatments that are not normally used"*** We have heard that some of these drugs, used in primary care have been helpful. Capsaicin patches have very useful characteristics, most especially for patients on many drugs. When more clinicians are trained in their use, the lack of adverse effects will make them very suitable for neuropathic pain. New clinical guidelines by the European Federation of Neurological Societies and recommendations by the Scottish Medicines Consortium and All Wales Medicines Strategy Group state a place for capsaicin patches having, in some cases, assessed the cost-effectiveness	The guideline development group (GDG) felt that there were specific reasons why each of these drugs should not be started in non-specialist settings, including difficulties with establishing correct dosages, issues related to potential dependency of these drugs, or related to the risk of side effects which could be alleviated if these drugs are administered in specialist settings where clinicians are more familiar with these issues. However, the GDG have now clarified in the recommendation that these treatments should not be started in non-specialist settings.
UK Clinical	7	Full	12	17	Should lidocaine patch be included in list of treatments	The list of treatments that the GDG felt should not be

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Pharmacy Association					that should be not used?	initiated in non-specialist settings were those where evidence presented to the GDG suggested that those options do not represent an effective use of NHS resources, or where the GDG felt that there were specific concerns that were best dealt with by a specialist with more knowledge and experience. The GDG did not feel that there was enough research that met the inclusion criteria specified in the review protocol to include recommendations about the use of lidocaine. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
The Walton Centre for Neurology and Neurosurgery NHS Foundation Trust	2	Full	70	1.1.13	I agree not to offer these treatments in non-specialist setting but think the 8% capsaicin patch should be available in a specialist neuropathic pain clinic to treat a confirmed diagnosis of PHN, post traumatic nerve injury and some forms of small fibre neuropathies. This is recommended by the EFNS guidelines and the MAP of medicine. Our clinical experience and outcomes support the use of capsaicin. Weaning of other drugs is often possible and well received by patients. We also have encouraging results with lamotrigine in central neuropathic pain syndromes after slow titration in 25mg increments per week to 200mg bd to avoid withdrawal due to side effects. It also has a beneficial effect on patients mood. Venlafaxine between 150 and 225 mg mane is an alternative to duloxetine in patient without hypertension and works better for comorbid depression.	Recommendation 1.1.13 (now recommendation 1.1.12) recommends that capsaicin patch, lamotrigine, and venlafaxine should not be used in non-specialist settings. It is beyond the remit of this guideline to make recommendations about the use of these treatments in specialist pain service settings.
British Pain Society	14	Full	12	20	There should be a statement to say that it is ok to continue prescribing medications outside of these guidelines IF they have been initiated in Specialist care The application process for Qutenza is becoming	The guideline development group (GDG) have now inserted a recommendation about continuing existing treatments for people whose neuropathic pain is already effectively managed.

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					progressively simpler (no requirement for lidocaine gel to the skin of target area), and could become available as a Primary Care administered therapy in the near future.	The GDG felt it was unnecessary to state 'if they have been initiated in specialist care' as this recommendation covers continuing treatments when the pain is effectively manage, regardless of what setting it was initiated.
Royal College of General Practitioners	17	General			There should be a statement to say that it is ok to continue prescribing medications outside of these guidelines IF they have been initiated in Specialist care **(MJ)**	The guideline development group (GDG) have now inserted a recommendation about continuing existing treatments for people whose neuropathic pain is already effectively managed. The GDG felt it was unnecessary to state 'if they have been initiated in specialist care' as this recommendation covers continuing treatments when the pain is effectively manage, regardless of what setting it was initiated.
Royal College of Anaesthetists - Faculty of Pain Medicine	21	Full	13	Table 2	CRPS 1 is not a neuropathic pain condition according to IASP definition used. CRPS 2 is. "Mixed neuropathic pain" is not a diagnosis we understand. Too vague. Suggest omit from table.	Complex regional pain syndrome was added in responses scope consultation. However, there was no literature on CPRS that met the inclusion criteria for the guideline. The GDG considered that CPRS is probably best managed in specialist pain services. The title of the table referred to has been clarified so it is now clear these are not a list of neuropathic conditions but that it is a list of search terms used.
Shingles Support Society	16	FULL	13	3	Venlafaxine is a good alternative to amitriptyline.	The guideline development group (GDG) felt that it can be difficult to establish an effective dosage and manage toxicity with venlafaxine so did not feel they were able to recommend venlafaxine outside of specialist pain services.
Royal College of Anaesthetists - Faculty of Pain Medicine	22	General	General esp page 14	10-14	The statement, and consequential detrimental effect upon the analysis decisions, that "similar underlying causes of neuropathic pain could be expected to respond to treatment analogously " is simply inaccurate and contrasts with available evidence on the topic. This is quite apart from the issue of individual treatment responses referred to elsewhere. We acknowledge that the decision to "lump" or "split" evidence obtained from	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone.

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					different conditions is not easy. We are pleased that a decision was made to separate trigeminal neuralgia. A decision was made not to analyse evidence or base recommendations on diagnosis-specific categories (other than trigeminal neuralgia). On one hand this is probably appropriate in non-specialist settings, yet there is good evidence that some conditions respond differently to drugs than others. This is particularly true for HIV neuropathy, where both amitriptyline and pregabalin have been shown NOT to have greater efficacy than placebo in trials identified in the search and also those unpublished trails referred to in point 3. Diabetic neuropathy is pathologically and clinically a similar condition and yet responds differently. We suggest for this reason that HIV neuropathy be analysed separately, as for trigeminal neuralgia. Furthermore, two conditions often studied in RCTs (diabetic neuropathy and post herpetic neuralgia) respond very differently to interventions- efficacy being more often demonstrated in PHN. Perhaps a comment to this effect across all conditions is required.	When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings. It should also be noted that NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
UK Clinical Pharmacy Association	8	General			We welcome the use of 'all neuropathic pain' as an indication for non-specialist use, excepting only trigeminal neuralgia, in this version of the guidance.	Thank you for your comment.
Eli Lilly and Company	6	General			Lilly welcomes the opportunity to respond to this draft guideline. Our comments are outlined in detail in the rows below. Our main concern is that the guideline is too one-dimensional in considering all neuropathic pain (with the exception of trigeminal neuralgia) as a blanket condition and that this simplification may be to the detriment of specific subpopulations such as patients with diabetic neuropathic pain. The NICE GDG commented at the scoping consultation stage that "the development group would be able to	This guideline is a full update of clinical guideline 96 (CG96). Therefore all recommendations within the new guidance should be considered as updating those in CG96. The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone.

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					make different recommendations for specific subgroups if supported by the evidence." We note the previous consideration in CG96 that thorough data was available for the subpopulation with diabetic neuropathic pain. Over the last few years the evidence base for diabetic neuropathic pain has become even more extensive and these guidelines should provide specific recommendations for this patient group as was done previously. The GDG from CG96 similarly decided at the outset of their assessment that neuropathic pain would be treated as a 'blanket condition' where possible or necessary. However, they noted that it was clear that the treatment of various subpopulations would differ considerably and that it would not be possible to extrapolate from one subgroup to all people with neuropathic pain. Since the development of CG96 there has been the publication of new evidence, not only in diabetic neuropathic pain but also other types of neuropathic pain. If anything the larger evidence base would allow an increased ability for considering specific populations rather than fewer. We don't agree that the new evidence in any way supports the change in approach taken in CG96 and we think this has the potential to create confusion amongst clinicians and patients alike to the detriment of patient outcomes. In addition, when the NHS has set up a clear strategy and significant focus on the management of diabetes within the NHS we do not understand why diabetic neuropathic pain has been grouped with other types of neuropathic pain. This change seems to go against the objectives of the NHS to better manage patients with diabetes which is one of the main priorities and prevalent conditions and may result in confusion amongst physicians and patients as it gives the impression that diabetes is less important than before.	When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings.

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					We are also concerned that an evidence based approach has largely given way to expert opinion in these draft guidelines. The cost-effectiveness evidence base for the majority of off-label treatments is poor and understandably associated with a good deal of uncertainty. Disappointingly the high levels of uncertainty have tainted the evidence base as a whole and led to the guidelines being largely determined by expert opinion.	
Eli Lilly and Company	7	Full	11 - 12		The draft guideline provides recommendations for 'all neuropathic pain' and 'trigeminal neuralgia' only. We believe that it would be in the best interests of patients to also consider the subgroup of patients with diabetic neuropathic pain as a specific population in the guidelines. We believe this is appropriate because: ***1)*** *Diabetic Neuropathic Pain is one of the most common causes of neuropathic pain (CG96) and it makes clinical sense for recommendations to be specific to the largest subpopulations in any condition. Approximately 16-26% of diabetes patients will have diabetic neuropathic pain (NICE CG96).* ***2)*** *Diabetic Neuropathic Pain is easily identifiable* The ability to manage diabetes and the associated neuropathy is already present in primary care. Diabetes is a well identified condition and practices should be able to produce a register of diabetic patients (Quality Outcomes Framework indicator DM001). In addition the QOF includes an indicator relating to the percentage of diabetic patients on the register with a record of a foot examination and risk classification (which includes neuropathy testing) (DM012).	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would be made in specialist settings. The recommendation has now changed. Amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.

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					Given that patients presenting with neuropathic pain will be known to have diabetes (or not) this means that the identification of diabetic neuropathic pain is relatively straightforward and allows for diagnosis to occur in a non-specialised setting. ***3)*** *Diabetes is a complex disease that needs tailored management. It is not good clinical practice to manage a patient with neuropathic pain without consideration of the underlying diabetes and associated comorbidites such as cardiovascular disease.* In a patient with diabetes the presence of neuropathic pain is indicative of advanced disease. In this group of patients cardiovascular disease is relatively common (>60% of patients)[1]. Treatment of diabetic patients presenting with neuropathies therefore needs to take into account potential cardiovascular disease. In particular, both amitriptyline and nortriptyline are contraindicated and/or have special precautions for use in patients with certain cardiovascular disorders. In the interests of patient safety we suggest that as a minimum the contraindications and precautions relating to amitriptyline and nortriptyline in patients with cardiovascular disorders should be highlighted in the guideline. Ideally it should be stated within the guidelines that tricyclic antidepressants are not a first line option for patients with cardiovascular conditions. ***4)*** *There is a significant evidence base for the treatment of diabetic neuropathic pain from which to make specific recommendations*	

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					In table 4 of the full guideline it can be seen that the trial evidence base for diabetic neuropathic pain is very large and many of the treatments (licensed and off-label) considered in the guidelines have been studied in this population. ***5)*** *The cost-effectiveness of different treatment options is likely to differ in a subpopulation of patients with diabetic neuropathic pain* As one of the most common causes of neuropathic pain it makes economic sense to consider cost-effectiveness specifically in this group. 1. Chen S et al. Factors associated with pain medication selection among patients diagnosed with diabetic peripheral neuropathic pain: a retrospective study. J Med Econ 2011;14(4):411-20	
Eli Lilly and Company	8	Full	14	11-13	An assumption that efficacy data from a trial in one type of neuropathic pain is equally valid for all types of neuropathic pain has been made in considering the evidence base in the guideline. We do not believe that this is appropriate. The evidence base in some subpopulations such as diabetic neuropathic pain is extensive and comes from thousands of patients taking numerous different treatments. This evidence base is more than sufficient for the development of robust evidence networks specifically for recommendations for the management of diabetic neuropathic pain. We consider that it is not appropriate that the lack of evidence for specific (mostly off- label) treatments drives the assumptions and analyses for the guideline as a	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would

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					whole. If a treatment does not have evidence in a specific population where the evidence for other treatments is extensive then that treatment should not be considered in that specific subpopulation. The short-comings of the evidence base for off-label treatments should not drive an evidence-based guideline. In the previous guideline (CG96) the GDG similarly decided at the outset that neuropathic pain would be treated as a 'blanket condition' where possible or necessary. However, they also noted that it was clear that the treatment of various subpopulations would differ considerably and that it would not be possible to extrapolate from one subgroup to all people with neuropathic pain. The evidence in the subpopulation of patients with diabetic neuropathic pain is robust and should be utilised for the development of specific recommendations for this population as done in CG96.	be made in specialist settings. The recommendation has now changed. Amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
NHS England		Full	11	23	There is an argument for keeping diabetics in a separate group (as per current guidance) because of their altered risk of detrimental effects.	The guideline development group (GDG) spent considerable time discussing the most appropriate way that the evidence on neuropathic pain should be presented. However, in light of the setting of the guideline being for non-specialists where a definitive cause of the pain may not be known, they felt that they should not be recommending drugs based on diagnosis alone. When breaking down the evidence to individual conditions, there are some conditions where there is little or no evidence to make recommendations. The GDG felt that the fact that more research has been performed in painful diabetic neuropathy, for example, may be partially due to its higher prevalence. The GDG felt that it would be appropriate to expect other peripheral conditions to respond similarly. Any further delineation of underlying conditions would

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						be made in specialist settings. There are risks related to many underlying causes of neuropathic pain. These should be considered on an individual patient basis for all patients, including those risks for specific patients with painful diabetic neuropathy. The recommendation has now changed. Amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Royal College of Anaesthetists - Faculty of Pain Medicine	23	Full	14	16	The "underlying cause … is not always known" by non-specialists, yet even a diagnosis of "Possible Neuropathic Pain" (a lowest sub-category of the IASP definition quoted in the guideline) requires: 1. Pain with a distinct neuroanatomically plausible distribution; and 2. A history of a relevant lesion or disease affecting the peripheral or central somatosensory system. This Guideline therefore needs to clarify the point which neuropathic pain is present with sufficient certainty to allow non-specialists to embark upon the process of applying the recommendations – if an underlying cause is not known, should we be giving people these drugs?	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Napp Pharmaceuticals Ltd	11	Full	14	16-20	The statements suggest that neuropathic pain is not well diagnosed. In relation to this could NICE make recommendations about training, the assessment and documentation of neuropathic pain within this SCG?	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Royal College of Nursing	11	General			This document should refer to the assessment and diagnosis of neuropathic pain e.g. such as that contained within the British Pain Society guidelines plus The Map of Medicine and the British Pain Society. Initial Assessment and Early Management of Pain. London: Map of Medicine, 2012. The Map of Medicine and the British Pain Society.	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.

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					Neuropathic Pain. England View. London: Map of Medicine, 2013	
NHS England					There is guidance on diagnosis and assessment of neuropathic pain. We recommend that this document should include it. (British Pain Society / Map of Medicine: Pain – initial assessment and early management and Neuropathic Pain)	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Physiotherapy Pain Association	1	General			Dear Colleagues, I believe that the document misses a number of highly significant opportunities to reinforce the importance of appropriate diagnosis of Neuropathic Pain (NeP) through the supported use of a choice of widely available assessment tools (DN4, LANSS, PainDETECT) which then itself underpins more appropriate treatment choices. The lack of such baseline information then reduces validated objective measurement of efficacy of treatment and therefore the appraisal of cost utility of any care given. There is, in my view, insufficient reference to the use of rehabilitation services as an alternative to pharmacotherapy but also to capitalise upon gains made with pharmacotherapy to maximise physical, functional, psychological and vocational recovery. By adjusting the thrust of the document this could have improved the Public Health message about the management of pain in general and specifically NeP.and reinforced the multidimensional nature and impact of pain but also the multi-professional potential management of pain. In terms of the recommendations of the medications I am broadly in support however I see the above shortfalls as significantly reducing the value of the document. There are some omissions of recommendations from the original document that just seem to have dropped off the radar and are puzzling. Regretably it very much seems a real missed opportunity for the betterment of care delivery in this field	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.

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Royal College of General Practitioners	18	General			The document should contain guidance on assessment and diagnosis of neuropathic pain (as per British Pain Society guidelines The Map of Medicine and the British Pain Society. Initial Assessment and Early Management of Pain. London: Map of Medicine, 2012. The Map of Medicine and the British Pain Society. Neuropathic Pain. England View. London: Map of Medicine, 2013 **(MJ)**	NICE recognises the importance of assessment and diagnosis but these were outside of the remit for this guidance, referred to us by the Department of Health. For this reason we have only been able to consider the pharmacological management of neuropathic pain and were unable to make any specific recommendations about diagnosis.
Cochrane Pain, Palliative Care and Supportive Care Group	1	Full	15	23-29	The CDG rightly considered that while pain is important, physical and emotional functioning, as well as sleep, fatigue, and depression were part of the overall goals of treatment. Pain relief of 30% or 50% cutpoints have become important criteria for judging pain relief. Since the GDG began work, several quite important pieces of work have shed more light on this. 1. A systematic review of studies of what patients want from treatment of acute and chronic pain concluded that the goal in any pain state was "no worse than mild pain" or pain intensity reduction of at least 50% (*Anaesthesia. 2013 68(4):400-12*). 2. A systematic review of , inter alia, benefits of pain relief, demonstrated from a range of data sources that achievement of "no worse than mild pain" or pain intensity reduction of at least 50% resulted in major improvements in physical and emotional functioning, quality of life, work, and sleep, depression, and fatigue (mainly from individual patient data analyses of randomised trials) (*Pain Pract. 2013 Mar 6. doi: 10.1111/papr.12050*). 3. This means that achieving good levels of pain relief are likely to be a prerequisite of improving other symptoms and functioning.	1–3. Utility values used in the model (which, themselves, are an empirical reflection of patient experience and societal preference) largely reflect these conclusions. In particular, the very large difference in utility between no pain relief (0.16) and pain relief of 50% or greater (0.67) reinforces the significant impact of substantial reductions in pain. 4 – Issues related to missing data in the studies are now discussed in appendix D. The 'evidence to recommendations' section now mentions this as well. 5–6 Although we acknowledge the intuitive appeal of these suggestions, the absence of any evidence on sequential treatment strategies made it impossible to model such approaches. However, recommendation 1.1.5 stresses that, after starting or changing a treatment, clinicians should 'carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.'

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					4. The measurement of benefit in chronic pain trials is subject to significant biases beyond randomisation and blinding. One of the largest of these is imputation bias deriving from the practice of using a last-observation-carried-forward imputation in the presence of large adverse event withdrawal rates with active drug (*Pain. 2012;153(2):265-8*). They may apply to some drugs evaluated, but not all (see *Eur J Pain. 2013 Jun 3. doi: 10.1002/j.1532-2149.2013.00341.x*). There are other biases (*Pain. 2010;150(3):386-9*). It is not clear that these biases have necessarily been taken into account in the review, though this can be difficult. Cochrane reviews from PaPaS have been attempting to adhere to the newer, higher, standards of evidence for some years now. 5. There is a strong argument that any health economics arguments should relate to those patients who achieve good pain relief, who are the only patients for whom benefit exceeds risks, given that pain responses are bimodal (a lot of pain relief, or very little). Good relief is typically established early, within 2-4 weeks. Patients with little pain relief should not be treated further. 6. There is case for treatment to be directed towards the achievement of useful pain relief, with early treatment change in the face of failure (*BMJ. 2013 May 3;346:f2690*).	
Cochrane Pain, Palliative Care and Supportive Care Group	2	Full	16	1-17	As above- comments above refer to Section 2.1.5 **Critical and important outcomes for clinical evidence** which falls across these two pages, 15 (lines 23-29) and 16 (lines 1-17).	Thank you for your comment. These queries are addressed above.

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Grünenthal Ltd	8	Full	15	26-29	Given that the GDG considered that the outcome 'patient's global (or overall) experience of the pain and its impact on daily physical and emotional functioning (including sleep)' to be critical to their decision making, it is surprising that amitriptyline and capsaicin cream have been recommended without any evidence of their impact on any of the critical efficacy outcomes.	Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience

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						of its use in non-specialist settings. The available evidence on capsaicin cream was incorporated into the health economic model in the same way as all other drugs. Withdrawal due to adverse effects is part of the simulated pathway and, consequently, the cost effectiveness of capsaicin cream is attenuated by an appropriate amount as a result of its relatively high withdrawal rates. Despite this, the analysis identifies this treatment as providing good value for money to the average patient. The GDG had concerns about the underlying evidence that suggested the model may somewhat overestimate the cost effectiveness of capsaicin cream (as detailed in the LETR table in section 3.1.4). However, they were confident that it could be recommended it as an option for some patients.
Grünenthal Ltd	9	Full	15	21-22	This statement implies all RCTs were included in the guideline. Given the GDG's concern over the overall lack of data on most critical outcomes it should be made clear that a number of RCTs which included such data were not included in the guideline (e.g. all non-blinded and enriched enrolment RCTs)	This statement has been amended to be clear that this applies to randomised controlled trials (RCTs) which met the inclusion criteria in the guideline.
Napp Pharmaceuticals Ltd	12	Full	16	5-12	Given the extent of validation and regulatory acceptance of the 10 point pain scale the GDG should provide evidence for their apparent concern that decreases at different points may have greater or lesser clinical significance. Since "pain is what the patient says it is" (McCaffery and. Beebe, 1989) a 2 point change on a 10 point scale is highly clinically relevant to each and every patient no matter what the initial pain score is. Pain is so subjective and such a personal issue that severe pain for one person could be scored at 6 and for another 10: the reduction in pain is highly relevant for both. Not only is a	The analyses for continuous outcomes in the guideline are focused on absolute rather than the relative reductions in pain.

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					decrease in pain important but it can often accompany improvements in function, sleep, mood and overall QOL. This could equate to a 20% change in improvement for some patients. The figure of 30% chosen seems to be quite arbitrary. See also 14 below.	
Grünenthal Ltd	10	Full	16	14-17	It is unclear why the additional use of rescue medication was identified as an important outcome included in the evidence review whilst other factors which may impact whether the drug appears to improve the patient experience, eg enriched enrolment, open label, short duration of treatment were regarded as potential sources of bias and excluded from the evidence review.	Use of rescue medication was seen as important as an outcome because a patient may reduce their medication usage to retain a particular level of pain relief and, so, their response to the drug may not be reflected as a reduction of pain.
British Pain Society	15	Full	17	Table 3	The document currently only recognises 'neuropathic cancer pain' as 'chemotherapy-induced neuropathy and neuropathy secondary to tumour antigens'. It does not recognise the numerous cancer-induced regional neuropathic pain syndromes such as brachial plexus, celiac axis and pelvic pains, as well as spinal cord compression. It also should explicitly recognise post-surgical pain following operations carried for cancer.	The introduction section has been amended so it is clear that the types of pain associated with neuropathic cancer pain are not exhaustive.
Royal College of Anaesthetists - Faculty of Pain Medicine	24	full	3 and table 2 page 13	15	Need a better term than "pain after surgery" so as to draw a clear distinction between with acute post operative pain & post surgical chronic non neuropathic pain and post surgical chronic neuropathic pain. The latter is the only condition relevant to this guideline. This distinction is very important since use of some of these drugs in creeping into perioperative practice without great justification and this guideline should avoid any unintended support for that practice.	This section of the guideline has been amended to be clear that it is 'post-surgical chronic neuropathic pain' that is being referred to.
Royal College of Anaesthetists - Faculty of Pain Medicine	25	Full	20	4	The Review Questions are specific to non-specialist settings, yet the RCT inclusion criteria specifically include those conducted in specialist settings. This is not quite consistent (though reasonable). At the very least, it would be helpful to present the setting in which RCTs were conducted, upfront, for example in Table 4.	The guideline development group (GDG) considered only considering studies in a non-specialist setting would further limit the evidence to be considered. In addition, despite acknowledging that in practice, there is more knowledge out the administration of some of these drugs in a specialist setting, the efficacy of the

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						drugs should be expected to be similar, regardless of setting, if they are used in accordance with that specified in the SPC.
Royal College of General Practitioners		Full	22 - 34		We note that the vast majority of studies used in preparing the guidelines were conducted in patients with specific types of neuropathic pain such as diabetic, post-herpetic, MS-related, HIV-related, cancer-related, post-stroke or after spinal cord injury. Very few of these studies are likely to have included patients with substance misuse backgrounds, and therefore are very unlikely to have raised the issues relating to problems of abuse with gabapentin and pregabalin that doctors working with substance abusers and in secure environments are dealing with every day. **(SEG)**	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
GW Pharmaceuticals plc	3	Full	22	Table 4	Several studies of Sativex are missing from this table. They are, as follows, 1. Berman JS et al. Efficacy of 2 cannabis medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 2004. 112; 299-306 2. Langford RM et al. A double-blind randomised placebo-controlled parallel group study of THC/CBD oromucosal spray in combination with existing treatment regimen, in the relief of central neuropathic pain in patients with Multiple sclerosis. J Neurol 2012 DOI: 10.1007/s00415-012-6739-4. 3. Rog DJ et al. Oromucosal delta-9 THC/CBD for neuropathic pain associated with multiple sclerosis. An uncontrolled open-label 2 year extension study. Clin Ther 2007; 29: 2068-2079.	The review protocol specifies inclusion and exclusion criteria which aim to reduce bias in the evidence considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process. The studies referred to either did not meet the inclusion criteria specified in the review protocol (see reasons below) or were published after the search was completed. It is not possible to include studies published after our search was completed as this is a short guideline where a re-run of the search is not customary. Further, the complex analyses would need to be re-run and the process does not support the additional work required.

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					4. Portenoy RK et al. Nabiximols for opioid treated cancer patients with poorly-controlled chronic pain: a randomized placebo-controlled graded dose trial. J Pain 2012:13; 438-449. 5. Johnson JR et al. Multicentre, double-blind, randomized, placebo-controlled, parallel group study of the efficacy, safety and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symp Management 2010; 39: 167-179. 6. Johnson JR et al. Open label extension study to investigate the long term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer related pain refractory to strong opioid analgesics. J Pain & Symptom Management 2012. 7. Lynch M et al. A Double-Blind, Placebo-Controlled, Crossover Pilot Trial With Extension Using an Oral Mucosal Cannabinoid Extract for Treatment of Chemotherapy-Induced Neuropathic Pain. J Pain Management 4th June 2013. This stakeholder would draw attention to the fact that the majority of studies with Sativex have been in the area of central neuropathic pain. We believe firmly (along with the US FDA and most other regulatory authorities) that this should be regarded as a different therapeutic target than peripheral neuropathic pain. They are simply different conditions. We do not believe that all neuropathic pain can be lumped together in the way of this guideline, and urge the guideline group to treat them separately.	There were only 11 studies on central pain that met the criteria for high-quality RCTs specified in the review protocol. This literature often did not report the outcomes which were critical to decision making for central pain and only covered 6 possible drugs for central pain which the GDG felt did not cover the drugs considered relevant in clinical practice. As they felt it was not possible to meaningfully compare treatments for central pain from this evidence and to make any conclusions about central pain, they felt it was most appropriate to consider the evidence on all neuropathic pain conditions and apply to central pain rather than give no recommendations for central pain. The first line recommendation has now changed; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Grünenthal Ltd	11	General			The systematic literature searches conducted by the Institute were inappropriately restrictive and, as a	The review protocol specifies inclusion and exclusion criteria which aim to reduce bias in the evidence

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					consequence, failed to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group (GDG). The evidence reviewed by the GDG did not include estimates of clinical and cost effectiveness for 23 of the 43 products in the guideline's scope; including two products, the lidocaine 5% medicated plaster (Versatis) and tapentadol (Palexia), which are particularly suited to the treatment of neuropathic pain by non-specialists. The highly selective review of evidence has resulted in a draft guideline that:- • is based on the availability of 'best' evidence rather than the best available evidence and • puts clinical opinion above consideration of RCT and other study evidence which is in clear contradiction to the Institute's intent set out in the Methods Guide Implementation of the guideline as it stands would:- • unnecessarily restrict physician and patient access to efficacious care in the non-specialist setting, which is entirely contrary to the GDG's desire to take patient preference into account and • increase the number of avoidable referrals into secondary care ○ few patients will remain under the long-term care of the specialist so will ultimately still need to be managed in the community by non-specialists. **The draft recommendations, including the recommendations for further research, should be reconsidered in light of a review of all available RCT**	considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process. Accordingly, the GDG made an a priori judgement that forms of evidence such as those recommended for consideration, here, were subject to greater risk of internal bias and poorer generalisability to the population in question. The fact that some 115 RCTs meeting the protocol's criteria were identified demonstrates that it has been possible for numerous investigators to perform trials that the GDG considered to be of adequate quality. This evidence-base enabled the GDG to make recommendations covering a range of options for people with neuropathic pain. Therefore, it would not be appropriate to disregard prespecified eligibility criteria in order to accommodate evidence on additional options that have not been studied with similar rigour.

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					evidence (including open label and enriched enrolment RCTs) and observational studies where appropriate.	
Grünenthal Ltd	12	General			The lidocaine 5% medicated plaster (Versatis) is a well-established, efficacious option for the treatment of localised neuropathic pain associated with post herpetic neuralgia (PHN). Significant analgesia is achieved whilst the low level of lidocaine absorbed systemically results in minimal systemic side effects or drug interactions and without the intense administration site burning sensation during initial treatment associated with topical capsaicin. The RCT by Baron et al[1] in 311 patients with PHN or painful diabetic neuropathy (PDN), one of 6 topical lidocaine RCTs included in the existing guideline (NICE CG96) but excluded from the current review, demonstrated comparable efficacy with pregabalin (<30, 30-49, >50% responder rates; 41.0, 20.1, 38.9% compared with 46.0, 21.9 and 31.2% for the lidocaine 5% medicated plaster and pregabalin respectively) but fewer adverse events (dizziness; 0% vs 11.8%, nausea; 0.6% vs 2.6%) and fewer withdrawals due to adverse events (5.8% vs 25.5%). These findings were mirrored by improvements in health related quality of life (EQ-5D) and PGIC (50.0% vs 47.4% patients very much / much improved with the 5% lidocaine plaster and pregabalin respectively). These benefits are particularly useful in the elderly PHN population many of whom are unable to tolerate systemic treatments. The favourable risk benefit of the lidocaine 5% medicated plaster, without the requirement for complicated up-titration, makes it particularly suitable for use by the non-specialist in primary care, compared to the other medications considered in this guideline. Whilst the preference is for blinded studies, a double	Baron (2009) was excluded because it is an open-label study and did not meet the inclusion criteria specified in the review protocol. The guideline development group (GDG) felt that because of the lack of literature that met the inclusion criteria specified in the review protocol, that they were unable to make recommendations for the use of lidocaine. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain. The available evidence on capsaicin cream was incorporated into the health economic model in the same way as all other drugs. Withdrawal due to adverse effects is part of the simulated pathway and, consequently, the cost effectiveness of capsaicin cream is attenuated by an appropriate amount as a result of its relatively high withdrawal rates. Despite this, the analysis identifies this treatment as providing good value for money to the average patient. The GDG had concerns about the underlying evidence that suggested the model may somewhat overestimate the cost effectiveness of capsaicin cream (as detailed in the LETR table in section 3.1.4). However, they were confident that it could be recommended it as an option for some patients. However, this has now been commented on in the evidence to recommendations section.

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					blind, double dummy study of the lidocaine plaster vs an oral treatment would be prone to bias due to the cooling and protective effect of the hydrogel 'placebo' plaster, which forms an intrinsic component of the active lidocaine product. The impact on the robustness of the evidence base and the relative quality of the Baron study compared with those currently included should be considered before excluding this RCT on the grounds that it is not blinded. Grünenthal contend that this large, well conducted, active comparator study provides estimates of efficacy and safety of the lidocaine 5% medicated plaster which are as robust and valid as those obtained for the products currently recommended in the draft guideline. For example, not only does the effectiveness evidence for capsaicin cream come from very small trials in highly selected populations, but the authors confirm that attempts to blind the studies were thwarted by the incidence and severity of burning, stinging, or redness of the skin on initial application of the active treatment. The Baron study contains the requisite critical and important efficacy and safety outcomes to enable the lidocaine 5% medicated plaster to be included in the health economic model. This in turn would enable the GDG to consider recommending the lidocaine 5% medicated plaster as a non-systemic treatment option for the treatment of neuropathic pain. Failure to do so significantly disadvantages patients unwilling or unable to take oral systemic treatments. **Grünenthal request that the outcomes from the Baron study be included in the network meta-analysis and the evidence synthesis for the health economic model and the findings be considered by the GDG with a view to recommending the lidocaine 5% medicated plaster as a non-systemic treatment**	

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					option for the treatment of neuropathic pain. [1] Baron et al. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open label, non-inferiority two-stage RCT. Curr Med Res Opin 2009; 25(7): 1663 – 1676	
Grünenthal Ltd	13	General			Tapentadol is a centrally acting analgesic combining two mechanisms of action, μ-opioid receptor agonism and noradrenaline reuptake inhibition (MOR – NRI), in a single molecule. This synergistic mode of action with the potential for a reduced reliance on the opioid component, may explain the comparable efficacy to a strong opioid (oxycodone CR)[2], more favourable GI side effect profile[2], lower rates of withdrawal[2] and no evidence of acquired tolerance over 1 year[3]. During the 24 months following its introduction in the US, population-based rates of abuse and diversion for tapentadol were clearly lower than rates for oxycodone and hydrocodone[4]. These attributes suggest a more favourable risk benefit profile than existing strong opioids, supporting its role in the management of severe, chronic neuropathic pain in the non-specialist setting. Efficacy has been verified in nociceptive and neuropathic chronic pain conditions including two placebo controlled RCTs in DPN (Schwartz et al[5], Vinik et al[6].) which were not identified by the Institute in its systematic review of evidence for this guideline. **Grünenthal request that the outcomes from the Schwartz and Vinik studies be included in the network meta-analysis and the evidence synthesis for the health economic model and the findings be**	The studies referred to did not meet the inclusion criteria specified in the review protocol.

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					considered by the GDG with a view to recommending tapentadol as an option for the management of severe, chronic (mixed) neuropathic pain. [2] Lange B. et al. Efficacy and Safety of Tapentadol Prolonged Release for Chronic Osteoarthritis Pain and Low Back Pain. Adv Ther. 2010; 27(6): 381-399 [3] Wild J.E. et al. Long-term Safety and Tolerability of Tapentadol Extended Release for the Management of Chronic Low Back Pain or Osteoarthritis Pain. Pain Pract. 2010; 10(5): 416-427 [4] Dart R.C. et al. Assessment of the abuse of tapentadol immediate release: The first 24 months. J. Opioid Management 2012; 8(6): 395-402 [5] Schwartz S et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy. Results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011; 27(1): 151-162 [6] Vinik A et al. (2012) Efficacy and Tolerability of Tapentadol Extended Release in Patients With Chronic, Painful Diabetic Peripheral Neuropathy: Results of a Phase 3, Randomized-Withdrawal, Placebo-Controlled Study. Poster presented at the 31st Annual Scientific Meeting of the American Pain Society (APS). 16 – 19th May 2012, Honolulu, Hawaii	
Grünenthal Ltd	14	General			Enriched enrolment, randomised withdrawal (EERW) study designs are increasingly being employed in the evaluation of treatments for neuropathic pain following their acceptance as an appropriate methodology by regulatory authorities. The Food and Drug Administration (FDA) recently approved an extension to the marketing authorisation for tapentadol prolonged-	The guideline development group (GDG) felt it was inappropriate to include enriched enrolment studies (full or partial) alongside traditional RCTs in the same synthesis as they felt they are less generalizable to the population who would present in non-specialist settings.

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					release tablets in the US to include the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN). Approval was based on the risk-benefit observed in two EERW studies (Schwartz et al. Vinik et al). By selecting a cohort of patients who respond to a drug, the treatment effect can be observed in the subset of patients who are likely to receive continued treatment in the real-world clinical setting. In contrast, estimates of treatment effect derived from traditional RCT designs are often diluted by averaging in results for patients who in a clinical setting would be switched to an alternative effective therapy rather than simply continued on a medication that is not effective or well tolerated. With the EERW design, these patients are excluded during the enrichment phase, leaving a patient sample that more closely approximates actual clinical practice. It is more clinically relevant to report the proportion of patients who respond, and then describe the magnitude of response in the subgroup of patients categorized as responders. The response rate during the enrichment phase provides useful information in its own right, being an important predictor of what will happen with the drug in clinical practice. Combining results of classic and EERW trials is possible by setting the denominator in the calculation of the relevant efficacy outcome in the EERW trial to the number of patients entering the open label phase, thus accounting for patients who were not subsequently randomised. **Whilst we recognise that evaluating EERW studies alongside traditional RCTs may add methodological complexity, as such studies provide valuable**	

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					evidence of effectiveness in routine clinical practice, Grünenthal propose they should be included in the evidence synthesis for this guideline.	
Grünenthal Ltd	15	General			By failing to consider anything other than RCTs, the GDG have little or no evidence on: • The long-term efficacy of treatments, which for ethical reasons tend to be collected in open-label extension studies and • The relative risk of tolerance, dependency and abuse of treatments o No mention of the growing abuse of pregabalin and gabapentin o No mention of the lower risk of tapentadol compared to strong opioids Failure to consider these factors has the potential to put patients' safety at risk. The results of 3 of the 5 key research recommendations proposed in this guideline would not be identified by the current evidence search strategy, begging the question as to whether the evidence already exists but has not been identified and included in the evidence review.	The review protocol specifies inclusion and exclusion criteria which aim to reduce bias in the evidence considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process.
Astellas Pharma Ltd	2	Full	22 - 34 26	Table 4	**Identification of Studies for Evaluation** We would like to highlight the following inconsistencies in the systematic review undertaken: One of the studies identified for inclusion is not an RCT (Irving 2012), but an integrated analysis of four other capsaicin patch studies. Also, the literature search failed to identify a systematic literature review that was conducted by The Cochrane Collaboration and was first published in 2009 (Derry S et al Cochrane Database of Systematic Reviews 2009,	Thank you for your comment. Irving 2012 has now been removed from the guideline. The review by Derry 2009 was missed from the excluded studies list in error. It has now been added to the excluded studies list. Simpson 2008 has now been included in the guideline.

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					Issue 4). There is a more recent version of this review that was published after the cut-off date for this guideline, and the GDG might like to review this prior to publication of the final guideline. (Derry S et al Cochrane Database of Systematic Reviews 2013, Issue 2). Additionally, an RCT of capsaicin patches in HIV-AN (Simpson Neurology 2008; 70:2305-2313) has not been included, (or excluded in Appendix D). We have additional concerns regarding the inclusion of HIV studies (see point 9 below) We have not checked the literature review for all drugs included in this guideline, and have concerns that there may be other omissions and erroneous inclusions.	
GW Pharmaceuticals plc	4	General			In the majority of the studies cited in the draft guidelines, the patients have been withdrawn from concomitant analgesia, and then only randomised if their pain score exceeds 4, thus enriching the study for patients who have the capacity to respond to analgesia. In the Sativex studies, such an enrichment technique has not been used, and Sativex has been added on to an established analgesic regimen, on which patients were failing to gain adequate relief. That is to say that Sativex was only being studied in a setting where there analgesic needs were not being met by several lines of existing treatment. This stakeholder believes that it is not appropriate to lump together these very different clinical study strategies in a single economic analysis. The former approach is likely to result in much larger differences in response between drug and placebo, while also providing analgesia to patients who may have been adequately treated with existing agents. By limiting study recruitment to those patients whose pain was not being adequately addressed by existing	Any studies where assessment for inclusion into the study and randomisation occurred after withdrawal from concomitant analgesia were excluded.

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					analgesia, the Sativex studies cannot be directly compared to 'first-line' types of treatment.	
Cochrane Pain, Palliative Care and Supportive Care Group	3	General			We note that enriched enrolment studies have not been included. It is unclear to what extent of enrichment this extends. Partial enrichment of studies in this area is common, but makes little or no difference to results (*Br J Clin Pharmacol. 2008 Aug;66(2):266-75*). Complete enrichment – typically in enriched enrolment randomised withdrawal (EERW) trials – poses a slightly different challenge, but there is no prior evidence to suggest that they give any different results in a population. Indeed, there are arguments that EERW designs are the ideal way to investigate efficacy and harm in neuropathic pain (*Br J Anaesth. 2013 Jul;111(1):38-45*).	The guideline development group (GDG) felt it was inappropriate to include enriched enrolment studies (full or partial) alongside traditional RCTs in the same synthesis as they felt they are less generalizable to the population who would present in non-specialist settings. This is because patients who respond to placebo are effectively removed from the trial so the population then included in the study is no longer representative of the population of patients which present in non-specialist settings.
Royal College of Anaesthetists - Faculty of Pain Medicine	26	General			We are gravely concerned that no attempt appears to have been made to access evidence from the considerable number of unpublished trials in this field. For example our own search of the clinicaltrials.gov databases locates about the same number of completed studies in postherpetic neuralgia, which are unpublished as those that are published. Furthermore accessible unpublished studies can, for example, be identified by searching the 2010 Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database (which is no longer available): We found one trial examining gabapentin 3600 mg, which relieved painful polyneuropathy with an NNT of 7.0 (4.3-20), and four positive and three negative trials with pregabalin, revealing a combined NNT of 9.5 (6.8-16.0). We are about to publish a further major multicentre trial of pregabalin and one of amitriptyline in HIV neuropathy in which no superior efficacy over placebo is seen for either drug. Inclusion of these data would fundamentally change the conclusions of the draft guideline. At the very	Following the NICE Guidelines Manual 2012 we only consider published literature unless in discussion with the guideline development group (GDG) we have reason to believe that significant unpublished data exist. No substantive unpublished literature was highlighted during development of the guideline so a formal call for evidence was not conducted. For more information on this, please see pages 47, 80 & 86 of the NICE Guidelines Manual.

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					least a formal publication bias impact analysis should be included for each drug/condition as well as generically across field.	
Royal College of Anaesthetists - Faculty of Pain Medicine	27	Full	28	Table 4	Nikolajsen et al. 2006 (pregabalin) is a preemptive trial, which is an exclusion criteria	This study has now been excluded.
Eli Lilly and Company	9	General			Part of the scope of the guidelines was to investigate combination therapy in neuropathic pain however very little data was retrieved by the literature search. Attached for your reference is the recently published manuscript for the COMBO-DN study[1]. This is the largest randomised double-blind study in diabetic neuropathic pain and it investigated whether patients with insufficient pain relief on duloxetine 60mg/day or pregabalin 300mg/day would benefit from combination therapy of duloxetine + pregabalin versus increased doses of each agent alone. This study demonstrated that at usual maintenance doses, duloxetine showed superior pain relief versus pregabalin after 8 weeks of treatment. 1.Tesfaye S et al. Duloxetine and pregabalin: High-dose monotherapy or their combination? The "COMBO-DN study" - a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013 May 31. [Epub ahead of print]	The guideline does not recommend the use of combination therapy as there was little data to consider combination therapy. There was substantial overlap in the estimated costs and effects of pregabalin and duloxetine. In the revised model, pregabalin was estimated to provide superior value for money to duloxetine in over 40% of simulations, and the costs of the two options were estimated to be broadly similar. This recommendation has now changed; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. This study by Tesfaye S et al was published after the literature search so it was not possible to include in the analyses, as per the NICE Guidelines Manual 2012.
Grünenthal Ltd	16	Full	65		**In light of the acknowledged 'overall lack of data on most critical outcomes' the GDG should expand the search to include all RCTs in the first instance followed by good-quality non-randomised studies, if necessary. Searching step-by-step by study design as set out in the NICE Guidelines Manual - Process and Methods Guide 2012**	The review protocol specifies inclusion and exclusion criteria which aim to reduce bias in the evidence considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process.

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						RCTs are the ideal study design, particularly for pharmacological agents. As some studies on some drugs did report the critical outcomes, it would be inappropriate to reduce the threshold for study quality overall.
Astellas Pharma Ltd	3	Full	35	Table 5	**Evaluation of the Quality of Evidence** The evaluation of the quality of the evidence of capsaicin patches as "low" or " very low" is inconsistent with other published evaluations. The current European Federation of Neurological Societies (EFNS) guidelines for the pharmacological treatment of neuropathic pain (Attal N et al 2010) state that *'Capsaicin patches are promising for painful HIV neuropathies or PHN (level A)'*.* Additionally, the previous draft consultation guideline that was produced by NICE in September 2011, stated that '*High quality evidence from four studies with 1272 patients with PHN, showed that topical capsaicin (8% patch) is more effective than placebo in achieving at least 30% pain reduction and global improvement/impression of change from baseline up to 12 weeks follow up'* In addition to these guidelines a recent review of capsaicin patches by The Cochrane Collaboration (Derry S et al Cochrane Database of Systematic Reviews 2013, Issue 2) reported "*All six included studies were of generally high quality..."* It is of concern that the current draft guideline reaches different conclusions regarding the quality of the data to EFNS, the Cochrane Collaboration and the previous	Unlike the reviews quoted, NICE guidelines use GRADE to assess the quality of the evidence across the whole evidence for each outcome (please refer to The Guidelines Manual). The use of GRADE helps to inform recommendations and is used by many organisations. While traditionally an assessment of quality includes an assessment of the risk of bias, GRADE requires assessment of imprecision, inconsistency, and indirectness of the evidence to support making recommendations. Furthermore, as we have assessed GRADE for a network meta-analysis, we are assessing the evidence across a number of interventions in each network, not the evidence for each individual intervention.

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					GDG when the same evidence has been reviewed. * Where 'Level A' rating is defined as "*(established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies*" and where a class I study is defined as "*A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy"* and a class II study is defined as "*a prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy*". (Brainin et al, Eur J Neurol 2004, 11: 577–581).	
NHS England		Full	37	4	A simplified summary may be helpful. E.g.: "Left side good, right bad. Colour intensity reflects probability."	Thank you for your comment. This information is stated in each graphic.
NHS England		Full	38	1	Drugs should be grouped by pharmacological similarity (not simply in alphabetical order). Combinations should be separated from monotherapy.	These are mutually exclusive options, and we have no a priori belief about the comparability or otherwise of any of them. Therefore, it is appropriate to present them in a neutral way.
Napp Pharmaceuticals Ltd	13	Full	39,40, 41, 108,	Tables	The tables are confusing and not easy to understand, perhaps they are trying to convey too much information and the colour gradation is difficult to see.	This is a novel mode of presentation and one that seeks to summarise a large number of analyses, to enable a single overview of all relevant results. Full details of each individual analysis are available elsewhere in the guideline, if readers wish to look into them more closely. The colour gradation would be easier to see if the results were more conclusively in favour of particular treatments; it is an appropriate reflection of uncertainty

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						in the data that it is sometimes hard to distinguish between options.
Faculty of Pharmaceutical Medicine	4	full	39	1	The data display is highly uninterpretable and unhelpful to directly compare treatments and demonstrate why choices for some of the treatments are made We are further concerned that the working algorithms that (presumably) led to these data being used are not being made freely available. This conflicts with the transparency that is being demanded elsewhere, and prevents independent 'What if?' and sensitivity analyses. Moreover, the restrictions on file storage, sharing, etc., effectively restricts algorithm investigation by potentially requiring huge amounts of re-work.	The fact that the summary graphic does not provide a clear demonstration of why one treatment should be preferred over others is an appropriate reflection of uncertainty in the data (as discussed in detail throughout the guideline), not a shortcoming of the mode of presentation. All data included in the synthesis models and all methods of synthesis are fully detailed in the guideline and its appendices. The analyses are entirely replicable without access to the developers' working files.
Napp Pharmaceuticals Ltd	14	Full	43	21-30	With regard to the point here all of the products tested "showed consistent direction of effect estimates compared with placebo. If we accept that this is true why has the guideline been written to exclude certain medicines which obviously would have positive benefits for patients with NP?	The statements referred to are about the clinical effectiveness of amitriptyline, duloxetine, pregabalin, as well as capsaicin cream, gabapentin, morphine, nortriptyline, and tramadol. Tramadol was recommended as acute rescue only but the use of this and morphine as maintenance therapy was not recommended. Capsaicin cream was recommended 'for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments'. Nortriptyline did not appear cost-effective compared to the other drugs and the estimates of effectiveness were highly uncertain. This recommendation has now changed, amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Astellas Pharma Ltd	4	Full	44	1	**Conclusions Regarding Efficacy of Capsaicin Patches**	The evidence statement on capsaicin patch and the evidence to recommendations section has now been amended.

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					The current draft states that '*there is inconclusive evidence on the effectiveness of capsaicin patch,..... in reducing pain compared with placebo'* We are concerned that this differs from the conclusions reached by regulatory authorities and all other guidelines/publications. The EPAR for capsaicin patch concluded that the '*Results of the integrated analysis performed separately for each indication (PHN, HIV-AN) and duration of application (60 and 30 minutes, respectively) showed a significant reduction in pain from baseline to weeks 2 to 12 after 30 minute Qutenza application in HIV-AN (-27%) and 60 minute Qutenza application in PHN (-29.6%) compared to the control (-15.7% and -22.3%, respectively) for all 12-week controlled efficacy studies'* A recent review by the Cochrane Collaboration (Derry S et al Cochrane Database of Systematic Reviews 2013, Issue 2) states that *"High-concentration topical capsaicin used to treat post-herpetic neuralgia and HIV-neuropathy generates more participants with high levels of pain relief than does control treatment using a much lower concentration of capsaicin".* Additionally, the draft consultation guideline that was produced by NICE, dated September 2011, stated that '*High quality evidence from four studies with 1272 patients with PHN, showed that topical capsaicin (8% patch) is more effective than placebo in achieving at least 30% pain reduction and global improvement/impression of change from baseline up to 12 weeks follow up'*	Unlike the reviews quoted, NICE guidelines use GRADE to assess the quality of the evidence across the whole evidence for each outcome (please refer to The Guidelines Manual). The use of GRADE helps to inform recommendations and is used by many organisations. While traditionally an assessment of quality includes an assessment of the risk of bias, GRADE requires assessment of imprecision, inconsistency, and indirectness of the evidence to support making recommendations. Furthermore, as we have assessed GRADE for a network meta-analysis, we are assessing the evidence across a number of interventions in each network, not the evidence for each individual intervention.
Napp	15	Full	44	1-5	We do not agree with the statement that there is	With the exception of the Hanna 2008 and Gimbel

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Pharmaceuticals Ltd					inconclusive evidence on the effectiveness of....gabapentin +oxycodone.....oxycodone.....in reducing pain compared with placebo. We refer you to the following published clinical papers: Zin 2010, Fan 2008, Watson 1998, Hanna 2008, Gimbel 2003, Barrera-Chacon 2011, Xiao-mei 2010, Gatti 2009, Ong 2008.Some of these use active comparators to demonstrate efficacy. A complete list is provided at the end of this response table (see separate Appendix A attached).	2003 studies which were included in the guideline, the other studies you refer to did not meet the inclusion criteria specified in the review protocol. Full details of the Hanna 2008 and Gimbel 2003 studies can be found in the GRADE tables (appendices G, H, and J) and Evidence Tables (appendix E).
British Medical Association	4	Full	44 - 69		The Health Economic Model is fairly impregnable. Although the document does try to explain it, there are a large number of tables that only confuse. The document repeats all of the tables again when discussing central rather than peripheral neuropathic pain, even though it can be summarised as "there are few specific studies, so we will repeat all the same recommendations again". Repeating the tables and figures is confusing, and it would be helpful if this is section was made more clear and easy to follow.	The section has been simplified by the removal of the dose adjusted model. However the analysis is complex and we have endeavoured to make it as transparent as possible
Eli Lilly and Company	10	General			**Economic model comments** As we don't agree with the inputs to the economic model we have concerns about its outputs. Regarding the clinical inputs, as already highlighted, the evidence for many of the treatments was based on very small trials in specific populations and using an assumption of transferability of these results to all patients with neuropathic pain. In addition the model uses doses for amitriptyline and gabapentin that are not likely to be reached in practice (see comment below). Regarding cost inputs we consider these would be more appropriate if they factored in costs associated with titrating to maintenance doses and did not round costs to the next whole tablet. Given this we do not think that the outputs of the economic model are appropriate for	The dosages were the average of dosages in clinical trials. Even though some trials were small, this treats all drugs equally. Costs to titration were not considered as efficacy was assumed to be that seen once titration was completed. As such, it would be inconsistent to consider costs during titration but not efficacy during titration.

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					decision making.	
Astellas Pharma Ltd	5	general			Thank-you for the opportunity to comment on the draft guideline for neuropathic pain. Astellas accept that the model is useful for initial treatments in the primary care setting. We are however concerned that the simple way in which the drug treatments have been modelled is inappropriate for capsaicin patches and as a consequence has resulted in provisional recommendations for capsaicin patches which are misleading. Our main concerns relate to: • The inaccurate assumption of the capsaicin study control arm being a placebo • The failure to take into account the retreatment period for capsaicin patches, which extends beyond the time horizon of the model • The failure of the economic model to reflect clinical practice with regard to capsaicin patches In order to accurately compare the cost-effectiveness of capsaicin patches with other treatments the model would need to be changed substantially. If this is not possible we request that capsaicin patches are **removed** from this economic evaluation, and in order to still provide guidance to the NHS a statement of use based on clinical efficacy added. Currently capsaicin patches are used in specialist pain settings, but with the direction of travel for the NHS of chronic conditions being treated in primary care we had anticipated that capsaicin patches would be recommended as a potential treatment, in line with the previous draft guideline (September 2011) which stated: *The GDG agreed that topical capsaicin (8% patch) should not be initiated without an assessment by a*	The available evidence on capsaicin patch was incorporated into the model in the same way as all other drugs. The costs associated with administration of the patch are likely to be higher than the other drugs considered as at least initially it requires a specialist to place the patch. This additional cost is not included in the model. As explained in the methods in appendix D, the GDG felt it was appropriate to group active placebo with placebo as they felt the active placebos used in the studies would not be likely to have a clinical effect. The included evidence did not substantiate the claim that capsaicin patches can be expected to retain efficacy beyond the timeframe of the model. In the absence of peer-reviewed (ideally, randomised) evidence on this subject, the GDG were content to adopt the simplifying assumption that response rates calculated for 20 weeks of treatment would apply throughout the time horizon of the model. While there may be individuals for whom this represents an underestimate of efficacy, there are others for whom the assumption would be anticonservative. The GDG felt that this was an appropriate reflection of the available data. The health economic model is deliberately focused on the relatively early stages of treatment that are typically accomplished in non-specialist settings. It does not suggest that capsaicin patches represent an effective use of NHS resources in this setting. The use of capsaicin patches (or any other treatment) in a specialist setting following the failure of other options is beyond the scope of this guideline. Therefore, it would not be helpful to alter the health economic model to

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					specialist pain service or a condition-specific service. However, the GDG acknowledged that in the near future, there may be more healthcare professionals trained in using this treatment in non-specialist settings, and therefore the recommendation on topical capsaicin (8% patch) should be re-assessed during the routine 3-year review of this guideline. Astellas consider that in order to provide the NHS with guidance whilst avoiding the issues surrounding the current model it would be useful to have a similar statement in the final version of the guideline.	simulate such eventualities. Evidence available on capsaicin patch compared to other treatments in the economic model suggests it is not cost effective. The current GDG did not speculate explicitly about the future of capsaicin patches in non-specialist settings so it would not be appropriate to make the comment suggested. However, this does not exclude the possibility for this to be reconsidered when this guideline is updated if the training for capsaicin patches has become more widespread outside of specialist settings.
Astellas Pharma Ltd	6	General			**Existing Cost-effectiveness Evaluations** We are also concerned that the findings of the GDG are in contrast to recent HTA recommendations. Using more appropriate models that more closely reflect clinical practice capsaicin patches have been recognised as cost-effective with positive appraisals from SMC and AWMSG.	The model compared a wider range of potential treatments with a broader evidence base than previous studies. . The conclusions reached by the Guideline Development Group may be different to those reached in previous evaluations.
Astellas Pharma Ltd	7	General			In conclusion we have concerns regarding the points made above, and we would recommend that the model is revised. If this is not possible we request that capsaicin patches are **removed** from this economic evaluation. Astellas consider that in order to provide the NHS with guidance whilst avoiding the issues surrounding the current model it would be useful to have a similar statement in the final version of the guideline, as in the	Capsaicin patches were considered as part of the guideline and were not found to be a cost effective option in the treatment of people with neuropathic pain in non-specialist settings. It is therefore not appropriate to remove capsaicin patches from the economic evaluation.

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					September 2011 draft: *The GDG agreed that topical capsaicin (8% patch) should not be initiated without an assessment by a specialist pain service or a condition-specific service. However, the GDG acknowledged that in the near future, there may be more healthcare professionals trained in using this treatment in non-specialist settings, and therefore the recommendation on topical capsaicin (8% patch) should be re-assessed during the routine 3-year review of this guideline*.	
Grünenthal Ltd	17	Full	45	7	It is incorrect to imply that the published economic evaluations involving the lidocaine plaster were inconsistent or contradictory. It should be noted that the lidocaine plaster was included in 3 of the 13 cost–utility studies identified and included in the economic evidence review on peripheral neuropathic pain and was considered cost effective in all 3 studies.	The text in the guideline has been amended to "Results for some of the treatments were inconsistent and occasionally contradictory between analyses."
Royal College of Anaesthetists - Faculty of Pain Medicine	28	full	45	24	Placebo treatment for pain is <u>not</u> the same as no treatment.	The practice of using data from placebo arms of RCTs to assess the benefits and harms of providing no treatment is ubiquitous in health technology assessment in general and health economic modelling in particular. We agree with what you suggest – there may be particular circumstances (and the assessment of treatments for pain may be amongst them) where this might lead to a bias against borderline cost-effective treatments. Methodological research on this subject would be extremely valuable. However, we are confident, in this particular instance, that none of the assessed technologies has been substantively biased against in this way: the decision-making is driven by the relative costs and effects of active comparators, and comparisons against placebo are only relevant in the absence of other options, and all recommended options were judged to represent an

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						effective use of NHS resources, in this regard.
GW Pharmaceuticals plc	5	Full	46	21	The GDG argue that central neuropathic pain should not be considered separately because "efficacy networks too sparse for any individual conditions or subgroups outside of peripheral pain to be able to produce informative models". This stakeholder would argue that this assertion is not evidence-based. There are 3 placebo-controlled, randomised high quality studies of Sativex in central neuropathic pain, together with data from very long term open label use. In Rog et al (2005), Sativex produced a 30% improvement from baseline in 62% vs 41% in placebo, and a 50% improvement in 35% vs 9% on placebo. The Neuropathic pain scale, sleep scale and global impression of change were also highly significant in favour of Sativex. There were no serious adverse events. Patients from this study went on to maintain their improvement over a 2 year period. In Langford et al (2012), a high proportion of 30% responders (55% of all patients) were seen on Sativex, which at 10 weeks of treatment was statistically superior to placebo, but failed to reach statistical significance at 14 weeks due to a sudden surge in placebo responders in the last few weeks of the study. Nonetheless, in a second randomised withdrawal phase to the study, Sativex was clearly and significantly superior to placebo. In Berman et al (2004) Sativex was significantly superior to placebo with an NNT for an improvement vs placebo of 2 units on a 0-10 pain scale of 7.5 and an NNT for sleep improvement of <4. These results taken together have led to the regulatory approval of Sativex in Canada and in Israel for the treatment of CNP in people with MS. While this stakeholder would accept that there are some questions remaining about the extent of efficacy, it cannot be appropriately argued that these data are too sparse to produce uninformative results, especially in a form of neuropathic pain that is known to be resistant to pharmacotherapy.	Rog (2005) is included in the guideline and as a result of the health economic model, Sativex was not considered to be a cost effective option for people with neuropathic pain in non-specialist settings.

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Astellas Pharma Ltd	8	Full	46 54	27 Table 9	**Time to Retreatment** In the model developed for this draft guideline patients have two treatments of capsaicin patches in a 20-week period. The 20-week time horizon is insufficient to capture the benefit of one application of capsaicin patches. The minimum retreatment period for capsaicin patches (as per the SmPC) is 90 days, however this does not mean that patients should be treated every 90 days. Retreatment is indicated when patients who have achieved satisfactory pain relief start to experience pain again. In one of the post herpetic neuralgia (PHN) studies (Webster LR et al Journal of Pain 2010; 11 (10): 972-982) patients could receive additional treatments in an open label extension phase. A total of 282 patients received capsaicin patches, and 123 (44%) responded. The median duration of response was **22 weeks**. Seventeen patients (14%) responded for more than 40 weeks and 10 patients (8%) became and remained pain free for up to 52 weeks (Webster LR Journal of Pain 2010; 11 (Suppl 1) S51). This longer retreatment period is also seen in clinical practice. In patients being treated at the Christie Hospital, Manchester the mean retreatment period was **23.6 weeks** (England J & Bhaskar A. European Journal of Oncology Nursing 2012; 16(Suppl. 1): S25, Abstr. 68). Similarly, in an ongoing observational study of capsaicin patch use in six European countries, median time to retreatment is **31 weeks** (Poole C, Value in Health 2013;16(3):A112).	The available evidence on capsaicin patch was incorporated into the model in the same way as all other drugs. The costs associated with administration of the patch are likely to be higher than the other drugs considered as at least initially it requires a specialist to place the patch. This additional cost is not included in the model. Evidence available on capsaicin patch compared to other treatments in the economic model suggests it is not cost effective. The included evidence did not substantiate the claim that capsaicin patches can be expected to retain efficacy beyond the timeframe of the model, and the evidence cited here is from observational studies that are, as yet, only available as conference abstracts. During development of this guideline, the GDG advised that resolution of symptoms can and does occur with any treatment (and without treatment); therefore, it would introduce unwarranted bias to assume that capsaicin patch is unique in this respect. In the absence of peer-reviewed (ideally, randomised) evidence on this subject, the GDG were content to adopt the simplifying assumption that response rates calculated for 20 weeks of treatment would apply throughout the time horizon of the model. While there may be individuals for whom this represents an underestimate of efficacy, there are others for whom the assumption would be anticonservative. The GDG felt that this was an appropriate reflection of the available data.
British Pain Society	16	Full	46	27	Capsaicin patch application can produce analgesia	The available evidence on capsaicin patch was

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					lasting longer than 20 weeks. Costing a duration of effect at this time point, will artificially increase the cost of treatment.	incorporated into the model in the same way as all other drugs. The costs associated with administration of the patch are likely to be higher than the other drugs considered as at least initially it requires a specialist to place the patch. This additional cost is not included in the model. Evidence available on capsaicin patch compared to other treatments in the economic model suggests it is not cost effective.
Napp Pharmaceuticals Ltd	16	Full	47		In the economic model it is assumed that pain relief of less than 30% is in fact no pain relief? Where does the evidence for this come from? On a scale of 0-10 change of 2 units is recognised as being of benefit to patients.	The model is constrained by the availability of data. As recommended by IMMPACT, trials commonly report 30% and 50% pain relief. We have not seen any trials reporting dichotomised pain relief of >0 but <30%.
Pfizer	10	Full	47	12-30	As noted above, the following utilities are assumed for the health states in the economic model. • Less than 30% pain reduction: 0.16 • 30–49% pain reduction: 0.46 • More than 50% reduction: 0.67 For the adverse events, the following utilities are applied: • Dizziness: Absolute disutility of 0.065 • Nausea: Absolute disutility of 0.12 • Intolerable AE leading to withdrawal: Relative reduction in utility of 10% Therefore, for the intolerable AEs, this corresponds to absolute disutilities of: • Less than 30% pain reduction: 0.016 • 30–49% pain reduction: 0.046 • More than 50% reduction: 0.067	Disutility is a function of both the utility of being in a state and the time a patient remains in that state. The disutility of AEs leading to withdrawal lasts for a longer period than the minor AEs. There are however some circumstances where the total disutility of the 'minor' AEs are higher than those leading to withdrawal. This is not necessarily unreasonable – the AEs leading to withdrawal may be intolerable and, importantly, unmanageable whereas some 'minor' AEs such as nausea may have a more significant impact on utility in the short term but can be mitigated with appropriate treatment. Overall however the difference in the loss of utility from AEs is minor and similar for most drugs and makes little difference to the overall utility generated on a drug.

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					In all health states, therefore, patients experience a greater disutility for a minor episode of nausea compared to a serious AE leading to withdrawal. This does not appear to be clinically plausible. Furthermore, there is no explanation provided of how long the disutility for intolerable AEs is applied for or of the ongoing utility levels for patients who withdraw from treatment. According to the analysis performed for the economic model, pregabalin is associated with low rates of withdrawal leading to AEs. However, it is likely that pregabalin is being penalised, in terms of QALY gain, compared to those drugs with high withdrawal rates overall, but low rates of the specific adverse events considered in this model, nausea and dizziness. Pfizer first requests that all methodology and assumptions relating to utilities associated with adverse events is fully explained in the guideline. Pfizer also suggests that the disutility associated with an intolerable adverse event relative to a minor adverse event is considered and more clinically appropriate values are selected.	
Pfizer	11	Full	47	9-18	Pfizer notes the use of discrete variables with pain reductions of less than 30%, 30-49% and 50% or more in the model as the health states within the model. Pfizer notes that there are a number of limitations with using relative effects as health states within the model. In particular, there is no consideration of the absolute condition of the patients within the model, as a situation may arise in clinical practice where a patient who has a pain reduction of less than 30% may end up in a better health state than a patient that has reduction in pain of	The HRQoL literature we surveyed did not provide evidence to support your comment.. The construction of a patient-level simulation accounting for first-order uncertainty is inappropriate in this situation: it would place yet greater demands on an already inadequate evidence-base.

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					more than 50% depending on their initial pain level. Pfizer suggests that the first order uncertainty be introduced into the model to reflect the variation in patients' baseline pain scores which will allow more realistic absolute health states to be modelled and accordingly quality of life to be generated in the model.	
Pfizer	12	Full	47	8	There is limited explanation or rationale of how the structure or type of economic model was informed from the existing economic evaluations. Pfizer notes that the CDG undertook a systematic review of the economic literature (pg.44, line 14) and understands that economic evaluations identified had low generalisability to the clinical guideline due to the limited number of comparators included in the studies. Nevertheless, there appears to be little or no consideration of how previous economic evaluations from the literature have modelled the condition and how these previous economic models have informed the development of the current model for the clinical guideline. As a result, it appears that the choice of the current economic model is somewhat arbitrary given the use of different outcomes, time horizons, model structures, inputs and treatment sequences identified from the literature. Accordingly, Pfizer suggests that the choice of model structure, choice of inputs and type of model chosen be set in context of the previous models identified in the literature to reduce the perception the model has been created to fit short-term RCT clinical effectiveness data.	The choice of model was not arbitrary but based upon the available data for all the drugs that were considered. Other models did not incorporate the number of drugs considered by the guideline development group (GDG).
Faculty of	5	full	47	20	Important and drug-utility limiting side effects such as	Side effects were incorporated where data was

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Pharmaceutical Medicine					sedation and dry mouth have been inappropriately left out. Consideration should be given to include in the models (perhaps an aggregate of) the most important "rare but serious" side effects of the drugs, as both QoL and cost-driving safety aspects. We again refer to the nortriptiline / amitriptyline example (above and below) as agents (off-label) that share similar unwanted effects and cannot therefore rationally be offered with the same priority in the same patient when one of them has already failed for pharmacodynamic and/or tolerability reasons.	available for all drugs considered in the analysis. Inclusion of partial side effect evidence on those drugs where it was available was not considered appropriate as this would bias results away from drugs where better safety data was available.
Royal College of Anaesthetists - Faculty of Pain Medicine	29	full	48	table	"No pain relief, minor AEs" and "No pain relief, no AEs" should also have a "terminate drug" box added	The patient will continue on the drug for the full 20 weeks so it would not be appropriate to add a "terminate drug" box as suggested.
Astellas Pharma Ltd	9	Full	48	Figure 3	**Model Structure/Treatment Pathway** We understand that economic models cannot completely reflect complex clinical treatment pathways, but the model developed for this draft guideline is a major oversimplification of what occurs in clinical practice, for the following reasons: **Treatment Pathway** The pathway in the model does not reflect clinical practice**.** All seventeen treatments in the model are inappropriately evaluated as first line treatments, irrespective on when they would actually be used in the treatment pathway. We would not envisage that capsaicin patches would be used as a direct alternative to generic tricyclic antidepressants (TCAs), and it is inappropriate for treatment with capsaicin patches to be evaluated for cost-effectiveness in this first line primary care position.	No evidence was available on the drugs considered on their effectiveness as part of a sequential strategy. The model therefore looks at all drugs as first line strategies to assess their effectiveness in this situation. The model highlights drugs that are most likely to be cost effective first line and if they fail/are not tolerated then it suggests which drugs may be cost effective second line treatments. Using available data capsaicin patch is less effective and more expensive than a number of other treatments. Even when other treatments fail capsaicin patch has an unfavourable ICER compared to placebo. Withdrawal through lack of efficacy would lower the costs of capsaicin patch in terms of treatment with the patch, but additional costs would be incurred from a new treatment. The amitriptyline second line scenario that was modelled for withdrawal due to AEs suggested it had little impact on the cost effectiveness of any particular drug and there is no reason to

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					Capsaicin patches are typically used in patients who have failed to respond to or not tolerated standard treatment. e.g. amitriptyline and pregabalin. However this doesn't mean that capsaicin patches are not a useful and cost-effective treatment later in the pathway. In clinical practice CCGs may consider the usage of capsaicin patches in non-specialist settings as a treatment option to avoid referral to specialist pain services and possible more costly procedures. **Withdrawal for lack of efficacy** In the model patients who experience no pain relief are assumed to remain on that treatment for the remainder of the 20 week model. Pain treatment is characterised by analgesic failure (BMJ 2013; 346: 19-21), and a high percentage of patients in the model will follow the 'no pain relief' branch of the decision tree (ref: Tables 7/8 of the current draft guideline). The idea that most patients would remain on ineffective treatment for 20 weeks is entirely inaccurate. In the case of capsaicin patches, this would mean that according to the draft guideline model non-responders would have a repeat application, which does not happen in real life. In clinical practice capsaicin patches are applied by the healthcare professional, and retreatment would only be considered after consultation with the patient to confirm efficacy. This is contrary to other treatments in the pathway where treatment is by repeat prescription and which would involve intervention by the clinician to discontinue.	suspect this would be different for withdrawal due to lack of effectiveness.
Pfizer	13	Full	49	13-25	It is noted that a separate network meta-analyses (NMA)	These analyses are now presented together in the

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					(p. 49 line 13-25) has been undertaken to inform the economic model from the NMAs conducted in the clinical section of the guideline. Pfizer was unable to find any explanation within the clinical guideline of why this was done. We presume that this was done to allow modelling of missing data for comparators at different time points and therefore increase the number of comparators for the economic model as suggested in the Section 5.2 of Appendix F pg 60, pg.7-10. <u>We would suggest that a rationale is inserted into the guideline which explains why different NMAs were conducted for the clinical section and the economic section of the guideline.</u> Pfizer was unable to find any explanation of the inclusion or exclusion criteria for the studies included in the NMA for the economic analysis. Pfizer also notes that there are differences in the studies included in the NMAs in the clinical section for 30% pain relief (all time points) and 50% pain relief (all time points) [Clinical section Table 5, p35 and Appendix G] and the economic section for the 30% and 50% pain relief NMA [Appendix K]. For example, the following studies were included in the economic NMA, but not in the clinical NMA for pain relief and as such, the quality of the evidence has not been comprehensively reviewed: • Boureau et al. (2003), Dongra et al. (2005), Eisenberg et al.(2001), Richter et al (2005), Rowbotham et al. (2004), Vinik et al (2007a), Shaibani et al. 2009, Zeigler et al (2010),	guideline, and it is clarified that the GDG reviewed all evidence together. GRADE profiles detailing the GDG's appraisal of the strength of the evidence for these outcomes have been provided. The methods for conducting the NMA that was used to feed the economic model are described in appendix D. The inclusion and exclusion criteria are essentially the same as for the NMAs performed for the clinical section of the guideline apart from that it was possible to include more evidence in the combined 30% / 50% pain relief since it includes outcomes reported at all follow-up times. The discrete-time analyses are limited to data available at those times. This is one advantage of the approach. The additional studies that are included are those that do not report at any of the discrete timepoints analysed (e.g. those that report at 42 days [too late for 4-wk analysis; too early for 8-wk] and those that report at >14wks).

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					Watson & Evans (1992), Vinik et al (2007b), Wu et al (2008). [NMA 30and 50% pain relief Appendix K, pg 5] <u>Pfizer requests clarification on why there are differences in studies included for economic and clinical NMAs for the same outcomes of 30% and 50% pain relief and what were the differences in the inclusion and exclusion criteria for the different NMAs.</u> It appears from the clinical guideline that no formal quality assessment of the trials identified for the NMA used in the economic evaluation has been undertaken and therefore it is arguable whether a data synthesis of trials should have been undertaken. Pfizer notes from the quality assessment for the NMA of 30% and 50% pain relief (at 28 days, 56 days and 84 days) that that there were 'serious' and 'very serious' limitations, inconsistencies and imprecision with the trials and that the trials were of 'low' or 'very low' quality. (Appendix G, pg 32, 56, 40, 44, 49 and 53). These inherent limitations and biases are likely to be compounded further by pooling studies across different time points and by the inclusion of new studies in the NMA used for the economic evaluation. Pfizer notes that a number of covariates (fixed versus flexible dose regimens, baseline pain status, age, sex and diagnosis) were included to explore difference in the trial characteristics, but these did provide informative results or improve model fit (Appendix K, pg 4, lines 1-4). Pfizer argues that these do not take account of the underlying biases due to the quality of the trials,	

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					differences in trial design, methods of randomisation, and other baseline characteristics differences not included as covariates. On this basis, we suggest that a quality assessment of the all studies included in NMA for the economic evaluation be undertaken to ascertain the overall suitability of these studies for data synthesis. We suggest that the economic NMA point estimates are likely to be severely biased due to difference in trials and that a scenario analysis should also be included in the model that uses data from the clinical NMAs to reflect available observed data from quality assessed trials at comparable time points (rather than modelled data from the economic NMA).	
Grünenthal Ltd	18	Full	49	20-23	The Versatis SPC indicates that 'when needed, the plasters may be cut into smaller sizes with scissors prior to removal of the release liner' and that 'long-term use of Versatis in clinical studies showed that the number of plasters used decreased over time. Therefore treatment should be reassessed at regular intervals to decide whether the amount of plasters needed to cover the painful area can be reduced, or if the plaster free period can be extended. A review of GP prescription data in the UK, from commercially available database of prescribing practice (CSD Patient Data, Cegedim Strategic Data UK Ltd) showed that average overall use was 1.0 lidocaine 5% medicated plaster per day for PHN.	Lidocaine patches are not included in the HE model, due to lack of robust efficacy data.
Pfizer	14	Full	49	6-9	Page 49 of the draft guideline (CG96, 2013) notes that the GDG assumed that the most cost-effective strategy overall is to try treatments in order of their individual probability of cost-effectiveness. However, there is no	Final approval prior to publication is required from NICE. NICE highlighted the following issues:

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					consideration of the appropriateness of this approach, which assumes that a treatment used at 1st line would be equally effective at 2nd or later line, regardless of what treatments had previously failed. So, for example, nortriptyline is as effective in 1st line patients as in patients who have already failed on amitriptyline. A systematic review to evaluate the use of treatments in refractory NeP found that pregabalin was the only drug with refractory evidence available in the licensed NeP population (Plested 2010) – see comment 5 above. As such, whilst the recommendation to use pregabalin after patients have failed on TCAs and gabapentin can be supported by evidence, there is no evidence to suggest that use of the other recommended drugs sequentially would be beneficial to patients. As such, this assumption potentially leads to clinically inappropriate recommendations, such as the recommendation to use amitriptyline and nortriptyline sequentially. Pfizer disagrees with the assumption noted above and its application in the formation of treatment recommendations. Pfizer requests that NICE consider the evidence base available (including real-world observational data) for the sequential use of NeP treatments and re-consider the clinical plausibility of the recommendations made in light of this flawed assumption.	• The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings.

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British Pain Society	17	Full	49	29-30	It is noted that adverse effects are estimated using models that don't adjust for dose. It is well established that many drug adverse event profiles change dramatically with dose. This is a major safety issue.	There was insufficient evidence to model AEs as a dose dependent variable. The guideline recommends that 'After starting or changing a treatment,' healthcare professionals should 'carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.'
Royal College of General Practitioners	19	Full	49	29-30	Noted that adverse effects are estimated using models that don't adjust for dose – everyone that treats pain knows that many of these drugs adverse event profiles change dramatically with dose. This is a major safety issue . **(MJ)**	There was insufficient evidence to model AEs as a dose dependent variable. The guideline recommends that 'After starting or changing a treatment,' healthcare professionals should 'carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.'
NHS England		Full	49	30	Add: "Adverse effects are acknowledged to be dose-related therefore this guidance may not accurately reflect clinical use and risk."	The guideline recommends that 'After starting or changing a treatment,' healthcare professionals should 'carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.'
Astellas Pharma Ltd	10	Full	51-52	Tables 7 & 8	**Placebo vs. Active Control** The calculation of the probability of response of capsaicin patches relative to placebo is confounded because the control arm in the capsaicin patch studies is a low strength capsaicin patch, and not a placebo. This underestimates the efficacy of capsaicin patches when compared to placebo controlled studies of other treatments, and as a result reduces the cost-effectiveness estimate for capsaicin patches. The control treatment, used in the studies considered, was a 0.04% capsaicin patch that was specifically designed as a control for these studies in order to facilitate blinding. The control patches produced reddening of the skin and a local burning sensation, as is seen with the active treatment, but were designed to have minimal clinical efficacy.	As explained in the methods in appendix D, the GDG felt it was appropriate to group active placebo with placebo as they felt the active placebos used in the studies would not be likely to have a meaningful clinical effect. The suggestion that response to 'placebo' may vary according to type of intervention is intuitively reasonable though remains speculative. In the absence of any means of proving and quantifying any bias this introduces into RCTs of capsaicin patch, the GDG had little option but to assume the equivalence of all active and inert placebo arms. If future research, such as that mentioned, is able to provide evidence that illuminates this issue, it will be considered for inclusion in any future update of this guideline.

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					In all of the studies, whether due to an exaggerated placebo effect or a true analgesic effect, the response in the control group was higher than expected, and was sustained over the assessment period. The greater than expected response with the control patch and the demonstrable effect on the epidermis means that the possibility of the control patch exerting a therapeutic effect cannot be excluded (Backonja Lancet Neurology 2008; 7:1106-12). Astellas has recognised the potential impact of the low dose active control on study interpretation, and recent capsaicin patch studies, that do not have an alternative treatment as control, now use a placebo patch.	
Grünenthal Ltd	19	Full	51	1	Tables 7 and 8 suggest that an unprecedented 68% to 71% of patients treated with capsaicin cream achieve greater than 50% reduction in pain scores from baseline. Such estimates of efficacy are more than 20% higher than any other treatment considered in the guideline and are inconsistent with the GDG's consideration of the treatment, namely 'there is some evidence that capsaicin cream is better than placebo at reducing pain'. The only estimate of responder rate for capsaicin cream comes from the Bernstein study which suggests that 9/16 (56.3%) of patients achieve a 30% response at 6 weeks of treatment. In addition to lacking precision small studies, in this case in just 16 patients, are likely to overestimate the true response rate and should therefore be treated with caution. **The economic model should be re-run with more appropriate estimates of efficacy and the recommendation on the use of capsaicin cream reconsidered accordingly.**	All evidence was incorporated into the model in the same way for all drugs to be consistent. However, the guideline development group (GDG) considered the strength of clinical evidence for specific treatments in making their recommendations.
Grünenthal Ltd	20	Full	51	1	The relationship between dose and response for a	The dose-adjusted model is now provided as a

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					number of treatments in the dose adjusted economic model appear inconsistent and to lack clinical plausibility. Comparing Table 7 with Table 8 indicates that the dose of gabapentin has been reduced by approximately 1/3 however the probability of achieving a ≥ 50% response rate has increased. The dose of nortriptyline has been reduced by 60% with no impact on efficacy but with a 20% reduction in the proportion of patients withdrawing due to AEs. Such changes serve to implausibly increase the probability that these products provide greatest net benefit.	scenario analysis, with the model based on unadjusted inputs as the base case.
GW Pharmaceuticals plc	6	Full	51	3rd row of table	The table lists the probability of withdrawal due to AEs on Cannabis extract as 0.46 (0.14 to 0.98). In the Central Neuropathic pain studies cited above, a total of 453 patients were included. Overall, 16 withdrew from Sativex due to an AE, compared with 11 on placebo. It is clearly incorrect to state that the probability of withdrawal due to AEs is 0.46 on drug and 0.09 on placebo. By selecting only two particular adverse events in this table we believe the results stated are incorrect and biased against Cannabis extract.	As stated in your earlier comment, the studies of Sativex for central pain did not meet the inclusion criteria specified in the review protocol or were published after our searches were completed. Moreover, it is not valid to draw inferences from individual arms of studies in the way you suggest. The data synthesis that was undertaken preserved randomisation of all included evidence to arrive at an estimate of relative likelihood of events. These data are then used to estimate withdrawals over the entire 20-week treatment period simulated (and the relatively short follow-up of the included cannabis sativa extract trials means that additional events will be predicted beyond the observed follow-up). The incorporation of individual AEs in the model was limited by the availability of data across all relevant comparators. It is an acknowledged limitation of the model that it cannot account for a wider range of AEs. However, it is not clear why this would results in a particular bias against cannabis sativa extract.
GW Pharmaceuticals plc	7	Full	51	3rd row of table	The table lists the probability of efficacy (responders>30%) as 0.16 (0.10 to 0.17) in cannabis extract. Yet the references that I have referred to, and which have been cited as sources in the guidelines	As stated in your earlier comment, the studies of Sativex for central pain did not meet the inclusion criteria specified in the review protocol or were published after our searches were completed.

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					above show a 30% responder rate in Rog et al (2005) of 62% on Sativex vs 41% on placebo. Similar numbers were seen in Berman et al (2004). Even in the study of Sativex in PNP which the guidelines reference (Nurmikko et al, 2005), the 30% responder rate on Sativex was 28% vs 16% on placebo (p=0.03). In light of these numbers, we believe that the calculation can only have been made incorrectly, and would ask the GDG to re-calculate both the efficacy and safety numbers. As all the relevant trials for Sativex have not been included in this analyses we believe it has affected the outcome stated.	The review protocol specifies inclusion and exclusion criteria which aim to reduce bias in the evidence considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process.
Eli Lilly and Company	11	Full	53	9-10	It would be more appropriate in the both versions of the model to use costs as they relate to the actual dose of the drug rather than rounding to the nearest whole tablet. The estimate of efficacy is the average for the population and for consistency the average dose for the population should be used for estimating costs. Rounding up to the nearest whole tablet biases against non-generic treatments and those agents whose average dose is only just above a whole tablet.	The guideline development group (GDG) felt that no pill splitting should be allowed in the model and rounding up to the nearest whole tablet was the most appropriate way to model drug costs. However, it is acknowledged that pill splitting may occur in practice.
Astellas Pharma Ltd	11	Full	54	9	**Patch Use** The guideline 'dose-adjusted' model uses 2 patches per application of capsaicin, based on clinical opinion. This is an over-estimate and does not reflect clinical practice where less than 2 patches are used. In a published study of 1044 patients treated with capsaicin patches the mean number of patches used was 1.4 $\pm$ 0.9 (SD) per patient at the initial visit with 61% of patients having up to one patch applied (Mainhofener C and Heskamp ML CMRO 2013; 29: 673-683). In an interim analysis of the ASCEND (Observation of the Use of QUTENZA™ in Standard Clinical Practice) study (NCT01737294) (Poole CD et al Value in health	The available evidence on capsaicin patch was incorporated into the model in the same way as all other drugs. The costs associated with administration of the patch are likely to be higher than the other drugs considered as at least initially it requires a specialist to place the patch. This additional cost is not included in the model. Evidence available on capsaicin patch compared to other treatments in the economic model suggests it is not cost effective. The model does not assume two patches simultaneously but two patches sequentially over the 20 week period.

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					2013; 16: A112) a mean of 1.5 patches per treatment were used. The indications included post-operative/post-traumatic PNP (43%), post-herpetic neuralgia (20%), 'other' neuropathies (26%), and neuropathic back pain (11%). In a study of 39 patients with peripheral neuropathic pain of mixed aetiology (reflecting real life clinical practice) at the University Hospitals of Leicester NHS Trust the mean treatment area size was 247cm^2, which is less than the size of one patch (280cm^2) (Bone ME et al. Poster presented at the 15th World Congress of Pain Clinicians, June 27-30, 2012)	
British Pain Society	18	Full	54	Table 9	Capsaicin patch cost is based on treating TWO feet. Whilst that is usually the case for HIV neuropathic pain, most other neuropathic conditions will be a unilateral condition. You have effectively doubled the cost of this treatment by analysing it this way. Also, the side effect profile for topical therapy is reduced compared to systemic therapy. This is also not factored in with the costing process.	The number of patches is taken from trial data. The side effects for capsaicin patch are the same as those considered for all drugs and so are incorporated. In addition, it is two patches sequentially over 20 weeks not two patches given at the same time.
Pfizer	15	Full Appendix F	54 31-32	Table 9 Table F19 & F20	In Table 9 in the Full Guideline, which presents the dosages and costs of drugs used in the economic model, states that for the dose-adjusted model, the recommended dose is 1800mg and the price of £54.60 corresponds to three 600mg tablets/day at the March 2013 tariff price – in other words the simplest administration with the least pill burden. Conversely, in Appendix F, in the GDG advised dose, for the 1800mg gabapentin a pill combination of 4x400mg + 2x100mg is used (i.e. 6 pills per day), costing much less at only £33.80. For the trial dosage analysis, the dose is 2600mg and	The cost in Table 9 (£54.60) is the cost that has been included in the model. Thank you for drawing our attention to the fact that this was not correctly given in Appendix F; this has now been corrected.

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					for this a cost of £46.73 is presented, corresponding to 6x400mg and 2x100mg day, which is the most efficient dosing at a total of 8 pills per day. If gabapentin was administered according to the least pill burden for patients (3x600mg and 1x800mg) the total cost for the trial dose of 2400mg would in fact be £108.82. Pfizer requests that NICE correct the price for gabapentin so that the actual price used in the economic model is presented in both table 9 in the full guideline and table F20. Furthermore, if the GDG-advised dosing was in fact 600mg tds, this is the price (£54.60) that should be used in the economic model, not the cheaper 'more-efficient' price of £33.80. The same principle of minimising pill burden should also be considered for the non-dose adjusted (trial) model. As an alternative, a weighted approach based on the tablets and doses actually used in clinical practice should be considered. Regardless of the approach used, the tablet combination assumptions should be made clear for both the dose-adjusted and trial dose analyses in Table 9 of the Full Guideline.	
Pfizer	16	Full	55 56	11-30 1-2	Pfizer is concerned about the use of absolute health utilities (Severe, (0.16) Moderate (0.46) and Mild (0.67)) from McDermott 2006 for model health states that are defined as a relative effect i.e. pain relief of <30%, 30-49% and ≥50%. This is a significant assumption as this will be dependent on the baseline pain scores of patients. We note that the other study identified from the systematic literature review (McCrink 2006) uses same relative treatment effects of ≥50% improvement (0.78), partial response 30-40% (0.70) and no response <30%	It is not clear that the McCrink utilities are relative and not absolute. The study is an abstract only. We acknowledge that the utilities are absolute and this is a limiting factor in the analysis.

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					(0.61) and is arguably more relevant for the health states chosen in the economic model . Pfizer realises that this data (McCrink 2006) is taken from an abstract, but would argue that this study should be included as a sensitivity analysis to explore the uncertainty within the model. If McDermott source is continued to be used in the model then baseline pain scores should be simulated to allow absolute health states to be modelled and all assumptions relating to the use of this data should be clearly documented. It is also worth noting that the full reference details for these two publications (McDermott 2006 and McCrink 2006) are not provided in the list of references.	
Pfizer	17	Full	55	4-10	Pfizer suggests that the costs associated with adverse effects are likely underestimated for those drugs associated with high rates of AEs and withdrawal due to AEs. NICE assume 1-2 visits to the GP for an AE (nausea or dizziness), and 2-4 visits to a GP for a withdrawal. This approach does not take into account potential drug-drug interactions that are likely to happen in practice. For example, a recent retrospective cohort study compared patients in the US who were initiated on pregabalin (n=2499) to those patients initiated on duloxetine (n=1354) (Johnston et al. 2013). In the pregabalin cohort, no patients experienced a drug-drug interaction, whilst around 37% of duloxetine patients experienced a drug-drug interaction. After multivariable adjustment, duloxetine patients who had a potential drug-drug interaction or drug-condition interaction (71%	Thank you for your comment. Evidence would be required on all drug interactions for inclusion.

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					in total) were associated with a significant increase in mean healthcare costs of $3,346 compared to those without an interaction. Pfizer requests that the potential additional burden of drug-drug interactions is considered within the cost of treating adverse events.	
Faculty of Pharmaceutical Medicine	6	full	55	157	The equation of mild/moderate etc pain to reductions of <30%, 30-49% etc seems very questionable. As well, instead of 2 course and arbitrary "efficacy categories" (30-49% and 50 or more% reduction) that inadequately dichotomizes and will both obscure and at the same time erroneously generate the presence of differences between drugs, one could better express the drug/placebo difference (a continuous difference) as a % reduction of baseline value (either of the placebo or drug group baselines), and maintain the continuity of the data and use that metric in all calculations and inter-drug comparisons. We presume that this is an algorithm outcome. However, we cannot confirm it with the restrictions currently in place on the algorithm(s).	Although arbitrary, this distinction had to be drawn to allow synthesis of the maximum number of studies and also to apply utility values to pain reduction. The categorisation of pain relief into 30% and 50% levels is recommended by IMMPACT guidelines, and commonly adopted by trial investigators. Any attempt to rely on continuous data would have necessitated far more significant and speculative assumptions about the relationship between pain and quality of life, so an approach of this type was rejected.
Pfizer	18	Full	57 61	Table 10 Table 12	Pfizer questions the efficacy and safety results presented for gabapentin in the dose-adjusted study compared with the trial dose analysis. Additionally, Pfizer questions the clinical plausibility of the impact of the dose adjustment on the QALY due to the changes in efficacy and safety.	The dose-adjusted model is now provided as a scenario analysis, with the model based on unadjusted inputs as the base case. This is in line with the stakeholder's suggestion, as is the final recommendation of pregabalin as a second-line option. The methods by which dose-adjusted efficacy and safety estimates were computed are fully detailed in appendix D, and the results presented in detail in appendix G. The stakeholder is correct to note that the effect of

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						dose-adjustment is not uniform: this is to be expected, and merely confirms that the evidence-base for some treatments may underestimate their effectiveness while others may be overestimated. In the case of gabapentin, the point-estimate of the dose–response coefficient (see appendix G, table 55) does, indeed, suggest that lower dosages may be associated with better response-rates (in other words: the assembled evidence may underestimate the true efficacy of gabapentin by including higher-dose trials in which lesser efficacy was seen). However, this estimate is subject to substantial uncertainty, which may suggest the effect comes about through random error alone. Importantly, though, this uncertainty is propagated throughout the synthesis model and appropriately reflected in probabilistic cost–utility modelling. Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed

	Trial Dose					Dose-Adjusted				
	Dose (mg)	Cost (£)	QALY	>50% pain relief	Withdrawal Due to AE	Dose (mg)	Cost (£)	QALY	>50% Pain relief	Withdrawal Due to AE
Amitriptyline	100	£8.20	0.133	0.37	0.24	50	£4.10	0.123	0.30	0.23
Nortriptyline	125	£406.00	0.131	0.40	0.33	50	£162.40	0.133	0.39	0.27
Gabapentin	2600	£46.73	0.134	0.35	0.17	1800	£33.80	0.146	0.43	0.18
Pregabalin	400	£322.00	0.144	0.41	0.19	300	£322.00	0.139	0.37	0.12
Duloxetine	90	£250.60	0.138	0.41	0.23	60	£138.60	0.139	0.40	0.21

See below for full size version of table
Blue = Value reduced compared to trial dose analysis
Yellow = Value increased compared to trial dose analysis

Table 9 in the full guideline outlines that for the 5 drugs recommended in the guideline, the dose from the trial is much higher than the dose recommended by the GDG and used in the dose-adjusted analysis.

Despite this, according to tables 7 and table 8 in the full guideline, for gabapentin, the reduction in dose corresponds to an improved efficacy (50% responder rate), but a slightly worse safety (i.e. higher withdrawal rates), and these inputs lead to an improvement in the QALY gained of 0.134 to 0.146 for the trial dose vs dose-adjusted.

It seems counter-intuitive that improved response rates are seen with reduced doses. In a pooled analysis of gabapentin patients with PDN, Backonja and Glanzman (2003) find that patients treated with gabapentin >1800mg/d had statistically lower pain scores at endpoint compared to placebo, whilst those who had gabapentin <1800mg did not have a statistically different response from placebo. Similarly, the only study included in the economic model that compared fixed

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					doses of gabapentin, found that patients receiving gabapentin achieved >50% reduction in pain in 32% of the 1800mg group compared to 34% of the 2400mg group (both significant improvements over placebo) (Rice and Maton 2001). For the other recommended drugs, it appears that with the lower (dose-adjusted) dose, the efficacy worsens and the safety improves by varying degrees. It is not clear what evidence has been used to support these changes, or how the dose adjustment has been performed. For example, the only study used in the economic model for nortriptyline did not appear to consider the impact of dose on efficacy/safety (Chandra 2006). Furthermore, the impact on the ICER of these changes has not been adequately considered or explored. For amitriptyline and pregabalin, the dose reduction appears to result in a net worsening of the QALY gain, but for duloxetine and nortriptyline, this leads to a substantial increase in the QALY gain. As such, Pfizer request that additional methodological details are provided around how the dose adjustment analysis has been conducted and greater exploration of the uncertainty and assumptions underpinning this analysis. On the basis of the apparent issues with the dose-adjusted analysis, Pfizer suggests that the dose-adjusted analysis should be of secondary importance to the actual trial data analysis.	pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience of its use in non-specialist settings. This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.

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					Under this analysis, at the £20K threshold, amitriptyline provides the greatest net benefit of the 5 drugs recommended for routine use, followed by gabapentin and then pregabalin, then duloxetine and finally nortriptyline. At the £30K threshold, pregabalin provides the greatest net monetary benefit of the recommended drugs, followed (in order) by amitriptyline, gabapentin, duloxetine and finally nortriptyline. Furthermore, there is considerably more uncertainty around the nortriptyline cost-effectiveness estimate, due to the lack of evidence available, compared to pregabalin. This does not appear to have been considered when making the recommendations for this guideline. As such, based on the cost-effectiveness results in the non-adjusted dose analysis, but recognising the cost concerns arising from the original CG96 recommendations, Pfizer suggests that pregabalin should be an option at second-line or later, after amitriptyline and/or gabapentin have failed in all types of peripheral neuropathic pain (see above for request around central NeP).	
Faculty of Pharmaceutical Medicine	7	full	59	2	From this analysis nortr comes out far more likely than ami and the recommendation for ami as initial choice is not supported. Also topiramate and capsaicin come out far superior.	We have updated our analyses. This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Grünenthal Ltd	21	Full	64		Whilst judging the acceptability of different	The drug recommendations state that other drugs

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					pharmacological treatments could be made at the individual patient level, individual adverse effects should impact the overall assessment of individual drugs when their incidence and severity serve to limit the usefulness of the treatment. In recommending capsaicin cream for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments, the guideline should make some reference to the fact it is associated with significant adverse effects and higher rates of withdrawal due to adverse effects than alternative treatments.	should be attempted if initial treatment options are not tolerated. The 'evidence to recommendations' section states highlights that the guideline development group (GDG) felt that decisions of what individual adverse events were acceptable to patients would vary from patient to patient and that this decision should be made on an individual patient basis. The available evidence on capsaicin cream was incorporated into the health economic model in the same way as all other drugs. Withdrawal due to adverse effects is part of the simulated pathway and, consequently, the cost effectiveness of capsaicin cream is attenuated by an appropriate amount as a result of its relatively high withdrawal rates. Despite this, the analysis identifies this treatment as providing good value for money to the average patient. The GDG had concerns about the underlying evidence that suggested the model may somewhat overestimate the cost effectiveness of capsaicin cream (as detailed in the LETR table in section 3.1.4). However, they were confident that it could be recommended it as an option for some patients.
Royal College of Anaesthetists - Faculty of Pain Medicine	30	full	64	4	The recommendations need to clearly state that pharmacological treatment should be individualised on the basis of adverse effects	The drug recommendations state that other drugs should be attempted if initial treatment options are not tolerated. The 'evidence to recommendations' section states highlights that the guideline development group (GDG) felt that decisions of what individual adverse events were acceptable to patients would vary from patient to patient and that this decision should be made on an individual patient basis.
GW Pharmaceuticals plc	8	Full	64	42	The draft states that cannabis sativa extract "did not reduce pain compared with placebo". In the light of the evidence contained in the published studies listed above, and with special regard to central neuropathic pain, especially that caused by multiple sclerosis, this	The evidence statement about cannabis sativa and the evidence to recommendations' section have now been amended.

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					stakeholder believes that the statement is not evidence based. Even the references cited by the guideline do not support this conclusion.	
The Walton Centre for Neurology and Neurosurgery NHS Foundation Trust	3	Full	65	4th line from end of table	Capsaicin patch was given level 1 evidence in the new EFNS guidelines. Mechanism of action is defunctionalising of C-fibres which can lead to reversal of secondary changes at spinal cord level. Clinical experience in nearly 100 patients demonstrated improvement of pain, sleep and quality of life in 50% of patients. Around 2 patches are used per patient but a reduction in the painful area and an extension of the interval between patches has been observed which make it likely that less patches are required than the cost effectiveness analyses predicts. Our patients are tertiary referrals refractory to previous treatments including neuromodulation. Many elderly patients are unable to tolerate TCAs, gabapentinoids or opioids and prefer topical treatments which does not interfere with other treatments for common co-morbidities in this population. Compliance issues and adverse events do not seem to be taken into consideration during the modelling.	Clinical experience does not meet the study design criteria specified in the review protocol. The true effectiveness of a drug must be tested in randomised controlled clinical trials. Withdrawal due to intolerable adverse effects and the incidence of 2 specific tolerable AEs (dizziness and nausea) are included in the HE model. It is an acknowledged limitation of the model that it is not possible to account for all reported AEs without biasing results in favour of treatments with poorly reported AE profiles.
Grünenthal Ltd	22	Full	66		Summary of the GDG considerations - Lidocaine (topical): the suggestion 'there was only 1 small crossover study on topical lidocaine, which showed no effect on pain reduction' is a misrepresentation of the available RCT evidence. There are an additional 8 RCTs in 930 patients, 5 of which were included in the current guideline (CG96). The 8 RCT studies, excluded from the current systematic review, all demonstrate that topical lidocaine is effective in reducing neuropathic pain.	These studies were excluded because they did not fit the study design specified in the review protocol. The review protocol specifies inclusion and exclusion criteria which aim to reduce bias in the evidence considered and increase confidence in the results of the included studies. These criteria which were specified in the review protocol were agreed with the guideline development group (GDG) at the start of the process.
NHS England		Full	66	7	We appreciate that the evidence base for lignocaine (lidocaine) plasters is, at best, weak (low grade evidence). Nonetheless, anecdotal clinical experience strongly supports its use in those patients found to respond. We recommend, at the very least, a trial of	The GDG did not feel that there was enough research that met the inclusion criteria specified in the review protocol to include recommendations about the use of lidocaine.

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					topical lidocaine for localized allodynia before referral to a specialist service.	The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
Napp Pharmaceuticals Ltd	17	Full	66		Morphine has been excluded as the GDG considered the potential risk of opioid dependency. However whilst we acknowledge these concerns, the GDG may wish to review current advice from the British Pain Society on the use of opioids for persistent pain: http://www.britishpainsociety.org/book_opioid_main.pdf "**Types of pain that might benefit from opioids** Pain of both nociceptive and neuropathic origin (including pain related to nervous system injury or disease) might respond to opioid therapy. Good evidence for efficacy or otherwise of therapeutic interventions for a variety of pain syndromes is now available. For some conditions, evidence based guidelines suggest that interventions other than medications are likely to be more successful. There are no conditions under which opioid therapy is contraindicated, but prescribers must be aware of the likely efficacy of a range of interventions for a given condition and use this information to guide management. In most situations, for most patients and most pains, opioids should not be considered as the first choice treatment. To understand where opioids fit into the treatment pathway, refer to validated, evidence-based guidance such as Cochrane Reviews or the Map of Medicine. Discussion with a specialist in pain medicine may be helpful if a prescriber has concerns about starting a patient on opioid treatment".	The guideline development group (GDG) has now included morphine in the treatments that should not be started in non-specialist settings due to the complex issues, such as the risk of dependency. The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Royal College of Anaesthetists - Faculty of Pain	31	Full	66		The draft guidelines state that ONE study showed that gabapentin did not have an effect on pain (and on page 101 on peripheral neuropathic pain that the evidence is	We are not able to include the results from all these studies in our syntheses (due to use of median or follow-up at times not synthesised). The statement

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Medicine					consistent and the negative trial is in central pain), but all these trials (which are included) are "negative" on the primary outcome measure: Hahn et al. 2004 HIV Rintala et al. 2008 SCI Gordh et al. 2088 Nerve injury Smith et al. 2005 Phantom limb pain Except the Hahn study which claims efficacy although there is none demonstrated on the primary efficacy outcome compared to placebo.	referred to in the 'evidence to recommendations' section has been amended to clarify this. In error, 30% and 50% response were not extracted from the Gordh study – these have now been included in the analyses.
Faculty of Pharmaceutical Medicine	8	full	66	Nortriptyline part	Since side effect profiles of ami and nortr are very similar, it is not appropriate to suggest that nortr be used if ami is not tolerated	This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options.
Cambridge University Hospitals NHS Foundation Trust	5	Full	66	7	We acknowledge the lack of robust evidence for use of the lidocaine 5% patch, but would suggest that this, at least, should be included in the list of drugs not to be used in non-specialist settings (implying that it may be used in a specialist setting). See recommendation 1.1.13.	The GDG did not feel that there was enough research that met the inclusion criteria specified in the review protocol to include recommendations about the use of lidocaine. No inferences should be made from this guideline about what should and what should not be used in specialist care settings. The GDG has recommended formal research into the clinical and cost effectiveness of lidocaine for localised peripheral pain.
Royal College of General Practitioners	20	Full	66,68	Lines not numbered	The GDG were rightly concerned about recommending morphine due to the well-known problems of abuse and dependence. The RCGP SEG strongly suggests that similar caution is advanced with gabapentin and pregabalin for those patients who already abuse opiates, or are at risk of doing so. **(SEG)**	The guideline development group (GDG) felt it was important for clinicians to be aware of the potential for dependency issues with a number of drugs for neuropathic pain, including for those with a history of addiction problems. This should be considered along with the overall risks and benefits of each treatment for a particular patient. However, they were concerned that patients with a history of drug misuse may not be

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						given effective treatment when needed. They noted these concerns in the 'evidence to recommendations' section that this should be taken into consideration among the balance of overall risk and benefits of each treatment on an individual patient basis.
Faculty of Pharmaceutical Medicine	9	full	67		The rationale why e.g. topiramate, pregabalin and capsaicin cannot be recommended as first choice is questionable. The suggested first choice drugs all have substantial adverse effects that do not appear to be less important or complex than those of drugs not recommended. Since for their "primary" indications (depression and seizures resp) both ami and nortr and gabapentin are typically prescribed by specialists only and not initiated in non-specialist care settings, among others also because of their side effect profiles, the choice for the now recommended initial treatments appears arbitrary and is not supported by much of the evidence that rates especially capsaicin cream as superior.	The guideline development group (GDG) considered that the particular issues around adverse events associated with topiramate mean that it should only be used in settings which may better understand this profile, such as specialist pain services. This recommendation has now changed. Nortriptyline is no longer recommended as a treatment option; amitriptyline, duloxetine, pregabalin or gabapentin are now recommended as initial treatment options. The evidence around capsaicin cream did not support its use as initial treatment, however the GDG did recommend its use 'for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments'. NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
Primary Care Neurology Society	5	Full	67		Lidocaine patches are excluded on the grounds of poor trial evidence. The drug is specifically licensed for PHN and clinically is very useful in focal allodynia. Many Local Health Boards have carried out their own audits on patients with focal painful conditions and have found it to be clinically effective and have thus included it in their formularies. Despite this practical evidence it is excluded from the guidance.	Clinical experience does not meet the study design criteria specified in the review protocol. The true effectiveness of a drug must be tested in randomised controlled clinical trials. The GDG has recommended formal research into the clinical and cost-effectiveness of lidocaine for localised peripheral pain.
UK Clinical	9	Full	67	46-	Given the fact that patents expire and cost is now a	As part of the NICE reviews process, each clinical

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Pharmacy Association					predominant factor in determining the hierarchy of treatments for NeuP within the guidance, regular review should be made when patents expire (and prices change) to ensure that guidance remains current and appropriate.	guideline is considered for an update at regular defined intervals and if significant new evidence is identified or if the costs of the drugs change considerably, the guideline may be considered for an update.
Faculty of Pharmaceutical Medicine	10	full	67	Capsaicin cream part	Given the results presented before, capsaicin cream would be an appropriate additional initial choice for patients who would prefer a topical rather than systemic treatment, or have a small localized area of pain.	Thank you for your comment. Capsaicin cream has been recommended for 'people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments'.
GW Pharmaceuticals plc	9	Full	68	HE model	The draft makes the comment that some treatments (including Cannabis sativa extract) appeared to be less effective than placebo. This conclusion is entirely unjustified by the evidence. In no study has placebo been shown to be significantly superior to Sativex in the treatment of neuropathic pain.	It is not stated that placebo has been shown to be significantly superior to any other treatment. However, the base-case estimate of the health economic model is that some treatments have lower expected health gains than placebo (cannabis sativa extract is one such option). It should be noted that the cost-effectiveness model incorporates data on efficacy, safety and tolerability to estimate a net health effect. Therefore, the analysis synthesises the empirical findings that cannabis sativa extract appears no more effective than placebo whereas it is subject to higher rates of adverse effects (and withdrawals due to them). These data combine to suggest that the average patient taking cannabis sativa extract will have lower expected benefit than one taking placebo.
Napp Pharmaceuticals Ltd	18	Full	68		The mean cost per QALY.....The GDG, although agreeing with the probability that morphine might provide maximum net benefit was not trivial, decided that opioids should be relegated to acute pain only and that tramadol was the safer option in non-specialist settings. GPs in primary care are familiar with using a wide range of opioids and aware of the risks and benefits. The BPS guidelines already mentioned also serve to guide GPs in the safe use of these medicines.	The GDG felt that the long term safety implications of morphine use that were not captured by the model outweighed its potential efficacy as maintenance medication.

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					This guideline is clearly restricting choice of medication and limiting options for the clinician treating NP patients. The GDG has also urged caution with tramadol in the elderly patient. Alternatives such as oxycodone, morphine and oxycodone / naloxone could be included in this treatment position.	
The Walton Centre for Neurology and Neurosurgery NHS Foundation Trust	4	Full	68	Line 15 from end of the table	According my knowledge the capsaicin patch was never compared to placebo. An active control was used to mimic the burning sensation.	The evidence tables show if placebo or active placebo was used in each study. However, the guideline development group (GDG) felt it was appropriate to combine placebo and active placebo as 'placebo' for the analysis as they considered that any analgesic effect was likely to be minimal. This has now been explained in appendix L.
NHS England		Full	70	15	We welcome the view taken on capsaicin cream.	Thank you for your comment
The Walton Centre for Neurology and Neurosurgery NHS Foundation Trust	5	Full	71	2	I agree with the research recommendation and we are planning a UK registry for neuropathic pain patients where data could be stratified.	Thank you for your comment
Napp Pharmaceuticals Ltd	19	Full	90	29-31	Please see clinical papers listed at the end of the comments for further evidence for oxycodone.	Thank you for these references which have been checked. However, they do not meet the inclusion criteria specified in the review protocol.
Napp Pharmaceuticals Ltd	20	Full	101		In relation to the GDG decision to include amitriptyline (un-licensed) when the evidence is reduced to a single trial is not balanced when other treatments which are licensed are excluded in spite of more evidence being available. More pragmatism needs to be used by the GDG when evaluating evidence.	We have removed the separate health economic analysis for peripheral neuropathic pain from the guideline, as the GDG did not make separate recommendations for this population. It should be emphasised that there is more than a single trial supporting the recommendation for amitriptyline. Volume of evidence alone cannot be a reason for recommending a treatment; rather, a thoroughgoing analysis of the available evidence is necessary, as was undertaken here. It should be noted that the uncertainty inherent in estimates of efficacy and safety drawn from smaller numbers of study participants is appropriately reflected in data analysis and propagated throughout the health economic decision model.

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						Final approval prior to publication is required from NICE. NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are

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						provided in the BNF) and there is extensive experience of its use in non-specialist settings.
Napp Pharmaceuticals Ltd	21	Full	101	3.2.4	The evidence for tramadol is mixed and the duration of the study is very short. However the GDG felt it was possible to recommend tramadol in PNP. The trade off between benefits and harms is assumed to be generalisible from all neuropathic pain to PNP and that the recommendations from all NP could apply to PNP. We would suggest that again there needs to be some consideration of alternatives to tramadol for elderly patients or those who have contraindications or who have side-effects.	NICE clinical guidance provides recommendations and does not replace individual clinical judgement when considering the most appropriate treatment for people with neuropathic pain.
Napp Pharmaceuticals Ltd	22	Full	102	Quality ...	Comments are made about insufficient follow up periods and yet, as stated above, a 4 week trial was deemed adequate for amitriptyline.	The guideline development group (GDG) considered 4 weeks as a minimum follow-up time but felt that ideally the studies should be longer than 8 weeks.
Pfizer	19	Full	110	18	NICE assert, in the draft guideline, that there is insufficient evidence to differentiate recommendations for central NeP from the 'all neuropathic pain' (p110, 'Evidence to Recommendations'). Pfizer disagrees that the paucity of evidence in central NeP (for drugs other than pregabalin) provides a sufficient rationale to recommend amitriptyline, nortriptyline, gabapentin and duloxetine in all types of NeP including central NeP patients. Pregabalin is the only treatment licensed for central neuropathic pain in the UK. Its use in central neuropathic pain is supported by a number of RCTs as noted in the draft guideline, plus one study not included in the guideline evidence review (Cardenas 2013). This study demonstrated, in agreement with earlier studies, that pregabalin treatment resulted in statistically significant	The GDG felt it was inappropriate to rely on such a small number of trials that covered only 6 drugs of interest and which only small numbers reported the efficacy outcomes which they considered critical and important to decision-making. The lack of evidence on relevant drugs and on outcomes of interest made it difficult to assess the evidence for central pain. In the absence of relevant data, the GDG felt it would be most appropriate to consider the evidence for all neuropathic pain for conditions with central pain. The GDG felt that trigeminal neuralgia was distinct from all other causes of neuropathic pain and that it was inappropriate to recommend the same drugs for this condition. Final approval prior to publication is required from NICE.

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					improvements over placebo for the primary outcome of change in pain and in key secondary outcomes. Furthermore, the EFNS guideline recommends pregabalin as a first-line treatment option in central neuropathic pain and considered pregabalin to be the only drug with Level A (highest level) evidence in central neuropathic pain (Attal 2010). Comparatively, there was virtually no evidence found to support the use of the other pharmacological options recommended in the draft guideline. A single study comparing amitriptyline to placebo and carbamazepine, involving 15 patients was found and another study compared duloxetine to placebo in 40 patients was found. No studies for nortriptyline or gabapentin were found. In light of the robust evidence for pregabalin, which consistently demonstrates efficacy in this difficult-to-treat population, compared to the virtually non-existent evidence base for the other pharmacological options recommended in this guideline, Pfizer requests that NICE and the GDG consider whether a specific recommendation for pregabalin as the first-line treatment of choice in central neuropathic pain would be appropriate.	NICE highlighted the following issues: • The uncertainty of the clinical evidence of efficacy included within the guideline and the consequent low reliability of the health economic model. • The requirement for the guideline to cover all types of neuropathic pain by a licensed or best available treatment. • The recommendation of an off-label preparation above a licensed preparation based on cost alone but in the absence of clear evidence of greater clinical efficacy in the outcomes identified as critical by the GDG. These issues have led NICE to the decision that we are unable to endorse a recommendation for an off-label pharmacological preparation ahead of a licensed pharmacological preparation in the absence of strong clinical evidence. For this reason, recommendation 1.1.8 includes duloxetine and pregabalin as initial treatment options for neuropathic pain alongside amitriptyline and gabapentin. Nortriptyline is no longer recommended in the guideline. Regarding amitriptyline the GDG felt it was appropriate to recommend amitriptyline as an alternative first line treatment despite the fact that it is off label in Neuropathic Pain, as analysis showed that it has a high probability of providing effective use of NHS resources, it is well established as a treatment for Neuropathic Pain (for example, details of dosages are provided in the BNF) and there is extensive experience

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						of its use in non-specialist settings.
Napp Pharmaceuticals Ltd	23	Full	115		Quality of evidence The GDG agreed that a formal evidence review is not necessary to support good principles of care. This seems contrary to the process which has taken place and has eliminated treatment options for the non-specialist at a time when the NHS has been committed to delivering as much care as possible to the patient at local level.	Thank you for your comment. The drug recommendations provide a number of options for the treatment of neuropathic pain and do not recommend specific drugs where there is no or conflicting evidence about their efficacy. Performing a formal review of evidence for the principles of care would not have an impact on the number of drugs that have been recommended. The GDG recognised that the management of some patients and the use of some drugs would require specialist input. This would not preclude services still being delivered at local level, and recommendation 1.1.11 contains provision for interaction between specialist and non-specialist healthcare providers for this reason.
Pfizer	20	Full	115	8	On page 115, under the trade-off between benefits and harms, the GDG note that: *"Clear statements about drug dosage and titration in the recommendations are crucial for non-specialist settings, to emphasise the importance of titration to achieve maximum benefit and also to minimise dose-related adverse effects."* However, Pfizer notes that in the actual recommendations for key principles of care outlined at the start of the guideline, no specific recommendations are made about dose and titration. Pfizer agrees that the addition of such practical recommendations would make	We are aware the previous version of the guideline reported dosages. However, NICE guidelines do not normally include dosages for recommended drugs. Suggested dosages are found in the summary of product characteristics (SPC) and British National Formulary (BNF) for each drug, including for situations when they are used off-label. Furthermore, the GDG felt it was inappropriate to list them in the recommendations as the dosages required for each patient will be assessed on an individual patient basis. The guideline development group (GDG) felt this was important but that sufficient information would be found in the SPC. This statement has been amended.

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					the guidelines much more useful for non-specialists and request that the GDG consider the addition of these.	
NHS England		Full	118		1.1.5 should include assessment of psychological state, as above.	This has been added to the recommendations for what should happen at the regular clinical review.
NHS England		Full	139	13	Reference needs updating as this consultant is now at National Hospital for Neurology and Neurosurgery, University College London Hospitals.	Thank you for your comment, this has been updated within the guideline
Royal College of General Practitioners	21	Full	155	2	We suggest that the potential for addiction and withdrawal syndromes and cumulative toxicity with opiates with pregabalin and gabapentin are subject to further research. **(SMAH)**	This has been added to the recommendations for research.
Eli Lilly and Company	12	Appendix F	31	Table F19	The GDG provided estimates of what they believe to be the most common doses of each drug used to treat neuropathic pain. With respect to amitriptyline and gabapentin doses of 50mg/day and 1800mg/day respectively were used in the dose-adjusted analyses. However, in the UK most patients receive suboptimal doses and hence lower efficacy i.e. a paper published by Gore et al in 2007 using data from the GPRD database showed that only 18% of patients received 50mg or greater of amitriptyline per day. With respect to gabapentin only 0.2% received 1800mg or greater per day. A recent analysis from Cegedim database (Data on File 2013) supports that the situation from 2007 has not changed significantly. From this database an average dose of 26mg/day for amitriptyline and 1028mg/day for gabapentin was estimated for patients diagnosed with neuropathic pain. Based on the above we believe that the efficacy and costs parameters pertaining to the higher doses used in the economic modelling are not reflective of the efficacy and costs that would be observed in clinical practice and therefore cannot be relied upon for decision making.	The dose-adjusted model is now not relied on as a primary analysis. Nevertheless, decision-making should be based on the appropriate dosage of an agent. If there is evidence that prescribers are failing to provide treatments at an appropriate dose, this should not be used to penalise those treatments in analysis. We will pass on your comments to the implementation team, who may be able to highlight this issue in the material accompanying this guideline.

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					1. Gore et al. Clinical characteristics and pain management among patients with painful peripheral neuropathic disorders in general practice settings. European Journal of Pain 11 (2007) 652–6 2. Data on File: CSD Patient Data, Cegedim Strategic Data UK Ltd, May 2013	
Eli Lilly and Company	13	Appendix F	32	4-5	The modelling does not include resource use costs associated with dose titration. There are differences between the treatments in terms of the number of titrations needed to achieve the maintenance doses used in each of the two economic models. For example, gabapentin and amitriptyline are initiated at lower doses and in practice will require several titrations to get to the doses used in the economic modelling. Each titration may be associated with HCP contacts and hence resource costs which should be considered in the model. These costs could have a meaningful impact on the economic results.	The GDG advised that, in practice, administration costs of all options could be assumed to be similar. We did not identify any evidence of systematic differences in resource-use in the published evidence included in the review.
Astellas Pharma Ltd	12				References: Neuropathic Pain. The pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline. Draft for consultation, September 2011 Backonja M, Wallace MS, Blonsky ER et al. NGX-4010, a high concentration capsaicin patch, for the treatment of post-herpetic neuralgia: a randomised, double blind study. Lancet Neurology 2008; 7: 1106-1112 Webster LR, Malan TP, Tuchman MM et al. A multicenter, randomized, double blind, controlled dose finding study of NGX-4010, a high concentration capsaicin patch for the treatment of postherpetic neuralgia. The Journal of Pain 2010; 11: 972-982	Thank you for these references.

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					Webster LR. Duration of treatment response to NGX-4010, a high concentration capsaicin patch, in patients with postherpetic neuralgia. The Journal of Pain 2010; 11: (Suppl 1) S51 0 England J and Bhaskar A. Management of cancer-related neuropathic pain using the 8% capsaicin patch. European Journal of Oncology Nursing 2012; 16(Suppl. 1): S25, Abstr. 68 Poole CD, Chambers C, Odeyemi I, Currie CJ. Treatment of peripheral neuropathic pain with the capsaicin 8% patch: an observational study in six European countries. Value in Health 2013; 16 (3): A112 Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. BMJ 2013;346:f2690 doi: 10.1136/bmj.f2690 (Published 3 May 2013) Maihofner C and Heskamp ML. Prospective, non-interventional study on the tolerability and analgesic effectiveness over 12 weeks after a single application of capsaicin 8% cutaneous patch in 1044 patients with peripheral neuropathic pain: first results of the QUEPP study. Current Medical Research & Opinion 2013; 29: 673-683 Bone ME et al. Clinical evaluation of the efficacy of capsaicin 8% topical patch in the management of neuropathic pain. Poster presented at the 15th World Congress of Pain Clinicians, June 27-30, 2012 Attal N et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology 2010; 17: 1113-1123	

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<tr><td></td><td></td><td></td><td></td><td></td><td>Brainin M et al. Guidance for the preparation of neurological management guideline by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol 2004; 11: 577-581

Derry S et al. Topical capsaicin (high concentration) for chronic neuropathic pain in adults (Review). The Cochrane Library 2013, Issue 2

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Irving GA, Backonja M, Rauck R et al NGX-4010 a capsaicin 8% dermal patch, administered alone or in combination with systematic neuropathic pain medications, reduces pain in patients with postherpetic neuralgia. Clin J Pain 2012; 28: 101-107

Derry S et al. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. The Cochrane Library 2009, Issue 4

Simpson DM et al. Controlled trial of high-concentration capsaicin patch in painful HIV neuropathy. Neurology 2008; 70: 2305-2313</td><td></td></tr>
<tr><td>Pfizer</td><td>20</td><td></td><td></td><td></td><td><u>Additional Table</u>

Table comparing Trial Dose and Dose Adjusted Analyses: Costs, QALYs, Efficacy and Safety
<table>
<tr><td></td><td colspan="5">Trial Dose</td><td colspan="5">Dose-Adjusted</td></tr>
<tr><td></td><td>Dose</td><td>Cost</td><td>QA</td><td>>50%</td><td>Withdra</td><td>Dose</td><td>Cost</td><td>QA</td><td>>50%</td><td>Withdra</td></tr>
</table></td><td>The dose-adjusted analysis now only used as a scenario analysis in the appendices.</td></tr>
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	(mg)	(£)	LY	pain relief	wal Due to AE	(mg)	(£)	LY	Pain relief	wal Due to AE
Amitriptyline	100	£8.20	0.133	0.37	0.24	50	£4.10	0.123	0.30	0.23
Nortriptyline	125	£406.00	0.131	0.40	0.33	50	£162.40	0.133	0.39	0.27
Gabapentin	2600	£46.73	0.134	0.35	0.17	1800	£33.80	0.146	0.43	0.18
Pregabalin	400	£322.00	0.144	0.41	0.19	300	£322.00	0.139	0.37	0.12
Duloxetine	90	£250.60	0.138	0.41	0.23	60	£138.60	0.139	0.40	0.21

Blue = Value reduced compared to trial dose analysis
Yellow = Value increased compared to trial dose analysis

References

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- Attal et al. EFNS guidelines on NeP. 2009 revision. European Journal of Neurology 2010

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					• Backonja, Glanzman. Clin Ther 2003;25(1):81–104. • Beith et al. Pain. 2011; 152(7): 1511-1516 • Cardenas et al. Neurology 2013;80;533-539 • Chandra (2006) International Journal of Clinical Pharmacology & Therapeutics 27 44: 358-63 • Douglas et al. Poster presented at British Pain Society, April 2007, Liverpool • Dworkin et al. Pain 2005, 113:9-19. • EMA report on Duloxetine new indication. (Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000572/WC500128545.pdf (accessed July 2013). • Freynhagen et al. Current Medical Research and Opinion. Vol. 22, No. 10, 2006, 1911–1920 • Freynhagen et al. Int. J. Clin. Pract. 2007;61(12):1989-1996 • Geisser et al. Clin J Pain 2000, 16:110-120. • Hall et al. Pain 122 (2006) 156-162 • Hanu-Cernat et al. Poster presented at Poster presented at 2005 IASP, Sydney, Australia • Hope-Simpson. Journal of the Royal college of Practitioners 1975;25;571-575 • Johnston et al. (2013) AJHP In Press.	

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					• Lampl et al. J Neurol 2010; 257: 1265-1273 • Lesser et al. (2004) Neurology 63: 2104-10 • Lunn et al. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD007115. DOI: 10.1002/14651858.CD007115.pub2. • Morera-Domínguez et al. 2010 Adis Data Information BV, Clin Drug Investigation : 1-15 • Plested et al. BMC Neurol. 2010; 10:116 • Rice, Maton (2001) Pain 94: 215-24. • Saarto T, Wiffen PJ. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005454. DOI: 10.1002/14651858.CD005454.pub2. • Smith, Haythornthwaite. Sleep Med Rev 2004, 8:119-132 • Solaro et al. J Neurol 2009; 256:1773–1774 • Smith and Roberts, Journal of Pain (Vol 8) No.5, 2007 396-404 • Stacey et al. Pain Med. 2008;9(8):1202-1208. • Tanenberg et al. Mayo Clin Proc July 2011; 86 (7): 615-624 • Toth C et al. Pain Medicine 2010; 11:456-465 • van Seventer et al. Health & Quality of Life Outcomes. 9:17, 2011.	

These organisations were approached but did not respond:

AbbVie
Abertawe Bro Morgannwg University NHS Trust
Action for ME
Aintree University Hospital NHS Foundation Trust
Alder Hey Children's NHS Foundation Trust
Allergan Ltd UK
Allocate Software PLC
Archimedes Pharma Ltd
Arden Cancer Network
Ark Therapeutics Ltd
Arthritis and Musculoskeletal Alliance
Arthritis Research UK
Association for Palliative Medicine of Great Britain
Association of Anaesthetists of Great Britain and Ireland
Association of British Clinical Diabetologists
Association of British Insurers
Association of Chartered Physiotherapists in Neurology
Association of Chartered Physiotherapists in Women's Health
Back Care
Basildon and Thurrock University Hospitals NHS Foundation Trust
Bedfordshire and Hertfordshire Tissue Viability Nurses Forum
Black and Ethnic Minority Diabetes Association
Blackpool, Fylde and Wyre Hospitals NHS Foundation Trust
Boehringer Ingelheim
Bolton Primary Care Trust
Boots
Boston Scientific
Bowel Cancer UK
Brain and Spine Foundation
Brighton and Sussex University Hospital NHS Trust
Bristol-Myers Squibb Pharmaceuticals Ltd
British Acupuncture Council
British Association for Counselling and Psychotherapy
British Association of Art Therapists

British Association of Hand Therapists
British Association of Neuroscience Nurses
British Association of Otorhinolaryngologists, Head and Neck Surgeons
British Association of Prosthetists & Orthotists
British Association of Psychodrama and Sociodrama
British Association of Stroke Physicians
British Medical Journal
British National Formulary
British Nuclear Cardiology Society
British Orthopaedic Association
British Paediatric Neurology Association
British Psychological Society
Brunel University
Cambridgeshire Primary Care Trust
Camden Link
Capsulation PPS
Capsulation PPS
Care Quality Commission (CQC)
Chartered Society of Physiotherapy
Chronic Pain Policy Coalition
Citizens Commission on Human Rights
Clarity Informatics Ltd
Commission for Social Care Inspection
Countess of Chester Hospital NHS Foundation Trust
Coventry and Warwickshire Cardiac Network
Covidien Ltd.
Croydon Clinical Commissioning Group
Croydon Health Services NHS Trust
Croydon University Hospital
Daiichi Sankyo UK
Department for Communities and Local Government
Department of Health, Social Services and Public Safety - Northern Ireland
Diabetes UK
Dudley Primary Care Trust
East and North Hertfordshire NHS Trust
East Kent Hospitals University NHS Foundation Trust

East Lancashire Hospitals NHS Trust
Economic and Social Research Council
Expert Patients Programme CIC
Faculty of Dental Surgery
Faculty of Occupational Medicine
FibroAction
Fibromyalgia Association UK
Five Boroughs Partnership NHS Trust
Galil Medical
Golden Jubilee Regional Spinal Cord Injuries Centre
Goldshield
GP Care
Greater Manchester Neurosciences Network
Hammersmith and Fulham Primary Care Trust
Harrogate and District NHS Foundation Trust
Harrow Local Involvement Network
Health Protection Agency
Health Quality Improvement Partnership
Healthcare Improvement Scotland
Heart of England NHS Foundation Trust
Herpes Viruses Association
Herts Valleys Clinical Commissioning Group
Hindu Council UK
Hockley Medical Practice
Humber NHS Foundation Trust
Hywel Dda Local Health Board
Independent Healthcare Advisory Services
Inspirability
Institute Metabolic Science
Integrity Care Services Ltd.
iQudos
Kidney Cancer Support Network
Knowsley Primary Care Trust
Lancashire Care NHS Foundation Trust
Leeds Community Healthcare NHS Trust
Leeds Primary Care Trust (aka NHS Leeds)

Lincolnshire Teaching Primary Care Trust
Livability Icanho
Liverpool PCT Provider Services
London Borough of Hounslow
London cancer alliance
Lundbeck UK
Luton and Dunstable Hospital NHS Trust
MASCIP
Maternity and Health Links
MBB Connections Healthcare
McCallan Group, The
Medicines and Healthcare products Regulatory Agency
Medtronic
Merck Sharp & Dohme UK Ltd
Ministry of Defence
MIPCA
Motor Neurone Disease Association
Multiple Sclerosis Society
Multiple Sclerosis Trust
Musculoskeletal Association of Chartered Physiotherapists
Myeloma UK
National Association of Primary Care
National Cancer Action Team
National Cancer Research Institute
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health
National Diabetes Nurse Consultant Group
National Hospital for Neurology & Neurosurgery
National Institute for Health and Clinical Excellence
National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research
National Patient Safety Agency
National Public Health Service for Wales
National Spinal Injuries Centre

National Treatment Agency for Substance Misuse
Neuromodulation Society of UK & Ireland
NHS Barnsley Clinical Commissioning Group
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Cornwall and Isles Of Scilly
NHS County Durham and Darlington
NHS Cumbria
NHS Direct
NHS England
NHS Greater Manchester Commissioning Support Unit
NHS Luton CCG
NHS Manchester
NHS Plus
NHS Plymouth
NHS Sefton
NHS Sheffield
NHS Warwickshire North CCG
NHS Warwickshire Primary Care Trust
NHS West Suffolk CCG
NICE technical lead
North and East London Commissioning Support Unit
North Lincolnshire and Goole Hospitals NHS Foundation Trust
Northumbria Diabetes Service
Northumbria Healthcare NHS Foundation Trust
Nottingham City Council
Oxleas NHS Foundation Trust
Paget's Association
Pain Concern
Pain Relief Unit
Pain Solutions
Parenteral and Enteral Nutrition Group
Pelvic Pain Support Network
PERIGON Healthcare Ltd
PharMAG
Pharmametrics GmbH

Primary Care Partnerships
Primary Care Pharmacists Association
Primrose Bank Medical Centre
Pseudomyxoma Survivor
Public Health Wales NHS Trust
Queen Elizabeth Hospital King's Lynn NHS Trust
Queen Victoria Hospital NHS Foundation Trust
Rarer Cancers Foundation
Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust
Royal Berkshire NHS Foundation Trust
Royal Brompton Hospital & Harefield NHS Trust
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Free Hospital NHS Foundation Trust
Royal Hallamshire Hospital
Royal National Institute of Blind People
Royal National Orthopaedic Hospital NHS Trust
Royal Pharmaceutical Society
Royal Society of Medicine
Salford Primary Care Trust
Salford Royal Foundation Hospital
Sandoz Ltd
Sandwell Primary Care Trust
Sanofi
Scottish Intercollegiate Guidelines Network
Sheffield Primary Care Trust
Sheffield Teaching Hospitals NHS Foundation Trust
Sherwood Forest Hospitals NHS Foundation Trust

Shine
Social Care Institute for Excellence
Social Exclusion Task Force
Society for Back Pain Research
Society of British Neurological Surgeons
South East Staffordshire and Seisdon Pennisula CCG
South London & Maudsley NHS Trust
South West Yorkshire Partnership NHS Foundation Trust
Southport and Ormskirk Hospital NHS Trust
Special Products Ltd
Spinal Injuries Association
Spinda Bifida . Hydrocephalus . Information . Networking . Equality
St James Priory Project
St Jude Medical UK Ltd.
St Lukes Hospice
St Mary's Hospital
St Michaels Hospice
Staffordshire and Stoke-on-trent NHS Partnerships
Staffordshire University
Stockport Primary Care Trust
Sutton and Merton Community Services
Tenscare Ltd
Teva UK
The Association of the British Pharmaceutical Industry
The College & Fellowship of Podiatric Medicine
The For All Healthy Living Centre
The Haemophilia Society
The Patients Association
Torbay and Southern Devon Health and Care NHS Trus
Transverse Myelitis Society
Trigeminal Neuralgia Association UK
Trinity-Chiesi Pharmaceuticals
UCB Pharma Ltd
UK Acquired Brain Injury Forum
UK Multiple Sclerosis Specialist Nurse Association
United Kingdom Council for Psychotherapy

United Kingdom National External Quality Assessment Service
University College London Hospital NHS Foundation Trust
University Hospital Birmingham NHS Foundation Trust
University Hospital of North Staffordshire NHS Trust
University Hospitals Birmingham
Velindre NHS Trust
Walsall Local Involvement Network
Welsh Association of ME & CFS Support -
Welsh Government
Welsh Pain Society
West Herts Hospitals NHS Trust
Western Cheshire Primary Care Trust
Western Health and Social Care Trust
Western Sussex Hospitals NHS Trust
Westminster Local Involvement Network
Wockhardt UK Ltd
Wound Care Alliance UK
York Hospitals NHS Foundation Trust
Yorkshire and Humber Strategic Clinical Networks