

National Institute for Health and Clinical Excellence

Neuropathic pain

Stakeholder Comments

Please enter your name and the name of your registered stakeholder organisation below. If you are a non-registered organisation, please register via the [NICE website](#) before submitting the proforma. If you are an individual then please contact the [registered stakeholder organisation](#) that most closely represents your interests and pass your comments to them.

Stakeholder Organisation:		British Pain Society	
Name of commentator:		Dr Nick Allcock	
Order number (for internal use only)	Page Number Number only (do not write the word 'page/pg'). Alternatively write ' general ' if your comment relates to the whole document.	Line Number Number only (do not write the word 'line'). See example in cell below	Comments Please insert each new comment in a new row. Please do not paste other tables into this table, as your comments could get lost – type directly into this table.

Example	116	15	My comments are as follows
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Proformas that are not correctly submitted as detailed in the line above may be returned to you

1	General		The British Pain Society welcomes these guidelines as important in guiding the management of Neuropathic pain in non-specialist settings.
2	4	25	Whilst we can understand the GDG's desire to include the information obtained in the pending HTA report, and we note that some of the main arguments are included in the guidelines, the lack of a reference or access to the report does make it difficult for the reader of the guidelines to make an informed judgement on the accuracy of the economic arguments.
3	7	22	We welcome the inclusion of coping strategies as the first key principle, but a brief discussion may not mean very much to patients. We suggest the addition of a third bullet point e.g.: "referral to a community-based pain management service - such as Primary Care Pain Services, E.P.P. Pain Management, or condition-specific, voluntary sector pain management services". Ideally this should also be in the Recommendations as a Key Principle of Care- say as 1.1.4.
4	7	24	While this is a good principle to include, adding the statement of 'start low go slow' could make the concept of titration clearer.
5	9	1-2	We would suggest for clarity "If there is satisfactory improvement, consider continuing the treatment. When a stable period of 3-6 months is achieved, consider trial of weaning down/discontinuation to ensure treatment is still required"
6	9	4	Clinical experience would suggest that the recommended starting dose of 150mg for pregabalin is too high, especially in the older person with potential renal and liver function impairment.
7	9	9	Giving pregabalin three times a day instead of twice a day increases the cost by 50%- a major cost effect, and is not required

			pharmacokinetically.
8	9	18	From clinical experience the starting dose of duloxetine seems high. We would suggest that 30 mg is a more appropriate starting dose.
9	9	9-21	It is surprising that pregabalin and not pregabalin/gabapentin is suggested as first line treatment and that duloxetine is suggested as first line treatment over TCAs for PDN; recommendations which seem to be based on the economic evidence. However we are concerned that there may be a distorting effect of a lack of relative investment in trials for TCAs such as imipramine, compared to the large number of trials of pregabalin and duloxetine sponsored by Pfizer and Eli Lilly.
10	9	17-21	It is unclear why a specific recommendation is made for PDN and not PHN particularly in light of the specific evidence of the efficacy of treatments for PHN (see comment 19) and the statement that PHN is a 'common example' of neuropathic pain (page 4 line 4-5). duloxetine has a specific recommendation for PDN, why is lidocaine excluded for PHN?
11	10	9	We would suggest adding "Consider combination therapy if a) partial improvement with 1 st agent or b) pain is severe and requires aggressive management." There is emerging evidence that combination therapy is more effective but often results in an increased side effect profile. Until evidence is clearer, combination therapy should be restricted to a) & b). Gilron. (2005) Morphine and Gabapentin in PHN. NEJM; 352: 1324-34
12	10	23	We suggest a note is added that the combination of tramadol with amitriptyline or SSRI has only a low risk of serotonin crisis.
13	10	25	We suggest that the guidelines make clear if this recommendation is for immediate or slow release tramadol. While there is a consensus that the slow release form should be used in chronic pain, there are cost implications.
14	11	5-7	Whilst dependency to morphine and oxycodone is mentioned, dependency to tramadol is not. Clinical experience suggests that there is a group of patients who suffer withdrawal symptoms when stopping tramadol and so it should be used with caution.
15	11	8	While the guideline's recommendations are limited to non-specialist settings this does raise issues in relation to the recommendations for conditions managed almost entirely in primary care such as PHN. In this case limiting the recommendations to particular pharmacological agents and suggesting other treatments can be used only after specialist consultation will deny access to potentially useful treatments or require patients to go through additional specialist pain service consultation potentially leading to treatment delay. This would for example not allow topical lidocaine to be used in primary care when there is evidence of efficacy (see comment 19)
16	12	1	It would be advisable to include the contraindications to amitriptyline (glaucoma, arrhythmogenic cardiac disease and prostatic hypertrophy, urinary retention) in the algorithm as this may be the most frequently read and referred to section
17	13	9-13	The definition of neuropathic pain used in the guidelines is out of date. NICE is urged to use the definition proposed by Treede et al ¹ . Particularly problematic is the use of the word "dysfunction" in this definition. A definition which includes "dysfunction" could be inappropriately used to include a variety of conditions where there is dysfunction of the sensory nervous system, but which are probably not neuropathic (e.g. fibromyalgia, whiplash injury, irritable bowel syndrome). This could lead to inappropriate prescribing (and promoting) of drugs which have efficacy in neuropathic pain, but not

			necessarily other conditions where dysfunction is a feature. (1) Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. <i>Neurology</i> 2008; 70(18):1630-1635.
18	15	18 -21	The current wording is hopeful rather than advisory. We would suggest: "Better management of neuropathic pain in non-specialist settings should aim to ensure that people who require specialist assessment and interventions are referred appropriately and in a timely fashion to a specialist pain service and/or condition-specific services."
19	16	9	<p>Whilst the approach of "lumping" neuropathic pain conditions together in the draft guidelines, when evidence is only available for specific conditions, is pragmatic and understandable, it may be inappropriate and too much of an oversimplification. There are increasing data from basic and clinical research which suggest important heterogeneities of presentations of neuropathic pain and the response to therapeutic interventions. The draft guidelines do address this issue for some conditions, but not sufficiently nor consistently. Certainly, more effort should be made to differentiate the evidence bases for central and peripheral neuropathic pain. The "lumping" approach can lead to problems in certain important conditions- for instance a systematic review has demonstrated that certain interventions have efficacy specifically in postherpetic neuralgia (e.g. certain topical NSAIDs, topical lidocaine, topical capsaicin 0.075% and, perhaps controversially, intrathecal methylprednisolone)². Another example is pain related to HIV-associated polyneuropathies: here, as the draft guidelines partially identify, there is evidence of a lack of effectiveness for interventions which the guideline recommends for generic use in neuropathic pain, most notably amitriptyline and gabapentin³⁻⁵. A large registered trial has been published in abstract form which demonstrates a lack of efficacy for pregabalin in this condition⁶. NICE should attempt to access these data from Pfizer. Although there are good reasons to not recommend it as a therapy⁷, it is of concern that the search appears not to have located two major trials of cannabis^{8;9} in HIV-associated polyneuropathies. For the benefit of prescribers being approached by patients, at least a view on this issue would be helpful in the guidelines. Finally, it is perhaps salient to note that for regulatory purposes the FDA have apparently not seen fit to "lump" and generically approve drugs for neuropathic pain, but rather grant approval for use in individual conditions. However, the EMEA seem to have adopted the converse approach in their guidelines¹⁰.</p> <p>(2) Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern R, Rice ASC. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. <i>Public Library of Science -Medicine</i> 2005; 2(7):628-644.</p> <p>(3) Hahn K, Arendt G, Braun JS, von Giesen HJ, Husstedt IW, Maschke M et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. <i>J Neurol</i> 2004; 251(10):1260-1266.</p> <p>(4) Kiebertz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. <i>AIDS Clinical Trial Group 242 Protocol Team. Neurology</i> 1998; 51(6):1682-1688.</p> <p>(5) Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. <i>Terry Bein Community Programs for Clinical Research on AIDS. JAMA</i> 1998; 280(18):1590-1595.</p> <p>(6) Simpson DM, Murphy TK, Durso-De Druz E, Glue P, Whalen E. A randomized, double-blind, placebo-controlled, multicenter trial of pregabalin vs placebo in the treatment of neuropathic pain associated with HIV neuropathy. <i>AIDS</i> 2008 abstract . 2008.</p> <p>(7) Rice ASC. Should cannabinoids be used as analgesics for neuropathic pain?</p>

			<p>Nature Clinical Practice Neurology 4, 654-655. 2008.</p> <p>(8) Ellis RJ, Toperoff W, Vaida F, van den BG, Gonzales J, Gouaux B et al. Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial. <i>Neuropsychopharmacology</i> 2008; doi: 10.1038/npp.2008.120.</p> <p>(9) Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. <i>Neurology</i> 2007; 68(7):515-521.</p> <p>(10) Committee for Medicinal Products for Human Use. Guideline on clinical investigation of medicinal products intended for use in the treatment of neuropathic pain. CHMP/EWP/252/03. 18-11-2004. London, European Medicines Agency.</p>
20	18	2	Complex regional pain syndrome (CRPS) does not appear to be included in the search terms, was this condition specifically excluded in the search strategy?
21	21	6	We are concerned with the statement that 'where there was significant heterogeneity a random effects model was used'. Although a random-effects meta-analysis may be used to incorporate heterogeneity among studies this is not a substitute for a thorough investigation of heterogeneity and is primarily for heterogeneity that cannot be explained.
22	25	2	The studies relating to topical Lidocaine include patch, cream and gel applications. The appropriateness of including very different application methods under one category is questionable.
23	29	19	The attempt to generic classify together as "anticonvulsants" a pharmacologically diverse group of drugs which happen to also poses some degree of efficacy in epilepsy is, although historically conventional, over-simplistic and potentially misleading. Not all anticonvulsants have efficacy in neuropathic pain and <i>vice versa</i> . This approach could lead to misguided thinking and prescribing. NICE is strongly urged to properly classify these drugs according to their mechanism of action (e.g. sodium channel blocker, calcium channel subunit ligands etc). At least for the "antidepressants" some attempt is made to classify these according to the mechanism of action.
24	30 & 30 & 31	4-17 27-28 1-13	<p>The apparent difference in benefit and harm between gabapentin and pregabalin is perplexing and at odds with most other systematic reviews and guidelines in the area^{2;13;14}. This is particularly so since, as the draft guideline points out, these two drugs are pharmacologically very similar. Has NICE rigorously attempted to access all unpublished data relating to both these drugs? Pfizer should be approached with a request for access to its full evidence base for both drugs, including registered but unpublished trials. Since pregabalin is still patent protected and gabapentin is now generic there could be cost implications if the difference in cost effectiveness is actually not as great as the draft guideline analysis purports. It was difficult to see where <i>actual current</i> cost of these drugs was taken into account in developing the guidelines. Members have witnessed recent major decreases in the cost of gabapentin. Furthermore, as mentioned above, a large registered trial has been published in abstract form which demonstrates a lack of efficacy for pregabalin in HIV neuropathy - NICE should attempt to access these data from Pfizer⁶.</p> <p>2) Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern R, Rice ASC. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. <i>Public Library of Science -Medicine</i> 2005; 2(7):628-644.</p> <p>(6) Simpson DM, Murphy TK, Durso-De Druz E, Glue P, Whalen E. A randomized, double-blind, placebo-controlled, multicenter trial of pregabalin vs placebo in the treatment of neuropathic pain associated with HIV neuropathy. <i>AIDS</i> 2008 abstract . 2008.</p> <p>(13) Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS et</p>

			<p>al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132(3):237-251.</p> <p>(14) Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118(3):289-305.</p>
18	38	8	<p>The appraisal of topical capsaicin therapies is flawed. It fails to distinguish between low concentration (0.025-0.075%) and high concentration therapies (8%). Indeed, it is of concern that the guidelines appear to not have identified at all two high quality published trials (in HIV and diabetic neuropathies) for capsaicin 8%^{11;12}. Also, as pointed out in the draft guidelines, and above the low concentration preparations do have efficacy in some conditions, but not others. Whilst the generic recommendations for capsaicin 0.025-0.075% across neuropathic pain cannot be made, the evidence does support the guidelines making recommendations for use in specific conditions, notably post herpetic neuralgia.</p> <p>(11) Backonja M, Wallace MS, Blonsky ER, Cutler BJ, Malan Jr P, Rauck R et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. The Lancet Neurology 2008; 7(12):1106-1112.</p> <p>(12) Simpson DM, Brown S, Tobias J. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. Neurology 2008; 70(24):2305-2313.</p>
19	39	6	<p>The failure of the guidelines to extract pain efficacy data from the trials of topical lidocaine is perplexing, specifically for focal peripheral neuropathic pain conditions. Other robust systematic reviews and guidelines have succeeded in achieving this^{2;13;14 15}. This should be reassessed before the guidelines are published.</p> <p>(2) Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern R, Rice ASC. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. Public Library of Science -Medicine 2005; 2(7):628-644.</p> <p>(13) Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007; 132(3):237-251.</p> <p>(14) Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118(3):289-305.</p> <p>(15) O'Conner AB, Dworkin RH. Treatment of Neuropathic Pain: An overview of Recent guidelines. The American Journal of Medicine 2009; 122;S22-32.</p>
21	42	18-29	<p>In light of this evidence, although considered to be of low quality, why is the use of topical lidocaine not considered in the recommendations particularly in light of the difference in adverse effects? Duloxetine has a specific recommendation for PDN, why is Lidocaine excluded for PHN in this "blanket" Neuropathic pain guideline?</p>
22	84	3-5	<p>While this statement highlights that different doses of gabapentin and pregabalin were modelled the statement that 5% lidocaine is included gives no indication of the number of patches that were included in the modelling, was this the maximum of average number of patches used? This would have impact on the economic outcomes of the model.</p>
23	108	1-8	<p>The advice re tramadol reads as contradictory and concerning. The GDG state that evidence re effectiveness of opioids is of moderate to low quality and lacked reliability (pg 107, lines 26-28). Use of tramadol is however recommended partly because it's commonly used in non-specialist settings already.</p> <p>The recommendation is for use of tramadol as a third line treatment, or as a combination "while a patient is waiting for referral to a condition specific service and/or a sepcialist pain service." However acquisition costs are described as relatively low and it is suggested may be offset by savings of referrals to specialist services "(where the patient and clinician agree that referral is not required)". (pg 108 lines 9-19)</p>

			<p>The CDG seem to be recommending tramadol whilst the patient is waiting for referral, whereas the comments re cost imply trade-off where tramadol can be used instead of referral. There is a danger that a patient may not know enough about referral to specialist services to make a genuinely informed choice to "agree that referral is not required".</p> <p>There is also a danger of appearing to recommend pain management services as end-of-line, costly last resort, rather than a genuine option which should be offered to patients from a very early stage. These underlying contradictions and implied messages need to be resolved. This is especially important given the moderate to low quality evidence of efficacy and long-term adverse effects.</p>
24	112	11-19	<p>We strongly support the reasoning and the principle that "the gateway for referrals to pain specialist services as well as other condition-specific services, should not be at the end of the care pathway." It is a clear, strong message that many patients have voiced for a long time. It needs to have far higher profile in the report and should be firmly integrated into the Key Principles of Care and the Care Pathway in the Recommendations - ideally:</p> <p>A) By adding the whole paragraph (pg112 lines 11 - 19) at the end of the recommendation 1.1.3 (pp 7 - 8).</p> <p>B) By adding a new Key Principle as 1.1.4. "Better management of neuropathic pain in non-specialist settings should aim to ensure that people who require specialist assessment and interventions are referred appropriately and in a timely fashion to a specialist pain service and/or condition-specific services."</p> <p>C) As a clear expansion of Recommendation 1.1.8 (pg. 8 - 9) re Clinical review: "If there is satisfactory improvement, consider continuing or stepping down the treatment. If improvement is not satisfactory or there is deterioration, follow the care pathway (see page 14) or refer the person to a specialist pain service and/or a condition-specific service. (see Key principle of care 1.1.3. above)."</p> <p>D) By an addition to the care pathway as follows: Addition of "If improvement is not satisfactory or there is deterioration, refer the person to a specialist pain service and/or a condition-specific service." in the right hand, blue vertical box re Clinical review.</p> <p>If this firming up of the recommendations isn't made, there's a danger that any non-specialist practitioner who only reads the summary and recommendations may still focus on medication rather than making appropriate early referral to pain management services.</p>
25	119	5	<p>We welcome the recommendation for research into the efficacy of non-pharmacological treatments although assessment of these treatments as components of treatment packages rather than as individual components against placebo is also important. The MRC has published guidance on complex interventions which could be used to inform this type of research. The comment section in the table in 3.3 doesn't seem to relate to non-pharmacological interventions.</p>
26	Appendix 10.4 29		<p>The justification for exclusion of the Shlay study is unclear</p>
27	Appendix 10.4 10		<p>The Scottish Medical Consortium in their cost analysis which resulted in approval of its use in PHN included Baron R et al. Current Med Research and Opinion 2009; 25 (7):1663-76 & 1677-87. A clearer justification for exclusion is needed in these guidelines.</p>
28	General		<p>These comments include comments submitted by a number of contributors some of whom have declared interests including:</p> <p>Andrew SC Rice Professor of Pain Research, Imperial College London who declares the following interests:</p> <p>In the last 12 months ASCR has received consultancy fees and</p>

		<p>expenses via Imperial College Consultants from: Pfizer, Eisai, Spinifex, Astellas, Allergan, NeuroGsx, Daiichi Sanky, GSK.</p> <p>In the last 12 months ASCR has received research funding from Pfizer and Spinifex</p> <p>ASCR is a member of the EU research collaboration Innovative Medicines Initiative “Europain”. Industry partners in this grant are: Pfizer, Esteve, GlaxoSmithKline, Astra Zeneca, Boehringer Ingelheim, UCB Pharma, Wyeth, Eli Lilly, Sanofi-Aventis.</p> <p>Professor Sam H Ahmedzai: funding for research/consultancy/lectures from Pfizer, Napp, Grunenthal.</p> <p>Dr Nick Allcock: has received research grants from Pfizer and acted as a consultant for Grunenthal.</p>
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Please add extra rows as needed

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Closing date: 5pm on 11 November 2009

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