National Institute for Health and Care Excellence

4-year surveillance 2016 – Palliative care for adults: strong opioids for pain relief (2012) NICE guideline CG140

Appendix B: stakeholder consultation comments table

Consultation dates: 13 to 26 May 2016

Stakeholder	Do you agree with the proposal not to update the guideline?	Comments	NICE response
Association for Palliative Medicine of Great Britain & Ireland	Agree	–	Thank-you for your comment.
British Pain Society	Disagree	Whilst we would agree with most of the specific decisions made in this surveillance programme, we feel that the overall decision not to update would be missing some important messages and potential benefits to patients and the NHS. These relate specifically to: 1. Breakthrough pain (page 13) We are unconvinced that the recent RCTs on fast-acting fentanyl products (oral transmucosal and intranasal) would 'not have a substantial effect on the evidence base'. The evidence shows that these agents give meaningful pain relief 5-10 minutes earlier than oral morphine, and this difference could be of great importance to many patients with advanced and terminal conditions. We recommend that further analyses including, where possible, conventional meta-analyses and network analyses should be attempted and reported. We disagree with the statement 'the population in the study predominantly had non-cancer pain. Therefore, this study may be only partly relevant to palliative care'. We consider it unhelpful to imply that the guideline is restricted to the care of	Thank-you for your comments. The evidence reviewed when developing the recommendations also found that fentanyl relieved pain faster than oral morphine. The guideline committee also looked at the costs per dose of fast-acting fentanyl formulations, including buccal tablets, and oral morphine, and concluded: 'it felt the cost impact of recommending fentanyl over immediate-release morphine or oxycodone would be considerable and therefore could not be justified'. Our surveillance has indicated that the costs of fentanyl buccal tablets have not reduced considerably since the recommendation was made. In light of your comment, however, the impact statement in the evidence summary document has been updated to include consideration of costs. Overall, as there has been no major change in evidence or costs since the guideline was developed, we have not identified a strong reason to conduct further in-depth analysis in this area at this time. In selecting studies through the surveillance review, consideration was given to studies of palliative pain treatment in progressive conditions other than cancer. For example, we included studies of pain

		patients with cancer-related pain. Furthermore, we reject the notion that palliative care only applies to cancer patients.	management in Parkinson's disease in the section 'Starting strong opioids – titrating the dose'. However, we excluded studies that primarily focused on chronic pain from conditions such as back pain or osteoarthritis. This was consistent with the approach taken when developing the guideline. The statement: 'the population in the study predominantly had non-cancer pain. Therefore, this study may be only partly relevant to palliative care' was made about Webster et al. (2013). We further investigated this study and noted that only 2 of the 213 participants had cancer. More than two-thirds of participants had back pain, and a further 20% of participants had neck pain, osteoarthritis, or fibromyaligia. Therefore the reference to 'patients with chronic cancer' pain' in the title of the study is substantially misleading. This study has now been excluded from consideration as part of this surveillance review because it mostly covers chronic pain so it is not relevant to the scope of NICE guideline CG140.
		2. Management of constipation (pages 14-16) This is an area where we believe substantial advances have been made in recent years, notably with the peripherally acting mu-opioid receptor antagonists. However, the original question was phrased in such a way that it cannot capture these innovations. It also denies the evidence that opioids are not all the same and some cause more or less constipation, which is very important for many patients who suffer this serious adverse effect. We believe that the question should be removed and replaced with more clinically meaningful questions, such as: a. Which opioids are associated with the least constipation? b. Do peripherally acting mu-opioid receptor antagonists prevent or relieve constipation more effectively than standard laxative treatment? With respect to the specific drugs mentioned in this section, we agree that there is unlikely to be any new evidence about Lubiprostone and 'General laxatives'. However, we contend	When considering opioid-induced constipation in the guideline, the guideline committee recognised that the evidence base for laxative treatment was insufficient. Recommendations were made based on clinical experience, including the observation that laxatives may not always be taken 'The GDG felt that adherence to laxative treatment was important. It was felt that a significant proportion of patients in primary and secondary care did not take laxatives regularly, if at all'. The mu-opioid receptor antagonists methylnaltrexone and naloxegol have licenses stipulating use after inadequate response to laxatives. The current recommendations around use of laxatives provide a reasonable method of determining inadequate response. It would be clinically inappropriate to declare an inadequate response to laxatives (or any drug treatment) without attempting to improve adherence, allowing them time to work, and making sure that the dose is effective. As noted in the comment, current evidence for mu-opioid receptor antagonists is in addition to laxatives. Optimising laxative therapy remains clinically appropriate when mu-opioid receptor antagonists are added to the regimen. However, as noted in the summary of evidence, no studies of optimum laxative therapy compared with mu-opioid receptor antagonists were identified. Therefore, it is not possible to

		that the evidence regarding peripherally acting mu-opioid receptor antagonists represent a step change in the prevention and management of opioid-induced constipation and therefore, they should be revisited but with a more meaningful question, as in (b) above. The guideline fails to appreciate the current oral and rectal laxative treatments are themselves poorly evidence based, and are largely ineffective (Ahmedzai, Boland, *Clinical Evidence* 2010). We therefore find the statement that "evidence of the efficacy of these drugs in palliative care, particularly when compared with optimised laxative therapy, was limited" to be unhelpful. The point is that the newer opioid antagonists are used on top of, rather than instead of, so-called 'optimised laxative therapy'.	answer the suggested review question 'Do peripherally acting mu-opioid receptor antagonists prevent or relieve constipation more effectively than standard laxative treatment?' The peripheral opioid receptor antagonists that are licensed in the UK for opioid-induced constipation are methylnaltrexone, naloxegol, and naloxone. Methylnaltrexone bromide is licensed when response to laxative therapy 'has not been sufficient in adult patients'. As noted in the summary of evidence, a technology appraisal for methylnaltrexone bromide is currently being developed. The clinical guideline will defer to the technology appraisal decision, which is expected in early 2017. Naloxegol is licensed for use in people with opioid-induced constipation 'who have had an inadequate response to laxative(s)'. The SPC additionally says: 'When naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined.' NICE technology appraisal 345 recommends naloxegol in accordance with its marketing authorisation. The clinical guideline defers to the technology appraisal decision. Targinact (naloxone/oxycodone) is the only combination medicine available in the UK licensed for severe pain, in which the naloxone is added to counteract opioid-induced constipation. All opioids are associated with constipation and the health economic analysis produced during guideline development considered the differing rates of constipation. Furthermore, although we approach surveillance by considering the review questions in the clinical guideline, we include all new evidence relevant to the scope, and will suggest new questions if necessary. We did not identify any new studies that addressed rates of constipation associated with different opioid products. The systematic review by Ahmedzai and Boland (2010) was published before the NICE guideline was issued, so the studies would have been available for consideration during guideline development. We thus would not consider this study to be new evidence, so cannot include it in the surveillance review. Additionally, its conclusions on the evidence-base are much the same as those of the Cochrane review (Candy et al. 2015) that we included in the summary of evidence from surveillance.

			The guideline recommends providing information about side-effects (recommendation 1.1.2) and frequent review of pain control and side effect (recommendation 1.1.3) in addition to the specific recommendations about managing constipation. Overall, we did not identify evidence to support the suggested changes to review questions at this time. Technology appraisal guidance will cover use of methylnaltrexone bromide and naloxegol.
		3. Management of nausea (page17) As with the original question on the management of opioid-induced constipation, we believe that this question on management of nausea is also poorly constructed. It does not capture the clinical thinking and judgement made in palliative care when dealing with opioid-induced side-effects. As with constipation, it denies the evidence that opioids are not all the same and some cause more or less side-effects. The clinician (and patients) are more interested in knowing which opioid drugs are more or less likely to cause a specific side-effect, and to be able to take that into account when prescribing and advising patients. Thus we recommend that the original question on nausea is deleted and replaced with questions such as: a. Which opioids are associated with the least nausea and vomiting? b. Which anti-emetics are effective in reducing opioid-induced nausea and vomiting?	In assessing the review question on nausea during guideline development, little evidence was found to support the view that specific opioids are associated with less nausea. 'Lauretti et al. (2003) reported fewer nausea events with oral sustained-release oxycodone but this was based on a very small study population (n=22). Other studies in larger populations didn't show significant differences in nausea (four out of five studies showed no statistically significant differences in side effects).' Although we approach surveillance by considering the review questions in the clinical guideline, we include all new evidence relevant to the scope, and will suggest new questions if necessary. We did not identify any new studies that addressed rates of opioid-induced nausea and vomiting in different opioid products, or use of anti-emetics in opioid-induced nausea and vomiting. The guideline recommends providing information about side-effects (recommendation 1.1.2) and frequent review of pain control and side effect (recommendation 1.1.3), in addition to the specific recommendations about managing nausea. Overall, we did not identify evidence to support the suggested changes to review questions at this time.
		4. Management of drowsiness (page 17) Once again, we believe that the original question is worded in an unhelpful way that does not reflect clinical thinking and decision-making in palliative care. The clinician – and the patient – need to know if some opioids are more or less likely to cause drowsiness. They can then use that information to guide their prescribing and adjustment of other medication, such as	In assessing the review question on drowsiness during guideline development, no evidence was found. Although we approach surveillance by considering the review questions in the clinical guideline, we include all new evidence relevant to the scope, and will suggest new questions if necessary. We did not identify any new studies that addressed rates of sedation and drowsiness in different opioid products, or use of stimulants in reducing

		the reduction of dose or switching opioids if necessary. Thus we recommend that the original question on drowsiness is deleted and replaced with questions such as: c. Which opioids are associated with the least sedation and drowsiness? d. Which stimulants are effective in reducing opioid-induced sedation and drowsiness?	opioid-induced sedation and drowsiness. The guideline recommends providing information about side-effects (recommendation 1.1.2) and frequent review of pain control and side effect (recommendation 1.1.3) in addition to the specific recommendations about managing constipation. Overall, we did not identify evidence to support the suggested changes to review questions at this time.
Medtronic Ltd	Disagree	We appreciate that the guideline is focused on addressing first-line treatment with strong opioids for patients who have been assessed as requiring pain relief at the third level of the WHO pain ladder and it is not intended to cover second line treatment with strong opioids where a change in strong opioid treatment is required because of inadequate pain control or significant toxicity. New approaches to pain control, such as neuromodulation and intrathecal drug delivery, have been developed since the WHO pain ladder was created in 1986 and we now have a better understanding of the multiple mechanisms underlying cancer pain and breakthrough pain. The Faculty of Pain Medicine, Royal College of Anaesthetists, Core Standards for Pain Management Services in the UK. October 2015 states that "Individualised cancer-pain management, with a selection of conservative and invasive treatment options depending on pain presentation, should now be considered the gold standard". We believe that this guideline needs to be updated to include the recommendations from the Faculty of Pain Medicine and to provide information, and raise awareness, of new approaches to pain control that may be available for inadequately controlled patients, via specialist pain centres. This may inform referral to specialist pain services	Thank-you for your comments. Although we approach surveillance by considering the review questions in the clinical guideline, we include all new evidence relevant to the scope, and will suggest new questions if necessary. We can also suggest extensions to the scope. However, we cannot look outside the remit of the guideline, as set by the Department of Health. As you note, non-opioid treatments are outside of the remit of this guideline. In terms of second-line treatment with strong opioids, in several places NICE guideline CG140 recommends seeking specialist advice if pain relief is inadequate. NHS England's specialised pain commissioning service specification notes: 'The Faculty of Pain Medicine of the Royal College of Anaesthetists is the statutory body that sets standards for pain services nationally. The British Pain Society also sets out standards for this service and unless advised otherwise by commissioners, providers are expected to work to the standards set by these bodies and any successor organisations standards and objectives.' NHS England's specialised pain commissioning service additionally has clinical commissioning policies on intrathecal pumps for severe pain. As such, we consider that second-line treatment with strong opioids or other interventions is covered by specialised pain services, and the scope of NICE guideline CG140 should not be extended to cover these treatments.

Royal College of Nurses	–	Nurses have reviewed the proposal and have no comments to submit at this stage Thank you for the opportunity to participate.	Thank-you for your comments.
NHS England	–	Thank you for the opportunity to comment on the above CG surveillance review proposal. I wish to confirm that NHS England has no further comments to add in regards to this consultation.	Thank-you for your comments.

Stakeholder	**Do you agree with the proposal to put the guideline on the static list?**	**Comments**	**NICE response**
Association for Palliative Medicine of Great Britain & Ireland	Agree	–	Thank-you for your comments.
British Pain Society	Disagree	The research base for pain in palliative care and in particular the reduction and management of opioid side-effects is growing. It is unhelpful to ignore these changes which could come to clinical relevance in the coming years.	Thank-you for your comments. As noted in the responses above, we did not identify sufficient new evidence in any area to warrant an update. We also did not identify any major ongoing studies due to publish in the next 3–5 years. Although guidelines on the static list are reviewed every 5 years, if we are notified of any major new evidence during this time, we will give it due consideration.
Royal College of Psychiatrists	Agree	–	Thank-you for your comments.
Medtronic Ltd	Disagree	As per comment 1	Thank-you for your comments. As noted in the response above: We consider that second-line treatment with strong opioids or other interventions is covered by specialised pain services, and the scope of NICE guideline CG140 should not be extended to cover these treatments.

			Additionally, non-opioid treatments for pain are outside the remit of the guideline and cannot be considered.
Royal College of Nurses	–	Nurses have reviewed the proposal and have no comments to submit at this stage Thank you for the opportunity to participate.	Thank-you for your comments.
NHS England	–	Thank you for the opportunity to comment on the above CG surveillance review proposal. I wish to confirm that NHS England has no further comments to add in regards to this consultation.	Thank-you for your comments.
Stakeholder	**Do you agree with the removal of the research recommendations?**	**Comments**	**NICE response**
Is prophylactic prescription of anti-emetic treatment or the availability of anti-emetic treatment at the patient's home more effective in reducing nausea than the availability of prescription on request for patients starting strong opioids for the treatment of pain in advanced or progressive disease? The outcomes of interest are nausea, time to control of nausea, patient acceptability of treatment, concordance and use of healthcare resources.			
Association for Palliative Medicine of Great Britain & Ireland	Agree	–	Thank-you for your comments.
British Pain Society	Agree	Although we agree this research recommendation should be removed, we suggest that it should be replaced with a clinical more relevant – and more measurable – question, namely: "Which opioids are associated with the least nausea and vomiting?" This question would provoke a review of the evidence on currently available opioids and should also include the newer opioids, namely Tapentadol and Cebranapadol.	Thank-you for your comments. Although we can suggest removing research recommendations, we cannot suggest any new additions. New additions can only be proposed by guideline committees during guideline development, including updates. We summarised several studies of tapentadol, but identified no clear evidence of statistically or clinically significant reductions in nausea and vomiting. Cebranapandol is not currently licensed in the UK, so cannot be considered.
Is early switching of opioid, on development of side effects, more effective at reducing central side effects than persisting with current opioid and dose reduction in patients starting strong			

opioids? The outcomes of interest are time to clinically effective pain control with acceptable side effects.			
Association for Palliative Medicine of Great Britain & Ireland	Agree	–	Thank-you for your comments.
British Pain Society	Agree	Although we agree this research recommendation should be removed, we suggest that it should be replaced with a clinical more relevant – and more measurable – question, namely: "Which opioids are associated with the least amount of central side-effects?" This question would provoke a review of the evidence on currently available opioids and should also include the newer opioids, namely Tapentadol and Cebranapadol. There should be clarification of what is meant by 'central side-effects.	Thank-you for your comments. The guideline noted: 'The degree of sedation in patients taking opioids can vary from mild sleepiness and fatigue to severe drowsiness or coma, and may be accompanied by other central nervous system side effects, such as hallucinations, cognitive impairment, agitation, myoclonus, respiratory depression and delirium.' The recommendations made in the guideline were for drowsiness only, however; the research recommendation applied to any effects of opioids in the central nervous system. Although we can suggest removing research recommendations, we cannot suggest any new additions. New additions can only be proposed by guideline committees during guideline development, including updates. We summarised several studies of tapentadol, but identified no clear evidence of statistically or clinically significant reductions in nausea and vomiting. Cebranapandol is not currently licensed in the UK, so cannot be considered.

We received no comments about equalities issues.