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Single Technology Appraisal (STA)

Naloxegol for treating opioid induced constipation [ID674]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Paul Farquhar-Smith

Name of your organisation
The Royal Marsden NHS Foundation Trust

Are you (tick all that apply):

✓a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?

Currently, opioid induced constipation (OIC) is treated by a number of strategies and guidelines are followed that are often similar to guidelines for of constipation of other and differing aetiologies. Due to the relative lack of high quality experimental data guidelines often have to rely on expert opinion and this has often led to a lack of consensus for the treatment of constipation, let alone OIC. Although there are some guidelines published from national and international bodies (for example American Society of Colon and Rectal Surgeons 2007[1], World Gastroenterology Organisation 2007, 2011 [3], Pan European Working Group into Constipation 2008 [2]) , in many cases individual establishments often use localised guidelines that allow for local practice and demographics (interalia Solihul Marie Curie Hospice Constipation Guidelines, St Richards Hospice constipation guidelines 2010).

Overall these general guidelines suggest 3 major therapeutic avenues which may be combined

(1) dietary and lifestyle adjustments,
(2) stool softeners and bulk forming agents
(3) stimulant laxatives

Specifically for OIC other strategies may be enlisted including opioid rotation (changing the type of opioid the patient is taking) that may include opioids for which there is evidence of a lower incidence of gastrointestinal side effects, and use of combination of opioids with naloxone (mu opioid receptor antagonist).

There are few high quality data to confirm the clinical efficacy of these guidelines. There are also specific peripherally acting mu opioid receptor antagonists (PAMORA). Methylnaltrexone is the only PAMORA licensed in the UK and can only be given by injection (subcutaneous). Although there is evidence of its efficacy, its use is potentially curtailed by high unit cost and adverse effects.

Historically opioid use and therefore OIC has predominated in patients with cancer but the last 10 years has seen a near exponential increase in opioid prescription in patients with non-malignant pain and the problem of OIC has increased accordingly. There is some evidence that suggests OIC may be more prevalent in non-malignant chronic pain than in pain in cancer patients. Current treatment guidelines do not usually differentiate between these patients although some laxatives (e.g. combination stool softeners and stimulants) are licenced only for use in cancer patients.

Therefore, although the main tenets of treatment of constipation and OIC treatment usually have consensus, local demographics, economics and experience leads to some variation in local practice.

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What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

As stated, OIC treatment recommendations often mirror guidelines for treatment of constipation with the added strategies noted above. However, the specific alternatives to naloxegol are the other PAMORA molecules currently available. The rational for their use is that their lack of transit across the blood brain barrier leads to

antagonism of mu opioid receptors in the periphery, including the gut, without reversing the central analgesic actions of mu opioid receptor.
In the UK, the only PAMORA licenced for use is the previously mentioned, methylnaltrexone. The evidence for its efficacy is reasonably robust, with one of the major randomised controlled trials reporting 60% of patients experiencing a bowel movement within 4 hours. However the limitation of route of administration (subcutaneous) ,reported side effects of abdominal pain and diarrhoea and unit cost have limited the initiation of the use of methylnaltrexone, to secondary or tertiary in patient care. In some cases, after the initial treatments, continuing use of methylnaltrexone can occur in primary care or the community.
Another PAMORA, alvimopan has only been licensed in the USA and only for a limited indication and not for OIC.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
There is some evidence that OIC in the non-cancer population is not as well treated as patients with cancer taking opioids for pain. In addition, patients with hepatic and renal impairment will be limited in the laxative treatment options and therefore potentially have a poorer prognosis.
In some cases patients with cancer bowel obstruction may be a contributing aetiology of their constipation and contraindicates the use of stimulant laxatives. Severe OIC may also precipitate bowel obstruction either mechanically or functionally.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Given the mechanism of action is similar to methylnaltreone, I would expect the use of naloxegol to be more suitable to secondary and tertiary care at least for the intial treatment. An argument could be made (partially dependent upon the final deliberation of the guidance for its use) for its starting use being restricted to specialist clinics. Depending on the clinical experience, maintenance therapy could be performed in primary care or the community.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
At present naloxegol has only just been approved by the FDA in the USA for adults with non-cancer chronic pain who have OIC refractory to laxatives. Although the technology has been filed with the European Commission, to my knowledge no decision has been made and it is not currently available in the UK.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*
There are many iterations of guidelines for constipation and OIC specifically at local, national and international levels (vide supra). As discussed, the lack of robust and high quality data to support the treatment of constipation is even more marked for OIC. Although the methodology for many of the guidelines is sound, the criticism of

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

their paucity of supporting evidence is incontestable. The guidelines cited are however, pragmatic and rational. Nevertheless, there is a reasonable evidence base for the use of PAMORAs in OIC [5].
The Pan European Working group that formulated guidelines for constipation in palliative care (where OIC is a key issue) acknowledged that the dearth of data required expert opinion and extrapolation of evidence from other forms of constipation to inform their recommendations. This paucity of evidence was exemplified by a Cochrane review of treatment of constipation in palliative care that identified only 3 studies of sufficient quality suitable for meta-analysis [6].
More recent consensus statements have promoted the importance of PAMORAs for the treatment of OIC [4]. The use of a mechanism-based approach by targeting the underlying pathophysiology is intuitive and credible.

1. Dis Colon Rectum. 2007 Dec;50(12):2013-22. Practice parameters for the evaluation and management of constipation. Ternent CA, Bastawrous AL, Morin NA, Ellis CN, Hyman NH, Buie WD; Standards Practice Task Force of The American Society of Colon and Rectal Surgeons.
2. Palliat Med. 2008 Oct;22(7):796-807. The management of constipation in palliative care: clinical practice recommendations. Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B, Gootjes JR, Nabal M, Noguera A, Ripamonti C, Zucco F, Zuurmond WW; European Consensus Group on Constipation in Palliative Care
3. J Clin Gastroenterol. 2011 Jul;45(6):483-7 World Gastroenterology Organisation global guideline: Constipation--a global perspective. Lindberg G, Hamid SS, Malfertheiner P, Thomsen OO, Fernandez LB, Garisch J, Thomson A, Goh KL, Tandon R, Fedail S, Wong BC, Khan AG, Krabshuis JH, LeMair A; World Gastroenterology Organisation.
4. Neurogastroenterol Motil. 2014 Oct;26(10):1386-95. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Camilleri M, Drossman DA, Becker G, Webster LR, Davies AN, Mawe GM
5. J Pain Symptom Manage. 2008;35(5):458-68. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. Portenoy RK, Thomas J, Moehl Boatwright ML, Tran D, Galasso FL, Stambler N, Von Gunten CF, Israel RJ.J Pain Symptom Manage. 2008;35(5):458-68.
6. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD003448. Laxatives for the management of constipation in palliative care patients. Miles CL, Fellowes D, Goodman ML, Wilkinson S.
7. Am J Gastroenterol. 2013 Oct;108(10):1566-74; Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. Ford AC, Brenner DM, Schoenfeld PS

The advantages and disadvantages of the technology
NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The direct comparator available in the UK is methylnaltrexone. One major advantage of naloxegol will be the oral administration. However, given the clinical experience of methylnaltrexone this still may not enable it use in a primary care setting at least for commencement of the treatment. Available data also suggests that modest renal and moderate hepatic impairment does not adversely affect the pharmacokinetics of this product.
Similarly to methylnaltrexone, the effective use of naloxegol does not appear to adversely influence opioid-mediated analgesia.
Much of the data for methylnaltrexone has been gleaned from patients with more advanced cancer and few from OIC in non-cancer chronic pain.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
Although cost and health economic analysis should be key to assessment of this technology, the likely position of naloxegol would be in the treatment of refractory OIC and therefore the clinical indications would be relatively narrow and selective.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
I am familiar with some, but not all of the data for naloxegol. Trail subjects included were taking a wide range of opioid doses and OIC appears to have been reasonable robustly and appropriately defined. From my knowledge of the trial data, the trial conditions did not deviate significantly from current UK practice. However it is notable that the major paper in the New England Journal of Medicine reported on OIC in non-cancer patients. Ideally a direct comparison of naloxegol with methylnaltrexone in the two potentially diverse patient groups of cancer and non-cancer patients would influence and guide the recommendations for the clinical indications of these drugs. This would also identify relative risks of benefits of the two agents by direct comparison of their efficacy and effectiveness (efficacy and tolerability).

Longer term follow up data indicated a high incidence of adverse effects but were comparable to the adverse effects of the control group who had ‘usual care’ laxatives. Nonetheless, abdominal pain, diarrhoea and nausea were more prevalent with naloxegol.
There is some debate about the key outcomes for treatment of constipation and there is no consensus about which are the most clinically meaningful. However, the naloxegol trials have used outcomes that are commonly used in similar research. Although these measures of bowel function are important and were for the most part adequately assessed and indeed were significantly improved, quality of life data was not so prevalent or obviously reported.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient’s quality of

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As with methylnaltrexone, adverse effects included abdominal pain, diarrhoea and nausea. These affected a significant number of patients and potentially could adversely affect the patients' quality of life. However, the drug is not available in the UK at present and its use only recently authorised in the USA so to my knowledge there have not been any unexpected adverse effects picked up in post market surveillance.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
- *Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
- *Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

There are no obvious issues with equality and diversity. The main limitation would be expected to be cost which could compromise the equitable distribution and exposure of the drug.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I am unsure if there would be any additional evidence not identifiable by the usual process of comprehensive systematic review specifically for this product. As for many other medications, data from unpublished trials could potentially be considered given the recognised general publication bias towards studies with positive outcomes.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

This would depend on how the NICE guidance was stated and how specific the recommendations for its use were such as which patient groups (i.e. in cancer patients or non-cancer patients) and which clinical scenarios (e.g. primary or secondary care) were suggested. In my experience with other medications especially for analgesics, NICE guidance can have a significant negative effect on the ability to deliver high quality care. If NICE guidance does not support the use of some relatively high cost drugs and even of there are favourable health economic data, unit cost potentially compromises the ability to prescribe. Drugs that are included in NICE guidance often do not share the same confines.

Those centres already familiar with the use of methylnaltrexone would be unlikely to require significant extra training and indeed the oral administration would facilitate its use. There would be no a priori expectation of increased facilities or equipment for the use of this technology.