NICE National Institute for Health and Care Excellence

2019 exceptional surveillance of neuropathic pain in adults: pharmacological management in non-specialist settings (NICE guideline CG173)

Surveillance report

Published: 5 December 2019

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Surveillance decision

An update of the NICE guideline on neuropathic pain in adults, to reassess gabapentin and pregabalin across most types of neuropathic pain is not necessary. However, the roles of gabapentin and pregabalin for the treatment of sciatica need consideration but this would be most appropriate within an update to the NICE guideline on low back pain and sciatica in over 16s.

Reasons for the decision

Based on clinical- and cost-effectiveness evidence, the guideline on neuropathic pain in adults currently recommends: 'Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)'. Concerns about dependence and misuse of gabapentin and pregabalin were discussed by the committee when the guideline was being developed. At that time, the committee had not experienced problems with dependence and misuse of these drugs in their patients. Warnings about misuse, dependence and withdrawal are clearly recorded in the summary of product characteristics for all preparations of gabapentin and pregabalin.

Overall, prescribing of gabapentin and pregabalin has increased, and alongside this, there has been increased incidence and awareness of problems of misuse and dependence with these drugs. In April 2019, the Medicines and Healthcare products Regulatory Agency published a Drug Safety Update notifying healthcare professionals that pregabalin and gabapentin are now controlled under the Misuse of Drugs Act 1971 as class C substances and scheduled under the Misuse of Drugs Regulations 2001 as schedule 3. Although a note to this effect was added to the guideline, the impact of the alert needed to be further explored in an exceptional surveillance review.

Topic experts suggested that the guideline had led to widespread prescribing of gabapentin and pregabalin for a very broad definition of neuropathic pain in non-specialist settings. They noted that more clinicians would now have direct experience with patients who had problems with dependence and withdrawal than when the guideline was developed.

The recommendation for initial treatment currently includes all forms of neuropathic pain (except for trigeminal neuralgia) but topic experts also indicated that many prescriptions of

gabapentin and pregabalin are for treatment of sciatica, yet the evidence for this indication is very limited.

We noted that for sciatica, a common type of neuropathic pain, evidence for gabapentin and pregabalin appears to be insufficient, and topic experts were concerned about using these drugs in this condition. Therefore, we decided that an update to the guideline should focus on treating sciatica, particularly whether gabapentin and pregabalin are suitable treatments for this condition.

However, we concluded that an update of the guideline to reassess gabapentin and pregabalin in other forms of neuropathic pain was not necessary because:

- the evidence for gabapentin and pregabalin consistently indicates that these drugs are effective in most neuropathic pain
- the reclassification means that clinicians must prescribe in accordance with the more stringent requirements for schedule 3 controlled drugs
- the summaries of product characteristics already warn about misuse, dependence and withdrawal
- the guideline has already been amended to include a footnote covering the reclassification and actions to mitigate against dependence and abuse
- NICE has published a guideline on the safe use and management of controlled drugs and is also developing a new guideline on safe prescribing and withdrawal management of prescribed drugs associated with dependence and withdrawal.

Exceptional surveillance summary

The NICE guideline on neuropathic pain in adults recommends gabapentin and pregabalin as options for the initial treatment of neuropathic pain:

'Offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia).

'If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs, and consider switching again if the second and third drugs tried are also not effective or not tolerated.'

The Medicines and Healthcare products Regulatory Agency (MHRA) published a Drug Safety Update advising that from 1 April 2019, gabapentin and pregabalin are reclassified as schedule 3 controlled drugs under the Misuse of Drugs Regulations 2001 and class C of the Misuse of Drugs Act 1971.

The MHRA's advice for healthcare professionals detailed the reclassification and noted that clinicians should:

- 'evaluate patients carefully for a history of drug abuse and dependence before prescribing pregabalin and gabapentin
- 'observe patients on pregabalin and gabapentin for possible signs of abuse and dependence, for example, drug-seeking behaviour, dose escalation, and development of tolerance
- 'ensure patients are aware of the risk of potentially fatal interactions with other medicines that cause central nervous system depression, particularly opioid medicines, and with alcohol
- 'report suspected adverse drug reactions to pregabalin and gabapentin on a Yellow Card, including cases of abuse and dependence.'

NICE has added a footnote to the recommendations on these drugs to draw attention to this change in legislation. The footnote also notes the need to: 'evaluate patients carefully for a history of drug abuse before prescribing and observe patients for development of signs of abuse and dependence'. This is consistent with the summary of product

characteristics for both gabapentin and pregabalin, which also recognise the issues of central nervous system depression, particularly when used with opioids, and withdrawal symptoms.

We then undertook this exceptional review of the guideline to examine in detail any new evidence on the use and misuse of gabapentin and pregabalin and how this might impact on the current recommendations.

Methods

We checked for evidence on effectiveness and safety of gabapentin and pregabalin by checking:

- the evidence considered when developing the guideline in 2013
- the evidence considered in the 2017 surveillance review of the guideline
- recent updated Cochrane reviews on gabapentin and pregabalin.

We decided that the large pool of published evidence already identified meant that further literature searches were not needed.

We also considered:

- topic experts' views on the efficacy and safety of gabapentin and pregabalin, including how those views have changed since the guideline was developed
- reports from government bodies on prescribing levels and observed harms of gabapentin and pregabalin
- whether any other NICE guidelines covering drug dependence and misuse adequately cover this issue
- whether any new information had equalities implications.

Information considered in 2013 when developing the guideline

When developing the guideline (see the NICE full guideline on neuropathic pain), the

guideline committee assessed the clinical and cost effectiveness of medicines for the management of neuropathic pain. A network meta-analysis of drug treatments was conducted, which included 115 randomised controlled trials (RCTs) of 18 drugs including gabapentin and pregabalin, as well as amitriptyline, capsaicin cream, lidocaine and tramadol.

Gabapentin and pregabalin were assessed in 35 of these studies. Patients had a range of neuropathic pain disorders, including painful diabetic neuropathy, post-herpetic neuralgia, and pain after stroke or spinal cord injury.

The network meta-analysis concluded that overall:

- the results from the analyses showed that amitriptyline, duloxetine and pregabalin consistently reduce pain compared with placebo
- most results from the analyses showed that capsaicin cream, gabapentin, morphine, nortriptyline and tramadol consistently reduce pain compared with placebo
- some adverse effects were more frequent with particular drugs; however, it was difficult to draw conclusions on which particular drugs were best or worst for particular adverse effects.

The guideline committee considered that individual patients would have differing preferences about which adverse events were acceptable to them. Consequently, 'the frequency of individual adverse effects did not weigh heavily in the overall assessment of individual drugs'. This led the committee to recommend a choice of the 4 drugs as initial treatment and to switch to other drugs if those previously offered were not effective or not tolerated.

The guideline committee discussed concerns that had been raised about people becoming dependent on drugs such as gabapentin and pregabalin. At that time, the committee was not aware of any such issues, either in their clinical experience or in the evidence included in the guideline. The committee further agreed that the potential for dependency was not limited to these drugs and is associated with several drugs, including opioids. The committee was also concerned that people with a history of addiction or drug dependency could possibly be denied effective drugs. Based on this concern and the lack of evidence in the area, the committee could not make a specific recommendation about the potential for dependency with certain drugs but felt that the issue could be explored when assessing the risks and benefits for the individual person.

Information considered in 2017 surveillance of this guideline

The NICE guideline on neuropathic pain in adults underwent a surveillance review in 2017 to check whether it should be updated. This followed standard surveillance processes, involving a search for new evidence, feedback from topic experts, and stakeholder consultation. A total of 12 systematic reviews and 17 RCTs assessed gabapentin or pregabalin in various populations (including patients with diabetic neuropathy, post-herpetic neuralgia, neuropathic pain after spinal injury, trigeminal neuralgia, and 'all neuropathic pain'). Most of the new evidence was for pregabalin (21 analyses) rather than gabapentin (11 analyses).

Gabapentin improved pain compared with placebo in 7 analyses and was more effective than carbamazepine in 1 analysis. Pregabalin was more effective than placebo in 12 analyses, but 1 comparison with placebo suggested no effect of pregabalin on pain. In 2 analyses of gabapentin compared with pregabalin, no difference in pain was seen between the groups. Pregabalin was more effective than amitriptyline in 1 analysis.

Gabapentin was associated with more adverse events than placebo (4 analyses) but with fewer adverse events than carbamazepine (1 analysis). Pregabalin was associated with increased adverse events compared with placebo (2 analyses) or amitriptyline or duloxetine (1 analysis). There was no significant difference in adverse events between gabapentin and pregabalin (1 analysis).

Topic expert feedback on the 2017 surveillance review noted:

- increasing reports of misuse of drugs recommended in the guideline, including gabapentin and pregabalin
- although gabapentin and pregabalin improve function and quality of life, there was concern that clinicians may be more reluctant to prescribe them because of potential risks of abuse and dependence. This precautionary prescribing could conversely lead to increases in illegal procurement.

The topic experts also referred to Public Health England's 2014 publication on advice for prescribers on the risk of the misuse of pregabalin and gabapentin. This document notes increased prescribing of gabapentin and pregabalin from 2011 to 2013 – the period before the NICE guideline on neuropathic pain in adults was published.

Overall, the 2017 surveillance review concluded that an update of the guideline was not needed at that time.

Additional information considered in this 2019 exceptional surveillance review

In April 2019, the MHRA Drug Safety Update informed healthcare professionals that pregabalin and gabapentin had been reclassified as class C controlled substances (under the Misuse of Drugs Act 1971) and scheduled under the Misuse of Drugs Regulations 2001 (as amended) as schedule 3.

We also considered:

- information on the background to reclassification:
  - the government consultation document on the reclassification of gabapentin and pregabalin
  - the Advisory Council on the Misuse of Drugs' letter to the government recommending the change in classification status
  - Public Health England's 2014 publication on advice for prescribers on the risk of the misuse of pregabalin and gabapentin
  - Public Health England's 2019 report on dependence and withdrawal associated with some prescribed medicines – an evidence review
- other NICE guidance on controlled substances and treatments that are associated with dependence and withdrawal
- Cochrane reviews on gabapentin and pregabalin that have been updated since the previous surveillance review.

Prescribing rates

Public Health England's report and the government's consultation on the reclassification of gabapentin and pregabalin indicate that prescriptions of gabapentin increased from 4.9 million prescriptions in 2013 (before implementation of NICE's guideline on neuropathic pain in adults, which published in November 2013) to 7.1 million prescriptions in 2017.

Prescriptions of pregabalin increased from 3.3 million to 6.2 million prescriptions over the same period. Overall, about 1.5 million people received at least 1 prescription for gabapentin or pregabalin in 2017/18.

Death certificates in England and Wales mentioning pregabalin rose from 36 in 2014 to 111 in 2016, and for gabapentin the increase was from 26 to 59.

Since authorisation and up to 10 April 2019, the MHRA received 113 reports of abuse and 98 reports of dependence with pregabalin, and 11 reports of abuse and 9 reports of dependence associated with gabapentin.

Clinical effectiveness in all neuropathic pain

We found new Cochrane reviews on gabapentin and pregabalin in neuropathic pain that have published since the 2017 surveillance of this guideline.

- The updated Cochrane review of gabapentin for neuropathic pain (Wiffen et al. 2017) included 37 studies (n=5,914). It concluded: 'gabapentin can provide good levels of pain relief to some people with post-herpetic neuralgia and peripheral diabetic neuropathy. Evidence for other types of neuropathic pain is very limited. Over half of those treated with gabapentin will not have worthwhile pain relief but may experience adverse events... Conclusions have not changed since the previous update of this review.'

- An updated Cochrane review of pregabalin for neuropathic pain (Derry et al. 2019) included 45 studies (n=11,906). It concluded that pregabalin has an 'important effect' on pain in some people with painful diabetic neuropathy or post-herpetic neuralgia, 'is effective after trauma due to stroke or spinal cord injury' but may not be effective in neuropathic pain associated with HIV. 'Very limited evidence is available for neuropathic back pain, sciatica, neuropathic cancer pain, and some other forms of neuropathic pain'. The authors additionally noted that it is not possible to know beforehand who will benefit and who will not.

We considered that the findings of these Cochrane reviews were consistent with current recommendations. We decided that a full literature search was not necessary for this surveillance review because a substantial weight of new evidence would be needed to change the conclusions on the effectiveness of these drugs. However, the studies included in these Cochrane reviews did not appear to specifically look at dependence or abuse potential. Trials in the reviews were probably too short term (4 weeks to 12 weeks

for gabapentin and 2 weeks to 16 weeks for pregabalin) to reliably assess this outcome.

Related NICE guidelines

NICE has published a guideline on the safe use and management of controlled drugs and is developing a new guideline on safe prescribing and withdrawal management of prescribed drugs associated with dependence and withdrawal, which is expected to publish in November 2021.

The guideline on the safe use and management of controlled drugs provides broad principles for prescribing controlled drugs, but does not provide specific advice for different drugs or indications. The in-development guideline on safe prescribing and withdrawal management of prescribed drugs associated with dependence and withdrawal is expected to provide more specific advice on these medicines, which were mentioned in the scope.

Topic expert feedback

We sent topic experts a summary of the new information we had identified alongside the considerations the guideline committee used to develop current recommendations. Three of the 4 topic experts who responded thought that the guideline should be updated.

These 3 topic experts explained that since the guideline was published, clinicians will have had more direct experiences with misuse and dependency associated with gabapentin and pregabalin. They advised that a guideline committee looking at all the evidence available today may make different recommendations on the use of gabapentin and pregabalin in neuropathic pain.

One topic expert thought the guideline should not be updated. The expert noted that there are few alternative treatments and that clinicians must always weigh up the benefit compared to issues such as potential misuse, harm and long-term side effects when prescribing any drug treatments.

Two of the topic experts noted a large amount of prescribing of gabapentin and pregabalin for sciatica (lumbar radiculopathy). NICE's guideline on low back pain and sciatica in over 16s directs clinicians to the NICE guideline on neuropathic pain in adults for recommendations on pharmacological management of sciatica. However, they thought that there was little evidence supporting use of gabapentin and pregabalin in sciatica.

Clinical effectiveness in sciatica

After feedback from topic experts on the lack of evidence for use of gabapentin and pregabalin in sciatica, we investigated this specific issue further.

The guideline included only 3 studies in populations with radiculopathy (2 of which specified lumbar radiculopathy), but none of these studies assessed either gabapentin or pregabalin. The surveillance review in 2017 did not identify any new evidence for these drugs in sciatica or any radiculopathy.

The updated Cochrane reviews discussed above both noted that evidence was 'very limited' for neuropathic pain conditions other than post-herpetic neuralgia and diabetic neuropathy. The topic experts also provided 2 new studies that show little effect of gabapentin and pregabalin on sciatica.

Topic experts highlighted 2 relevant studies on treating sciatica:

- A randomised controlled trial of pregabalin compared with placebo in 209 people with sciatica (Mathieson et al. 2017). After 8 weeks, and after 1 year, there was no significant effect of pregabalin on leg pain, disability, back pain or quality of life.
    - This study was excluded from the Cochrane review of pregabalin by Derry et al. (2017) because it was 'not clearly chronic pain'. Derry et al. (2017) included 1 study in chronic lumbosacral radiculopathy (sciatica, n=217). This study assessed people whose pain had responded to pregabalin in an initial phase, who were then randomly assigned to continue with pregabalin or switch to placebo. There was no difference in the proportion of people maintaining their response in the pregabalin or placebo groups.

- An RCT comparing epidural steroid injection plus placebo pills or sham injection plus gabapentin in 145 people with sciatica (Cohen et al. 2015). After 1 month and 3 months, there was no significant effect of gabapentin on leg pain compared with steroid injection. At 1 month, people who received the epidural steroid injection had significantly greater reduction in 'worst leg pain' and were more likely to experience a 'positive successful outcome'.
  - This study was included in the Cochrane review by Wiffen et al. (2017), alongside an additional study of gabapentin compared with placebo in 108 people, 46 of whom had radicular leg pain. No differences between gabapentin and placebo were seen for reductions in pain intensity or 'patient estimation of pain improvement'.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

We concluded that for sciatica, a common type of neuropathic pain, evidence for gabapentin and pregabalin appears to be insufficient, and topic experts were concerned about using these drugs in this condition. Therefore, we decided that an update to the NICE guideline on low back pain and sciatica in over 16s should focus on treating sciatica, particularly whether gabapentin and pregabalin are suitable treatments for this condition.

However, an update of the guideline to reassess gabapentin and pregabalin in all other types of neuropathic pain was not necessary because:

- the evidence for gabapentin and pregabalin consistently indicates that these drugs are effective in most neuropathic pain
- the reclassification means that clinicians must prescribe in accordance with the more stringent requirements for schedule 3 controlled drugs
- the summaries of product characteristics already warn about misuse, dependence and withdrawal
- the guideline has already been amended to include a footnote covering the reclassification and actions to mitigate against dependence and abuse

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ISBN: 978-1-4731-3619-9