Neuropathic pain: Pregabalin and gabapentin prescribing

There has been an increase in pregabalin prescribing recently and across the PrescQIPP membership (approximately 16.4 million patients) over £60 million is spent annually on pregabalin. (ePACT May 2013).

QIPP projects in this area are aimed at either dose optimisation for pregabalin or reviewing pregabalin prescribing to ensure a pathway has been followed which includes prescribing of amitriptyline or gabapentin before pregabalin is initiated. This bulletin reviews the place in therapy of pregabalin (and gabapentin) and offers guidance and support material for organisations considering reviewing pregabalin and gabapentin prescribing as a QIPP project.

Recommendations

- Ensure that pregabalin and gabapentin are prescribed at an appropriate place in therapy for neuropathic pain (see algorithm, p.11 and attachment 1). Ensure patients understand where treatments are unlicensed and that informed consent is given. Patient information leaflets are available to support this.

- Where pregabalin and gabapentin are being prescribed outside of their licenced indication for other non-neuropathic pain, review the need to continue treatment.

- Ensure careful consideration is given before pregabalin and gabapentin are prescribed to patients with a history of substance misuse or those that have recently been released from prison and review treatment regularly.

- Review treatment 8 weeks after initiation and discontinue if ineffective (withdrawal from treatment should be gradual).

- Ensure prescribed (and taken) doses of pregabalin and gabapentin are not outside the therapeutic dose range.

- Prescribing of pregabalin capsules should be optimised to the minimum number per dose with a twice daily frequency. See PrescQIPP bulletin 9: Pregabalin dose optimisation for further information available at http://www.prescqipp.info/resources/bulletins/09preg/finish/43-pregabalin-dose-optimisation/266-bulletin-9-pregabalin-dose-optimisation

- Review patient records for compliance – patients requesting ad hoc prescriptions and not taking the medication regularly will not benefit from the treatment, such patients may benefit from prn (when required) use of other types of analgesia such as paracetamol or NSAIDs.

- Consider switching patients on pregabalin whose neuropathic pain is not effectively managed to gabapentin or amitriptyline if these drugs have not been tried previously or the dose of treatment had not been previously titrated and maximised. If undertaking a switch programme, ensure that the switching methodology has been agreed locally by GPs, consultants, pain nurses, and other relevant healthcare professionals.
National guidance

The NICE Clinical Guideline 96 for neuropathic pain included pregabalin or amitriptyline as first line treatment options for neuropathic pain. The exclusion of gabapentin in this recommendation was seen as controversial at the time of publication of the guideline; the Drug and Therapeutics Bulletin questioned whether switching away from gabapentin was a justifiable and affordable option as gabapentin was in common use prior to this time. Gabapentin is available as a generic treatment which is significantly less costly than pregabalin.

This Guideline has recently been updated to, NICE Clinical Guideline 173 which, states:

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

The full guideline explains that the guideline development group (GDG) agreed to make its recommendations on the basis that the sequential strategy with the highest probability of cost effectiveness for any individual patient is to try treatments in order of their individual probability of cost effectiveness.

Looking at the cost effectiveness of treatments, the GDG found that gabapentin had the highest net benefit which is why it was recommended as an initial treatment option. Amitriptyline had closely comparable costs per quality adjusted life year (QALY) to gabapentin and lower net costs so was also recommended as an initial treatment option.

Pregabalin and duloxetine were recommended as initial treatment options due to their wider licences, however the GDG did acknowledge that both these treatments represented poor value for money and further state:

"Probabilistic sensitivity analysis showed a negligible probability that either of these options provides greatest net benefit at conventional QALY values. For these reasons, the GDG felt it would not be possible to support recommendations that suggested either option as an initial treatment for neuropathic pain. However, the GDG noted that, when compared with placebo alone (that is, no treatment), both drugs appeared to be viable options from a health economic point of view. Therefore, it would be appropriate to recommend these treatments in a context where other options were removed from the decision-space – that is, when they are contraindicated or when they have been tried and proved ineffective or were not tolerated."

A Scottish Medicines Consortium review of pregabalin in 2009 placed its use 3rd line after conventional 1st and 2nd line therapies such as amitriptyline and gabapentin. This position is supported by the recent SIGN guideline in the management of chronic pain published in December 2013.

A Canadian review stated that the benefits and harms of pregabalin are similar to gabapentin but at a higher cost. A more recent Australian RADAR review stated that there was currently a lack of robust data in the form of head to head randomised controlled trials directly comparing efficacy pregabalin with other drugs for neuropathic pain.

The NICE Clinical Guideline for neuropathic pain also recommends early and regular assessment for patients prescribed treatments for neuropathic pain. The early review after starting or changing treatment needs to include dosage titration, tolerability and adverse effects to assess suitability of chosen treatment.

Regular clinical reviews should assess and monitor effectiveness of chosen treatment and need to include assessment of:

- Pain control
- Adverse effects
- Impact on lifestyle, daily activities (including sleep disturbance) and participation (such as ability to work and drive)
- Physical and psychological wellbeing
- Continued need for treatment.
In the majority of cases a drug treatment should be reduced gradually and stopped if the patient has not shown sufficient benefit within 8 weeks of reaching the maximum tolerated dose except when moving to combination therapies.

NICE Clinical Guideline 173 did not provide advice on combination therapies as it was difficult to assess the cost effectiveness of these. It did acknowledge that combination therapy is commonly used in practice and that it may be more practical and effective than switching to another treatment in some patients. If combination therapy is used and is not showing sufficient benefit within 8 weeks, one drug should be reduced gradually and stopped before the other.\textsuperscript{1,8}

Clinical Guideline 173 also recommends several treatments that are commonly used outside of their product licences in "off label use". The Clinical Guideline recommends that where these medicines are prescribed, prescribers should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented and patients should be given information about the unlicensed/off label status of their prescribed medicines.\textsuperscript{3}

Special consideration should be given to patients who have a current or known history of substance misuse or who have been released from prison. Gabapentin and pregabalin are known to be traded and sought after in secure environments (i.e. prisons).\textsuperscript{9} An audit in prisons showed that over 50\% of prisoners prescribed these medicines have a history of substance misuse.\textsuperscript{10} These medicines are likely to be sought after by released prisoners (especially if this has been stopped during custody) and their abuse potential communicated into the wider community. A recent publication by Public Health England\textsuperscript{11} recommends that amitriptyline or nortriptyline are used as first line agents for neuropathic pain in this patient group.

### Clinical effectiveness

Neuropathic pain is often difficult to treat because it is resistant to many medications and/or because of the adverse effects associated with effective medications. No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patient responses and diseases, treatment must be individualised. Other than analgesia, factors to consider when individualising therapy include tolerability, other benefits (e.g. improved sleep, mood, and quality of life), co-morbidities, concomitant therapies and contra-indications, low likelihood of serious adverse events and cost effectiveness to the patient and the health economy.\textsuperscript{3,12}

Gabapentin and pregabalin are structurally related epilepsy drugs which are also licenced for the treatment of peripheral neuropathic pain in adults. In addition pregabalin is licenced for the treatment of central neuropathic pain and generalised anxiety disorder in adults.\textsuperscript{13,14} There are no direct comparative studies between pregabalin and gabapentin for the treatment of neuropathic pain. Gabapentin has nonlinear pharmacokinetics which means careful titration of dose is required whereas pregabalin possesses linear pharmacokinetics which means dosing regimens are more straightforward.\textsuperscript{15}

There is published evidence that both gabapentin and pregabalin are subject to abuse and misuse.\textsuperscript{10,16,17} Both medicines have known psychiatric side effects including euphoria and hallucinations.\textsuperscript{13,14} Care should be taken to avoid exposing patients to these risks when the expected benefits are not properly documented.

In addition:

- The SPC for pregabalin states that cases of abuse have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin abuse.\textsuperscript{14}
- Although pregabalin appears to have low potential for abuse, certain populations e.g. those with a history of substance abuse may be more liable to abuse or misuse it.\textsuperscript{16}
- Gabapentin dependence/abuse is generally related to withdrawal effects and syndromes rather than abuse directly, although case reports of abuse in secure environments have been reported.\textsuperscript{17}

The recent audit undertaken in prisons by the East and South East England specialist pharmacy services\textsuperscript{10} found that there was considerable off-label (and outside national guidelines) use of pregabalin and gabapentin within prisons and immigration removal centres (22\% of prescribing was for off-label use). The
recommendation was to review any prescribing for gabapentin or pregabalin that was off label and not within national guidelines.

There was also a significant amount of co-prescribing of gabapentin or pregabalin with opiates which is of concern in particular groups of patients where addiction may become a problem. Recommendations in the report were to review co-prescribing of opiates given the main indications for gabapentin and pregabalin were for neuropathic pain.\textsuperscript{10}

The PrescQIPP team have previously reviewed the evidence of clinical and cost effectiveness of the treatments available for the management of neuropathic pain and also anecdotal evidence on use of pregabalin and gabapentin in practice across the East of England PCTs. A treatment pathway was produced which has now been updated to incorporate information from the latest NICE Clinical Guideline on neuropathic pain, the summary of product characteristics (SPC) and specific treatments for trigeminal neuralgia and diabetic neuropathy. The pathway is in \textbf{attachment 1} and can be used and adapted locally by CCGs and acute trusts.

\textbf{Costs}

Table 1 below shows the costs for generic gabapentin three times a day and also comparative costs for pregabalin at a twice a day and three times a day dose. Pregabalin can be prescribed as either a twice a day or three times a day dose for all indications, and as the three times a day is considerably more expensive, CCGs should review any prescribing for three times a day pregabalin and switch to an equivalent dose twice a day. Guidance is available in the pregabalin dose optimisation bulletin: \url{http://www.prescqipp.info/resources/bulletins/09preg/finish/43-pregabalin-dose-optimisation/266-bulletin-9-pregabalin-dose-optimisation}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Product} & \textbf{Price for 28 tablets} & \textbf{Dose: one twice a day (28 days cost)} & \textbf{Dose: one three times a day (28 days cost)} \\
\hline
Gabapentin 100mg capsules & £0.72 & n/a & £2.16 \\
Gabapentin 300mg capsules & £0.99 & n/a & £2.97 \\
Gabapentin 400mg capsules & £1.27 & n/a & £3.81 \\
Gabapentin 600mg tablets & £3.22 & n/a & £9.66 \\
Gabapentin 800mg tablets & £10.11 & n/a & £30.33 \\
Pregabalin 25mg capsules & £32.20 & £64.40 & £96.60 \\
Pregabalin 50mg capsules & £32.20 & £64.40 & £96.60 \\
Pregabalin 75mg capsules & £32.20 & £64.40 & £96.60 \\
Pregabalin 100mg capsules & £32.20 & £64.40 & £96.60 \\
Pregabalin 150mg capsules & £32.20 & £64.40 & £96.60 \\
Pregabalin 200mg capsules & £32.20 & £64.40 & £96.60 \\
Pregabalin 225mg capsules & £32.20 & £64.40 & Above maximum licenced dose \\
Pregabalin 300mg capsules & £32.20 & £64.40 & Above maximum licenced dose \\
\hline
\end{tabular}
\caption{Costs of gabapentin and pregabalin\textsuperscript{18,19}}
\end{table}
Switching from pregabalin to gabapentin

NICE Clinical Guideline 173 suggests that patients whose neuropathic pain is already effectively managed should have their existing treatments continued, taking into account the need for regular clinical reviews which would include a review of efficacy as well as continued need for treatment.

Organisations considering a review and switch from pregabalin to gabapentin (or amitriptyline) for patients who have not previously tried these products (especially for those patients whose neuropathic pain is not effectively managed) should ensure that the process and switching methodology has been agreed locally by all key stakeholders including GPs, practice nurses, pain consultants, pain nurses and other relevant healthcare professionals/patients. Community pharmacists should also be informed of any switch processes. Organisations should consider the information below before deciding on a switching protocol.

The audit and patient letter in attachments 2 and 3 can be used to identify patients who would be suitable for a therapy review which may include discontinuing medication that is ineffective or not being taken, reviewing patients being prescribed or taking a dose that is outside the therapeutic range for the drug and switching patients to a different class of drug if appropriate (based on co-morbidities or indication). The audit tool used for the prescribing of these medicines in prisons is also available on the East and South East Specialist Pharmacy Services website:


If considering a switch from pregabalin to gabapentin in appropriate patients, patients on the lower doses of pregabalin should be switched first as patients on high dose pregabalin, who are compliant and stabilised on their treatment are more likely to experience a disruption in pain control and therefore less likely to accept change of medication.20

There have been no studies looking at a switch from pregabalin to gabapentin however there have been a few studies looking at a switch from gabapentin to pregabalin which have used various strategies and dosing regimens to undertake the switch - some strategies including direct switch and dose tapering are discussed below.

The manufacturer of both pregabalin and gabapentin advises that if they are to be discontinued, or the dose reduced or substituted with an alternative medicine, the dose should be tapered gradually over a minimum of one week.13,14 This withdrawal is however to minimise the risk of increased seizure frequency where they are being used for patients with seizure disorders. The clinical importance of a slow withdrawal in patients with neuropathic pain remains unknown.20

A pharmacokinetic simulation study21 looked at two different gabapentin to pregabalin transition designs based on respective population pharmacokinetic profiles. The first simulation involved immediate discontinuation of gabapentin therapy with initiation of pregabalin therapy at the next scheduled dose period and the second design featured a gradual transition involving co-administration of 50% of the gabapentin dose and 50% of the desired pregabalin dose for four days followed by discontinuation of gabapentin and fully targeted doses of pregabalin. Both designs were studied at three dose levels (total daily dose):

- Gabapentin 900mg daily to pregabalin 150mg daily
- Gabapentin 1800mg daily to pregabalin 300mg daily
- Gabapentin 3600mg daily to pregabalin 600mg daily

Overall drug exposure was expressed as pregabalin equivalent concentrations. The simulations showed that during the transitions, the predicted pregabalin concentrations did not depart from those calculated during periods of steady state gabapentin or pregabalin monotherapy. The authors suggested that changing patients from gabapentin to pregabalin could theoretically be achieved by either of the two approaches assessed.
An open label study substituted gabapentin with pregabalin in patients with neuropathic pain due to peripheral neuropathy. The author describes an overnight switch from gabapentin to pregabalin, based on a conversion table which is described in the paper as “of the author’s creation” (table 2). No serious adverse effects appeared to have been caused by the switch. Patients who had not responded to gabapentin therapy appeared to have a higher likelihood of adverse effects such as sedation and dizziness, although these did not lead to treatment discontinuation after one week.22

Table 2: Dose conversion of gabapentin to pregabalin used in the above study22

<table>
<thead>
<tr>
<th>Daily dose of gabapentin pre-switch (mg/day)</th>
<th>Daily dose of pregabalin per day post switch (mg/day)</th>
<th>Dosing schedule of pregabalin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-900</td>
<td>150</td>
<td>75mg twice daily</td>
</tr>
<tr>
<td>901-1500</td>
<td>225</td>
<td>75mg in the morning and 150mg in the evening*</td>
</tr>
<tr>
<td>1501-2100</td>
<td>300</td>
<td>150mg twice daily</td>
</tr>
<tr>
<td>2101-2700</td>
<td>450</td>
<td>150mg in the morning and 300mg in the evening</td>
</tr>
<tr>
<td>2700 or higher</td>
<td>600</td>
<td>300mg twice daily</td>
</tr>
</tbody>
</table>

*The table in the published study actually reads 75mg in the morning and 225mg in the evening. This error has been corrected in the above table which is taken from the UKMi medicines Q&A document.20

A small (n=32) study of patients with post-herpetic neuralgia saw patients switched from gabapentin to pregabalin at one sixth of the gabapentin dose. No serious side effects occurred, and no significant difference was found before and after substitution in the number of patients with somnolence and dizziness. A significant (p<0.05) increase in the number of patients with peripheral oedema was found after the switch.23

In practice it may be preferable to start titrating down pregabalin and then gradually adding in and titrating up gabapentin to the lowest dose that will give pain relief rather than just switching over to an equivalent dose.

Gabapentin can be started at a dose of 300mg once daily on day 1 then 300mg twice daily on day 2 then 300mg three times a day.13

The SPC for pregabalin states pregabalin dose reduction should occur over a minimum of one week.14 Assuming 300mg of gabapentin is approximately equivalent to 50mg pregabalin, then as 300mg of gabapentin was added, the dose of pregabalin could be reduced by 50mg. Practically the prescriber may have to prescribe a lower strength of capsule and have multiple capsules are taken in one dose so that the dose reduction can take place over a week.

So for example if a patient was taking pregabalin 150mg twice daily at a dose of 1 capsule twice a day - this could be converted to 50mg capsules so they are taking three capsules twice a day - the dose reduction (and titration up) may then look something like that suggested in table 3 on the following page.
Table 3: An example dose reduction of pregabalin for conversion to gabapentin for a 150mg twice daily pregabalin dose

<table>
<thead>
<tr>
<th>Day</th>
<th>Pregabalin dose</th>
<th>Gabapentin dose</th>
<th>Total pregabalin equivalent daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3x50mg capsules twice daily</td>
<td>Nil</td>
<td>300mg</td>
</tr>
<tr>
<td>2</td>
<td>2x50mg pregabalin in the morning and 3x50mg pregabalin in the evening</td>
<td>1x300mg capsule in the morning</td>
<td>300mg</td>
</tr>
<tr>
<td>3</td>
<td>2x50mg capsules twice daily</td>
<td>1x300mg capsule twice daily</td>
<td>300mg</td>
</tr>
<tr>
<td>4</td>
<td>1x50mg capsule in the morning and 2x50mg capsules in the evening</td>
<td>1x300mg capsule three times a day</td>
<td>250mg</td>
</tr>
<tr>
<td>5</td>
<td>1x50mg capsule in the morning</td>
<td>1x300mg capsule three times a day</td>
<td>200mg</td>
</tr>
<tr>
<td>6</td>
<td>Nil</td>
<td>1x300mg capsule three times a day</td>
<td>150mg</td>
</tr>
<tr>
<td>7</td>
<td>Nil</td>
<td>1x300mg capsule in the morning and afternoon</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Nil</td>
<td>1x300mg capsule three times a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 plus extra for continuing dose titration</td>
<td></td>
</tr>
</tbody>
</table>

After day 8 titrate up gabapentin according to tolerability and response.

Local decision makers will need to agree whether this switch will be undertaken and also the protocol that is to be used for switching.

**Savings available**

(ePACT prescribing data analysis and charts attached in data pack)

Spend on pregabalin (both generic and branded Lyrica®), branded Neurontin® and gabapentin liquid specials is almost £56 million annually across the PrescQIPP membership. Prescribing should be reviewed to ensure it is appropriate and treatment is effective.

Note: The prescriptions for liquid specials could be for epilepsy in children which would be inappropriate to change.

The PrescQIPP scorecard has a suggested target of 65% or more for generic gabapentin prescribing. **The average potential savings across the PrescQIPP membership are over £6,131 per 100,000 population annually. Total savings over £1 million across a 16.4 million population.**

The maximum achievement across the PrescQIPP membership is 74.49% and **achieving this target could release potential savings of £135,000 per 100,000 population annually. Total savings £22 million over the 16.4 million population.**
Summary

- Pregabalin and gabapentin are both epilepsy drugs licenced in the treatment of neuropathic pain. Pregabalin is considerably more expensive than gabapentin and costs of prescribing are rising significantly. The NICE clinical guideline 96 on neuropathic pain recommends pregabalin as a first line option to treat neuropathic pain,¹ however this recommendation has been widely criticised.² The updated Clinical Guideline 173 on neuropathic pain recommends amitriptyline, gabapentin, duloxetine and pregabalin as initial treatment options for neuropathic pain but does suggest that these should be used in order of cost effectiveness.³ Most organisations that have developed treatment pathways for neuropathic pain recommend gabapentin as a treatment option before pregabalin is initiated.

- Prescribing for neuropathic pain treatments should be reviewed in line with the criteria set out in the NICE clinical guideline for neuropathic pain and discontinued (gradually) if it is ineffective. Where gabapentin has not been previously tried (and particularly if treatment is currently not effective) a switch may be considered, however this should be agreed with local pain specialists and other relevant healthcare professionals.

- Both drugs have the potential to be abused (particularly when prescribed with opiates) and prescribing should be reviewed in light of this. Any prescribing should also be within recommended therapeutic dose ranges.

References

20. Johnson H. How do you switch between pregabalin and gabapentin for neuropathic pain and vice versa? UKMi QA 408.1 November 2012

Additional resources to accompany this bulletin include:

- Briefing
- Data pack
- Implementation pack (audit tool, treatment pathway and patient letters)


Non-subscriber publication on 15 May 2014.
Attachment 1: Template Guidance on the Management of Neuropathic Pain (Adults)

Guidance which includes a flow chart indicating a stepwise approach to the management of neuropathic pain and additional treatment notes has been developed to guide prescribers. This guidance is based on feedback from several organisations across the east of England on current practice when prescribing for neuropathic pain. Organisations can use this guidance as a template to develop their own local guidance in partnership with key stakeholders such as pain consultants, GPs, pharmacists, nurses and other healthcare professionals.

In clinical practice a combination of two or more drugs is often needed to achieve satisfactory pain relief. The flow chart reflects this need and proposes that combination therapy is an option before specialist referral. This does not reflect the guidance in the updated NICE Clinical Guideline 173 on neuropathic pain.

Many of the treatment options suggested by the NICE Clinical Guideline 173 for neuropathic pain are not licenced for all forms of neuropathic pain but have been used in clinical practice for many years and have an established role in the treatment of neuropathic pain.

NICE CG173 recommends that the GMC good practice in prescribing and managing medicines and devices (2013) guide is followed when treating neuropathic pain. This states:

“You should usually prescribe licensed medicines in accordance with the terms of their licence. However, you may prescribe unlicensed medicines where, on the basis of an assessment of the individual patient, you conclude, for medical reasons, that it is necessary to do so to meet the specific needs of the patient.”

“When prescribing an unlicensed medicine you must:

a. be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy,

b. take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring, and any follow up treatment, or ensure that arrangements are made for another suitable doctor to do so,

c. make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing an unlicensed medicine.”

Information for patients about the licence for their medicines.

“Some medicines are routinely used outside the terms of their licence, for example in treating children. In emergencies or where there is no realistic alternative treatment and such information is likely to cause distress, it may not be practical or necessary to draw attention to the licence. In other cases, where prescribing unlicensed medicines is supported by authoritative clinical guidance, it may be sufficient to describe in general terms why the medicine is not licensed for the proposed use or patient population. You must always answer questions from patients (or their parents or carers) about medicines.”

PrescQIPP draft patient information leaflets are available for Prescribers to use as an aid to discuss the unlicensed status of some medicines prescribed in neuropathic pain and then give to the patient as a reminder of the information discussed.
Neuropathic pain algorithm

- If a treatment is not licenced for the prescribed indication ensure the patient understands the unlicensed status of the medicine, and has been given patient information and gives informed consent.
- Consider co-morbidities, side effects and potential for abuse before commencing treatments.
- Prescribe on acute prescriptions (not repeat) until treatment is stabilised.
- Review all treatments after 8 weeks once the dose is titrated to an adequate dose. Discontinue treatments that are ineffective.
- Ongoing review: treatment should be reviewed regularly for continued need. Discontinue repeats for medication no longer being taken.

**Trigeminal neuralgia**
Use carbamazepine first line for trigeminal neuralgia.

**Amitriptyline**
10-75mg at night

If not tolerated or inadequate response, replace with Gabapentin
300-3600mg/day

If not tolerated or inadequate response, replace with Duloxetine
60-120mg/day
or
Pregabalin
150-600mg/day

If first choice not tolerated or ineffective discontinue and try other drug.

If not tolerated or inadequate response:

**STOP and refer**

Refer to pain clinic for specialist assessment if inadequate response to treatment or treatments not tolerated. Whilst patient is awaiting assessment by specialist, consider adding short term treatment with tramadol for acute rescue therapy only.

**DO NOT START THE FOLLOWING TREATMENTS IN NON SPECIALIST SETTINGS**

- Cannabis sativa extract
- Capsaicin patch
- Lacosamide
- Lamotrigine
- Levetiracetam
- Morphine
- Oxcarbazepine
- Topiramate
- Tramadol-long term
- Venlafaxine
Prescribing notes

For Trigeminal neuralgia only: Carbamazepine (first line)

This is one of several antiepileptics that can be of use for trigeminal neuralgia in addition to the tricyclic antidepressants and gabapentin etc.

Notes

- Initially 100mg (once or divided into twice daily dose) increased gradually according to response. Usual dose 200mg three to four times daily, up to 1.6g total daily dose in some patients.
- If ineffective follow neuropathic pain pathway from step 1.

For all other neuropathic pain

Step 1 – Amitriptyline

Notes

- Amitriptyline is unlicensed for use in neuropathic pain but there is a large evidence and practice base to support its use and this is an established indication.
- Typical starting doses are 10mg-25mg at night and should be gradually increased according to the patient’s needs. Doses above 50mg are seldom required although up to 75mg may sometimes be tolerated. Pain relief may be seen after 1-7 days but it may take two to six weeks for the drug to be effective.
- Advise patient to take at about 8pm; if morning sedation is problematic the dose may be taken earlier in the evening.
- Particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.
- A typical amitriptyline dosage regimen:
  - Step 1: - 10mg at night* for 1 week
  - Step 2: - 20mg at night* for 1 week then evaluate response
  - Step 3: - 30mg at night* 
  - Step 4: - 40mg at night*
  - Step 5: - 50mg at night*

  * Ensure patient tolerates dose at each step before increasing dose.
  
  After step 2 the dose can be increased gradually according to tolerance and the patient’s needs.

  - If amitriptyline is not tolerated or is ineffective it should be withdrawn gradually over 1-2 weeks and gabapentin tried.

Step 2 – Gabapentin

Notes

The anticonvulsant drug of choice is gabapentin (licensed indication for peripheral neuropathy, not licenced for central neuropathy). Capsules are the most cost-effective formulation. Where appropriate for patients with a low tablet/capsule load, using multiple capsules to make up a dose should be considered. Gabapentin should be started slowly according to the regimen below. In renal impairment, the elderly or drug sensitive patients, this titration may need to be done in 100mg increments. Refer to the SPC for more details. Slower titration and particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.
A typical dosage regimen for gabapentin

For neuropathic pain dose range is 900mg to 3600mg daily (dose reduced in renal impairment). Treatment can be initiated at a dose of 900mg/day given as three equally divided doses or at a slower rate as described below:

Step 1: Gabapentin 300mg once daily on day 1.
Step 2: Gabapentin 300mg twice daily on day 2.
Step 3: Gabapentin 300mg three times daily on day 3.
Slower titration of gabapentin may be appropriate for individual patients to improve tolerability.

Once a patient is on a 900mg dose, the dose can be increased in 300mg increments every two to three days until tolerated. The dose should be increased to either the dose that provides sufficient pain relief or the maximum tolerated dose. The maximum daily dose is 3600mg, however in practice many patients do not go over a dose of 1800mg.

An example of a dose increase regimen is shown below:

Step 4: Gabapentin 300mg morning and 300mg mid-day + 600mg night until tolerated*.
Step 5: Gabapentin 600mg morning and night and 300mg mid-day until tolerated*.
Step 6: Gabapentin 600mg morning, 600mg mid-day and 600mg night until tolerated*.

*usually 2-3 days but may take up to a week in some patients.

The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

- Side effects are usually minor and subside within 4 weeks.
- Gabapentin can make patients drowsy or dizzy and occasionally causes severe headaches. Headache does not tend to resolve. Serious adverse effects are rare.

If there is no improvement within 8 weeks of reaching the maximum tolerated therapeutic dose, consider alternative treatment. Gabapentin should not be stopped abruptly and should be reduced gradually over a minimum of 1 week, depending on dose and duration of treatment.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient’s clinical status and determine the need for additional therapy.

### Step 3: Duloxetine or Pregabalin

**Duloxetine**

This can be considered a third line treatment for neuropathic pain (licenced for the treatment of diabetic neuropathy only) in patients who have not achieved adequate pain relief from, or who have not tolerated, first and second line treatments i.e. with amitriptyline or gabapentin.\(^4\,5\) In secure environments duloxetine is recommended for consideration prior to prescribing gabapentin or pregabalin due to the risk of abuse and diversion of these medicines.\(^7\)

- The dose is 60mg once daily, increased to a maximum of 120mg daily in divided doses.
- Treatment should be discontinued after 8 weeks if there is an inadequate response.

Treatment should be reviewed at least every three months for continued need

**Pregabalin**

Pregabalin is an alternative to gabapentin in patients who have not achieved adequate pain relief from, or have not tolerated, first and second line treatments. This drug can be used in combination with a tricyclic anti-depressant, but it should not be co-prescribed with gabapentin (note there may be some crossover when titrating treatments at change of therapy). Cases of abuse have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of pregabalin abuse.
Pregabalin is licensed for neuropathic pain.

Pregabalin should be started slowly and titrated to response and tolerability as detailed below.

The dose must be reduced in renal impairment and may need to be reduced in older people, or drug sensitive patients.

Twice daily dosing is more cost-effective than three times a day dosing.

Pregabalin can make patients drowsy or dizzy and may cause confusion.

Dose range is 150mg to 600mg daily (reduce dose in renal impairment).

A typical dose regimen for pregabalin

Pregabalin 75mg morning and night until tolerated (usually 3 to 7 days), if a dose increase is needed use Pregabalin 150mg morning and night until tolerated (after 7 days), if a further dose increase is needed use Pregabalin 300mg morning and night until tolerated- no further dose increase is recommended as 600mg daily is the maximum dose.

The starting dose may need to be reduced in drug sensitive or elderly patients. A suitable starting dose may be 25mg twice daily (morning and night). This should be titrated slowly to response and tolerability. Slower titration and particular caution is advised on initiation and after an increase in dose in patients who drive or operate machinery.

Dosage reduction is required in patients with compromised renal function. Refer to the SPC for details.

Pregabalin should be stopped if the patient has not shown sufficient benefit within 8 weeks of reaching the maximum tolerated therapeutic dose and referred to the Pain Clinic. It should not be stopped abruptly but should be reduced gradually over a minimum of 1 week.

Review long term use and assess the need to continue treatment.

References