Guidance for Review of Patients taking Pregabalin for Neuropathic Pain

Aim
To review effectiveness of pregabalin in patients who have been taking this medication for more than 12 month for the treatment of neuropathic pain.

Background
Pregabalin is locally recommended as a third line treatment for neuropathic pain (after amitriptyline/nortriptyline and gabapentin). This is expected to be its positioning in the revised NICE guidance currently under consideration. Pregabalin is not licenced for use in any other type of pain.

After 6 to 12 months of use, the initial benefit that some patients may have obtained from pregabalin for the treatment of their neuropathic pain may no longer exist. Gloucestershire Hospitals Chronic Pain Specialists therefore support the principle of the gradual trial withdrawal of pregabalin in appropriate patients, after a period of 12 months, to assess whether pregabalin continues to provide a significant benefit.

Pregabalin is currently the highest cost growth drug (23% pa) in Gloucestershire. The current primary care prescribing costs of pregabalin in Gloucestershire are £1.6 million pa, with average costs per prescription of £58.42. Local audits have shown that the largest part of this prescribing is for neuropathic pain (although mental health indications are increasing). All neuropathic pain products prescribing costs at shown in Appendix 6.

Review Process

1. Identify patients taking pregabalin for neuropathic pain for longer than 12 months.
2. Obtain relevant information from patient notes to support potential pregabalin review (see Appendix 1: Patients reviewed summary form).
3. Select patients considered as potential candidates for trial withdrawal.
4. Invite patients in for review. (Sample patient letter attached in Appendix 2)
5. Complete the PAIN DETECT questionnaire (Appendix 3) as a baseline assessment as part of the initial review. (Consider asking the patients to complete the PAIN DETECT questionnaire themselves in advance and bring to the review.)

6a) If the pain score is LOW at time of review (ie. pain well controlled):
   a) Provide patient with dosage reduction instructions. A blank patient dosage instruction form can be found in Appendix 4. A suggested dosage reduction regime is:
**Pregabalin Dosage Reduction**: Reduce dose by 50-75 mg per week *e.g. starting dose*: Pregabalin 150mg bd then dosing would be:

<table>
<thead>
<tr>
<th>Dosage Reduction Guidance</th>
<th>Week 1 Dose</th>
<th>Week 2 Dose</th>
<th>Week 3 Dose</th>
<th>Week 4 Dose</th>
<th>Week 5 Dose</th>
<th>Week 6</th>
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<tbody>
<tr>
<td>Morning</td>
<td>150mg</td>
<td>75mg</td>
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b) Give patient a blank PAIN DETECT questionnaire to complete at the end of the dosage reduction period.
c) Invite patient back for review at end of trial withdrawal or sooner if experiencing problems
d) Complete **Patient Review Summary Form (Appendix 1)** to as part of summary of outcomes of all patient trial withdrawals.

6b) **If pain score is HIGH** at time of review (i.e. pain is not well controlled) and PAIN DETECT questionnaire **confirms** pain is neuropathic in nature

   a) Consider additional/change in neuropathic agent or,
   b) Referral to Secondary Care Pain Clinic if:
      i. Patient’s symptoms are unresponsive to treatment and an acceptable reduction in pain is not achieved
      ii. There is response to treatment but unacceptable side-effects and all options have been considered
      iii. Bio-psychosocial needs and difficulty in coping ("yellow flags")
      iv. Further advice or diagnosis is needed on the particular clinical symptom set

6c) **If pain does not appear to be neuropathic in nature** and is not currently well controlled – consider a change of treatment as pregabalin is only licenced for neuropathic pain.

**Appendices:**
- Appendix 1: Patients reviewed summary form
- Appendix 2: Sample patient letter
- Appendix 3: Diagnostic screening tool - Pain Detect questionnaire
- Appendix 4: Dose reduction instructions for patients
- Appendix 5: Management & Treatment of Neuropathic Pain & Diabetic Neuropathy
- Appendix 6: Neuropathic pain drugs treatment costs
- Appendix 7: Additional information

This local guidance is based on advice from Gloucestershire Hospitals Pain Specialists
Appendix 1:

Pregabalin for Neuropathic Pain - Patients Reviewed Summary Form

<table>
<thead>
<tr>
<th>Patient Identifier</th>
<th>DOB</th>
<th>Pregabalin strength &amp; dose</th>
<th>Indication</th>
<th>Initiated By GP/Specialist etc</th>
<th>Duration of Treatment</th>
<th>Other neuropathic agents tried</th>
<th>PAIN detect questionnaire score</th>
<th>Action taken: T- Tapering S-Switched R-Referral C- Continued O - Other</th>
<th>Outcome of follow up review &amp; any additional comments</th>
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This local guidance is based on advice from Gloucestershire Hospitals Pain Specialists
Appendix 2:

Sample patient letter

Dear

We are currently undertaking a review of patients at the Practice who are taking medication to treat “nerve pain”.

We notice from your records that you have been taking pregabalin for some time now and may benefit from a review. We may be able to reduce your pain medication if your pain is now well controlled, or review it to another medication/change your dose if the pain is not well controlled.

We would like to invite you to a clinic to discuss this with you. Please could you phone the surgery to book an appointment. Prior to seeing you, it would be useful if you could complete the enclosed questionnaire, so that we can assess how well your pain is being controlled on your current medication.

Yours sincerely,

_________________________________________________________________________

Appendix 3:

The PAIN DETECT Questionnaire – neuropathic pain assessment tool can be found at:


An internet based version for online scoring is available at:

http://www.virtualmedicalcentre.com/calc_pfizer_pain_detect.asp

This local guidance is based on advice from Gloucestershire Hospitals Pain Specialists
Appendix 4:

Pregabalin for neuropathic pain – dosage reduction instructions for patient

<table>
<thead>
<tr>
<th>Dosage Instructions:</th>
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<tbody>
<tr>
<td>Week 1</td>
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<tr>
<td>Morning</td>
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<tr>
<td>Lunchtime</td>
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<td>Evening</td>
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Please attend for a further review once the above pregabalin dosage reduction is complete, or sooner if you experience any problems or worsening pain.

It would be useful if you kept a symptom diary over the dosage reduction period, including details of activities undertaken, ability to work and drive, quality of sleep and general mood (e.g. depression/anxiety) and the associated pain experienced.

Please also complete the PAIN DETECT Questionnaire again at the end of the dosage reduction period and bring it with you to the follow up review.
Appendix 5:

Guidelines for the Management of Neuropathic Pain in Primary Care

Neuropathic pain is caused by abnormally damaged nerves. Possible causes include nerve damage due to trauma or conditions such as diabetes, herpes zoster (shingles) and trigeminal neuralgia. Neuropathic pain may be considered in ongoing conditions e.g. sciatica, neck pain and low back pain. It may also be a feature of underlying conditions e.g. malignancy, that require investigation.

Neuropathic pain may present as:

- **Dysasthesia** - an unpleasant, abnormal sensation
- **Hyperalgesia** - increased sensitivity to normal pain stimulus e.g. temperature
- **Allodynia** - pain caused by a stimulus that does not normally produce pain – e.g. wearing clothes
- **Motor-dystonia**, weakness and paralysis, fasciculations
- **Autonomic signs** including skin changes such as shininess, oedema, change of perspiration

Neuropathic pain may be spontaneous or evoked, continuous or intermittent and is often worse at the end of the day. Patients’ descriptors of the pain include:

- **Shooting**, **Tingling**, **Burning**, **Sharp**, **Nagging**, **Electric shock**

2-4% of the general population is thought to be affected by neuropathic pain. Adequate assessment and accurate diagnosis is essential for specific treatment options to be considered. Diagnostic screening tools can be useful such as PAIN DETECT.

All treatment strategies need to be individualised to specific patient requirements and tolerance. Patients’ beliefs and perception of the pain and its cause, disturbed sleep, anxiety, mood changes and coping strategies will also need to be addressed and treating anxiety or depression first may reduce the need for analgesics.

Consider non-pharmacological elements to the management eg. address physical and emotional aspects, as well as pain, by encouraging physical activity, improving poor sleep.

Pharmacological interventions should be increased to full therapeutic and tolerated dose before switching or adding a different agent. As pain is a biologically complex phenomenon, there is rationale for combining drugs with different mechanisms of action. Realistic goals need to be set – pain free status is not usually achievable and 20-50% reduction in pain is a commonly used end-point in clinical trials.

If complex regional pain syndrome is suspected, refer urgently to Pain clinic, since there is a window of opportunity to treat this before it becomes chronic and untreatable.

Please note: these guidelines are not intended to cover Palliative Care.
Treatment of Neuropathic Pain (for diabetic Neuropathy see next section)

- Review periods at 2, 4 and 8 weeks is recommended to assess effectiveness of the neuromodulatory medication. However, the median effective dose should have been achieved at 8 weeks i.e. gabapentin 600mg tds; or pregabalin 150mg bd or amitriptyline 25-50mg on to assess accurately
- If the drug is effective, continue for 12 MONTHS and then consider dosage reduction and trial withdrawal to assess continuing benefit being obtained, if any.

### Step 1
Non-opioid analgesia/baseline analgesia  
Paracetamol 1g qds

### Step 2
Tricyclic Antidepressant (TCA) unless contra-indicated (Unlicensed use but proven efficacy)  
**Amitriptyline** – titrate slowly to reduce side effects

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
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</thead>
<tbody>
<tr>
<td>10mg</td>
<td>20mg</td>
<td>30mg</td>
<td>40mg</td>
<td>50mg</td>
</tr>
</tbody>
</table>
- Take at night to reduce hangover effect and to promote sleep.  
- Usual maximal dose is 50mg but 75mg may be used if patient deriving benefit with limited side effects  
- Titrate down slowly if stopping therapy (see pg------)  
- Avoid co-prescribing of tramadol as increases risk of CNS toxicity

For contra-indications refer to SPC in Electronic Medicines Compendium – www.medicines.org.uk

Consider use of nortriptyline if patient not tolerating side effects of amitriptyline or in patients with cardiac disease. Patients should be encouraged to persist with treatment as tolerance to side –effects is possible

### Step 3
Anticonvulsant (first choice if TCA contra-indicated or lancinating pain (electric shock like piercing or stabbing sensation)

**Gabapentin**

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<td>Night</td>
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<td>300mg</td>
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<td>600mg</td>
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</table>
- Continue increasing as above to maximum of 1200mg tds. Minimum time to reach dose of 3600mg is total of 3 weeks, determined by efficacy and side effects. May need to wait for up to 2 weeks to experience maximal benefits.  
- Titrate down slowly if stopping therapy (see pg------). Advise patient and carer(s) of possible drowsiness and effect on driving

Consider **pregabalin** if gabapentin is effective but not well tolerated. When gabapentin is ineffective consider a trial of pregabalin (initial dose 75mg bd increasing after 3-7 days if required to a maximum dose of 300mg bd)

Pregabalin is not recommended as first line treatment for neuropathic pain contrary to NICE guidance. Valid clinical reasoning supports current PCT recommendations based on a health economics analysis

ALWAYS PRESCRIBE AS BD DOSING (MORE COST EFFECTIVE THAN TDS)

May need to reduce dose in renal impairment

### Step 4
If patient has mixed symptoms and not pure neuropathic pain consider initiation of **Tramadol** (check for cautions and contra-indications first e.g. unstable epilepsy). Increase dose according to response to a maximum dose of 100mg qds

### Step 5
Refer to Secondary care pain clinic if:
- Patient’s symptoms are unresponsive to treatment and an acceptable reduction in pain is not achieved  
- There is response to treatment but unacceptable side-effects and all options have been considered  
- Bio-psychosocial needs and difficulty in coping (“yellow flags”)  
- Further advice or diagnosis is needed on the particular clinical symptom set

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Treatment of Diabetic Neuropathy

- In patients with diabetes, poor glycaemic control is a key risk factor for developing peripheral diabetic neuropathy.

### Step 1

**Tricyclic Antidepressant (TCA) unless contra-indicated (Unlicensed use but proven efficacy)**

**Amitriptyline** – titrate slowly to reduce side effects

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<thead>
<tr>
<th>Week 1</th>
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**Anticonvulsant (first choice if TCA contra-indicated or lancinating pain (electric shock like piercing or stabbing sensation)**

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<tr>
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<td>Night</td>
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ALWAYS PRESCRIBE AS BD DOSING (MORE COST EFFECTIVE THAN TDS)

May need to reduce dose in renal impairment.

### Step 3

**Duloxetine 60mg od.** In trials a total daily dose of 120mg (60mg bd) was not found to be superior to 60mg od (ref).

Response is seen within ONE WEEK and is unlikely if not seen within 8 weeks. PATIENT TO BE REVIEWED ON A REGULAR BASIS EVERY 3 months (see pg--)

Contraindicated in liver disease and severe renal impairment (CrCl<30ml/min). For full details see [www.medicines.org.uk](http://www.medicines.org.uk)

Titratedown slowly if stopping therapy (over a period of at least 1-2 weeks (see pg ----))

Duloxetine is classed as ▼ which means it is under intensive surveillance by the MHRA. All suspected adverse drug reactions should be reported via the yellow card scheme.

### Step 5

Refer to Secondary care pain clinic if:

- Patient's symptoms are unresponsive to treatment and an acceptable reduction in pain is not achieved.
- There is response to treatment but unacceptable side-effects and all options have been considered.
- Bio-psychosocial needs and difficulty in coping (“yellow flags”)
- Further advice or diagnosis is needed on the particular clinical symptom set.

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Appendix 6:

Neuropathic Pain - 1 year treatment costs (Oct 2012)

(Doses stated below do not imply therapeutic equivalence due to significant patient variability in response in management of neuropathic pain.)

- Pregabalin (100mg tds)$1,400
- Lidocaine patch (1/day)$1,200
- Pregabalin (150mg bd)$1,000
- Duloxetine (60mg od)$800
- Carbamazepine (200mg qds)$600
- Capsaicin 0.075% cream 91/5g/day)$400
- Nortriptyline (25mg od)$200
- Gabapentin (600mg tds)$200
- Gabapentin (2x300mg tds)$200
- Amitriptyline (25mg od)$200
- Amitriptyline (25mg od)$200

Appendix 7: Additional Information

Local specialists have developed a pain management guidance section on the Gloucestershire Hospitals intranet site. This included further information on the management of neuropathic pain at:


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