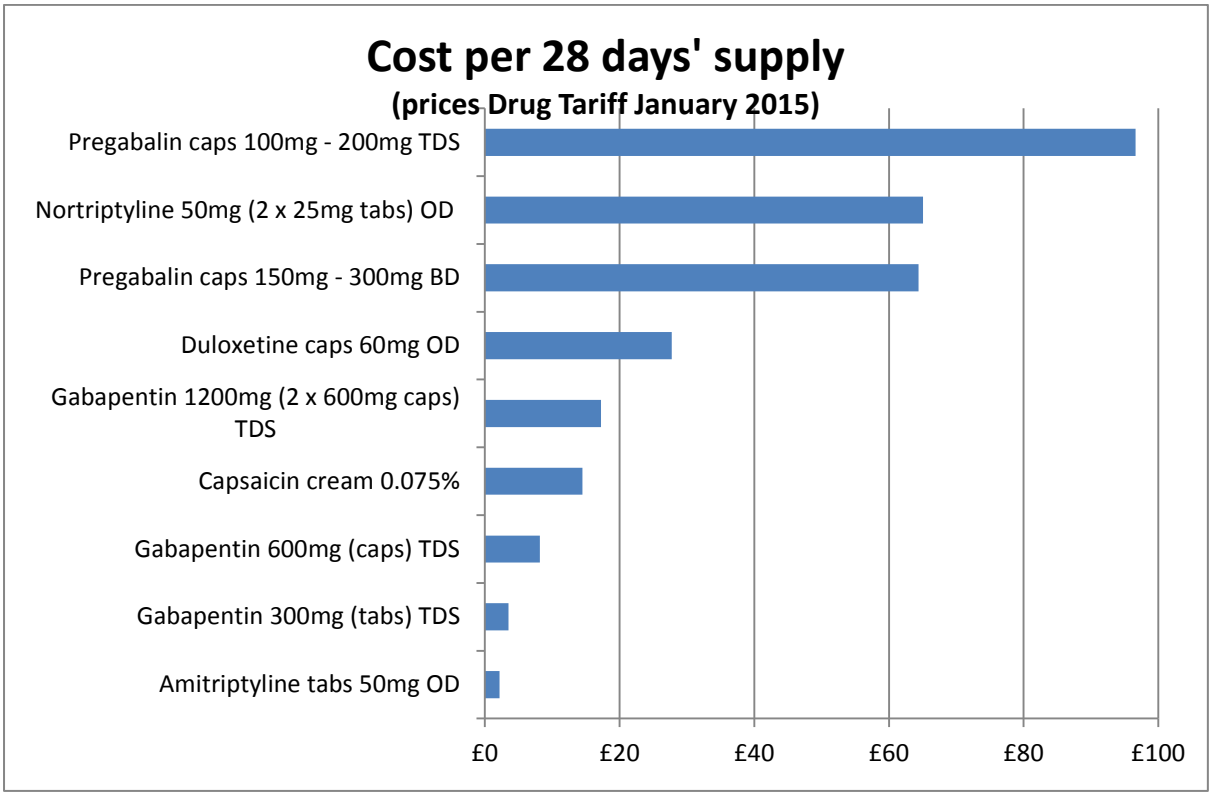
Review of Pregabalin for Neuropathic Pain
A Guide for Prescribers

What are the issues with pregabalin?

In a 12 month period (Jan-Dec 2013) NHS Eastbourne, Hailsham and Seaford and NHS Hastings and Rother Clinical Commissioning Groups spent approximately £1.6 million on pregabalin (prescribing for all indications). The average cost was £56.63 per prescription.

Spend on pregabalin prescribing in NHS Eastbourne, Hailsham and Seaford and NHS Hastings and Rother Clinical Commissioning Groups is much higher than expected based on national prescribing patterns. If prescribing of pregabalin was reduced to national levels, an additional £1million would be available to the local health economy. Locally there is significant variation in prescribing between practices.



- NICE guideline for the pharmacological management of neuropathic pain in the non-specialist setting (CG173) was issued in November 2013. NICE recommends offering a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain.
- There are no head to head trials of these agents in neuropathic pain; all of the recommended agents have been shown to consistently reduce pain compared to placebo.
- As there is no evidence of superior clinical efficacy for any one agent, amitriptyline and gabapentin were not recommended ahead of other agents. However, it is noted that pregabalin and duloxetine offer poor value for money.
- Amitriptyline does not have a UK marketing authorisation license for neuropathic pain, however use for this indication is well established and there is extensive experience of primary care prescribing. Duloxetine is only licensed for diabetic peripheral neuropathy.

With kind acknowledgement to NHS Surrey Downs CCG, NHS Gloucestershire CCG and NHS Wirral CCG

- Choice of initial drug should be governed by the patient's vulnerability to specific adverse effects because of comorbidities, safety considerations and contraindications, lifestyle factors (such as occupation) and any mental health problems (such as depression or anxiety).
- Pregabalin is structurally related to gabapentin and has a similar pharmacological action and side-effect profile.
- Therapy should be reviewed **regularly** – taking account of pain control, impact on lifestyle, activities of daily living (including sleep), physical/psychological wellbeing, adverse events and continued need. Patients in whom the drug is effective should continue for 6 months, after which a trial withdrawal should be attempted to assess if benefit persists. Following this the drug should be reviewed at least annually.

- Side effects of both gabapentin and pregabalin are significant and include:
    - Dizziness and somnolence (common). Particular care is needed in the elderly who may be at risk of falls.
    - Increased appetite and weight gain.
    - Euphoria, hence the significant abuse potential and street value for both drugs. Abuse has been reported to be a particular problem in prisons.

How can prescribing of pregabalin be improved?

- To help ensure current prescribing for neuropathic pain is safe and effective, introduction of pain management review of patients prescribed pregabalin is recommended.
- Patients currently taking pregabalin, who have not had a review of this medicine for at least 12 months should be prioritised for review.

Review Process

- Identify patients prescribed pregabalin **for neuropathic pain** who would benefit from a review of pregabalin prescribing (as above)
- Invite patients in for review (see sample patient invite letter (Appendix 1)
- Complete review template for each review undertaken (Aide Memoire Appendix 2). This assessment of chronic pain may be undertaken by the patient prior to the consultation with their GP (e.g. in the waiting room) although it is the view of local pain team that better results may be obtained by asking questions in the face to face consultation.

If pregabalin does not appear to be helpful (pain management, improved functioning or quality of life); initiate gradual drug withdrawal. Provide patients with full dose reduction instructions (Appendix 3) and an appropriate supply of medication. Prescriptions should be provided to cover a 2 week reduction process and should include the exact number of capsules required.
Each patient should be advised that a trial withdrawal of their medication is being attempted as the medicine does not seem to be particularly helpful. In addition, patients should be informed that initial benefit seen may not persist, but medicines are associated with long term adverse effects. Patient should be given written information to support them in reducing their medication (Appendix 3).

Withdrawal regimen

Suggested pregabalin withdrawal : Reduce dose of pregabalin by 50-75mg every 2 weeks

During the dose reduction multiple capsules may need to be taken per dose for simplicity. This is an expensive short term measure to aid effective withdrawal.

In order to reduce potential waste and risk of diversion, no more than 2 weeks supply of pregabalin capules should be supplied in the initial stages of withdrawal. Patients must be advised of the importance of telephoning their GP to request the next prescription stage in their withdrawal regime early in their 2nd week of withdrawal to ensure supplies is available. Alternatively following discussion with the patient and their normal pharmacy, post-dated prescriptions could be written which would enable the patient to collect the next part of their withdrawal regime without needing to contact their GP. Community pharmacists are able to offer support to patients throughout the process through the Medicines Use Review process.

Reduction from pregabalin **300mg twice daily**

	Week 1	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**
Morning	3 x 75mg	3 x 75mg	2 x 75mg	2 x75mg	75mg	75mg		Stop
Evening	4 x 75mg	3 x 75mg	3 x 75mg	2 x 75mg	2 x 75mg	75mg	75mg	
Total number of capsules to be supplied for this 2 week period	98 x 75mg	84 x 75mg	70 x 75mg	56 x 75mg	42 x 75mg	28 x 75mg	14 x 75mg	

Reduction from pregabalin **150mg twice daily**

	Week 1	**Week 3**	**Week 5**	**Week 7**
Morning	75mg	75mg		Stop
Evening	2 x 75mg	75mg	75mg	
Total number of capsules to be supplied for this 2 week period	42 x 75mg	28 x 75mg	14 x 75mg	

Unsuccesful withdrawal

- If during a trial withdrawal a patient experiences an unacceptable worsening of their pain, they should be advised to increase the dose back to a therapeutic dose and make an appointment with their GP.

- Dosing of pregabalin should be normally consist of ONE capsule TWICE a day. During the dose reduction more than one capsule may need to be taken per dose for simplicity. If the withdrawal is unsuccessful and treatment needs to be continued, remember to change the prescription back to ONE capsule TWICE DAILY if necessary.

If patients pain/function level is unacceptable at time of review

- Reassess patient's condition to exclude any red flags
- Review psychosocial needs and difficulty in coping (yellow flags)
- Consider advice/referral to specialist pain team for additional support (e.g. TENS, acupuncture, pain rehabilitation programs)
- Switch to one of the other three drug options (for example if on pregabalin; switch to amitriptyline, duloxetine or gabapentin). If the treatment is still poorly tolerated, consider switching again until a treatment is found that is tolerable or all four drugs have been tried.
- When introducing a new drug, consider overlapping it with the old treatment to avoid deterioration in pain control. Taper the dose of the drug to be withdrawn to prevent discontinuation symptoms (see Withdrawal regimens above)
- Clinical Knowledge Summaries has Prescribing information for additional information on starting and withdrawing drug treatments

If pregabalin is helpful; consider whether a switch to gabapentin is appropriate. A straight switch to an equivalent dose is possible in patients with normal renal function (See Appendix 4 for dose conversion information).

Complete Patient Review Summary Form (Appendix 5) as part of record of outcomes of all patient trial withdrawals. Part A can be completed following assessment of the patient and agreed treatment plan, Part B will need to be completed following the trial withdrawal. If a read code is added to patients who have had their pain management review using the Aide Memoire (Appendix 2) it will be possible to run a search to identify patients to review the outcome achieved. The completed form will need to be submitted to the CCG Medicines Management Team in order to receive payment for undertaking reviews as part of the Prescribing Support Scheme 2015/16.

References

1. Neuropathic pain-pharmacological management: the pharmacological management of neuropathic pain in adults in non-specialist settings. NICE Clinical Guideline 173 November 2013. http://www.nice.org.uk/guidance/CG173 Accessed 11.11.14
2. Side effects of pregabalin and gabapentin, BNF online. Accessed 23.4.14.
3. Management of chronic pain. Scottish Intercollegiate Guidelines Network (SIGN) December 2013
4. Clinical Knowledge Summaries at www.cks.nice.org.uk Accessed on 11.11.14
5. Toth C. Substitution of gabapentin therapy with pregabalin therapy in neuropathic pain due to peripheral neuropathy. Pain Medicine 2010; 11:456-465

Appendix 1. Sample patient invite letter

Dear

We are currently undertaking a review of patients at our practice who are taking medicine to help manage “nerve pain”.

We notice from your records that you have been taking pregabalin for some time now. You may benefit from a review to ensure that you are not suffering from any harmful side effects and to check the medication is still helping you.

We would like to invite you to come into the practice to discuss this further.

Yours sincerely

Appendix 2.

Aide Memoire for Review of Chronic Non-malignant Pain

Pain Problem ……..

Which medicines are currently being taken for pain? (List below)

……

……

Are side effects currently causing problems? (Tick as appropriate)

Headache (Yes/No)	Tiredness (Yes/No)	Poor memory (Yes/No)
Confusion (Yes/No)	Drowsiness (Yes/No)	Constipation (Yes/No)
Weight gain (Yes/No)	Dry mouth (Yes/No)	Unsteadiness (Yes/No)
Nausea (Yes/No)		

Does this medicine help you manage your pain? (Tick as appropriate)

No, it's not helpful Yes, it is helpful

Does this medicine help you in your day to day life?

Tick the response that describes whether you feel your medicine helps you with:

General activity? Not helpful Helpful	**Sleep?** Not helpful Helpful
Mood? Not helpful Helpful	**Anxiety?** Not helpful Helpful

On balance, do you feel this medicine is helpful? (Yes/No)

Would you be willing to consider other options that might help you manage your pain (e.g. pain rehabilitation programme)? (Yes/No)

Clinician assessment of pain medicine

Is the medicine helpful?

Yes

Efficacy/safety balance acceptable

Consider switch to gabapentin if appropriate (Appendix 5)

If no change to treatment, review annually

No/Unsure

Withdrawal of medicine (as per review protocol)

Consider alternatives and/or advice/referral

Assess Yellow Flags – psychosocial needs and difficulty in managing/coping *(indicators suggestive of increased risk of progression to long term distress, disability and pain)*

Attitudes and Beliefs	• Pain is harmful or severely disabling • Expectation that passive treatment rather than active treatment may help • Feeling that 'no-one believes the pain is real' –may relate to previous encounters with healthcare professionals
Emotions and Behaviour	• Fear-avoidance behaviour (avoiding activity due to fear of pain) • Low mood and social withdrawal • Lack of job satisfaction
Other psychosocial factors	• Poor family relationships or history of abusive relationships • Financial concerns particularly related to ill-health or ongoing pain • Poor social support from colleagues • Company policy on sick leave • Threats to financial security (e.g. benefit changes) • Ongoing litigation related to persistent pain problem • Lack of contact with work

Consider obtaining specialist advice or referral if:

Presence of Red Flags/Yellow Flags

Patient's symptoms are unresponsive to treatment

Patient does not want drug therapy

Further advice required for particular clinical symptom set

Appendix 3.

Pregabalin for neuropathic pain – dosage reduction instructions for patient

Dosage instructions:								
	Week 1	**Week 3**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**
Morning								
Evening								

Your GP has provided you with an initial prescription for pregabalin capsules. During the dose reduction multiple capsules may need to be taken per dose for simplicity. Please ensure that you request your next prescription in plenty of time to ensure you don't run out.

Please contact your GP for advice 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. Try to remember to bring your symptom diary with you if you need to see your GP again.

Appendix 4. Pregabalin to gabapentin dose conversion information

Switching pregabalin to gabapentin in patients with normal renal function

This would be a straight switch, rather than titrating down the pregabalin dose and titrating up the gabapentin dose.

Pregabalin total daily dose pre-switch	Gabapentin total daily dose post switch (Toth study[5])	Suggested daily dose of gabapentin
150mg	900mg	300mg tds
225mg	901mg to 1500mg	400mg tds
300mg	1501mg to 2100mg	2x300mg tds
450mg	2101mg to 2700mg	2x400mg tds
600mg	2701mg to 3600mg	3x300mg tds

For daily doses of pregabalin below 150mg daily, e.g. 100mg, 75mg – **switch to gabapentin 100mg tds**, and titrate up if necessary (see gabapentin titration schedules below)

Gabapentin dose adjustment based on renal function

Creatinine Clearance (ml/min) or eGFR	Total Daily Dose (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	*150-600
<15**	150*-300

*To be administered as 300 mg every other day.

** For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency

Gabapentin titration schedule

Gabapentin – Standard Titration

	Day 1-3	Day 4-6	Day 7-9	Day 10-12	Day 13-15	Day 16-18
Morning		100mg	100mg	100mg	300mg	300mg
Midday			100mg	100mg	100mg	300mg
Night	100mg	100mg	100mg	300mg	300mg	300mg

Gabapentin – Rapid Titration

	Day 1-3	Day 4-6	Day 7-9	Day 10-12	Day 13-15	Day 16-18
Morning		300mg	300mg	300mg	600mg	600mg
Midday			300mg	300mg	300mg	600mg
Night	300mg	300mg	300mg	600mg	600mg	600mg

- A longer titration starting at initial lower dose may frequently be required depending on the patient's general health.
- Dosage will need to be reduced in patients with renal impairment. Access Prescribing information (Clinical Knowledge Summaries) for additional information.
- Median effective dose is 600mg three times daily
- Continue increasing as above to maximum 1200mg three times a day – determined by efficacy and side-effects (especially unsteadiness, drowsiness).
- May need to wait up to 2 weeks to experience maximum benefit, a therapeutic trial of 8 weeks at median effective dose is required before assessment of efficacy can be undertaken

Discontinuing gabapentin

If gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week. Clinical Knowledge Summaries has Prescribing information for additional information on starting and withdrawing drug treatments.

Appendix 5. Patient Review Summary Form

	Past and current treatment details					Outcome of initial review	Outcome of following withdrawal
Patient Identifier (to be removed prior to sending to CCG)	Pregabalin strength and dose	Indication	Duration of treatment	Previous medication for neuropathic pain tried (please list)	Assessment of chronic pain completed (Aide Memoire) Copy in electronic patient notes (Y/N)	Action taken: W – Withdrawal S – Switched R – Referred C- Continued O –Other (please state)	Outcome (assess after withdrawal complete **or** after 4 month period) W- Pregabalin withdrawn D – Pregabalin dose reduced U – Unsuccessful withdrawal/switch – pregabalin dose returned to baseline S – Successfully switched to gabapentin N/A – not applicable for patients who did not attempt withdrawal or switch to gabapentin