Neuropathic pain: Pregabalin and gabapentin prescribing

There has been a 17.2 % increase in pregabalin prescribing across England since 2013/14 with over £256 million spent annually on pregabalin (ePACT July 2015).

QIPP projects in this area are aimed at reviewing pregabalin prescribing in neuropathic pain to ensure a pathway has been followed, which includes prescribing of amitriptyline or gabapentin before pregabalin (Lyrica®) is initiated. In this bulletin, dose optimisation of pregabalin and use of the most cost effective forms of pregabalin in appropriate indications in line with guidance from NHS England are reviewed. The use of nortriptyline in neuropathic pain is also reviewed in light of current costs.

Support material: Briefing, pathway, invitation to review letter, audit, patient information leaflet and presentation, available: https://www.prescqipp.info/pregabalin-in-neuropathic-pain/viewcategory/202

Note – While the document refers to pregabalin for neuropathic pain, only Lyrica® brand is licensed for neuropathic pain.

Recommendations

- Ensure that pregabalin and gabapentin are prescribed at an appropriate place in therapy for neuropathic pain. For diabetic neuropathy, consider duloxetine as a third line option after amitriptyline (unlicenced) and gabapentin (see pathway). 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 their licensed indication for indications other than neuropathic pain, review the need to continue treatment.
- Consider switching patients on pregabalin whose neuropathic pain is not effectively managed to gabapentin or amitriptyline if these medicines have not been tried previously or the dose of treatment has 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.
- Ensure careful consideration is given before pregabalin and gabapentin are prescribed to patients with a history of substance misuse, co-prescribed with opiates or to those that have recently been released from prison. Review treatment regularly.[1]
- Review treatment eight 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.
- Where pregabalin is prescribed for neuropathic pain, prescribe under the brand name Lyrica®[2]
- When prescribing pregabalin for the treatment of Generalized Anxiety Disorder (GAD) or epilepsy, continue to prescribe as generic pregabalin. For organisations wishing to prescribe branded generics as a cost effective option, prescribe pregabalin as a branded generic, e.g. Rewisca, for GAD and epilepsy; this will help incur savings as pregabalin is currently a category C drug and any generic prescribing will be priced at the Lyrica® price.[2]

- Prescribing of pregabalin capsules should be optimised to the minimum number per dose with a twice daily frequency.
- Where nortriptyline is prescribed consider a change to a more cost-effective option such as amitriptyline if not previously tried or a step up the treatment pathway to gabapentin.
- 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 "when required" use of other types of analgesia such as paracetamol or NSAIDs.

Background

Pain is an unpleasant sensory and emotional experience that can have a significant impact on a person's quality of life, general health, psychological health, and social and economic wellbeing. Neuropathic pain is defined as '*pain caused by a lesion or disease of the somatosensory nervous system*'. Central neuropathic pain is defined as '*pain caused by a lesion or disease of the central somatosensory nervous system*', and peripheral neuropathic pain is defined as '*pain caused by a lesion or disease of the peripheral somatosensory nervous system*'.[3]

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. Pain and anxiety symptoms are subjective with wide variation in reported prevalence.[3] No single drug works for all neuropathic pain, and given the diversity of pain mechanisms, patients' 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.[3,4]

Licenced indications

- Gabapentin and pregabalin are structurally related epilepsy drugs and are also licensed for the treatment of peripheral neuropathic pain, such as painful diabetic neuropathy and post-herpetic neuralgia in adults.[5,6] Only the Lyrica® brand of pregabalin is licensed for neuropathic pain.[6]
- Pregabalin is also licenced for the treatment of central neuropathic pain and generalised anxiety disorder in adults.[6]
- Amitriptyline (and nortriptyline) do not have a UK marketing authorisation (not licenced) for pain.
- Duloxetine is licensed for diabetic peripheral neuropathic pain and generalised anxiety disorder.[7]

Several treatments are used outside of their product licences in "off label use". Although the drugs are commonly prescribed for non-neuropathic pain syndromes, e.g. fibromyalgia, there is little evidence to support the practice and prescribers should consider interventions more likely to help such as physical rehabilitation for back pain and musculoskeletal pain.[1,8]

If a decision is made to prescribe the drugs for unlicensed indications, 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.[3]

In addition, the Lyrica® brand of pregabalin has patent protection until July 2017 for its licensed indication of treatment of peripheral and central neuropathic pain; until such time as this patent expires generic pregabalin products will not be licensed for this indication and their use for this condition would be off-label and may infringe the patent.[3] Due to this patent protection, Warner-Lambert Company LLC is engaged in a dispute with a number of generic pharmaceutical suppliers. As part of that dispute, the Court has required NHS England to issue guidance which states that "*Pregabalin should only be prescribed for the treatment of neuropathic pain under the brand name Lyrica® (unless there are clinical contra-indications or other special clinical needs e.g. patient allergic to an excipient, branded product*

unavailable etc. which apply to Lyrica®, when you should not prescribe Lyrica® or pregabalin)"[2] The outcome of the court judgement has recently been reported, stating that Pfizer has lost its patent infringement case against generic drug manufacturers.[9] NHS England is awaiting a court order to cover the new situation and consequently current guidance still applies.

National guidance and clinical effectiveness

The NICE Clinical Guideline CG173 recommends to *"offer a choice of amitriptyline, duloxetine, gabapentin or pregabalin as initial treatment for neuropathic pain (except trigeminal neuralgia)"*[3] This recommendation was seen as controversial at the time of publication of the guideline, as gabapentin was in common use prior to this time.

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 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 states:

"*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 proven ineffective or were not tolerated.***"[3]

The British Pain Society (BPS) pathway for the care of patients with neuropathic pain (2013) recommend gabapentin among the choice of first-line drugs (along with amitriptyline, pregabalin, duloxetine for painful diabetic neuropathy and carbamazepine for trigeminal neuralgia).[10]

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.[11] This position is supported by the recent Scottish Intercollegiate Guidelines Network (SIGN) guideline in the management of chronic pain published in December 2013.[12]

A Canadian review stated that the benefits and harms of pregabalin are similar to gabapentin but at a higher cost.[13] 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 of pregabalin with other drugs for neuropathic pain.[14]

In one Cochrane review which considered 29 studies (3571 participants) gabapentin was demonstrated to be effective for the treatment of a variety of neuropathic pain conditions. The number needed to treat (NNT) to benefit, as measured by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definition, were 6.8 (95% confidence interval [CI] 5.6 to 8.7) for substantial pain relief (50% over baseline) and 5.8 (95% CI 4.8 to 7.2) for moderate pain relief (35% over baseline).[15] An update of this review (with a further 1919 participants), showed that for an outcome of at least 50% pain intensity reduction, gabapentin was significantly better than placebo in postherpetic neuralgia (34% gabapentin versus 21% placebo; NNT 8.0, 95% CI 6.0 to 12) and painful diabetic neuropathy (38%

versus 21%, NNT 5.9, 95% CI 4.6 to 8.3). There was insufficient information in other pain conditions to reach any reliable conclusion. There was no obvious difference between standard gabapentin formulations and recently-introduced extended-release or gastro-retentive formulations, or between different doses of gabapentin.[16]

In another Cochrane review, pregabalin at doses of 300 mg, 450 mg, and 600 mg daily was effective in patients with postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, and fibromyalgia (19 studies, 7003 participants). Pregabalin at 150 mg daily was generally ineffective. Efficacy was demonstrated for outcomes equating to moderate or substantial pain relief, alongside lower rates for lack of efficacy discontinuations with increasing dose. The best NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for 600 mg pregabalin daily compared with placebo were 3.9 (95% confidence interval 3.1 to 5.1) for postherpetic neuralgia, 5.0 (4.0 to 6.6) for painful diabetic neuropathy, 5.6 (3.5 to 14) for central neuropathic pain, and 11 (7.1 to 21) for fibromyalgia. With 600 mg pregabalin daily somnolence typically occurred in 15% to 25% and dizziness occurred in 27% to 46%. Treatment was discontinued due to adverse events in 18 to 28%. The proportion of participants reporting at least one adverse event was not affected by dose, nor was the number with a serious adverse event, which was not more than with placebo. Higher rates of substantial benefit were found in postherpetic neuralgia and painful diabetic neuropathy than in central neuropathic pain and fibromyalgia.[17]

A recent systematic review and meta-analysis concluded that tricyclic antidepressants, duloxetine, gabapentin or pregabalin could all be recommended as first-line treatments in neuropathic pain. NNTs (for 50% pain relief) were 7.7 for pregabalin and 7.2 for gabapentin.[18]

NICE CG173 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.[3]

In addition, regular clinical reviews should be conducted to 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.[3]

Organisations may use questionnaires such as PainDETECT or Leeds assessment of Neuropathic signs and symptoms (LANNSS) to identify if neuropathic pain is likely or the British Pain Inventory (BPI) questionnaire for a baseline global assessment of symptoms (see Appendix 1). Expert based recommendations from the BPS suggest asking the patient to keep a short term diary of response to a drug and how it is taken, because patients often do not adhere to the instructions. Also patients may expect a 100% response which is only possible for trigeminal neuralgia, where as a likely improvement of 30-50% is suggested. The diary should be discontinued after initial use to prevent too much focus on one aspect of the condition. Expert advice from the BPS states that many patients are often under-treated with a drug; as a result titration to the maximum tolerated dose is important.[19]

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 licensed for neuropathic pain.

In the majority of cases a drug treatment should be reduced gradually and stopped if the patient has not shown sufficient benefit within eight weeks of reaching the maximum tolerated dose except when moving to combination therapies. If they are successful, it is suggested that there should be a reduction on an annual basis to ascertain ongoing effectiveness.[1]

Potential for abuse

There is published evidence that both gabapentin and pregabalin are subject to abuse and misuse.[1,20-22] Both medicines have known psychiatric side effects including euphoria.[1,5-6] Individuals misusing gabapentin and pregabalin variably describe improved sociability, euphoria, relaxation and a sense of calm. Gabapentin and pregabalin have the propensity to cause depression of the central nervous system, resulting in drowsiness, headache, sedation, respiratory depression and at the extreme, death.[1] These adverse effects are additive when used with other centrally acting drugs, particularly opioids. Where patients are receiving concomitant opioids they should be monitored for signs of CNS and/or respiratory depression.[5]

Gabapentin and pregabalin are structurally similar drugs acting via the alpha-2-delta subunit of voltage-gated calcium channels. Pregabalin misusers take large quantities, ranging from 200mg to 5g as a single dose (Note - the recommended therapeutic dose range is 150mg to 600mg daily).[1]

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.[6]
- 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.[21]
- Gabapentin dependence/abuse is generally related to withdrawal effects and syndromes rather than abuse directly, although there are case reports of abuse in secure environments.[22]

The pharmacokinetic properties of pregabalin make it relatively more dangerous than gabapentin in high doses.[1]

Special consideration should be given to people 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).[23] Whilst prescribing of gabapentin or pregabalin occurs in only 2.82% of the prison population, an audit showed that over 50% of those prescribed these medicines have a history of substance misuse.[20] These medicines are likely to be sought after by those released from prison (especially if this has been stopped during custody) and their abuse potential communicated into the wider community. A publication by Public Health England recommends that amitriptyline or nortriptyline are used as first line agents for neuropathic pain in this patient group.[24]

The recent audit undertaken in prisons by the East and South East England specialist pharmacy services 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.[20]

There was also significant 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.[20] Morphine can increase the bioavailability of gabapentin. Caution is needed when these drugs are co-prescribed and the doses of both drugs may need to be modified. Similarly, pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.[1]

Patients who are offered these drugs need to have sufficient information to consent to the treatment plan. Patients should be aware of the likely efficacy of the drugs for management of their symptoms and also about the risk of harms, including dependence.

While no patient should normally be excluded from access to medications that may help them simply because of a current or past problem with misuse or dependence (or because of a concern about propensity to such risk), that concern is a proper and relevant consideration in how, and even whether to prescribe these drugs. Prescribing decisions should be discussed in full with patients and they should be made aware of the importance of their co-morbidities and context in making a safe prescribing decision.[20]

Other treatment options

Combinations

NICE states that there is a lack of trial evidence comparing the clinical and cost effectiveness and tolerability of different drug combinations; further research is a recommendation.[1] NICE 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 eight weeks, one drug should be reduced gradually and stopped before the other.[1,23]

A Cochrane review concluded that while the superior efficacy of two-drug combinations for neuropathic pain has been demonstrated, it was not possible to recommend any one specific drug combination.[26] BPS through their expert consensus statement states that combinations are not generally recommended.[19] Complex combinations of analgesics need careful supervision because of the potential for adverse effects and interaction.[10] However, if a patient is already taking a selective serotonin re-uptake inhibitor (SSRI) or serotonin and noradrenaline re-uptake inhibitor (SNRI) for their mood, some specialists would consider adding in amitriptyline starting at 10mg but not going above 25mg daily.[19]

Tramadol

NICE CG173 recommends to consider tramadol only if acute rescue therapy is needed. Tramadol long term is not recommended in non-specialist settings and must not be used.[3]

Capsaicin cream

Capsaicin cream is recommended for people with localised neuropathic pain who wish to avoid, or who cannot tolerate, oral treatments.[3] The BPS (2013) also recommends use of topical treatments for localized causes of neuropathic pain, such as post-herpetic neuralgia, perhaps even before first-line treatment is given. They state that there is good clinical consensus that topical agents are effective in certain circumstances, they may prevent the need for systemic therapies and contingent adverse reactions and interactions, and there was strong patient-representative preference expressed for their use during the development of the pathway.[10] As capsaicin cream (Axsain®) has a UK marketing authorisation for post-herpetic neuralgia and painful diabetic peripheral polyneuropathy, use for other conditions would be off-label.[3] The SPC states that this should only be used for painful diabetic peripheral polyneuropathy 'under the direct supervision of a hospital consultant who has access to specialist resources'.[27] The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented.[3]

Nortriptyline

NICE did not provide explicit recommendations for nortriptyline and does not recommend it in its main recommendations. NICE states that whilst the mean cost-per-QALY appeared to represent poor value for money, the GDG did not exclude the possibility that it may be an extremely effective option and noted that in 7 of 10 safety network meta-analyses it appeared to be somewhat better tolerated than amitriptyline with lower incidence of events.[3] A Cochrane review found little evidence to support the use of nortriptyline to treat neuropathic pain conditions.[28] Also an increase in cost of nortriptyline (i.e. Drug Tariff cost for 75mg is £104.64) means that it is not currently a cost effective choice.[29] Prescribing as the brand Allegron® is less costly.[30]

A treatment pathway incorporates information from the latest NICE CG173 on neuropathic pain, the SPCs and specific treatments for trigeminal neuralgia and diabetic neuropathy. The pathway is in attachment 1 and can be used and adapted locally by CCGs and acute trusts. An 'invitation to review' letter is found in attachment 2. Both attachments can be downloaded here: https://www.prescqipp.info/pregabalin-in-neuropathic-pain/viewcategory/202

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. Costs for amitriptyline, duloxetine and nortriptyline are provided for comparison (Note – no explicit recommendation for nortriptyline [3]). Pregabalin can be prescribed as either a twice a day or three times a day dose for all indications. However as all pregabalin doses are flat priced and the three times a day dosing is considerably more expensive, CCGs should review any prescribing for three times a day pregabalin and switch to an equivalent dose twice a day.

Table 1: Costs of treatments[29,30]

Product	Price for 28 tablets	Dose: one twice a day (28 days cost)	Dose: one three times a day (28 days cost)
Amitriptyline 10 - 75mg night	£0.95 - £2.94	n/a	n/a
Nortriptyline 10mg - 25mg night	£21.49 - £34.88 (Note 75mg dose = £104.64) (N.B. Allegron®:£3.38 - £6.73, 75mg - £20.18)	n/a	n/a
Duloxetine 60mg-120mg daily	£21.82 -£36.14	n/a	n/a
Gabapentin 100mg capsules	£0.79	n/a	£2.36
Gabapentin 300mg capsules	£1.06	n/a	£3.19
Gabapentin 400mg capsules	£1.21	n/a	£3.64
Gabapentin 600mg tablets	£3.04	n/a	£9.12
Gabapentin 800mg tablets	£8.48	n/a	£25.44
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

Switching from pregabalin to gabapentin

NICE CG173 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.[1] Comparator studies and switching options from pregabalin to gabapentin are discussed below.

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.[31] A recent UKMi document states that there have been no clinically relevant pharmacokinetic interactions found between pregabalin and gabapentin although pregabalin displaces gabapentin from receptors.[32]

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.

Cross tapering

A pharmacokinetic simulation study 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 3600mmg 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.[33]

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.[5,6] 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.[32]

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. NHS England in its recommendations states that a more gradual dose taper allows observation of emergent symptoms that may have been controlled by the drug. Recommendations by NHS England are to reduce the daily dose of pregabalin at a maximum rate of 50-100mg/week and to reduce the daily dose of gabapentin at a maximum rate of 300mg every four days.[1]

Gabapentin can be started at a dose of 300mg once daily on day one, then 300mg twice daily on day two, then 300mg three times a day.[5] Assuming 300mg of gabapentin is approximately equivalent to 50mg pregabalin, then as 300mg of gabapentin is 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 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 one capsule twice a day - this could be converted to 50mg capsules so they are taking three capsules twice a day. An example of a dose reduction is illustrated in table 3 below. After day eight titrate up gabapentin according to tolerability and response. Based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of two weeks, and to reach 3600 mg/day is a total of three weeks.[5]

Table 3: Example dose reduction of pregabalin for conversion to gabapentin for a 150mg twice daily pregabalin dose

Note: The dose does decrease after day 5 then increases again. This is intentional to allow titration to the lowest effective gabapentin dose.

Day	Pregabalin dose	Gabapentin dose	Total pregabalin equivalent daily dose
1	3x50mg capsules twice daily	Nil	300mg
2	2x50mg pregabalin in the morning and 3x50mg pregabalin in the evening	1x300mg capsule at night	300mg
3	2x50mg capsules twice daily	1x300mg capsule twice daily	300mg
4	1x50mg capsule in the morning and 2x50mg capsules in the evening	1x300mg capsule three times a day	300mg
5	1x50mg capsule twice daily	1x300mg capsule three times a day	250mg
6	1x50mg capsule in the morning	1x300mg capsule three times a day	200mg
7	Nil	1x300mg capsule three times a day	150mg
8	nil	1x300mg capsule in the morning and afternoon and 2x300mg capsules in the evening	200mg
Total number of capsules needed on prescription	**21**	**19 plus extra for continuing dose titration**	

Direct switch

The pharmacokinetic simulation study described above demonstrated that patients' therapy could be changed by a direct discontinuation of gabapentin and pregabalin (as well as a gradual transition).[33]

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, page 10). 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.[34]

Table 2: Dose conversion of gabapentin to pregabalin used in the above study[34]

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

*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.[32]

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.[35]

Dosage adjustment of gabapentin in renal impairment

Elderly patients (over 65 years) and patients with compromised renal function may require dosage adjustment because of declining renal function. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency. Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.[5] See table 4 below.

Table 4: Dosage of gabapentin in renal impairment[5]

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).

Other considerations

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 individual commissioning groups, GPs, practice nurses, pain consultants, pain nurses and other relevant healthcare professionals/patients. **A process for a direct switch or cross taper as described above should be agreed.** Community pharmacists should also be informed of any switch processes.

When considering a switch from pregabalin to gabapentin in appropriate patients, a suggested strategy would be to switch patients on the lower doses of pregabalin 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.

If pain does not appear to be neuropathic in nature (consider using questionnaires, i.e. LANSS and PainDETECT) and is not currently well controlled, consider a change of treatment as pregabalin is only licensed for neuropathic pain.

The audit (attachment 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 (www.medicinesresources.nhs.uk/en/Communities/NHS/SPS-E-and-SE-England/Meds-use-and-safety/Service-deliv-and-devel/OffenderHealth/Gabapentin-and-Pregabalin-Offender-Health-Audit-Report-and-Audit-Tool/). A patient information leaflet is available (attachment 4).

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

Pregabalin prescribing for indications other than neuropathic pain

For the treatment of conditions other than neuropathic pain, pregabalin can be prescribed generically. However as pregabalin remains as category C in the drug tariff[29] organisations may consider prescribing branded generics as a more cost effective option, i.e. Rewisca®, Alzain®, Lecaent® are licensed for generalised anxiety disorder and epilepsy. All preparations are also available in all eight strengths. The pharmacokinetic profile of these preparations is the same as Lyrica®, e.g. the oral bioavailability is estimated to be ≥ 90% and is independent of dose; following repeated administration, steady state is achieved within 24 to 48 hours; the rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25-30% and a delay in Tmax to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.[36-38]

Table 5 illustrates the cost difference between pregabalin and the branded generic preparations

Table 5: Cost of different pregabalin formulations[39]

Product	Cost for 28 days (1 bd)[39]			
	Lyrica®	Rewisca ®	Alzain®	Lecaent®
Pregabalin 25mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 50mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 75mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 100mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 150mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 200mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 225mg capsules	£64.40	£48.30	£61.18	£64.39
Pregabalin 300mg capsules	£64.40	£48.30	£61.18	£64.39

Nortriptyline

There has been a recent high increase in cost of notriptyline. Where notriptyline has been prescribed, consider reviewing if the patient has not been prescribed amitriptyline in the past. The brand Allegron® is a more cost effective alternative and organisations may wish to consider this.

There are no specific recommendations for switching nortriptyline to amitriptyline for doses up to 100mg. Whilst a slow withdrawal of tricyclic anti-depressants is normally required, both drugs display similar pharmacokinetic profiles, with nortriptyline being the specific active metabolite of amitriptyline.[40] Consequently it may be possible to substitute amitriptyline for nortriptyline. Another suggested approach to reduce side effects is to stop one anti-depressant and start another at a low dose and escalate upwards immediately after stopping.[39]

Savings available

Spend on pregabalin (both generic and branded Lyrica®), branded Neurontin® and gabapentin liquid specials is over £256 million across England (ePACT July 2015). 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 suggested achievement of 67% or more for generic gabapentin prescribing (based on top 10% achievement). **Potential savings across England are £68.8 million or over £120,509 per 100,000 population annually** (ePACT July 2015).

Where pregabalin needs to be continued it should be prescribed as Lyrica® for neuropathic pain. For conditions other than neuropathic pain, organisations may consider prescribing branded generics as a more cost effective option.

NICE does not recommend the use of nortriptyline in neuropathic pain and as the costs have escalated recently, this is not a cost-effective treatment for neuropathic pain. Treatment should be reviewed and discontinued or switched to an alternative depending on what the patient has previously tried for neuropathic pain. Amitriptyline is the most appropriate choice if it has not been tried previously. In England, over £30 million is spent on nortriptyline, which represents a 17.5% growth in cost from 2013/14. (ePACT September 2015 - PrescQIPP financial deep dive report)

Summary

- Pregabalin and gabapentin are both medicines originally used to treat epilepsy and have a similar pharmacological and adverse event profile. Pregabalin is considerably more expensive than gabapentin and costs of prescribing are rising significantly. NICE 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] There are no comparative studies between pregabalin and gabapentin for neuropathic pain (including post-herpetic neuralgia, diabetic neuropathy, and spinal cord injury related neuropathic pain), however indirect comparisons show a similar efficacy and tolerability profile. Most organisations that have developed treatment pathways for neuropathic pain recommend gabapentin as a treatment option before pregabalin is initiated. Recently NHS England, due to patent protection, has issued guidance for pregabalin to be prescribed as Lyrica® for neuropathic pain.[1]
- Prescribing for neuropathic pain treatments should be reviewed in line with the criteria set out in the NICE CG173 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 process should be agreed with local pain specialists and other relevant healthcare professionals.
- Both drugs have the potential to be abused by individuals with a history of substance abuse (particularly when prescribed with opiates) and prescribing should be reviewed in light of this. Any prescribing should also be within recommended therapeutic dose ranges.

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Appendix 1. Pain screening tools and questionnaires

PainDETECT

http://www.specialistpainphysio.com/wp-content/uploads/2010/07/painDETECT-Questionaire-01.pdf

Leeds assessment of Neuropathic signs and symptoms (LANSS)

http://www.endoexperience.com/documents/Apx4_LANSS.pdf

British Pain Inventory

http://www.healthcare.uiowa.edu/igec/tools/pain/briefpain.pdf

Additional PrescQIPP resources

 Briefing  Data pack  Implementation resources

Available here: https://www.prescqipp.info/pregabalin-in-neuropathic-pain/viewcategory/202

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