NHS
Shropshire, Telford and Wrekin
Clinical Commissioning Group

Shropshire, Telford and Wrekin CCG Guidance for Primary Care

Gabapentinoid Prescribing In Chronic Pain

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Appropriate Prescribing of Gabapentinoids

Background Information

Prescription of pregabalin and gabapentin items in Shropshire, Telford and Wrekin CCG has increased by 22% between 2018/19 and 2020/21. Although this is below the national average increase of 38% within the same timeframe, the prescribing of these items is still following an upwards trajectory. In 2020/21 £543,385 was spent on pregabalin and gabapentin.[epact2 2021]

There is published evidence that both gabapentin and pregabalin are subject to abuse and misuse. Both medicines have known psychiatric side effects including euphoria. 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 in extreme circumstances, death.

Misuse Potential

Gabapentinoids have the potential for misuse and dependence, particularly in patients with a history of misuse of other drugs and in specific settings such as prisons. Their mechanism for producing dependence is not yet well understood, though there may be direct or indirect effects on the dopaminergic 'reward' system.

There appears to be more evidence of misuse than for dependence, however the summaries of product characteristics for both medicines caution about dependence.

It is recommended that practitioners give careful consideration to the individual patient when prescribing pregabalin and gabapentin to minimise the risk of misuse, dependence, and diversion. Assessment of the balance of benefits and risks is essential.

Patients may source gabapentinoids illicitly. Referral to specialist substance misuse services is advised, for assessment and psychological treatment of the underlying difficulties where the whole substance misuse picture will be considered.

Individuals at high risk of misusing or diverting gabapentinoids may include those who:

- Have a history of substance misuse
- Make specific requests for initiation of either gabapentin or pregabalin
- Request pregabalin or gabapentin following release from the prison service
- Make repeated early prescription requests
- Contact out of hours services for supplies of medication

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.

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.

Gabapentinoids and Opiates

Use of gabapentin/pregabalin with opioid medicines or other central nervous system (CNS) depressant medicines has been previously associated with reports of respiratory failure, coma, and deaths. Studies show use of high doses of the gabapentinoids alongside opioid medicines to be particularly associated with an increased risk of opioid-related death. Drug safety updates from the MHRA highlight the significant safety concerns and risks of respiratory depression associated with gabapentoid use.

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.

Co-prescribing of gabapentin or pregabalin with opioids is also of concern in particular groups of patients where addiction may become a problem. It is recommended that the co-prescribing of opiates with gabapentinoids is reviewed. There are safety searches available to practices to help identify these patients.

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.

Legal Status

Gabapentinoids have been reclassified as Schedule 3 CDs under the Misuse of Drugs Regulations 2001 and Class C controlled substances under the Misuse of Drugs Act 1971 from 1st April 2019. The law change means there are stronger controls in place to ensure accountability and minimise the chances of pregabalin and gabapentin falling into the wrong hands or being stockpiled by patients.

- Clinicians are encouraged to only prescribe 30 days' supply.
- Gabapentin and pregabalin are subject to additional prescription requirements for CDs.
- In addition, pharmacists must dispense the drugs within 28 days of the prescription being written.
- The change means it is illegal to possess pregabalin and gabapentin without a prescription and it is illegal to supply or sell them to others.

Off label use

Several treatments are used outside of their product licences in “off label use”.

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.

Further information may be found here:

https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities

Risk Management

Patients should be made aware of the risks associated with the prescribing of gabapentinoids including the risk of harms.

In high risk patients the following may be helpful (see appendix 5 Resources):

The risk of misuse - opioid risk tool

Whether there is a neuropathic component to pain. The following tools help to classify pain

- LANSS tool
- PainDETECT

Gabapentinoids are not licensed for non-neuropathic pain.

Review previous management options:

- ✓ Ensure 1st and 2nd line options have been trialled adequately as per local or national guidance
- ✓ A discussion on the risks of dependence
- ✓ Consider daily or weekly dispensing in *at risk* patients
- ✓ A *prescribing agreement, (Appendix 1)* which may be of help with some patients to ensure all parties are clear on how to proceed.

Indications and assessment

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)"

	Amitriptyline	Duloxetine	Gabapentin	Pregabalin
Neuropathic Pain CG173	✓	✓	✓	✓
Peripheral neuropathic pain e.g. painful diabetic neuropathy, post herpetic neuralgia		✓	✓	✓
Central neuropathic pain				✓
Generalised anxiety disorder		✓		✓
Major depressive disorder	✓			
Chronic tension type headache	✓			
Prophylactic treatment of migraine	✓			

Gabapentinoids are **not licensed** for non-neuropathic pain. Questionnaires such as PainDETECT or LANSS can help to identify if neuropathic pain is likely or in determining if there is a neuropathic component to the pain.

Gabapentinoids have historically been commonly prescribed for non-neuropathic pain syndromes, e.g. fibromyalgia. However there is little evidence to support the practice and prescribers should consider interventions more likely to help such as physical rehabilitation for back and musculoskeletal pain.

Gabapentinoids should **not be initiated** for the treatment of chronic primary pain as per the new NICE guidelines released in April 2021 (NICE Clinical Guideline 193). If a patient has already commenced treatment with gabapentinoids, it is important to review the prescribing as part of a shared decision making process. It would be prudent to first explain the lack of evidence for gabapentinoids for the treatment of chronic primary pain. If patients report little improvement and/or significant harm, encourage and support the patient with a reduction or withdrawal plan.

Recommendations from the British Pain Society (BPS) suggest asking the patient to keep a short term diary of response to a drug and dose. Patients often do not adhere to the instructions.

Symptom diaries should be discontinued after initial use to prevent too much focus on one aspect of the condition.

Managing expectations is paramount to success. Patients may expect a 100% response; where as a likely improvement of 30-50% is suggested.

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.

If pain does not appear to be neuropathic in nature and is not currently well controlled, consider a change of treatment.

Initiation

How to achieve the correct dosage.

Useful patient information leaflets on medicines for long term pain are available in appendix 5 Live Well with Pain

The following principles may be useful in the process of determining the correct dose for a patient:

A titrated approach for initiation of both gabapentin and pregabalin is recommended, taking into consideration patient characteristics, e.g. elderly, renal impairment, breast feeding which may affect the suitability for prescribing or the dosage.

Gabapentin usually starts at 300mg once a day (at night) and titrates upwards, adjusted according to response to a maximum of 3600mg daily in divided doses. Evidence suggests that a minimum of 1200mg is usually needed and doses may need to be increased to the maximum of 3600mg.

Pregabalin usually starts at 75mg twice daily up to a maximum of 300mg twice daily.

Titration of doses should be managed according to side effects and clinical effectiveness.

Patient should be reviewed following each escalation of dose to review clinical effectiveness and any side effects. Medication should be stopped if there is no, or insufficient effect at maximally tolerated doses.

Stepping up should be closely monitored. Dispense daily or weekly in high-risk patients.

Aim to maintain patients on the minimum dose which controls pain.

Review

New Patients:

Individual patient review should take place. NICE CG173 states after starting or changing a treatment, carry out an early clinical review of dosage titration, tolerability and adverse effects to assess the suitability of the chosen treatment.

Further reviews and titration may be required for the next few months. If no improvement or insufficient improvement is seen after several months the gabapentinoid should be gradually reduced and stopped or switched to an alternative treatment.

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.

Long-term gabapentinoid treatment:

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 should be reviewed at least annually.

Many patients whose pain is well controlled manage eventually to successfully reduce their dose of gabapentinoids, and they should be invited to try this, with support. Subsequent review should take place at least annually but may need to be more frequent.

Where treatment appears to be ineffective or response is poor:

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.

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 one gabapentinoid has not been previously tried (and particularly if treatment is currently not effective) a switch may be considered.

Where there is evidence of non-adherence:

It is important that practices monitor gabapentinoid prescriptions both in the individual patient and at practice level. Patients requesting ad-hoc prescriptions and not taking the medication regularly will not benefit from the treatment.

Other indications necessitating review

- Patients with a history of misuse or recently released from prison should be reviewed monthly.
- High risk patients who are co-prescribed opioids and those who are having their dose changed (increased or decreased) should be reviewed monthly.
- At the request of the patient
- If there are side effects
- Where the gabapentinoid is being used outside of its licenced condition
- Where the gabapentinoid is being used outside of evidence based guidance e.g. in chronic primary pain
- If the patient is pregnant or breastfeeding or planning to conceive (unless the benefits of treatment outweigh the risks)

Additional measures that may help support safe prescribing of gabapentinoids

✓ Repeat prescribing of gabapentinoids must be avoided in high-risk patients unless there are strict processes in place to monitor for over-ordering and dispensing.

✓ Patients may require support and advice about pain management. These include the PAIN TOOLKIT and Live Well with Pain, see appendix 5.

✓ Self-management support should be actively encouraged/ offered as required. All review of medicines should be conducted in a structured and holistic way.

Reducing the dose

How to reduce the dosage for patients on long-term treatment

Both gabapentin and pregabalin doses should normally be gradually reduced to minimise symptoms of withdrawal and allow assessment of response. The following principles may be useful:

A trial of dose reduction/cessation should be undertaken after two months of relative improvement in pain following stabilisation on treatment.

A suggested reduction regimen would be:

- Gabapentin – reduce at maximum daily rate of 300mg every week
- Pregabalin – reduce at maximum daily rate of 50-100mg every week

A full suggested reduction regimen is available in appendix 2.

In high risk patients, temporarily halt reduction, in preference to re-escalating the dose when required.

Rapid reduction to stop is justified if there is clear evidence of attempts to divert or obtain illicit supplies of gabapentin or pregabalin.

In practice, a reduction regimen may be adjusted depending on individual response and degree of associated risk.

Evidence for cross tapering

A pharmacokinetic simulation study looked at two different gabapentin to pregabalin transition designs.

The first simulation involved immediate discontinuation of gabapentin therapy with initiation of pregabalin therapy at the next scheduled dose period.

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:

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

The simulations showed that levels of gabapentinoid remained at steady state. The authors suggested that changing patients from gabapentin to pregabalin could theoretically be achieved by either of the two approaches assessed.

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.

The withdrawal simulated was to minimise the risk of increased seizure frequency where the medications are being used for patients with seizure disorders. The clinical importance of a slow withdrawal in patients with neuropathic pain remains unknown.

Cross tapering guidance

In practice it may be preferable to start down titrating 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 proposes that a more gradual dose taper allows observation of emergent symptoms that may have been controlled by the drug.

Recommendations are:

- Reduce the daily dose of pregabalin at a maximum rate of 50-100mg/week
- Reduce the daily dose of gabapentin at a maximum rate of 300mg every four days.

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 and so on. 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 to enable dose adjustment and reduction for a week. 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. They would now be taking three capsules twice a day. An example of a dose reduction is illustrated in appendix 3.

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.

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).

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.

Dosing for a direct switch such as that used in the study is in appendix 4.

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.

Renal function

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. See table below.

Dosage of Gabapentin in Renal Impairment

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). See SPC for further information on renal dosing: Gabapentin 300mg Capsules - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Summary of 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 (unlicensed) 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.
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.
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.
Early and ongoing review is essential for all patients prescribed gabapentinoids. Extreme care should be taken when co-prescribing gabapentinoids and opioids.
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.

Acknowlegements

This guidance has been adapted from a resource developed by NHS Forth Valley and Prescqipp Bulletin 119. We are very grateful to the original authors both for their work and for their agreement to the development of this version for use in Shropshire, Telford and Wrekin.

Appendix 1 – Prescribing agreement

The below Pain Management Prescribing Agreement may be useful in some cases (for instance with high risk patients), to ensure and document the patient's understanding of their treatment. **It is not recommended for all patients** and clinical judgment is required. Practices may wish to tailor it to their needs.

Pain Management Prescribing Agreement

Name .....

Date of birth.....

As part of my treatment plan which includes prescribing pain relief medicines I agree to the following conditions:

1. I am currently taking _____mg of _____daily
2. I agree to fully participate in the pain management plan as outlined in my medical record. As part of this plan I will be referred to other specialist and agree to engage fully in all treatments offered.
3. If I do not adhere to the agreed programme, I accept that my prescribed pain relief medicines will be reviewed and may be reduced.
4. I acknowledge that I should not take any additional pain relief medicines unless under the advice of a clinician.
5. I agree not to sell or otherwise dispose of medication prescribed to me.
6. I agree to the medicines being dispensed daily / weekly [delete as appropriate].
7. I understand that early requests for medicines will not be granted.

Signed (patient) .....

Signed (on behalf of service) .....

Date.....

Appendix 2 – Example dose reduction

Gabapentin - Suggested gabapentin reduction regime from 1200mg TDS

Gabapentin	Morning	Afternoon	Night	No. 300mg capsules
Week 1	1200mg (i.e. 4 x 300mg)	900mg (i.e. 3 x 300mg)	1200mg (i.e. 4 x 300mg)	**77**
Week 2	900mg	900mg	1200mg	**70**
Week 3	900mg	900mg	900mg	**63**
Week 4	900mg	600mg	900mg	**56**
Week 5	600mg	600mg	900mg	**49**
Week 6	600mg	600mg	600mg	**42**
Week 7	600mg	300mg	600mg	**35**
Week 8	300mg	300mg	600mg	**28**
Week 9	300mg	300mg	300mg	**21**
Week 10	300mg	-	300mg	**14**
Week 11	-	-	300mg	**7**

Pregabalin - Suggested pregabalin reduction from 300mg BD

Pregabalin	Morning	Night
Week 1	250mg	300mg
Week 2	250mg	250mg
Week 3	200mg	250mg
Week 4	200mg	200mg
Week 5	150mg	200mg
Week 6	150mg	150mg
Week 7	100mg	150mg
Week 8	100mg	100mg
Week 9	50mg	100mg
Week 10	50mg	50mg
Week 11	25mg	25mg
Week 12	-	25mg

In practice, the reduction regimen may be adjusted depending on individual response and degree of associated risk

Appendix 3 – Example cross taper

Pregabalin → gabapentin

Usual pregabalin dose = 150mg twice daily

Note: The dose decreases after day 5 and 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 twice a day	NIL	300mg
2	2x50mg in the morning and 3 x 50mg in the evening	1 x 300mg night	300mg
3	2 x 50mg twice a day	1 x 300mg twice a day	300mg
4	1 x 50mg in the morning and 2 x 50mg in the evening	1 x 300mg three times a day	300mg
5	1 x 50mg twice a day	1 x 300mg three times a day	250mg
6	1 x 50mg in the morning	1 x 300mg three times a day	200mg
7	NIL	1 x 300mg three times a day	150mg
8	NIL	1 x 300mg in the morning and lunch and 2 x 300mg at night	200mg
Total number of capsules needed on prescription	21	19 plus extra for continuing dose titration	

Appendix 4 - Direct switch between gabapentinoids

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 a day
901-1500	225	75mg morning 150mg evening
1501-2100	300	150mg twice a day
2101-2700	450	150mg morning 300mg evening
2700 or higher	600	300mg twice a day

Appendix 5 - Resources

Patient resources

Live well with pain	Resources for your patients - Live Well With Pain

Clinician resources

Opioid Risk Tool	https://www.mdcalc.com/opioid-risk-tool-ort-narcotic-abuse
LANSS tool - Leeds Assessment of neuropathic signs and symptoms LANSS score	https://www.thecalculator.co/health/LANSS-Scale-for-Neuropathic-Pain-Questionnaire-Calculator-948.html
Pain Detect - Pain Detect Questionaire	pdq_us_enreview_only_3_1_1.pdf (pfizerpcoa.com)