The risk of harm from Pregabalin and Gabapentin (gabapentinoids)

Pregabalin is licensed for focal seizures, central and peripheral neuropathic pain and generalised anxiety disorder. Gabapentin is licensed for treatment of partial seizures and for peripheral neuropathic pain. Whilst it is recognised that gabapentinoids can be useful medications, there is a significant risk of potential misuse and subsequent harm. From April 2019, due to the risk of dependence and misuse, gabapentinoids were re-classified as Class C controlled substances and Schedule 3 controlled drugs under the Misuse of Drug Regulations 2001.

There have been other MHRA alerts for gabapentinoids, including:

- Gabapentin: risk of severe respiratory depression (October 2017)
- Pregabalin: reports of severe respiratory depression (February 2021)

These reports highlight advice to healthcare professional about the risk of respiratory depression (with and without concomitant opioid medication), they advise:

- Consider whether adjustments in dose or dosing regimen are necessary for patients at higher risk of respiratory depression, this includes people:
    - with compromised respiratory function, respiratory or neurological disease, or renal impairment
    - taking other central nervous system depressants (including opioid-containing medicines)
    - aged older than 65 years
- Studies show use of high doses of pregabalin (over 300mg a day) alongside opioid medicines to be particularly associated with an increased risk of opioid-related death[1], [2]

NHS England (March 2023) developed guidance, to support adults by optimising personalised care for those with prescribed medications associated with dependence or withdrawal symptoms. As with all dependence-forming medication, patients should be involved in shared-decision making decisions with extensive discussions about the risks involved, including the risk of dependence, respiratory depression and withdrawal symptoms if discontinuing.

If gabapentinoids are prescribed, it is important to minimise polypharmacy with medicines that also act on the central nervous system due to the increased risk of respiratory depression.

The responsibility for safe prescribing decisions, as well as to communicate the benefits and risks, lies with the clinician.

Following a review of the risks and benefits, if a prescriber thinks that a medicine is not in the person's best interests but a shared decision about starting or continuing a medicine cannot be reached with the person, the prescriber should follow the advice on 'handling patient requests for medicines you don't think will benefit them' in the General Medical Council guidance: good practice in prescribing and managing medicines and devices. The prescriber should:

- not prescribe a medicine if they believe it is not in the person's best interests
- explain the reasons for the decision to the person, offering a second opinion if needed
- document all discussions carefully, any advice given and provide a copy to the person

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[1] Gomes T and others. Pregabalin and the risk for opioid-related death: a nested case-control study. Ann Intern Med. 2018; issue 169: 732–34

[2] MHRA, Drug Safety Update, 18th February 2021, Pregabalin (Lyrica): reports of severe respiratory depression https://www.gov.uk/drug-safety-update/pregabalin-lyrica-reports-of-severe-respiratory-depression#fn:1

Opioid dependency and gabapentinoids prescribing Advice - "Dos and Don'ts"

In view of the evidence available and BNSSG ICB's commitment to patient safety, BNSSG urge clinicians to **exercise caution when considering co-prescribing gabapentinoids alongside opioids, especially those with opioid substitution therapy or known opioid misuse** (prescribed or illicit) particularly in those patients where there is a risk of dependence, withdrawal symptoms and in those at highest risk of respiratory depression.

While no patient should generally be denied access to medications that may offer some benefit, due to current or historic issues with misuse, dependence or the risk thereof, these factors should be a major consideration when deciding whether to prescribe gabapentinoids. Medication reviews should be done to identify patients that would benefit from a discussion regarding the withdrawal of medication. Where dependence or issues with misuse are of concern it would be advisable to encourage patient engagement with the local substance misuse services who can help them through the psychosocial aspects.

Do…

Practice policy

- Have a PCN/practice wide approach/policy to gabapentinoid prescribing and de-prescribing. This will help to ensure all patients are treated consistently and to assure clinicians and surgery staff that everyone is giving the same clear message, help, and advice.
- Publicise message to patients and wider staff group advising of changes, such as a review of patients concurrently prescribed opioids with gabapentinoids.

Starting gabapentinoids

- Consider all other pharmacological and non-pharmacological options before contemplating starting a gabapentinoid prescription. Medicines may not always be effective and can cause harm, and so always consider the option of not prescribing as well as non-pharmacological options.[3]
- If initiating gabapentinoids, explain the unpleasant side effects/feelings that gabapentinoids may give a patient: Life threatening breathing problems, irritability, aggression, feeling anxious and on edge, loss of libido, blurred vision, increased appetite, addiction, demanding behaviours, erectile dysfunction, difficulty going to the toilet, confusion, loss of memory, headache. Highlight that all these above side effects will reduce on discontinuation and clearer thoughts will return.
- On initiation, advise the patient they will be reviewed to assess effectiveness and highlight that where gabapentinoids are ineffective, a plan will be made to taper and stop the medication.

Reviewing and deprescribing gabapentinoids

- Taper gradually – as below. Consider use of post-dated prescriptions for those with dependence.
- Short duration prescriptions may be helpful to allow regular review of the tapering.
- Take a cautious approach to requests for early or lost prescriptions.
- If pregnancy is possible, highlight the risks. This MHRA leaflet can support for Pregabalin.
- Provide patients with a clearly documented treatment reduction plan. Offer psychosocial support in a collaborative manner, this may involve referral to the local specialist drug and alcohol service.
- Consider multidisciplinary team input where appropriate e.g. from drug and alcohol services

[3] NICE Guideline NG 193, Chronic pain (primary and secondary in over 16s: assessment of all chronic pain and management of chronic primary pain, April 2021 https://www.nice.org.uk/guidance/ng193

- Advise patients to carry naloxone if they are co-prescribed or co-use opioids, particularly if they are at increased risk of opioid overdose. Advise this will only be helpful in opioid respiratory depression toxicity, it will not reverse effects of gabapentinoids alone. Naloxone is a relatively safe medication and should be considered where there is the possibility of a polypharmacy overdose involving an opioid. Prescribe take home naloxone formulations if necessary.

Don't…

- Don't initiate any new prescriptions in patients with current opioid dependence/opioid substitution therapy unless in very exceptional circumstances where a team/multidisciplinary discussion of risks vs benefits has taken place. In this circumstance, document the rationale and ensure ongoing reviews. Discontinue in these patients using the suggested tapering scheme below on discussion with the patient over an agreed time period.
- Don't stop gabapentinoids abruptly, this can precipitate significant withdrawal symptoms. Tapering must be gradual.
- Don't use gabapentinoids for non-licensed indications.
- Do not attempt a reduction for any patient who has been prescribed gabapentinoids for epilepsy.

Suggested tapering schedules

The summary of product characteristics for gabapentin and pregabalin indicate that both drugs can be discontinued over one week. Public Health England (PHE), suggest a more gradual dose tapering with safety netting advice to allow observation of emergent symptoms that may have been controlled by the drug.

- Pregabalin: reduce the daily dose at a maximum of 50-100mg/week.
- Gabapentin: reduce the daily dose at a maximum rate of 300mg every four days.

However, please note this reduction schedule **may not be appropriate for all patients** with some finding it challenging, for example, those with complex substance use histories and co-presenting PTSD. A rapid reduction in some patients could make them less likely to engage. Clinical judgement should therefore be used considering individual patient factors and if the reduction rates are too difficult to achieve, prescribers should consider **tapering more slowly for example smaller weekly decrements or monthly reductions to enable better support and encourage engagement**.

There should be flexibility in lengthening the time between dose reductions but aim not to reverse the reduction. Regular monitoring of the tapering to assess progress is important.

- Advise patients of usual withdrawal symptoms which include feeling anxious, insomnia, sweating, body aches, restlessness, nausea, withdrawal seizures (epilepsy). It is possible to prevent withdrawal seizures and other symptoms by gradually reducing the dose of gabapentinoids. The reduction schedule can be modified to allow intolerable withdrawal symptoms to improve before making the next reduction
- Always consider psychosocial support to support with any tapering and engagement and ensure the person knows who to contact if problems occur.
- Deprescribing of gabapentinoids can cause anxiety for patients; pre-planned appointments can ease this process and alleviate concerns.