Medicines & Healthcare products Regulatory Agency

DRUG SAFETY UPDATE (DSU)

Improving Information Supplied with Gabapentinoids (Pregabalin/Gabapentin), Benzodiazepines and Z-Drugs

Specialisms: *General Practice, Pain management and palliation, Psychiatry.*

Summary

The MHRA has reviewed the warnings regarding addiction, dependence, withdrawal, and tolerance for gabapentin, pregabalin, benzodiazepines, and z-drugs. The findings (detailed in the Public Assessment Report) were that it was necessary to strengthen these warnings in the product information and on packaging to better inform healthcare professionals and patients of these known risks.

Advice for Healthcare Professionals:

- gabapentinoids (pregabalin and gabapentin), benzodiazepines and z-drugs are three classes of medicines used to treat a variety of conditions such as neuropathic pain, anxiety and insomnia. Specialist use of these medications for conditions such as epilepsy, or sedation during medical procedures are not included in this review
- all three classes of medications are known to pose risks of addiction, dependency, withdrawal and tolerance
- the Summary of Product Characteristics, Patient Information Leaflets and Outer Packaging of these medicines will have strengthened warnings to better communicate the risks of addiction, dependency, withdrawal and tolerance to healthcare professionals and patients. Updates are in progress and will be rolled out over the coming months
- prior to starting treatment with these medicines, a discussion should be held with patients to put in place a strategy for reducing or ending treatment. By doing this the risk of addiction, dependence, and drug withdrawal syndrome is reduced. NICE guideline, NG215, has resources that include visual summaries which are available to support these discussions. The Agency has also developed additional patient resources for benzodiazepines, gabapentinoids and z-drugs which highlight key messages concerning these risks and should be made available to patients when these medications are prescribed
- addiction and dependence are related but have distinct presentations. Healthcare professionals are reminded of the importance of using non-judgmental language when discussing these terms

- patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. This could be a sign that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient
- drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to reduce symptoms of withdrawal. Tapering from a high dose may take weeks or months. Patients should be informed of this when the medication is first prescribed and should be encouraged to speak to their healthcare professional or prescriber before stopping their medicine. See NICE guideline NG 215 for identifying and managing withdrawal symptoms
- provide regular support especially to individuals at increased risk of drug withdrawal syndrome, such as those with current or past history of substance use disorder (including alcohol misuse) or mental health disorder
- addiction, dependence, withdrawal or tolerance in response to these medications can be reported via the Yellow Card scheme

Advice for Healthcare Professionals to Provide to Patients:

- as these medicines carry risks of addiction, dependence and withdrawal reactions, before starting treatment with these medicines, your healthcare professional should explain how long you might need to take them for, and how to stop safely. This helps reduce the risk of addiction, dependence, and drug withdrawal syndrome
- anyone can become physically dependent on these medicines, meaning that their body gets used to it, and this can cause them to have withdrawal symptoms if the medicine is suddenly stopped, or the dose is reduced
- drug addiction can feel like a strong desire to take the medicine, and difficulties in controlling medicine use (for example feeling like you want to take more or use the medicine when you shouldn't)
- addiction and dependence are related but they are not the same, being physically dependent on a medicine does not necessarily mean you are addicted to it
- drug tolerance can mean no longer feeling like the medicine is working well, or feeling that a higher dose is required to achieve the same symptom relief as before
- if you want to stop taking your medicine there are additional resources to help you. Never stop taking your medication without asking a healthcare professional first
- if you are taking this medicine for epilepsy, you should keep taking it for as long as your doctor says it's needed
- if you find that your treatment is not working as well, you should speak to your healthcare professional about possible alternative treatment options, and you should never take more of your medicine than you have been prescribed
- when it is time to stop your medication, your healthcare professional will tell you how to gradually reduce the amount of medicine you are taking over time (known as dose tapering). This is very important to reduce the risk of drug withdrawal syndrome. Dose tapering can sometimes take weeks or months. Mild symptoms may still occur,

but you should contact your healthcare professional if the withdrawal symptoms become intolerable

Background

Review of the communication of the known risks of addiction, dependence, withdrawal and tolerance.

The MHRA undertook an assessment of awareness and understanding of information supplied with dependency-forming medicines and whether potential improvements were needed. The first two phases of the review included gabapentinoids, benzodiazepines and z-drugs. The scope of the review included review of the existing warnings in the product information and labelling of these medicines. Specific assessment of the efficacy, dose and indications of these medicines was outside of the aims of this specific review. A similar review of opioids has previously been undertaken by the Agency.

The MHRA assessed data and evidence that included UK Yellow Card data (voluntary reporting of side effects from healthcare professionals and the public), data from companies which hold the licences for these medicines (marketing authorisation holders), data from other international regulators, clinical practice research datalink data (a database of anonymised GP practice data from across the UK) and accounts of lived experience from patient charity groups and discussions with related professional stakeholders.

The MHRA presented the data and evidence to the Commission on Human Medicines (CHM) who were asked to provide independent advice and recommendations. Other independent expert groups consulted included the Pharmacovigilance Expert Advisory Group (PEAG) and the Neurology, Pain and Psychiatry Expert Advisory Group (NPPEAG) who provided their recommendations to the CHM.

Overall, it was considered that the current wording contained within the product information and labelling of gabapentinoids, benzodiazepines and z-drugs did not sufficiently communicate the extent of the known risks of addiction, dependence, withdrawal and tolerance associated with these medications. It was concluded that improved wording should be agreed which reflected current post-marketing experience of the use of these medications so that patients could be appropriately informed about the risks before starting the medication, and can be adequately supported to stop their medications appropriately. Furthermore, CHM considered that the Agency should generate additional patient resources for benzodiazepines, gabapentinoids and z-drugs in order to highlight key messages to patients.

Additionally, further support from other healthcare stakeholders will be sought in order to influence clinical guidelines and clinical practice which extends beyond the scope of the Agency.

The information considered by the CHM and the advice issued is presented in a Public Assessment Report.

Addiction, dependence, withdrawal and tolerance.

Product information and outer-packaging for gabapentinoids, benzodiazepines and z-drugs in the UK will have consistent warnings of the risks of addiction, dependence, withdrawal and tolerance.

For all patients, prolonged use of these medications may lead to drug addiction and dependence, but these effects can also occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol use disorder) or mental health disorder (e.g., major depression). Addiction and dependence are related but have distinct presentations. Healthcare professionals are reminded of the importance of the use of non-judgmental language.

Patients should be closely monitored for signs of misuse, abuse or addiction.

Signs of addiction and misuse could include:

- Expression of craving for the medicine, even if it is causing adverse effects on overall health
- Expression of a need for more e.g. requesting early prescription refills, or reporting additional use of other equivalent medicines
- Taking medicines for reasons other than the approved indications
- Experiencing withdrawal side effects when the medicines are stopped suddenly

Note that if this medicine is being used for the treatment of epilepsy, it should be used for as long as the prescriber considers it necessary, in discussion with the patient.

Tapering Doses

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. Prior to starting treatment with gabapentinoids, benzodiazepines or z-drugs, a discussion should be held with patients to put in place a reduction strategy for ending treatment with these medicines. There may be exceptions to this in specific clinical situations such as symptom management in end-of-life palliative care and for use in epilepsy.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person’s preferences when appropriate, changes to their circumstances and the response to dose reductions.

If the patient is taking more than one of these medicines e.g. gabapentin and diazepam, the reduction strategy should include a discussion to determine which medicine will be tapered first.

If a patient develops intolerable withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

Resources for prescribers and dispensers

The Agency has developed additional patient resources for benzodiazepines, gabapentinoids and z-drugs on the risks of addiction, dependence, withdrawal and tolerance for these classes of medications, which should be provided to patients when these medicines are prescribed. This advice for patients and their families/ carers was developed following consultation with a number of stakeholder organisations, charities and the CHM/ relevant expert advisory groups. We encourage healthcare professionals to use this information alongside the statutory patient information leaflet supplied with these medicines. Prescribers are reminded to consult the Repeat Prescribing Toolkit when considering the appropriateness of providing a dependency-forming medicine on repeat prescription.

In addition, NICE have a relevant guideline, NG215, with resources that include visual summaries and patient decision aids which may aid discussions with patients concerning these risks. NHS England have also devised actions to help local healthcare systems develop plans that can support people who are taking medicines associated with dependence and withdrawal symptoms.

The Scottish Government have also published guidance on prescribing of benzodiazepines and z-drugs: Quality prescribing for Benzodiazepines and z-drugs: guide for improvement 2024 to 2027

The All Wales Medicines Strategy Group (AWMSG) have published guidance on Appropriate Prescribing of Hypnotics and Anxiolytics across Wales and All Wales Analgesic Stewardship Guidance

The Northern Ireland Formulary provides information for healthcare professionals on Benzodiazepine and Z drug withdrawal and Neuropathic pain. You can also find patient resources on use of Benzodiazepines and Z Drugs and Gabapentinoids.

Reporting advice

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website.
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates.

Additional information

You can sign up to receive email notifications for Drug Safety Updates.

You can sign up to receive our monthly round-up of safety communications.

Stakeholder Engagement

- Scottish Government
- The Faculty of Pain Medicine of the Royal College of Anaesthetists
- NHS Specialist Pharmacy Service
- MSO Network

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