Public Health England

NHS England

Advice for prescribers on the risk of the misuse of pregabalin and gabapentin

Purpose of this advice

This document has been produced by healthcare professionals with support from policy observers to provide:

- information regarding the potential for misuse of pregabalin and gabapentin
- suggestions for a balanced and rational use of these medications

Who should read this advice on risk of misuse?

The statement will be useful to medical and non-medical prescribers of pregabalin and gabapentin, and other healthcare professionals in primary and secondary care and in secure environments including those working in:

- general practice
- pain medicine (acute and chronic)
- substance misuse treatment and recovery
- neurology and neurosurgery
- rheumatology
- orthopaedics

Key messages

Professionals prescribing pregabalin and gabapentin should be aware not only of the potential benefits of these drugs to patients, but also that the drugs can lead to dependence and may be misused or diverted.

Pregabalin and gabapentin have a well-defined role in the management of a number of disabling long-term conditions, including epilepsy and neuropathic pain; and, for pregabalin, generalised anxiety disorder. When used for pain the drugs do not work for everyone but a proportion of patients benefit sufficiently to notice an improvement in quality of life.

Practitioners should prescribe pregabalin and gabapentin appropriately to minimise the risks of misuse and dependence, and should be able to identify and manage

problems of misuse if they arise. Most patients who are given these drugs will use their medicines appropriately without misuse.

Prescribing for patients with a known or suspected propensity to misuse, divert or become dependent on these drugs may place these people at greater risks from their use. Prescribers must make a careful assessment to balance the potential benefits against the risks. However, it should be noted that such patients may also have a higher prevalence of the indicated conditions for these drugs and some may benefit from their use.

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 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.

Less harmful, alternative drugs can often be first-line treatments for the indicated conditions for which pregabalin and gabapentin are now used, and may be tried preferentially in higher risk settings or in patients who may be more likely to be harmed by the drugs.

Clinical indications for gabapentin and pregabalin

The drugs are licensed in the UK for treating focal seizures and managing neuropathic pain; pregabalin is licensed for treating generalised anxiety disorder. In Canada and the US, the drugs are licensed for treating pain associated with fibromyalgia and, although not licensed for this indication in Europe, are an established part of the pharmacological repertoire of fibromyalgia management. When these drugs are prescribed for neuropathic pain or fibromyalgia, they should be prescribed for a test period to ascertain if they are effective. The dose should be titrated up to the maximum tolerated within the suggested dose range. If the patient has no improvement in symptoms, the drug should be reduced and stopped. If they are successful, it is suggested that there should be a reduction on an annual basis to ascertain ongoing effectiveness.

Gabapentin and pregabalin should usually be prescribed for their licensed indications. Although the drugs are commonly prescribed for non-neuropathic pain syndromes 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. If a decision is made to prescribe the drugs for unlicensed

indications, the rationale should be discussed with the patient, appropriate consent acquired and all discussions clearly documented.

The pharmacology of pregabalin and gabapentin

The drugs have a similar mechanism of action and both have propensity for misuse. Gabapentin and pregabalin are structurally similar drugs acting via the alpha-2-delta subunit of voltage-gated calcium channels. The mechanism by which the drugs may induce dependence is not well worked out.

Gabapentin and pregabalin are associated with significant euphoric effects. 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, sedation, respiratory depression and at the extreme, death.

Both gabapentin and pregabalin have adverse effects on the central nervous system, which are additive when used with other centrally acting drugs, particularly opioids (see below).

The pharmacokinetic properties of pregabalin make the drug relatively more dangerous than gabapentin in high doses. Pregabalin misusers are achieving these effects by taking large quantities, ranging from 200mg to 5g as a single dose.

Evidence for misuse of pregabalin and gabapentin

Misuse of gabapentin and pregabalin has been noted for some years in clients attending substance misuse treatment and recovery services, and within secure environment settings. Currently, pregabalin appears to be more sought after for misuse than gabapentin. There is a growing illegal market, and these drugs are also being bought through online pharmacies.

There have been numerous anecdotal reports of misuse of gabapentin and pregabalin, and the literature has been reviewed systematically. The abuse liability of pregabalin has been described in Scandinavia and other parts of Europe. Pregabalin was also listed as a new recreational psychoactive substance by the relevant EU agencies in 2010. Concerns about misuse of pregabalin in the US have led to it being scheduled, indicating that it has abuse potential. Gabapentin and pregabalin have been mentioned on death certificates as adjunctive substances in patients dying of drug poisoning.

In the UK there is evidence that the drugs are readily available among those held in secure environment settings, where they may be abused or used as a commodity for trade. Prescribing per capita of pregabalin and gabapentin in secure settings is double that in the community and this appears unlikely to represent differences in prevalence of the licensed indications for the drugs in these populations.

Prescribing trends

Analysis of electronic prescribing data (ePACT) for primary care prescribing of these medicines during 2011 to 2013 reveals the following headlines:

- in 2013 the total use in England of both these medicines was 8.2 million prescriptions. This represents a 46% rise in prescribing of gabapentin and 53% rise in pregabalin prescribing since 2011
- there is a wide variation in prescribing across the four NHS regions which may, in part, be explained by social and demographic differences between populations, but these may not fully account for three times the prescription numbers seen in the north of England compared to London (further data on gabapentin and pregabalin prescribing is in appendix A)

Drug interactions

Pregabalin and gabapentin are predominantly excreted unchanged in the urine; they undergo respectively negligible or no metabolism in humans. They do not inhibit drug metabolism in vitro and are not bound to plasma proteins, so they are unlikely to produce, or be subject to, pharmacokinetic interactions.

If more than one central nervous system depressant is taken (eg, alcohol even in small amounts, antidepressants, anti-emetics, anti-epileptics, antihistamines, antipsychotics, anxiolytics, barbiturates, hypnotics, opioid analgesics, skeletal muscle relaxants), the central nervous system depressant effects may be additive (of drowsiness, sedation, respiratory depression and, at the extreme, death). There are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system-depressant medicinal products. Cumulative central nervous system depression, ranging from drowsiness to stupor, is particularly dangerous in situations where alertness is needed. In 1994 it was estimated that as many as 600 traffic accident fatalities each year in the UK could be attributed to the sedative effects of psychoactive drugs.

There are particular issues in secure settings where deaths have been found to involve drug and alcohol misuse or dependence, combined with physical and mental health issues and illicit and/or diverted medication. In some cases, pregabalin or gabapentin is found in combination with other central nervous system depressants in addition to methadone and/or chlordiazepoxide prescribed for the management of opiate and/or alcohol withdrawal.

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.

Tapering gabapentin and pregabalin

If dependence on pregabalin or gabapentin, or other misuse or diversion, is suspected or identified the patient should be reviewed and the concerns of the prescriber should be discussed sensitively and documented clearly.

If dependence on prescribed medication is suspected or confirmed, the problem may require specialist advice on managing the dependence. It may simply require agreement on suitable controls on access to, and maximum daily use, of the drugs being misused (when it is felt the medication is still needed for the management of the original indication). Careful reassessment of the patient may lead to an appropriate decision to offer a planned withdrawal of the medication, particularly if the medication does not appear any longer to be required for the main clinical indication.

If completely inappropriate use is confirmed (eg, if there is unequivocal objective evidence that the drugs are simply being diverted) the drugs should be stopped. However, in some cases patients may have diverted a portion of their treatment, such as to a family member, and so adequate assessment is needed to try and determine the most suitable approach in each case and context.

Suggested tapering schemes

The summary of product characteristics for gabapentin and pregabalin indicate that both drugs can be discontinued over one week. A more gradual dose taper allows 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.

Patient information

Patients need to be given information on the potential benefits of the use of pregabalin and gabapentin for their conditions and the risks and reported side effects of the drugs. Patients should be told about the potential for pregabalin and gabapentin to lead to abuse or dependence. It is important for prescribers to have a complete list of medications (including any over-the-counter products or illicit drugs) that patients are taking so that hazardous drug interactions can be minimised or avoided.

If there are features in the patient’s history that increase the likelihood of pregabalin and gabapentin being misused, these should be discussed openly with the patient and the rationale for prescribing suggestions and decisions should be discussed fully and documented. Prescribers should evaluate the risks of continued prescribing and make appropriate decisions regarding quantity of drugs prescribed and the intervals at which the patient should be reviewed.

Further reading

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Spence D. Bad medicine: gabapentin and pregabalin. BMJ 2013;347:6747

Summary of Product Characteristics - Lyrica capsules. Pfizer Limited, last updated 4 March 2014. Accessed 23/05/14 via www.medicines.org.uk/emc

Summary of Product Characteristics - Neurontin 100mg, 300mg & 400mg hard capsules and 600mg & 800mg film coated tablets. Pfizer limited, last updated 26 June 2013.Accessed 23/05/14 via www.medicines.org.uk/emc

US Drug Enforcement Agency (DEA). Drug scheduling. www.justice.gov/dea/druginfo/ds.shtml

Appendix A. FP10 prescribing trends for pregabalin and gabapentin in England 2011-13

The source of the following data is ePACT, which is centrally analysed by NHS Prescription Services from FP10 prescriptions dispensed in the community. The data has not been adjusted for population demographics so the information cannot be used for detailed comparisons but provides an overview of the volume and cost of prescribing of pregabalin and gabapentin.

Headlines

Figure 1 shows the number of prescriptions dispensed for pregabalin and gabapentin during 2011, 2012 and 2013. Figure 2 shows the net ingredient cost for the same time periods:

- in 2013 the total cost in England for both these medicines was £237.9m for 8.2 million prescriptions. Costs of pregabalin were £211.2m for 3.3 million prescriptions. This compares to £26.7m for 4.9 million prescriptions for gabapentin
- the average net ingredient cost per prescription in 2013 for pregabalin was £63.60 compared to £6.37 for gabapentin
- since 2011, when generic preparations became available, there has been a 30% decrease in costs of gabapentin against a 46% rise in the number of prescriptions. This compares to a 40% increase in costs and a 53% rise in the number of prescriptions for pregabalin
- there are significant regional variations in prescribing across the four NHS regions as shown in figure 3. Even though the data has not been adjusted for population or social demographics, these differences are unlikely to be due to social and demographic reasons alone

Figure 1. Number of prescription items across England for gabapentin and pregabalin

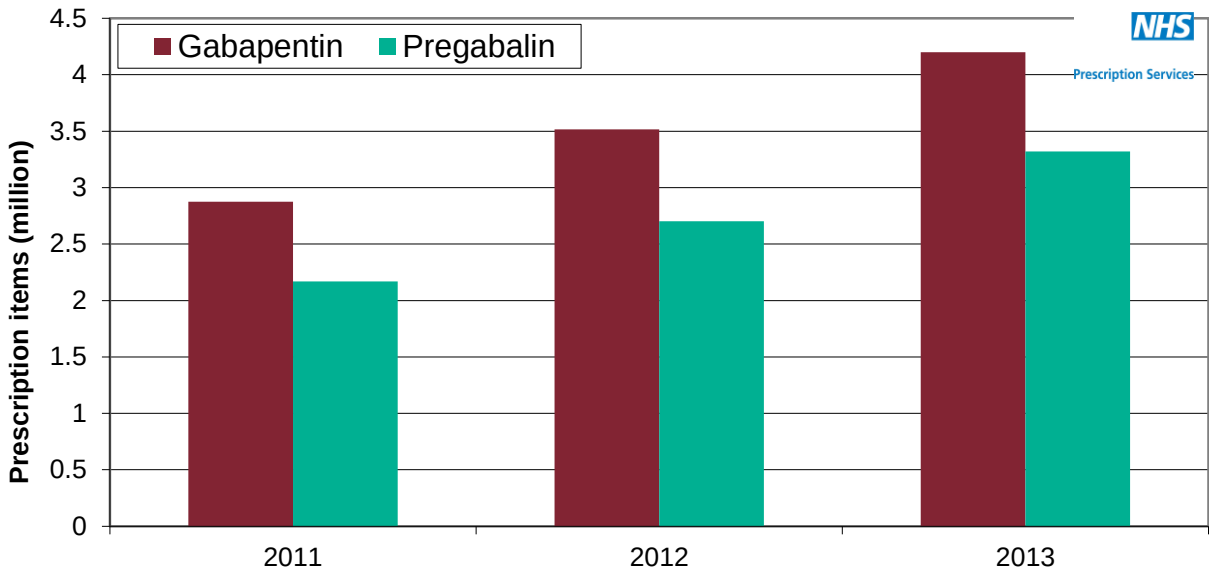


Figure 2. Net ingredient cost (NIC) in England of gabapentin and pregabalin

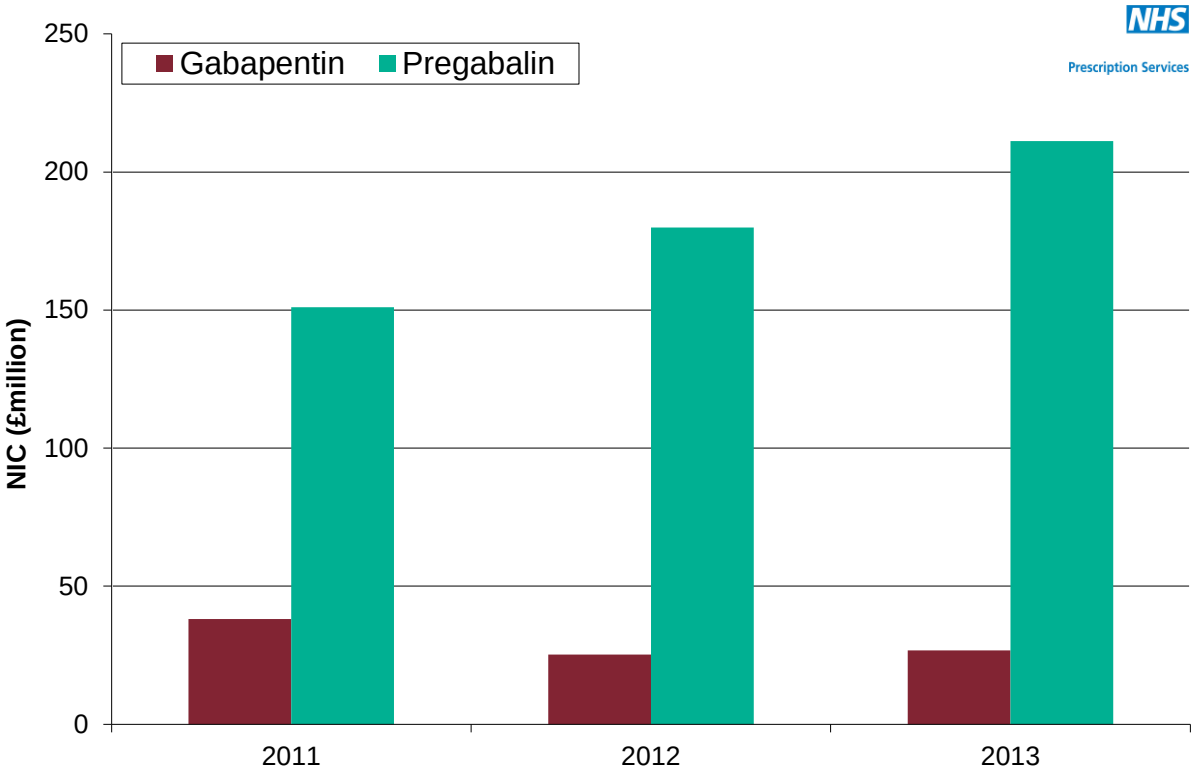
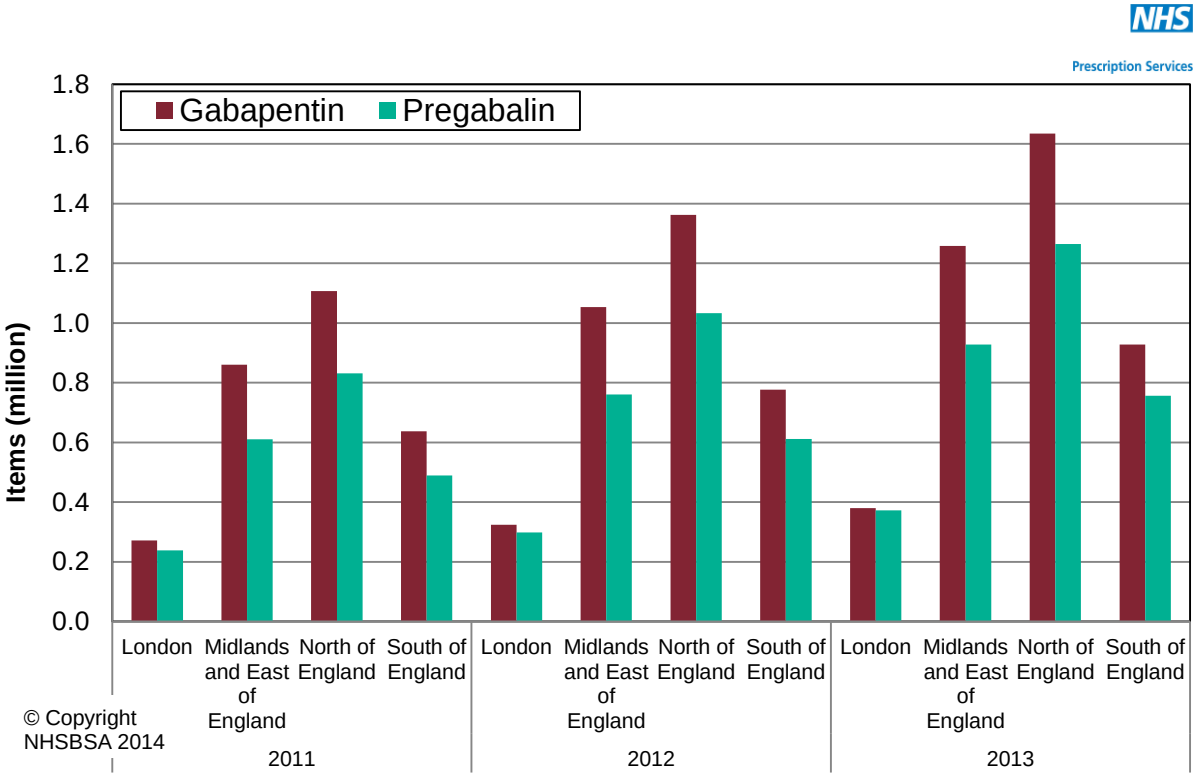


Figure 3. Variation between regional offices in prescribing of gabapentin and pregabalin (BNF 4.8.1)



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- given regard to the need to reduce inequalities between patients in access to, and outcomes from, healthcare services and in securing that services are provided in an integrated way where this might reduce health inequalities

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