



## Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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### **Gabapentin and pregabalin associated with increased risks of suicidal behaviour, injuries, unintentional overdose, and road traffic incidents**

A large population-based cohort study in Sweden found that prescriptions for gabapentinoids were associated with increased risk of suicidal behaviour, unintentional overdoses, head and body injuries, and road traffic accidents and offences. However, the observational study design means the results are subject to confounding and can only suggest an association, not causation. In April 2019, pregabalin and gabapentin were reclassified as schedule 3 controlled drugs because of the risk of abuse and dependence. A Public Health England report has called for better services and support to reduce dependence and withdrawal associated with some prescribed medicines, including gabapentinoids.

#### **Overview and current advice**

Gabapentinoids have an important role in the management of some significant conditions, they are mentioned in several NICE products, including the NICE guidelines on [epilepsy](#), [neuropathic pain](#) and [generalised anxiety disorder](#). The [MHRA has warned](#) that antiepileptic drugs as a group are associated with an increased risk of suicidal thoughts and behaviour, although this was not shown for gabapentinoids (pregabalin and gabapentin) specifically. Nevertheless, the summaries of product characteristics (SPCs) of [gabapentin](#) and [pregabalin](#) note these as possible problems. Other possible adverse effects noted in the SPCs include hostility, emotional lability, confusion and problems with co-ordination and balance.

In April 2019, pregabalin and gabapentin were reclassified as schedule 3 controlled drugs because of the risk of abuse and dependence. Public Health England (PHE) and NHS England have published [advice for prescribers on the risk of misuse of pregabalin and gabapentin](#). In September 2019 PHE published [an evidence review of dependence and withdrawal problems](#) associated with 5 commonly prescribed classes of medicines in England. The review found that prescriptions for gabapentinoids are rising.

The NICE Pathway on [suicide prevention](#) brings together everything NICE has said on suicide prevention in an interactive flowchart. See also the NICE key therapeutic topics on [suicide prevention: optimising medicines and reducing access to medicines as a means of suicide](#) and [medicines optimisation in chronic pain](#).

## New evidence

A large prospective cohort study has investigated the association between prescription use of gabapentinoids and suicidal behaviour, unintentional overdoses, head/body injuries, road traffic incidents and offences, and arrests for violent crime. The cohort comprised 191,973 people in the Swedish Drug Register who collected prescriptions for gabapentin (n=85,360) or pregabalin (n=120,664) between 2006 and 2013, of whom 14,051 received both medicines. Participants acted as their own controls whereby periods during which they were treated with a gabapentinoid were compared with periods where they did not receive a gabapentinoid.

During the study period, 5.2% of people were treated for suicidal behaviour or died from suicide, 8.9% had an unintentional overdose, 6.3% had a road traffic accident or were arrested for a road traffic offence, 36.7% had fatal or serious nonfatal head or body injuries requiring emergency department attendance, and 4.1% were arrested for a violent crime against another person, including sexual offences.

Within-person analyses for the whole cohort adjusted for age, found a statistically significant increase in the risk of: suicidal behaviour and deaths from suicide (age-adjusted [hazard ratio](#) [a-aHR] 1.26, 95% [confidence interval](#) [CI] 1.20 to 1.32), unintentional overdoses (a-aHR 1.24, 95% CI 1.19 to 1.28), head or body injuries (a-aHR 1.22, 95% CI 1.19 to 1.25), and road traffic accidents and offences (HR 1.13, 95% CI 1.06 to 1.20). There was no statistically significant association with arrests for violent crime (a-aHR 1.04, 95% CI 0.98 to 1.11). In an age-stratified analysis, the authors found an increased risk of all outcomes with gabapentinoid use in the younger age groups, with the highest risk of all outcomes being in people aged 15 to 24 (including a statistically significant association with arrest for violent crime) and the lowest risk in those aged 65 and over. When the whole cohort was analysed by specific drug, pregabalin was associated with risks of similar magnitude to the combined exposure, whereas gabapentin was either not statistically significantly associated with increased risk or significantly associated with a reduction in risk.

In an analysis that excluded people with a previous event of the examined outcome, hazard ratios increased for all outcomes. There were also greater hazard ratios for some outcomes associated with use of higher doses. Among people with epilepsy, gabapentinoids were associated with a reduced risk of all outcomes except suicidal behaviour and among people with psychiatric disorders they were associated with a reduced risk of all outcomes.

Using within-person analysis reduced the risk of [confounding](#) by indication (that is, the reason for prescribing the drug is itself a cause of the outcome of interest) and the influence of factors such as individual vulnerability. However, confounding by changes in disease severity were not accounted for and outcomes within each indication were not reported. It is possible that worsening disease could be associated with increased likelihood of being prescribed a gabapentinoid and could also be responsible for the increased risk of some observed outcomes such as major head and body injuries, road accidents and suicidal behaviour. Furthermore, the authors did not account for transient changes in concomitant medicine prescribing which could be associated with gabapentinoid prescribing.

## Commentary

### Commentary provided by NICE

The findings of the study by Molero et al. are consistent with previous warnings that gabapentinoids could be associated with an increased risk of suicidal behaviour. Moreover, the study suggests an increased risk of other adverse outcomes possibly arising from noted adverse effects such as unintentional overdose, head or body injuries and road traffic incidents and, in younger people, violent behaviour. However, because of the observational study design, the contribution of other factors such

as worsening disease, alcohol consumption, illicit drug use and co-prescription of some medicines is unknown.

Although gabapentinoids can be an essential treatment option for some people with certain conditions, prescribers should be aware of this new evidence, the advice provided by the MHRA, and the PHE evidence review on dependence. Prescribing of these medicines has increased in recent years and prescribers should review their use of these to ensure they are in line with current guidance. The MHRA advises that people taking gabapentinoids should be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment. They should be advised to seek medical advice if they develop such thoughts or behaviour, and should be referred for appropriate treatment if necessary. Prescribers and people taking gabapentinoids should also think about the possible effects on their ability to drive safely: see the [advice from the MHRA on drugs and driving](#).

The NICE key therapeutic topic on [medicines optimisation in chronic pain](#) discusses possible approaches that avoid long-term prescription of gabapentinoids for chronic pain.

## Study sponsorship

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## References

Molero Y, Larsson H, D'Onofrio B et al. 2019. [Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic accidents, and violent crime: population based cohort study in Sweden](#). BMJ 365:12147

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