Increased heart failure risk in older people with pregabalin versus gabapentin

Pregabalin initiation increased the risk of new heart failure (HF) compared to gabapentin initiation in people with chronic non-cancer pain, including diabetic neuropathy, in this retrospective cohort study published in *JAMA Network Open*. Data from more than 246 000 US Medicare beneficiaries aged 65–79 years without HF at baseline who were initiated on the drugs demonstrated a significant extra six cases per 1000 person-years in pregabalin recipients, translating to an adjusted hazard ratio of 1.48. The risk was higher in those with cardiovascular disease at baseline (hazard ratio 1.85). The authors caution that it was not possible to measure ejection fraction or natriuretic peptide levels and, although they made significant effort to adjust for confounders, some factors which may contribute to HF risk could not be captured. The American Heart Association has already acknowledged that pregabalin, but not gabapentin, may exacerbate HF.

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Around 50% of people with diabetes will develop neuropathy at some stage, with many already having neuropathy at the time of diagnosis with type 2 diabetes, and 20–30% will develop painful diabetic neuropathy. With the growing recognition of risks associated with opioids, including addiction, overdose and mortality, especially in older people, clinicians are encouraged to limit their use.

The NICE guideline on neuropathic pain, including that resulting from diabetic neuropathy, recommends use of amitriptyline, duloxetine, gabapentin or pregabalin as the first line. However, all of these may have adverse effects, including sedation, dizziness, falls and fractures, particularly in older people. Likewise, the cardiovascular effects of pregabalin and gabapentin, especially in the elderly, who are at increased risk of cardiac conditions, may influence drug choice; however, the small studies carried out to date have been contradictory regarding the associated risk of heart failure (HF).

The American Heart Association highlights that pregabalin, but not gabapentin, may exacerbate HF, but the BNF does not differentiate between these two drugs. Pregabalin binds with greater affinity to the α2δ subunits of calcium channels – subunits which are also found in vascular smooth muscle and heart muscle cells – and it is thought that this could contribute to fluid retention and exacerbation of subclinical cardiac dysfunction (Zhang and Birati, 2025).

The present study

In this retrospective cohort study published in *Jama Network Open*, Park and colleagues reviewed data collected from 246 237 US Medicare beneficiaries aged 65–89 years (median age 73 years) with chronic, non-cancer pain, including a significant percentage (around 12%) with diabetic neuropathy, with no history of HF.

The researchers adjusted for more than 231 covariates to reduce confounding and sought to emulate a hypothetical target trial (i.e. to use observational data to mimic a randomised clinical trial to estimate causal effects and reduce common observational study biases). Stratified analysis was undertaken to also assess risks in those who had cardiovascular disease in the 1 year leading to study enrolment date.

The primary outcome was hospital admission or emergency department attendance with a discharge diagnosis of any type of HF. Secondary outcomes were diagnosis of HF as an outpatient and all-cause mortality.

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Practice points

1. Raise the subject of painful diabetic neuropathy regularly so that it can be identified and managed optimally.
2. Given the increased risks of incident and worsening heart failure associated with pregabalin in people over age 65, careful consideration should be given before prescribing this drug for painful diabetic neuropathy.
3. Consider assessing cardiovascular disease and heart failure risk in people already taking pregabalin to decide whether it is safe to continue.

Initiation of pregabalin vs gabapentin and development of heart failure

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Results

Data from 18 622 people initiating pregabalin and 227 615 initiating gabapentin were analysed. In total, 1470 people (1.3%) developed new HF, with an incidence of 18.2 versus 12.5 per 1000 person-years in those initiated on pregabalin and gabapentin, respectively, giving an adjusted hazard ratio (aHR) of 1.48 (95% confidence interval [CI], 1.19–1.77). In people with pre-existing cardiovascular disease, the aHR was higher, at 1.85. Outpatient diagnoses of HF were also increased, with an aHR of 1.27 (95% CI, 1.02–1.58), but all-cause mortality did not differ between those treated with pregabalin versus gabapentin.

When the numbers of older people treated with these drugs is taken into account, six extra cases of new HF per 1000 people treated per year reflects a significant burden of new chronic disease, potentially damaging quality of life and increasing mortality risk and management workload. The increased risk of HF with pregabalin versus gabapentin was identified in the overall cohort and also in some specific subgroups; for example, in women and white participants, but not in men or in racial or ethnic minority groups.

In an accompanying editorial, Zhang and Birati (2025) describe this as "a large, well-designed study that addresses an area of ongoing clinical uncertainty." However, limitations include that it was not possible to measure ejection fraction or natriuretic peptide levels, and that the results are not generalisable to younger or more diverse populations. Two-thirds of the study population were female. Some factors which may contribute to HF risk, such as BMI, diet, smoking history and physical activity, could not be captured. The authors attempted to compensate for unmeasured confounders using hip fracture as a negative control (as this has no relationship with pregabalin, gabapentin or heart failure), and found no difference between use of the two drugs, which strengthens the HF findings.

Implications for practice

Painful diabetic peripheral neuropathy is common in people with diabetes and has significant impact on sleep, mood and all aspects of quality of life, yet we do not always remember to ask about it, to fully titrate treatments, or to review and optimise treatment benefits, adding or switching treatment when appropriate. Giving people the opportunity to talk about their pain, and possibly referring them to a pain programme, can have a significant beneficial impact alongside drug therapy.

Evaluation of addiction risk is important before initiating and during treatment with pregabalin or gabapentin. Many older people will not tolerate the doses required to make a significant impact on their neuropathic pain, and careful cross-tapering is important if switching from one neuropathic pain drug to another. There is evidence that adding a second drug for diabetic neuropathy may be more effective than switching (Tesfaye et al, 2022).

Although this study showed only a small increased risk of HF, this is clearly something which we want to avoid when prescribing for older people, who are often already frail with multiple long-term conditions. In addition, many clinicians may not be fully aware of the risks of worsening HF with pregabalin when initiating treatments for painful peripheral neuropathy.

Pregabalin and gabapentin have similar efficacy in painful diabetic neuropathy, but the NHS tariff price is slightly lower for pregabalin than gabapentin, so formularies may recommend the former, although the cost differences are small now that generic drugs can be prescribed. However, this study should prompt us to consider carefully before initiating pregabalin for painful diabetic neuropathy in people over 65 years of age, with or without previous HF, unless they have previously failed on gabapentin, duloxetine and amitriptyline, the other first-line options. Opportunistically, we may also choose to assess cardiovascular disease and HF risk in people already taking pregabalin to consider whether it is safe to continue. ■

Park EE, Daniel LL, Dickson AL et al (2025) Initiation of pregabalin vs gabapentin and development of heart failure. *JAMA Netw Open* **8**: e2524451

Tesfaye S, Sloan G, Petrie J et al; OPTION-DM trial group (2022) Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): A multicentre, double-blind, randomised crossover trial. *Lancet* **400**: 680–90

Zhang RS, Birati EY (2025) Pregabalin for chronic noncancer pain – when pain relief comes at a cardiac cost. *JAMA Netw Open* **8**: e2524457