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Pregabalin and gabapentin-induced heart failure

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The association of widely used neurological agents gabapentin and pregabalin and heart failure (HF) is not widely known, although fluid retention after their use in the form of peripheral edema has been recognized. Meanwhile, some evidence suggests that both drugs may be related to HF, especially to new onset HF.

The pharmacokinetics and side effects of pregabalin and gabapentin tend to be similar because both belong to a class of drugs called gabapentinoids. These agents bind to the voltage-gated calcium channels in the brain. In the information from the Food and Drug Administration, neither HF or cardiomyopathy is listed as a contraindication/precaution or side effect of these drugs, although both are associated with increased risk of peripheral edema. This risk is estimated as up to 8% for gabapentin and up to 16% for pregabalin, in a dose-dependent manner (https://www.accessdata.fda.gov/drugsatfda_docs/ accessed 11/18/23). Several case reports have suggested an association of HF with both pregabalin and gabapentin [1, 2]. This association has now been explored in a number of large studies.

Pan et al. studied 210,064 patients with diabetic neuropathy [3]. Propensity score matching the baseline co-variates of the 2 groups were used: pregabalin/gabapentin and control. Regarding gabapentin, the matched cohorts consisted of 7,049 patients taking gabapentin and the same number of controls. Gabapentin increased the risk of HF by 14% over a 5-year period compared to not using gabapentin, and pregabalin increased such risk by 20% (Table 1).

All cases of peripheral edema or HF involving gabapentin or pregabalin were reported to the French Pharmacovigilance Centers between January 1, 1994 and April 30, 2020 [4]. A total of 58 reports were included (gabapentin n = 5, pregabalin n = 53). Only pregabalin was associated with acute HF, with the onset of a median of 17 days after the start of therapy. The timing is consistent with that of previous reports [1, 2]. The majority of their patients had reversal of the condition after discontinuation of pregabalin, confirming the causality. Also, the difference between non-cardiogenic edema and HF should be supported by objective data, especially the biomarkers.

The data are more controversial when it comes to worsening HF in patients, who already had this diagnosis before the initiation of gabapentin or pregabalin. Wynn et al. performed a retrospective study of patients taking pregabalin and found no significant association with worsening HF [5] (Table 1). Curiously, the same group of authors earlier presented an abstract demonstrating that pregabalin was associated with an increased risk of acute HF in patients with existing HF with a 13% increase in per-patient-per-year hospitalizations ($p < 0.036$) (published as abstract only) [6].

Several large cohort studies compared the rates of heart failure between pregabalin and gabapentin and found no difference. A population-based study was conducted in Denmark using data from nationwide registers, from 1 January 2008 to 31 December 2017 [7]. The study population consisted of patients 50 years of age or older with a diagnosis of HF who were new users of pregabalin

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Table 1. Cohort studies on association of heart failure with gabapentin and pregabalin

Author, date	Design	Population	Drug	Findings
Pan, 2022 [3]	The multicenter retrospective cohort study	210,064 patients with diabetic neuropathy divided into those exposed to gabapentin or pregabalin or not exposed to either drug and then propensity-matched	Gabapentin	Increased the risk of new HF by 14% over a 5-year period (HR: 1.14, 95% CI 1.07–1.21)
			Pregabalin	Increased the risk of HF by 20% over a 5-year period (HR: 1.2, 95% CI 1.11–1.3)
Wynn, 2024 [5]	The University of Utah retrospective cohort study	Patients with pre-existing HF, 346 pregabalin users and propensity-matched 3460 pregabalin nonusers	Pregabalin	Hazard ratio for a composite of HF-related hospitalizations, HF-related emergency room visits, and all-cause mortality. 1.099 (95% CI: 0.789-1.530; p = 0.58)
Lund, 2020 [7]	The retrospective cohort study from nationwide registry in Denmark	Patients with pre-existing HF, 1395 new users of pregabalin propensity-matched to 1395 new users of gabapentin, then 847 new users of pregabalin vs. 847 new users of duloxetine	Pregabalin	Worsening HF: HR 0.79 (95% CI 0.50–1.23) vs. gabapentin HR 1.08, 95% CI 0.60–1.94 vs. duloxetine

HF — heart failure; HR — hazard ratio; CI — confidence intervals

or gabapentin. Both groups had 1395 patients and the end point was exacerbation of HF within 90 days. There were 33 patients with worsening HF among users of pregabalin (incidence rate 105.7 per 1000 person-years vs. 133.8 per 1000 person-years among users of gabapentin, the difference was not significant). There was also no difference with patients who were taking duloxetine (Table 1).

Another population-based cohort study was conducted on Ontarians aged 66 and older who received pregabalin or gabapentin [8]. The primary outcome was an emergency department visit or hospitalization for HF within 90 days. The study included 9855 patients who initiated pregabalin and an equal number treated with gabapentin. Like in the prior study, no difference in the incidence of HF was found with pregabalin compared to gabapentin (incidence rate 1.2% vs. 1.3%).

The mechanism of gabapentin-induced toxicity is unknown. However, Awwad. et al [9] studied the effect of pregabalin-induced cardiotoxicity in rats and showed a 44% decrease in left ventricular ejection fraction and sevenfold increase in plasma N-terminal pro-brain natriuretic peptide. Histopathological examination also showed prominent vacuolar changes and edema in cardiomyocytes.

Concerning the renin-angiotensin system, Awwad et al found significantly increased angiotensin II, angiotensin converting enzyme and angiotensin II type 1 receptor levels suggesting that mechanism of cardiotoxicity is probably mediated via this pathway [9, 10]. Also, pregabalin's inhibition of the calcium channels in the myocardium can also play a role.

The limitations of the above studies in humans include incomplete drug dosage, and limited information about the time onset of new or exacerbation of HF. Importantly, in the studies involving patients without pre-existing HF, there are incomplete criteria for the diagnosis of HF, BNP determination, and echocardiographic data.

Clinically, the situation is compounded by the fact that the two drugs are associated with non-cardiogenic vasodilatory edema with a dose-dependent incidence as high as 8%–16% of patients. In fact, this raises the concern that some patients with edema, as reported by FDA, may have had HF. In the presence of edema, one should therefore consider ruling out HF with a meticulous physical examination coupled with BNP determination and echocardiography. Furthermore, it is important to look for clinical deterioration when administering the drugs or increasing their dosage in patients with compensated HF. The incidence of HF, potentially induced by the two drugs, is rare in patients with and without pre-existing compensated HF. Heart failure tends to occur early, within days after the onset of treatment with gabapentin or pregabalin. The characteristics, dose dependence, genetic predisposition, pathophysiology and the type of HF remain to be clarified. In patients without pre-existing HF,

the favorable outcome or reversibility upon discontinuation of drug therapy should be confirmed with serial echocardiographic monitoring.

In conclusion, the accumulated evidence suggests that both gabapentin and pregabalin may increase the incidence of new onset heart failure. Clinical symptoms may occur days after the beginning of treatment and are mostly reversible upon its discontinuation. Cases of new peripheral edema on either drug should be worked up with echocardiography and testing for natriuretic peptides to rule out HF.

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