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Gabapentinoid-induced peripheral edema and acute heart failure: a translational study combining pharmacovigilance data and in vitro animal experiments

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Abbreviations: ADR, adverse drug reaction; Cav, voltage-gated calcium channels; GABA, gamma-aminobutyric acid; HEPES, Hydroxyethyl piperazineethanesulfonic acid; I_{CaL}, L-type calcium inward current; KB, Kraft-Bruhe; KRB, Krebs-Ringer Bicarbonate Buffer; MedDRA (Medical Dictionary for Regulatory Activities).

1 **ABSTRACT**

2 **INTRODUCTION:** Gabapentinoids are ligands of the $\alpha 2\text{-}\delta$ subunit of voltage-gated calcium
3 channels (Cav) that have been associated with a risk of peripheral edema and acute heart
4 failure in connection with a potentially dual mechanism, vascular and cardiac.

5
6 **OBJECTIVES & METHODS:** All cases of peripheral edema or heart failure involving
7 gabapentin or pregabalin reported to the French Pharmacovigilance Centers between January
8 1, 1994 and April 30, 2020 were included to describe their onset patterns (e.g., time to onset).
9 Based on these data, we investigated the impact of gabapentinoids on the myogenic tone of
10 rat third-order mesenteric arteries and on the electrophysiological properties of rat ventricular
11 cardiomyocytes.

12
13 **RESULTS:** A total of 58 reports were included (gabapentin n=5, pregabalin n=53). The female-
14 to-male ratio was 4:1 and the median age was 77 years (IQR 57-85, range 32-95). The median
15 time to onset were 23 days (IQR 10-54) and 17 days (IQR 3-30) for non-cardiogenic edema and
16 acute heart failure, respectively. Cardiogenic and non-cardiogenic peripheral edema occurred
17 frequently after a dose escalation (27/45, 60%), and the course was rapidly favorable after
18 discontinuation of gabapentinoid (median 7 days, IQR 5-13). On rat mesenteric arteries,
19 gabapentinoids significantly decreased the myogenic tone to the same extent as verapamil and
20 nifedipine. Acute application of gabapentinoids had no significant effect on Cav1.2 currents of
21 ventricular cardiomyocytes.

22
23 **CONCLUSION:** Gabapentinoids can cause concentration-dependent peripheral edema of
24 early onset. The primary mechanism of non-cardiogenic peripheral edema is vasodilatory
25 edema secondary to altered myogenic tone, independent of Cav1.2 blockade under the
26 experimental conditions tested.

27
28
29 **KEYWORDS:** Edema; Heart failure; Gabapentin; Pregabalin; Pharmacovigilance

1. INTRODUCTION

The gabapentinoids, gabapentin and pregabalin, are both indicated in partial seizure and neuropathic pain. The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) also approved pregabalin for the treatment of generalized anxiety disorder and fibromyalgia, respectively. Recent United States and European data have shown that the use of gabapentinoids has tripled over the past 15 years [1,2]. While gabapentinoids were synthesized as GABA-mimetics, the discovery of their pharmacological target succeeded their approval by several years. These are high-affinity ligands for the subtypes 1 and 2 of the auxiliary $\alpha 2\text{-}\delta$ subunit of voltage-gated calcium channels (Ca_v) [3]. Subtype $\alpha 2\text{-}\delta 1$ is particularly expressed within $\text{Ca}_v 1.2$ (L-type) and affects the electrophysiological properties of the channels [3].

Meta-analyses have shown a substantial risk of peripheral edema in 7-10% of patients taking gabapentinoids [4,5]. In the face of underinvestigated clinical features and pharmacological mechanism with only a few case reports published [6,7], it has been shown that this inadequate knowledge of gabapentinoid-induced peripheral edema places patients at substantial risk for hazardous prescribing cascade with diuretics [8]. Indeed, misinterpretation of gabapentinoid-induced peripheral edema as a new or worsening medical condition (e.g., heart failure) may lead to subsequent prescribing of diuretics of uncertain efficacy and that can be harmful (e.g., electrolyte imbalance, acute kidney injury) especially in the elderly [8,9]. In addition, case reports [10] and post-marketing surveillance [11] have highlighted an underappreciated risk of worsening heart failure with gabapentinoids. Acute heart failure, which may be associated by peripheral edema (i.e., cardiogenic peripheral edema), seems to be a risk specific to pregabalin exposure that is not found with gabapentin [10]. Thus, this apparent polymorphism of gabapentinoid-associated edematous states (i.e., of non-cardiogenic or cardiogenic origin) could be due to several distinct pathophysiological mechanisms affecting vascular smooth muscle and cardiomyocytes, respectively.

Clinical observations reported to date on these aspects are limited in scope by their small sample size and the onset modalities (e.g., time to onset, patient comorbidities) are unknown. The aim of this study was to characterize the onset patterns of gabapentinoid-induced peripheral edema, whether or not involving heart congestion, by reviewing the cases reported to the French regional pharmacovigilance centers. Based on these data, we investigated the pharmacological mechanisms underlying non-cardiogenic and cardiogenic peripheral edema secondary to gabapentinoids that have not been addressed to date. Since gabapentinoids share a common pharmacological target (Ca_v) with calcium channel blockers (CCBs), with which these same adverse drug reactions (ADRs) are described [9,12], we hypothesized that gabapentinoids, just like CCBs, reduce myogenic tone on perfused isolated mesenteric arteries and inhibit $\text{Ca}_v 1.2$ currents on isolated ventricular cardiomyocytes explaining the risk of non-cardiogenic peripheral edema and acute cardiac failure, respectively.

2. METHODS

2.1 Pharmacovigilance study

This study was conducted using the French Pharmacovigilance Database, in which reported ADR cases have been registered since 1985. Patient informed consent was not required as the database is deidentified to protect subject confidentiality. All cases of peripheral edema or heart failure [Medical Dictionary for Regulatory Activities (MedDRA) High-Level Term 'total

77 volume fluid increased' or High-Level Group Term 'heart failures'] involving gabapentin or
78 pregabalin and recorded between January 1, 1994 and April 30, 2020 were selected. Extraction
79 of these reports identified cases of peripheral edema in which acute heart failure was co-
80 reported (cardiogenic peripheral edema) or not (non-cardiogenic peripheral edema). Cases of
81 localized edema (e.g., face or eyelids only) or edema that was part of a hypersensitivity
82 reaction were excluded from this study. Cases were included if they met the following criteria
83 1/ development of peripheral edema or acute heart failure while receiving gabapentinoid and
84 recovery or marked improvement if gabapentinoid was stopped, and 2/ no other reported
85 triggers that could explain the occurrence of non-cardiogenic peripheral edema (e.g.,
86 hypoproteinemia) or acute heart failure (e.g., sepsis, myocardial ischemia). Only cases in
87 which a gabapentinoid was the only suspect drug and with sufficient data regarding exposure
88 were included. For each report, extracted data included patient demographics and
89 comorbidities, characteristics of gabapentinoid exposure (e.g., dose, drug withdrawal,
90 rechallenge) and characteristics of ADR (time course, outcome). Based on the European
91 summary of products characteristics and the published literature [9,13], concomitant drugs
92 were labelled as either a known cause of non-cardiogenic peripheral edema or acute heart
93 failure or not yet recognized as such. Causality was assessed for each drug according to the
94 French causality method as previously described [14]. Briefly, this method allows for each
95 drug a clear distinction between data related to the individual characteristics of the case and
96 published information. This method determines the intrinsic imputability combining a
97 chronological score (temporal link) and semiological score (etiological link), and an extrinsic
98 score, based on previous published similar cases. For each case, drugs were classified
99 according to the intrinsic imputability as suspect (highest score) or concomitant (lower score)
100 according to the World Health Organization criteria.

101

102 2.2 Animal studies

103 2.2.1 Animals

104 Male Wistar rats weighting 350-450 g (n=20) were purchased from Janvier (Le Genest Saint
105 Isle, France). Animals were kept under a 12h-12h light-dark cycle and allowed free access to
106 food and water.

107

108 2.2.2 Tissue collection

109 Rats were anesthetized with pentobarbital (60 mg/kg, intraperitoneal) and heparined (500
110 UI/kg, intravenous). Heart-lung block then intestine were immediately removed and placed
111 in ice-cold cardioplegic solution (in mmol/L: 110 NaCl, 16 KCl, 1.20 CaCl₂, 16 MgCl₂, 10
112 NaHCO₃, and 10 glucose) and ice-cold Krebs solution (in mmol/L: 119 NaCl, 4.7 KCl, 1.36
113 CaCl₂, 1.17 MgSO₄, 1.18 KH₂PO₄, 25 NaHCO₃ and 5.5 glucose), respectively. Heart and aorta
114 were cleaned up from lungs, conjunctive tissues and atriums. Mesenteric arteries were cleaned
115 up from fat, conjunctive tissues and third-order mesenteric arteries were harvested.

116

117 2.2.3 Pressurized mesenteric arteries experiments with Halpern's arteriography

118 Isolated third-order mesenteric arteries were cannulated on two glass micropipettes (diameter
119 150 µm) and secured with nylon thread (diameter 25 µm) in a pressure arteriography (Living
120 System Instrumentation, Burlington, VT, USA) filled with Krebs solution warmed to 37°C and
121 oxygenated with 95% O₂ and 5% CO₂. Endothelium was removed by passing 1 mL of air in the
122 vessel. Arteries were then pressurized to 80 mmHg with no flow condition, i.e., at ~ 80% of the
123 animal's mean arterial pressure to approximate in vivo perfusion pressure (~ 100 mmHg). The

124 chamber was placed atop an inverted microscope connected to a video camera. The video
 125 acquisition was performed by HF_IDS_Cam software [15] to obtain lumen diameter and wall
 126 thickness measurements in micrometers. Vessels were kept to equilibrate for 30 minutes to
 127 allow the development of myogenic tone. Viability of the arteries was then tested by the
 128 vasoconstriction of a high KCl Krebs solution (100 mmol/L). Then, arteries were washed to
 129 baseline and constricted with phenylephrine 10^{-6} mol/L and relaxed with acetylcholine 10^{-6}
 130 mol/L to confirm the absence of endothelium. A dilatory response of less than 15% was
 131 considered indicative of a denuded vessel. Arteries were then washed to baseline and
 132 incubated for 30 minutes with verapamil (10^{-5} mol/L, Sigma-Aldrich), nifedipine (10^{-5} mol/L,
 133 Sigma-Aldrich), gabapentin (10^{-5} mol/L, Sigma-Aldrich), Lyrica® oral solution 20 mg/mL (10^{-5}
 134 mol/L, Pfizer), excipients with known effects of Lyrica® [i.e., methyl parahydroxybenzoate
 135 (6.08×10^{-7} mol/L, Sigma-Aldrich), propyl parahydroxybenzoate (7.2×10^{-8} mol/L, Sigma-Aldrich)
 136 and ethanol (0.01 g/L, Sigma-Aldrich)], or nothing for the control group. The concentrations
 137 of gabapentinoids used correspond to those found in the serum of patients taking these drugs
 138 (12-117 μ mol/L of gabapentin and 13-50 μ mol/L of pregabalin) [16]. Of note that the excipients
 139 of Lyrica® did not affect the myogenic tone of arteries (**supplemental eFigureS1**). Myogenic
 140 tone, i.e., the percentage of contraction of the artery in response to the increase internal
 141 pressure, was determined after increasing pressure by 20 mmHg steps from 0 to 160 mmHg
 142 with first normal Krebs and in a second time with calcium-free Krebs (in mmol/L: 119 NaCl,
 143 4.7 KCl, 1.17 MgSO₄, 1.18 KH₂PO₄, 25 NaHCO₃, 5.5 glucose and 2 EGTA). The percentage of
 144 myogenic tone was determined by the following formula:

$$145 \quad \% \text{ myogenic tone} = \frac{ID_{Kcf} - ID_K}{ID_{Kcf}} \times 100$$

146 where ID_{Kcf} = internal diameter with calcium-free Krebs and ID_K = internal diameter with
 147 Krebs at the same pressure.

148 The structural properties of third-order mesenteric arteries were also evaluated by calculating
 149 the wall-to-lumen ratio (M/L ratio) and the cross-sectional area (CSA). The mechanical
 150 properties were assessed by calculating stress-strain relationships and the tangential elastic
 151 modulus β , as previously described [17]. We also assessed the percentage of arterial
 152 vasodilation after 30-minutes incubation with the active molecules. The percentage of
 153 vasodilation was determined by the following formula:

$$154 \quad \% \text{ vasodilation} = \frac{ID_{30'} - ID_{baseline}}{ID_{baseline}} \times 100$$

155 where $ID_{30'}$ = internal diameter after 30 minutes of incubation and $ID_{baseline}$ = internal diameter
 156 before 30 minutes of incubation.

157

158 2.2.4 Rat ventricular cardiomyocytes isolation

159 Cardiomyocyte's isolation was proceeded, as mentioned previously [18]. Briefly, isolation was
 160 performed using a Langendorff system with 0.17 U/mL liberase™ in KRB (in mmol/L: 35 NaCl,
 161 4.75 KCl, 1.19 KH₂PO₄, 16 Na₂HPO₄, 25 NaHCO₃, 134 sucrose, 10 HEPES, and 10 glucose, pH
 162 adjusted to 7.4) under 95% O₂/5% CO₂ until the heart changed in shape and color (white areas
 163 appeared). After enzymatic digestion, the heart was recovered in a KB solution (in mmol/L: 50
 164 glutamic acid, 30 KCl, 30 KH₂PO₄, MgSO₄, 20 taurine, 0.5 EGTA, 10 HEPES, 10 Glucose, 10
 165 KOH, pH adjusted to 7.4). The ventricles were then separated and cut up into fine pieces for
 166 mechanical digestion, then the KB solution was replaced by Tyrode's solution (in mmol/L: 140
 167 NaCl, 5.37 KCl, 1.36 CaCl₂, 1 MgCl₂, 0.33 NaH₂PO₄, 10 HEPES, and 11 glucose; pH adjusted to
 168 7.4) and stored at room temperature until use.

169

170 2.2.5 Whole-cell voltage-clamp experiments

171 An Axopatch 200A amplifier linked to Digidata 1200 A interface, was used to control voltage
172 and record currents. A computer with Clampex (pClamp 9 software, Axon Instruments) was
173 used to acquire data at a sampling frequency of 10 kHz and low-pass filtered with an 8-pole
174 lowpass Bessel filter at 5 kHz.

175 L-type calcium inward current (I_{CaL}) was recorded from a holding potential of -70 mV as
176 previously described [19]. Briefly, cardiomyocytes were superfused with a solution containing
177 (in mmol/L: 144 TEACl, 2 $CaCl_2$, 1 $MgCl_2$, 5 4-aminopyridine, 10 HEPES, and 11 glucose; pH
178 adjusted to 7.4 with TEAOH). The recording pipettes used had a tip resistance of 1.5–2.5 M Ω
179 and were filled with (in mmol/L): 10 TEACl, 2 $MgCl_2$, 115 DL-aspartic acid, 5 di-tris
180 phosphocreatine, 10 HEPES, 10 EGTA, and 5 Mg-ATP; pH adjusted to 7.2 with CsOH. These
181 solutions were used to block ionic currents other than I_{CaL} .

182 Background currents were recorded from a holding potential of -70 mV during a ramp of
183 voltage from -120 mV to $+60$ mV at an increasing speed of 36 mV/s. Recording pipettes had a
184 tip resistance of 2-3 M Ω and were filled with (in mmol/L): 115 K-aspartate, 25 KCl, 1 $MgCl_2$, 5
185 ATP-Mg, 0,1 GTP-Tris, 5 di-Na phosphocreatine, 10 HEPES, 10 EGTA; pH adjusted to 7.2 with
186 KOH. During experiments, cells were superfused with Tyrode solution in the absence and the
187 presence of 10^{-5} mol/L of pregabalin or gabapentin.

188 All recorded currents were normalized to membrane capacitance. Membrane capacitance was
189 measured by integration of the capacitive currents in response to a series of 10 hyperpolarizing
190 pulses (10 mV, 10 ms) applied from the holding potential and then averaged. The pipette and
191 cell capacitances were compensated by 80%.

192

193 2.3 Data analysis and statistics

194 In the pharmacovigilance study, categorical variables are presented as absolute number
195 (percentage) and continuous variables as median [interquartile range (IQR)] with minimum
196 and maximum values. In the animal studies, values are presented as means \pm standard error
197 of mean (SEM). Data were analyzed using GraphPad Prism software (version 5.3).
198 Comparisons of means between each group were tested by a one-way analysis of variance
199 (ANOVA). Myogenic tone curves (active vs. control) were compared by two-way ANOVA for
200 repeated measures followed by an appropriate post-hoc test using the Bonferroni correction.
201 Two-sided P values of less than 0.05 were considered to indicate statistical significance.

202

203 2.4 Ethical standards

204 Per the Jardé law in France regarding research involving human participants, this study did
205 not require ethical review or informed consent because an existing anonymized database was
206 used. The experimental procedures were approved by the local committee for ethics in animal
207 experimentation No. 2016-090711251954 of Tours University (Tours, France) and complied
208 with the “Animal Research: Reporting In Vivo Experiments” ARRIVE guidelines.

209

210 3. RESULTS

211 A total of 58 ADR reports were included involving gabapentin and pregabalin in 5 and 53
212 cases, respectively (**Figure 1**). The female-to-male ratio was 4:1 and the median age was 77
213 years (IQR 57-85, range 32-95).

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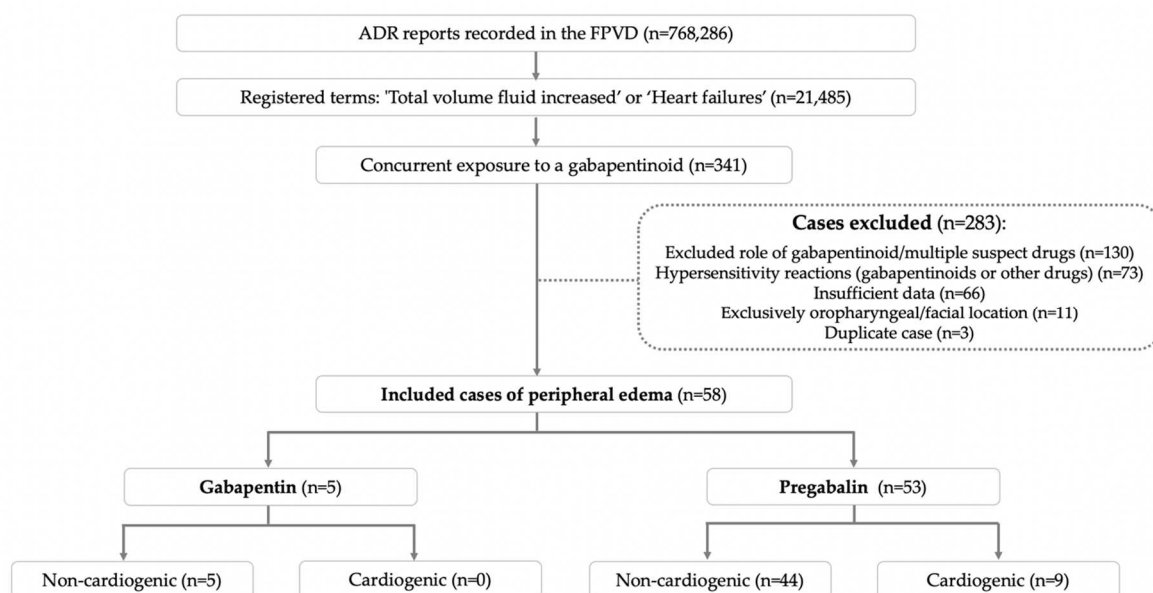


Figure 1 – Flowchart of the study.

ADR, adverse drugs reactions; FPVD, French pharmacovigilance database

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3.1 Non-cardiogenic peripheral edema

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Non-cardiogenic peripheral edema occurred in 49 cases, involving gabapentin and pregabalin in 5 and 44 patients, respectively. Case characteristics are summarized in **Table 1**. The female-to-male ratio was 4:1 and the median age was 73 years (IQR 56-85, range 32-94). A concomitant drug known to cause edema was reported in 78% of cases (29/37). The role of these concomitant drugs was not retained because the edema improved after discontinuation of gabapentinoid and despite the continuation of concomitant drugs or because the edema recurred after restarting gabapentinoid alone. The main pharmacological classes involved were opioids (15/25, 60%) and CCBs (9/29, 31%). Drugs involved are shown in **supplemental eTable S1**.

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The median time from gabapentinoid initiation to peripheral edema was 23 days (IQR 10-54, range 1 day-3 years, n=41). In 68% of cases (26/38), peripheral edema occurred after a dose escalation. In these cases, the median time to onset after dose titration was reduced to 7 days (IQR 3-15, range 1-44, n=21). In all but one case, peripheral edema was bilateral (48/49, 98%). Gabapentinoid was stopped in 94% (46/49) of cases and the dosage was reduced in the other three cases. Of the 46 patients who discontinued gabapentinoid, 10 also received diuretic therapy. Ineffectiveness of diuretics was documented in the four cases where their efficacy could be assessed (i.e., when discontinuation of gabapentinoid and diuretic initiation were not simultaneous). In the three cases where gabapentinoid was continued at a reduced dosage (17%, 33% and 40% dose reduction), a marked improvement was reported. When the follow-up was sufficient (n=47), the outcome was favorable in all cases. After discontinuation of gabapentinoid, the time to recovery ranged from 2 to 55 days (median 7, IQR 4-10, n=22). Of the four rechallenges with pregabalin, three resulted in a recurrence of peripheral edema (unchanged dose n=2, dose unknown n=1) and rechallenge was negative in the last case (dose reduced by 33%). No patient was rechallenged with gabapentin. Switch from pregabalin to gabapentin was performed in three patients, with no cross-ADR reported.

Table 1 – Cases characteristics of gabapentinoid-induced non-cardiogenic peripheral edema.

	Gabapentin (n=5)	Pregabalin (n=44)
Demographics		
Sex ratio (female/male)	4:1	4:1
Age, median [min-max]	82 [71-94]	73 [32-93]
Comorbidities, n (%)		
Hypertension	1/5 (20)	13/36 (36)
Diabetes	1/5 (20)	4/36 (11)
Heart failure	1/5 (20)	3/38 (8)
Gabapentinoid exposure		
Therapeutic indication, n (%)		
Neuropathic pain/neuropathy	4/5 (80)	44/44 (100)
Seizure	1/5 (20)	0 (0)
Dose in mg/day, median [min-max]	1800 [600-2400]	150 [50-1800]
TTO and dose titration		
TTO, median [min-max]	383 [6-1095] n=4	20 [1-240] n=37
Occurrence after dose titration, n (%)	4/4 (100)	22/34 (65)
TTO after dose escalation, median [min-max]	20 [2-44] n=4	7 [1-30] n=17
Location of peripheral edema, n (%)		
Lower limbs	5/5 (100)	40/44 (91)
Multiple location	3/5 (60)	18/44 (41)
Generalized edema	0 (0)	8/44 (18)
Upper limbs	2/5 (40)	7/44 (16)
Face/eyelids	2/5 (40)	5/44 (11)
Management and outcome, n (%)		
Gabapentinoid withdrawal	4/5 (80)	42/44 (95)
Gabapentinoid dose reduction	1/5 (20)	2/44 (5)
Favorable	3/5 (60)	44/44 (100)
Not recovered	2/5 (40)	0 (0)
Time to recovery, median [min-max]	6 [2-10] n=2	7 [2-55] n=20
TTO, time to onset		

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245

3.2 Acute heart failure

247 Only pregabalin was associated with acute heart failure (n=9). Patient age ranged from 62 to
248 95 years (median 84, IQR 77-84) and 89% (8/9) of cases occurred in women. The case
249 characteristics are described in **Table 2**. The main cardiovascular comorbidities of patients
250 were heart failure (3/9, 33%), hypertension (3/9, 33%), atrial fibrillation (2/9, 22%) and coronary
251 heart disease (2/9, 22%). Pregabalin was indicated for neuropathy/neuropathic pain in all
252 cases. The daily dose ranged from 50 to 600 mg (median 150, IQR 100-150). The time to onset
253 of acute heart failure ranged from 1 to 112 days after initiation of pregabalin (median 17, IQR
254 3-30, n=9). In one case (patient #5), heart decompensation occurred after a dose increase (1/7,
255 14%). In the absence of data on possible pre-therapeutic imaging, no cases described the
256 impact of pregabalin on echocardiographic parameters. In all but one case (patient #1),

257 pregabalin was stopped. The outcome was favorable in all cases except for patient #1, in whom
 258 the continuation of pregabalin resulted in three occurrences of acute heart failure in the
 259 months following the first episode. The time to recovery ranged from 7 to 32 days (median 30,
 260 IQR 24-31, n=4). No rechallenge was performed with pregabalin. A switch to gabapentin was
 261 made in one patient (#6) with no recurrence of the ADR at 1-month follow-up.
 262

263 3.3 Myogenic tone

264 To explain non-cardiogenic peripheral edema, we explored the impact of gabapentinoids on
 265 the myogenic tone of endothelium denuded third-order mesenteric arteries. All the vessels
 266 included in the study generated a constriction to high KCl superior to 50% and a vasodilation
 267 to acetylcholine less than 15% (data not shown). Given that subtypes 1 and 2 of the auxiliary
 268 $\alpha 2\text{-}\delta$ subunit are expressed in $\text{Ca}_v1.2$ (the pharmacological target of CCBs), the effects of
 269 gabapentinoids were compared to two CCBs known to cause peripheral edema (verapamil
 270 and nifedipine), in order to perform a comparative effect size estimate of the impact of
 271 gabapentinoids on myogenic tone [9]. Compared to control, gabapentin and pregabalin
 272 dramatically decreased the myogenic tone (**Figure 2A**) to the same extent as verapamil and
 273 nifedipine (**Figure 2B**). The loss of myogenic tone observed was not the consequence of
 274 impairments of structural or mechanical proprieties of vessels because M/L ratio, CSA, stress-
 275 strain curve, and tangential elastic modulus β were not different between control and treated
 276 groups (**Supplemental eFigure S2**). In contrast to the effects of CCBs, incubating 30-minutes
 277 vessels with gabapentin or pregabalin did not induce a significant vasodilatation compared to
 278 the control group (**Figure 2C**).

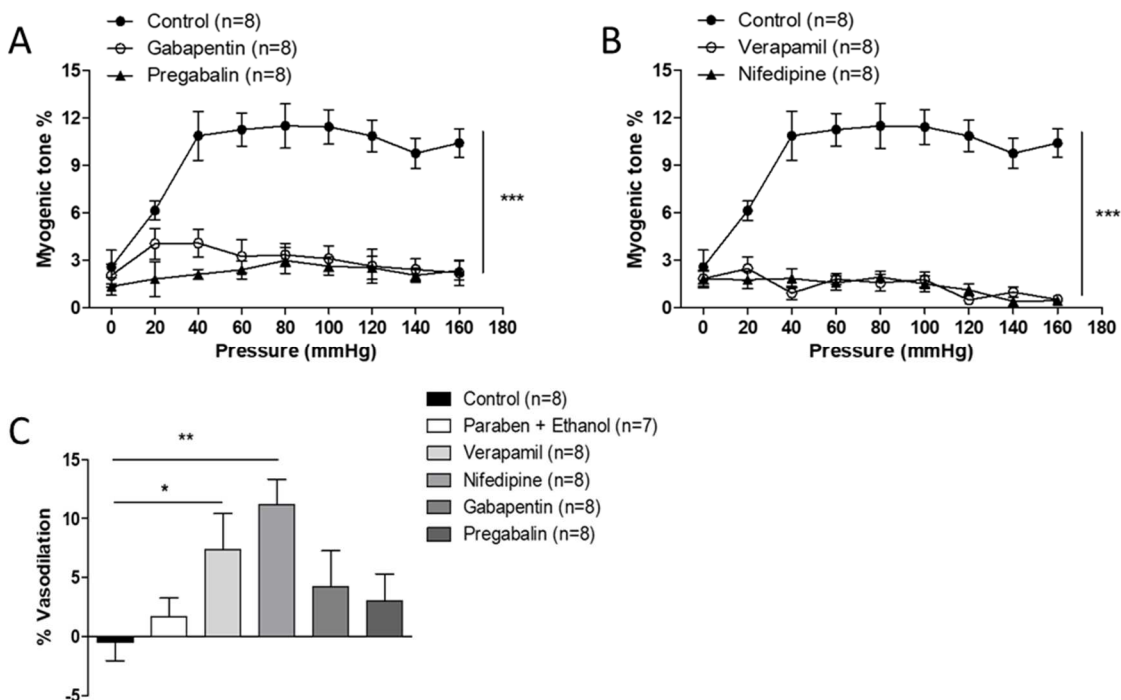


Figure 2 – Results of pressurized mesenteric arteries experiments.

Myogenic tone of endothelium-denuded third-order mesenteric arteries control or incubated with (A) verapamil or nifedipine or (B) gabapentin or pregabalin and (C) vascular dilation of these same vessels after incubation for 30 minutes. The Bonferroni post-hoc test showed a significant difference at $p < 0.0001$ for all pressure steps except 0 mmHg.

Values are means \pm SEM from n = number of artery segments from 7 to 8 rats per group. * p<0.05, ** p<0.01, *** p<0.0001.

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3.4 Electrophysiology studies

Gabapentin and pregabalin at the concentration of 10^{-5} mol/L in acute superfusion had no significant effect on the L-type calcium current nor on the background currents from -120 mV to +60 mV (n=6, **Figure 3**).

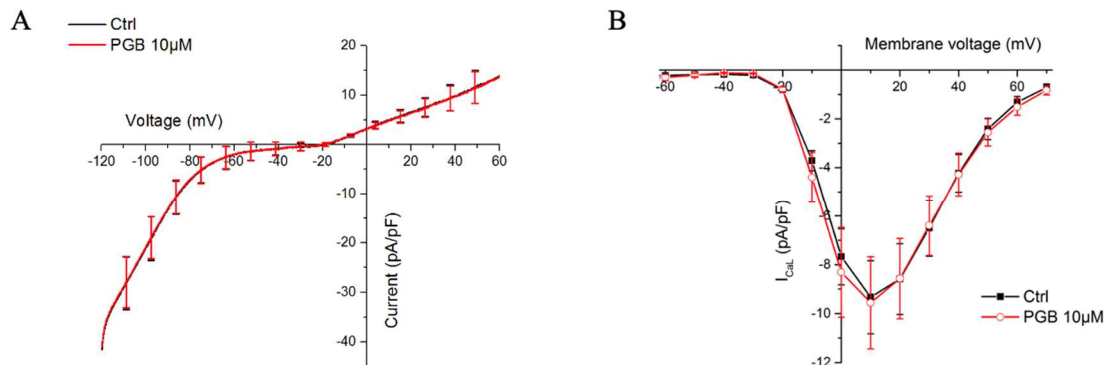


Figure 3 – Results of whole-cell voltage-clamp experiments on rat ventricular cardiomyocytes.

I_{CaL} current-voltage curve in absence (ctrl, black), in the presence of pregabalin (10^{-5} mol/L, PGB, red) in ventricular cardiomyocytes (n=6 cells from 2 rats) (**A**). Background currents in absence (ctrl, black), and in the presence of pregabalin (10^{-5} mol/L, PGB, red) in ventricular cardiomyocytes (n=6 cells from 2 rats) (**B**).

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4. DISCUSSION

This study, the largest case series to date on gabapentinoid-induced non-cardiogenic and cardiogenic peripheral edema, provides an accurate description of their onset modalities. Compared to non-cardiogenic peripheral edema, gabapentinoid-induced acute heart failure had a numerically shorter time to onset (median 17 days, IQR 3-30 vs. median 23 days, IQR 10-54) and a longer time to regression after discontinuation of gabapentinoid (median 30 days, IQR 24-31 vs. median 7 days, IQR 4-10). Whatever the origin of peripheral edema this ADR frequently occurred after a dose escalation (27/45, 60%), pregabalin was most often involved (53/58, 91%), and women (47/58, 81%) and older patients (median 77 years, IQR 57-85) were highly represented.

Gabapentin and pregabalin bind with a strong affinity to $\alpha 2$ - δ subtype 1 which is particularly expressed within $Ca_v 1.2$ of vascular smooth muscle and cardiac tissue [3]. The pore-forming $\alpha 1$ -subunit of $Ca_v 1.2$ is the pharmacological target of CCBs, responsible, according to their tissue selectivity, for vascular ADRs (e.g., vasodilatory peripheral edema) and cardiac ADRs (sinus bradycardia, atrioventricular block, left ventricular dysfunction) [9,12]. These cardiac ADRs, explained by the negative chronotropic, dromotropic and inotropic properties of verapamil and diltiazem [12], are also reported with pregabalin [10,20,21]. Interestingly, quite

306 specific off-target ADRs of CCBs such as parkinsonism [22], gynecomastia [23] and gingival
307 overgrowth [24] are also reported with gabapentinoids [23–25]. Taken together, the safety
308 profile and the pharmacodynamics properties of gabapentinoids on Cav1.2 appear to overlap
309 with those of CCBs. It suggests that the pathophysiological mechanisms of peripheral edema
310 secondary to gabapentinoids may be the same as those induced by CCBs. To test this
311 hypothesis, we investigated the impact of gabapentinoids on the mechanisms involved in non-
312 cardiogenic and cardiogenic peripheral edema induced by CCBs such as altered myogenic
313 tone [9] and reduced Cav1.2 current into cardiomyocytes [12], respectively.

314
315 As the same way as verapamil and nifedipine, gabapentin and pregabalin dramatically
316 decreased the myogenic tone of third-order mesenteric arteries (**Figures 2A and 2B**). Although
317 non-significant, gabapentin and pregabalin also induced a weak vasodilatation in
318 endothelium-denuded vessels (**Figure 2C**). These results are consistent with the observations
319 of Bannister *et al.*, [26] who demonstrated that pregabalin is a weak Cav1.2 pore channel
320 blocker that reduced myogenic tone and caused concentration-dependent vasodilation in
321 pressurized rat cerebral arteries. These elements together with a shared pharmacological
322 target (Cav) support a common pathophysiological mechanism between non-cardiogenic
323 peripheral edema induced by CCBs and gabapentinoids [9]. The corollary being that if the
324 pathophysiological mechanisms of these ADRs are the same as those observed with CCBs,
325 gabapentinoid-induced non-cardiogenic peripheral edema should share similar features such
326 as 1/ diuretic-resistance, 2/ higher prevalence in women and in older subjects and 3/ a
327 concentration-dependent effect [9].

328
329 As gabapentinoid-induced non-cardiogenic peripheral edema may be primarily related to
330 selective arteriolar vasodilatation combined with autoregulation disruption and not to fluid
331 retention, diuretic therapy should not be effective. In this study, resistance to diuretics was
332 found in all four cases in which diuretic efficacy could be assessed, providing further support
333 for vasodilatory edema [9]. Consistently, women and older subjects were highly represented
334 in this study. Although there are more women than men treated with gabapentinoids in France
335 [2], women still appear to be over-represented in this series. One explanation of the effect of
336 sex could be pharmacokinetic. Indeed, pregabalin clearance was 17% lower in female than
337 male [27] and gabapentin peak plasma concentration was about 25% higher for women than
338 for men [28]. In this study, several features argue for a concentration-dependent ADR: 1/ the
339 high proportion of non-cardiogenic peripheral edema that occurred after increasing the dose
340 of gabapentinoid (26/38, 68%) (**Table 1**) and 2/ the absence of positive rechallenge with a
341 reduced dose of pregabalin. In the literature, pregabalin-induced peripheral edema is dose-
342 dependent [4] whereas it is less pronounced for gabapentin [29–31]. Gabapentin has non-linear
343 pharmacokinetics, so the dose-ADR relationship is likely to be attenuated. Indeed, due to its
344 saturable absorption, high plasma exposure values are more difficult to obtain [32]. This
345 difficulty in achieving a high level of exposure to gabapentin could also partly explain a
346 greater propensity of pregabalin to cause non-cardiogenic peripheral edema and acute heart
347 failure. In this study, pregabalin was involved in 44 cases of non-cardiogenic peripheral edema
348 compared to only 5 cases with gabapentin. It could be explained by the greater use of
349 pregabalin in France, with approximately four times more new users between 2006 and 2014
350 compared to gabapentin [2]. Although reporting rates do not reflect the prevalence of ADR,
351 this very uneven distribution may suggest a different risk within this pharmacological class.
352 Indeed, at equivalent doses (1:6 ratio of pregabalin to gabapentin [33]), the literature suggests

353 a greater risk of peripheral edema with pregabalin (10%, between 150 and 300 mg/day) [4]
354 than with gabapentin (7%, at 1200 mg/day) [5].
355

356 A total of 9 cases of cardiac decompensation were included, involving only pregabalin.
357 Consistently, 10 cases of worsening heart failure have been published with pregabalin [10],
358 compared with only one case with gabapentin (in the context of a possible new-onset non-
359 ischemic cardiomyopathy) [34]. Thus, unlike gabapentin, the EMA's assessment of this risk
360 leads a warning for the use of pregabalin in patients who are cardiovascular compromised due
361 to the potential risk of developing/worsening congestive heart failure [35]. One explanation
362 for a potentially different safety profile between gabapentin and pregabalin could be
363 pharmacodynamics. Nevertheless, the only known pharmacological difference between these
364 two drugs is a stronger dose-response effect with pregabalin [32], partly explained by its
365 greater pharmacological potency [33] and its linear pharmacokinetics [32]. This may explain
366 the greater propensity of pregabalin to cause non-cardiogenic peripheral edema and acute
367 heart failure.

368 Some authors have suggested that heart failure exacerbations may be related to the negative
369 inotropic effect of pregabalin, similar to that of cardiotropic CCBs with cardiac tropism [10,11].
370 This hypothesis is supported by preclinical studies showing that pregabalin is a weak $Ca_v1.2$
371 channel pore blocker [36] and that pregabalin can reduce left ventricular ejection fraction in
372 rats [37]. However, we did not find a significant impact of acute application of gabapentinoids
373 at 10 $\mu\text{mol/L}$ on $Ca_v1.2$ currents of rat cardiomyocytes. These results are consistent with the
374 study of Bannister *et al.*, [36] which showed that, although pregabalin is a weak $Ca_v1.2$ channel
375 pore blocker, acute application of pregabalin 100 $\mu\text{mol/L}$ does not directly alter $Ca_v1.2$ current
376 voltage dependence in arterial myocytes of normotensive rats. Conversely, chronic application
377 (24 hours) of pregabalin 100 $\mu\text{mol/L}$ was shown to significantly reduce $Ca_v1.2$ currents in both
378 normotensive and hypertensive rat arterial myocytes through depletion of plasma membrane
379 insertion of $\alpha_2\text{-}\delta_1$ and $Ca_v1.2$ α_1 subunits [36]. These data suggest that gabapentinoid-
380 associated cardiac decompensation could be mediated by a mechanism involving a reduction
381 in trafficking of $Ca_v1.2$ $\alpha_2\text{-}\delta_1$ and α_1 subunits related to chronic exposure rather than a direct
382 pore-blocker effect on the membrane-resident pore channel subunit.
383

384 Alteration of myogenic tone secondary to CCBs is considered to be a $Ca_v1.2$ -dependent
385 mechanism explaining in part the occurrence of vasodilatory edema frequently reported with
386 these drugs [9]. We observed that, as with CCBs, acute exposure to gabapentinoids at 10
387 $\mu\text{mol/L}$ significantly reduced the myogenic tone of third-order mesenteric arteries. The lack of
388 observed impact of gabapentinoids on calcium currents under the same conditions while
389 impairing vascular autoregulation raises two main hypotheses with either an effect of
390 gabapentinoids on pathways upstream of $Ca_v1.2$ activation (e.g., mechanosensitive channels)
391 or downstream (e.g., contractile protein). However, to our knowledge, no studies have focused
392 on the effects of gabapentinoids on channels involved in myogenic tone through
393 depolarization-induced Ca_v activation such as transient-receptor-potential channels (i.e.,
394 TRPC3, TRPC6, TRPM4, TRPP2, TRPV2) or on the contractile machinery [38,39]. Another
395 explanation could be that the effect of gabapentinoids on $Ca_v1.2$ currents is different between
396 those expressed by smooth muscle cells or cardiomyocytes because of a different association
397 of the $\alpha_2\text{-}\delta_1$ subunit with the accessory β protein, known to regulate the voltage dependencies
398 of $Ca_v1.2$ channels (β_2 and β_3 are predominant subunits expressed in ventricular and vascular

399 smooth muscle cells, respectively [40]). Finally, some data suggest that gabapentinoids are
400 potassium channel activators [41].

401
402 The nine patients who experienced pregabalin-related acute heart failure had numerous
403 cardiovascular comorbidities including heart failure (3/9, 33%), hypertension (3/9, 33%) and
404 coronary heart disease (2/9, 22%). These data may suggest that the cardiac effects of
405 gabapentinoids are insufficient, in most instances, to cause cardiac decompensation in subjects
406 with normal heart function. The fact that hypertension was common in patients with
407 gabapentinoid-induced non-cardiogenic peripheral edema (14/41, 34%) could be explained by
408 the increased expression and function of $Ca_v1.2$ channels in hypertension, contributing to
409 increased myogenic tone [42]. Indeed, the effects of pregabalin on reducing the membrane
410 density $\alpha1$ and $\alpha2\text{-}\delta1$ subunits of the $Ca_v1.2$ were significantly greater in hypertensive rats
411 than in normotensive rats [36]. Similarly, the vasodilatory properties of pregabalin [36] and
412 gabapentin [43] are greater in hypertensive rats, supporting the hypothesis that the vasomotor
413 effects of gabapentinoids could be closely related to patients comorbidities, especially
414 hypertension.

415
416 Our results should be viewed in light of the known limitations of the spontaneous reported
417 cases. First, in France, as in other countries, there is under-reporting, estimated at less than
418 10% for serious ADRs, and even lower for non-serious ADRs [44]. Thus, the selective nature
419 of spontaneous reporting may lead to a lack of representativeness. The results of this
420 pharmacovigilance study should therefore be interpreted in the light of the profile of patients
421 treated with gabapentinoids. According to a recent drug utilization study on the pattern of
422 gabapentinoids prescription in France, their use involves a predominantly female population
423 (60%) with a mean age of about 60 years [2]. Therefore, the potential risk factors identified
424 (e.g., age, sex, hypertension) will need to be confirmed by studies specifically designed to meet
425 such objectives. Second, some important data such as details of clinical and imaging signs (e.g.,
426 echocardiography parameters), and time to recovery were missing. Finally, especially for
427 gabapentin-related cases, the small sample size limits the scope of our results.

428

429 **5. CONCLUSION**

430 This nationwide pharmacovigilance study showed that gabapentinoid can induce
431 concentration-dependent peripheral edema of early onset (within the first month) and
432 involving two different clinical entities, either isolated or as part of cardiac decompensation.
433 While the pharmacological substrate of gabapentinoid-induced cardiac decompensation
434 deserves further investigations, the primary mechanism of non-cardiogenic peripheral edema
435 is vasodilatory edema secondary to altered myogenic tone, independent of $Ca_v1.2$ blockade
436 under the experimental conditions tested. Given their high prevalence and rapid favorable
437 course upon discontinuation or dose reduction of gabapentinoids, it would be interesting for
438 clinicians to be alert to this risk and to the management of gabapentinoid-induced peripheral
439 edema in order to limit any risk of prescribing cascade with diuretics.

440 **CONFLICT OF INTEREST STATEMENT**

441 The authors declare that there are no conflicts of interest.

442

443 **AUTHOR CONTRIBUTIONS**

444 **Bérenger Largeau**: conceptualization, methodology, formal analysis, writing original draft;

445 **Romain Bordy**: methodology, software, formal analysis, resources, investigation, writing

446 original draft; **Côme Pasqualin**: methodology, software, formal analysis, resources,

447 investigation, writing original draft; **Pierre Bredeloux**: methodology, formal analysis, writing

448 – review & editing; **Jean-Luc Cracowski**: investigation, writing – review & editing; **Céline**

449 **Lengellé**: investigation, writing – review & editing; **Valérie Gras-Champel**: investigation,

450 writing – review & editing; **Marine Auffret**: investigation, writing – review & editing;

451 **Véronique Maupoil**: conceptualization, supervision, methodology, writing – review &

452 editing; **Annie-Pierre Jonville-Béra**: conceptualization, supervision, methodology,

453 investigation, writing – review & editing

454

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458

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SUPPLEMENTARY MATERIAL

- **eTable S1:** Concomitant drugs known to cause peripheral edema in patients with non-cardiogenic peripheral edema
- **eFigure S1:** Impact of known effects of Lyrica® on the myogenic tone of endothelium-denuded third-order mesenteric arteries
- **eFigure S2:** Impact of actives molecules on the structural and mechanical properties of endothelium-denuded third-order mesenteric arteries

Table 2 – Cases characteristics of pregabalin-induced acute heart failure.

N°	Sex/age	Comorbidities	Dose (mg/d)	TTO (days)	Acute HF features	CV concomitant drugs	Management	Outcome
#1	F/77	None reported	600	30	Global HF	None	Furosemide initiation	3 occurrences of acute HF [‡]
#2	F/90	Aortic valve replacement, pacemaker (AV block)	50	30	Global HF LVEF 42%	Eplerenone Furosemide	- Pregabalin discontinuation - Furosemide titration	6-day regression of edema
#3	F/78	Triple coronary bypass, atrial fibrillation, Hodgkin lymphoma in remission, diabetes	75	5	Global HF Heart rate: 110 bpm	Carvedilol Perindopril Furosemide	- Pregabalin discontinuation - Furosemide titration	Favorable
#4	F/84	Hypertension, chronic kidney disease	300	112	Global HF	Unknown	- Pregabalin discontinuation - Bumetanide initiation	Favorable
#5	F/95	HF, hypertension, asthma on oral corticosteroid	150	17	Sinus bradycardia 45 bpm (holter) increasing with dose pregabalin titration and complicated by an episode of acute HF	Lercanidipine Urapidil Furosemide	Pregabalin discontinuation	Favorable at day 8 after pregabalin discontinuation with heart rate of 60 bpm
#6	F/84	HF (LVEF 35%), pacemaker, atrial fibrillation, hypertension, diabetes	100	80	Global HF Atrial fibrillation BNP 237 ng/L	Digoxin Spironolactone Furosemide	Furosemide titration	Recurrence at 3 months (switch to gabapentin without recurrence at 1-month follow-up)
#7	F/84	Mitral insufficiency, atrial flutter ablation, pacemaker (AV block), pulmonary arterial hypertension	150	3	Global HF TTE: LVEF 50%, dilated right chambers with right ventricular dysfunction NT-proBNP 3511 ng/L	Bisoprolol Perindopril Spironolactone Furosemide	- Pregabalin discontinuation - Furosemide titration	Favorable
#8	M/73	None reported	75	2	Right-sided HF Sinus tachycardia (120 bpm)	None	- Pregabalin discontinuation - Furosemide titration	7-day regression
#9	F/62	HF (hypothesis of a pre-existing HF revealed by pregabalin), coronary artery disease	150	1	Dyspnea evolving for 2 months with worsening NYHA IV and signs of right-sided HF at day 1 Heart rate: 101 bpm TTE: LVEF 20% with very dilated left ventricle BNP 1695 ng/L	None	- Pregabalin discontinuation - Initiation of therapies for HF [§]	Asymptomatic at 2 months with persistent LVEF at 20%

†Recurrence of 3 episodes of congestive heart failure in a few months with no etiology found

§Bisoprolol, sacubitril/valsartan and furosemide initiation

AV, atrioventricular; BNP, brain natriuretic peptide; bpm, beat per minute; CV, cardiovascular; F, female; HF, heart failure; LEVF, left ventricular ejection fraction; M, male; TTE, transthoracic echocardiography; TTO, time to onset

Gabapentinoid-induced peripheral edema and acute heart failure: a translational study combining pharmacovigilance data and in vitro animal experiments

Nationwide study using the French Pharmacovigilance database (1994 to 2020)

Gabapentinoid-induced peripheral edema (n=58)

Ligands of the $\alpha 2$ - δ subunit of voltage-gated calcium channels (Cav)



median 77 years
(IQR 57-85)



81% ♀

Peripheral edema (n=49)

Gabapentin (n=5)

Pregabalin (n=43)

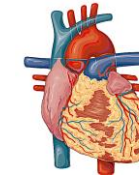
Acute heart failure (n=9)

Pregabalin (n=9)

Median time to onset



23 days (IQR 10-54)



17 days (IQR 3-30)

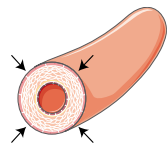
Median time to recovery

7 days (IQR 4-10)

30 days (IQR 24-31)

In vitro animal studies: Are the mechanisms of gabapentinoid-induced edema the same as those of CCBs?

Methods

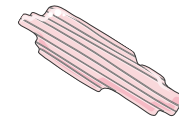


Pressurized 3rd order mesenteric arteries experiments with Halpern's arteriography

Whole-cell voltage-clamp experiments on rat ventricular cardiomyocytes

Results

As the same way as verapamil and nifedipine, gabapentinoids dramatically decreased the myogenic tone



Gabapentinoids (10^{-5} mol/L) in acute superfusion had no significant effect on the L-type calcium current