

1 **Anxiety disorders in patients with noncardiac chest pain: association with health-related**
2 **quality of life and chest pain severity**

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Abstract

25
26 **Background:** Patients with noncardiac chest pain (NCCP) report more severe symptoms
27 and lowered health-related quality of life when they present with comorbid panic disorder (PD).
28 Although generalized anxiety disorder (GAD) is the second most common psychiatric disorder in
29 these patients, its impact on NCCP and health-related quality of life remains understudied. This
30 study describes and prospectively compares patients with NCCP with or without PD or GAD in
31 terms of (1) NCCP severity; and (2) the physical and mental components of health-related quality
32 of life. **Methods:** A total of 915 patients with NCCP were consecutively recruited in two
33 emergency departments. The presence of comorbid PD or GAD was assessed at baseline with the
34 Anxiety Disorder Schedule for DSM-IV. NCCP severity at baseline and at the six-month follow-
35 up was assessed with a structured telephone interview, and the patients completed the 12-item
36 Short-Form Health Survey Version 2 (SF-12v2) to assess health-related quality of life at both time
37 points. **Results:** Average NCCP severity decreased between baseline and the six-month follow-up
38 ($p < .001$) and was higher in the patients with comorbid PD or GAD ($p < .001$) at both time points
39 compared to those with NCCP only. However, average NCCP severity did not differ between
40 patients with PD and those with GAD ($p = 0.901$). The physical component of quality of life
41 improved over time ($p = 0.016$) and was significantly lower in the subset of patients with PD with
42 or without comorbid GAD compared to the other groups ($p < .001$). A significant time x group
43 interaction was found for the mental component of quality of life ($p = 0.0499$). GAD with or
44 without comorbid PD was associated with a lower mental quality of life, and this effect increased
45 at the six-month follow-up. **Conclusions:** Comorbid PD or GAD are prospectively associated with
46 increased chest pain severity and lowered health-related quality of life in patients with NCCP. PD
47 appears to be mainly associated with the physical component of quality of life, while GAD has a

48 greater association with the mental component. Knowledge of these differences could help in the
49 management of patients with NCCP and these comorbidities.

50

51 **Keywords:** Anxiety; chest pain severity; generalized anxiety disorder; noncardiac chest
52 pain; panic disorder; quality of life.

Background

Chest pain is a frequent cause of visits in medical emergency and cardiology settings (1-4). In approximately 50% of cases, patients present with noncardiac chest pain (NCCP), that is, chest pain in the absence of identifiable cardiac etiology (4-9). Even though NCCP is often medically benign, its negative impact on quality of life is long-lasting and comparable to that of cardiac disease (10-15).

NCCP is associated with a high prevalence of psychiatric comorbidity (41-88%) (12, 16-21). The two most common psychiatric disorders in patients with NCCP visiting an emergency department are panic disorder (PD; 14-50%) and generalized anxiety disorder (GAD; 6-33%) (19, 21-27). These psychiatric comorbidities are associated with a less favourable NCCP presentation and have a serious impact on the patient's quality of life (21, 24, 28).

Indeed, in patients with NCCP, PD is associated with increased NCCP frequency and severity and an increased risk of NCCP recurrence (21, 28-31) and lowered health-related quality of life (28-30). However, only the physical component of health-related quality of life of the SF12-v2 appears to be significantly affected in patients with NCCP who present with comorbid PD (28). However, these results need to be interpreted with caution, as some are from cross-sectional studies and have yet to be confirmed prospectively (21, 30).

The impact of comorbid GAD on NCCP and health-related quality of life has yet to be assessed. However, the presence of at least one psychiatric disorder is associated with elevated pain severity and life interference due to NCCP (21). Moreover, GAD has been linked to lowered quality of life in primary care patients, especially with regard to emotional health (32-34). In fact, the

77 quality of life of patients with GAD has also been found to be similar to that of patients with major
78 depressive disorder and chronic medical conditions, such as arthritis (35-37). Based on these data,
79 it is likely that the presence of comorbid GAD negatively affects the presentation of NCCP and its
80 consequences on health-related quality of life.

81
82 Even if PD and GAD are both anxiety disorders, they are independent diagnostic entities
83 that are likely to have a differential impact on NCCP severity and health-related quality of life in
84 patients with NCCP. Currently, it remains unclear how patients with NCCP and PD compare to
85 patients with NCCP and GAD in terms of patterns of symptoms and health-related quality of life.
86 Therefore, the objectives of the present study were to describe and prospectively compare patients
87 with NCCP, with or without comorbid PD or GAD, in terms of (1) NCCP severity; and (2) the
88 physical and mental components of health-related quality of life. Assessing each component of
89 health-related quality of life is essential in order to understand how PD and GAD respectively and
90 differentially affect patients and to guide clinical decision-making.

91
92 Considering that PD is more specifically characterized by interoceptive fear and
93 hypervigilance than GAD (38, 39), it was expected that patients with PD would report greater
94 NCCP severity than those with GAD. Based on the literature, it was also hypothesized that patients
95 with PD would report a lower physical quality of life, while patients with GAD would report a
96 lower mental quality of life. Overall, it was expected that patients with NCCP and comorbid PD or
97 GAD would present with higher NCCP severity and lower health-related quality of life than those
98 with NCCP without comorbid PD or GAD (21).

99

100

101 **Methods**

102 **Design**

103 This prospective cohort study was aimed at describing and comparing patients with NCCP
104 with or without comorbid PD of GAD in terms of NCCP severity and health-related quality of life.
105 Recruitment took place between March 2014 and February 2016 and was part of a larger
106 longitudinal research project. The ethics board at the research centre of the Centre hospitalier affilié
107 universitaire de Lévis of the Centre intégré de santé et de services sociaux de Chaudière-
108 Appalaches approved the research protocol (CER-1314-022).

110 **Participants**

111 Patients were recruited consecutively in two emergency departments (Centre hospitalier
112 affilié universitaire de Lévis and Centre Paul-Gilbert de Charny of the Centre intégré de santé et
113 de services sociaux de Chaudière-Appalaches). To be included in the study, patients had to meet
114 the following criteria: (1) be 18 years old or older; (2) be fluent in English or French; (3) have
115 visited an emergency department for NCCP with a low risk of death or cardiovascular disease,
116 which was defined as chest pain with no objectively identifiable cause (i.e., normal chest
117 radiography, electrocardiogram and serial cardiac enzymes) and a Modified Thrombolysis in
118 Myocardial Infarction score of two or less (40, 41); and (4) have completed the Anxiety Disorders
119 Interview Schedule for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
120 (ADIS-IV) (42). The exclusion criteria were as follows: (1) an unstable or terminal medical
121 condition; and (2) a condition that could invalidate the interview (e.g., an objective medical cause
122 explaining the chest pain, a psychotic state or intoxication, an intellectual disability, or a major
123 cognitive impairment). Patients with missing data on the main study variables were also excluded.

125 **Procedure**

126 Eligible and consenting patients were invited to undergo a telephone interview and to
127 complete a self-report questionnaire on health-related quality of life (by mail or via the PIANO
128 secured Web portal (43) in the month following their initial emergency department visit and again
129 six months later. The interviewers were doctoral students in psychology who had received initial
130 training and subsequent weekly clinical supervision. All the telephone interviews were audio-
131 recorded, and a randomly selected sample of 20% of the recordings was reviewed for inter-rater
132 reliability of the diagnoses of PD and GAD.

133

134 **Measures**

135 **Telephone interview.** A structured interview was used to collect sociodemographic data.
136 Average NCCP severity during the previous six months was assessed using the following question:
137 “On a scale of 0 to 10, where 0 is no pain and 10 is the worst pain imaginable, how would you rate
138 your pain?”. This item was adapted from Eslick and Talley (8) and from Jonsbu, Dammen, Morken,
139 and Martinsen (44). At follow-up, a medical interview was used to document medical diagnoses
140 received after the emergency department visit, and the abbreviated version of the Health Cost
141 Interview (45-48) was used to assess medical visits between the two time points. PD and GAD
142 diagnoses were assessed with the ADIS-IV (42). This instrument has good psychometric properties,
143 most notably, good inter-rater reliability for PD ($k = 0.79-0.82$) in patients visiting an emergency
144 department (19, 22) and for GAD ($k = 0.67$) (42, 49).

145

146 **Self-report questionnaire.** The 12-item Short-Form Health Survey Version 2 (SF-12v2)
147 measures patients’ perception of their health-related quality of life. The instrument enables one to
148 calculate a Physical Component Summary (PCS) score and a Mental Component Summary (MCS)

149 score (50). The PCS concerns physical functioning, role limitations due to physical problems,
150 bodily pain, and general health perceptions, while the MCS concerns vitality, social functioning,
151 role limitations due to emotional problems, and mental health. Both are norm-based scores with a
152 mean of 50 and a range of 0–100. Higher scores indicate better health-related quality of life (50).
153 This scoring method permits comparisons with the 36-item Short-Form Health Survey. The SF-
154 12v2's reliability and validity have been confirmed in a variety of populations (50, 51). The
155 validated French adaptation was used in the present study (52).

156

157 **Statistical analyses**

158 Descriptive statistics were used to describe the sample according to four mutually exclusive
159 groups (patients with NCCP and PD, patients with NCCP and GAD, patients with NCCP and PD
160 and GAD, and patients with NCCP but without PD or GAD). One-way analyses of variance
161 (ANOVAs) were performed to detect differences between the groups according to age, while chi-
162 square tests were used to compare the groups with regard to categorical sociodemographic
163 characteristics. In addition, the participants in the final sample were compared to the patients who
164 did not complete the final evaluation to assess the risk of selection bias. As well, sensitivity
165 analyses were conducted to determine the impact of the missing data.

166

167 Descriptive statistics were used to present average NCCP severity and the scores on both
168 components (PCS and MCS) of health-related quality of life at baseline and the six-month follow-
169 up according to the different groups in the study. Generalized linear mixed models were then
170 conducted to assess time and group effect on average NCCP severity and health-related quality of
171 life. The interaction effect between time and group was assessed for both objectives, and multiple
172 comparisons were conducted to identify significant differences. Effect sizes were estimated by

173 calculating partial eta-squares (η_p^2). Generalized linear mixed models were adjusted for potential
174 confounding variables (i.e., civil status and family income), which had been identified with
175 backward selection. Analyses were also performed to control for medical visits and diagnoses made
176 after the emergency department visit but no significant effect was found for these variables (data
177 not shown). All the analyses were performed with IBM SPSS Statistics, version 23.0 (IBM,
178 Armonk, NY), and SAS 9.4 (SAS Institute Inc., Cary, NC) for Windows.

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Results

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Description of sample

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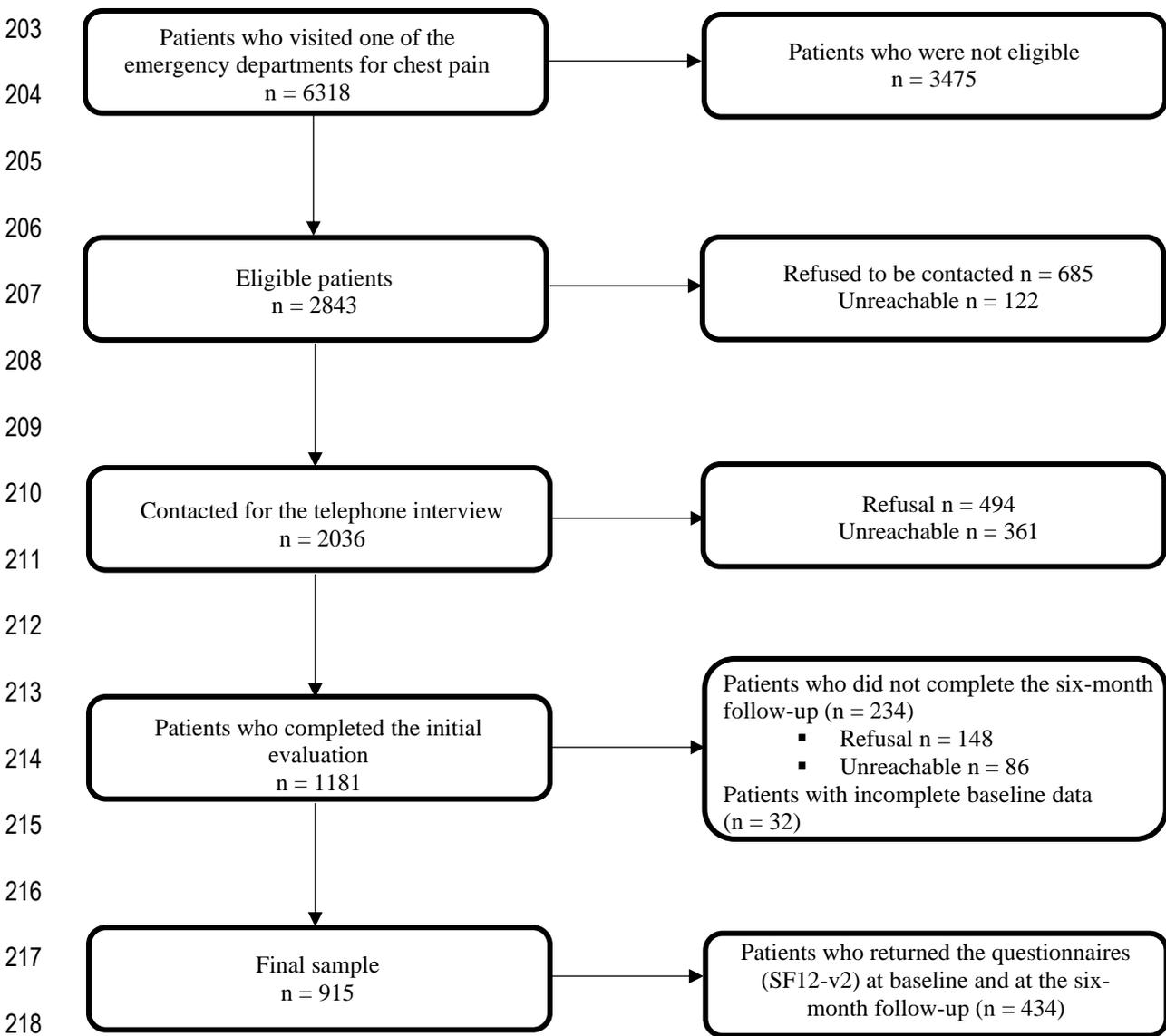
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As shown in Figure 1, 45% (n = 2843) of the patients who visited the emergency departments for chest pain were eligible for the study, and 71.6% (n = 2036) of them consented to be contacted for the telephone interview. Of these patients, 58% (n = 1181) completed the initial evaluation, and of these, 80.2% (n = 947) completed the six-month follow-up. The final sample consisted of 915 patients with complete data from the telephone interviews (ADIS-IV and average NCCP severity). No statistically significant differences in sociodemographic characteristics were found between the groups (PD, GAD, PD and GAD, no PD or GAD; see Table 1). The patients in the final sample were more likely to have a college or university education (54.0% vs. 37.3%; $\chi^2 = 21.623$; $p < 0.001$) and to be married/in a common-law relationship (69.1% vs. 61.8%; $\chi^2 = 4.790$; $p = 0.032$) and less likely to have a low income (58.9% vs. 66.5%; $\chi^2 = 5.032$; $p = 0.027$) than patients who did not complete the final evaluation. The two groups did not differ in terms of average NCCP severity at baseline ($t(1144) = 0.214$; $p = 0.831$). Inter-rater agreement on the ADIS-IV for PD ($k = 0.78$) and GAD ($k = 0.79$) was excellent.

196 A subgroup of 434 patients (47.4%) completed the health-related quality-of-life measure at
 197 both time points (SF12-v2). They were significantly older (57.2 vs. 50.6; $t(913) = -6.527$; $p <$
 198 0.001) and less likely to be working (50.0% vs. 60.3%; $\chi^2 = 7.617$; $p = 0.006$) than those who did
 199 not. The two groups did not differ in terms of average NCCP severity at baseline ($t(913) = -0.689$;
 200 $p = 0.491$) or at the six-month follow-up ($t(913) = 1.098$; $p = 0.272$). However, the patients who
 201 completed the health-related quality-of-life measure only at baseline had a lower mental component
 202 score than the patients in the final sample (44.99 vs. 48.32; $t(732) = 4.218$; $p < 0.001$).



219 Figure 1. *Sample selection process*

220 Table 1
 221 Sociodemographic characteristics ($N = 915$)

	PD ($n = 77$)	GAD ($n = 56$)	PD and GAD ($n = 48$)	No PD or GAD ($n = 734$)	t or chi- square	p
Age, mean (SD)	54.1 (16.6)	48.6 (14.4)	52.3 (14.5)	54.2 (15.7)	2.329	0.073
Female, % (n)	41.6 (32)	58.9 (33)	56.3 (27)	50.8 (373)	1.562	0.197
Married or in a common-law relationship, % (n) ^a	63.6 (49)	66.1 (37)	64.6 (31)	70.3 (515)	0.745	0.526
Family income (\leq \$59,999), % (n) ^b	68.0 (51)	58.9 (33)	58.7 (27)	55.3 (384)	1.540	0.203
Education (college/ university), % (n) ^a	54.5 (42)	57.1 (32)	56.3 (27)	53.6 (393)	0.124	0.946
Employed, % (n) ^c	53.2 (41)	60.7 (34)	54.2 (26)	55.5 (406)	0.269	0.848

222 PD: Panic disorder; GAD: Generalized anxiety disorder; SD: Standard deviation; ^a One missing
 223 data; ^b 34 missing data; ^c Two missing data.

224
 225
 226 **NCCP severity**

227 As shown in Table 2, average NCCP severity significantly decreased from baseline to the
 228 six-month follow-up ($F(1, 911) = 176.60; p < .001; \eta_p^2 = 0.162$) for all the patients, regardless of
 229 the group. Average NCCP severity also differed significantly according to the group ($F(3, 911) =$
 230 $7.29; p < .001; \eta_p^2 = 0.029$). More specifically, average NCCP severity was higher in the patients
 231 with PD or GAD than in those without these comorbidities. The patients with PD did not differ
 232 from those with GAD ($t(911) = 0.12; p = 0.901$). The interaction between time and group was not

233 significant ($F(3, 911) = 1.50; p = 0.212; \eta_p^2 = 0.005$). Descriptive statistics on average NCCP
 234 severity are provided in Supplementary Table 1.

235

236 Table 2

237 *Panic disorder, generalized anxiety disorder and average NCCP severity (N = 915)*

	β (SD)	p
Time effect		
6-month follow-up vs. baseline	-2.59 (0.19)	<.001*
Group effect		
	-	<.001*
PD vs. no PD or GAD	0.68 (0.23)	0.003*
GAD vs. no PD or GAD	0.64 (0.26)	0.015*
PD and GAD vs. no PD or GAD	0.89 (0.28)	0.002*
PD vs. GAD	0.04 (0.33)	0.901
PD and GAD vs. PD	0.21 (0.35)	0.540
PD and GAD vs. GAD	0.25 (0.37)	0.494
Time x group effect	-	0.212

238 SD: Standard deviation; PD: Panic disorder; GAD: Generalized anxiety disorder;

239 * $p < 0.05$.

240

241 **Health-related quality of life**

242 As shown in Table 3, the PCS scores improved significantly over time for all the patients
 243 ($F(1, 405) = 5.90; p = 0.016; \eta_p^2 = 0.014$) and differed between the groups ($F(3, 405) = 7.88; p$
 244 $<.001; \eta_p^2 = 0.260$). More specifically, the PCS scores were significantly lower in both groups of
 245 patients with PD than those of the other two groups (GAD and no PD or GAD). The time effect

246 was independent of the group effect ($F(3, 405) = 0.65; p = 0.585; \eta_p^2 = 0.005$). Descriptive statistics
 247 of the PCS scores are provided in Supplementary Table 2.

248
 249 Table 3
 250 *Panic disorder, generalized anxiety disorder and the Physical Component Summary (PCS) score*
 251 *(N = 434)^a*

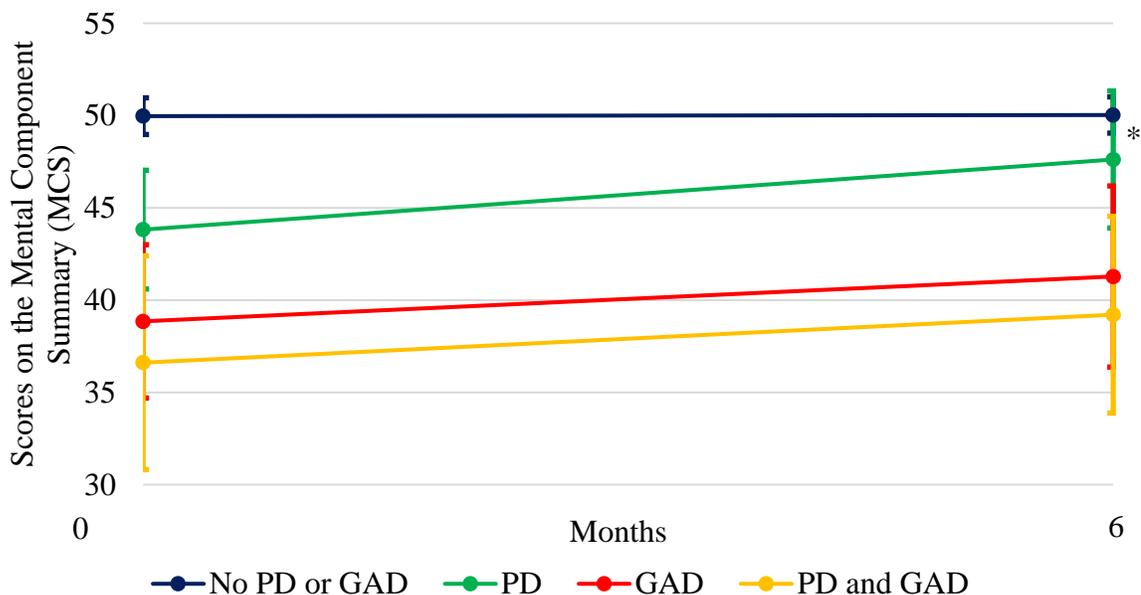
	β (SD)	p
Time effect		
6-month follow-up vs. baseline	1.77 (0.73)	0.016*
Group effect	-	<.001*
PD vs. no PD or GAD	-6.24 (1.46)	<.001*
GAD vs. no PD or GAD	0.64 (1.79)	0.720
PD and GAD vs. no PD or GAD	-5.66 (2.31)	0.015*
PD vs. GAD	-6.89 (2.20)	0.002*
PD and GAD vs. PD	-0.58 (2.64)	0.826
PD and GAD vs. GAD	-6.30 (2.83)	0.027*
Time x group effect	-	0.585

252 ^a Adjusted for civil status and family income; SD: Standard deviation; PD: Panic
 253 disorder; GAD: Generalized anxiety disorder; * $p < 0.05$.

254
 255 There was a significant group x time interaction for the MCS ($F(3, 428) = 2.63; p = 0.0499$
 256 $\eta_p^2 = 0.018$). At baseline, the patients with no comorbidities had a significantly higher MCS score
 257 than those in the three other groups with comorbidities. Furthermore, the patients with GAD, with
 258 or without comorbid PD, had a lower MCS score than those with PD and no GAD. At the six-
 259 month follow-up, both groups of patients with GAD still had a significantly lower MCS score than
 260 those with no comorbidities. They also had a lower MCS score than the patients with PD only, this

261 effect being greater at the follow-up than at baseline. Finally, the patients with PD and those with
 262 no comorbidities did not differ significantly from each other at this time point compared to baseline.
 263 See Figure 2 for further details. Descriptive statistics of the MCS scores are provided in
 264 Supplementary Table 2.

265
 266



267 Figure 2. Interaction effect of the Mental Component Summary (MCS) score

268 * Significant time x group interaction effect after adjustment for difference in civil status.
 269

270 Discussion

271 The first objective of this study was to describe and compare NCCP severity in patients
 272 with or without comorbid PD or GAD at baseline and at the six-month follow-up. Overall, the
 273 patients still reported episodes of NCCP at the six-month follow-up, which corroborates the well-
 274 documented persistence of these symptoms in the literature (1, 7, 30, 53). A time effect of moderate
 275 size was found for all the patients ($\eta_p^2 = 0.162$), as average NCCP severity tended to decrease from
 276 baseline to the six-month follow-up, which supports the results of Dammen and colleagues (29).
 277 This improvement in symptom severity in the absence of any specific intervention could be

278 explained by some form of reassurance obtained during the emergency department visit. Still,
279 average NCCP severity was higher in the patients with comorbid PD or GAD at both time points
280 ($\eta_p^2 = 0.029$). This result is in line with those indicating that comorbid psychiatric disorders are
281 associated with increased NCCP severity (21, 28-31). Surprisingly, no significant differences were
282 found between the patients with PD and those with GAD in terms of average NCCP severity. This
283 does not support the primary hypothesis, namely, that patients with PD would report more severe
284 NCCP. The greater-than-expected association of GAD with NCCP severity may be explained by
285 intolerance to uncertainty. The impact of medical uncertainty associated with diagnoses of
286 exclusion, such as NCCP (2, 24), might be underestimated in patients with GAD, who are already
287 well-known for their intolerance to uncertainty. Indeed, intolerance to uncertainty is associated
288 with pain severity through the catastrophizing of pain in patients with chronic pain (54, 55).
289 Therefore, it is possible that the medical uncertainty associated with NCCP, coupled with the
290 intolerance to uncertainty of patients with GAD, increases anxiety significantly, leading these
291 patients to catastrophic interpretations and an amplified perception of bodily symptoms, as
292 experienced by patients with PD as well. Moreover, tolerance of negative emotional states could
293 also explain the strong association of GAD with NCCP severity. Indeed, tolerance of negative
294 emotional states has been independently associated with chronic pain severity, while being closely
295 linked to avoidance of internal experiences and difficulties in emotion regulation found in patients
296 with GAD (56, 57).

297
298 Another surprising result is that the presence of two comorbid anxiety disorders (PD and
299 GAD) was not associated with greater NCCP severity than the presence of a single disorder (PD
300 or GAD). This result is not consistent with that of White and colleagues (21), namely, that patients

301 with more anxiety disorders report greater pain severity. The absence of a cumulative effect of PD
302 and GAD suggest that these disorders affect NCCP through the same mechanisms.

303
304 The second objective of this study was to describe and compare health-related quality of
305 life in patients with NCCP, with or without comorbid PD or GAD, at baseline and at six-month
306 follow-up.

307
308 Physical quality of life improved over time for all the patients, regardless of the group,
309 which is consistent with previous studies of patients with NCCP with or without PD (8, 29).
310 However, because of the negligible effect size ($\eta_p^2 = 0.014$) obtained, the observed statistically
311 significant difference may not be clinically meaningful. As well, the presence of PD, with or
312 without comorbid GAD, was significantly and meaningfully ($\eta_p^2 = 0.260$) associated with a
313 diminished physical quality of life, which is in line with the primary hypothesis and results of Bull
314 Bringager and colleagues (28). The results also show a lower physical quality of life in the patients
315 with PD than in those with GAD. This observation corroborates reports that PD is the anxiety
316 disorder that affects the physical functioning subscale the most in patients without NCCP (32, 34).

317
318 As regards mental quality of life, a time x group interaction effect of small size ($\eta_p^2 = 0.018$)
319 was obtained. Indeed, the presence of GAD, alone or in comorbidity with PD, was significantly
320 associated with a lower mental quality of life than PD alone, this effect being greater at the follow-
321 up than at baseline. These results support the primary hypothesis of a greater association of GAD
322 with lowered MCS scores and are also consistent with the positive association found by White and
323 colleagues (21) between the number of disorders and the impairment reported by patients.
324 Moreover, the absence of a significant difference between the patients with PD and those with no

325 comorbidities at the six-month follow-up also suggests that PD has a significant but limited impact
326 on mental quality of life.

327
328 In summary, this study highlights the considerable negative impacts of GAD on NCCP and
329 health-related quality of life of patients, which confirms that they represent a particularly
330 vulnerable subgroup of patients, just like patients with NCCP and PD. Therefore, GAD should also
331 be identified early in the process so that patients can benefit from appropriate treatment or referral.
332 Some brief self-report instruments have been shown to be useful in screening for PD in patients
333 with NCCP, such as the Revised Panic Screening Score (58, 59) and the Psychiatric Diagnostic
334 Screening Questionnaire (60, 61). A similarly brief instrument, such as the GAD-2, could be used
335 to screen for GAD during a patient's initial visit for NCCP (62). This study also highlights the
336 differential impact of PD and GAD on health-related quality of life, which reinforces the relevance
337 of assessing specific domains of quality of life because they appear to vary across anxiety disorders.
338 These findings shed light on specific needs of these patients that could be targeted in order to
339 improve their quality of life.

340
341 Currently, psychological interventions for NCCP are offered to patients to prevent pain
342 from becoming chronic (63). While a Cochrane review recommends cognitive-behavioural therapy
343 for these patients, its benefits appear to be modest and largely limited to the first three months after
344 the intervention (63). As for offering psychological treatment for the comorbid anxiety disorder
345 itself in patients with NCCP, studies show that cognitive-behavioural therapy is effective in
346 reducing PD severity, but little is known about its impact on NCCP (45, 64-66). With regard to
347 GAD, no study to date has assessed the effectiveness of cognitive-behavioural therapy in patients

348 with NCCP. Based on the findings of the present study, the current intervention for patients with
349 NCCP only is likely to be insufficient to treat patients with NCCP and comorbid PD or GAD.

350
351 The primary strengths of this study are its prospective nature, the consecutive sampling,
352 the high retention rate at the six-month follow-up (80.2%) and the large sample size, especially for
353 the assessment of NCCP severity, thanks to the high measure completion rate. Another strength of
354 this study is the application of a standardized psychiatric interview and the high diagnostic
355 reliability achieved. Moreover, the use of generalized linear mixed models helped minimize
356 potential type I errors, as dependence between time points for each patient was considered. Finally,
357 this study was able to address a current knowledge gap by prospectively assessing NCCP severity
358 and health-related quality of life in patients with NCCP and GAD. It also prospectively compared
359 NCCP severity and health-related quality of life according to the patients' anxiety disorder profile.

360
361 This study has some limitations that should be taken into consideration when interpreting
362 the results. First, one should bear in mind that the presence of PD and GAD was not reassessed at
363 follow-up. Considering the chronic course of these disorders over time (31, 67), a potential impact
364 on the results appears unlikely. Second, certain analyses were conducted on small subgroups of
365 patients, and a lack of statistical power could explain some of the negative results. However, group
366 effects were obtained by combining certain subgroups, which made it possible to draw relevant
367 conclusions. Third, significant differences between patients in the final sample and those who were
368 not included in the study have potential implications for the findings' internal validity and
369 generalizability. The patients in the final sample (N= 915) for the first objective (NCCP severity)
370 were more educated, more likely to be married or in a common-law relationship, and had a higher
371 family income. One could argue that the patients in the final sample might have had a better

372 understanding of research and better health, which might have resulted in an underestimation of
373 NCCP severity in the present study. The patients in the final sample (N= 434) for the second
374 objective (health-related quality of life) were older and less likely to be working than those who
375 did not complete the measure at either time point. The age difference may mean that the PCS scores
376 were lower than they should have been, while the MCS scores were higher than they should have
377 been (34). The difference regarding employment status may have led to a lowered health-related
378 quality of life in the study since the patients who were not working might have had poorer health.

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Conclusions

381 Like PD, GAD is prospectively associated with higher NCCP severity and lowered health-
382 related quality of life. PD appears to be more closely associated with a decrease in the physical
383 component of quality of life, while GAD is more strongly associated with impairment in the mental
384 quality of life. These results highlight the fact that patients with PD or GAD represent a particularly
385 vulnerable subgroup of patients with NCCP. Considering the specific and distinct effect of these
386 disorders on patients could help improve care for this subset of patients with NCCP.

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Abbreviations

389 ADIS-IV: Anxiety Disorders Interview Schedule Fourth Edition; ANOVA: Analyses of
390 variance; GAD: Generalized anxiety disorder; MCS: Mental Component Summary; NCCP:
391 Noncardiac chest pain; η_p^2 : Partial eta-squared (effect size); PD: Panic disorder; PCS: Physical
392 Component Summary; SD: Standard deviation; SF-12v2: 12-item Short-Form Health Survey
393 Version 2.

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Declarations

Ethics approval and consent to participate

The Centre intégré de santé et de services sociaux de Chaudière-Appalaches ethics board authorized this research protocol (CER-1314-022).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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420 **Authors' contributions**

421 The main author, SH, participated to the development of the study, recruitment of patients, data
422 collection, data analysis and wrote all sections of the article. All stages of this study were conducted
423 under the careful guidance of GFB. ST contributed to the study design and analysis. PA, RF, CD,
424 and ID meaningfully contributed to the design of the study and data collection and reviewed the
425 manuscript critically for important intellectual content. All authors read and approved the final
426 manuscript.

427

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Supplementary data

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448 **Supplementary Table 1**449 *Average NCCP severity (N = 915)*

	PD (n = 77)	GAD (n = 56)	PD and GAD (n = 48)	No PD or GAD (n = 734)
Baseline	5.32 ± 2.14	5.61 ± 2.31	5.94 ± 2.14	5.07 ± 2.43
Six-month follow-up	3.31 ± 2.69	2.95 ± 2.91	3.13 ± 2.68	2.20 ± 2.66

450 PD: Panic disorder; GAD: Generalized anxiety disorder.

451

452 **Supplementary Table 2**453 *SF-12v2 Physical and Mental Component Summary of health-related quality of life (N = 434)**

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	PD (n = 38)	GAD (n = 24)	PD and GAD (n = 16)	No PD or GAD (n = 356)	
PCS	Baseline	38.58 ± 12.15	45.82 ± 8.28	40.25 ± 8.28	46.59 ± 9.09
	Six-month follow-up	41.22 ± 11.51	48.14 ± 8.83	41.36 ± 10.47	47.51 ± 9.32
MCS	Baseline	43.82 ± 9.82	38.85 ± 9.88	36.61 ± 10.93	49.97 ± 9.56
	Six-month follow-up	47.62 ± 11.33	41.28 ± 11.67	39.21 ± 10.05	50.03 ± 9.22

455 * A higher score indicates a higher health-related quality of life; PCS: Physical Component Summary;
456 MCS: Mental Component Summary; PD: Panic disorder, GAD: Generalized anxiety disorder.

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References

- 460
461 1. Eslick GD, Talley NJ. Non-cardiac chest pain: Predictors of health care seeking, the types of
462 health care professional consulted, work absenteeism and interruption of daily activities. *Aliment*
463 *Pharmacol Ther.* 2004;20(8):909-15.
- 464 2. Mayou R. Chest pain, palpitations and panic. *J Psychosom Res.* 1998;44(1):53-70.
- 465 3. McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2002 emergency
466 department summary. *Adv Data.* 2004;340(340):1-34.
- 467 4. Pope JH, Ruthazer R, Beshansky JR, Griffith JL, Selker HP. Clinical features of emergency
468 department patients presenting with symptoms suggestive of acute cardiac ischemia: A multicenter
469 study. *J Thromb thrombolysis.* 1998;6(1):63-74.
- 470 5. Bahr RD. Chest pain centers: Moving toward proactive acute coronary care. *Int J Cardiol.*
471 2000;72(2):101-10.
- 472 6. Christenson J, Innes G, McKnight D, Boychuk B, Grafstein E, Thompson CR, et al. Safety and
473 efficiency of emergency department assessment of chest discomfort. *CMAJ.* 2004;170(12):1803-
474 7.
- 475 7. Dumville JC, MacPherson H, Griffith K, Miles JN, Lewin RJ. Non-cardiac chest pain: A
476 retrospective cohort study of patients who attended a Rapid Access Chest Pain Clinic. *Fam Pract.*
477 2007;24(2):152-7.
- 478 8. Eslick GD, Talley NJ. Natural history and predictors of outcome for non-cardiac chest pain: A
479 prospective 4-year cohort study. *Neurogastroenterol Motil.* 2008;20(9):989-97.
- 480 9. Fass R, Achem SR. Noncardiac chest pain: Diagnostic evaluation. *Dis Esophagus.*
481 2012;25(2):89-101.
- 482 10. Chambers J, Bass C. Chest pain with normal coronary anatomy: A review of natural history
483 and possible etiologic factors. *Prog Cardiovasc Dis.* 1990;33(3):161-84.

- 484 11. Cheung TK, Hou X, Lam KF, Chen J, Wong WM, Cha H, et al. Quality of life and
485 psychological impact in patients with noncardiac chest pain. *J Clin Gastroenterol.* 2009;43(1):13-
486 8.
- 487 12. Eifert GH, Hodson SE, Tracey DR, Seville JL, Gunawardane K. Heart-focused anxiety, illness
488 beliefs, and behavioral impairment: Comparing healthy heart-anxious patients with cardiac and
489 surgical inpatients. *J Behav Med.* 1996;19(4):385-99.
- 490 13. Fagring AJ, Gaston-Johansson F, Kjellgren KI, Welin C. Unexplained chest pain in relation to
491 psychosocial factors and health-related quality of life in men and women. *Eur J Cardiovasc Nurs.*
492 2007;6(4):329-36.
- 493 14. Fagring AJ, Kjellgren KI, Rosengren A, Lissner L, Manhem K, Welin C. Depression, anxiety,
494 stress, social interaction and health-related quality of life in men and women with unexplained
495 chest pain. *BMC Public Health.* 2008;8(1):165.
- 496 15. Wong WM, Lai KC, Lau CP, Hu WH, Chen WH, Wong BC, et al. Upper gastrointestinal
497 evaluation of Chinese patients with non-cardiac chest pain. *Aliment Pharmacol Ther.*
498 2002;16(3):465-71.
- 499 16. Alexander PJ, Prabhu SG, Krishnamoorthy ES, Halkatti PC. Mental disorders in patients with
500 noncardiac chest pain. *Acta Psychiatr Scand.* 1994;89(5):291-3.
- 501 17. Bass C, Wade C. Chest pain with normal coronary arteries: A comparative study of psychiatric
502 and social morbidity. *Psychol Med.* 1984;14(1):51-61.
- 503 18. Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal
504 coronary arteries: Clinical and psychosocial state 12 months after angiography. *Br Med J.*
505 1983;287(6404):1505-8.
- 506 19. Foldes-Busque G, Marchand A, Chauny JM, Poitras J, Diodati J, Denis I, et al. Unexplained
507 chest pain in the ED: Could it be panic? *Am J Emerg Med.* 2011;29(7):743-51.

- 508 20. Hadlandsmyth K, White KS, Krone RJ. Quality of life in patients with non-CAD chest pain:
509 Associations to fear of pain and psychiatric disorder severity. *J Clin Psychol Med Settings*.
510 2013;20(3):284-93.
- 511 21. White KS, Raffa SD, Jakle KR, Stoddard JA, Barlow DH, Brown TA, et al. Morbidity of DSM-
512 IV Axis I disorders in patients with noncardiac chest pain: Psychiatric morbidity linked with
513 increased pain and health care utilization. *J Consult Clin Psychol*. 2008;76(3):422-30.
- 514 22. Fleet RP, Dupuis G, Marchand A, Burelle D, Arsenault A, Beitman BD. Panic disorder in
515 emergency department chest pain patients: Prevalence, comorbidity, suicidal ideation, and
516 physician recognition. *Am J Med*. 1996;101(4):371-80.
- 517 23. Srinivasan K, Joseph W. A study of lifetime prevalence of anxiety and depressive disorders in
518 patients presenting with chest pain to emergency medicine. *Gen Hosp Psychiatry*. 2004;26(6): 470-
519 4.
- 520 24. White KS. Assessment and treatment of psychological causes of chest pain. *Med Clin North*
521 *Am*. 2010;94(2):291-318.
- 522 25. Worthington JJ 3rd, Pollack MH, Otto MW, Gould RA, Sabatino SA, Goldman L, et al. Panic
523 disorder in emergency ward patients with chest pain. *J Nerv Ment Dis*. 1997;185(4):274-6.
- 524 26. Wulsin L, Liu T, Storrow A, Evans S, Dewan N, Hamilton C. A randomized, controlled trial
525 of panic disorder treatment initiation in an emergency department chest pain center. *Ann Emerg*
526 *Med*. 2002;39(2):139-43.
- 527 27. Yingling KW, Wulsin LR, Arnold LM, Rouan GW. Estimated prevalences of panic disorder
528 and depression among consecutive patients seen in an emergency department with acute chest pain.
529 *J Gen Inter Med*. 1993;8(5):231-5.

- 530 28. Bull Bringager C, Arnesen H, Friis S, Husebye T, Dammen T. A long-term follow-up study of
531 chest pain patients: Effect of panic disorder on mortality, morbidity, and quality of life. *Cardiology*.
532 2008;110(1):8-14.
- 533 29. Dammen T, Bringager CB, Arnesen H, Ekeberg O, Friis S. A 1-year follow-up study of chest-
534 pain patients with and without panic disorder. *Gen Hosp Psychiatry*. 2006;28(6):516-24.
- 535 30. Dammen T, Ekeberg O, Arnesen H, Friis S. Health-related quality of life in non-cardiac chest
536 pain patients with and without panic disorder. *Int J Psychiatry Med*. 2008;38(3):271-86.
- 537 31. Fleet RP, Lavoie KL, Martel JP, Dupuis G, Marchand A, Beitman BD. Two-year follow-up
538 status of emergency department patients with chest pain: Was it panic disorder? *CJEM*.
539 2003;5(4):247-54.
- 540 32. Luo N, Fones CS, Thumboo J, Li SC. Factors influencing health-related quality of life of Asians
541 with anxiety disorders in Singapore. *Qual Life Res*. 2004;13(2):557-65.
- 542 33. Mendlowicz MV, Stein MB. Quality of life in individuals with anxiety disorders. *Am J*
543 *Psychiatry*. 2000;157(5):669-82.
- 544 34. Schonfeld WH, Verboncoeur CJ, Fifer SK, Lipschutz RC, Lubeck DP, Buesching DP. The
545 functioning and well-being of patients with unrecognized anxiety disorders and major depressive
546 disorder. *J Affect Disord*. 1997;43(2):105-19.
- 547 35. Grant BF, Hasin DS, Stinson FS, Dawson DA, Patricia Chou S, June Ruan W, et al. Co-
548 occurrence of 12-month mood and anxiety disorders and personality disorders in the US: Results
549 from the national epidemiologic survey on alcohol and related conditions. *J Psychiatr Res*.
550 2005;39(1):1-9.
- 551 36. Murray CJ, Lopez AD. *The Global Burden of Disease: A comprehensive assessment of*
552 *mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*.
553 Cambridge, MA: Harvard University Press; 1996.

- 554 37. Wittchen HU. Generalized anxiety disorder: Prevalence, burden, and cost to society. *Depress*
555 *Anxiety*. 2002;16(4):162-71.
- 556 38. Eifert GH, Zvolensky MJ, Lejuez CW. Heart-focused anxiety and chest pain: A conceptual and
557 clinical review. *Clin Psychol Sci Pract*. 2000;7(4):403-17.
- 558 39. Olatunji BO, Deacon BJ, Abramowitz JS, Valentiner DP. Body vigilance in nonclinical and
559 anxiety disorder samples: Structure, correlates, and prediction of health concerns. *Behav Ther*.
560 2007;38(4):392-401.
- 561 40. Hess EP, Perry JJ, Calder LA, Thiruganasambandamoorthy V, Body R, Jaffe A, et al.
562 Prospective validation of a modified thrombolysis in myocardial infarction risk score in emergency
563 department patients with chest pain and possible acute coronary syndrome. *Acad Emerg Med*.
564 2010;17(4):368-75.
- 565 41. Jaffery Z, Hudson MP, Jacobsen G, Nowak R, McCord J. Modified thrombolysis in myocardial
566 infarction (TIMI) risk score to risk stratify patients in the emergency department with possible
567 acute coronary syndrome. *J Thromb Thrombolysis*. 2007;24(2):137-44.
- 568 42. DiNardo PA, Brown TA, Barlow DH. Anxiety Disorders Interview Schedule for DSM-IV
569 (ADIS-IV): Lifetime Version (ADIS-IV-L). San Antonio, TX: Graywind Publications; 1994.
- 570 43. Vézina J, Camateros C. La plate-forme PIANO afin de rejoindre plus facilement les proches
571 aidants isolés. *Vie et vieillissement*. 2012;9(4):54-6.
- 572 44. Jonsbu E, Dammen T, Morken G, Martinsen EW. Patients with noncardiac chest pain and
573 benign palpitations referred for cardiac outpatient investigation: a 6-month follow-up. *Gen Hosp*
574 *Psychiatry*. 2010;32(4):406-12.
- 575 45. Poirier-Bisson J, Marchand A, Pelland ME, Lessard MJ, Dupuis G, Fleet R, et al. Incremental
576 cost-effectiveness of pharmacotherapy and two brief cognitive-behavioral therapies compared with
577 usual care for panic disorder and noncardiac chest pain. *J Nerv Ment Dis*. 2013;201(9):753-9.

- 578 46. Roberge P, Marchand A, Reinharz D, Savard P. Cognitive-behavioral treatment for panic
579 disorder with agoraphobia: A randomized, controlled trial and cost-effectiveness analysis. *Behav*
580 *Modif.* 2008;32(3):333-51.
- 581 47. Roberge P, Marchand A, Reinharz D, Cloutier K, Mainguy N, Miller JM, et al. Healthcare
582 utilization following cognitive-behavioral treatment for panic disorder with agoraphobia. *Cogn*
583 *Behav Ther.* 2005;34(2):79-88.
- 584 48. Roberge P, Marchand A, Cloutier K, Reinharz D. Entrevue sur les coûts de la santé. Montréal,
585 Québec: Université du Québec à Montréal; 2000.
- 586 49. Brown TA, Di Nardo PA, Lehman CL, Campbell LA. Reliability of DSM-IV anxiety and mood
587 disorders: Implications for the classification of emotional disorders. *J Abnorm Psychol.*
588 2001;110(1):49-58.
- 589 50. Montazeri A, Vahdaninia M, Mousavi SJ, Asadi-Lari M, Omidvari S, Tavousi M. The 12-item
590 medical outcomes study short form health survey version 2.0 (SF-12v2): A population-based
591 validation study from Tehran, Iran. *Health Qual Life Outcomes.* 2011;9(1):12.
- 592 51. Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the
593 medical expenditure panel survey. *Qual Life Res.* 2009;18(6):727-35.
- 594 52. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation
595 of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the
596 IQOLA project. *J Clin Epidemiol.* 1998;51(11):1171-8.
- 597 53. Glombiewski JA, Rief W, Bosner S, Keller H, Martin A, Donner-Banzhoff N. The course of
598 nonspecific chest pain in primary care: Symptom persistence and health care usage. *Arch Intern*
599 *Med.* 2010;170(3):251-5.

600 54. Hadjistavropoulos HD, Hadjistavropoulos T. The relevance of health anxiety to chronic pain:
601 Research findings and recommendations for assessment and treatment. *Curr Pain Headache Rep.*
602 2003;7(2):98-104.

603 55. Trépanier A, Cormier S. L'effet de l'intolérance à l'incertitude sur le fonctionnement des
604 individus souffrant de douleur chronique. Montréal, Québec: Congrès de la Société Québécoise
605 pour la Recherche en Psychologie; 2017.

606 56. Dugas MJ, Marchand A, Ladouceur R. Further validation of a cognitive-behavioral model of
607 generalized anxiety disorder: Diagnostic and symptom specificity. *J Anxiety Disord.*
608 2005;19(3):329-43.

609 57. Trépanier A, Foldes-Busque G. Tolérance à la détresse et douleur chronique. Québec:
610 Université Laval; 2021.

611 58. Foldes-Busque G, Denis I, Poitras J, Fleet RP, Archambault P, Dionne CE. The Revised-Panic
612 Screening Score for emergency department patients with noncardiac chest pain. *Health Psychol.*
613 2018;37(9):828-38.

614 59. Foldes-Busque G, Fleet R, Poitras J, Chauny JM, Belleville G, Denis I, et al. Preliminary
615 investigation of the Panic Screening Score for emergency department patients with unexplained
616 chest pain. *Acad Emerg Med.* 2011;18(3):322-5.

617 60. Sung SC, Ma J, Earnest A, Rush AJ, Lim LEC, Ong MEH. Screening for panic-related anxiety
618 in emergency department patients with cardiopulmonary complaints: A comparison of two self-
619 report instruments. *Psychiatry Res.* 2018;263:7-14.

620 61. Zimmerman M, Mattia JI. The Psychiatric Diagnostic Screening Questionnaire: Development,
621 reliability and validity. *Compr Psychiatry.* 2001;42(3):175-89.

622 62. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-
623 7 and GAD-2: A systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry*.
624 2016;39:24-31.

625 63. Kisely SR, Campbell LA, Yelland MJ, Paydar A. Psychological interventions for symptomatic
626 management of non-specific chest pain in patients with normal coronary anatomy. *Cochrane*
627 *Database Syst Rev*. 2015(6):Cd004101.

628 64. Foldes-Busque G, Hamel S, Belleville G, Fleet R, Poitras J, Chauny JM, et al. Factors
629 associated with pain level in non-cardiac chest pain patients with comorbid panic disorder.
630 *Biopsychosoc Med*. 2016;10(1):30.

631 65. Lessard MJ, Marchand A, Pelland ME, Belleville G, Vadeboncoeur A, Chauny JM, et al.
632 Comparing two brief psychological interventions to usual care in panic disorder patients presenting
633 to the emergency department with chest pain. *Behav Cogn Psychother*. 2012;40(2):129-47.

634 66. van Beek MH, Oude Voshaar RC, Beek AM, van Zijderveld GA, Visser S, Speckens AE, et
635 al. A brief cognitive-behavioral intervention for treating depression and panic disorder in patients
636 with noncardiac chest pain: A 24-week randomized controlled trial. *Depress Anxiety*. 2013;30(7):
637 670-8.

638 67. Yonkers KA, Bruce SE, Dyck IR, Keller MB. Chronicity, relapse, and illness-course of panic
639 disorder, social phobia, and generalized anxiety disorder: Findings in men and women from 8 years
640 of follow-up. *Depress Anxiety*. 2003;17(3):173-9.