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# Pain related factors in newly diagnosed Generalized Anxiety Disorder patients

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**Purpose.** To determine the prevalence and factors associated to painful physical symptoms (PPS), pain as presentation, and neuropathic pain in generalized anxiety disorder (GAD) at primary care setting.

**Methods.** Multicenter, cross-sectional, observational study conducted on 404 Spanish primary care centers with 2,232 patients. Data was collected at once and included demographic data, main reason for visit, psychiatric and medical illnesses, healthcare resource utilization. Validated scales used for GAD diagnosis were the MINI interview and GAD-7 scale. Depression was measured with the Hospital Anxiety and Depression Scale, sleep disturbances with the MOS-Sleep Scale, and pain with the Brief Pain Inventory, short version.

**Results.** Most patients reported PPS (93.5%). The main associated factors of PPS were consultation for gastrointestinal disease (OR=3.9) or for depression (OR=2.2), and being women (OR=1.5). PPS were the reason for visiting in 72.4 % of the sample. The main associated factors of PPS as the reason for consultation were clinical discomfort due to anxiety (OR=2.0), being female (OR=1.6), comorbid social anxiety (OR=1.4), and high Body Mass Index (OR=1.04). Neuropathic pain was present in 59.4% of all patients. Patients with diabetes (OR=2.6), social anxiety (OR=1.6), and depression (OR=1.6) suffered more frequently from neuropathic pain.

**Conclusion:** This is the first study to establish the associated factors of PPS, neuropathic pain and pain as main reason for visiting in primary care patients with newly diagnosed GAD. Better knowledge factors associated to GAD

could help to reduce its underdiagnosis and undertreatment at the primary care level.

**Keywords:** Generalized, Anxiety Disorder, Pain, Primary care, Painful physical symptoms

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## Factores relacionados con dolor en pacientes recién diagnosticados de Trastorno de Ansiedad Generalizada

**Objetivo.** Determinar la prevalencia y factores asociados a los síntomas físicos dolorosos (SFD), presencia de dolor y dolor neuropático en el servicio de atención primaria para el trastorno de ansiedad generalizada (TAG).

**Método.** Estudio multicéntrico, transversal y observacional llevado a cabo en 404 centros españoles de atención primaria con 2.232 pacientes. Los datos se recogieron de una vez y se incluyeron datos demográficos, principal motivo de consulta, enfermedad psiquiátrica o médica y utilización de los recursos de salud. Las escalas validadas para el diagnóstico del TAG fueron la escala GAD-7 y la entrevista MINI. La depresión se midió con la *Hospital Anxiety and Depression Scale* HADS, las alteraciones de sueño con la escala de sueño MOS, y el dolor con el *Inventario Breve de Dolor*, versión corta.

**Resultados.** La mayoría de los pacientes comunicaron SFD (93,5%). La mayor parte de los factores asociados a los SFD fue la consulta por trastornos gastrointestinales (OR=3,9) o por depresión (OR=2,2), y ser mujer (OR=1,5). Los SFD fueron el motivo de consulta en un 72,4 % de la muestra. Los principales factores asociados a SFD como motivo de consulta fueron el malestar clínico debido a la ansiedad (OR=2,0), ser mujer (OR=1,6), ansiedad social comórbida (OR=1,4), y un alto Índice de Masa Corporal (OR=1,04). El dolor neuropático estuvo presente en el 59,4% de todos los pacientes. Los pacientes con diabetes (OR=2,6), ansiedad social (OR=1,6), y depresión (OR=1,6) sufrieron dolor neuropático con más frecuencia.

**Conclusión:** Este es el primer estudio para establecer los factores asociados a los SFD, el dolor neuropático y el

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dolor como motivo principal de consulta en pacientes recién diagnosticados de TAG en atención primaria. Un mejor conocimiento de los factores asociados al TAG pueden ayudar a reducir el sub-diagnóstico y sub-tratamiento a nivel de atención primaria.

**Palabras claves:** Trastorno de ansiedad generalizada, dolor, atención primaria, síntomas físicos dolorosos

## Introduction

Generalized anxiety disorder (GAD) is quite prevalent in primary care (PC), with figures around 3–8%.<sup>1–4</sup> In PC, GAD is underdiagnosed and undertreated,<sup>5</sup> because the main reason for visiting is not anxiety, but other complaints such as painful physical symptoms (PPS). In fact, GAD patients report that main reasons for seeing the physician are somatic complaints (38.3%) and pain (29.2%).<sup>4</sup>

Several reports have studied the prevalence of anxiety among pain sufferers;<sup>6</sup> however, the opposite, prevalence of pain among GAD patients, has been the focus of research only recently.<sup>7–9</sup> One PC study reported that more than half (61%) of patients seeking treatment reported significant pain; with anxiety treatment resulting in an improvement of their pain symptoms.<sup>8</sup> Another study has shown a high prevalence of PPS among GAD patients and even higher on comorbid GAD–major depression (MDD) patients.<sup>9</sup> Finally, the strong association of medically unexplained pain and GAD has important consequences, such as lower quality of life, and higher disability and healthcare resources utilization.<sup>7</sup>

Neuropathic pain (NP) has been recognized as one the most difficult pain syndromes to treat. Patients with NP present with comorbid psychiatric diseases including anxiety, depression and sleep disorders.<sup>10</sup>

Better knowledge of the GAD associated factors in PC patients could help to better identify them and implement proper treatment. The aim of this study was to determine the prevalence and clinical features of PPS, pain as presentation and NP features of GAD patients at the PC setting, and to determine pain related associated factors for GAD.

## METHODS

### Study design

This multicenter, cross-sectional, observational study was conducted on 404 Spanish PC centers between April 2009 and September 2009. The study was approved by the local ethics committee. Patients gave written informed consent before participating in the study. A total of 447 PC

physicians recruited 2,232 patients. Participation in the study did not modify the usual clinical practice of physicians. Data from patients was collected at once at the only study visit, which included demographic data, current GAD symptoms, main reason for visit, sleep quality, psychiatric and medical illnesses information, current pharmacological and non-pharmacological treatments, healthcare resource utilization, and productivity.

### Study Sample

Eligible patients were individuals over 18 years of age with a GAD-7 score  $\geq 10$ . Exclusion criteria included previous GAD diagnosis and difficulty to understand questionnaires. A stratified multistage probabilistic sample without replacement was drawn. Sampling frame included all public and private health systems within the 17 regions of Spain. First stage consisted on selection of the PC centers in each region. The number of PC centers selected was proportional to the region's population, being the probability of choosing each center relative to the population in the area it covered. In the second stage, one PC physician per center was chosen randomly. Finally, physicians were asked to screen all patients attending on a given day for GAD following the GAD-7 scale, regardless of their reason for visiting. The first 5 patients with a GAD-7 score  $\geq 10$  that fulfilled all inclusion criteria and none of the exclusion criteria were invited to participate.

Sample size was calculated taking into account study's main variable: pain prevalence among GAD patients in primary care setting. A sample of 2,250 evaluable patients was estimated assuming a 30% rate of non-evaluable data and a 2-tailed 95% confidence interval to determine the prevalence of pain symptoms with an estimated error  $\leq 2.5\%$ .

### Functional Outcome Measures

GAD (Generalized Anxiety Disorder)-7 Scale: This scale,<sup>11</sup> validated in Spanish,<sup>12</sup> is a useful tool to screen for GAD symptoms. It consists on 7 questions related to presence and frequency of anxiety feelings, uncontrollable worry, etc. over the past 15 days. Scores for each question range from 0 (not at all) and 3 (nearly every day). Only patients with a GAD-7 score  $\geq 7$  were included in the study.

Hospital Anxiety Depression Scale (HADS): This is a 14-item, self-administered scale for the diagnosis of anxiety and depression.<sup>13</sup> It has been validated in Spanish.<sup>14</sup> Each disorder is assessed by 7 items each, all following a Likert scale from 0 to 3. Each domain (anxiety and depression) score from 0 (worst) to 21 (best). Scores  $\geq 14$  are considered as severe anxiety.

Mini Neuropsychiatric Diagnostic Interview (MINI): This is a short structured diagnostic interview, developed for DSM-IV and ICD-10 psychiatric disorders.<sup>15</sup> It has been validated in Spanish.<sup>16</sup> It can be used for non-psychiatrist physicians. It consists on 7 closed questions with a yes or no answer. This interview was used to confirm the diagnosis of GAD.

Brief Pain Inventory-Short Form (BPI-SF): This is a patient-rated instrument validated for Spain<sup>17</sup> to measure pain intensity and interference with daily activities. For our study, the 11-items short form was used. Each item ranges from 0 (no pain or interference) to 10 (most severe pain or complete interference).

DN4 questionnaire: This 10 items questionnaire allows for diagnosis of NP.<sup>18</sup> The first seven are related to the quality of pain and its association to abnormal sensations; the other 3 items are related to neurological examination in the painful area. Each positive item is assigned a 1, while negative scores are assigned a 0; then the sum of all 10 items gives the total score. A score of 4 or higher is considered as neuropathic pain.

## Statistical analysis

For statistical analysis, only patients that fulfilled all inclusion criteria and none exclusion criteria were included. Descriptive statistics were prepared for the continuous variables, including the assessment of central position and dispersion (two-tailed 95% confidence interval). The Kolmogorov-Smirnov test was applied to check adjustment of data to a Gaussian distribution. For comparisons, Student *t* tests and chi-square test were used for continuous and categorical variables, respectively.

Multivariate linear regression analysis were fitted to explore for possible predictive factors for the presence of PPS in GAD patients, for pain being the main reason for visiting, and for NP. All variables with differences rendering *p* values <0.05 in each corresponding patient group were included in each model. A forward stepwise procedure was applied and a *p* value <0.05 level for the Wald statistic was used as a criterion for maintaining variables in the model. Data were analyzed using SAS version 8.2 statistical software.

## RESULTS

A total of 2,232 patients were finally recruited and 66 patients were excluded from the study (Figure 1). From the remaining 2,144 patients, most reported PPS (93.5%) with a mean duration of 13.3 months ( $\pm 22.3$ ). More than half of the patients (66.6%) reported that PPS were moderate and 14.9% (310 patients) reported severe intensity, as measured by the

BPI-SF. The mean number of pain locations was  $2.7 \pm 1.6$ . Back pain was the most frequently reported reason behind pain with 74.4% of patients (cervical neuralgia 52.3%, low back pain 49.7%, upper back pain 23.6%) followed by headache (33.2%), arthrosis (28%), NP (18.5%), radiculopathy (15.8%), shoulder pain (15.2%), etc. Finally, 1510 patients (72.5%) considered that PPS interfered with their daily activities with a score higher than 5 (in a scale from 1 to 10), while only 27.5% (574 patients) considered PPS symptoms <5.

For all subsequent analyses, only those patients with substantial psychiatric impairment were included. A threshold for both anxiety and depression impairment was set at HADS scores  $\geq 11$ , and only patients with scores above this threshold were included. First, a comparison was made between patients with severe anxiety with and without PPS. Table 1 shows sociodemographic characteristics and healthcare resources utilization of these patients.

In order to identify factors associated with PPS in patients with GAD, a multivariate logistic regression analysis was performed with all significantly different variables resulting from the comparison of patients with and without PPS, as shown in Table 2.

PPS were the reason for visiting in 72.4 % of the sample. Table 3 describes the features of patients presenting with and without PPS.

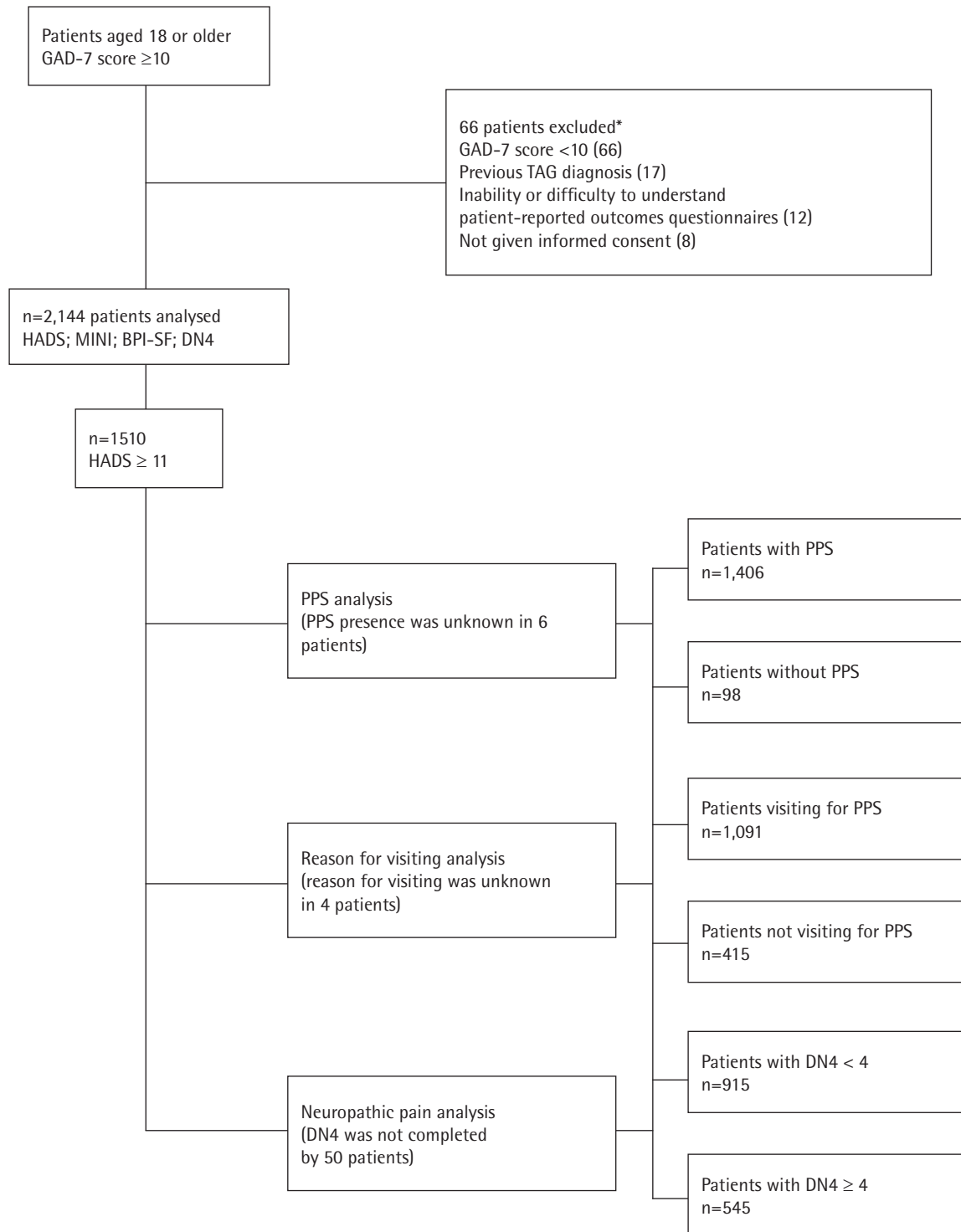
A multivariate stepwise linear regression analysis was performed with all significantly different variables resulting from the comparison of patients visiting for PPS with patients visiting for another reason, and excluding those variables directly related to pain (see Table 3 and above). These results are presented on Table 4.

In our study, 59.4% of all patients suffered from NP; which accounts for 63.3% of all patients with PPS. The mean score for the DN4 questionnaire was  $4.2 \pm 2.4$ , with more than 50% of patients describing the pain as burning, tingling, pins and needles, and numbness. Table 5 describes the main features of patients with and without NP.

Finally, all significantly different variables among patients with and without NP were used in multivariate stepwise linear regression, as shown in Table 6.

## DISCUSSION

Results from our study demonstrate the high prevalence of PPS symptoms among newly diagnosed GAD patients. Our study is first on identifying factors associated to GAD in patients with PPS, in patients with PPS as their main reason for visiting, and in patients with NP



\* Some patients reported more than one exclusion criteria

Figure 1

Study design

**Table 1** Features of patients presenting with and without PPS

	Total	Without PPS	With PPS	p value
N	1504	98	1406	
Gender (Female) (%)	70.8%	57.3%	71.7%	0.0053
Age (years)	52.6 ± 13.8	43.3 ± 13.1	53.3 ± 13.6	<0.0001
Anxiety*				
Severe (score ≥ 15)	46.4	52.3	45.9	0.2688
Moderate (score 10-14)	53.6	47.7	54.1	
GAD symptom duration (months)	33.3 ± 44.7	16.9 ± 30.1	34.5 ± 45.4	<0.0001
Age at symptom onset (years)	50.0 ± 13.3	42.1 ± 12.8	50.6 ± 13.2	<0.0001
Comorbid psychiatric diseases (%)	69.9	76.9	69.5	0.2678
Comorbid medical illnesses (%)	97.0	72.3	98.2	<0.0001
Physician Visits (last 3 months)	5.7 ± 4.1	3.5 ± 2.8	5.9 ± 4.2	<0.0001
Primary Care	3.5 ± 3.0	2.6 ± 2.3	3.6 ± 3.0	0.0002
Psychologist	0.4 ± 2.3	0.3 ± 1.1	0.4 ± 2.4	0.6941
Psychiatrist	0.5 ± 1.0	0.2 ± 0.6	0.5 ± 1.0	<0.0001
Emergency room	0.7 ± 1.6	0.1 ± 0.4	0.8 ± 1.6	<0.0001

\* As measured by GAD-7 scale

**Table 2** Predictors of PPS presence among severe GAD patients

Predictors	β-coefficient	Standard error	Wald $\chi^2$	p-value	OR	95% CI
Gender (female)	0.465	0.253	3.390	0.0656	1.592	0.97-2.611
Age	0.032	0.011	7.771	0.0055	1.032	1.009-1.055
Months with anxiety symptoms	0.020	0.008	6.840	0.0087	1.021	1.005-1.036
Main reason for visiting						
Anxiety	-0.687	0.322	4.552	0.0329	0.503	0.267-0.946
Depression	0.801	0.309	6.719	0.0095	2.227	1.216-4.080
Gastrointestinal disease	1.374	0.610	5.076	0.0243	3.952	1.196-13.065
Anxiety level (severe vs.moderate)	-0.765	0.251	9.265	0.0023	0.465	0.284-0.762

 $\chi^2$ : 105.5, p<0.0001, the explained variance of the model is 80.2%.

## Prevalence and factors associated with pain in GAD patients

Prevalence of PPS among GAD patients in our sample is quite high (93%) when compared to other studies, with figures around 60%<sup>7, 9</sup> or up to 78% when comorbid

depression is associated with GAD.<sup>9</sup> However, these studies used a threshold for PPS of a VAS score ≥ 30. We did not set any pain threshold as the aim was to study relevant PPS from the patient's point of view, which could explain the higher PPS prevalence observed in our study.

Table 3

## Features of patients presenting with PPS as their main reason for visiting

	Total	Without PPS	With PPS	p value
N	1506	415	1091	
Gender (Female) (%)	70.8	65.6	72.7	0.0126
Age (years)	52.6 ± 13.8	49.5 ± 14.4	53.8 ± 13.4	<0.0001
Height (cm)	166.3 ± 9.0	166.3 ± 9.0	164.7 ± 8.1	0.0021
BMI (Kg/m <sup>2</sup> )	26.5 ± 4.3	25.9 ± 4.4	26.7 ± 4.2	0.0006
Highest educational level (%)				<0.0001
No studies	6.7	4.8	7.4	
Elementary school	38.9	32.6	41.3	
High school	37.3	39.1	36.6	
College or higher	17.1	23.4	14.6	
Employment status (%)				<0.0001
Employed	46.0	52.0	43.6	
Unemployed	7.8	10.2	6.9	
Housewife	26	22	27.5	
Retiree	14.3	9.7	16.1	
Other	6	6	6	
Marital status (%)				<0.0001
Single	14.9	22.3	12.1	
Married/ Living together	64.7	59.5	66.7	
Divorced	9.7	10.7	9.4	
Widowed	10.7	7.5	11.8	
Anxiety	14.5 ± 2.7	14.3 ± 2.6	14.5 ± 2.7	0.0901
GAD symptom duration (months)	33.3 ± 44.7	27.9 ± 38.2	35.4 ± 46.8	0.0023
Age at symptom onset (years)	50.0 ± 13.3	47.2 ± 13.7	51.1 ± 13.1	<0.0001
Comorbid psychiatric diseases (%)	69.9	68.2	70.5	0.2678
Comorbid medical illnesses (%)	97.0	93.2	98.3	<0.0001
Pain duration (months)	13.3 ± 23.0	11.2 ± 21.5	13.9 ± 23.4	0.0816
Sleep quality*	6.6 ± 1.7	6.4 ± 1.8	6.6 ± 1.7	0.0065
HADS-Depression subscale score	12.4 ± 3.5	12.1 ± 3.6	12.6 ± 3.4	0.0196
Physician Visits (in the last 3 months)	5.7 ± 4.1	4.8 ± 3.4	6.1 ± 4.3	<0.0001
Primary Care	3.5 ± 3.0	3.1 ± 2.6	3.7 ± 3.2	<0.0001
Psychologist	0.4 ± 2.3	0.2 ± 0.8	0.4 ± 2.7	0.0567
Psychiatrist	0.5 ± 1.0	0.4 ± 0.9	0.5 ± 1.0	0.0108
Emergency room	0.7 ± 1.6	0.5 ± 1.1	0.8 ± 1.7	0.0002

**Table 4** Predictors of patients with PPS as the main reason for visiting

Predictors	$\beta$ -coefficient	Standard error	Wald $\chi^2$	p-value	OR	95% CI
Gender (female)	0.466	0.158	8.680	0.0032	1.593	1.169-2.172
Age	0.016	0.006	7.267	0.0072	1.016	1.004-1.027
BMI	0.039	0.018	4.639	0.0314	1.040	1.004-1.078
MINI-item E	0.713	0.283	6.374	0.0116	2.041	1.173-3.550
Social anxiety	0.338	0.155	4.750	0.0293	1.402	1.035-1.900

$\chi^2$ : 66.7 p<0.0001, the explained variance for this model was 66.2%

**Table 5** Features of patients with and without neuropathic pain

	Total	Without NP	With NP	p value
N	1460*	545	915	
Gender (Female) (%)	70.8	68.3	72.8	0.0871
Age (years)	52.6 $\pm$ 13.8	50.2 $\pm$ 13.5	54.6 $\pm$ 13.4	<0.0001
Anxiety (GAD-7)	14.5 $\pm$ 2.7	14.2 $\pm$ 2.7	14.6 $\pm$ 2.7	0.0061
Main reason for visiting				
Depression	36.9	26.9	44.4	<0.0001
Metabolic disease (diabetes)	5.8	2.6	8.0	<0.0001
Comorbid psychiatric diseases (%)	69.9	60.8	75.1	<0.0001
Comorbid medical illnesses (%)	97.0	96.0	98.3	0.0111
Pain duration (months)	13.3 $\pm$ 23.0	11.1 $\pm$ 18.7	14.5 $\pm$ 25.0	0.0065
Number of pain locations	2.8 $\pm$ 1.7	2.2 $\pm$ 1.4	3.1 $\pm$ 1.7	<0.0001
Sleep quality** (global index)	57.8 $\pm$ 13.1	54.8 $\pm$ 13.5	59.5 $\pm$ 12.5	<0.0001
HADS-Depression subscale score	12.4 $\pm$ 3.5	11.7 $\pm$ 3.4	12.9 $\pm$ 3.4	<0.0001
Physician Visits (in the last 3 months)	5.7 $\pm$ 4.1	4.7 $\pm$ 3.4	6.4 $\pm$ 4.4	<0.0001
Primary Care	3.5 $\pm$ 3.0	2.9 $\pm$ 2.7	3.9 $\pm$ 3.1	<0.0001
Psychologist	0.4 $\pm$ 2.3	0.4 $\pm$ 3.6	0.4 $\pm$ 1.1	0.9470
Psychiatrist	0.5 $\pm$ 1.0	0.3 $\pm$ 0.7	0.6 $\pm$ 1.1	<0.0001
Emergency room	0.7 $\pm$ 1.6	0.5 $\pm$ 2.0	0.9 $\pm$ 1.3	0.0001

\*From the 1510 patients with HADS anxiety scores  $\geq 11$ , on 50 patients the presence of neuropathic pain was unknown

\*\*As measured by the MOS-Sleep scale

**Table 6** Predictors of neuropathic pain in GAD patients

	$\beta$ -coefficient	Standard error	Wald $\chi^2$	p-value	OR	95% CI
Age	0.014	0.005	6.675	0.0096	1.014	1.003-1.025
GAD-7	0.282	0.133	4.466	0.0346	1.325	1.021-1.721
Main reason for visiting						
Depression	0.459	0.139	10.945	0.0009	1.583	1.206-2.078
Metabolic disease (diabetes)	0.981	0.350	7.844	0.0051	2.666	1.342-5.295
Social Anxiety	0.452	0.139	10.519	0.0012	1.571	1.196-2.064
MOS-Sleep Scale						
Awaken short of breath or with a headache	0.007	0.003	5.056	0.0244	1.007	1.001-1.014
Sleep disturbances	0.018	0.006	8.720	0.0031	1.018	1.006-1.030
$\chi^2$ : 116.6, $p < 0.0001$ , the explained variance for this model was 68.6%						

Features of patients presenting with PPS are similar to those found in somatizers.<sup>18, 19</sup> In our study, GAD patients with PPS presented with chronic pain (mean duration 13.3 months) and several pain locations (mean 2.7), which is similar to the two thirds of somatizers presenting with chronic pain previously observed.<sup>18, 19</sup> In addition, back pain was the most frequent somatic symptom (71.4% for somatizers and 74.4% for GAD patients with PPS in our study). These similarities are expected, since patients complaining from PPS and with a diagnosis of GAD fulfil somatizer criteria.<sup>18, 19</sup>

GAD patients with and without PPS do not differ significantly in GAD severity; however, the use of healthcare resources was significantly higher among these patients, due to the higher number of visits to the primary care physicians. Another study at PC has also reported this increase in healthcare resources utilization, being patients with GAD and PPS higher users than GAD patients alone and non-anxious patients with PPS.<sup>7</sup> One of the reasons for the increase in resource utilization could be explained by the longer symptom duration observed among patients with PPS in our study. In this regard, a recent study has demonstrated that GAD patients that reported high pain interference had a more severe anxiety and a lower likelihood of responding to anxiety treatment.<sup>20</sup> Moreover, back pain has been associated with reduced chance of remission in GAD patients.<sup>21</sup> Therefore, simultaneous treatment of both pain and anxiety could result in a synergistic effect that will greatly help GAD patients with PPS by improving their quality of life, and reducing their healthcare resources utilization.

Results from our regression analysis show that the most important factors associated with GAD in patients with PPS are gastrointestinal disorder (OR: 3.9) and depression (OR: 2.2) as the main reason for visiting, followed by female gender (OR: 1.6), age (OR: 1.03), and the number of months with anxiety symptoms (OR: 1.02). Other studies in GAD patients have previously reported pain and somatic complaints as the main reasons for visiting the primary care physicians.<sup>4</sup> In fact, anxiety patients with HADS>11 have a higher risk of presenting uninvestigated dyspepsia, which does not occur in depressed patients.<sup>22</sup> One explanation could be that the existence of pain and other somatic symptoms make the patient choose a somatic symptom as the reason for consultation, instead of his/her anxiety. As previously mentioned, choosing somatic symptoms as the reason for visiting fulfils the somatization criteria. To our knowledge, our study is the first one to establish gastrointestinal disorder and depression as predictors for GAD, which could help primary care physicians in the diagnosis of anxiety patients.

### PPS as main reason for visiting the primary care physician in GAD patients

PPS being the main reason for visiting the primary care physician can mislead GAD diagnosis. In almost 3 out of 4 patients (72.9%) pain was their main complaint. These results are in line with those of Zhu et al. reporting 63% pain prevalence among GAD patients, with or without comorbid depression.<sup>23</sup> Also, GAD patients with painful symptoms were more likely to be treated at the primary care level than GAD patients alone.

Our regression analysis shows that the main variables associated with presenting with PPS to the PC physician and having GAD are disorder duration (OR=2.04), being female (OR=1.6), social anxiety (OR=1.4), BMI (OR= 1.04) and age (OR= 1.01). A review has previously demonstrated the association of PPS to females, to disease duration, and increasing age in somatisation disorder, which further supports our results for GAD patients.<sup>24</sup> To our knowledge, this is the first study to define BMI as a predictive factor for PPS as the main complaint in GAD patients. Previous studies have associated being overweight with GAD.<sup>25, 26</sup> In particular, BMI  $\geq 30$  was associated with increased odds for subsequent GAD (6.27, after adjusting for other significant risk factors).<sup>25</sup> Also, this is the first time to describe an association between social anxiety and PPS as presentation. Taking into account the tendency among social anxiety patients to avoid conflicts, one explanation for the observed association could be that social anxiety patients tend to present with pain because they infer this will be better understood by their physician.

## Neuropathic pain

NP was explored since it has been demonstrated to respond to several pharmacological agents used for GAD treatment. Our results show that NP is prevalent among newly diagnosed GAD patients (59.4%) and even more among GAD patients with PPS (63.3%). To our knowledge, ours is the first study on the prevalence of NP among GAD patients. Studies aimed at NP patients have determined a high rate of GAD among these patients (35% among diabetic neuropathy patients).<sup>10</sup> In this regard, pain, anxiety and depression seem to have a common neurochemical basis as suggested by the efficacy observed with treatments targeting the serotonergic system.<sup>27</sup>

Multivariate analysis show that the factors associated with NP among GAD patients are main reason for visiting being diabetes (OR= 2.66) or depression (OR= 1.58), and comorbid social anxiety (OR=1.57). Diabetes is frequently associated with NP,<sup>10</sup> which could explain why GAD patients may choose their diabetes as the main reason for visiting above its anxiety. Our results suggest that GAD patients with NP consider depression above pain and anxiety as the main reason for visiting the PC physician. Finally, we have previously hypothesized about why social anxiety is a risk factor for pain, which also seems to apply for neuropathic pain.

## Characteristics of the study

This study has several strengths. First, this is a multicentre (447 centres) study, with a wide and representative sample (N=2232 patients). Second, its naturalistic study design

allows for the generalization of the results to PC patients suffering from GAD.

Among the limitations is its cross-sectional design; that does not allow to infer causality but only to show associations. Also, comorbid psychiatric diseases were not diagnosed with a psychiatric structured interview, which could result in the under diagnosis of these diseases in our sample. Although a validated questionnaire (BPI-SF) was used for measuring pain interference with the daily activities, pain symptoms report by the GAD patients may be influenced by the inherent worry of these patients. Also, pain intensity, comorbidities, treatment and physician visits data relied on self-report by patients, which could be biased by recall. However, previous studies have demonstrated the acceptable reliability of these reports.<sup>28</sup> In addition, GAD patients already treated for their anxiety were excluded from our study (one of the exclusion criteria was a previous diagnosis of GAD). Thus, patients with not very efficacious treatment or with relapsing episodes of GAD were not included, and the population in our study may not be representative of the whole GAD population at the PC level. However, the study of GAD associated factors of those patients not yet diagnosed is key to better recognised then and to reduce the under diagnosis observed in this population.

In conclusion, our study is the first one to establish the associated factors of PPS, neuropathic pain and pain as main reason for visiting in PC patients with newly diagnosed GAD. Given the high degree of underdiagnosis and undertreatment reported for this disorder,<sup>4</sup> PC physicians can greatly benefit from knowing the predictive factors in GAD patients with PPS and could reduce the challenge of managing GAD at the PC level.

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## DECLARATION OF INTEREST

María Pérez and Vanessa Lopez are employed by Pfizer España, the body funding the study. All other authors declare no conflicts of interest.

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