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# Pathological Worry is Related to Poor Long-Term Pharmacological Treatment Response in Patients With Panic Disorder

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**Objective** Several predictors of unfavorable pharmacological treatment response (PTR) in panic disorder (PD) patients have been suggested, such as the duration of the illness, presence of agoraphobia, depression, being a woman, and early trauma. This study aimed to examine whether pathological worry is associated with PTR in PD patients.

**Methods** This study included 335 PD patients and 418 healthy controls (HCs). The Penn State Worry Questionnaire (PSWQ), the Early Trauma Inventory Self Report-Short Form (ETISR-SF), Beck Depression Inventory (BDI), Panic Disorder Severity Scale (PDSS), and Anxiety Sensitivity Inventory-Revised (ASI-R) were administered. We measured the PTR at 8 weeks and 6 months. Student t-test, chi-square tests, Pearson's correlation analyses, and binary logistic regression model were used.

**Results** Our results showed that the total scores of the PSWQ correlated with the ETISR-SF, BDI, and ASI-R were significantly higher in patients with PD compared with HCs. The PSWQ and BDI could predict unfavorable PTR at 6 months in PD patients.

**Conclusion** This is the first study to demonstrate that pathological worry may contribute to poor long-term PTR in PD patients. Therefore, our research suggests that clinicians must be aware of worry to optimize PTR for PD patients.

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**Keywords** Panic disorder; Pathological worry; Penn State Worry Questionnaire; Pharmacotherapy; Treatment response.

## INTRODUCTION

Generally, worry, which is defined as "a chain of thoughts and images, negatively affect-laden and relatively uncontrollable," is a cognitive characteristic of anxiety that can be seen in normal individuals.[1] In contrast, excessive worry is the cognitive component of anxiety and is closely associated with anxious apprehension, which may be an attempt at coping with unfavorable events.[2]

Panic disorder (PD) is an anxiety disorder whose main symptoms are recurrent and unexpected panic attacks, excessive worry about future panic attacks, and physical symptoms such as the sensation of shortness of breath, palpitation, and fear of dying.[3] In particular, excessive worry in PD consists of persistent concern or worry about the implications of a panic attack or its consequences such as losing control and having a heart attack, with a tendency to cause considerable distress and functional impairment. Therefore, in patients with PD, excessive worry is might be explained "trait worry" more than "state worry," which is named pathological worry.[4] In particular, the contents of pathological worry in PD differs from excessive worry about various events or activities in generalized anxiety disorder (GAD).[3] However, patients with PD similar to GAD who experience pathological worry may tend to be focused on future negative outcomes that are vague in nature, resulting in problem generation rather than problem resolution.[5]

To reduce symptoms like pathological worry in patients with PD, pharmacological treatment and second wave cognitive-behavioral therapy (CBT) have been well-established so far as effective methods.[6-9] In addition, previous research has shown that pharmacotherapy is effective in reducing pathological wor-

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ry symptoms in patients with GAD.[10] However, diagnostic comorbidities such as anxiety disorders in patients with GAD having pathological worry is associated with lack of recovery.[11] Furthermore, in clinical settings, even when such patients with PD are treated, the pharmacological treatment response (PTR) may not be quite satisfactory because approximately 20%−40% of patients with PD are non-responsive to pharmacotherapy with antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and anxiolytics.[12,13] In some clinical trials in which patients with PD were treated with SSRIs and anxiolytics for a period of 8 to 12 weeks, but 17%−61% of PD patients didn't respond to pharmacotherapy.[14,15] Therefore, it is important to early detect patients with PD having pathological worry in advance so that other different alternative treatments can be considered for each patient. Moreover, further studies are needed to identify additional predictors of pharmacological treatment for patients with PD.

Several baseline predictors that could contribute to the PTR in patients with PD have been suggested. Previous short-term as well as long-term research has suggested several predictors in PD such as duration of the illness, the symptom severities of PD, presence of agoraphobia, comorbidities with other psychiatric disorders including depressive disorders and personality disorders, and the female gender.[16-22] In addition, some studies have found that recent emergency room visits and medical comorbidities in PD were might be predictors of poor PTR in patients with PD.[23] Another study found an correlation between early sexual trauma and neuroticism, and unfavorable long-term PTR in patients with PD.[24] However, few studies thus far have determined whether pathological worry is a predictor of PTR in PD. Further research about long-term pharmacotherapy needs to be done due to the lack of studies on the responses to long-term pharmacological treatment for pathological worry.

Our study addresses this gap in the literature by examining whether pathological worries are associated with long-term PTR in patients with PD using a relatively larger sample size than those used in previous studies. We hypothesized that patients with PD who experience pathological worry will have an unfavorable response to pharmacological treatments in long-term follow-ups.

## METHODS

### Participants

Between 2011 and 2021, 335 patients with PD and 418 healthy controls (HCs) participated in this study. We recruited participants from patients with PD who were treated in the Department of Psychiatry at CHA Bundang Medical Center. All participants were Koreans aged between 18 and 70 years old. The participants' family histories of PD were established through interviews. Participants with PD with or without agoraphobia met the DSM-IV-TR Axis I Disorder, as diagnosed by trained psychiatrists using the Structured Clinical Interview for DSM-IV-TR. Although DSM-5 was published in 2013, we recruited patients with PD with the previous criterion, DSM-IV-TR, to collect data on a consistent basis from 2011 to 2021. Only patients primarily diagnosed as experiencing PD were included, and PD patients with additional major medical comorbidities were excluded. In addition, PD patients who followed up to 6 months after pharmacotherapy were included.

Participants with a primary diagnosis of any schizophrenia spectrum disorders, bipolar disorders, depressive disorders, anxiety disorders including GAD other than PD, substance use disorders, personality disorder, mental retardation, major medical disorders including neurological disorders, and pregnancy were excluded. Furthermore, all patients with PD who had been treated with individual or group psychotherapy such as mindfulness-based cognitive therapy or CBT were excluded. In addition to, HCs with a history of psychiatric disorders were excluded.

All patients with PD had pharmacotherapy with SSRIs such as escitalopram, paroxetine, and sertraline (escitalopram equivalence dosage=9.97±7.50 [mean±SD] mg/day),[25] and BDZs including alprazolam, clonazepam, and diazepam were primarily permitted on a pro re nata (PRN; as required) basis. Some patients with PD were undergoing pharmacological treatment with antidepressants and anxiolytics according to the Korean Mediation Algorithm for PD[26] or the Clinical Practice Guidelines: Treatment of PD.[27] When analyzing several factors for the PTR in PD, interview and clinical assessments were performed during patients' first visit to the hospital. Participants were administered all self-report scales on the same day to rule out memory recall bias after medication commencement.

All study procedures complied with to the Institutional Review Board regulations and principles of Good Clinical Practice at the CHA Bundang Medical Center. After participants were provided with an enough explanation of the study process, methods, and purpose, their written informed consent was obtained.

### Clinical assessments

#### Penn State Worry Questionnaire

To evaluate pathological worry in patients with PD in clinical settings, the Penn State Worry Questionnaire (PSWQ) is used.[28] The PSWQ consisting of 16-item is made to assess the generality, excessiveness, and uncontrollability of pathological worry. Items of this inventory are rated on a 1−5-point scale and are known to have high internal consistency and excellent test-

retest reliability. In this study, we also used the Korean version of the PSWQ,[29] which represented high internal consistency (Cronbach's alpha: 0.952).

### Other clinical assessments

Early trauma was evaluated using the Korean version of the Early Trauma Inventory Self Report-Short Form (ETISR-SF) with a Cronbach's α of 0.869. ETISR-SF is significantly positively associated with the scores on the Childhood Trauma Questionnaire-Short Form (r=0.691),[30] which consists of 27 "yes" or "no" questions in total evaluating the four domains of general, physical, emotional, and sexual trauma histories before the age of 18 years. In addition, each of the domains is evaluated using 11, 5, 5, and 6 questions, respectively.

The Korean version of the Anxiety Sensitivity Inventory-Revised (ASI-R) to assess potential anxiety trait markers in patients with PD at baseline.[31,32] The ASI-R is the most commonly performed measure of anxiety sensitivity (AS), consisting of fears of respiratory symptoms, publicly observable anxiety reactions, cardiovascular symptoms, and cognitive dyscontrol.

To measure the clinical severity of the participants' anxiety and depressive symptoms at baseline in PD, we performed the Panic Disorder Severity Scale (PDSS)[33] and the Beck Depression Inventory (BDI),[34] respectively.

The PTR was evaluated after a minimum of 8 weeks and 6 months of pharmacotherapy in an adequate dose. It was defined as a total PDSS score reduction of 40% or more from the baseline score after 8 weeks and 6 months of treatment in an adequate dose.[35-37]

### Statistical analyses

To analyze the sociodemographic characteristics and clinical symptom severities including the PSWQ of patients with PD and HCs, the Student t-test and chi-square tests were performed.

In addition, Pearson's correlation analyses were applied to determine whether an association existed among continuous variables such as age, ETISR-SF, ASI-R, BDI, PDSS, and PSWQ at baseline.

Further, a binary logistic regression model with treatment response as the dependent variable and with those that can influence the treatment response at 8 weeks and in 6 months as covariates was performed in PD. All statistical analyses used the IBD SPSS Statistics 26.0 software (IBM Corp., Armonk, NY, USA). All reported probability values were two-tailed where $p<0.05$ was considered statistically significant.

## RESULTS

### Sociodemographic and clinical characteristics

The sociodemographic and clinical characteristics of all study participants are summarized in Table 1. There were no significant differences between patients with PD and HCs in terms of age and gender at baseline. However, patients with PD had significantly lower levels of education than HCs ($\chi^2$=90.12, p< 0.001). Also, patients with PD were relatively less likely to live without a partner ($\chi^2$=5.98, p=0.014), and their monthly incomes were relatively lower than those of HCs ($\chi^2$=9.10, p= 0.003). All clinical scale scores such as ETISR-SF (e.g., total sum, general, emotional, and sexual subtypes), ASI-R (e.g., total sum, all subtypes), and BDI at baseline were significantly higher in patients with PD compared with HCs ($p<0.01$). Over time, the total scores of PDSS in patients with PD gradually decreased from 12.33 (±6.33) (mean [±SD]) at baseline to 9.89 (±5.01) at 8 weeks, then 8.85 (±4.77) at 6 months.

### Comparison of pathological worry between patients with panic disorder and healthy controls

The total scores of the PSWQ at baseline were significantly higher in patients with PD compared with HCs {PD: 52.73 (±12.68) (mean [±SD]), HCs: 38.64 (±9.14), t=14.14, $p<0.001$} (Table 2). The result remained the same after the ANCOVA analysis controlling for education levels, marital status, and monthly income.

### Association between pathological worry and categorical variables in each panic disorder and healthy control group

The mean PSWQ scores of patients with PD did not significantly differ by gender, level of education, monthly income, and marital status (all, $p>0.05$). Furthermore, there was no statistical difference in the mean PSWQ scores by gender, level of education, and marital status in HCs (all, $p>0.05$). However, in HCs, the mean PSWQ scores differed significantly in monthly income levels, and the lower the monthly income, the higher the PSWQ scores (Fisher's exact test, p=0.01).

### Pearson's correlation analyses among continuous variables in healthy controls and patients with panic disorder

Table 2 presents the correlations among continuous variables in HCs. The total scores of the PSWQ at baseline presented significant positive associations with the total sum of all subtypes ETISR-SF, emotional early trauma scores, sexual early trauma scores, ASI-R, and BDI at baseline among HCs ($p<0.05$). However, there was a significant negative correlation between the PSWQ scores at baseline and age ($p<0.05$).

In patients with PD, the total PSWQ scores at baseline showed significantly positive correlations with the total sum of all subtypes of ETISR-SF, the emotional early trauma scores, ASI-R, BDI, and PDSS at baseline, at 8 weeks, and 6 months (all, p<

**Table 1.** Socio-demographic and clinical characteristics of patients with panic disorder and healthy controls

| | PD (N=335) | HCs (N=418) | Statistics (t or $\chi^2$) | p-value |
|---|---|---|---|---|
| Age at baseline (years, mean±SD) | 37.91±11.41 | 36.84±11.31 | 1.29 | 0.199 |
| Gender (male [%]/female) | 149 (44.5)/186 | 195 (46.7)/223 | 0.35 | 0.552 |
| Years of education (high school or less [%]/college or more) | 174 (53.0)/154 | 76 (19.3)/318 | 90.12 | <0.001*** |
| Marital status (living without partner [%]/with partner) | 136 (41.1)/195 | 190 (50.3)/188 | 5.98 | 0.014* |
| Monthly income (below 1,800 $USD [%]/above 1,800 $USD) | 33 (10.2)/290 | 14 (4.2)/322 | 9.10 | 0.003** |
| Agoraphobia, yes (%) | 242 (73.8) | - | - | - |
| Duration of illness (months, mean±SD) | 56.05±43.61 | - | - | - |
| Baseline ETISR-SF total score (mean±SD) | 4.96±4.00 | 3.28±3.01 | 4.04 | <0.001*** |
| General trauma sub-scale score | 1.34±1.49 | 0.89±1.15 | 2.89 | <0.001*** |
| Physical trauma sub-scale score | 1.89±1.62 | 1.58±1.65 | 1.63 | 0.104 |
| Emotional trauma sub-scale score | 1.37±1.69 | 0.66±1.19 | 4.21 | <0.001*** |
| Sexual trauma sub-scale score | 0.39±0.88 | 0.16±0.41 | 2.95 | 0.001** |
| Baseline ASI-R total score (mean±SD) | 52.03±29.79 | 8.23±10.47 | 24.76 | <0.001*** |
| Fear of respiratory symptom | 19.76±11.80 | 1.51±2.82 | 27.24 | <0.001*** |
| Fear of cardiovascular symptom | 14.14±9.74 | 2.80±4.98 | 18.98 | <0.001*** |
| Fear of publicly observable anxiety reaction | 11.06±7.54 | 3.35±4.27 | 16.39 | <0.001*** |
| Fear of cognitive dyscontrol | 6.99±6.97 | 0.84±1.76 | 15.58 | <0.001*** |
| Baseline BDI total score (mean±SD) | 17.77±10.83 | 6.05±6.28 | 17.32 | <0.001*** |
| PDSS total score at baseline (mean±SD) | 12.33±6.33 | - | - | - |
| PDSS total score at 8 weeks (mean±SD) | 9.89±5.01 | - | - | - |
| PDSS total score at 6 months (mean±SD) | 8.85±4.77 | - | - | - |
| Pharmacotherapy, yes (%) | 244 (72.8) | | | |
| Kinds of SSRI {escitalopram (N [%])/paroxetine (N [%])} | 71 (29.1)/149 (61.1) | - | - | - |
| SSRI equivalent dosage (mg, mean±SD)† | 9.97±7.50 | - | - | - |

*p<0.05; **p<0.01; ***p<0.001; †the approximate equivalent oral doses to 10 mg Escitalopram are given. PD, panic disorder; HCs, healthy controls; ETISR-SF, Early Trauma Inventory Self Report-Short Form; ASI-R, Anxiety Sensitivity Inventory-Revised; BDI, Beck Depression Inventory; PDSS, Panic Disorder Severity Scale; SSRI, Selective Serotonin Re-uptake Inhibitor

0.001). However, there were significant negative associations between the PSWQ scores at baseline and age (p<0.01) (Table 3).

### Binary logistic regression analysis predicting the pharmacological treatment response at 6 months in patients with panic disorder

To evaluate which factors contributed to the response of pharmacological treatment at 6 months, a binary logistic regression analysis was performed (Table 4). This model only included the essential variables (i.e., age, gender, education level, marital status, monthly income, PSWQ, BDI, PDSS, ASI-R, and early trauma at baseline).

After 6 months, the PSWQ at baseline (B=-0.072, p=0.018) and BDI (B=-0.089, p=0.047) were significantly negatively associated with the response of pharmacological treatment in patients with PD. In particular, higher total scores of PSWQ reduced the possibility of PTR in 6 months (OR=0.930, 95% CI=0.876−0.988). However, the monthly income and the total score of PDSS at baseline were positively significantly associated with the PTR in patients with PD in 6 months. Higher PDSS scores were associated with a significantly better PTR in 6 months (OR=0.284, 95% CI=1.158−1.524).

This research model proved to be significant at p<0.05, with the $\chi^2$ value for the -2 log likelihood difference between the null model in which the independent variable was excluded, and these models with the independent variable. The explanatory powers of these models at 6 months were 30.5% based on the Cox and Snell's $R^2$, and overall percentage was 67.8%.

## DISCUSSION

This is the first study to demonstrate that pathological worry can influence the poor long-term PTR in patients with PD. The findings of our study suggest that patients with PD with pathological worry are more vulnerable and show more severe symptoms, which may lead to a chronic course of illness. There-

**Table 2.** Pearson's correlations among continuous variables in healthy controls

| Continuous variables | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| [1]PSWQ at baseline | - | | | | | | | | |
| [2]Age | -0.181* | - | | | | | | | |
| ETISR-SF | | | | | | | | | |
| [3]Total sum of all subtypes | 0.179* | -0.034 | - | | | | | | |
| [4]General | -0.080 | 0.160* | 0.647** | - | | | | | |
| [5]Physical | 0.075 | -0.069 | 0.795** | 0.275** | - | | | | |
| [6]Emotional | 0.367** | -0.125 | 0.673** | 0.213** | 0.292** | - | | | |
| [7]Sexual | 0.179* | -0.056 | 0.381** | 0.208** | 0.141 | 0.221** | - | | |
| [8]ASI-R at baseline | 0.324** | 0.017 | 0.218* | 0.133 | 0.096 | 0.255** | 0.037 | - | |
| [9]BDI at baseline | 0.472** | 0.072 | 0.326** | 0.176* | 0.137 | 0.416** | 0.142 | 0.370** | - |

*p<0.05; **p<0.01. PSWQ, Penn State Worry Questionnaire; ETISR-SF, Early Trauma Inventory Self Report-Short Form; ASI-R, Anxiety Sensitivity Index-Revised; BDI, Beck Depression Inventory

fore, our study shows that it is important for clinicians to check for these features at an early stage in patients with PD in initial interviews and to choose appropriate treatments for such individuals.

Previous studies showed the several risk factors contributing to worse PTR of patients with PD.[16,18,19,21] In addition, our study showed that pathological worries affect long-term poor PTR in patients with PD. It is not clear why this occurs, but a neurobiological study showed that pathological worries were positively significantly correlated to the both medial orbitofrontal cortex (mOFC) volume playing a role in emotional decision-making under uncertain conditions in patients with GAD ($p<0.001$).[38,39] Also, previous studies about PD have consistently reported volume reductions in mOFC.[40,41] The OFC related to pathological worry contributes to preservative and inflexible thoughts and behaviors, and pathological worries suggest that repetitive nonreinforced thoughts and behaviors might be over-engaged when attempting to solve problems. Therefore, in patients with PD with pathological worries, maladaptive coping strategies related to the inability to activate a switch-off mechanism for fear might be reinforced, aggravating PTR.

From a psychological perspective, pathological worry is associated with coping strategies such as attempts to avoid negative events, interpersonal control, and cognitive failures. In the cognitive model of worry process presented by Eysenck,[42] worry has three major functions: alarm, prompt, and preparation. In particular, the prompt function brings threat-related negative thoughts. The preparation function permits individuals to anticipate negative anticipatory scenarios in the future and to act with inappropriate coping strategies to prevent the anticipated negative events such as panic attacks, which makes the worry continue.

Our findings have shown a positive association between pathological worry and secondary depressive symptoms. In addition, it has shown that the severity of secondary depressive symptoms in PD were correlated with unfavorable long-term treatment responses, although we excluded participants with primary major depressive disorder consistent with prior literature.[18,43-46] Patients with secondary depression might have an earlier age at onset their panic symptoms and appeared to be more agitated, according to a previous study.[47] As a result, patients with PD with severe secondary depression might be more likely to suffer from maladaptive patterns of their behaviors and thoughts, which is associated with responses to pharmacological treatment at long-term follow-ups.

In addition, our findings have shown that high symptom severity of PD at baseline in patients with PD was associated with good long-term PTRs inconsistent with prior literature.[44] It is unclear why high PDSS scores were related to better PTR in our findings. However, we assume that the participants whose high symptom severity scores at baseline and decreased scores rapidly over time may have been included in our study. Because we recruited patients with PD in the acute care hospital equipped with an emergency room, this environment might have affected the PTR in our study.

Furthermore, we found that the AS associated with pathological worry in patients with PD does not significantly directly influence the PTRs at long-term follow-ups. Previous studies have suggested AS as a predictor of panic-related pathology, which may affect the frequency of panic attacks.[48-50] Although AS is significantly positively associated with pathological worry[51] and increases the level of symptom severities, it is unknown whether it has a direct relationship with the unfavorable long-term PTR. Therefore, further studies are needed to examine whether AS directly contributes to long-term poor PTR.

Notably, previous studies showed an correlation between early trauma and the frequency of panic attacks or the age of

**Table 3.** Pearson's correlations among continuous variables in patients with panic disorder

| Continuous variables | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| [1]PSWQ at baseline | - | | | | | | | | | | | |
| [2]Age | -0.178* | - | | | | | | | | | | |
| ETISR-SF | | | | | | | | | | | | |
| [3]Total sum of all subtypes | 0.274** | -0.313*** | - | | | | | | | | | |
| [4]General | 0.108 | -0.153 | 0.708*** | - | | | | | | | | |
| [5]Physical | 0.149 | -0.227** | 0.717*** | 0.306*** | - | | | | | | | |
| [6]Emotional | 0.335*** | -0.302*** | 0.817*** | 0.411*** | 0.429*** | - | | | | | | |
| [7]Sexual | 0.065 | -0.072 | 0.450*** | 0.171* | 0.076 | 0.302*** | - | | | | | |
| [8]ASI-R at baseline | 0.600*** | -0.257*** | 0.440*** | 0.283** | 0.223** | 0.451*** | 0.221** | - | | | | |
| [9]BDI at baseline | 0.682*** | -0.202*** | 0.350*** | 0.183* | 0.209* | 0.389*** | 0.141 | 0.654*** | - | | | |
| [10]PDSS at baseline | 0.378*** | -0.235*** | 0.170* | 0.148 | 0.131 | 0.153 | -0.025 | 0.579*** | 0.538*** | - | | |
| [11]PDSS at 8 weeks | 0.399*** | -0.271*** | 0.235** | 0.170* | 0.197* | 0.183* | 0.027 | 0.566*** | 0.547*** | 0.820*** | - | |
| [12]PDSS at 6 months | 0.417*** | -0.285*** | 0.247** | 0.123 | 0.257** | 0.202* | 0.037 | 0.529*** | 0.551*** | 0.753*** | 0.883*** | - |

*p<0.05; **p<0.01; ***p<0.001. PSWQ, Penn State Worry Questionnaire; ETISR-SF, Early Trauma Inventory Self Report-Short Form; ASI-R, Anxiety Sensitivity Index-Revised; BDI, Beck Depression Inventory; PDSS, Panic Disorder Severity Scale

onset of disease in patients with PD.[52] In addition, one such study suggested that early physical or sexual trauma are risk factors related to increased frequency of panic attacks in patients with PD.[52] Another study showed that a past history of early trauma was related to an earlier onset of symptoms in patients with PD.[53] Although our findings showed that the early trauma is positively correlated with pathological worry in patients with PD, there was no significant direct association between early trauma and long-term PTR in PD.

Our findings showed that the higher the patient's income level, the better the long-term PTR. We assume that individuals with a higher level of income generally tend to show less symptoms and disability, resulting in better PTR after long-term follow-up, which is consistent with a previous study.[54] However, our study findings showed that old age, gender, education level, and marital status are not significant potential sociodemographic predictors of long-term PTR. Therefore, further research on this is necessary in the future.

In addition, CBT effectively reduced pathological worries with a large overall effect size showing improvement following treatment at the 6-month follow-up in patients with GAD.[55] According to Well's metacognitive model in GAD, negative beliefs about the uncontrollability, danger, and meaning of worry may cause patients to worry about worrying, which in turn intensifies anxiety symptoms.[56] Further, changes in panic-related cognitions predicted the improvement of symptom severity for PD, mediating worry for CBT but not for pharmacotherapy.[57] Therefore, patients with PD with pathological worries might experience more severe anxiety symptoms than PD patients without pathological worries, and this might also be related to PTR.

Our study has several limitations. First, it is believed that in addition to self-reported evaluation measures such as PSWQ, objective evaluation measures evaluated by clinicians are necessary. Second, recall bias can happen when evaluating early trauma. Third, we recruited patients with PD in an acute care hospital, some of which might have depressive episodes in the long-term follow-up, as happens in the natural course of PD. Therefore, the possibility cannot be ruled out that the sampling bias influenced the response to long-term pharmacological treatment.

In conclusion, the current findings suggest that the symptoms of pathological worries could be associated with poor long-term PTRs in patients with PD. Therefore, our study highlights the need to detect the symptoms of pathological worry early to determine the direction of medical treatment and predict the results of pharmacotherapy for patients with PD. The optimization of pharmacological treatments and CBT will be necessary for individuals with PD in the future.

**Table 4.** Binary logistic regression results predicting the pharmacological treatment response at 6 months in patients with panic disorder

| Variables | Pharmacological treatment response at 6 months | | |
|---|---|---|---|
| | B | p-value | Odds ratio (95% CI) |
| Age (years) | 0.018 | 0.467 | 1.018 (0.970−1.069) |
| Gender (male) | 0.582 | 0.267 | 1.789 (0.641−4.996) |
| Level of education (high school or less) | -0.381 | 0.495 | 0.683 (0.229−2.041) |
| Marital status (living without partner) | -0.815 | 0.150 | 0.443 (0.146−1.344) |
| Monthly income (below 1,800 $USD) | 3.854 | 0.001** | 47.166 (4.571−486.658) |
| PSWQ at baseline (total sum) | -0.072 | 0.018* | 0.930 (0.876−0.988) |
| BDI at baseline (total sum) | -0.089 | 0.047* | 0.915 (0.839−0.999) |
| PDSS at baseline (total sum) | 0.284 | <0.001*** | 1.329 (1.158−1.524) |
| ASI-R at baseline (total sum) | 0.017 | 0.283 | 1.017 (0.986−1.050) |
| Early trauma (ETISR-SF, total sum of all subtypes) | -0.068 | 0.346 | 0.934 (0.810−1.076) |
| -2 log likelihood | 108.163 | | |
| $\chi^2$ (df) | 43.959 (10) (p<0.001***) | | |
| Cox & Snell $R^2$ | 0.305 | | |
| Overall percentage (%) | 67.8 | | |

Criteria for response of pharmacological treatment in patients with panic disorder is classified as the total PDSS score of 40% or greater reduction compared to the PDSS total score at baseline. *p<0.05; **p<0.01; ***p<0.001. CI, confidence interval; PSWQ, Penn State Worry Questionnaire; BDI, Beck Depression Inventory; PDSS, Panic Disorder Severity Scale; ASI-R, Anxiety Sensitivity Inventory-Revised; ETISR-SF, Early Trauma Inventory Self Report-Short Form

## Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available because all participants did not consent their information exposure.

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

## Author Contributions

Conceptualization: all authors. Data curation: all authors. Formal analysis: all authors. Funding acquisition: Sang-Hyuk Lee. Investigation: all authors. Methodology: all authors. Project administration: all authors. Resources: all authors. Software: all authors. Supervision: Sang-Hyuk Lee. Validation: all authors. Writing—original draft: all authors. Writing—review & editing: all authors.

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