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# Psychological characteristics of early remitters in patients with panic disorder

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ABSTRACT

We aimed to examine whether anxiety sensitivity and agoraphobic fear could affect the time taken to remission after 24 weeks of open-label escitalopram treatment of patients with panic disorder (PD). We recruited 158 patients, and 101 patients completed the study. Clinical severity and psychological characteristics were assessed at baseline and 4, 12, and 24 weeks after the treatment, using the Clinical Global Impression-Severity (CGI-S), the Hamilton Rating Scales for Anxiety and Depression, the Anxiety Sensitivity Index-Revised (ASI-R), the Albany Panic and Phobia Questionnaire (APPQ), and the Panic Disorder Severity Scale (PDSS). Remission was defined as the absence of full panic attacks and PDSS scores of 7 or less. Completing patients were stratified according to the time taken to remit: early ($n=20$) and late ($n=58$) remission and non-remission groups ($n=23$). There were no significant differences among the three groups at baseline on the CGI-S and the PDSS mean scores. However, early remitters had significantly lower scores than late remitters and non-remitters on the ASI-R and APPQ. In conclusion, anxiety sensitivity and agoraphobic fear can affect the time to remission after pharmacotherapy, and clinicians should consider the psychological characteristics of PD patients in order to achieve an optimal response to pharmacotherapy.



## 1. Introduction

Panic disorder (PD) is a disabling condition characterized by recurrent unexpected panic attacks, persistent anticipatory anxiety about additional attacks, and worry about the implications of the attacks or significant related changes in behavior (Goodwin et al., 2005). The negative effects of PD on social, familial and occupational functioning are comparable to those of depression and even many chronic medical conditions (Kessler et al., 2006). Patients with PD face problems associated with impaired work performance, and the long duration of PD has negative impacts on subjective well-being, contact with friends, and self-realization (Cramer et al., 2005; Waghorn et al., 2005). The longer PD persists, the greater the difficulty PD patients may experience in their social, familial and occupational functioning (Kessler et al., 2006; Hendriks et al., 2011).

PD is known to be very responsive to pharmacotherapy in the acute phase, but the long-term response to pharmacotherapy seems to be variable. Even with medication, about a third of PD patients do not improve and one in five follows an unremitting and chronic course (Bruce et al., 2005; Heldt et al., 2006; Marchesi et al., 2008). It is known that the sooner PD patients achieve a remission, the better their prognosis and future quality of life (Kampman et al., 2008).

Previous findings suggest some clinical factors associated with remission in PD patients. Pollack et al. (2002) found that early responders to anti-panic medications were more likely to be in remission at the end of treatment. In several studies, co-morbidity with depressive disorders, generalized anxiety disorder, or social phobia and severity of panic symptoms have been reported to result in a poorer prognosis (Keller et al., 1994; Chavira et al., 2009). Other studies also suggest that agoraphobic fear and avoidance behavior predict an unfavorable outcome and a chronic course of PD (Scheibe and Albus, 1996; Chavira et al., 2009). In previous long-term studies, PD patients without agoraphobia showed more improvement and a higher remission rate after pharmacotherapy when compared with those with agoraphobia (Carpiniello et al., 2002; Bruce et al., 2005). Batelaan et al. (2010) recently suggested that the presence of agoraphobia predicts a higher proportion of time with PD, and that agoraphobic fear could be one of the most important predictors of treatment outcome in PD. Although a number of studies to investigated predictors of treatment

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response in PD, only a few variables such as severity of PD and agoraphobic fear and avoidance have been suggested to be relatively consistent predictors of treatment outcome (Slaap and den Boer, 2001; Kampman et al., 2008).

Anxiety sensitivity (AS) is a dispositional cognitive construct that reflects an excessive fear of anxiety-related bodily sensations, and is caused by beliefs that these sensations are harmful and lead to physical, psychological, or social consequences (Reiss, 1991). According to AS theory, an individual with a high level of AS will experience amplified fear in response to stimuli that elicit anxiety and finds his/her own anxiety symptoms to be particularly aversive. Thus, AS is known to be one of the strong predictors of prognosis in anxiety disorders, such as generalized anxiety disorder, social phobia and especially PD (McNally, 2002; Plehn and Peterson, 2002; Struzik et al., 2004; Schmidt et al., 2006). In addition, AS has been found to be useful for identifying individuals at risk for the emergence or relapse of panic attacks in some prospective longitudinal studies (Ehlers, 1995; Schmidt et al., 2006). Previous studies have found that AS reduction is unlikely to occur after pharmacotherapy (Fava et al., 1994; McNally, 2002; Simon et al., 2004), and that AS remains higher in PD patients after 3 months of drug treatment even though their severity of illness decreased after the treatment (Choi et al., 2004). These findings indicate that AS is a dispositional and cognitive variable, which could be related to treatment response.

The purpose of this study was to investigate whether the psychological characteristics of PD patients affect the time to remission after pharmacotherapy, and we examined the relationship between psychological characteristic and clinical remission after escitalopram treatment. We hypothesized that early remitters would have less severe panic symptoms and have lower AS and agoraphobic fear at baseline than late remitters or non-remitters.

## 2. Methods

### 2.1. Subjects

The Structured Clinical Interview for the DSM-IV (SCID-IV) was administered to all subjects by experienced psychiatrists. Patients with a high suicidal risk or mental illnesses including major depressive disorder, bipolar affective disorder, schizophrenia, other psychotic disorders, and alcohol or other substance abuse were excluded from the study. Patients with personality disorders were also excluded from the study through psychiatric interview and history taking. Finally, we recruited 158 PD patients — 87 male (55.06%) and 71 female (44.94%) from six university hospitals in South Korea (Samsung Medical Center, Seoul Paik Hospital, Ilsan Paik Hospital, Wonkwang University Hospital, Ewha-Womans University Mokdong Hospital, and Chonbuk National University Hospital). All gave their informed consent as participants after being provided with complete information about the study, and the study was approved by the institutional review board of Samsung Medical Center.

### 2.2. Assessment

At the first visit, the patients were assessed using the Clinical Global Impression-Severity (CGI-S) (Guy, 1976), the Hamilton Rating Scales for Anxiety (HAM-A) (Hamilton, 1959) and Depression (HAM-D) (Hamilton, 1960), the Anxiety Sensitivity Index-Revised (ASI-R), the Albany Panic and Phobia Questionnaire (APPQ) and the Panic Disorder Severity Scale (PDSS).

The ASI-R (Taylor and Cox, 1998) is a 36-item revised and expanded version of the original 16-item ASI. Each item is rated on a 5-point Likert scale from 0 to 4, so that total scores range from 0 to 144. The scale consists of four sub-factors: fear of cardiovascular symptoms, fear of publicly observable anxiety reactions, fear of respiratory symptoms, and fear of cognitive dyscontrol. For this study, we used the Korean version of the ASI-R (Kim et al., 2004b), which was shown to have high internal consistency (0.92) and test-retest reliability (0.82).

The APPQ (Rapee et al., 1995) is a 27-item instrument that is designed to measure interoceptive, agoraphobic, and social situational fear. Subjects respond to each item on a 9-point Likert scale from 0 to 8, according to how much fear they think they would experience in a given situation so that total scores range from 0 to 216. In this study, we used the Korean version of the APPQ (Kim et al., 2004a), which was found to have high internal consistency (0.95) and test-retest reliability (0.77).

The PDSS (Shear et al., 1997) is a 7-item scale to assess multiple dimensions of PD severity. Each item is rated on a 0-4 scale so that total scores range from 0 to 28. We used the Korean version of the PDSS (Kim, 2001), which has high inter-rater reliability (0.88) and test-retest reliability (0.96).

All patients were assessed on the CGI-S, HAM-A, HAM-D, ASI-R, APPQ and PDSS at baseline and 4, 12, and 24 weeks after beginning treatment.

### 2.3. Treatment

The minimal effective dose of escitalopram is usually set at 10mg for Caucasian patients. However, there is an ethnic difference in the effective dose of antidepressants between Asian and Caucasian people (Lin et al., 1986), and in Korea, physicians usually use a starting dose of escitalopram that ranges from 5 or 10mg per day in order to help PD patients tolerate possible adverse effects of the medication (Kim, 1998). Thus, all PD patients were treated with escitalopram at an initial dose of 5 or 10 mg per day with the dose being increased up to 20 mg per day according to the clinician's judgment.

If patients were taking any other anti-panic medication before participating in this study, they did not start our treatment until 2 weeks after the other medication had been withdrawn. The mean daily doses (±SD) of escitalopram was 11.94±4.23mg/day, and there was no difference in the mean escitalopram dose between completers and dropouts (12.24±3.93mg/day vs. 11.38±4.74mg/day). During the first 4 weeks, alprazolam was allowed for 71 patients (63 patients in the completer subgroup and 8 patients in the dropout subgroup, respectively), but it was tapered down and finally stopped by 3 months after excitalopram treatment began. Zolpidem was allowed for insomnia and was prescribed for 16 patients (13 patients in the completer subgroup and 3 patients in dropout subgroup, respectively).

### 2.4. Remission criteria

Ballenger et al. (1998) described the remission of PD as no or minimal anxiety, no functional impairment, no or minimal symptoms of depression, essentially free of panic attacks, and no or only mild agoraphobic avoidance. Formal criteria for defining remission in PD in accordance with Ballenger et al. (1998) have been proposed, but the issue is still under discussion. In previous studies, the clinical progress of PD patients was assessed in terms of a reduction in HAM-A scores, but these scores measure general anxiety symptoms and are not specific for panic symptoms (Pollack et al., 2002; Marchesi et al., 2008). As previously stated, the PDSS assesses multiple dimensions of PD severity and covers the remission criteria suggested by Ballenger et al. (1998). We therefore defined clinical remission as the absence of full panic attacks and a PDSS score ≤7, which is in line with the suggestion made by Furukawa et al. (2009).

### 2.5. Analysis

To control missing values for a given evaluation, we used the last-observation-carried-forward (LOCF) method. The Statistical Package for the Social Science (SPSS) for Windows (version 17.0) was used for all statistical analyses, and statistical significance was defined at the 0.05 level (two-tailed tests). The Bonferroni correction for multiple comparisons was used when needed. Chi-square tests were conducted to examine group differences in nominal and categorical variables. After normality of the data was confirmed by the Shapiro-Wilk test, scores on continuous variables, such as those on the PDSS and HAM-A, were compared using analysis of variance (ANOVA) and Scheffé *post-hoc* tests. The comparisons of scores on other variables (CGI-S, HAM-D, ASI-R, and APPQ) were performed using the Kruskal–Wallis test as the data were not normally distributed, and the Mann–Whitney *U* test with Bonferroni correction was used for *post-hoc* analyses. Finally, logistic regression was performed to confirm the predictors of remission in PD patients. Age, sex, and scores on the PDSS, HAM-A, HAM-D, APPQ and ASI-R were entered as independent variables in the logistic regression analysis.

## 3. Results

Of the 158 PD patients who were initially enrolled, 57 withdrew from the study for the following reasons: lost to follow-up ($n=48$), adverse events ($n=3$), withdrawal of consent ($n=4$), and no need to continue the treatment due to clinical improvement ($n=2$). There were no significant differences in the demographic data and mean scores of the psychological rating scales at baseline between the 101 study completers and the 48 patients who were lost to follow-up. Of the 101 PD patients completing the study, 56 (55.4%) were males and 45 (44.6%) were females. Their mean age was 42.14 years (SD=11.0), and 56 (55.4%) had comorbid agoraphobia.

After 24 weeks of pharmacotherapy, 78 patients (77.2%) had attained remission. All participants were then stratified into three groups: an early remission group who attained remission within the first 4 weeks ($n=20$), a late remission group who attained a remission from 4 weeks to 24 weeks ($n=58$) after beginning treatment and a non-remission group who had not attained remission by the end of the study ($n=23$). There were no differences between these three