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Trajectories of recovery in depressed Parkinson's disease patients treated with paroxetine or venlafaxine

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ABSTRACT

Introduction: Depression is considered a syndrome with a constellation of symptoms that are frequently categorized into 3 domains including affective, somatic and cognitive. There has been limited research into the domain specific magnitude or relative timing of treatment response in patients with Parkinson's disease (PD). In addition, antidepressant trials involving patients with PD have demonstrated a similar robust placebo response to that seen in other populations. However, the timing of the placebo response has not been carefully studied.

Methods: We studied differential responses to antidepressant treatment in affective, somatic and cognitive domains of depression. Patients were treated for twelve weeks with placebo, venlafaxine or paroxetine as part of the Study of Antidepressants in Parkinson's Disease (SAD-PD) randomized controlled trial. Depressive symptoms were evaluated with three commonly used rating scales.

Results: All symptom domains improved during the study period, There was a significant placebo effect, especially in the first two weeks that had diminished by week 12. Compared to placebo, the affective symptoms significantly improved during treatment as early as week 4, followed by the somatic symptoms of depression in week 6 and cognitive symptoms in week 8. The largest response was seen in the affective domain.

Conclusion: In depressed PD patients treated with venlafaxine or paroxetine, affective symptoms improved first, followed by somatic symptoms and cognitive symptoms. These findings could guide patient counselling and increase patient compliance by informing about the expected treatment responses. The substantial placebo effect underlines the importance of a sufficiently long study period in future studies.

1. Introduction

Clinically significant depressive symptoms are found in up to 50% of Parkinson's disease (PD) patients, with an estimated prevalence of major depressive disorder of 17% [1]. Depressed PD patients report a decreased quality of life and consistently rate the effect of their psychiatric disturbances as more detrimental to their well-being than the severity of motor symptoms [2,3]. However, only about 20% of depressed PD patients receives treatment for depression [4] and despite extensive research, there is still discussion about the optimal treatment strategy [5,6]. In addition, several studies showed that up to 67% of PD patients have a low medication adherence [7–9]. Mood disorders, especially depressive disorders, seem to be the most important factor for non-adherence [10]. Studies in psychiatric populations show that education of depressed patients when starting antidepressants greatly improves compliance [11].

Symptoms of depression are frequently subdivided in three

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domains including affective, somatic and cognitive symptoms (concentration and ideational). Research exploring domain specific magnitude or timing of treatment response is scarce. A more thorough understanding of this response in depressed PD patients could aid patient counselling by informing the patients about the expected response. In addition, although antidepressant trials involving PD patients have demonstrated robust placebo responses similar to that seen in other population, there is no thorough study of the timing of this response.

The aim of this analysis is to explore differential response patterns to treatment with venlafaxine or paroxetine in the affective, somatic and cognitive domains of depressed PD patients using data of the largest placebo-controlled randomized controlled trial (RCT) of antidepressants for the treatment of depression in PD patients to date.

2. Methods

This study is a secondary analysis on the dataset of the Study of Antidepressants in PD (SAD-PD) [12]. This study showed superior efficacy of treatment with venlafaxine or paroxetine over placebo treatment in depressed PD patients.

2.1. Participants

The SAD-PD study enrolled 115 participants from 20 centres in the United States, Canada, and Puerto Rico from 2005 through 2009. Patients with idiopathic PD, diagnosed according to the Queen Square Brain Bank criteria [13] had to meet diagnostic criteria of the 4th edition of the Diagnostic and Statistical Manual (DSM-IV) [14] for major depressive disorder, dysthymic disorder or minor depression. Patients with dementia as defined by the DSM-IV criteria, or those with a Mini Mental Sate Examination (MMSE) [15] score <23 were excluded. Antidepressant medication other than the study drugs, as well as antipsychotics and MAO inhibitors were not permitted.

2.2. Standard protocol approvals, registrations, and patient consents

The study was approved by the local Medical Ethics Committees of all participating institutions. Patients gave written informed consent before inclusion in the study. The study was registered with clinicaltrials.gov (registration no. NCT00086190).

2.3. Assessment and randomization

During a screening visit informed consent was obtained and eligibility criteria were verified. During the baseline visit ($t = 0$) the participants were randomized to venlafaxine, paroxetine or placebo in a 1:1:1 ratio. Double-blind treatment lasted 12 weeks and consisted of a 6-week dosage titration and a 6-week maintenance period. The first two weeks participants received 10 mg of paroxetine or 37,5 mg of venlafaxine XR or matching placebos. The following 4 weeks the investigator then adjusted the dosage as necessary and tolerated up to a maximum daily dosage of 40 mg for paroxetine and 225 mg for venlafaxine XR to achieve the optimal dosage. Patients were evaluated at 2, 4, 6, 8 and 12 weeks after randomization. During these evaluations participants were assessed in the “on” state. Antidepressant efficacy was rated by the 17-item Hamilton Depression Rating Scale (HAMD) [16], Montgomery-Åsberg Depression Rating Scale (MADRS) [17] and the Beck Depression Inventory II (BDI-II) [18].

2.4. Statistical methods

None of the depression rating scales used in the study has a satisfactory factorial structure on the basis of which symptom domains could be defined [19]. In order to formulate symptom domains we subdivided the items of the HAMD, BDI-II and MADRS into “affective”, “somatic” or “cognitive”, based on face validity (Table 1). Only items with clear affective, cognitive or somatic characteristics were included. Items that could not be easily attributed to one of these domains, such as agitation, were not included. The cognitive domain consisted of both symptoms of cognitive dysfunction (such as concentration difficulties, lack of insight) as well as of depressive-related ideation. The final affective domain included 14 items, the cognitive domain 14 items and the somatic domain 16 items. All three domains showed excellent internal consistency with Cronbach's α 0.96, 0.95 and 0.94 respectively. Since the three depression scales had different ranges, means and standard deviations, we standardized the scores by calculating z-scores of each domain. First we calculated the z-score of the patient per scale and per domain, after which we averaged the domain-specific z-scores on the three scales into one single score.

Since there was no difference in the depression outcome between patients treated with venlafaxine and paroxetine [12], we decided to combine these two treatment groups to increase the power of our analysis. The between group difference in change in domain-specific z-scores compared to baseline was evaluated at 2,4,8 and 12 weeks using a repeated measures analysis of variance (rm-ANOVA). The dependent variable was the domain-specific averaged z-score, and the within-subject factor was “time” (6-levels: baseline, week 2,4,6,8 and 12). Since Mauchly's test of sphericity was significant, all F- and df -values were adjusted following the method of Greenhouse-Geisser if Epsilon was <0.75 (cognitive domain) or Huynh-Feldt if Epsilon was >0.75 (affective and somatic domain). The between-subject factor was group (“placebo” or “active treatment”). The interaction between treatment and time was of most interest as it indicates differential improvement between groups in the dependent variable. All analyses were computed with SPSS 21 (Chicago). In order to further test whether change across domains was significantly different, we compared the delta scores per domain (defined as the score at last observation minus the score at baseline) using three paired-sample t-tests in a post-hoc analysis.

3. Results

A total of 115 subjects were randomized to receive paroxetine ($n = 42$), venlafaxine XR ($n = 34$), or placebo ($n = 39$). Eighteen subjects (16%) withdrew participation and 4 (3%) were not assessed on all measurement points (2,4,6,8,12 weeks). For the final analyses the placebo group consisted of 32 subjects and the treatment group of 61 (33 on paroxetine and 28 on venlafaxine). The demographic and disease characteristics of the two groups are listed in Supplementary table 1. Fifty-nine percent of patients in the active treatment group had a diagnosis of major depressive disorder versus 56% in the placebo treated group. The active treatment group was slightly older than the placebo treated group (64.2 years versus 61.4 years), mean disease duration in the treatment group was 5.3 years, in the placebo group 5.5 years. Mean scores on the HAM-D, MADRS and BDI-II at baseline were comparable in both groups.

RM-ANOVA showed a significant time effect in all three domains for both groups, with a significant group-by-time interaction in the 3 depression symptom domains (affective: Wilks' Lambda = 0.86, F