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Therapeutic effects of escitalopram and reboxetine in seasonal affective disorder: A pooled analysis

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ABSTRACT

The monoaminergic neurotransmitters serotonin and noradrenaline have both been implicated in the pathogenesis of seasonal affective disorder (SAD). However, the differential therapeutic value of selective serotonin reuptake inhibitors (SSRI) and selective noradrenaline reuptake inhibitors (NARI) in SAD has not been assessed until now. This study compares data from two open-label trials with similar methodology investigating the SSRI escitalopram and the NARI reboxetine. 20 SAD patients were treated with escitalopram (10–20 mg) and 15 patients received treatment with reboxetine (fixed dosage: 8 mg) over 6 weeks. Ratings included the structured interview guide for the Hamilton depression rating scale, SAD version (SIGH–SAD), the clinical global impression of severity (CGI-S) and improvement (CGI-I) and the UKU side effect rating scale. Treatment led to a significant reduction in SIGH–SAD score, CGI-S and CGI-I after one week in the reboxetine group and after two weeks in the escitalopram group. SIGH–SAD score was significantly lower in the reboxetine group at weeks 1, 2 and 4 but not at the end of the study. The response rate (SIGH–SAD <50% of baseline value) and the remission rate (SIGH–SAD <8) were not significantly different after 6 weeks of treatment, but the time to response and to remission was significantly shorter in the reboxetine group. The number and severity of side effects were higher in patients treated with reboxetine at all time points. Thus escitalopram and reboxetine were equally effective in treating SAD on all primary and secondary outcome measures. Reboxetine displayed a faster onset of action, but was associated with more pronounced side effects. Further studies comparing SSRI and NARI in SAD are warranted.

1. Introduction

Seasonal affective disorder (SAD) is a relatively frequent mood disorder in temperate climates. It is defined by reoccurence of depressive episodes in autumn and winter (fall-winter depression) alternating with remission or hypomania, more seldom mania, during the successive spring and summer (Rosenthal et al., 1984). Preliminary data indicate a high degree of social impairment and socioeconomic costs for patient suffering from SAD (Pjrek et al., 2008), highlighting the necessity of early recognition and adequate treatment. Bright light therapy is a first choice treatment for SAD patients (Winkler et al., 2006). However, light therapy is either not entirely effective or not suitable for other reasons in about 50% of cases (Pjrek et al., 2004). For those patients antidepressant drug treatment has been established as a viable alternative (Winkler et al., in press).

Several studies have been conducted to elucidate the pathogenetic background of SAD: studies in drug-free patients employing monoamine depletion (Neumeister et al., 1998; Stastny et al., 2003) and challenge tests (Coiro et al., 1993; Schwartz et al., 1997), neuroimaging studies (Neumeister et al., 2001; Willeit et al., 2000) and findings from studies exploring serotonin transporter function in SAD (Willeit et al., 2008) have suggested an involvement of the serotonergic, but also noradrenergic and dopaminergic neurotransmitter systems. However, the differential value and the specific clinical advantages and disadvantages of selectively influencing one of these monoaminergic neurotransmitters in the pharmacotherapy of SAD have not been assessed until now.

The aim of this study was to compare existing data on treatment of SAD with escitalopram and reboxetine in regard to clinical efficacy and tolerability. Escitalopram is a selective serotonin reuptake inhibitor (SSRI) with high affinity to the serotonin transporter. It has been postulated that escitalopram binds to a secondary allosteric binding site on the serotonin transporter molecule, which is able to augment the efficacy of reuptake inhibition (Chen et al.,

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2005; Klein et al., 2007). Reboxetine on the other hand is a potent and highly selective noradrenaline reuptake inhibitor (NARI), which is devoid of any relevant affinity to other neurotransmitter receptors (Kasper et al., 2000).

2. Method

We submitted data from two observational studies with similar methodology to a comparative reanalysis. These trials had both been conducted by the same working group at the outpatient clinic for SAD of the Department of Psychiatry and Psychotherapy, Medical University of Vienna. Twenty patients had been treated with escitalopram in a flexible dosage of 10–20 mg (Pjrek et al., 2007) and 15 patients had received reboxetine 8 mg per day (Hilger et al., 2001). One patient of the reboxetine group, who had been reported in the original publication, and who had been lost to follow up after the baseline visit, was not included in this study. Patients had to fulfill the Rosenthal criteria for SAD (Rosenthal et al., 1984) and the DSM-IV criteria for major depressive disorder (American Psychiatric Association, 1994). Study subjects with psychiatric comorbidity and severe somatic illness were excluded by the protocol. Patients received open-label treatment as monotherapy. Data of the first 6 weeks of treatment of the escitalopram study were used to match the duration of the reboxetine trial. Assessments were performed at baseline and at weeks 1, 2, 4 and 6 for both groups using the same psychometric instruments including the structured interview guide for the Hamilton depression rating scale, SAD version (SIGH–SAD, 29 items) (Williams, 1988; Williams et al., 2002), the clinical global impression of severity (CGI-S), the clinical global impression of improvement (CGI-I), the CGI efficacy index (CGI-EI), a composite measure that reflects efficacy and tolerability (Guy, 1976) and the social adaptation self-evaluation scale (SASS) (Bosc et al., 1997). Side effects were systematically assessed with the udvalg for kliniske undersogelser (UKU) side effect rating scale (Lingjærde et al., 1987). Additional information on the protocols of the two underlying studies are documented in the original reports (Hilger et al., 2001; Pjrek et al., 2007).

Primary outcome measures were SIGH–SAD total score as well as response and remission rates that were calculated from SIGH–SAD score. The criterion for response was a reduction in baseline SIGH–SAD total score of more than 50%. Remission was defined as a SIGH–SAD total score of 7 or lower. Secondary outcome variables included three subscores of the SIGH–SAD (Hamilton 21 item scale, atypical 8 item scale and Hamilton 6 item scale (Bech et al., 1981) consisting of the items depressed mood, guilt, work and activities, retardation, psychic anxiety and general somatic symptoms), CGI-S, CGI-I, CGI-EI, SASS score, number of adverse events and UKU grading of side effects.

Statistical analysis was performed with SPSS 15.0 for Windows (SPSS Inc., 1989–2006). A last observation carried forward (LOCF) procedure was utilized to account for early terminators. Data were tested for outliers and departures from normality. We used a two-way, mixed design analysis of variance (ANOVA) for each outcome parameter with time of treatment (week 0, 1, 2, 4, 6) as within subjects factor and treatment group (escitalopram or reboxetine) as between subjects factor. Mauchly's W was calculated to check for violations of the sphericity assumption, and the Huynh–Feldt correction was applied, whenever the assumption was not met. In case of a significant time *x* group interaction we examined simple main effects with one-way repeated measures ANOVA. Bonferroni-corrected post-hoc tests were performed, when there was a significant effect of time. Data were analyzed for group differences at all time-points with Student's *t*-test. We carried out a Levene test for equal variances before computation of the *t*-tests and applied a correction, whenever the assumption was not met. Furthermore, we corrected the significance levels of the *t*-tests for multiple testing using the Holm–Bonferroni method (Holm, 1979). The adjusted significance level is given in square brackets after the respective *p*-value. Fisher's exact test was employed to assess group differences between the two treatments in categorical variables. The Mann–Whitney test was calculated for differences between groups for the median time to response and to remission. Kaplan–Meier survival analysis was used for estimation and graphical presentation of response and remission. The $p \leqslant 0.05$ level of significance was adopted unless otherwise specified. All statistical comparisons were two-tailed.

3. Results

There were no statistically significant differences in the demographic and clinical variables between the escitalopram and the reboxetine group (Table 1). At baseline we found no significant group differences with regard to SIGH–SAD score (escitalopram: 28.2 ± 4.8; reboxetine: 32.7 ± 8.3; $t = -1.905$, df = 20.961, $p = 0.071$ [<0.025]), Hamilton 21 item score, atypical 8 item score, Hamilton 6 item score and CGI-S. The SASS score was slightly higher in the reboxetine group at baseline (37.7 ± 7.4 vs. 31.2 ± 8.3), but the difference was not statistically significant after employing the Holm–Bonferroni correction ($t_{(33)} = -2.389$; $p = 0.023$ [<0.010]).

Two-way ANOVA of SIGH–SAD score (Fig. 1) yielded a significant effect of time ($F_{(3.165,104.453)} = 89.929$; $p < 0.001$) and group ($F_{(1,33)} = 14.341$; $p = 0.001$) and a significant time *x* group interaction ($F_{(3.165,104.453)} = 8.082$; $p < 0.001$). Using one-way ANOVA we observed a progressive reduction in SIGH–SAD score in both groups (escitalopram: $F_{(4,76)} = 97.133$; $p < 0.001$; reboxetine: $F_{(3.325,46.554)} = 29.168$; $p < 0.001$) with statistical significance from week 1 on ($p < 0.001$) in patients treated with reboxetine and from week 2 on ($p < 0.001$) in escitalopram treated patients. SIGH–SAD score was lower at week 1 ($t_{(17.530)} = 4.813$; $p < 0.001$ [<0.010]), week 2 ($t_{(33)} = 2.575$; $p = 0.015$ [<0.017]) and week 4 ($t_{(33)} = 2.886$; $p = 0.007$ [<0.013]) in the reboxetine group than in the escitalopram group, but not at week 6 ($t_{(33)} = 1.423$; $p = 0.164$ [<0.050]).

Consecutively performed two-way ANOVAs resulted in a significant within subjects factor and a significant interaction term for Hamilton 21 item score (time: $F_{(3.245,107.082)} = 61.153$; $p < 0.001$; interaction: $F_{(3.245,\ 107.082)} = 2.896$; $p = 0.035$), atypical 8-item score (time: $F_{(2.931,96.736)} = 62.522$; $p < 0.001$; interaction: $F_{(2.931,96.736)} = 9.976$; $p < 0.001$) and Hamilton 6 item score (time: $F_{(3.677,121.345)} = 80.667$; $p < 0.001$; interaction: $F_{(3.677,121.345)} = 4.542$; $p = 0.003$). Simple main effects were significant in both groups for Hamilton 21 item score (escitalopram: $F_{(4,76)} = 62.351$;

Table 1
Demographic and clinical characteristics of the two samples. Variables are presented as arithmetic mean ± standard deviation or percentage values. Escitalopram vs. reboxetine: $p > 0.05$ for all comparisons.

	Escitalopram	Reboxetine
N	20	15
Sex		
Female	14 (70.0%)	13 (86.7%)
Male	6 (30.0%)	2 (13.3%)
Age (years)	40.8 ± 13.4	41.6 ± 9.6
Body mass index (kg/m^2)	23.3 ± 3.8	22.9 ± 3.1
Family history for psychiatric disorders (first degree relatives)	10 (50%)	7 (50.0%)[a]
Age at onset of illness (years)	27.3 ± 12.0	31.4 ± 12.3
Number of depressive episodes	10.2 ± 7.3	6.6 ± 5.0
Global seasonality score (SPAQ)	14.6 ± 3.9	15.9 ± 3.9
DSM-IV feature specifier		
Atypical	10 (50.0%)	10 (66.7%)
Melancholic	1 (5.0%)	2 (13.3%)

[a] Missing information on one subject.