

## Reboxetine in seasonal affective disorder: an open trial

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Received 27 June 2000; accepted 5 September 2000

### Abstract

Seasonal affective disorder (SAD), winter type, is a condition characterized by the annual recurrence of depressive episodes during fall/winter, alternating with spring/summer euthymia or hypomania. Various neurotransmitters have been implicated in the etiology of SAD, the strongest evidence involving serotonin. Recently, increasing attention has been paid to the potential role of catecholaminergic pathways in the pathophysiology of SAD. We investigated the efficacy and tolerability of reboxetine, a selective noradrenaline inhibitor, in patients with SAD. Eleven out of sixteen patients who were included in a 6-week drug surveillance during winter season experienced full remission of depressive symptoms. Nine patients reported a rapid relief of preexistent severe atypical depressive symptoms within the first treatment week. Reboxetine might therefore be an effective and well-tolerated treatment option for SAD patients. In conclusion, our preliminary results are in line with evidence from recent studies suggesting that catecholaminergic systems might also be involved in the pathophysiology of SAD. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Seasonal affective disorder; Depression; Atypical symptoms; Noradrenaline; Reboxetine

### 1. Introduction

Seasonal affective disorder (SAD) is a condition characterized by annually occurring depressive episodes, the most usual pattern being symptom onset in fall and winter followed by full remission or hypomanic states during spring and summer (Rosenthal et al., 1984). Furthermore the optionally present so-called atypical depressive symptoms, e.g. hypersomnia, fatigue, hyperphagia, carbohydrate craving, and subsequent weight gain often precede impaired functioning (Tam et al., 1997).

Emphasis has been put in evaluating treatment options for patients with SAD. The antidepressant effect of bright light therapy (BLT) in the treatment of seasonal depression is well documented (Eastman et al., 1998; Lewy et al., 1998; Terman et al., 1998). In case patients do not respond sufficiently to light treatment or object to the usage of light therapy for logistical reasons, the best evidence so far for efficacy of antidepressants in SAD involve the selective serotonin reuptake inhibitors (SSRIs) with sertraline and

fluoxetine having been studied predominantly (Lam et al., 1995; Blashko, 1995; Kasper et al., 2000).

Studying the biological basis of SAD, several studies focused on alterations in brain serotonergic systems (Wirz-Justice and Richter, 1979; Carlsson et al., 1980; Arora and Meltzer, 1988; Neumeister et al., 1997; Schwartz et al., 1997; Yatham et al., 1997; Neumeister et al., 2000a, Willeit et al., 2000). Little is known about the potential role of catecholaminergic pathways in the etiology of SAD. Evidence for the importance of catecholamines in the pathophysiology of SAD can be inferred from studies showing that (a) resting plasma norepinephrine levels are inversely correlated with the level of depression in drug-free SAD patients (Rudorfer et al., 1993), (b) BLT decreases the urinary output of norepinephrine and its metabolites (Anderson et al., 1992), (c) catecholamine depletion disrupts the beneficial effects of light therapy (Neumeister et al., 1998) and (d) dopamine transporter availability is reduced in untreated symptomatic depressed SAD patients (Neumeister et al., 2000b). In addition, mirtazapine, an antidepressant drug providing a dual mechanism by increasing noradrenergic and serotonergic neurotransmission, was found to be effective in a drug surveillance with patients suffering from SAD (Hessel-

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mann et al., 1999). However, plasma concentrations of the major norepinephrine metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) did not differentiate depressed patients with SAD from controls or patients with SAD in BLT-induced remission, nor did cerebrospinal fluid levels in relation to either MHPG or the 5-HT metabolite 5-hydroxyindolaecetic acid (Rudorfer et al., 1993).

Reboxetine is a novel selective noradrenaline reuptake inhibitor with proven antidepressant efficacy in the treatment of non-seasonal depression (Kasper, 1999) which has recently become available in a number of European countries. Reboxetine specifically inhibits the noradrenaline transporter and has shown to have negligible affinity for adrenergic, muscarinic, serotonergic, and histaminergic receptor systems (Montgomery, 1999)

So far, in the pharmacological treatment of SAD efficacy has been documented predominantly for serotonergic agents (Kasper et al., 2000). In the present drug surveillance we investigated the efficacy and tolerability of the noradrenergic compound reboxetine in patients with SAD.

## 2. Experimental

Sixteen symptomatic depressed outpatients (see Table 1), who met the Rosenthal criteria for SAD (Rosenthal et al., 1984) and the diagnostic criteria for a major depressive disorder outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV, American Psychiatric Association, 1995), entered a 6-week drug surveillance with reboxetine. Patients were investigated between October 1998 and February 1999. All patients had been free of psychotropic drugs for at least 6 months and were screened to be medically healthy. Five patients had been drug-naive.

Patients were treated with reboxetine 8 mg p.o./day as monotherapy. Treatment response was evaluated using the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD), which consists of the 21-item version of the HDRS (Hamilton, 1976) and is

supplemented by eight additional items with particular relevance to the atypical symptoms of SAD (Rosenthal et al., 1987). Side-effects were assessed using the UKU-Side Effect Scale and by spontaneous report. In addition, a new scale for the assessment of quality of life from the patients perspective, the Social Adaption Self Evaluating Scale (SASS) (Bosc et al., 1997) was employed. Ratings were performed on day 0, 7, 14, 28 and 42.

Positive treatment response was defined as a decrease of at least fifty percent from the baseline SIGH-SAD score and a total SIGH-SAD score  $\leq 12$ .

Statistical evaluation of the clinical response was done by comparing baseline SIGH-SAD scores and SIGH-SAD scores after 6 weeks of treatment using a paired two-tailed *t*-test. Changes in atypical depressive symptoms after 1 week and changes in social functioning by comparing baseline SASS total scores with SASS total scores on day 42 were also calculated using a paired two-tailed *t*-test. Results were considered significant at  $P < 0.05$ . Reported values are means  $\pm$  S.D. Analyses were performed with SPSS for Windows 95, V.7.0.

## 3. Results

Twelve out of sixteen patients completed the 6-week observation period. Eleven patients were classified as treatment responders according to the remission criteria noted above (SIGH-SAD D0:  $33.3 \pm 6.7$  vs. SIGH-SAD D42:  $4.0 \pm 6.5$ ; two-tailed  $t = 12.5$ ;  $df = 11$ ;  $P < 0.001$ ), (see Fig. 1).

Interestingly, nine out of eleven treatment responders who suffered from severe atypical symptoms (e.g. hypersomnia, fatigue and hyperphagia) experienced a rapid relieve of their atypical symptoms within the first week of treatment (HRDS Suppl. D0:  $14.3 \pm 4.9$  vs. D7:  $5.4 \pm 5.8$ ; two-tailed  $t = 5.4$ ;  $df = 11$ ;  $P < 0.001$ ), (see Fig. 2).

Comparison of SASS total scores between baseline (SASS D0:  $36.8 \pm 5.3$ ) and day 42 (SASS D42:  $40.7 \pm 6.7$ ) showed a trend towards statistical significance (two-tailed  $t = -2.07$ ;  $df = 10$ ;  $P < 0.065$ ).

Of the sixteen patients initially enrolled, four did not complete the protocol. Two patients dropped out because of non-compliance, two patients discontinued reboxetine because of side-effects in the early treatment phase: One patient (m/37a) experienced moderate urinary retention which resolved after drug discontinuation, another patient (f/41a) reported insomnia and psychomotor agitation.

Reported side-effects in the responder group were orthostatic dysregulation, dry mouth, constipation, psychomotor agitation, sleep disturbances, increased heart rate, palpitations, and nocturnal sweating. Side-effects were observed in the early treatment phase and disappeared within the first 2 weeks of treatment. No concomitant medication was necessitated.

Table 1  
Clinical and demographic characteristics<sup>a</sup>

Number		16
Gender		M/F=2/14
GSS		$16.3 \pm 3.6$
Age of onset		$31.5 \pm 12.0$
Number of episodes		$6.2 \pm 5.0$
Previous treatments	SSRIs	$n = 5$
	BLT	$n = 9$
	Drug naive	$n = 5$

<sup>a</sup> GSS, global seasonality score (Rosenthal et al., 1984); SSRIs, selective serotonin reuptake inhibitors; BLT, bright light therapy.

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