HUMAN PSYCHOPHARMACOLOGY
*Hum. Psychopharmacol. Clin. Exp.* **14**, 59–62 (1999)

# Mirtazapine in Seasonal Affective Disorder (SAD): A Preliminary Report

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Beside light therapy, selective serotonin reuptake inhibitors (SSRI) are the recommended treatment for patients suffering from Seasonal Affective Disorder (SAD). They seem to particularly resolve the atypical symptoms of SAD, while tricyclic antidepressants tend to worsen them. The latter has been linked to the broader spectrum of neurotransmitter modulation tricyclics enfold. Mirtazapine is a novel antidepressant providing a broad spectrum of neurotransmitter modulation on a basis of high selectivity. In order to evaluate the antidepressant efficacy of mirtazapine in the treatment of SAD, eight depressed and drug-naive SAD patients entered a 4 week drug surveillance and received 30 mg of mirtazapine per day. Clinical response was assessed using the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder Version (SIGH-SAD). Our preliminary results show that mirtazapine was not only well tolerated by the patients but also efficacious in the treatment of SAD. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS — seasonal affective disorder; treatment; mirtazapine; efficacy

## INTRODUCTION

Seasonal affective disorder (SAD)/winter type is a variant of the major depressive or bipolar disorder where recurrent depressive episodes during fall/winter alternate with spring/summer euthymia or hyperthymia (Rosenthal *et al*., 1984). Typically, the depressive episodes are associated with atypical symptoms, e.g. increased appetite, carbohydrate craving, weight gain, fatigue and hypersomnia. The pathogenesis of SAD is yet undetected. Previous studies showed that light therapy is an effective antidepressant therapy for SAD (Kasper *et al*., 1989; Terman *et al*., 1989).

It seems likely that monoaminergic pathways are involved in both the pathophysiology of SAD and the mechanism of action of light therapy. Evidence for serotonergic mechanisms can be inferred from studies showing (1) a seasonal rhythm of (a) human hypothalamic 5-HT concentrations, (b) platelet 5-HT uptake and $^{3}$[H]-imipramine binding, (c) levels of 5-HT and its metabolites in plasma and cerebrospinal fluid, (2) abnormal activation-euphoria responses induced by meta-chlorophenylpiperazine (m-CPP) in symptomatic depressed SAD patients but not after successful light therapy or during summer or in healthy controls (3) abnormal hormonal responses after administration of m-CPP or sumatriptan in depressed SAD patients, (4) efficacy of serotonergic agents such as fenfluramine or the selective 5-HT reuptake inhibitors such as fluoxetine or sertraline in the treatment of SAD, (5) tryptophan depletion studies suggesting that serotonergic dysfunction may be a trait marker in SAD (Neumeister *et al*., 1997a,b; Neumeister *et al*., 1998a). Evidence for the importance of catecholaminergic systems are as follows: (1) resting plasma norepinephrine levels have been shown to be inversely correlated with the level of depression in untreated SAD patients, (2) light therapy was shown to decrease the urinary output of norepinephrine and its metabolites, (3) studies reported increased, but also decreased basal plasma prolactin levels, (4) SAD patients showed an increased eyeblink rate and (5) catecholamine depletion disrupts the beneficial effects of light therapy (Neumeister *et al*., 1998b).

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CCC 0885–6222/99/010059–04$17·50

As an alternative to light treatment, several open and placebo-controlled trials investigated the efficacy of psychopharmacological treatments for SAD. Several studies suggest that selective serotonin reuptake inhibitors (SSRIs) are effective and well tolerated by the patients (for overview see Kasper *et al*., 1994). Older antidepressants, e.g. tricyclics, in comparison to SSRIs were found to rather aggravate atypical symptoms, which was linked to their broader spectrum of neurobiological modification (Kasper *et al*., 1995).

Mirtazapine is a novel antidepressant drug providing a dual mechanism of action (De Boer *et al*., 1994). Mirtazapine increases both noradrenergic and serotonergic neurotransmission, blocks adrenergic $\alpha_2$-auto- and $\alpha_2$-heteroreceptors as well as 5-$HT_2$- and 5-$HT_3$- receptors (De Boer *et al*., 1994). As a result of the 5-$HT_2$- and 5-$HT_3$-receptor blockage serotonin stimulate other 5-HT-receptors including the 5-$HT_{1A}$-receptor whose activation seems to produce antidepressant effects (De Vry *et al*., 1992). The inhibition of adrenergic $\alpha_2$-auto- and $\alpha_2$-heteroreceptors bypasses the down-regulation of the serotonergic neuronal body activity (De Boer *et al*., 1994). Blocking of 5-$HT_2$- and 5-$HT_3$-receptors has been shown to increase tolerability but the influence of mirtazapine on other neurotransmitters also may account for a small and rarely seen spectrum of side effects, e.g. sedation, increased appetite and weight gain (for overview see Kasper, 1997). In clinical trials including non-seasonal depressives mirtazapine proved to be effective, safe and well tolerated (for overview see Kasper, 1997).

So far no studies have been published addressing the question whether mirtazapine is an effective antidepressant to treat SAD. Thus, this drug surveillance of mirtazapine focuses on therapeutic effects as well as tolerability of mirtazapine in the treatment of SAD.

## MATERIALS AND METHODS

In this 4 week drug surveillance, eight SAD patients were included. Diagnosis was made according to the Rosenthal Criteria (Rosenthal *et al*., 1984) and the criteria outlined in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV American Psychiatric Association, 1995). All patients who entered the drug surveillance were drug-naïve and free of medical illness and substance abuse. Table 1 summarizes the patients' demographic and clinical characteristics.

Treatment was given as a fixed evening dose of 30 mg mirtazapine. Treatment response was assessed weekly during outpatients appointments using the Hamilton Depression Rating Scale Seasonal Affective Disorder Version (SIGH-SAD) (Williams *et al*., 1988). This questionnaire consists of the 21-item version of the Hamilton

Table 1. Patients characteristics, side effects and treatment outcome after 4 weeks of treatment with 30 mg of mirtazapine per day

| Patient | Sex | Age | Weight | Years of illness | SPAQ | HDRS | SIGH-SAD | Treatment outcome | Side effects/special comments |
|---|---|---|---|---|---|---|---|---|---|
| 1 | f | 55 | 67 | 20 | 12 | 20 | 26 | Remission | — |
| 2 | f | 22 | 50 | 2 | 11 | 19 | 36 | Remission | Sedation (day 1–3) |
| 3 | m | 41 | 71 | 7 | 17 | 27 | 46 | Remission | Sedation (1 week) increased appetite |
| 4 | f | 21 | 62 | 5 | 16 | 23 | 36 | Remission | — |
| 5 | f | 47 | 98 | 20 | 18 | 18 | 25 | Remission | Weight loss (4 kg) |
| 6 | m | 30 | 92 | 4 | 13 | 29 | 37 | Remission | Increased appetite weight gain (5 kg) |
| 7 | f | 30 | 58 | 2 | 13 | 25 | 40 | Discontinued (day 3) | Remission after sleep deprivation |
| 8 | f | 25 | 47 | 5 | 12 | 21 | 30 | Discontinued (day 2) | Vertigo, drowsiness |
| Mean | | 33·8 | 68·1 | 8·1 | 14 | 22·7 | 34·5 | | |
| SD | | 12·4 | 18·4 | 7·5 | 2·6 | 3·9 | 7·1 | | |

SPAQ: Seasonal Pattern Assessment Questionnaire.
HDRS: Hamilton Depression Rating Scale.
SIGH-SAD: Seasonal affective disorder version of the Hamilton Depression Rating Scale.
SD: Standard deviation.

 

Depression Rating Scale (HDRS) (Hamilton, 1967) and is supplemented by eight additional items with particular relevance to SAD. Positive treatment response was defined as a decrease of 50 per cent or more from the baseline SIGH-SAD score and a total SIGH-SAD score of 12 or less. Moreover self-rating assessments used the Profile of Mood States H(POMS). A one-way Analysis of Variance (ANOVA) with $p < 0{\cdot}05$ as the defined level of significance was applied for statistical evaluation of the outcome. All reported values are means $\pm$ SD.

## RESULTS

Six out of eight patients completed the 4 week observation period and fulfilled the remission criteria as noted above. After 4 weeks of treatment an 80 per cent decrease in SIGH-SAD ($df = 1$, $F = 49$, $p < 0{\cdot}001$) total scores was found (Figure 1).

Patient self-ratings on the POMS showed significant decreases of scores on the subscales 'depression' ($df = 1$, $F = 14$, $p = 0{\cdot}005$) and 'fatigue' ($df = 1$, $F = 18$, $p = 0{\cdot}002$), and an increase on the sub-scale 'vigor' ($df = 1$, $F = 13$, $p = 0{\cdot}005$).

As mentioned above, two patients did not complete the treatment period of 4 weeks. One patient took mirtazapine for 1 day and experienced a spontaneous total remission after she underwent a night of total sleep deprivation. The other patient discontinued the medication on the second day because of drowsiness and vertigo after the first intake of the mirtazapine.

Three of six patients, who completed the 4 week protocol, reported side effects. One patient reported increased sedation in the evening that resolved during the first week of treatment. Two patients reported increased appetite and one of them consecutive weight gain. None of the reported side effects influenced the clinical outcome of the patients.

## DISCUSSION

This is to our knowledge the first report on the antidepressant effects of mirtazapine in patients with SAD. The main finding is that mirtazapine proved to be effective and safe in the treatment of SAD. Side effects were rare, generally mild and mostly disappeared within the first week of treatment. Only one of eight patients discontinued the treatment due to side effects.

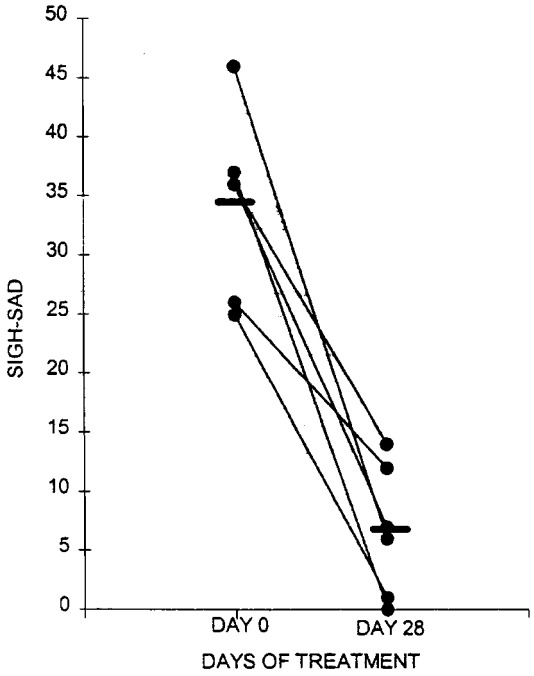


Figure 1. Individual scores and mean value of the SIGH-SAD of six patients with Seasonal Affective Disorder treated with 30 mg of mirtazapine for 4 weeks

Generally, side effects often limit the use of antidepressants. One advantage of the newer antidepressants is their good tolerability in comparison with the older tricyclics. So far, SSRIs can be recommended as the first treatment alternative to light therapy for patients with SAD (Kasper *et al.*, 1989). However, it has to be acknowledged that to date no studies are published assessing the efficacy and tolerability of tricyclic antidepressants in the treatment of SAD. Thus, it cannot be ruled out that tricyclics also may be effective to treat SAD.

Placebo-controlled trials in non-seasonal depressives show that administration of mirtazapine is significantly more often associated with sedation, dry mouth, drowsiness, increased appetite and weight gain than placebo (Kasper, 1997). These side effects can be possibly linked to mirtazapine's pharmacodynamic properties (De Boer *et al.*, 1994) but are generally less frequent than in tricyclics. In the present study side effects were generally mild and short-lived. However, since this is an uncontrolled trial the side effect frequency reported herein has to be regarded as preliminary.

Previous studies suggest that the antidepressant effects of mirtazapine are mediated via serotonergic and noradrenergic pathways. The efficacy of

mirtazapine in the treatment of SAD suggests that mirtazapine may compensate for a possible underlying deficit within the mentioned transmitter systems. Evidence for the importance of serotonergic and catecholaminergic mechanisms in the pathophysiology of SAD can be inferred from studies showing that lowering brain serotonin and catecholamine activity during tryptophan depletion and catecholamine depletion respectively, disrupted the beneficial effect of light therapy. Such studies support the hypothesis that the antidepressant effects of light therapy are mediated involving monoaminergic pathways. Such studies also suggest that these neurotransmitter systems may play a critical role in the pathophysiology of SAD.

Altogether, the monotherapy with mirtazapine (30 mg/day) was effective and well tolerated by the majority of our patients with SAD. It appears worthwhile to verify these results in placebo-controlled trials.

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