sleep disturbance and retardation factors of the HAMD. The efficacy analyses were performed on the Intent-To-Treat Group using the Last Observation Carried Forward method.

Results: On all efficacy variables treatment with mirtazapine has resulted in a larger magnitude of change from baseline than treatment with fluoxetine. During the first two weeks of treatment, the largest magnitude of change was observed in the anxiety/somatization and sleep disturbance factors, The changes in the 'depressed mood' and the retardation factor were similar in both groups. From week 2 onwards changes favoring mirtazapine were particularly prominent in the 'depressed mood' item and the retardation factor. The difference on the 'depressed mood' item favoring mirtazapine reached statistical significance at week 4.

Conclusion: The results demonstrate that treatment with mirtazapine is superior to fluoxetine in improving depressed mood. Pharmacological properties of mirtazapine, especially its specific actions on postsynaptic 5-HT receptors, may account for the consistent improvements in anxiety and sleep disturbances throughout the treatment period.

P.1.174 Effects of venlafaxine on REM sleep after short term and long term application in patients with major depression

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Venlafaxine, a novel antidepressant selectively inhibiting neuronal uptake of serotonin and norepinephrine has been proved to be effective in antidepressant treatment. However, sleep disturbance is frequently observed after venlafaxine application. While trimipramine, a long established antidepressant is known to beneficially affect sleep continuity without changing sleep architecture, a decrease in sleep efficiency and a suppression of REM sleep has been reported under venlafaxine treatment.

We registered in a still ongoing study the sleep EEG of 7 patients with major depression (HRS > 18) at baseline (unmedicated), under short term treatment (STT), one week of venlafaxine at least 3 days on 225 mg, and long term treatment (LTT), 6 weeks of 225 mg treatment of venlafaxine and compared it to the sleep EEG of patients under 200 mg trimipramine with the same time and evaluation schedule.

The preliminary results were the following:

Compared to unmedicated conditions, after the STT, venlafaxine markedly increased the duration of first sleep cycle, predominantly due to an increase of stage 2, and reduced total number of cycles. In addition, an increase of sleep efficiency, stage 2 and REM-latency and a marked decrease of REM density and REM-sleep, predominantly in the first half of the night was found.

Compared to STT, sleep efficiency after LTT decreased, slow wave sleep (SWS), predominantly stage 4 was augmented and advanced, being exclusively present in the first cycle. REM-sleep remained markedly suppressed, while REM-density showed a significant increase (predominantly in the later part of the night).

Compared to patients with trimipramine medication, after STT of venlafaxine (week 1), REM sleep and REM density were significantly reduced without differences in parameters of sleep continuity and Non-REM sleep. After LTT (week 6) patients with venlafaxine treatment presented worse in sleep continuity and time in REM sleep remained significantly suppressed, while the observed difference in REM density at week 1 between trimipramine and venlafaxine treated patients was markedly reduced.

These results are in line with animal data and one previous study on sleep EEG variables in depressed patients under venlafaxine treatment showing a pronounced reduction of REM sleep. The observed alterations of SWS and REM density after venlafaxine LTT may reflect sensitive indicators of a reorganisation towards a normal sleep pattern probably being related to remission of symptoms.

P.1.175 Effects of short and long-term lithium treatment on serum cortisol levels in patients with bipolar affective disorder

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Objective: The importance of lithium (Li) salts as prophylactic therapeutic agents in bipolar affective disorder is now well-known. However, both basic and clinical studies have shown that lithium treatment can be associated with a wide range of adverse effects on metabolic and endocrine functions. It has also been suggested that Li can affect the pituitary-adrenocortical axis (Souza et al, 1991). In this study, we sought to test the hypothesis that prophylactic lithium treatment can induce alterations in cortisol secretion in euthymic bipolar patients and the length of Li administration can affect the degree of alterations.

Methods: Twenty euthymic bipolar patients (4 females, 16 males; mean ± SD age: 34.90 ± 10.05) on long-term lithium carbonate treatment for more than 6 months (range: 18–180 months) and 15 euthymic bipolar patients (10 females, 5 males; mean ± SD age: 29.53 ± 8.76) on short-term Li therapy for shorter than 6 months (range: 2–6 months) who met DSM-IV criteria for bipolar affective disorder (APA, 1994) were included in the study. Seventeen healthy control subjects (7 females, 10 males; mean ± SD age: 33.88 ± 1.72) were chosen among the hospital staff. A single fasting morning blood specimen was obtained at 07.00–08.00 a.m. from all the subjects after 10–12 h after the previous lithium dose from the patients. Serum basal cortisol was determined using the standard RIA (ICN Biomedicals, Inc. US. Cortisol ^{125}I kits).

Results: There was no significant difference in mean age among the three study groups. The mean ± SD duration of Li use was 68.93 ± 46.31 months in the long-term group and 4 ± 3.42 months in the short-term group. Serum basal cortisol values were within the normal limits in all study groups but they were significantly lower in the Li-treated patients than those of the controls. However, there was no difference between the two patient groups in plasma basal cortisol values. There was no significant correlation between the plasma or red blood cell Li levels and serum cortisol values in the Li-treated groups.

Conclusion: In conclusion, our study documents that Li administration induces a significant reduction in cortisol release in bipolar patients compared to the normal control subjects, but cortisol secretion remains quite stable during the prolonged Li treatment. However, since basal cortisol concentrations show considerable intraindividual and interindividual variations further studies are needed.

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P.1.176 Venlafaxine withdrawal syndrome

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The abrupt withdrawal of antidepressants often produces symptoms requiring clinical attention. Autonomic, behavioural, and somatic symptoms have been observed following discontinuance of cyclic antidepressants (TCAs), selective serotonin reuptake inihibitors (SSRIs) and norepinephrine and serotonin reuptake inihibitors (SNRIs). Tryciclic antidepressants are known to carry the risk of withdrawal after abrupt discontinuation, which is believed to be associated with cholinergic and noradrenergic rebound. Common symptoms include headache, nausea, diarrhoea, myalgias, fatigue, and sleep disturbances. The existing data regarding SSRIs are not know to carry a substantial risk of withdrawal

syndromes. Some data suggest that fluoxetine discontinuation may precipitate withdrawal, but withdrawal is unexpected because of fluoxetine's long half-life. In phase II clinical trials, discontinuation of higher dose of venlafaxine therapy resulted in insomnia, headaches, and fatigue in some patients (Whyeth-Ayerst personal communications, 1995).

The authors reviewed 9 patients (8 female and 1 male), aged from 34 and 75, affected from Major Depression, treated for 6 months with venlafaxine, 150 mg/die (range 75 mg–250 mg) abruptly discontinuated. The common symptoms after discontinuation were headache, nausea, feeling of abdominal distension, fatigue, tinnitus, dizziness, panic sympatomalogy, anxiety. This severe symptomatology appeared when the patients abruptly discontinuated the venlafaxine and they were clinically significant and all completely resolved about 1–2 days upon reintroduction of the drug. The symptoms observed in these cases after abrupt discontinuation of venlafaxine are similar to those reported after withdrawal of SSRIs. Venlafaxine withdrawal may share a similar mechanism with SSRIs, but since it blocks the reuptake of both norepinephrine and serotonin, either or both of these neurotransmitters may be involved in withdrawal reactions. Given the possibility of venlafaxine withdrawal reactions, it should be aware that some patients may require tapering of venlafaxine before discontinuation.

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P.1.177 Once-daily venlafaxine XR vs. paroxetine in outpatients with major depression

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Objective: Evaluate the efficacy and tolerability of once-daily venlafaxine XR and paroxetine in outpatients with major depression.

Methods: This was a randomized, double-blind, placebo-controlled comparison of once-daily venlafaxine XR and paroxetine. Outpatients with DSM-III-R major depression were randomly assigned to venlafaxine XR 75 mg or 150 mg once daily, paroxetine 20 mg once daily or placebo for a maximum of 8 weeks.

Results: Three hundred twenty-three patients were evaluated for efficacy. Because of a high placebo response, there were no significant differences between active drugs and placebo. However, in pairwise comparisons, venlafaxine XR 75 mg was significantly superior ($p < 0.05$) to paroxetine on the HAM-D and MADRS at weeks 1, 2, 4, 6, and 8 and on the CGI severity scale at weeks 2, 4, 6, and 8. Venlafaxine XR 150 mg was significantly superior ($p < 0.05$) to paroxetine on the HAM-D at weeks 4, 6, and 8, on the MADRS at weeks 4 and 6, and on the CGI severity scale at weeks 4 and 6. The most common treatment-emergent adverse event with venlafaxine XR and paroxetine was nausea. Discontinuations due to nausea were similar for venlafaxine XR 75 mg (1%) and placebo (1%), and higher for venlafaxine XR 150 mg (6%) and paroxetine (4%). Discontinuations overall were less with venlafaxine XR 75 mg (20%) than with paroxetine (35%).

Conclusion: These results indicate that once-daily venlafaxine XR 75 mg is as effective and better tolerated than paroxetine 20 mg daily for treating major depression.

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P.1.178 Open-label evaluation of once-daily venlafaxine XR in depressed outpatients

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Background and Purpose: The tolerability and effectiveness of venlafaxine during long-term treatment for 6 to 12 months have been demonstrated (Shrivastava et al, 1994; Entsuah et al, 1996). Once-daily venlafaxine extended release (XR) is a new formulation of venlafaxine that provides the same total extent of drug absorption as the immediate release formulation but permits administration as a single daily dose. Short-term randomized controlled trials have demonstrated the efficacy and tolerability of venlafaxine XR in outpatients with major depression (Cunningham, 1997). The objective of this study was to evaluate the tolerability and effectiveness of once-daily venlafaxine XR during long-term treatment of outpatients with major depression.

Methods: This was a 12-month, open-label evaluation of venlafaxine XR in outpatients at least 18 years of age with DSM-III-R major depression. Treatment was maintained for at least 6 months, but could be continued for an additional 6 months if clinically indicated. Treatment was initiated with venlafaxine XR 75 mg/day; beginning on day 14, the dose could be increased to 150 mg/day at the investigator's discretion for increased response. Efficacy was assessed on the 21-item HAM-D and the CGI scales. Efficacy data were analyzed on an intent-to-treat basis using both LOCF and observed cases anlalysis.

Results: Two hundred and fifty-two patients were recruited, 159 (61%) completed 6 months and 113 (45%) patients completed 12 months. Data were available for 251 patients for the safety analysis and 240 for the efficacy analysis. Twenty-three (23) patients opted not to continue after 6 months and 115 (46%) patients withdrew during the study. The study population consisted of 191 female and 60 male patients with a mean age of 47.9 years. The mean dose from the second month on was approximately 110 mg/day; 51% of patients increased their dose to 150 mg/day.

The most frequent adverse events were nausea (23%), headache (20%), dry mouth (12%), and somnolence (9%). Nausea was mild to moderate and led to discontinuation in 4% of cases. The total number of patients who were withdrawn for adverse reactions as a primary reason was low (13%). A secondary objective was to assess the efficacy of venlafaxine XR. During the study there were significant decreases from baseline in HAM-D and CGI total scores, indicative of improvement of depression from week 2 onward. The response rates at 12 months for the HAM-D total score and the CGI improvement were 60% and 73%, respectively, in the LOCF analysis and 76% and 88%, respectively in the observed cases analysis.

Conclusion: Once-daily venlafaxine XR is well tolerated and appeared to be effective for the long-term treatment of major depression in outpatients.

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P.1.179 Antidepressive and anxiety-lowering effects of immunotherapy and aromatherapy

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Effect of thymus peptides is supposed to be associated with common immunotropic and psychotropic properties. Three groups of laboratory