to 9.5 and 13.9 (Mann-Whitney U Test, $p < 0.001$). Proportions of sertraline and imipramine patients with reduction of HAMA score $\geq 50\%$, and HAMA ≤ 8 were 66% versus 56% ($p < 0.001$), and 54% versus 38% ($p = 0.014$), respectively. The CGI-I response rate (was higher in sertraline group (76%) than in imipramine group (63%) ($p = 0.028$). The difference in efficacy may have been contributed to by the poorer tolerability of imipramine, leading to many dropouts for adverse event in the imipramine group (24%), relative to the sertraline group (24%) ($p = 0.004$).

Conclusion: Sertraline demonstrated greater effectiveness than imipramine in the acute treatment of depressive and anxiety symptoms in patients with non-melancholic depression

P02.231

24-WEEK PREVENTION OF RELAPSE OF GENERALIZED SOCIAL PHOBIA STUDY IN RESPONDERS TO 20-WEEKS OF SERTRALINE TREATMENT

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Objective: Demonstrate the efficacy and tolerability of sertraline in the prevention of relapse of generalized social phobia (GSP).

Method: Fifty adult GSP patients with CGI-I much or very much improved after 20-weeks sertraline-treatment (50–200 mg/day) were randomized double-blind in 1:1 ratio to continue sertraline or switch to placebo for 24-weeks. Primary efficacy assessments; number relapsing CGI-S increase of >2 points over continuation baseline and/or discontinuation for lack of efficacy (LOE); CGI-I 1 or 2; mean score changes from continuation baseline on CGI-S, social phobia sub-scale of Marks Fear Questionnaire (MFQ), and Duke Brief Social Phobia Scale (BSPS) at study endpoint.

Results: In ITT, LOCF analyses 1/25 (4%) in sertraline group and 9/25 (36%) in placebo-switch group had relapsed at study endpoint ($p = 0.01$). Mean CGI-S, MFQ social phobia subscale, and BSPS total scores were reduced by 0.07, 0.34, and 1.86 in the sertraline group and increased 0.88, 4.09, and 5.99 in the placebo-switch group ($p < 0.03$), respectively. There was no significant difference in CGI-I responders. Eighty-eight percent of sertraline and 40% of placebo-switch patients completed the study. Discontinuations for LOE were 4% in sertraline and 28% in placebo-switch ($p < 0.05$).

Conclusions: Sertraline is effective in preventing relapse in GSP.

P02.232

IMPACT OF RESIDUAL SYMPTOMS ON OUTCOMES IN GAD: EVIDENCE FROM PLACEBO-CONTROLLED TRIALS OF VENLAFAXINE ER

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Background: Residual symptoms are associated with greater risk of relapse and morbidity. Treatment response leaves patients with a significant burden of symptoms and impairment. The goal of treatment for chronic conditions such as GAD should look beyond treatment response to remission.

Methods: Data from 1,129 short-term (8 weeks) and 767 long-term (24 weeks) treatment responders (50% decrease in HAMA total) from placebo-controlled studies of venlafaxine ER in GAD were pooled to compare:

- the number of residual symptoms at the time of first response, and after short-and long-term treatment.
- the effect of residual symptoms on clinical outcomes

Residual symptoms were defined as anxiety symptoms (HAMA items) present at baseline with a score greater than zero at the time of first response.

Results: Regardless of treatment, responders had a similar number of residual symptoms at the time of first response. However, venlafaxine ER was associated with fewer residual symptoms overall at week 8 compared with placebo ($p < 0.001$) for all patients and those with moderate or severe anxiety (HAMA < 25 or ≥ 25) at baseline. In the long term and independent of treatment, patients who responded before week 8 had fewer residual symptoms at end-point than those who responded later. Patients who relapsed (HAMA total ≥ 18 or ≥ 20, EU and US studies, respectively) had the highest number of residual symptoms (9.1 and 9.1 for placebo and venlafaxine, respectively) and those who remitted (sustained HAMA < 8) the lowest number (7.3 and 7.5 respectively) at their first response.

Conclusions:

1. At the time of first response, patients still carry a significant burden of residual symptoms.
2. A higher number of residual symptoms is associated with a poorer outcome.
3. Venlafaxine ER is more effective than placebo in reducing residual symptoms.

P02.233

INFLUENCE OF SELECTED SSRI ON ACTIVITY OF CYTOCHROME P450 2D1 AND ARYLAMINE N-ACETYLTRANSFEARASE IN WISTAR RATS

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(a) Antidepressive therapy includes the use of selective serotonin reuptake inhibitors (SSRI). The elimination of the SSRI proceeds predominantly via oxidation catalyzed by cytochrome P450 in the liver. At our pre-clinical department, interactions on the drug-metabolizing enzyme level have been studied using rodent animal models. Only few data are available on the activities of cytochrome P450 2D1 (CYP2D1) and arylamine N-acetyltransferase (NAT) in Wistar albino rats after pretreatment with SSRI. In the study of Walter et al. (1996), which was performed using liver microsomes of Wistar rats after subacute (7 days) SSRI treatment, only paroxetine inhibited activity of CYP2D1, while citalopram and sertralin did not influence it and fluoxetine even showed stimulatory effect. Fluoxetine and paroxetine also inhibited NAT activity. (b) On the basis of this knowledge the present study was undertaken to characterize changes of the activity of CYP2D1 and NAT in the isolated perfused rat liver after 7 res. 14 days pretreatment of male Wistar rats with fluoxetine (20 mg/kg/day per se) or paroxetine (15 mg/kg/day per se.). Re-circulatory perfusion system by Miller (1951) was used with Williams' medium E as a perfusion medium. As model metabolic reactions was used: O-demethylation of dextromethorphan (DEM) to dextrorphan (DOR) for CYP2D1 and N-acetylation of procainamide (PA) to N-acetylprocainamide (NAPA) for NAT. (c) Concentrations of PA and NAPA was measured spectrophotometrically and those of DEM and DOR by HPLC. Capacity of the isolated liver for O-demethylation of DEM after pretreatment with both of tested antidepressants was significantly ($P < 0.01$) decreased. Fluoxetine (14 days administered) also decreased ($P < 0.01$) concentrations of NAPA in perfusate while paroxetine (14 days admin.) showed stimulatory effect on NAT activity ($P < 0.05$). (d) An inhibitory effect of tested drugs on CYP2D1 was proven. Concerning NAT: slow acetylators seem to preponderate amongst patients with psychiatric disorders. These

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