of coronary heart disease (CHD). Whether atypical neuroleptics differ regarding their impact on the CHD risk profile is not known.

Study Design: We conducted a cross-sectional, multicenter study to compare morphological indices of obesity, adipose tissue distribution and a full fasting metabolic risk profile in patients receiving either risperidone (RP) or olanzapine (OLZ). Inclusion criteria included drug exposition for 6 to 42 months. Exclusion criteria, among others, were previous exposition to atypicals, treatment with drugs altering blood pressure, plasma lipids, insulin and body weight. Anthropometric measurements, laboratory and psychiatric assessments were completed.

Results: Preliminary results on 44/120 subjects were analysed. Mean duration of treatment was 17.4 ± 8.8 months for RP and 17.9 ± 8.1 months for OLZ (p = NS). OLZ-treated subjects had significantly higher plasma triglyceride level (2.1 ± 1.3 for OLZ vs 1.3 ± 0.7 for RP, $p < 0.01$), higher cholesterol/HDL-cholesterol ratio (5.3 ± 1.7 for OLZ vs 4.3 ± 1.4 for RP, $p < 0.06$) and lower HDL-cholesterol level (0.95 ± 0.2 for OLZ vs 1.06 ± 0.2 for RP, $p < 0.08$). Finally, 32% of OLZ-treated patients presented the atherogenic metabolic triad (hyperinsulinemia, elevated apo-B, small dense LDL) as opposed to 5% in RP-treated patients.

Conclusion: This interim analysis suggests that OLZ-treated patients are characterized by a deteriorated metabolic risk profile compared to RP-treated patients. These results raise concerns about the potentially deleterious effects of OLZ therapy on cardiovascular health.

P02.228

SEXUAL DYSFUNCTION BURDEN IN A 24-WEEK STUDY OF SSRIS IN DEPRESSED PATIENTS

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Background: Secondary pharmacological characteristics among SSRIs may result in differing potential to induce/alleviate sexual dysfunction.

Objective: Examine adverse sexual experiences systematically recorded during a 24-week, prospective, randomized study comparing sertraline and paroxetine (mean daily doses completers 83.0 mg, 27.8 mg, respectively) in the treatment of depressed outpatients.

Methods: UKU symptom checklist recorded and quantitated adverse sexual effects experienced by patients receiving sertraline (n = 176) or paroxetine (n = 177). The interviewer rated UKU assesses increased sexual desire, decreased sexual desire, orgasm dysfunction, ejaculatory dysfunction, and erectile dysfunction: 0 = absent, 1 = mild, 2 = moderate, 3 = severe). The burden score is sum of 5 items for males and sum of 3 applicable items multiplied by 5/3 for females.

Results: Mean baseline burden scores for sertraline and paroxetine groups, respectively, were 2.2 and 2.2 (p = 0.969). Scores in sertraline and paroxetine groups, respectively, changed by 0.0 and +0.5 at week 6 (p = 0.105), −0.4 and +0.2 at week 12 (p = 0.035), −0.8 and −0.2 at week 24 (p = 0.120), and −0.6 and −0.1 at study endpoint (p = 0.050). Analysis by gender revealed a statistically significant difference between treatments amongst female, but not among male, patients.

Conclusions: The potential to induce or alleviate sexual dysfunction in depressed patients may differ significantly between sertraline and paroxetine.

P02.229

A PLACEBO-CONTROLLED STUDY OF SERTRALINE IN GENERALIZED SOCIAL PHOBIA

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Objective: To evaluate the efficacy, safety, and tolerability of sertraline, a selective serotonin reuptake inhibitor, in the treatment of generalized social phobia.

Method: Following a 1-week, single-blind, placebo run-in, 206 adult outpatients with generalized social phobia from 10 Canadian centers were randomized to 20 weeks of double-blind treatment with sertraline or placebo in a 2:1 ratio. The initial daily dosage of sertraline was 50 mg with increases of 50 mg/day every 3 weeks permitted after the fourth week of treatment (flexible dosing to a maximum of 200 mg/day). Primary efficacy assessments were the percentage of patients much or very much improved on the Clinical Global Impression of Improvement (CGI-I) scale, and the mean total score baseline to endpoint change on the social phobia subscale of the Marks Fear Questionnaire and the Duke Brief Social Phobia Scale (BSPS).

Preliminary Results: 71 (53%) of 134 persons receiving sertraline and 20 (29%) of 69 persons receiving placebo were CGI-I responders at the end of treatment ($p < 0.001$). Mean Marks Fear Questionnaire social phobia subscale and BSPS total score were reduced by 32.5% and 34.8% in the sertraline group and 8.6% and 16.7% in the placebo group ($p < 0.005$), respectively. Sertraline-treated patents also evidenced significant improvements relative to patients receiving placebo on all secondary efficacy parameters and on social/leisure functioning and mental health dimensions of quality of life assessments ($p < 0.05$). Overall, sertraline was well tolerated.

Conclusions: This study demonstrated sertraline to be an effective treatment for generalized social phobia. Future research should assess whether improvements may be maintained or further improved by either continued treatment or by augmentation with specific cognitive-behavioral techniques.

P02.230

SERTRALINE VERSUS IMIPRAMINE IN NON-MELANCHOLIC DEPRESSION

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Objective: To compare the acute treatment efficacy, tolerability, and effects on health related quality of life of sertraline (50–200 mg/day) and imipramine (75–225 mg/day) in outpatients with non-melancholic depression.

Method: In an open, parallel-group design, 116 patients were randomized to receive sertraline and 123 to imipramine for 8-weeks. The initial daily dose was sertraline 50 mg/day or imipramine 75 mg/day with increases in increments of 50 mg/day allowed at 2-week intervals.

Results: There were statistically significantly greater improvements in favour of sertraline on depressive and anxiety symptom reduction, response and remission on all scales from week 4 onwards (ITT, LOCF). In the sertraline and imipramine groups, respectively, baseline HAM-D_{21} scores of 24.9 and 24.4 were reduced to 10.3 and 13.4 (p = 0.011). Proportions of sertraline and imipramine patients with reduction of HAM-D_{21} score $\geq$ 50%, and HAM-D_{21} $\leq$ 8 were 69% versus 54% (p = 0.016), and 51% versus 38% (p = 0.041), respectively. In sertraline and imipramine groups, respectively, baseline HAMA scores of 21.8 and 21.9 were reduced

https://doi.org/10.1016/S0924-9338(00)94638-8 Published online by Cambridge University Press

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

https://doi.org/10.1016/S0924-9338(00)94638-8 Published online by Cambridge University Press