and severe depression in Austria, from the perspective of the *Gebietskrankenkassen.*

Methods: Clinical decision analysis techniques were used to perform a cost-effectiveness analysis to determine the cost per successfully treated patient. Treatment paths were developed from clinical trial data, interviews with Austrian physicians and the published literature.

Results: Mirtazapine was found to be the more cost-effective antidepressant, since it was clinically more effective. The cost per patient successfully treated with mirtazapine was between ATS15,157 and ATS17,404 less than with either amitriptyline or fluoxetine.

Sensitivity analyses showed the findings to be robust. Changing the proportion of patients absent from work, or the unit costs of psychiatric consultations with GPs and psychiatrists, or the proportion of hospital admissions had little effect on the cost-effectiveness of mirtazapine - the expected cost per patient successfully treated with mirtazapine remained less than for a patient successfully treated with amitriptyline or fluoxetine, due to its superior clinical profile.

Sick Fund payments to patients during their time off work accounted for up to 50% of the costs, whereas hospital stay accounted for up to 19% and the acquisition costs of antidepressants for between 6 and 18%.

Conclusion: Mirtazapine is more cost-effective than amitriptyline and fluoxetine. The cost per patient successfully treated with mirtazapine is between ATS15,000 and ATS18,000 less than with either amitriptyline or fluoxetine.

Tues-P36

PREGNANCY DURING USE OF MIRTAZAPINE

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We describe the first case of pregnancy during the use of mirtazapine. A 28-year old woman (1.68 cm, 63.3 kg) with a DSM-III-R diagnosis of a major depressive episode and a 17-HAMD score of 26, was included into a clinical study with mirtazapine. Both the patient and the husband were informed about the aim of the study, and were advised about the need for contraception. As the patient refused to use oral contraceptives, the couple agreed to use condoms in combination with contraceptive ovula. The patient responded well to short-term intravenous treatment with mirtazapine for 14 days (up to 45 mg/day), and continued with study medication for 6 months. At the last study visit, one week after the intake of last dose of mirtazapine, the pregnancy test was positive (β-HCG = 3728 mIU/ml). Last menstrual belleding was 26 days before the last dose of mirtazapine. The couple agreed to continue pregnancy. The patient was regularly followed by psychiatrist and gynecologist. Her depression remained in remission, while the course of the pregnancy was normal. In 39th week she gave a birth to a healthy baby girl (3360 gr. 51 cm, Apgar score 8/10/10). Delivery was spontaneous, placenta complete, and amniotic fluid normal.

In our patient, the use of mirtazapine during the first month of pregnancy did not cause any complications during its further course, nor any adverse events or defects in the newborn.

Tues-P37

EFFECTS OF MILNACIPRAN AND VENLAFAXINE ON EXTRACELLULAR LEVELS OF 5-HT AND NORADRENALINE IN GUINEA PIG HYPOTHALAMUS

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The antidepressants milnacipran and venlafaxine inhibit both the uptake of 5-hydroxytryptamine (5-HT, serotonin) and noradrenaline (NA) in rat brain synaptosomes. The aim of the present work was to compare the effects of milnacipran and venlafaxine on the extracellular levels of 5-HT and NA and their metabolites as a resulting increase in their synaptic amounts in the guinea pig brain. The output of 5-HT and NA, and their respective metabolites, 5-hydroxyindole acetic acid (5-HIAA) and 4-hydroxy-3-methoxyphenyl-glycol (MHPG), were determined by microdialysis in the hypothalamus of freely moving guinea pigs. The extracellular levels of 5-HT and NA were increased (% of basal values) in a dose-dependent manner and to a similar extent after the i.p. administration of milnacipran (by 197 and 440 for 5-HT; by 211 and 497 for NA, at 10 and 40 mg/kg, respectively). The i.p. administration of venlafaxine enhanced the output of 5-HT by 432 and 428% of basal values at 10 and 40 mg/kg, respectively, while the output of NA was not modified at 10 mg/kg and was slightly increased by 111% of basal values at 40 mg/kg. The basal extracellular levels of 5-HIAA were not modified by milnacipran at 10 and 40 mg/kg whereas those of MHPG were decreased by 57 and 47% of basal values at these doses, respectively. Venlafaxine reduced the output of 5-HIAA by 70 and 60% and of MHPG by 84 and 79% of basal values after the administration of 10 and 40 mg/kg, respectively. A more evident effect on the NA system was obtained by venlafaxine when the dose of 160 mg/kg was used (1334 and 790% of basal values for 5-HT and NA, respectively, and 50% of basal values for 5-HIAA and MHPG). These results indicate that milnacipran, by blocking the uptake of 5-HT and NA, increases about equipotently the extracellular levels of 5-HT and NA, confirming previous in vitro studies. In contrast in vivo venlafaxine is more potent on 5-HT than NA systems. It has been shown previously that a major metabolite of venlafaxine is less active on NA than on 5-HT uptake which could explain this point.

Tues-P38

MIANSERIN UND ALPRAZOLAM IN DER BEHANDLUNG VON HERZSCHMERZ-ZUSTANDEN

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Ziel: Auswirkung von Mianserin und Alprozalam auf die Perzeption des Herzschmerzes. Es wurden 82 Patienten untersucht (42- koronare Herzkrankheit, 36- funktionelle Kardialgie).

Methoden: psychopathologische Untersuchung Hamilton - Angst Skala (HARS), Fragebogen SCL-90, MPQ, sowie Tredmill-test.

Ergebnisse: Nach Kriterien ICD-10 wurden in beiden Gruppen keine wesentliche Unterschiede entdeckt. Es stellten sich deutliche Angst- und Depressionstorungen heraus. Das widerspiegelte sich bei den Herzschmerzpatienten im grossen Anteil der diagnostischen Kategorien, die zum Abschnitt F 3 (affektive Storungen) gehoren. Das Vorherrschen von Somatisation, Angst, Depression und Zwangstorungen wurde mit den Daten von SCL-90 bestatigt. Die Werte der HARS bestatigen die Rolle der Angst (der somatischen und psychischen). Die MPQ - Angaben Zeigen die grosse Rolle affektiver Bestandteile der subjektiven Schmerzperzeption

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bei Patienten der beiden Gruppen. 36 Patienten wurden mit Mianserin (Lerivon), Dosis 7.5–15 mg/Tag (max 30 mg/Tag) 46- mit Alprazolam (Cassadan), Dosis 0.06–0.125 mg/Tag (max 0.25 mg/Tag) behandelt. Bei der Behandlung mit Mianserin wurde eine positive Wirkung bei 83.3% der Kranken gefunden, bei der Behandlung mit Alprazolam - bei 78.3% Patienten. Die Dynamik des Patienten-zustandes wahrend der Behandlung war ahnlich. Unterschiedlich war die Auspragung der antidepressiven Wirkung (Mianserin starker, als Alprazolam).

Tues-P39

VENLAFAXINE IN ELDERLY DEPRESSED PATIENTS. A MULTICENTER STUDY

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Objective: To study the possible differences in the management of depression with Venlafaxine between patients aged 65 years and over, and patients under 65.

Design: A nation-wide observational, prospective, longitudinal study.

Subjects: 5012 Out-patients with DSM-IV major depression, with age ranging from 18 to 97 years, 30.6% male and 69.4% female, who received treatment with Venlafaxine for 6 months. 577 patients were[3] 65 years old, of which 75.3% were female and 24.7% male.

Assessment of depression was carried out over a total of 5 visits using Hamilton's 17 items scale and Clinical Global Impression Scale (CGI).

Results: The score in Hamilton's scale at baseline was 22.8 and 5.3 in the final visit at six months for patients[3] 65 versus 23.2 and 5.6, respectively, for patients <65 (NS). Total CGI at 6 months resulted in "a great deal of improvement or much improved" in 84.88% for patients[3] 65 versus 84.36% for patients <65 (NS). Mean dosing was 101.9 mg/day for patients[3] 65 versus 107.8 for patients <65 ($p = 0.006$).

Compliance with treatment was 94% for both age groups.

Out of the total 577 elderly patients, only 63 (10.9%) reported side-effects. For patients <65, the percent of side-effects was 11.8% (NS). The most frequent events were: nausea and vomiting, constipation, nervousness, tremors and dry-mouth.

Conclusions: Outcome of elderly patients being treated for depression does not vary in relation to that of the remaining population, either in terms of efficacy or tolerance.

Tues-P40

OPTIMAL LENGTH OF CONTINUATION THERAPY: A PROSPECTIVE ASSESSMENT DURING FLUOXETINE LONG-TERM TREATMENT OF MAJOR DEPRESSIVE DISORDER

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Objective: To prospectively determine optimal length of fluoxetine continuation therapy following successful acute treatment of major depressive disorder.

Design: Outpatients were treated for 12 to 14 weeks with fluoxetine (20 mg/day). Patients meeting response criteria were randomized to 50 weeks of double-blind continuation therapy comprised of placebo crossover periods as follows:

- immediate placebo crossover for 50 weeks (crossover group-1);
- fluoxetine for 14 weeks followed by placebo crossover for 36 weeks (crossover group-2);
- fluoxetine for 38 weeks followed by placebo crossover for 12 weeks (crossover group-3);
- fluoxetine for 50 weeks (no crossover).

Actual relapse rates and Kaplan-Meier estimates were determined during three fixed 12-week time intervals following each placebo crossover.

Results: Relapse rates were statistically significantly higher in patients initiating placebo in crossover group-1 (48.6% vs. 26.4% $p < 0.001$) and crossover group-2 (23.2% vs. 9.0% $p < 0.05$) than in patients remaining on fluoxetine. Relapse rates were not statistically significantly higher in patients initiating placebo in crossover group-3 than in patients remaining on fluoxetine (16.2% vs. 10.7%, NS).

Conclusions: These data suggest that following a successful 12-week course of acute therapy, additional protection against relapse is associated with continuation therapy of at least 26 further weeks (38 weeks total).

Tues-P41

ADVERSE EVENT PROFILES ASSOCIATED WITH LONG-TERM FLUOXETINE TREATMENT

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Background: The Agency for Health Care Policy and Research Guideline state that "most patients should receive the full therapeutic dosage of antidepressant drug for 4 to 9 months of continuation therapy after symptom remission is achieved." We examined the safety of fluoxetine 20 mg/day in long-term treatment in a large, prospective trial and report a comparison of early and late adverse events (AEs) and the course of AEs over time.

Design: AEs were recorded at each visit in a uniform format by open-ended questioning, regardless of perceived causality. The frequencies of common new/worsened AEs reported in the first four weeks (early) or the 22nd–26th weeks of treatment (late) were compared using McNemar's test.

Results: 299 patients with major depressive disorder responded to 12 weeks of fluoxetine treatment and entered continuation therapy and 174 completed 26 weeks of therapy. All early events which occurred in $\geq$ 5% of patients declined significantly ($p < .05$) over time and no events occurred significantly more frequently during continuation therapy.

Conclusions: Common adverse events associated with initiating fluoxetine in depressed patients resolve in the majority of patients and are significantly less frequent with ongoing treatment. Overall, therapy with fluoxetine 20 mg daily is well tolerated over a 6 month period.

Tues-P42

CHANGES IN INSOMNIA DURING TREATMENT OF DEPRESSION: ANALYSIS OF FLUOXETINE DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS

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Objective: Examine the effects of fluoxetine, a nonsedating antidepressant, on depression related insomnia symptoms.

Method: Retrospective analysis of data from 7 double-blind clinical trials of 2456 patients with major depression randomly assigned to fluoxetine or placebo treatment. Baseline HAMD-Sleep Disturbance Factor score was used to categorize patients

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