leading to further improvement of phobic symptoms, however with persistent edema. After one month, the dose was increased to 60 mg/day. Twelve hours after the dosage increase the facial edema disappeared. After 2 weeks overall depressive symptoms had improved so much that she was able to return to work. The second patient was a 37-year old patient with ICD-10 diagnosis of recurrent severe depression, previously unsuccessfully treated with moclobemide, fluoxetine and zolpidem. The treatment with mirtazapine started at 15 mg/day, but after dose increase to 45 mg/day edema appeared in her face and legs. In the second week of treatment with 60 mg/day, edema disappeared completely. In both patients treatment-emergent edema resolved upon dose increase of mirtazapine.

Conclusion: These cases illustrate that in the few patients in which edema appears at low doses of mirtazapine, further dosage increase may lead to resolution of this bothersome adverse event.

Tues-P32

THE USE OF MIRTAZAPINE IN PRIMARY CARE

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Aim: To assess overall antidepressant efficacy as well as effects on anxiety and sleep disturbance symptoms, and tolerability of mirtazapine in everyday clinical practice.

Methods: Depressed outpatients (n = 10405) of both sexes, older than 18 years, were treated with mirtazapine (15–45 mg/day) for 6 weeks in an open label-study. Clinical efficacy was assessed after 6 weeks of treatment by a German version of the CGI - Global improvement scale. Tolerability was assessed by registering treatment-emergent adverse events.

Results: Thirty-three percent of patients included into present study have switched from previous antidepressant treatment because of unsatisfactory efficacy. After 6 weeks of treatment with mirtazapine (mean dose: 30 mg/day), 82% of patients were classified as CGI responders. Prominent anxiety, present in 37% of patients at baseline, was present in only 1.1% at the end of the study. The respective percentages for prominent sleep disturbance are 44 and 2.1% and for agitation 47% and 1.5%. Adverse events were reported by only 5.3% of patients: somnolence by 1.3%, dizziness by 1.3%, dry mouth by 1.0% and weight gain by 0.4%.

Conclusion: Mirtazapine was effective and well tolerated treatment in depressed outpatients. The adverse events such as somnolence or weight gain, previously reported in placebo-controlled studies of mirtazapine, appear to be rare in everyday clinical practice.

Tues-P33

IN VITRO METABOLISM OF S-(+)- AND R-(−)-ENANTIOMERS OF MIRTAZAPINE

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Aim: To study the oxidative *in vitro* metabolism of S-(+)- and R-(−)-enantiomers of mirtazapine in microsomes from cells expressing a single human cytochrome P450 enzyme.

Materials and Methods: *In vitro* metabolism of enantiomers of mirtazapine was studied in microsomes derived from cells expressing a single human cytochrome P450 isoenzyme (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, CYP3A4), and human liver microsomes incubated with [^{3}H]-labeled S-(+)-mirtazapine and R-(−) mirtazapine. Cytochrome P450 isoenzyme selective substrates were used as a positive control for enzymatic activity.

Results: During *in vitro* experiments, 3 metabolites were formed: 8-hydroxymirtazapine, N(2)-demethylmirtazapine and the N(2)-oxide of mirtazapine. For S-(+)-mirtazapine a significant Spearman rank correlation ($p < 0.01$) was found between the formation of the 8-hydroxy metabolite and the 1′-hydroxylation of bufuralol, a reaction considered to be a selective indicator of CYP2D6 activity. For R-(−)-mirtazapine a significant Spearman rank correlation ($p < 0.01$) was found between the formation of both the N(2)-demethyl- and the N(2)-oxide metabolites and the 6β-hydroxylation of testosterone, a CYP3A catalyzed reaction.

Conclusion: Preferred metabolic *in vitro* route for the S-(+)-enantiomer of mirtazapine is 8-hydroxylation catalyzed by CYP2D6, and for R-(−)-enantiomer preferred route is the N(2)-demethylation- and the N(2)-oxidation catalyzed by CYP3A.

Tues-P34

THE INFLUENCE OF MIRTAZAPINE ON ANTERIOR PITUITARY HORMONE SECRETION IN HEALTHY SUBJECTS

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It is hypothesized that antidepressants interact with central aminergic neurons which for their part have an impact on the hormone secretion of the anterior pituitary gland. In this investigation the effects of acute p.o.-administration of 15 mg mirtazapine on the GH, COR, and PRL secretion were examined in six physically and mentally healthy male subjects, compared to placebo. After insertion of an intravenous catheter, blood samples were drawn one hour prior to the administration of mirtazapine or placebo, at time of application, and during the time of four hours after application in periods of 30 minutes. Plasma concentrations of GH, COR, and PRL were determined in each blood sample. The AUC (AUC = area under the curve) value was used as parameter for the GH, COR, and PRL response. With respect to GH and PRL secretion, mirtazapine did not show any effects in comparison with placebo. However, measurement of COR concentrations revealed a highly significant ($p < 0.01$) reduction of COR secretion compared to placebo. Since other antidepressant agents generally are known to acutely stimulate COR secretion, mirtazapine seems to be the first antidepressant which is proven to produce an acute reduction in COR secretion. Apparently, the results of our endocrinological investigation reflect the special mechanism of action of mirtazapine: unlike other antidepressants mirtazapine does not inhibit the reuptake of norepinephrine or serotonine but is an antagonist of presynaptic and, presumably, postsynaptic α_2-receptors as well as an antagonist of postsynpatic 5-HT_2 and 5-HT_3-receptors.

Tues-P35

ECONOMIC IMPACT OF USING MIRTAZAPINE IN THE MANAGEMENT OF MODERATE AND SEVERE DEPRESSION IN AUSTRIA

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Objective: This study aimed to estimate the economic impact of using mirtazapine (at ATS21.85 per 30 mg tablet), compared to amitriptyline (at ATS4.35 per 100 mg capsule) and fluoxetine (at ATS17.79 per 20 mg capsule), in the management of moderate

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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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