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

H.-J. Kreuzenbeck[1], J.Th. Helsdingen[2]*. [1]*Thieman, Walthorp, Germany*
[2]*NV Organon, Oss, The Netherlands*

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

L.P.C. Delbressine, R.M.E. Vos, R. Pinder*. *NV Organon, Oss, The Netherlands*

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

Gregor Laakmann*, Cornelius Schüle, Thomas Baghai, Jürgen Kraus. *Department of Psychiatry, University of Munich, Nussbaumstr. 7, D-80336 Munich, Germany*

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

M.C.J. Brown[1], A.A. Nimmerrichter[2]*, J.F. Guest[1]. [1]*Catalyst Health Economics Consultants, Pinner, Middlesex, UK*
[2]*Organon GesmbH, Vienna, Austria*

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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