Tues-P28

MIRTAZAPINE VS FLUOXETINE: EFFICACY ON SYMPTOMS ASSOCIATED WITH DEPRESSION

C.M.E. Kremer[1], M. Zivkov[2]*, J.T.H. Helsdingen[2]. [1]*Organon Inc, West Orange, JN, USA*
[2]*NV Organon, Oss, The Netherlands*

Aim: To compare the efficacy of mirtazapine and fluoxetine on depressed mood, as well as on anxiety, sleep and retardation symptoms in depressed in- and outpatients.

Methods: Patients with a Major Depressive Episode (DSM-IIIR), a baseline score of ≥ 21 on the 17 item-HAMD and ≥ 2 on depressed mood item, were randomized to a 6 week treatment with either mirtazapine (n = 66; 15–60 mg/day) or fluoxetine (n = 67; 20–40 mg/day). Changes from baseline in depressed mood were assessed by item 1 ('depressed mood') of the HAMD, while anxiety disturbances, sleep disturbances and retardation symptoms were respectively assessed by anxiety/somatization, sleep disturbance and retardation factors of the HAMD. The efficacy analyses were performed on the Intent-To-Treat Group using the Last Observation Carried Forward method.

Results: On all efficacy variables treatment with mirtazapine has resulted in a larger magnitude of change from baseline than treatment with fluoxetine. During the first two weeks of treatment, the largest magnitude of change was observed in the anxiety/somatization and sleep disturbance factors, The changes in the 'depressed mood' and the retardation factor were similar in both groups. From week 2 onwards changes favoring mirtazapine were particularly prominent in the 'depressed mood' item and the retardation factor. The difference on the 'depressed mood' item favoring mirtazapine reached statistical significance at week 4.

Conclusion: The results demonstrate that treatment with mirtazapine is superior to fluoxetine in improving depressed mood. Pharmacological properties of mirtazapine, especially its specific actions on postsynaptic 5-HT receptors, may account for the consistent improvements in anxiety and sleep disturbances throughout the treatment period.

Tues-P29

A NATURALISTIC STUDY OF MIRTAZAPINE IN THE GERMAN PSYCHIATRIC PRACTICE

A.-M. Pattenier[1], J.Th. Helsdingen[2]*. [1]*Organon GMBH, Oberschleißheim, Germany*
[2]*NV Organon, Oss, The Netherlands*

Aim: To assess clinical efficacy and tolerability of mirtazapine in everyday clinical practice in Germany.

Methods: Depressed in and outpatients (n = 2460) 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 1, 3 and 6 weeks of treatment by a German version of the CGI-Severity of illness and Global improvement scales. Tolerability was assessed by registering treatment-emergent adverse events.

Results: Forty eight percent of patients had an ICD-X diagnosis of a recurrent depressive episode at baseline, while 73% were treated with antidepressants prior to inclusion in the study. The most common reason for switching to mirtazapine was lack of efficacy. After 6 weeks of treatment with mean dose of 30 mg/day of mirtazapine, 72% of patients were classified as CGI responders. At the same time point, in 45.4% the severity of illness was assessed as 'mild', and in 22.6% as 'moderate'. Eighty-one percent of patients have not reported any treatment emergent adverse events. Somnolence was reported by 6% of patients, dizziness by 2.7, weight gain by 2.1% and restlessness by 2.1% of patients. Each of the remaining adverse events was reported by less than 2% of patients.

Conclusion: Mirtazapine was effective and well tolerated treatment in everyday clinical practice. Despite the methodological limitation, our results are in line with previously reported double-blind randomized studies of mirtazapine.

Tues-P30

ECONOMIC IMPACT OF USING MIRTAZAPINE

M.C.J. Brown[1], J.F. Guest[1], J. van Loon[2], R. Bruin[2]*. [1]*Catalyst Healthcare Communications, Pinner, UK*
[1]*NV Organon, Oss, The Netherlands*

Aim: To estimate the cost-effectiveness of mirtazapine vs amitriptyline and fluoxetine in management of moderate and severe depression in France.

Method: Clinical decision analysis techniques were used for retrospective estimate of the direct and indirect healthcare costs per patient; a cost-effectiveness analysis was performed to determine costs per successfully treated patient. Treatment paths for management of depression were developed from clinical data, interviews with French psychiatrists and published literature.

Results: After 28 weeks of treatment, both direct costs to Social Security and indirect costs to French society per patient were higher with amitriptyline than with mirtazapine (FF 786 and FF 4.814, respectively). A cost-effectiveness analysis shows that the expected direct costs to Social Security per patient successfully treated with mirtazapine are FF 24.212 less than for a patient successfully treated with amitriptyline. Estimates after 6 months of treatment with fluoxetine show that although direct costs are FF117 higher with mirtazapine, indirect costs are FF427 higher with fluoxetine. In addition, a cost-effectiveness analyses shows that the expected direct costs are FF25.914 less with mirtazapine compared to fluoxetine. Social Security payments to patients during their time off work emerged as the main cost driver and accounted for 86% of the direct cost per patient. In contrast, acquisition costs of antidepressants accounted for 1 to 3% of the expected costs per patient.

Conclusion: Mirtazapine is more cost-effective antidepressant compared to amitriptyline or fluoxetine. The cost per patient successfully treated with mirtazapine is FF24.212 lower than with amitriptyline, and FF25.914 lower than with fluoxetine.

Tues-P31

THE CLINICAL COURSE AND RESOLUTION OF MIRTAZAPINE-INDUCED EDEMA

L. Lahdelma[1], R. Bruin[2]*. [1]*Helsinki, Finland*
[2]*NV Organon, Oss, The Netherlands*

Objective: Edema is rare a adverse event reported with majority of antidepressants, with incidence ranging between 1%–11%. In placebo-controlled studies of mirtazapine, edema was reported in 1% of patients. We present 2 cases of edema with mirtazapine successfully resolved after dosage increase.

Method: Chart review of two outpatients presenting with facial edema.

Results: A 27-year old woman with the ICD-10 diagnosis of severe depression without psychotic symptoms, previously unsuccessfully treated with moclobemide and fluoxetine, started treatment with mirtazapine 30 mg/day. After one week there was a substantial improvement in sleep and anxiety, but facial edema appeared in the morning. The dose was increased to 45 mg/day,

https://doi.org/10.1016/S0924-9338(99)80481-7 Published online by Cambridge University Press

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

https://doi.org/10.1016/S0924-9338(99)80481-7 Published online by Cambridge University Press