SEROTONIN SYMPTOMS SCALE: AN INSTRUMENT FOR ASSESSMENT OF SEROTONIN RELATED SIDE EFFECTS

R. Bottlender, U. Hegerl, J. Gallinat, U. Preuss, H.-J. Kuss, M. Ackenheil, H.-J. Möller. *Department of Psychiatry, Ludwig Maximilians University of Munich, Nussbaumstrasse 7, 80336 Munich, Germany*

Selective serotonin reuptake inhibitors (SSRI) are generally better tolerated and less toxic than tricyclic antidepressents. Nevertheless there are side effects, that reflect a hyperserotonergic state in the CNS. Until now there is no instrument to assess these side effects, which are related to the serotonergic system. We want to close this gap with our serotonin symptoms scale. This scale includes a subscore for the diagnosis of the serotonin syndrome. In contrast to the diagnostic criteria for the serotonin syndrome proposed by Sternbach, our criteria consider not only the presence but also the severity of the serotonin related side effects and avoids overdiagnosis. In 15 patients treated with the SSRI paroxetine, relationships were studied between paroxetine plasma levels, side effects and EEG parameters. Paroxetine plasma levels were determined, using high-performance liquid chromatography with native fluorescence detection. This method is highly sensitive for paroxetine. Side effects were assessed using the serotonin symptoms scale. We found, that the subscore for the serotonin syndrome is highly correlated ($r = 0.6$) with the paroxetine plasma levels. Significant effects of paroxetine on the EEG could not be detected. The strong correlation between the subscore for the serotonin syndrome and the paroxetine plasma levels gives first evidence, that the serotonin symptoms scale is effective in measuring serotonin related side effects and a helpful instrument for the diagnosis of the serotonin syndrome.

CYCLOTHYMIC AND DYSTHYMIC DISORDER: HISTORY, CONCEPTS AND PERSPECTIVES — A REVIEW

P. Brieger, A. Marneros. *Klinik und Poliklinik für Psychiatrie, Martin-Luther-Universität Halle- Wittenberg, J.-Kühn-Str. 7, 06097 Halle, Germany*

The concepts of dysthymic and cyclothymic disorder in DSM-IV and ICD-10 have opended new perspectives. Both terms derive from 19th century German-speaking psychiatry. "Dysthymia" was first used by C.F. Flemming (1844), "cyclothymia" by E. Hecker (1877). Until now both dysthymia and cyclothymia have been used with various meanings. While dysthymia first lost its importance after Kraeplin's formulation of "manic-depressive insanity" (MDI), many authors (e.g. K. Schneider, H.J. Weitbrecht) used cyclothymia as a synonym for MDI. Other psychiatrists as Kraepelin himself and E. Kretschmer saw cyclothymia as a mild or constitutional form of MDI. H.S. Akiskal's research on "subaffective disorders" greatly influenced the development and reformulation of both diagnoses in DSM-III. Nowadays DSM-IV and ICD-10 do not differ substantially in how they define cyclothymic and dysthymic disorder. While current research on dysthymic disorder has lead to encouraging results concerning clinical presentation, familial loading, neurobiology, psychology and treatment, the concept of cyclothymic disorder needs further verification. Also the relation of both diagnoses to personality disorders is of future interest.

CLINICAL IMPLICATIONS OF THE ADRENERGENIC AND SEROTONERGENIC RECEPTOR BINDING PROFILE OF THE NEW ANTIDEPRESSANT MIRTAZAPINE

C. Broekkamp, H. Berendsen, G. Ruigt, A.M. Van Delft, N.V. Organon. *Department of Neuropharmacology, POB 20, Oss, The Netherlands*

Interactions with various receptors are the basis for explaining the therapeutic profile of new anti-depressant drugs. We report here on our progress in explaining the properties of the new antidepressant mirtazapine, by its spectrum of affinities for various G-protein linked receptors. The techniques used are receptor binding, micro-dialysis and animal behaviour. Mirtazapine has high affinity for the presynaptically located α_2 receptors. This leads not only to enhanced noradrenergic, but also to enhanced serotonergic transmission. Similar to noradrenergic terminals the serotonergic terminals undergo inhibitory control by α_2 receptor activation. Blockade of these receptors by mirtazapine leads to enhancement of noradrenergic and serotonergic transmission. However, this indirect serotonin enhancement does not lead to activation of all post-synaptic serotonin receptors, as the 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} and 5-HT_3 receptors are blocked by mirtazapine. Therefore the enhanced release of serotonin has only consequences for 5-HT receptors which are *not* blocked by mirtazapine, such as 5-HT_{1A} receptors. Several experiments confirmed that mirtazapine has effects similar to compounds which directly activate 5-HT_{1A} receptors. In rats, we studied overt unconditioned symptoms evoked by selective serotonin agonists and by serotonin reuptake inhibitors (SSRI's). Both mirtazapine as well as SSRI's indirectly activate 5-HT_{1A} receptors. Mirtazapine blocks 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} and 5-HT_3 receptors, whereas these receptors are indirectly activated by SSRI's. This suggests that 5-HT_{1A} receptor activation contributes to the antidepressant effect of mirtazapine. Blockade of 5-HT_{2B} and 5-HT_3 receptors can explain the low incidence of typical SSRI related side effects, such as nausea and headache, seen during the clinical use of mirtazapine. Furthermore, blockade rather than activation of 5-HT_{2C} receptors explains that mirtazapine neither has no negative impact on sexual functions nor induces appetite inhibition.

CHARACTERISTIC EFFECTS OF MIRTAZAPINE AND OTHER ANTIDEPRESSANTS ON RAT SLEEP EEG

Gé S.F. Ruigt, A.M.L. van Delft, C.L.E. Broekkamp. *Neuropharmacology department, N.V. Organon, Postbus 20, 5340BH Oss*

Most psychotropic drugs have clear effects on animal sleep, which may be used to separate various psychotropic drug classes [1]. Antipsychotics and anxiolytics increase quiet sleep; the "true" hypnotics increase deep sleep and stimulants enhance active waking. The most consistent finding for antidepressants is a combination of an increase in quiet waking and a preferential reduction of REM sleep. Furthermore, human studies on waking EEG [2] and studies in rat on forced waking EEG [3] have revealed that characteristic changes in EEG spectra can be delineated for several subgroups of antidepressant drugs. Very limited data are available on the way in which antidepressants and other psychotropic drugs affect the spectral characteristics of the EEG underlying the various sleep and waking stages. In the present study we have investigated the sleep-EEG effects of mirtazapine, a very effective antidepressant, which improves the onset of sleep and increases REM sleep latency in volunteers [4]. The effects of mirtazapine on rat sleep-waking behaviour fit to the general profile of sleep changes obtained for antidepressants.

In series of experiments we studied the effects of mirtazapine and other psychotropic drugs on EEG power spectra (a representation of

https://doi.org/10.1016/0924-9338(96)89052-3 Published online by Cambridge University Press

the contribution of different frequencies to the EEG signal) for the various sleep and waking stages. Power spectra were calculated per 2 sec epoch and were averaged for each of the 6 sleep-wake stages and for each rat on an hourly basis. These spectra were normalized with respect to the baseline power spectra obtained before drug administration. T-test comparisons were then made between placebo and drug treatment groups per 0.5 Hz spectral line. The ensuing t-profiles of power spectral changes were similar for all antidepressants studied and consisted of a broadband power decrease above 8 Hz, which was much more prominent for slow wave sleep and quiet sleep than for waking EEG. Mirtazapine in contrast to fluoxetine, moclobemide, desipramine further produced a 3–7 Hz power increase for all sleep and waking stages, which might be related to the observed enhancement of deep slow wave sleep after mirtrazapine. For REM sleep EEG complex patterns of spectral changes, consisting of a 1–7 increase combined with a power decrease between 7 and 10 Hz and from 20 to 60 Hz, were observed for all the antidepressants studied. This pattern of REM sleep changes could not be observed for other psychotropic drugs, suggesting that all antidepressants, including the novel antidepressant mirtazapine, produce a characteristic effect on rat REM sleep EEG.

[1] Ruigt et al, Neuropsychobiol., 28, 138, 1993.
[2] Saletu, In: Human psychopharmacology, measures and methods, vol 1 (Hindmarch, I et al, eds.), Wiley & Sons, 1987, pp. 173–200.
[3] Krijzer et al, Neuropsychobiol., 28, 122, 1993.
[4] Ruigt et al, Eur. J. Clin. Pharmacol., 38, 551, 1990.

DEPRESSION AND PERCEPTIONS OF HEALTH STATUS: EFFECT OF DEPRESSIVE SYMPTOMS ON SF-36 RATINGS IN CHRONIC PHYSICAL ILLNESS

Tom Sensky [1], Stefan Büchi [1,2], Natalie Timberlake [1], Louise Sharpe [1], Claus Buddeberg [2]. [1] *Department of Psychiatry, Charing Cross & Westminster Medical School, West Middlesex University Hospital, Isleworth, Middlesex TW7 6AF, United Kingdom;* [2] *Abteilung für Psychosoziale Medizin, Psychiatrische Poliklinik, Universitätsspital, CH-8091 Zürich, Switzerland*

Background and Objectives: The SF-36 questionnaire devised for the Medical Outcomes Study is widely used as an outcome measure in research on medical or surgical interventions, and as a measure of quality of life. Responses to the SF-36, as with other similar self-report measures, would be expected to be significantly influenced by the presence of depressive symptoms. Depression leads to systematic bias in appraisal, including that of illness and its consequences. Among people with a chronic physical illness, depressive symptoms lead patients to report more functional impairment and greater pain, regardless of objective measures of disease status. Given the high prevalence of depressive symptoms in patients with chronic illnesses, this effect of depression is likely to be clinically significant. The present study therefore aimed to test the hypothesis that SF-36 scores correlate significantly with depression ratings.

Methods: Patients with rheumatoid arthritis attending a rheumatology outpatient clinic at a district general hospital were asked to compete a battery of questionnaires, including the SF-36, the Hospital Anxiety and Depression Scales (HADS) and the Rheumatoid Arthritis Disease Activity Index (RADAI), a brief self-report measure which correlates with physician ratings of disease activity such as joint tenderness and swelling, and grip strength.

Results: Questionnaires were completed by 89 patients. Scores on the RADAI correlated significantly with each of the SF-36 subscales. However, there were also significant correlations ($p < 0.01$) between the HADS depression score and all the SF-36 subscales, with the exception of the emotional role subscale. These correlations were greatest for SF-36 general health ($r = -0.62$), mental health ($r = 0.62$) and social functioning ($r = 0.61$) subscales.

Conclusions: These results provide strong support for the study hypothesis. While the SF-36 may be a useful measure of overall quality of life or health service utilization (since depression and physical status may each influence these), the results cast doubt on the validity of the SF-36 as a global outcome measure for interventions in chronic illness, where depressive symptoms are common but often independent of the intervention under study.

CHANGES OF PATTERN IN UTILISATION OF HOSPITAL SERVICES AFTER ADMISSION TO THERAPEUTIC RESIDENTIAL FACILITIES

Jens Bullenkamp, Burkhardt Voges. *Central Institute of Mental Health, J 5, D-68159 Mannheim, Germany*

An analysis of utilisation data was conducted for 218 residents from nine different residential facilities, i.e. halfway houses, group homes and sheltered apartments. Data for each patient were obtained from the Division of Scientific Documentation of the Central Institute of Mental Health for five different categories: hospital admission, emergency and outpatient services, day clinic and liaison service within a general hospital.

Utilisation was calculated per year for the periods before and after admission to the current therapeutic facility. In all 1840 contacts were counted since the beginnings of the Central Institute in 1972, amounting to a mean of 8.4 contacts per patient with a range from 0 to 55 contacts. Utilisation of the Central Institute increased from 0.85/year before admission to 1.04/year after admission to the respective institution. Further analysis revealed this finding to be due to an increase in utilisation of emergency services (0.35/year vs. 0.6/year), while utilisation of services in all other categories remained stable or decreased. Especially the number and proportion of hospital admissions was reduced significantly as was the length of stay in hospital and day clinic.

We conclude that admission to therapeutic residential facilities does not reduce overall utilisation rates of hospital services. However, according to our results, it is associated with a substantial reduction in hospital admissions and length of stay in hospital. This indicates not only a higher level of quality of life for the respective population, but also a possible cost saving effect generated by therapeutic institutions like halfway houses and group homes.

DEPRESSION WITH AND WITHOUT CONCURRENT PANIC ATTACKS: DIFFERENCES IN THYROID ECONOMY

R. Bunevičius. *Institute of Eudocrinology, Eivenių 2, 3007 Kaunas, Lithuania*

The abnormalities of Thyroid stimulating hormone (TSH) response to Thyrotropin releasing hormone (TRH) has been reported both in depressed and panic patients. In the present study TRH test was performed in 28 depressed women. Patients were divided by the presence ($n = 10$) or absence ($n = 18$) of concurrent panic attacks and compared their TRH test results. All patients were screened for the microsomal thyroid antibodies.

There were no significant differences in basal thyroid hormones (thyroxin and triiodothyronine) levels. Basal TSH tended to be lower in depressives with panic attacks in comparison to depressives without panic (1.51 ± 1.08 vs. 3.38 ± 0.85, $p < 0.1$) and TSH response to TRH stimulation (dmaxTSH) was significantly lower (5.73 ± 3.01 vs. 12.91 ± 2.41, $p < 0.05$). Basal TSH correlated significantly to dmaxTSH in depressed patients without panic attacks only ($r = 0.80$, $p < 0.001$). One patient (10%) in panic group and three (16.7%) in depression group had titre of microsomal thyroid antibodies higher than 1:2560, suggesting autoimmune thyroiditis.

The present study suggests that depressed patients with concur-

https://doi.org/10.1016/0924-9338(96)89052-3 Published online by Cambridge University Press