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

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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

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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

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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

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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

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