post-operative psychiatric interview and scales: Montgomery and Asberg Depression Rating Scale (MADRS), Mini International Neuropsychiatric Inventory (MINI), Scale Inventory Personality Disorder (SIPD), Mania Assessment Scale (Bech), Assessment of Depression (Beck), Apathic scale and neuropsychologic tests.

Results: After six months, among 12 operated patients, temporary results show one case of hypomania with behavioral disorder (DSM-IV criteria disorder). This patient, without thymic history, presented a paranoid personality disorder. Using tools, we did not identified in the others 11 patients, acute depression or manic symptoms.

Conclusion: Data are still being analysed, but this case draw our attention to the effects of STN stimulation on mood and behavioural disorders and to the importance of the psychiatric follow-up.

Monday, April 4, 2005

LS-03. Satellite symposium: Implication of serotonergic and melatonergic systems: New perspectives for the treatment of depression

Supported by an unrestricted educational grant from Servier

Chairperson(s): Mario Maj (Naples, Italy), Dieter Naber (Hamburg, Germany)
12.30 - 14.00, Gasteig - Carl-Orff Hall

Introduction

M. Maj *University of Naples of SUN Dept. of Psychiatry, Naples, Italy*

LS-03-01

Biological rhythm disturbances in mood disorders

A. Wirz-Justice. *Universitätsklinik Psychiatrie Center für Chronobiologie, Basel, Switzerland*

The clinical observations of diurnal variation of mood and early morning awakening in depression are incorporated into the established diagnostic systems. Not only is sleep disturbed, but many circadian rhythms in depressive patients are abnormal: earlier in timing, diminished in amplitude, or of greater variability. Whether these disturbances are of etiologic significance for the role of circadian rhythms in mood disorders (are there allelic mutations in "circadian clock"– or "sleep"-related genes in depression?), or whether they are a consequence of altered behavior is not yet clear. Genetic vulnerabilty and stress influence circadian rhythms and sleep patterns, leading to the symptoms characteristic of affective disorders. Circadian regulation interacts with, and is determined by, neurotransmitter function; for example, the highest concentrations of CNS serotonin are found in the biological clock in the suprachiasmatic nucleus. CNS serotonin turnover undergoes marked circadian and seasonal rhythmicity, and is rapidly stimulated by light exposure. This links the important role of light as a zeitgeber or synchronizer of the circadian system to the role of serotonin in mood disorders. Zeitgebers ensure stable phase relationships between internal and external time, which is crucial for a stable mood state. Melatonin is also a zeitgeber for the circadian system. The specific pharmacological profile of agomelatine, as an agonist of melatonergic MT1 and MT2 receptors with 5-HT2C receptor antagonist properties, uniquely combines zeitgeber with neurotransmitter regulation properties, with evolving evidence for robust antidepressant efficacy. New to neuropharmacology is the zeitgeber aspect, providing innovative perspectives for drug development.

LS-03-02

Insights into the pharmacology of agomelatine: The first melatonergic antidepressant

E. Fuchs. *DPZ Deutsches Primatenzentrum Division of Neurobiology, Göttingen, Germany*

Depressive disorders represent a collection of psychological, physiological and behavioral symptoms whose frequency and chronicity together constitute a recognizable clinical condition. Despite extensive investigations, the exact neurobiological processes leading to depression and the mechanisms responsible for the therapeutic effects of antidepressant drugs are not completely understood. Limitations of current antidepressant medications such as the delay before there is a therapeutic response, a substantial rate of nonresponders, and bothersome side-effect profiles, merit the exploration of all plausible agents with novel antidepressant mechanisms of action. The well-established clinical finding that depressive disorders are often associated with desynchronization of internal rhythms has stimulated the idea that resetting normal circadian rhythms may have antidepressant potential. Initial attempts to prove an antidepressant activity for the powerful endogenous synchronizer melatonin were not successful. However, recent experiments using the novel melatonin receptor agonist agomelatine (S 20098; N[2-(7-methoxy-1-naphthyl) ethyl]acetamide) revealed clear antidepressant-like effects in a wide variety of rodent and non-rodent models. In vitro binding studies revealed that agomelatine is a high affinity agonist at both the melatonin MT1 and MT2 receptor types. In addition, these studies revealed that agomelatine - but not melatonin – blocks with high affinity 5-HT2C receptors. Interestingly, antagonism of 5-HT2C receptors is reported for various established antidepressant compounds. Therefore, one may assume that the agonistic activity at the melatonin receptors with blockade of 5-HT2C receptors probably contributes to the rapid onset and the efficacy of this novel compound at least in animal models for depression.

LS-03-03

Antidepressant efficacy of agomelatine: Clinical implications

P. Boyer. *Ottawa, Canada*

Agomelatine is a new antidepressant with a unique mechanism of action. It is the first melatonergic (MT1 and MT2 receptor) agonist antidepressant. Its antidepressant efficacy was demonstrated in a range of clinical trials. Due to its mechanism of action, agomelatine was proven to have special advantages in improving sleep and anxiety, without being sedative and affecting vigilance. In a multicenter, placebo-controlled, dose-ranging study over 8 weeks, agomelatine was shown to be an effective antidepressant at a dose of 25 mg once daily, by reducing the initial HAMD score to a similar extent to that of paroxetine (HAMD scale: 2.57 point difference between agomelatine and placebo; $P<0.05$). In 2 studies in an adult population aged 18 to 65, agomelatine 25 mg was

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significantly more effective than placebo in the overall population, and also in the severely depressed population (HAMD score >25, and with a combination of HAMD score of 25 or more and a CGI score of 5 or more; P<0.05). Similarly, in a trial in elderly patients aged 60 and above, agomelatine was shown to be effective in the more severely depressed patients. Another clinical trial demonstrated the same percentage of responders and remitters between venlafaxine (150 mg/day) and agomelatine (50 mg/day); the first results will be presented during the symposium. Updated data concerning the efficacy of this innovative melatonergic agonist and 5-HT2C antagonist antidepressant will be presented as well its action on anxiety symptoms and sleep within depression.

LS-03-04

Sleep as a marker of disrupted circadian rhythms in depression

C. Guilleminault. *Stanford Slee Disorders Center, Stanford, USA*

Sleep is one of the circadian rhythms often disturbed in depressed patients. A resetting of these disturbed rhythms is known to have beneficial effects on depressive states, with a normal circadian profile being restored after recovery. Agomelatine is a new antidepressant with an entirely innovative mode of action: it is the first melatonergic agonist antidepressant. Agomelatine is effective for the treatment of major depressive disorder, with particular advantages in improving sleep of depressed patients, without being sedative or increasing daytime clumsiness. Analysis of the HAMD sleep item results of efficacy studies showed agomelatine to be better than placebo on all three phases of sleep, early insomnia (P<0.001), middle insomnia (P=0.015), and early wakening (P=0.006), with a similar treatment size effect. Furthermore, using the Leeds Sleep Evaluation Questionnaire in clinical trials, agomelatine significantly improved the ability to get off to sleep and improved the quality of sleep. This effectiveness was seen versus placebo (P<0.001) and SSRIs (P<0.001). In order to confirm the subjective sleep improvements, a specific polysomnography study was performed to examine the effect of agomelatine on sleep architecture of depressed patients. There were clear changes in sleep structure and NREM sleep stage distribution following treatment. Agomelatine appears as an innovative treatment for depression, because of its chronobiotic activity regulating circadian rhythms, and its interaction with the serotonergic system. The ability of agomelatine to relieve sleep complaints, without being sedative, is a key advantage for depressed patients, who frequently suffer from sleep disturbances associated with their depression.

LS-03-05

Benefits and tolerability evaluation of agomelatine: A new approach to the treatment of depressed patients

S. Montgomery. *London, United Kingdom*

Agomelatine is a new antidepressant, being the first melatonergic (MT1 and MT2 receptor) agonist antidepressant. Its antidepressant efficacy at a mean dose of 25 mg daily has been shown in a dose-ranging study performed in major depressive disorder (MDD).1 Agomelatine's safety and tolerability has been examined across a wide range of studies. The pharmacological profile of agomelatine differs from standard antidepressants, and it has been shown to lack the typical antidepressant side effects (ie, gastrointestinal disorders, weight gain, insomnia). The effect of agomelatine on sexual function was compared with venlafaxine in a specific study using the SEX-FX scale in remitted MDD patients after 12 weeks of treatment. Significantly fewer remitters experienced sexual dysfunction in the agomelatine group than in the venlafaxine group measured on desire-arousal (P<0.05) and orgasm (P<0.01) dimensions. There are concerns about drug discontinuation syndromes, associated mainly with SSRIs and SNRIs. A double-blind study with discontinuation of either agomelatine or paroxetine on placebo or continued medication was performed.2 After one week of treatment discontinuation, no signs of discontinuation symptoms were observed in the agomelatine group compared with placebo, whereas the cessation of paroxetine treatment was associated with significant discontinuation symptoms. Agomelatine is an interesting antidepressant that is effective in both moderate and severe depression; it improves sleep without being sedative, and its efficacy is not compromised by sexual side effects, tolerability problems, or discontinuation symptoms.

References

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Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Int Clin Psychopharmacol. 2004;19:271-280.

Conclusion

D. Naber. *UKE UniversitätsKH Eppendorf Psychiatrische Klinik, Hamburg, Germany.*

Monday, April 4, 2005

LS-04. Satellite symposium: Overcoming common barriers to treatment adherence in bipolar disorder

Supported by an unrestricted educational grant from Eli Lilly

Chairperson(s): Siegfried Kasper (Wien, Austria)
12.30 - 14.00, Holiday Inn - Hall 1

LS-04-01

Medical comorbidities and bipolar disorder

S. Kasper. *Medizinische Universität Allgem. Psychiatrie, Wien, Austria*

Nearly 20% of all patients with bipolar disorder have a comorbid illness. Younger patients are more likely to have a comorbid psychiatric illness, while comorbid, physical illness is a greater problem in the elderly. The prevalence of comorbidity associated with bipolar disorder creates a unique diagnostic and treatment challenge. Illnesses such as epilepsy and cardiovascular disease are also strongly associated with bipolar disorder. This symposium will review the methods of assessing comorbid illnesses that may disguise the presence of, as well as affect the course and prognosis of, bipolar disorder. Comorbid illnesses also impact treatment; therefore, strategies for selecting appropriate treatment options will be discussed.

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