spectrum disorders, and the subtyping of OCD. An important issue was also of whether OCD should be considered as a distinct disorder, separate from the anxiety disorders. Based on the available evidence, it was proposed to remove OCD from the anxiety disorders and place it within a separate category of OCDs. To do justice to the complex and heterogeneous presentation of OCDs it was also proposed to utilize a combination of categorical and dimensional approaches in the diagnostic process. The consensus was that this would enable not only the tailoring of treatment, but would also be helpful to studies on the neurobiology and endophenotyping of OCD.

Key issues in the neurobiology OCD, including the role of serotonin and dopamine, the cortico-striatal circuits and genetic factors, were addressed with respect to their relationship to special populations, such as treatment resistant patients, tic disorders and "schizo-obsessive' patients, and the response to various treatments.

SAT2.04

Escitalopram - a new option in OCD treatment

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Substantial evidence from controlled studies demonstrate efficacy for clomipramine and SSRIs in the acute treatment of OCD across the lifespan. There have been fewer studies of long-term treatment and it remains less conclusively understood as to how well treatments that have been shown to be effective in short-term studies maintain their efficacy over the longer term, though placebo-referenced trials suggest efficacy for clomipramine, fluoxetine and sertraline up to twelve months. Most relapse prevention studies in acute responders revealed a significant advantage for remaining on active treatment (paroxetine, sertraline and fluoxetine at higher doses). For some of these studies methodological problems impaired their ability to discriminate active from placebo treatment on the chosen relapse criterion.

In a double-blind dose-finding study, 458 OCD patients were randomized to escitalopram (fixed at 10mg or 20mg), or 40mg paroxetine or placebo. At week 12 - the primary efficacy endpoint - 20 mg escitalopram showed a significant improvement in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) compared to placebo ($p<0.005$). At week 24, escitalopram 10mg ($p<0.05$) and 20mg ($p<0.005$) showed significantly greater improvements in Y-BOCS total scores than placebo - as did paroxetine 40 mg ($p<0.005$). In a relapse prevention study, 320 patients (ITT) who had responded following 16 weeks of open treatment with escitalopram, were randomized to placebo or escitalopram for a further 24 weeks of double-blind treatment. The primary analysis (time to relapse) showed a significant advantage for escitalopram (Log-rank test $p<0.001$), and the risk of relapsing was 2.7 times higher for placebo compared to escitalopram. These results suggest that escitalopram is effective for acute and long-term treatment and relapse-prevention in OCD.

SAT3 - Satellite symposium: RESETTING THE INTERNAL CLOCK IN DEPRESSION: A NEW THERAPEUTIC APPROACH

Sponsored by Servier

SAT3.01

Effective management of depressed mood with agomelatine, a melatonergic antidepressant

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Agomelatine is a new antidepressant with an unique pharmacological profile. It is a potent agonist of melatonin receptors (MT1 and MT2) and also an antagonist at 5-HT2C receptors Agomelatine's acute efficacy in treating MDD was seen in three placebo-controlled studies, including a dose-ranging study with paroxetine as active comparator.

The meta-analysis of these trials showed a significant difference between agomelatine and placebo in the main efficacy analysis, the HAMD score (= 2.86 0.56; $P<0.001$) and in the CGI scale (=0.47 0.10; $P<0.001$).

Furthermore, evidence of agomelatine's efficacy in severe depression was illustrated by the meta-analysis of the patient subgroup with a baseline HAMD 25. Analysis of pooled data demonstrated an increase in the magnitude of the agomelatine-placebo difference with increasing severity at baseline.

The antidepressant efficacy of agomelatine was also evaluated in direct comparison to venlafaxine in 2 trials. Agomelatine showed at least comparable efficacy to venlafaxine in depressed patients after 6 and 12 weeks of treatment.

Agomelatine did not show the typical side effects found with selective serotonin reuptake inhibitors (SSRIs) (ie, gastrointestinal disorders, weight gain, serotonergic syndrome, and insomnia).

Moreover, agomelatine was shown to lack discontinuation symptoms compared with placebo in a study showing significant discontinuation symptoms with paroxetine.

In conclusion, the experience with agomelatine across a wide range of clinical trials suggests that agomelatine offers an important alternative for the treatment of depression, combining efficacy, even in the most severely depressed patients, with a favourable side-effect profile.

SAT3.02

A new pharmacological step: The melatonergic approach

G. Racagni. *Center of Neuropharmacology, University of Milan, Milan, Italy*

A breakthrough has recently been made in antidepressant research with the development of agomelatine. Agomelatine has a distinct pharmacological profile compared with all other classes of clinically available antidepressants.

Agomelatine is a high-affinity agonist at both the melatonergic MT1 and MT2 receptor types, and, in addition, blocks 5-HT2C receptors. Agomelatine did not significantly bind to any other site studied. In accordance with this profile, agomelatine resynchronized circadian rhythms and elicited a dose-dependent elevation in extracellular levels of noradrenaline and dopamine in the frontal cortex of freely moving rats while exerting no effect upon serotonin levels. The antidepressant actions of agomelatine have been described in several validated animal models: learned helplessness, forced swim, chronic mild stress, mice with impaired glucocorticoid receptors, isolated aggressive mice, and the marble burying test, with antidepressant-like effects being shown in all behavioral paradigms examined. Based on these results, the nocturnal sleep pattern of psychosocially stressed male tree shrews (a valid animal model for depression) was investigated: agomelatine resynchronized disrupted circadian rhythms and antagonized the effect of stress on the total amount of rapid eye

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movement (REM) sleep and on the fragmented sleep pattern. In conclusion, the antidepressant efficacy of agomelatine may be due to its receptor profile, and it is hypothesized that melatonergic and 5-HT2C receptors may be acting in synergy, thus representing a novel approach to treating depression.

SAT3.03

How the internal clock interacts with mood and depression

C. Guilleminault. *Stanford Sleep Disorders Center, Stanford, CA, USA*

In all life forms, circadian rhythms are defined by a period of approximately 24 hours. The daily light/dark cycle governs rhythmic changes in behavior and physiological and mental functions, ie, in activity, core body temperature, hormones, sleep-wake cycle. All circadian rhythms are driven and controlled by the biological clock, which in mammals is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus.

Disruption of circadian organization is a characteristic of a variety of affective disorders, especially major depression, and, circadian abnormalities may constitute a core component of the pathophysiology of depression and may also determine the treatment response.

Depressed patients have documented abnormalities in mood, body-temperature, neuroendocrine secretion, and, most importantly and disabling, in sleep (approximately 90% of patients complain about their sleep). The sleep alterations are mainly related to poor sleep quality and maintenance and to difficulties in maintaining alertness during the day. Polysomnographic recordings show disruption of sleep continuity with prolonged sleep latency, increased wake time during the night, increased early morning wake time, decreased slow-wave sleep, and disinhibition of REM sleep. Most antidepressants can influence the architecture of sleep: SSRIs, SNRIs, and some TCAs (clomipramine) have "alerting" effects whereas others, among them, mirtazapine or trazodone, are sleep promoting often also causing sedation and daytime sleepiness. An important clinical goal in the treatment of major depression would therefore include antidepressants that improve both mood and quality of sleep without impairing daytime alertness.

SAT3.04

Beyond efficacy on the core symptoms of depression: Sex and sleep benefits

A.L. Montejo. *Departamento de Psiquiatría, Hospital Universitario de Salamanca, Salamanca, Spain*

The outcome of depression can be affected after chronic use of antidepressants, because of the spectrum of side effects affecting compliance and quality of life. Among the most disabling side effects are sleep disturbances and sexual dysfunction.

Agomelatine, with its unique pharmacological profile acting as an agonist at melatonergic receptors and as an antagonist at 5-HT2C receptors, improves sleep and does not affect sexual functioning in major depressive disorder. In one study, agomelatine 25 mg, increased slow-wave sleep and normalized its distribution throughout the night ($P<0.05$) without altering REM sleep. In another study, agomelatine 25-50mg, compared with venlafaxine 75-150 mg, showed similar antidepressant efficacy and demonstrated significant sleep improvement (LSEQ questionnaire) as early as from the first week of treatment ($P=0.007$ for getting off to sleep and $P=0.015$ for quality of sleep). This improvement was maintained throughout the entire 6-week treatment period, with a parallel improvement in daytime alertness.

A comparison of sexual functioning in depressed patients treated with agomelatine or venlafaxine indicated that agomelatine 50 mg had a better sexual profile than venlafaxine XR 150 mg in remitted patients after 12 weeks of treatment on both orgasm and preorgasm measures; both treatments showed comparable antidepressant efficacy. To confirm the favourable effects of agomelatine on sexual functions, a study in healthy volunteers has been carried out and these results will be discussed.

In conclusion, agomelatine is a novel antidepressant that ameliorates disturbed sleep and leaves sexual functioning unaffected, thus improving both depressive symptoms and quality of life of depressed patients.

SAT4 - Satellite symposium: THE INTEGRATED MANAGEMENT OF LONG-TERM PSYCHIATRIC AND MEDICAL NEEDS IN PATIENTS WITH SEVERE MENTAL ILLNESS

Sponsored by pfizer

SAT4.01

Impact of medical comorbidities on patients with severe mental illness

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Patients with schizophrenia and bipolar disorder carry a heavy burden of medical comorbidities. Patients with schizophrenia or bipolar disorder have a life expectancy that is 15 years less than that of the general population. This increased mortality is partly associated with factors inherent to the patients' psychopathology. For example, the risk of suicide is about 20 times higher than that of the general population. However, despite increased psychiatric mortality, cardiovascular disease is the primary cause of death in patients with schizophrenia. While some of this morbidity is the acknowledged result of long-term antipsychotic medication, not all can be explained by pharmacotherapy-for example, patient lifestyle choices may account for at least part of this elevated risk. Smoking, for example, is much more common among patients with schizophrenia than the general population. However, psychotic patients often have undetected general health problems despite a higher than average physician consultation rate, suggesting that there is inadequate monitoring and treatment of the physical health of individuals with mental health problems. This may reflect the fact that mental healthcare is separated from physical healthcare in many countries and access to primary healthcare is often limited for individuals with mental illness.

SAT4.02

Considerations in the treatment of severe mental illness: Differential profiles of antipsychotics

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