# ABSTRACTS FROM THE 6TH INTERNATIONAL FORUM ON MOOD AND ANXIETY DISORDERS

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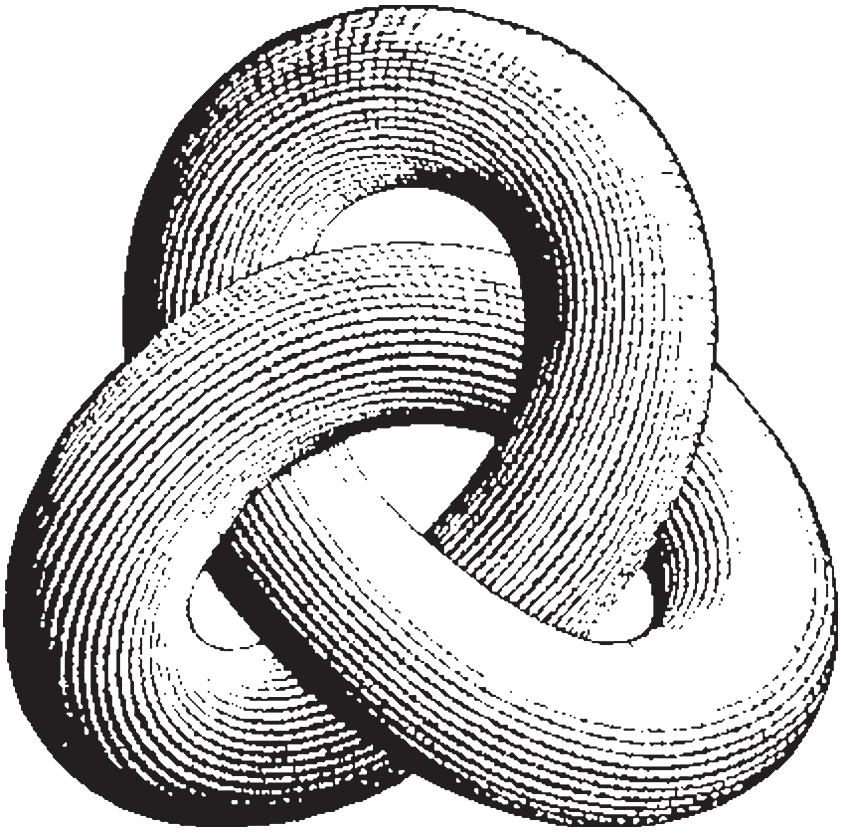

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# Speaker Abstracts

## SO 01. Treatment of comorbid depression

### SO 0101. Treatment of depression in schizophrenia

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Depressive symptoms are frequently found in schizophrenic patients during the longitudinal course of illness. The DSM-IV and the ICD-10 have operationalized postschizophrenic depression, which can follow after remission of a psychotic episode. However, a rational approach for treating depression in schizophrenia is to rule out other causes for depression-like symptoms: a number of organic factors and substance/medication-induced depressive syndromes have to be excluded. Furthermore, side effects of neuroleptic treatment such as extrapyramidal symptoms (i.e. akinesia and akathisia) and neuroleptic-induced dysphoria have to be distinguished from depressive features. Negative symptoms of schizophrenia may be particularly difficult to differentiate from postpsychotic depression. At last, prodromes of a psychotic relapse can resemble a depression-like state and have to be recognized by the clinician. Besides increased surveillance and unspecific support, optimization of antipsychotic treatment (switch from typical neuroleptic to atypical antipsychotic, dose adjustment, treatment of side effects) is the first step after the development of depression-like symptoms. Despite the limited literature on this topic, schizophrenic patients with persistent depression may respond to adjunctive antidepressant medication [1]. However, psychosocial strategies, such as stress reduction, social skills training and minimizing high expressed emotions, may also be beneficial and should be integrated in a holistic treatment approach [2].

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### SO 0102. Treatment of depression in OCD

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In the "real world", it is not always easy to disentangle depression from anxiety and vice versa. Moreover, long-life comorbidity of some of the anxiety disorders (e.g., PTSD, OCD, social anxiety, etc.) with depression is actually above 50%. The governing school of thought regarding this sizeable group of patients is the hierarchical or primary–secondary approach. The underlying hypothesis being that the affective component is secondary to the suffering induced by the anxiety disorder. According to this line of reasoning, only successful treatment of the primary cause will eventually lead to a subsequent resolution of the depression. Another conceptualization of mixed anxiety and depression is the symptomatic approach, i.e. treating equally (and appropriately) the different symptoms. Unfortunately, the way most studies in anxiety and depression were conducted does not give us good footing as they used to exclude depression in anxiety studies and vice versa. The selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) are now established as effective and well-tolerated treatments for mood and anxiety disorders. In randomized, double-blind, placebo-controlled studies in patients with OCD and comorbid depression, patients receiving SSRIs showed significantly higher response rates than placebo-treated patients. Alexander the Great, so the legend says, being frustrated with the complex Gordian knot, used his sword to cut through it. The authors will present less dramatic approaches including functional brain imaging and genetic reasoning along with some practical therapeutic hints, in an attempt to explore (and treat) the anxiety-depression knot.

### SO 0103. Treatment of depression in Parkinson's Disease

### SO 0104. Treatment of comorbid depression and anxiety

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As with most comorbid conditions there is no clear evidence-based state of the art treatment for comorbid depression and anxiety. There are only a few randomised controlled studies which address this issue under the aspect of acute treatment, while randomised controlled studies addressing the long-term treatment of this comorbid condition are lacking. As to the acute treatment studies addressing this issue, most deal with the co-medication with a

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benzodiazepine in addition to treatment with antidepressants. From these studies the treatment recommendation can be derived that acutely depressive patients suffering from severe anxiety in the context of the depression can benefit from adjunctive medication with a benzodiazepine. However, it should be considered that also antidepressants themselves reduce the anxiety score during the treatment of an acute depression. Thus the question is always from which threshold, expressed by a score of an anxiety scale, the co-medication should be started. At the moment there are no clear rules in this respect and the decision is still based on subjective clinical judgement. These studies in a descriptive sense do not deal with comorbidity but with co-syndromality in a dimensional way. As to comorbidity in the stricter sense, i.e. the coexistence of a depressive episode and anxiety disorder, principally it seems meaningful to prefer antidepressants that also have the indication for the respective anxiety disorder. However, there are no clear evidence-based data to support this clinically plausible rule.

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## SO 02. Bipolar depression

### SO 0201. Switch rates with antidepressants or placebo in bipolar depressed patients

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The rate at which patients switch from bipolar (BP) depression to the manic or hypomanic phase of the disorder during treatment with antidepressants (ADs) has not been firmly established. In older studies, higher rates of switching had been found for antidepressant monotherapy (67%) than with placebo (33%). Conversely, it had been supported, based on naturalistic observations, that the rate of induction of mania by tricyclic antidepressants (TCAs) was not greater than what would be expected from the natural history of the illness itself. This controversy about the rates of switches in mood polarity in BP patients who receive ADs may be due to differences among studies in definitions of switch and in population characteristics. More recent studies have demonstrated that in patients with BP depression, manic switch occurs substantially more often with TCAs (11.2%) than with selective serotonin reuptake inhibitors (SSRIs) (3.7%) or placebo (4.2%); these rates are supported by a meta-analysis of 12 randomized trials. It also appears that the risk with monoanine oxidase inhibitors (MAOIs) is between that of SSRIs and TCAs. Furthermore, recent randomized data support the view that there is a greater risk of a switch with the combined reuptake inhibitors with additional noradrenergic action, compared to the SSRIs. There have been no systematic studies on the risk of a manic switch using combined antidepressant treatments. An additional problem with AD use is the probability of cycle acceleration; 25% of depressed BP patients seem to worsen over time with ADs and the incidence of antidepressant-induced rapid cycling ranges from 23 to 73%. Since we are lacking knowledge about the mechanisms underlying the switch process on ADs, psychiatrists must be cautious in prescribing antidepressant monotherapy for BP depression. The use of ADs without the concomitant use of mood stabilisers is not recommended in BPI patients, although the danger of switch should not avert physicians from the use of ADs, since their premature discontinuation may elevate the risk of a depressive relapse.

### SO 0202. Efficacy of mood stabilisers in treatment of bipolar depression

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Certain anticonvulsants and lithium have been described as "mood stabilisers", although this term can be ambiguous unless it is defined, or unless the specific drugs are named. Until recently, lithium has had the best claim for being a mood stabiliser, improving both mania and depression and reducing the frequency of recurrences of both poles of bipolar illness. However, its efficacy in preventing depression is less impressive than in preventing episodes of mania. Likewise, similar to monotherapy in acute bipolar depression, lithium is slow and relatively weak in effect. Lithium has been used as an adjunct to other antidepressants, but the evidence for its efficacy in this context is mainly from studies in both which bipolar and unipolar patients were included. Among the anticonvulsants, only lamotrigine has proven antidepressant efficacy. Although the first large placebo-controlled trial showed antidepressant efficacy on one of the main outcome measures, other studies were not conclusive. However, a meta-analysis of all the trials of

lamotrigine in bipolar depression does demonstrate significant antidepressant efficacy, albeit with a small effect size. As a maintenance treatment, lamotrigine provides protection against further episodes of depression, and also of mania. Its prophylactic efficacy is most marked, in preventing a recurrence of depression, when lamotrigine is initiated after an episode of mania. Other drugs that have been studied in bipolar depression include carbamazepine, gabapentin and valproate.

#### SO 0203. Lamotrigine as add-on to lithium in bipolar depression

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*Introduction*: Lamotrigine is one of the pharmacological options in bipolar depression, but has so far only been studied in RCTs as monotherapy. In an 8-week, double-blind study we compared lamotrigine and placebo as add-on therapy to lithium in patients with bipolar depression.
*Method*: Inclusion criteria: age $\geq$18 years, bipolar I or II disorder, depressive episode, MADRS $\geq$18 and CGI-BP severity of depression $\geq$4, lithium levels between 0.6 and 1.2 mmol/l. Exclusion criteria: psychotic features, $\geq$10 episodes/year, recent alcohol or substance abuse, relevant somatic illness, current use of antidepressants, antipsychotics or benzodiazepines $\geq$2 mg lorazepam equivalent. Outcome measures: MADRS and CGI-BP
*Results*: In total we included 124 patients from 26 centers in The Netherlands and five centers in Spain. At time of submission of the abstract the database for the acute phase of the study has been closed. Results will be presented.

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#### S 0204. Atypicals in bipolar depression

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*Introduction*: Depression is the predominant mood disturbance in bipolar disorder, but limited progress has been made in the treatment of this disabling condition. New treatment options have appeared recently and raise the question as to what is the most effective strategy in bipolar depression. Moreover, the use of atypical antipsychotics is rapidly expanding in the management of bipolar disorder, and recently two compounds, olanzapine and quetiapine, have proved to be efficacious in controlled clinical trials in bipolar depressed patients.
*Methods*: Relevant papers were identified undertaking a literature search using MEDLINE and PubMed: preclinical and clinical studies that incriminate the dopaminergic system in bipolar depression, and recent controlled trials supporting the use of atypical antipsychotics, were reviewed. Data from recent scientific meetings were also scrutinized.
*Conclusions*: Bipolar depression has a severe impact on patients' lives and there is an urgent need for increased understanding of this condition and improvements in treatment. Atypical antipsychotics may ultimately prove effective in acute bipolar depression and maintenance treatment. Dopamine may still play an important role as a mediator of antidepressant response in bipolar depression. There is good evidence available for the efficacy of quetiapine, some evidence for the efficacy of olanzapine (particularly in combination with fluoxetine but also as monotherapy) and amisulpride, and some promise with ziprasidone and aripiprazole. Little or no evidence is available for clozapine, risperidone, and other antipsychotics. Longer-term trials, comparative studies, and research with novel compounds is urgently needed to confirm the great expectations that have been recently raised in this area.

### SO 03. Treatment of severe depression

#### SO 0301. Disability and risks in severe depression

#### SO 0302. TCAs in severe depression

#### SO 0303. SNRIs in severe depression

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Findings from main epidemiological studies indicate that major depressive disorder (MDD) is a highly prevalent illness. The lifetime prevalence of MDD is about 15–17%. Major depressive disorder is a serious illness often associated with significant morbidity and mortality for which prolonged treatment with antidepressant is often required to achieve satisfactory response, in particular in the most severe subjects. Although there is no generally accepted definition of severe depression, arbitrary criteria such as cut-offs on depression rating scales (Montgomery Asberg Depression Rating Scale or Hamilton Depression Rating Scale) have been used to define severity. Serotonin-norepinephrine reuptake inhibitors (SNRIs) work by blocking the presynaptic reuptake of 5-HT and NE resulting in an increased sustained level of both neurotransmitters. Some SNRIs have demonstrated efficacy in hospitalized subjects with severe melancholic depression and in some instances a higher rate of remission in severe depression as compared with either selective serotonin reuptake inhibitors

(SSRIs) or tricyclic antidepressants (TCAs). Desvenlafaxine is the latest SNRI to demonstrate efficacy with positive placebo-controlled studies and has been filed for a licence as an antidepressant with the FDA. The data show that desvenlafaxine is effective in severe depression.

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### SO 0304. Superior treatments in severe depression

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Severe depression represents a most important subgroup of patients to manage. The disability and dangers of the disorder are greater than with less severe subgroups, and frequent hospitalisation increases the health care costs. Severe depression is associated with a higher level of suicidal thoughts, and suicide and is associated with an increase in mortality from many physical conditions. Unfortunately regulatory authorities do not require evidence of efficacy in severe depression so that systematic data are not necessarily available for new treatments. For example, in the duloxetine registration studies there were too few patients with severe depression to provide any reassurance of efficacy in this subgroup. In a recent consensus meeting on the differential efficacy of antidepressants only two antidepressants were considered to have sufficient clearcut evidence of being superior to any other antidepressant in treating severe depression. Escitalopram was superior to citalopram and paroxetine in two separate placebo-controlled studies, and was found to be superior to comparator SSRIs and venlafaxine in pooled metanalysis in severe depression. Venlafaxine was superior to fluoxetine in hospitalised patients with severe depression in a specific study and in metanalysis. Milnacipran was thought to have probable superiority based on a subanalysis of data in severe depression.

## SO 04. Treatment of GAD

### SO 0401. Diagnosis, long-term course and pain comorbidity of generalised anxiety disorder (GAD)

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*Background*: The diagnosis of GAD remains problematic. The current temporal diagnostic criterion of 6 months has been repeatedly shown to be invalid; it misses 50% of treated cases. The description of the long-term course of the disorder as "chronic waxing and waning" is also controversial; a third interesting question is the comorbidity of pain with GAD.
*Method*: In the Zurich Study, GAD was assessed from age 20/21 to 40/41 by six interviews in combination with the SCL-90-R. Course and outcome were computed as follow-up of first episodes and follow-back of last episodes in terms of a severity spectrum: 1-month GAD, 2-weeks GAD, anxiety symptoms, no symptoms. From 1979 to 1999 (22 years) we assessed the presence of anxiety symptoms and treatment for every year. Headache and back pain were assessed as well as other pain.
*Results*: Onset: most GAD subjects manifested symptoms before the age of 20 but qualified for 1-month GAD much later; the cumulative incidence rate from age 20 to 30 was only 5.1%, but increased to 14% by the age of 40/41. Prospectively the diagnostic stability of the 75 subjects with 1-month GAD was 21%; another 17% developed 2-weeks GAD, 24% residual symptoms and 37% became symptom-free. Followed over 5 and 10 years, 15% of 6-month GAD were diagnosed again. Controlled for sex and depression, a significant association of GAD with pain was found for headache, back pain and insomnia that was in most cases independent of the duration of GAD (odds ratios between 2.1 and 4.8).
*Conclusions*: Up to the age of 41, 1-month DSM-III GAD takes a recurrent course with partial or full remission in 61% of cases. We can hypothesize that later onset GAD may have a poorer prognosis, but such pessimism is not supported by data. Important pain syndromes are associated with GAD.

### SO 0402. Selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors in the treatment of generalized anxiety disorder – met and unmet needs

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*Background*: The selective serotonin reuptake inhibitors (SSRIs) escitalopram, paroxetine and sertraline and the serotonin reuptake inhibitors (SNRIs) duloxetine and venlafaxine have proven efficacy in the acute treatment of generalized anxiety disorder, and some have efficacy in the prevention of relapse. Although undoubtedly efficacious and useful in clinical practice (and differing in their overall acceptability) they cannot be considered "ideal", due to

problems such as the delay in onset of efficacy in relieving anxiety symptoms, or tolerability concerns including treatment-emergent sexual dysfunction and weight gain.
*Methods*: A structured review of the efficacy of SSRIs and SNRIs in the treatment of generalized anxiety disorder, focusing on the onset of action, their efficacy in relieving psychic and somatic symptoms of anxiety, overall treatment response rates, the proportion of patients entering symptomatic remission, and the profile of treatment-emergent adverse events. Through comparison of the profile of efficacy and tolerability of SSRIs and SNRIs with that of the "ideal" treatment, it is possible to identify those needs which are satisfactorily met with current treatment approaches, and those which remain unfulfilled.

### SO 0403. Novel GAD treatments with evidence of efficacy

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*Aims*: This presentation will review the definition of efficacy in generalized anxiety disorder (GAD) therapy as well as the methodology for investigating the illness, including optimum clinical trial design. There are several guidelines outlining the appropriate management of GAD, and currently, benzodiazepines, antidepressants (SSRIs and SSNRIs) and buspirone are all frequently prescribed. New therapeutic agents will potentially provide safer, more effective GAD options. Pregabalin is an effective anticonvulsant, anxiolytic, and analgesic drug, recently approved for the treatment of GAD. It binds potently to the $a_2$-d subunit of voltage-gated calcium channels, modulating the influx of calcium ions ($Ca^{2+}$) into presynaptic terminals which, in turn, reduces the release of the excitatory neurotransmitters.
*Conclusions*: In a recent placebo-controlled study, pregabalin was shown more efficacious at improving HAM-A scores after only 1 week of treatment, as compared with placebo. Additional placebo-controlled studies have shown pregabalin therapy in doses of 300–600 mg/day to be consistently superior to placebo and comparable to lorazepam 6 mg/day, alprazolam 1.5 mg/day, and venlafaxine 75 mg/day in treating GAD, but without the negative side effects. Long-term efficacy in GAD has also been demonstrated with pregabalin therapy and some antidepressants as far out as 6 months. Psychotherapies are also effective in treating GAD and are often most effective when used in combination with pharmacotherapy. This presentation will explore the application of the aforementioned GAD treatment modalities.

### SO 0404. Specific outcome. Speed of onset and comorbidity

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*Aims*: Generalized anxiety disorder (GAD) is a syndrome with a high degree of comorbidity with other anxiety disorders, depression, dysthymia, chronic fatigue syndrome and alcoholism. Less well-known is the comorbidity with pain syndromes and sleep disturbances. The presence of GAD increases the likelihood of pain and vice versa. In GAD there exists also increased sleep latency and a reduced quality of sleep. Interestingly, around 90% of patients with GAD report never having experienced insomnia without having excessive worries. Not only the clinical course, but also speed of recovery and recovery rate has been shown to depend on the presence and type of the comorbid disorder. In this presentation I will focus on onset of efficacy of new psychotropic agents and focus on comorbidity with pain and sleep disturbances.
*Conclusions*: Older drugs such as TCAs and SSRIs have been shown to be effective in GAD but have considerable side effects. During the last decade several new anxiolytics have been developed, such as venlafaxin, mirtazapine, duloxetine, pregabalin and (not available yet) agomelatine. These newer compounds have an established or probable beneficial influence on pain and sleep within the context of GAD.

## SO 05. Newer antidepressants – From neurobiology to a differentiated choice

### SO 0501. The neurobiology of mood disorders: an update

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Behaviour is influenced by environmental, genetic and neurodynamic factors, leading to emotional, cognitive and behavioral processes. Neurobiological factors play a major role. In various models, such as animal experiments, fMRI studies the amygdala, the hypothalamus, and the orbitofrontal cortex have been identified as playing a major role in emotional processes. 5-HT-related polymorphisms or polymorphisms at the DA receptor have been identified as being related to fear conditioning. Volumetric and post-mortem studies have been used to identify neuroanatomical correlates of major depression and show reductions in the volume of the frontal lobe as well as other structures. Newer approaches try to identify specific changes in the circuitry of the brains of depressed patients. Monoamines (such as serotonin, norepinephine and dopamine) form the substrate for the current pharmacological treatment of

depression. The role of other factors, such as growth hormone, cortisol, adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) is also currently the object of intense investigation. This presentation will give a comprehensive overview on the current knowledge of neurobiological factors in mood disorders.

**SO 0502. Depression within OCD: from neurobiology and clinical responses toward endophenotypes**

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Up to two-thirds of individuals with obsessive compulsive disorder (OCD) suffer from co-morbid depression at some time during the course of their illness. Results from brain-imaging suggest depressive episodes in OCD patients may be mediated by different basal-ganglia–thalamic abnormalities from primary Major Depressive Disorder (MDD): hippocampal dysfunction was associated with MDD irrespective of the primary diagnosis, whereas metabolism in the thalamus and caudate differed according to the presence of OCD. Co-morbid depression within OCD also exhibited a different treatment response from MDD in that only those pharmacological agents with potent selective serotonin reuptake inhibition (SSRIs) were effective in alleviating depressive symptoms in treatment-trials. This contrasts with MDD, where a range of non-serotonergic agents are known to be efficacious. Moreover, in one study, cases of major depression with comorbid obsessive compulsive personality traits showed a significantly greater reduction of depression scores following treatment with the SSRI fluvoxamine, compared to their non-comorbid counterparts. This pattern raises the question whether co-morbid depression in OCD is integral or secondary to OCD, or a separate entity. We compared the depressive symptom profile of a group of OCD patients with co-morbid depression, with a group of patients with major depressive disorder (MDD), pair-wise matched on depression severity. The OCD group was significantly less symptomatic on items 4 (sleep) and 5 (appetite), that measure a vegetative response to depression. In contrast, the OCD group was significantly more symptomatic on items 3 (inner tension) and 9 (pessimistic thoughts). These items are close to core symptoms of OCD. Anxiety is considered integral to OCD. The increased frequency of depressive ruminations may reflect OCD-related neurocognitive failures in behavioural inhibition that spread to involve depressive as well as obsessive mentation. The phenotype in psychiatry is subject to great deal of variability, and emphasis is shifting toward examining endophenotypes, i.e. the biological substrates of the illness considered to lie closer to the genetic basis of the disorder. Further exploration of endophenotypes within depression and OCD, for example using domain-specific neurocognitive tests of behavioural inhibition, may bring us closer to the underpinning neurobiology and novel treatment strategies.

**SO 0503. Differentiated binding of escitalopram versus citalopram to the serotonin transporter: A SPECT study**

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Previous studies have investigated the occupancy of the serotonin reuptake transporter (SERT) after clinical doses of citalopram and other SSRIs using the PET ligand [$^{11}$C]DASB. Citalopram is a racemic mixture of the therapeutically active *S*- and the *R*-enantiomers [1]. In the current study programme, the occupancy of SERT after single [2] and multiple [3] doses of escitalopram and citalopram was compared using the radioligand [$^{123}$I]ADAM and single photon emission computer tomography (SPECT). Healthy subjects received escitalopram 10 or 20 mg or citalopram 10 or 20 mg (single dose study) or escitalopram 10 mg/day or citalopram 20 mg/day for a total of 10 days (multiple dose study). SERT occupancy level was determined from midbrain SERT binding potential, which was measured with [$^{123}$I]ADAM using SPECT at two different occasions: at baseline (no medication) and 6 h after medication (single dose) or at three different occasions: at baseline (no medication) and 6 and 54 h after last drug dose (multiple dose study). Blood samples for pharmacokinetic analysis were analysed using a stereoselective assay. In the single dose study, escitalopram but not citalopram demonstrated significant dose-dependent differences in SERT occupancies; however, similar SERT occupancies after equal doses of escitalopram and citalopram were detected. In the multiple dose study 6 h after last dose (Day 10), the mean SERT occupancy in midbrain was $81.5 \pm 5.4\%$ (mean $\pm$ SD) for escitalopram (10 mg/day) and $64.0 \pm 12.7\%$ for citalopram (20 mg/day) ($P < 0.01$). Fifty-four hours after last dose, the mean SERT occupancy was $63.3 \pm 12.1\%$ for 10 mg escitalopram and $49.8 \pm 10.9\%$ for 20 mg citalopram ($P < 0.05$). The serum concentrations of the *S*-enantiomer were very similar after both escitalopram and citalopram, whereas the concentration of the *R*-enantiomer was approximately twice that of the *S*-enantiomer. The significantly higher occupancy of SERT after multiple doses of escitalopram compared to citalopram indicates a more complete inhibition of SERT by escitalopram. Since the concentration of the *S*-enantiomer was essentially the same, the lower occupancy seen with citalopram is interesting and

cannot be explained by a competitive interaction of the *R*-enantiomer at the primary site of the SERT. The higher occupancy of escitalopram may be due to an allosteric mechanism.

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### SO 0504. Differentiated choice of newer antidepressants

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In the last decade, our knowledge of the neurological basis of depression has advanced considerably: changes in brain function as visualized by neuroimaging, identification of specific brain areas involved in the regulation of mood and motivation, specific targets of antidepressant action in the signal transduction cascade, genetic determinants of mood disorders. Specific depressive symptoms have been shown to respond differently to individual antidepressants. The introduction of selective serotonin reuptake inhibitors (SSRIs) into the treatment of depression and anxiety disorders offered new treatment options with a favourable side effect profile versus older tricyclic antidepressants or MAO inhibitors. However, the efficacy of SSRI was perceived as generally lower than that of older antidepressants and differences among SSRI were perceived as clinically irrelevant. The introduction of dual serotonin–norepinephrine reuptake inhibitors (SNRI) offered the latest new treatment option with a perception of higher efficacy, but a less favourable side effect profile. Newer preclinical and clinical research allows a clinically significant differentiation between individual members of the SSRI class (for example escitalopram versus citalopram or versus paroxetine) as well as between SSRIs and compounds with actions at various neurotransmitter transporters (e.g., escitalopram versus venlafaxine). The insights into the neurobiology of mood disorders, the differential response of symptoms to different pharmacotherapeutic agents as well as demonstrated differences between allow the differentiated choice of newer antidepressants based on their pharmacological–neurochemical profile and specific efficacy as well as on the specific symptomatology of the patient. The talk focuses on these differences and will give an overview on various strategies to improve the response to and to optimize the treatment with newer antidepressants.

## SO 06. Treatment of mania

### SO 0601. Mood stabilizers in mania

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*Introduction*: Mood stabilizers are considered one of the treatment options in acute mania. However, they are not as well studied as the recently introduced atypical antipsychotics.
*Method*: The double-blind, randomised controlled trials in which lithium or anticonvulsants were compared with placebo, with each other and/or with antipsychotics are reviewed.
*Results*: Both lithium and valproate are efficacious, while the efficacy of carbamazepine is less well proven. There is no evidence for effect of gabapentin, lamotrigine or topiramate. In a direct comparison with valproate, lithium was more effective than valproate in patients who had not received lithium before, while valproate was more effective in prior lithium non-responders (unpublished data), indicating that both drugs are effective in different subgroups. In a direct comparison with chlorpromazine, lithium was less effective in more severe manic patients, while in two direct comparisons with olanzapine, valproate appeared less effective.
*Conclusion*: Both lithium and valproate are effective in acute mania. However, in patients with more severe mania there is a preference for antipsychotics, either as monotherapy or as addition to (an ongoing treatment with) lithium or an anticonvulsant. In addition, the choice should be guided by the drug to be used in subsequent maintenance treatment, for which lithium is still the preferred drug, with valproate, carbamazepine and the atypical antipsychotics as best studied alternatives.

### SO 0602. Atypical antipsychotics in bipolar mania

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The accurate diagnosis and treatment of bipolar mania is extremely challenging. Therapeutic intervention for mania has traditionally relied on the use of lithium or valproate as a first-line treatment option. Due to the limited therapeutic range of these agents, conventional antipsychotics have also often been used. Conventional antipsychotics have

demonstrated efficacy in mania, but are often associated with significant side effects, especially extrapyramidal symptoms. The atypical antipsychotics are the increasingly preferred treatment for bipolar mania. Data from controlled studies of several atypical antipsychotics for treating mania are surveyed and issues involved in the selection of an appropriate atypical agent discussed. There are important differences among the atypical antipsychotic agents with respect to their side effect profiles. These profiles commonly influence the choice of agent from within the same drug class. Medications that have the same indication or putative mechanism of action can provide patients with very different subjective experiences. Clinicians must prescribe treatments that are effective and tolerable so that the patient can take the medication on an ongoing basis. The key to successful antipsychotic therapy is selecting the atypical best tolerated by an individual patient. To match a patient with the least medically disruptive atypical antipsychotic, physicians must be aware of the patient's unique medical history and susceptibility profile. The differences in side effect profiles will ultimately influence patient compliance patterns; because untreated bipolar patients are at increased risk of medical morbidities, the chosen therapeutic agents should not exacerbate existing medical morbidity risks. In this context, clinicians should consider the tolerability profiles of atypical antipsychotics with regard to the side effect susceptibilities in bipolar patients when formulating a treatment plan for mania.

**SO 0603. Speed of action of treatments in mania**

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Lithium has long been considered the treatment of choice for acute mania, but some studies have shown that it has a longer latency of action than newer mood stabilizing compounds, thus being disadvantageous for the treatment of severe manic patients. Valproate has been also used for acute manic episodes, and some studies have shown that the onset of its antimanic effect appears within 1–4 days of achieving a serum concentration 50 g/ml, with better clinical management of mania and cost savings due to shorter lenghts of hospital stay. The addition of antipsychotics to classical mood stabilizers appears to result in an even more rapid onset of action and in a better control of agitation and psychotic behavior during manic episodes. Recently there has been increasing evidence for the efficacy of atypical antipsychotics in the treatment of acute mania as add-on or monotherapy. Differences and similarity between traditional mood stabilizers and atypical antipsychotics with respect to the speed of action of antimanic effect will be discussed. In addition, new comparative data on the latency of antimanic effect for atypical antipsychotics with or without classical mood stabilizers will be also presented and discussed in the light of the advantages for the management of hypomanic, manic, and mixed states.

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**SO 0604. Treatment of mixed states**

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So far only a limited number of controlled studies has been published on the treatment of mixed states. An early study by Alan Swann et al. showed [1] that mixed (but not euphoric) mania is more responsive to valproate than to lithium salts. This study has launched a variety of questions on the assessment and diagnosis of mixed states [2] as opposed to "pure" episodes. In particular the risk of "switching" from and into a mixed state has been controversially discussed. Patients with mixed states have been thoroughly studied in a variety of randomized clinical trials [3] involving the atypical antipsychotic, olanzapine, as monotherapy or in combination with a mood stabilizer (lithium or valproate). New evidence has demonstrated the efficacy of ziprasidone and aripiprazole. In treatment-resistant mixed states, electroconvulsive therapy has been described as being highly beneficial. In summary, while treatment response remains worse [4] than in patients with "pure" mania or "pure" depression, clinical psychiatry is left with one of its greatest therapeutic challenges.

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## SO 07 Unmet treatment needs in major depressive disorders

### SO 0701. Expecting more from antidepressant treatment: what happens when conventional therapy fails?

#### a. The specialist perspective

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There are few data which inform the treatment of bipolar depression and specialists have for some time been forced to go to the limit of our knowledge in treating this common disorder. Antidepressants are widely used but have only been shown to have efficacy in single studies of fluoxetine and buproprion. Concern that antidepressants such as TCAs and SNRIs are associated with unacceptable switch rates to mania have further limited the use of antidepressants and have helped to promote the use of mood stabilisers such as valproate and lamotrigine which do not have sufficient evidence to be licensed for this indication. The two recent Bolder studies which have shown clearcut placebo-controlled efficacy for both quetiapine 300 and 600 mg have already persuaded significant numbers of specialists to increase their use of atypical antipsychotics in bipolar depression. Quetiapine shows efficacy early at 1 week in both studies in BPI and BPII depression in rapid cycling and non rapid cycling, in more severe and less severe bipolar depression, and in those with more or less sleep disturbance. So striking are these data that even the very conservative NICE committee in England now recommends the use of quetiapine in bipolar depression in advance of the licence being granted. The question also arises concerning efficacy in Major Depressive Disorder and anxiety disorders and such studies are urgently needed.

#### SO 0701b. The general practice perspective

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The majority of patients with major depression are treated in primary care. Recognition of these patients is generally poor but naturalistic outcome studies suggest that, even when treated, the outcome for the majority is unsatisfactory. The model of depression recognised by most PCPs is one of an acute, possibly recurring illness, whereas it is now accepted that depression is a chronic illness which requires long-term treatment and management. The aim of treatment must be to achieve true remission and its maintenance. Remission should not necessarily be defined in terms of a low score on a rating scale but a situation where the patient is relatively symptom-free and as close as possible to normal functioning. Even with the less rigorous definitions of remission, however, probably less than 30% of patients achieve this and fewer still remain in remission. Combinations of current medications can improve outcomes but some symptoms, particularly agitation and insomnia can be difficult to manage and leave the patients vulnerable to relapse and recurrence. There is a pressing need therefore for new antidepressants drugs without the disadvantages of current agents. Meantime exploration of currently used medications such as hypnotics and antipsychotics, to be used in combination with antidepressants, might offer a possible solution.

### SO 0702. Response in treatment resistant depression

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Treatment-resistant depression (TRD) is a common clinical occurrence among patients treated for major depressive disorder. TRD is usually defined as the failure to reach sufficient response or remission after two consecutive adequate treatments. Despite the availability of an increasing number of new antidepressants, it is estimated that TRD occurs in up to 30–40% of depressive episodes adequately treated with first line antidepressant therapy. Clinicians need to accurately diagnose TRD by examining primary and secondary (organic) causes of depression and acknowledging paradigm failures that contribute to a misdiagnosis of TRD. While several studies have identified predictors of nonresponse, clinical studies investigating the predictors of resistance following the failure of two or more antidepressant trials should be pursued. Three basic strategies exist for treating TRD: (1) optimizing antidepressant dose, (2) augmenting or combining therapies, and (3) switching therapies. In the augmentation strategy, the clinician seeks a synergistic interaction between agents such that the therapeutic some of the whole is greater than the parts. Combination strategies are those involving the concomitant use of two agents with well-established antidepressant efficacy. The typical rationale is that of broadening the central nervous system by combining agents affecting different neurotransmitter systems. Switching between drugs is often simpler with less risk of drug–drug interaction. The question remains if the clinician should switch from a failed SSRI treatment to a second SSRI or if it is best to switch out of the class to another antidepressant. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study sponsored by the US National Institute of Mental Health determine the best subsequent treatment strategies (i.e. identifying which combinations and which sequences of treatment are effective with minimal side effects) following nonresponse of an initial monotherapy with an SSRI. First results

suggest that approximately one in four patients achieved remission during a second antidepressant treatment, regardless of de medication used after switching (bupropion, sertraline or venlafaxine-XR).

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## SO 08 New evidence of long-term efficacy in chronic anxiety disorders

### SO 0801. Long-term efficacy in obsessive compulsive disorder

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Obsessive compulsive disorder (OCD) is a prevalent and disabling lifespan disorder. Untreated OCD usually runs a chronic course, fluctuating in intensity but rarely disappearing. Convincing evidence from large-scale placebo-referenced randomised controlled trials supports efficacy for clomipramine and selective serotonin reuptake inhibitors (SSRIs) in the acute treatment of OCD. Response is characteristically partial, with few cases achieving full remission. Fixed-dose comparator studies provide evidence of a dose–response relationship with SSRIs [1]. Long-term data is sparse and it remains less conclusively understood as to whether treatments that have been shown to be effective in short-term studies maintain their efficacy over the longer term. Studies of clomipramine, fluoxetine and sertraline investigated "responders" from the acute treatment phase and extended their controlled treatment up to twelve months versus placebo with the result that the response to SRI was sustained with no evidence of tolerance developing. In contrast, studies that have discontinued active treatment and randomised cases to placebo have, in the main, demonstrated re-emergence of symptoms in the placebo-treated cohort. Some, but not all relapse prevention studies investigating responders to acute treatment with an SSRI revealed a significant advantage for remaining on active medication (reviewed in Fineberg and Gale 2005). Difficulties agreeing clinically relevant criteria for response and relapse have hampered trial design in this area. Comparison of the efficacy of escitalopram 10 or 20 mg/day with that of placebo in preventing relapse during 24 weeks in 320 outpatients with OCD who had responded to 16 weeks prior open-label treatment with escitalopram showed a beneficial effect of escitalopram relative to placebo on the primary analysis (time to relapse) (log-rank test, $P < 0.001$). In addition, the proportion of patients who relapsed was statistically significantly higher in the placebo group (52%) than in the escitalopram group (24%) ($P < 0.001$, chi-square test) and the risk of relapse was 2.74 times higher for placebo than for escitalopram-treated patients. Escitalopram was well tolerated and improvements in obsessive-compulsive symptoms and social disability reported during the open-label period were sustained during the double-blind extension of treatment with active drug. However, 24% of escitalopram-treated patients relapsed according to trial criteria during the 24-week randomisation period with an estimated median time of 10 months. These results suggest that escitalopram is an effective long-term treatment and that improved long-term efficacy represents a realistic goal for treatment development in OCD.

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### SO 0802. The long-term efficacy of pregabalin and SSRIs in the treatment of generalized anxiety disorder

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Generalized anxiety disorder (GAD) is a chronic anxiety disorder characterized by persistent, excessive and uncontrollable worry which is accompanied by psychic and somatic symptoms. This disorder affects more women than men, and has a lifetime prevalence of 6% in the general population. GAD is highly associated with a multitude of social and occupational disabilities. Short-term studies have indicated a variety of agents to be efficacious in the treatment of GAD, including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenalin reuptake inhibitors (SNRIs), benzodiazepines, azapirones and anticonvulsants. Approximately 60% of patients demonstrated a satisfactory response to acute treatment, and a high percentage of these patients report continued problematic, persistent symptoms. Prospective data from the Harvard-Brown Anxiety Research Program (HARP) suggests that the remission rate is low, where only 40% of patients experienced at least a partial remission during the 5-year follow-up period. Given the chronic nature of this disorder, effective maintenance therapy is required. Currently, only a hand-full of studies have examined the long-term treatment of GAD. This presentation will review the available literature on the long-term pharmacological treatment of GAD and focus on treatment with SSRIs and the novel anticonvulsant pregabalin.

**SO 0803. Review of SNRIs in generalized anxiety disorder**

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Two serotonin norepinephrine re-uptakke inhibitors have been studied in the treatment of generalized anxiety disorder, venlafaxine XR and duloxetine. There were five short-term (8-week) and three longer-term (6-month) studies with venlafaxine XR in GAD. The five short-term studies included one flexible dose design, comparing venlafaxine XR to placebo in the dose range 75–225 mg/day. The four fixed dosed studies compared venlafaxine XR in doses of 37.5, 75, 150, 225 mg/day with placebo. In one of these studies there was an active comparator (buspirone) and in another (diazepam). In four of these five studies, venlafaxine XR was consistently superior to placebo on the primary and secondary outcome measures. The fifth study was a failed study with neither diazepam nor venlafaxine XR separating from placebo. There were three long-term studies (2 months acute phase plus 4 months extension) investigating the ability of venlafaxine XR to sustain its efficacy compared to placebo. One of these used a fixed-dose design, a second used a flexible dose design, and a third used a relapse prevention design. Venlafaxine XR provided sustained benefit over a 6-month period and protected patients from relapse compared to placebo. Duloxetine has been the subject of several recent studies in generalized anxiety disorder studies. One was a 10-week flexible dose design with 327 patients randomly assigned to duloxetine 60–120 mg/day or placebo. In a 9-week study, 507 patients with GAD were randomly assigned to a fixed-dose of either 60 or 120 mg of duloxetine or to placebo. The primary outcome measures in both studies included change from baseline on the Hamilton Anxiety Scale and improvement in functional impairment on the Sheehan Disability Scale. Duloxetine was statistically superior to placebo on both primary outcome measures and on several secondary outcome measures such as improvement in pain scores and quality of life scales (the QLESS-Q-SF and Euroquol-5D). These findings, if verified and approved by regulatory agencies, could make duloxetine the first psychiatric medication eligible for an indication in the improvement of functional impairment associated with a psychiatric disorder. The results of these studies will be presented.

**SO 0804. Long-term efficacy in social anxiety disorder (SAD)**

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Social phobia is a highly prevalent yet often overlooked psychiatric disorder. It is the most prevalent of any anxiety disorders and is the third most common psychiatric disorder after depression and alcohol abuse. Social anxiety disorder typically begins during childhood, with a mean age at onset 15 years if left untreated, is usually chronic, unremitting, and associated with significant functional impairment. A substantial number of patients start treatment after suffering from SAD for 10–20 years. Based on clinical experience, experts recommended that effective drug treatment be continued for at least 12 months. Only in recent years, have long-term studies with a duration of 24–28 weeks been conducted to establish sustained efficacy of drug treatment in SAD, triggered by the requirements of the regulatory authorities. Now, an expanding body of evidence from controlled trials demonstrates the long-term efficacy and tolerability of the serotonin selective reuptake inhibitors (SSRIs) escitalopram, fluvoxamine, paroxetine, sertraline, the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine, and the reversible inhibitor of MAO-A moclobemide for the treatment of social anxiety disorder. All these studies confirm the necessity of continuous treatment over at least several months, as differences to placebo were still observable after treatment over half a year. There is also evidence for the effectiveness of cognitive-behavioral therapy, including exposure-based strategies, and controlled studies suggest that the effects of this treatment are generally maintained at long-term follow-up.

## SO 09. Burden and treatment of chronic insomnia

**SO 0901. The burden of disease, guidelines in chronic insomnia**

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Chronic insomnia, defined as insomnia lasting 1 month or more, represents a significant public health and economic burden. In various population surveys, the prevalence of chronic insomnia in population surveys has been measured in the range of 10–15%. Insomnia is associated with various medical and psychiatric comorbidities, and the consequences of insomnia include impaired daytime functioning, an increased risk of developing depression and other psychiatric conditions, and worsening of outcomes in various medical illnesses. The direct economic costs of insomnia in the United States have been estimated at $14 billion per year, with indirect costs including loss of productivity, absenteeism, and work-related accidents totaling more than $57 billion per year. Daytime consequences of insomnia include fatigue, mood changes, performance

decrements, memory difficulties, irritability, daytime sleepiness, increased sensitivity to environmental stimuli, and decreased ability to accomplish daily duties. These daytime consequences have been associated with a decreased overall quality of life among insomnia sufferers, which is comparable in magnitude to that experienced by patients with congestive heart failure or major depressive disorder (MDD). Improved quality of life has been linked with treatment for insomnia, although not to the level of the normal population. Individuals with insomnia also have higher rates of medical illnesses than those without sleep problems. Population-based studies have shown that insomniacs had an increased number of medical consultations, medication use, number of medical tests performed, number of hospitalization days, and emergency visits compared with non-insomniacs. Furthermore, a greater severity of sleep disturbance is correlated with a worse outcome and increased pain severity among patients who experience pain. Insomnia is associated with worse outcomes in a number of medical illnesses, including an increased risk of mortality among institutionalized elderly individuals, greater disability among stroke patients, and increased risk of mortality among patients with cardiovascular disease. In June 2005, the US National Institutes of Health (NIH) held a State-of-the-Science conference on chronic insomnia that has helped standardize the definition and diagnosis of chronic insomnia in the US, and provided guidance on the various pharmacological and non-pharmacological treatments. At the time of the meeting, eszopiclone is the first agent to be studied for the long-term treatment of chronic insomnia and in comorbid conditions such as depression and anxiety. In Europe, practices and guidelines for the treatment of insomnia vary widely from country to country, and there has historically been less recognition of chronic insomnia as a distinct condition requiring long-term treatment. At the recent ECNP Consensus Elderly Conference from March 12 to 15, 2006, in Nice, France, data were presented on the use of eszopiclone for the long-term treatment of insomnia. The ECNP acknowledged that chronic insomnia should be recognized as a disease, and that long-term treatment seems feasible, providing safety is demonstrated.

**SO 0902. Eszopiclone in the treatment of chronic insomnia**

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Eszopiclone is a non-benzodiazepine sedative-hypnotic agent active at the GABA-A receptor, and it is the *S*-isomer of the sedative-hypnotic agent zopiclone. Eszopiclone is the first sedative-hypnotic agent to be studied in long-term randomized controlled trials for the treatment of insomnia, and it is also the first anti-insomnia agent to be approved for long-term usage in the United States. Two 6-month randomized placebo-controlled trials have demonstrated the safety and efficacy of eszopiclone in the long-term treatment of chronic insomnia, and a 6-month open-label extension of the first trial demonstrated safety and tolerability of the agent over 12 months, without the development of tolerance. In the first trial, a double-blind placebo-controlled study in adults with primary insomnia over 6 months of nightly usage, eszopiclone was found to show significant, sustained improvement in sleep and daytime function [1]. 593 subjects with primary chronic insomnia between the ages of 21 and 69 were randomized to eszopiclone, and 195 patients were randomized to placebo. Eszopiclone demonstrated significant and sustained improvements in comparison to placebo on all study endpoints, including various sleep endpoints (sleep latency, wake time after sleep onset, number of awakenings, number of nights awakened per week, total sleep time, and quality of sleep) and functional endpoints (next-day function, alertness, and sense of physical well-being). The most common side effects noted in eszopiclone-treated patients were unpleasant taste and headache. Tolerance was not observed in either group. A 6-month open-label extension phase [2] demonstrated the safety and tolerability of eszopiclone over 12 months of nightly treatment. Patients who received placebo in the first 6 months of treatment were switched to eszopiclone, and showed significant improvements in both sleep and daytime function; patients continuing with eszopiclone treatment maintained or improved treatment gains realized during the double-blind treatment phase. Eszopiclone was well tolerated over the full 12 months of treatment, and tolerance was not observed. This published data have since been replicated in a second 6-month placebo-controlled trial in adults with chronic primary insomnia (data on file, Sepracor). A total of 830 subjects with chronic insomnia aged 21–64 were enrolled. Consistent with the first 6-month study [1], treatment with eszopiclone was found to be safe and well tolerated. When compared to placebo, eszopiclone was effective in inducing and maintaining sleep, increasing total sleep time, improving sleep quality, and improving daytime measures and functional endpoints. Efficacy was sustained for 6 months of nightly use without evidence of tolerance or rebound insomnia, which was evaluated during a 2-week single-blind run-out period. The results of this study demonstrate the consistent efficacy of eszopiclone in the long-term treatment of primary chronic insomnia. In summary, the robust efficacy and safety of eszopiclone over long-term treatment, with no demonstrated evidence of tolerance or rebound insomnia, establish the agent

as a unique first-line option for the treatment of chronic insomnia.

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### SO 0903. Role of eszopiclone in treating co-morbid insomnia in depression

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Insomnia is now increasingly recognized as a significant co-morbidity in major depressive disorder (MDD) and other psychiatric diseases and as a common and important clinical problem that can significantly affect the quality of life of patients. Insomnia is a diagnostic symptom of MDD; various studies estimate the prevalence of insomnia in depression between 65 and 90% [1]. Insomnia often precedes the onset of depression, and sleep problems are the most common residual symptom when depression is treated to remission [2]. In addition, worsening of insomnia can often signal a relapse to full-blown depression. In general, insomnia is an important risk factor for new onset of psychiatric conditions, with insomniac patients exhibiting a significantly elevated risk of developing depression and other disorders in comparison to those without insomnia [1]. Various pharmacological agents are commonly used in clinical practice in combination with antidepressants to treat insomnia in depression, including benzodiazepines, non-benzodiazepine sedative-hypnotics, and sedating antidepressants, but few randomized controlled clinical trials have been conducted to investigate the acute co-administration of adjunctive anti-insomnia pharmacotherapy on depression endpoints. No studies of acute co-administration of non-benzodiazepines with antidepressants at the time point of diagnosis of MDD have been performed except for the study presented here. However, one study of zolpidem in conjunction with the antidepressants fluoxetine, sertraline or paroxetine was completed in MDD patients ($n = 190$) who had continued insomnia, but were no longer acutely depressed (HAM-D score of 12 or less at entry) and were on above antidepressants for at least 2 weeks. This study showed the expected improvement in sleep parameter, but did not demonstrate any positive impact on the underlying depressive symptoms over the 4-week treatment period [4]. Eszopiclone was studied in a population of patients with comorbid depression and insomnia [5]. Patients were initiated on 20 mg of daily fluoxetine and randomized to 8 weeks of nightly treatment with eszopiclone 3 mg ($n = 269$) or placebo ($n = 274$). Eszopiclone demonstrated statistically significant effects on all primary sleep endpoints at all study time points, consistent with its effects in previous trials of patients with both primary insomnia and insomnia associated with other conditions. In addition to its effects on sleep, eszopiclone co-therapy significantly improved the underlying depression, as measured by the significantly greater and clinically meaningful effect on HAM-D-17 scores at weeks 4 and 8 compared to fluoxetine alone. Similar and consistent positive effects were observed on HAM-D-17 response and remission rates. Furthermore, the combination of fluoxetine and eszopiclone resulted in significant effects on CGI-I and CGI-S at all time points after week 1, and resulted in a faster onset of antidepressant response. Antidepressant effects of the combination were greater in patients with more severe depression at baseline, and significant treatment effects were seen at Week 8 between groups, even with the removal of the insomnia items from the HAM-D-17. The combination of eszopiclone and fluoxetine was well tolerated, with unpleasant (metallic) taste reported as the most frequent adverse event. No major differences were observed between groups in CNS adverse events during treatment or the discontinuation phase. Dropout rates were similar between the two groups. Fluoxetine titration to 40 mg was allowed at week 4, but significantly fewer patients receiving the combination treatment required titration to the higher dose of fluoxetine. Further studies are required to understand whether the observed positive interaction between acutely administered eszopiclone and fluoxetine in the treatment of depression can be generalized to other antidepressants.

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## SO 10. Mood and anxiety disorders in old age

### SO 1001. The epidemiological evidence

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The Epidemiological Catchment Area study, investigating a representative sample of 5702 subjects older than 65 years, reported much lower rates of affective disorders among elderly subjects than in other age-groups. Moreover, anxiety disorders and panic disorder, especially, were found with lower prevalence than in younger age-groups. Otherwise, clinical impressions and investigations of symptoms of depressions or anxiety found that these symptoms are common, affecting up to 25% of persons aged 65 years or older. Depressive symptoms of both depression and anxiety have also been reported as increasing with advancing age. It has been suggested that methodological problems might have led to an underestimation of the prevalence of both depressive disorders and anxiety disorders in the elderly. Besides giving an overview on epidemiology of depression/anxiety in the elderly, this presentation reports the epidemiological evidence from a large epidemiological study in Vienna (Austria). The Vienna Transdanube Aging (VITA) study is a community-based age-cohort study starting at age 75. VITA tried to investigate the whole cohort of elderly born between May 1925 and June 1926, living in the geographical districts on the left shore of the Danube (Vienna Transdanube). Whether a patient suffers from dementia and/or depressive disorders (major depression, minor depression, subsyndromal depression) was diagnosed in a longitudinal setting every 30 months, applying DSM-IV criteria in a structured interview carried out by two experienced geriatric psychologists. Moreover, the Hamilton Depression Scale, the Short Geriatric Depression Scale, and the Spielberger Anxiety Inventory were applied. Only 8% of the sample ($n = 606$) were found somatically healthy at baseline. Irrespective of both physical health and dementia, the rate of minor/major depression at mean age 75.8 years (SD = 0.5 years) was 16.5% (9.1% minor; 7.4% major). Levels of anxiety significantly increased with increasing severity of depression. At mean age 78.3 years (SD = 0.5 years) the rate of minor/major depression increased to 22.9%. State anxiety at baseline predicted a depressive syndrome at follow-up even in subjects found never depressed throughout their life at baseline.

### SO 1002. Pharmacokinetics and interaction in old age

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Elderly patients suffering from mental diseases are frequently co-medicated with several psychopharmacological agents simultaneously, such as antidepressants, antipsychotics, anxiolytics, hypnotics, and anticonvulsants, used as mood stabilizers. In addition, somatic drugs are co-prescribed for the treatment of other concomitant diseases. This situation increases the risk for pharmacokinetic interactions with pharmacodynamic consequences in a population which is particularly sensitive to adverse effects. Indeed, drug absorption, distribution, metabolism and elimination (ADME) may be altered in the elderly. However, studies in very old patients ($>80$ years) are often lacking [1]. Therefore, treatment needs to be carefully and individually tailored. Therapeutic drug monitoring [2] may be a useful tool to optimise treatment, as some "classical" indications apply for this population: lack of compliance, adverse effects despite the use of generally recommended doses, suspected drug interactions, combination treatment with a drug known for its interaction potential, patients with pharmacokinetically relevant comorbidities (hepatic or renal insufficiency, cardiovascular disease). The increasing knowledge on the role of cytochrome P-450 isozymes in the metabolism of drugs and their interaction potential has fortunately led to a situation, which allows, to some extent, predicting risks for adverse effects after introducing a polymedication [3–6].

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### SO 1003. Biological changes in old age

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Although several biological functions alter with healthy aging, there seems to be no consensus for a

biological marker to serve as a guide for pharmacological treatment strategies in the elderly, or as a justification for a cut-off age. However, the question arises if there are age-related neurobiological changes in the brain that might not only explain age-associated memory impairments, but also indicate potentially changing sensitivities to psychopharmacological treatments. Such alterations might include loss of neuronal tissue, changes in neuronal morphology, synaptic plasticity and functioning, as well as changes in the amount and plasticity of vascular innervation and blood supply. In contrast to earlier beliefs, neuronal loss is minimal over the life span and differs slightly between brain regions. For example, in longitudinal studies the volume of the hippocampus, which is a critical brain structure in the limbic system and involved in memory functions, showed a yearly decline in the range of only 0.79–0.86%, up to the age of 80 years. This change appears not to be correlated with memory functions. The largest volumetric changes seem to appear in the prefrontal cortex, with yearly decreases of about 0.9%. Evidence has been reported of region-specific changes in dendritic branching, length and synapse numbers, whereas the biophysical properties of the neurons appeared to be stable over the life span. Functional responsiveness, connectivity and plasticity were shown to be related to age, possibly associated with an aging-dependent impairment of $Ca^{2+}$ homeostasis. Reports of diminished response of pyramidal cells to acetylcholine in the hippocampus may relate to age-associated memory impairments. Other neurotransmitter functions, such as dopamine transporter availability, have been described to decline with age with up to a 5% decline in the basal ganglia per decade. Such a decline may compromise episodic memory and executive control performance and explains the major part of age-related variance in recognition and working memory tasks. As far as the treatment of stress-related mental disorders and cognition is concerned, no evidence of age-specific changes of the HPA axis has yet been suggested, apart from the effects of chronic stress.

**SO 1004. Treatment response in old age**

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*Background*: Depression is common in old age, with a community prevalence of 12–15% in people aged 65 and over [1]. A recent systematic review has shown that, though older people may be as likely as younger adults to respond to acute treatment of their depression, they are significantly more likely to suffer relapse [2]. Reducing risk of relapse is therefore a particularly important element of the management plan for older depressed patients.

*Objective*: The present study investigated the efficacy and tolerability of escitalopram in the prevention of relapse of major depressive disorder (MDD) in older patients who had responded to acute treatment with escitalopram.

*Method*: A total of 405 patients, aged 65 years or older with a primary diagnosis of MDD and a MADRS total score of 22 or more, received a 12-week, open-label escitalopram 10 or 20 mg/day treatment. Remitters (MADRS 12) were randomised to a 24-week double-blind treatment with escitalopram or placebo. The primary efficacy parameter was the time to relapse, defined as either an increase in MADRS total score to 22 or more, or lack of efficacy as judged by the investigator.

*Results*: A total of 305 patients achieved remission and were randomly assigned to treatment with escitalopram ($n=152$) or placebo ($n=153$). The primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse (log-rank test, $P<0.001$). The risk of relapse was 4.4 times higher for placebo- than for escitalopram-treated patients ($\chi^2$-test, $P<0.001$). Significantly fewer escitalopram-treated patients relapsed (9%) compared with placebo (33%) ($\chi^2$-test, $P<0.001$). Escitalopram was well tolerated; with 53 patients (13%) withdrawn due to adverse events during the open-label period and three (2%) escitalopram-treated patients and six (4%) placebo-treated patients during double-blind treatment (NS). The overall withdrawal rate, excluding relapses, was 7.2% for escitalopram and 8.5% for placebo during the double-blind period (NS).

*Conclusion*: Escitalopram was effective in preventing relapse of MDD in older patients and was well tolerated as continuation treatment.

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# Poster Abstracts

### P 01. The impact of anxiety on components of sleep quality

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*Background*: There has been scant research regarding the comorbidity of psychiatric symptomatology and sleep complaints in medical patients. However, sleep problems and mental complaints seem to be highly interrelated and people with any medical condition have a higher prevalence sleep problems than general population. Both anxiety and depression have been associated with insomnia in this population.
*Method*: A total of 234 randomly selected adult outpatients with various physical complaints participated in the study. Sleep quality was measured with Pittsburgh Sleep Quality Index (PSQI) which assesses several aspects of sleep quality, including subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. Patients who reported anxiety on PSQI completed the Beck Anxiety Inventory (BAI) which consists of 21 descriptive statements of anxiety symptoms and measures the severity of self-reported anxiety.
*Results*: The findings showed a positive correlation between anxiety and sleep latency and a negative correlation between anxiety and sleep duration. Patients with anxiety complaints tended to have longer sleep latency and shorter amount of slept hours.
*Conclusion*: The interrelatedness between anxiety and sleep quality components in medically ill patients is highly relevant for both assessing and treating anxiety and sleep complaints in this population. Anxiety complaints such as worrying and rumination may affect more sleep complaints and should therefore be a focus of sleep research.

### P 02. Neurocognitive impairment in bipolar I and II disorders

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*Background and Aims*: Although neurocognitive dysfunctions were implicated in patients with bipolar disorders, studies that compared neurocognitive functioning across different subtypes of bipolar disorders are scarce. The aims of this study were to compare the neurocognitive performances of bipolar I and II patients with those of healthy normal controls and to address the differences in neurocognitive dysfunctions between the subtypes of bipolar disorders.
*Methods*: Nineteen euthymic patients with bipolar I disorder, 32 euthymic patients with bipolar II disorder and 27 age-matched healthy controls performed a neurocognitive test battery consisting of the Wisconsin Card Sorting Test, Trail Making Test, Continuous Performance Test, Gambling Test, Controlled Oral Word Association Test, Korean version of California Verbal Learning Test, Rey-Osterrieth Complex Figure Test. Performances on those tests were compared between the three groups.
*Results*: There were no significant differences in intelligence, attention and executive functions except the performances on the WCST, among the bipolar I patients, the bipolar II patients and the healthy control groups. Compared with the controls, patients with bipolar I disorder performed poorly with significance on the tests for verbal memory, visual memory and the verbal fluency. Patients with bipolar II disorder showed significant impairments in the long-term verbal memory and WCST, compared to the healthy control group. The cognitive impairments in each group were not related to the severity of subclinical depressive symptoms, onset age and duration of illness.
*Conclusions*: The findings of the current study replicated that there are neurocognitive dysfunctions in bipolar disorders and suggest that the memory impairment can be used as the endophenotype of the disorder. It is also suggested that the impairments in some executive functions can be conjugated as an index to differentiate the subtypes of bipolar disorders.

### P 03. Anxiety and cognitive function in the elderly: Preliminary results from a double-blind, placebo-controlled trial of pregabalin in generalized anxiety disorder

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*Background*: Benzodiazepine anxiolytics cause impairment in cognitive function, especially in the elderly. The goal of the current study was to obtain preliminary data on the effect of pregabalin in elderly patients diagnosed with generalized anxiety disorder (GAD).
*Methods*: Patients aged 65 years and older who met DSM-IV criteria for GAD, with a HAM-A $\geq$20 were randomized, in a 2:1 ratio, to 8 weeks of treatment with flexible doses of pregabalin, 150–600 mg/day or placebo. A subgroup of patients ($N$=89; 81% female; mean age, 70.4 years; mean

HAM-A, 27.3) completed a cognitive battery at baseline and endpoint consisting of the Digit Symbol Substitution Test (DSST) and the Set Test.
*Results*: At baseline, scores were comparable, on pregabalin and placebo, respectively, on the DSST ($13.75 \pm 3.51$ vs. $13.39 \pm 3.89$) and the Set Test ($37.88 \pm 3.25$ vs. $37.63 \pm 3.69$). There was a moderate but significant ($P < 0.05$) inverse Pearson correlation between HAM-A item-5 (intellectual) and scores on the DSST ($-0.32$) and the Set Test ($-0.30$). There were also moderate inverse correlations between the DSST and HAM-A total score ($-0.35$), age ($-0.25$), and previous use of benzodiazepines ($-0.31$). Weaker correlations (with the same directionality) were observed between the Set Test and the same variables. At 8-week LOCF-endpoint, scores were comparable on the DSST (13.82 vs. 14.54) and the Set Test (38.24 vs. 37.95). Endpoint improvement in the HAM-A was moderately correlated with improvement in the Set Test ($-0.23$; $P < 0.05$) but not with DSST. On both univariate and multivariate analyses, treatment with pregabalin had no effect on endpoint cognitive function.
*Conclusions*: Pregabalin was effective in reducing the symptoms of GAD in patients aged 65 years and older without causing impairment in cognitive function. Use of a more extensive cognitive battery is needed to confirm this preliminary finding.

### P 04. Improvement of quality of life in panic disorder with escitalopram *versus* citalopram, and placebo

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*Purpose*: Panic disorder is characterized by recurrent anxiety attacks that occur spontaneously and, over time, become associated with situations and places in which the patients fear that medical help might be unavailable. Patients with this anxiety disorder are also afraid of experiencing bodily injury during panic attacks, or of becoming severely ill. All these symptoms lead to substantial functional and social disability. Thus, although panic disorder is not the most frequent among the anxiety disorders, it is the one that leads most frequently to the utilization of psychiatric services. Quality of life is not only impaired by the panic attacks, but also by the other features of panic disorder. This study investigated the improvement in quality of life of patients with panic disorder treatment with either placebo, citalopram, or escitalopram in a randomized, double-blind clinical trial.
*Methods*: Data from a randomized prospective comparison of escitalopram, citalopram, and placebo in patients with panic disorder, were analyzed with regard to measurements of impairment of quality of life. The subscales of the Panic and Agoraphobia Scale (P&A) (Panic Attacks, Agoraphobic Avoidance, Anticipatory Anxiety, Functional and Social Disability, and Worries about Health) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) were analyzed.
*Results*: Treatment with escitalopram was associated with significant improvement on all five subscales of the P&A. Citalopram was different from placebo in only three of five P&A subscales. Escitalopram and citalopram were significantly better than placebo in improving quality of life (as measured by the total score of the Q-LES-Q Scale). Escitalopram was superior to placebo on 11 of 16 items of the Q-LES-Q, while citalopram was superior only on seven of 16 Q-LES-Q items.
*Conclusion*: Escitalopram led to improvement on a wide range of domains the impair quality of life in panic disorder. Measurement of severity of illness should not be only based on panic attack frequency, but should include all areas that are dysfunctional in panic disorder.
*Disclosure*: Professor B. Bandelow, D.S. Baldwin and D.J. Stein have received consultancy honoraria from Lundbeck. O.C. Dolberg and H.F. Andersen are employees of Lundbeck.

### P 05. Comparison of the standard scales and CGI scores in major depressive disorder, panic disorder, social anxiety disorder, and generalized anxiety disorder

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*Purpose*: The Clinical Global Impression [CGI] is commonly used as a global measure for disease severity and treatment-induced improvement in a variety of disorders. The objectives of the present study were to compare the CGI measures with disorder-specific scales that are considered to represent 'gold standard' measures in these disorders, and to define levels for response and remission for these standard scales, by reference to CGI definitions.
*Methods*: In a *post-hoc* analysis, randomized controlled studies with patients treated with escitalopram for major depressive disorder (n=5), panic

disorder (n=1), generalized anxiety disorder (n=4), or social anxiety disorder (n=2) were compared with regard to the standardized effect sizes in the Clinical Global Impression (CGI) score and the rating scales that represent the 'gold standard' for these disorders (MADRS, PAS, HAM-A, and LSAS).
*Results*: In all indications, treatment with escitalopram showed high standardized effect sizes on all efficacy measures. Standardized effect sizes of active drug-placebo differences were numerically higher in panic disorder than in the other disorders but this difference was not significantly different. Moderate to high correlations were found between CGI and the standard scales. The CGI was shown to be a consistent measure of disease severity and to be sensitive to change. When defining "response" to a treatment on a standard rating scale, a $\geq$50% decease from baseline scale score is conventionally used. However, in this analysis the CGI-I definition of at least 'much improved' corresponded to only 39%, 23%, 42%, and 31% reductions in the MADRS, PAS, HAMA and LSAS, respectively.
*Conclusion*: The comparison of the standard scales and CGI scores suggest that the traditional definition of response may be too conservative.
*Disclosure*: Professor B. Bandelow, D.S. Baldwin and D.J. Stein have received consultancy honoraria from Lundbeck. O.C. Dolberg and H.F. Andersen are employees of Lundbeck.

**P 07. Mood disorders in people living with HIV/AIDS in New York City: Review of published studies**

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Mood disorders, especially depression, are very common in the general US population and among people living with HIV/AIDS (PLWHA) in New York City, USA. A large body of literature documents lifetime and point prevalence of depression across different sectors of the PLWHA population,. Depending on study features, prevalence estimates can vary widely, and among women, for example, they range from 3 to 86%. Because of the relationship between depression and mortality and morbidity, understanding and addressing the impact of mood disorders in people living with HIV/AIDS has become an important priority in public health research and practice. With a large group of HIV/AIDS survivors who are aging and/or PLWHA who are becoming diagnosed at later age, identifying and addressing mood disorders is critically important for individual and public health outcomes. Furthermore, because of comorbid conditions commonly existing in this specific population, practitioners and researchers are to be aware of the impact of age and comorbidity when designing and implementing public health programs and research studies. Although studies recruit older subjects for research, it is not common that in their statistical analysis they account for variables such as age and other comorbidities, and defeat one of the main purposes of research which is to obtain reliable and generalizable results for the population of interest. This review examines research studies conducted among PLWHA in New York City, and identifies methodologies used for accounting for age and comorbid conditions in the aging PLWHA population. A systematic procedure was used to identify relevant studies. Findings are summarized and their contents are analyzed according to state-of-the-art research practices. Methodological procedures that studies use or could have used to account for age-related variables are presented and recommendations for future research are proposed.

**P 08. Panic disorder, depression and the risk of coronary heart disease: A cohort study of a national managed care database**

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*Objective*: The association between panic disorder (PD), depression and coronary heart disease (CHD) was examined in a large national managed care database.
*Methods*: The Integrated Health Care Information Services (IHCIS) managed care database is a fully de-identified, HIPAA-compliant database and includes complete medical history for more than 17 million managed care lives; data from more than 30 US health plans covering seven census regions; and patient demographics, including morbidity, age and gender. A total of 39,920 PD patients and an equal number of patients without PD were included in this cohort study. The Cox proportional hazards regression models were used to assess the risk of CHD adjusted for age at entry into the cohort, tobacco use, obesity, depression and use of medications including angiotensin-converting enzyme (ACE) inhibitors, -blockers and statins.
*Results*: Patients with PD were observed to have nearly a two-fold increased risk for CHD (HR = 1.87, 95% CI = 1.80–1.91) after adjusting for these factors. There was some evidence of a possible trend toward increased risk in a subgroup of patients diagnosed with depression. After controlling for the aforementioned covariates and comparing these patients to those without a diagnosis of depression, it was noted that patients with a comorbid diagnosis of depression were almost 3 times more likely to develop CHD (HR = 2.60, 95% CI = 2.30–3.01).

*Conclusions*: The risk of CHD associated with PD with or without comorbid depression suggests the need for cardiologists and internists to monitor panic disorder in order to ensure a reduction in the risk of CHD.

**P 09. The effect and safety of ziprasidone in patients with bipolar disorders: A naturalistic study**

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*Objectives*: A newer atypical antipsychotic, ziprasidone, has not been fully studied in Korean patients with bipolar disorders. In this retrospective study, the prescription patterns, efficacy and safety of ziprasidone were evaluated in patients with bipolar disorders under naturalistic conditions.
*Methods*: We analyzed medical records of bipolar patients who had been treated with ziprasidone at Seoul National University, Bundang Hospital. Eighty-three patients with bipolar disorder were reviewed for demographic data, current mood episodes, doses of ziprasidone, concomitant psychotropic medications, and adverse effects. They also were checked on change of body weight and blood cholesterol level.
*Results*: Ziprasidone was prescribed mainly to patients who showed limited response or intolerance to former treatment. The drug was effective to any kind of mood symptoms regardless of its polarity. The most frequently reported adverse effects were somnolence, akathisia, and insomnia. Notably, mean body weight and serum cholesterol level were significantly decreased.
*Conclusion*: Ziprasidone seems to be effective not only for manic symptoms but also for depressive symptoms, and to be well tolerated by patients with bipolar disorders.

**P 10. Does specialised inpatient treatment have a role for severe, chronic, resistant obsessive-compulsive disorder (OCD)?**

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*Aims*: A study examining the outcome on observer-rated and self-report measures in patients suffering from severe, chronic resistant obsessive-compulsive disorder admitted to a specialised inpatient unit over a 2-year period.
*Method*: ICD 10 diagnoses were made following a detailed psychiatric interview by a qualified psychiatrist. All cases fulfilling ICD 10 criteria for OCD were included in this study. Measures of severity of OCD and any depression as well as records of previous treatments were recorded. Outcome measures were repeated at the end of inpatient stay.
*Results*: Fifty-five patients were included in the study. This patient group comprised the most handicapped OCD patients. The mean age of patients was 34 years (SD 12; range 18–63 years) with a mean duration of OCD of 16 years (SD 11; range 1–50 years). Mean YBOCS score on admission was 32 (SD 5; range 20–40), which indicates extremely severe OCD. At discharge from inpatient treatment the mean YBOCS score had reduced to 21 (SD 10; range 2–40), which indicates moderate OCD.
*Comments*: This study demonstrates that specialised inpatient care can benefit a small group of severely ill OCD patients who fail to respond to treatment in primary care and community health teams. With current local emphasis on services and the small number of patients likely to require such specialised treatments, we suggest that these specialised services should be provided at a National level.

**P 11. Delayed sleep phase shift in chronic refractory obsessive-compulsive disorder**

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*Aim*: Potential biological markers for delayed sleep-phase (DSPS) in patients with severe, chronic, resistant obsessive-compulsive disorder (OCD)
*Background*: Iit has long been recognised by clinicians that some patients with severe OCD also suffer from DSPS but this has only recently been described in the literature. Our group found that in a retrospective analysis of patients admitted to a specialist unit, 17% met criteria for DSPS. Those most likely to be affected were younger and had an earlier age of onset of their OCD symptoms. A subsequent prospective study found that almost half of the patients admitted had evidence of DSPS. Younger patients; those who were male and those with the most profound OCD symptoms were most frequently affected. It was decided to repeat a prospective analysis but include actigraphy and measures of urinary melatonin and cortisol to obtain a more reliable marker of sleep phase disturbance.
*Method*: Successive admissions to the OCD Specialist Unit with OCD (DSM-IV) were invited to participate. Standard measures of severity of OCD and depression were administered. Patients were asked to wear an actigraph and keep a sleep diary for 2 weeks. Sleep records were kept by nursing staff. Urine samples were analysed for melatonin and cortisol.

*Results*:Nine patients have completed actigraphic recordings so far, of which seven exhibited severely disturbed rest and activity patterns. Specifically, patients showed abnormally high nocturnal activity throughout the night, a low interdaily stability (IS = $0.407 \pm 0.111$, $n = 7$) as well as a low rest-activity amplitude (RA) across day and night (RA = $0.702 \pm 0.04$, $n = 5$). These parameters indicate that the rest–activity regularity is severely disrupted in these patients. Extremely delayed and polyphasic sleep and activity phases were found in two patients suggesting changes in the circadian timing of rest–activity rhythms. Examples of these will be presented as well as the psychometric and urinalysis data.
*Conclusions*:DSP and other abnormal sleep patterns are common in the most profoundly ill OCD patients. They are associated with sleep-related neuro-endocrinological changes. The neurobiological clinical implications of these findings merit further exploration

**P 13. Effectiveness of brief cognitive therapy for depressive cases**

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This research investigated effectiveness of cognitive therapy (CT) for depression. The researchers used quasi experimental research design with pre-post treatment strategy to study the effectiveness of CT for Pakistani adult psychiatric patients suffering from depression. The sample consisted of 20 outdoor adult psychiatric patients diagnosed for depression drawn from a Government Hospital and a private clinic. All of them had already been diagnosed and referred by the same psychiatrist. Ten patients were given CT, of whom seven continued with their medications, while the other three volunteered to receive CT exclusively. The remaining 10 patients received pharmacotherapy (PT). Each subject was given 12 individual sessions (50 min each) over a time span of 2.5 months, using Beck's research protocol of CT (1978, 1995). The Post-therapy scores on *BDI (Urdu version, 1995) and Depression Checklist constructed by Syed and Farooqi (1998) showed significant decrease in the depression level of patients ($t = 3.87$; df = 18; $^{*}P < 05$ and $t = 4.60$; df = 18; $^{*}p < 05$, respectively) as compared to those of PT. The significant $F$-ratio ($F(2,17) = 13.47$; $^{*}P < 01$) further suggests that CT is more effective treatment modality for depression than pharmacotherapy.

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**P 15. Escitalopram in relapse prevention in patients with obsessive-compulsive disorder (OCD)**

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*Purpose*: The primary objective of this study was to compare the efficacy of escitalopram 10 or 20 mg/day with that of placebo in preventing relapse during 24 weeks in outpatients with obsessive-compulsive disorder who had responded to an initial 16-week open-label treatment with escitalopram.
*Methods*: This was a multinational, randomised, double-blind, placebo controlled, flexible to fixed dose relapse prevention study with escitalopram in outpatients with obsessive-compulsive disorder. Patients with comorbid depression and anxiety were excluded. The study consisted of two periods: a 16 week open-label period with 10–20 mg escitalopram followed by a 24-week double-blind, placebo-controlled period, and a 1-week taper period. Patients who had responded to treatment ($\geq$25% decrease in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score) by the end of the 16-week open-label period were eligible for randomisation to either escitalopram or placebo for a further 24 weeks.
*Results*: A total of 468 patients with obsessive-compulsive disorder were treated with open-label escitalopram (10 or 20 mg) for 16 weeks. There were 320 responders (68%) who were randomized to change to placebo ($n = 157$) or to continue with escitalopram (at the assigned dose) for further 24 weeks ($n = 163$). The primary analysis (time to relapse) showed a clear beneficial effect of escitalopram relative to placebo (log-rank test, $P < 0.001$). The proportion of patients who relapsed was statistically significantly higher in the placebo group (52%) than in the escitalopram group (23%) ($P < 0.001$, chi-square test). The risk of relapse was 2.74 times higher for placebo- than for escitalopram-treated patients (chi-square test, $P < 0.001$). Escitalopram was well tolerated. During the 16-week open-label period, 94 out of 468 patients (20%) were withdrawn, of whom 28 (6.0%) were due to adverse events. During the double-blind period the overall withdrawal rate, excluding relapses, was 9.6% for escitalopram and 9.4% for placebo (NS).
*Conclusion*: Escitalopram was effective in preventing relapse of obsessive-compulsive disorder and was well tolerated as continuation treatment.
*Disclosure*: N. Fineberg and D.J. Stein have received consultancy honoraria from H. Lundbeck A/S or Forest Laboratories. O. Lemming and B. Tonnoir are employees of H. Lundbeck A/S.

**P 16. Effect of bromocriptine in the patient with refractory depression**

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*Background*: The treatment strategy for refractory depression where a drug is given to augment the effect of foregoing antidepressants is called augmentation therapy. The augmentation therapy using lithium and triiodothyronine has been fairly established. Some reports have suggested that bromocriptine, a dopamine agonist, also has an augmentation effect on the antidepressant treatment. We report a patient with monopolar depression who showed a dramatic improvement with the bromocriptine augmentation therapy.
*Case*: The case was a 64-year-old male suffering from monopolar depression. Since antidepressants were not adequately effective, the modified electroconvulsive therapy (mECT) was performed 16 times. By mECT, depressed mood and delusion of belittlement were ameliorated, whereas loss of energy was not altered. Therefore, we chose bromocriptine augmentation therapy; with that, loss of energy was improved gradually and, finally, complete remission was achieved by 15 mg/day of bromocriptine. It is also reported that the patient with depression who had failed to respond to mECT showed a dramatic improvement with selegiline, a selective monoamine oxidase type-B inhibitor that slows down the degradation of dopamine in the human brain. These cases suggest that a certain subgroup of mood disorders would be associated with the dysfunction of the dopaminergic neural system.

**P 17. Efficacy and safety of desvenlafaxine succinate in the short-term treatment of adults with major depressive disorder**

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*Objectives*: This study evaluated the efficacy and safety of desvenlafaxine succinate (DVS) in adults with major depressive disorder (MDD).
*Methods*: In an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, adult outpatients with a primary diagnosis of MDD received once-daily, fixed doses of DVS 200 or 400 mg. The primary efficacy measure was change from baseline on the 17-item Hamilton Rating Scale for Depression (HAM-$D_{17}$); the key secondary efficacy measure was the Clinical Global Impressions–Improvement (CGI-I) scale. Other efficacy measures included response, remission, and the Visual Analog Scale–Pain Intensity (VAS-PI). Safety assessments included adverse events, physical exam, and laboratory determinations.
*Results*: Of the 375 subjects randomized to treatment, 373 were included in the safety analyses and 369 in the intent-to-treat efficacy analyses. At the final on-therapy evaluation, adjusted mean change from baseline in HAM-$D_{17}$ total score was greater for DVS 200 mg ($-12.6$, $P=0.002$) and DVS 400 mg ($-12.1$, $P=0.008$) versus placebo ($-9.3$); mean CGI-I scores were lower for DVS 200 mg (2.2, $P=0.004$) and DVS 400 mg (2.3, $P=0.028$) versus placebo (2.7). Both doses were significantly better than placebo on Montgomery–Åsberg Depression Rating Scale scores, CGI-Severity, and HAM-$D_{17}$ response. DVS 200 mg was also significantly better than placebo on remission, VAS-PI overall scores, and some component scores; DVS 400 mg was significantly better than placebo on some VAS-PI component scores. Adverse events were generally mild or moderate, and safety assessments revealed few clinically significant changes.
*Conclusions*: These data provide support for the efficacy and safety of DVS for treatment of MDD.

**P 18. Cognitive evaluation in 11 depressed patients**

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*Aims*: Many studies have objective neuropsychological deficits in depressed patients, especially quantitative and qualitative deficits of memory and executive functions. However, assessment of executive functions depends on the neuropsychological tests employed and which led to controversial results. We propose to assess inhibition with the model of Hasher and Zacks (1991), who divide inhibition into three functions: access function, deletion function and restraint function.
*Methods*: Eleven patients with major depression, responding to CIM 10 criteria and 11 normal controls were included in the study. All subjects were assessed with neuropsychological battery including: (a) mini-mental test; (b) to evaluate inhibition: reading task with distracting material (Connelly et al. 1991), TMT, Modified Wisconsin Card Sorting Test, BADS, Hayling Sentence Completion Test, Stroop test; (c) to evaluate the other executive functions: Brixton test, verbal fluency, six elements and all the tests of GREFEX battery; (d) the severity of depression was assessed with the Hamilton Depression Scale.
*Results*: Depressed patients exhibited deficits in Stroop test, Hayling test, BADS, reading with distracting material. There was no difference between depressed patients and controls at the TMT, WCST.

*Discussion*: Depressed patients exhibited deficits in inhibition, but only in two functions: access function and restraint function. We found no deficit in deletion function. The other executive functions were not significantly different.

**P 20. Comparison of cognitive behavioral psychotherapy and pharmacotherapy in the treatment of agoraphobia with panic disorder**

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*Background and aims*: Cognitive-behavioral psychotherapy /CBT/ based on scientific princip and psychotherapeutic the treatment of psychiatric disorders especially in out-patients from agoraphobia with panic and panic disorders.
The aim of our study was to compare the combination of CBT and treatment in patients with agoraphobia with panic disorder patients with panic disorder.
*Methods and assessment*: 6-months pilot retrospective follow-up of 10 patients with agoraphobia with panic disorder and 10 patients with panic disorder, severe form.

a. objective scales:Hamilton Anxiety Rating Scale, 21-item assessment Hamilton Rating Scale for Depression
b. subjective scales: Beck Questionnaire for the assessment of the most frequent anxiety symptoms. Test for the assessment of the incidence of panic attacks.

Statistic evaluation: SD, p value, student's test.
Inclusion criteria:

a. agoraphobia with panic disorder F.40.01 panic disorder, severe form, F.41.01
b. age between 18-60 years old
c. CBT
d. informed consent of the patients included to study.

Exclusion criteria: other mental disorder.

*Results*: Calculated results proved statistically significant differences. Agoraphobia with panic improvement frequency and intensity of panic attacks. Patients with panic disorder improved after first week of the treatment.Statistically significant differences were in Hamilton scale of depression /HAMD 0=0,0095, HAMD 1=0,0025, HAMD 6=0,0131/ Hamilton scale of anxiety during the first day, 1 first months and 6 months/HAMA 0=0,0754,HAMA 1=0,0354, HAMA 6=0,0167 and in one case-Beck scale during the first months the result were on the border of statistical significance/BECK 1=0,0424/
*Conclusion*: It has been shown, that a combination of CBT and PT is more effective in panic disorder with faster start of decreasing the frequency and intensity of panic attacks.Patients suffering from agoraphobia with panic disorder had more problems /agoraphobia symptoms/, anticipating anxiety, emotions, bodily reactions, behaviour and also consequences of this behavior than patients suffering only from panic disorder. Our study is a pilot, with significant differences in combination of CBT and PT patients suffering from agoraphobia with panic and panic disorders.

**P 21. Depersonalization as a trait in panic disorder**

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*Backgrounds/Aims*: Depersonalization (DP) is a common clinical phenomenon in neurology and psychiatry. It is an experience in which the person fells a sense of unreality and detachment from himself. A systematic review showed a high prevalence of DP in panic disorder (Hunter et al., 2004). All 16 studies except one assessed DP as a unique symptom or item during the panic attack. Our aim was to study DP as a dimension in panic disorder.
*Methods*: We assessed consecutive panic disorder (DSM-IV) outpatients. Written consent was obtained. We used the SCID DSM-IV for axis I ($n=104$) and axis II ($n=93$). DP was assessed with the Spanish validated version of the Cambridge Depersonalization Scale (S-CDS) (Molina et al., 2006; Sierra et al., 2000). It is a self-report instrument of 29 items (range 0–290) with a good reliability and validity at a cut-off of 71. This questionnaire captures the frequency (0–4) and duration (0–6) of DP symptoms over the last 6 months.
*Results*: Seventeen patients (16.3%) had DP symptoms and 43 patients (41%) had the DSM-IV item depersonatization/derealization ($P=0.017$). We did not find sex or age of onset statistical differences. Comparing panic with and without DP the subgroup with DP had a high Panic-Agorafobia (PA) score: 22.53 (12.69) versus 14.60 (10.5) ($P=0.007$) and high prevalence of personality disorders 10 (33%) versus 6 (10%) ($P=0.007$).
*Conclusions*: The results support a slightly moderate prevalence of DP as a dimensional trait in panic disorders associated with severity (high scores PA) and worse prognosis (co-morbid personality disorder). Only a small proportion of patients with the depersonalization/derealization item during the panic attack had DP as a trait.

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**P 22. Assessing European practicing psychiatrists' awareness of metabolic syndrome among patients with bipolar disorder**

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*Background*: Patients with bipolar disorder may be at elevated risk for metabolic syndrome or its components (obesity, insulin resistance, hypertension, elevated triglycerides, below-normal HDL). An online survey of experienced practicing European psychiatrists assessed awareness of metabolic issues and their impact on clinical management of bipolar disorder.
*Methods*: From April 24 to June 15, 2006, psychiatrists in UK, France, Germany, Spain and Italy were recruited from a European physician panel. Eligibility criteria were: practicing 4–30 years, spending greater than or equal to 50% of time in direct patient care, and treating greater than or equal to 10 bipolar patients in the last month. Aggregate European data were weighted to represent the population of practicing psychiatrists in each country.
*Results*: Of the 718 respondents, 22% were unfamiliar with the metabolic syndrome and half had diagnosed it. Yet 72% thought it poses significant health risks to patients, warranting monitoring and treatment. Based on the National Cholesterol Education Program criteria, respondents said the syndrome prevlance was $\sim$25% in bipolar patients and $\sim$20% in the general population. Overall, respondents were most concerned with medication side effects of weight gain, cognitive impairment, and glucose intolerance, while they viewed their patients' chief concerns as weight gain, sedation, and cognitive impairment. Treatments most often associated with increased risk of metabolic syndrome were olanzapine (76%), risperidone (42%), and quetiapine (36%). Olanzapine was also the drug most commonly associated with weight gain and adverse effects on lipid and glucose levels. Although 39% of respondents and metabolic concerns rarely or never led them to stop or switch bipolar medications, 65% said they have made interview and monitoring changes in the past 3 years regarding metabolic health.
*Conclusions*: European psychiatrists view metabolic syndrome as highly prevalent in the general population and even more so in bipolar patients, and they are especially concerned about weight gain. In recent years, two-thirds have changed their patient interviewing and monitoring habits pertaining to metabolic health.

**P 23. Escitalopram in the long-term treatment of major depressive disorder in elderly patients**

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*Purpose*: The primary aim was to investigate the long-term safety and tolerability of escitalopram (10 or 20 mg/day) treatment of elderly patients suffering from major depressive disorder (MDD). The secondary aim (also prospectively defined) was to examine response to treatment, as measured by change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score from study entry to each visit, using observed cases (OC).
*Method*: This 12-month extension trial included 225 elderly patients with MDD who had completed an 8-week, double-blind, placebo-controlled, lead-in study, which was performed in outpatients in primary care and in specialist clinics.
*Results*: The intent-to-treat (ITT) population comprised 223 patients and the overall withdrawal rate was 24%. The most common reason cited for withdrawal was adverse events (9%). The five most common adverse events were accidental injury, weight increase, arthralgia, coughing, and rhinitis, with an incidence ranging from 8 to 13%. No new types of adverse events were reported in this extension study, compared to the 8-week lead-in study. Mean weight increased from 69.2 kg at study entry to 70.0 kg at the last assessment. There were no clinically relevant safety findings with respect to changes in mean values for vital signs, electrocardiograms, weight, or clinical laboratory values. The mean MADRS total score decreased from 13.4 to 6.4 (OC) [8.5 last observation carried forward (LOCF)]. The percentage of patients in remission (MADRS total score $\leq$12) increased from 48% at study entry to 81% by Week 52.
*Conclusions*: Escitalopram (10 or 20 mg/day) demonstrated a favourable tolerability profile during 12 months of open-label treatment of elderly patients, and produced a further improvement in depressive symptoms during the study period.

**P 24. Cross-cultural evaluation of the self report version of the panic disorder severity scale in JAPAN**

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Since there are many patients who have suffered from panic disorders, they have been the focus of much research interest around the world. Various kinds of instruments are available to establish panic disorder

diagnoses and treatments, which make it difficult for researchers to make direct comparisons between different research settings and different strategies. To address this problem, the Panic Disorder Severity Scale (PDSS), a seven-item measure to rate overall severity of Panic Disorder, was developed by Shear et al. The instrument has been accepted in the world-wide and translated into seven languages. For instance, the Japanese version of PDSS (PDSS-J) [Furukawa et al., 2004] was associated with reliable and valid measurement of panic disorder severity and favorable levels of sensitivity to change. Afterwards, the self-report version of the PDSS (PDSS-SR), which can be a useful tool when an interviewer is not available or practical, was developed and demonstrated to be a reliable format by Houck et al. In the current study, we developed the Japanese version of the PDSS-SR (PDSS-SR-J), and both PDSS-J and PDSS-SR-J were administered to 73 Japanese outpatients with panic disorder with or without agoraphobia. The identical one-factor structure of PDSS-SR-J was confirmed and the internal consistency of the instruments was excellent. The individual items from the PDSS-SR-J were compared to those of the PDSS-J with a weighted Kappa, showing good to moderate agreement between the two forms. The total score of the PDSS-SR-J was strongly associated with that of PDSS-J by analyses of the intraclass correlation coefficient. Using the anchor-based approach, we confirmed the correlation between total score of PDSS-SR-J and the Clinical Global Impression-Severity (CGI-S) score. The PDSS-SR-J is a simple, reliable, and valid instrument to rate severity in patients with diagnoses of panic disorder with or without agoraphobia.

### P 25. Cost effectiveness of venlafaxine compared with generic fluoxetine and amitriptyline for the treatment of depression in primary care in the UK

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*Objective*: To estimate the economic impact of using venlafaxine compared with generic fluoxetine or amitriptyline to treat depressed patients from the perspective of the UK's NHS.
*Methods*: A decision tree modelling the management of depression over 6 months following initial treatment with venlafaxine XL, fluoxetine and amitriptyline was constructed using clinical outcomes obtained from randomised controlled trials. This was supplemented with estimates or resource utilisation which was derived following discussions with general practitioners and psychiatrists.
*Results*: Remission rates for venlafaxine, fluoxetine and amitriptyline were 40, 33 and 24%, respectively. The cost of treatment for depression over a 6-month period was £1530, £1539 and £1558 for venlafaxine, fluoxetine and amitriptyline, respectively
*Conclusions*: First line use of venlafaxine is a cost-effective treatment for depression in the UK, even when compared against generic and generic amitriptyline.

### P 26. Older people's chronic insomnia: Combined therapeutic approach throught the neuromuscolar and relaxing treatment integrated with melatonina

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*Methods*: We submitted 10 subjects, aged between 55 and 70 years, to a combined neuromuscular, relaxing and shiatzu treatment integrated with melatonin retard formulation, taking into consideration a possible positive function on the chronic insomnia of the examined patients. Twenty subjects were submitted, before call to study, to a psycodiagnostic evaluation using the Hamilton-A test which showed a point between 15 and 27, and Hamilton-D test which showed a point between 18 and 24. Subsequently, the study group (10 subjects) was submitted to the combined neuromuscular, relaxing and shiatzu treatment every week, integrated with melatonin retard. At the end of 6 months, both the study group and the reference group, that is all 20 patients, were submitted to another test evaluation.
*Results*: The results, obtained comparing the first Hamilton-A test with the check one, have shown a decrease of 11 points in 12%, 9 points in 28%, 8 point in 30%, with an immutable condition in 30% of cases for the subjects who practised Perfect Shape. The results obtained comparing the first Hamilton-D Test and the last, showed a decrease of 13 points in 10%, 11 points in 15%, 9 points in 30%, 6 points in 20%, with an immutable condition in 25% of cases for the examined subjects. Therefore, the results show, only for the examined patients, a reduction, although in a minor way, of the chronic insomnia, with an improvement of Hamilton-A test and Hamilton-D test.
*Conclusions*: An analysis of the study leads to assert, on the basis of the results, that in the study group, submitted to combined neuromuscular, relaxing and shiatzu treatment integrated with melatonina retard formulation, that chronic insomnia is reduced. This is a noteworthy result, above all in relation to the immutable sleep balance of the reference group.

### Reference

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**P 30. Interpersonal violence and symptoms of depression**

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*Objective*: The study was conducted to determine the prevalence of interpersonal violence in women attending mental health services. It also assessed the symptoms of depression in these women.
*Method*: Women coming to the Department of Psychological Disorders were screened for interpersonal violence. Women were excluded if they had psychosis or dementia. Their age range was 18–55 years. Structured interviews were conducted to probe the type of interpersonal violence. Later BDI-II was administered to diagnose and measure the severity of depression. Data was collected over a period of 6 months.
*Results*: A total of 72% of the women experienced interpersonal violence; 82% were married; 5% were divorced; 3% separated; and 10% unmarried. All the women reported experiencing different levels of emotional trauma including verbal abuse (100%), physical abuse (72%), forced sex (7%) and economic abuse (100%). A total of 51% of women had major depressive disorder, 4% had dysthymia and 45% had various anxiety disorders.
*Discussion*: Women suffering from various types of emotional abuse are more likely to develop symptoms of depression. Study reveals women of lower and middle socioeconomic classes commonly experience interpersonal violence. It was also true for partners having no or less education. Prolonged stressful life events increase their vulnerability for depression. The type of interpersonal violence and severity of depression are closely related. Women who experienced physical abuse (severe or long term) or two or more types of abuse suffered from major depressive disorder, while verbal abuse alone (long term) was related to dysthymia.

**P 32. Neuropetide Y, calcitonin gene-related peptide and CRH in brain of rats bred for high anxiety-related behaviors**

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*Background*: To elucidate the neurobiology of anxiety, a rat model exhibiting high (HAB) versus low anxiety behaviors (LAB) was developed by selective breeding of the Wistar strain. Since neuropeptides play a variety of roles in CNS we explored whether they are changed in brain of those animals.
*Methods*: Male and female HAB and LAB rats were tested in the elevated plus maze (EMP) and subjected to the Porsolt swim test. Neuropeptide Y (NPY), calcitonin gene-related peptide (CGRP) and corticotropin releasing hormone (CRH) were measured by radioimmunoassays in brain regions.
*Results*: Behavior: HAB rats exhibited higher anxiety-like behavior in the EPM and increased depression-like behavior in the swim test. Neuropeptides: NPY was increased in the frontal cortex, cingulate and striatum, while CGRP was increased in the frontal cortex and hippocampus of both male and female HAB. CRH was higher in the hypothalamus of male and female HAB and male LAB compared to female LAB.
*Comment*: This is the first demonstration that brain NPY and CGRP are altered in a genetic model of anxiety. In contrast to consistently decreased NPY in hippocampus of both genetic and environmental depression models, in our anxiety model no changes were observed in that region. Moreover, NPY was increased in regions with significant dopaminergic/glutamatergic input/activity. CGRP, a stress-sensitive peptide that interacts with dopamine, was also increased in HAB animals. Lastly, no changes were found in the brain CRH system, confirming the dominant role of vasopressin in this anxiety model.
*Conclusion*: We present the first evidence that neuropeptides NPY and CGRP are altered in selected brain regions in an animal anxiety model. Both the direction of change and the regions involved differ from those found in genetic and environmental models of depression, implying that we may have identified some neurobiological correlates of anxiety. These findings are likely to be diagnostically useful and contribute to understanding of the anxiety–depression comorbidity; they may also facilitate novel therapeutic approaches.

**P 33. Anxiety and depression symptoms in school age children**

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*Objectives*: Previous studies at Penteli Children's Hospital indicated that children with learning disabilities present secondary psychological problems (e.g., depression, anxiety, anger) and especially elementary school children. In the present study we aim to extend and systematize the typology of psychological problems on a larger clinical population of children with learning disabilities and confirm the hypothesis (it is expected that children with learning difficulties will present high levels of depressive, anxious, and aggressive symptoms, as well as low self-esteem) for the high school student group. We also aim to take into account variable gender, which seemed to be an interesting perspective, as the limited sample that we used did not permit us to have significant differences.

*Methods*: The sample consisted of 421 children, 292 boys and 129 girls, aged 7–14. The children were categorized into three different groups: (a) children with slight learning disabilities; (b) children with dyslexia; and (c) children with learning and intellectual disabilities. Children were given complete Beck Youth Inventory and their parents were asked to complete Achenbach parents' questionnaire. In order to compare the three groups we used the $\chi^2$-test.
*Results*: The Beck Youth Inventory indicated that 29% of children have low self-concept, 32.3% anxiety, and 22.1% depressive feelings, and 21.6% express anger and 20.9% disruptive behaviour. The Aschenbach test equivalent percentages were: 21.4% anxiety, 21.4% depression, 18.5% aggression and 16.2% delinquency tendencies. It seems that parents generally underestimate children's anxiety and focus on the treatment of the learning disabilities.
*Conclusions*: As expected the dyslectic children presented more anxiety than children with no dyslexia. This finding is valid for the two age groups. However, self-concept is affected by age: high school children present more symptoms of low self-esteem. The sex of the children proved to be an important factor: dyslectic girls have lower self concept, more anxiety and depression symptoms; on the contrary, boys have more aggressive and delinquency tendencies.

### P 35. Efficacy of 2 years of maintenance treatment with venlafaxine extended release 75–225 mg/day in patients with recurrent unipolar major depression

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*Background*: The efficacy of venlafaxine XR 75–300 mg/day has been demonstrated in patients with recurrent MDD over 2.5 years. As 300 mg/day is above the approved dose in most countries, this reanalysis focused on patients taking $\leq$225 mg/day.
*Methods*: In the primary multicenter, double-blind trial, outpatients with recurrent MDD ($n=1096$) were randomized to receive 10-week acute phase treatment with venlafaxine XR (75–300 mg/day) or fluoxetine (20–60 mg/day), then a 6-month continuation phase. Subsequently, at the start of two consecutive, double-blind, 12-month maintenance phases, venlafaxine XR responders were randomized to receive venlafaxine XR or placebo. Data from the 24-month maintenance treatment were analyzed for the combined endpoint of maintenance of response (i.e., no recurrence of depression and no dose increase >225 mg/day), and each component individually (a: no recurrence; b: no dose increase). Time to each outcome was evaluated with Kaplan–Meier methods using log-rank tests for comparisons between venlafaxine XR and placebo.
*Results*: The analysis population was comprised of 114 patients in the venlafaxine XR group who received doses $\leq$225 mg/day prior to maintenace phase baseline (venlafaxine XR: $n=55$; placebo: $n=59$). During the 24-month maintenance phase, seven patients in the venlafaxine XR group required dose increases >225 mg/day, four had recurrences; in the placebo group, 16 patients required dose increases, seven had recurrences. Kaplan–Meier probability estimates for maintaining response were 70% for venlafaxine XR $\leq$225 mg/day and 38% for placebo ($P=0.007$). Analysis of individual endpoints showed the probability of no dose increase above 225 mg/day was 76% for venlafaxine XR and 58% for placebo ($P=0.019$); the difference in the estimated probability of no recurrence between patients receiving venlafaxine XR $\leq$225 mg/day and those receiving equivalent placebo did not reach statistical significance (87 vs. 65%; $P=0.099$).
*Conclusion*: Venlafaxine XR is effective maintaining response at doses $\leq$225 mg/day for up to 2.5 years in patients with MDD. The findings are consistent with the results of the full data set.

### P 37. Efficacy of duloxetine versus SSRIs and placebo in treating major depressive disorders

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*Background*: The purpose of this study was to compare the efficacy of duloxetine with a SSRI group and placebo in the treatment of adults with major depressive disorder (MDD).
*Method*: Pooled data from all studies in patients diagnosed with MDD where duloxetine and SSRIs were compared: seven randomized, double-blind, fixed-dose, 8-week studies of duloxetine ($N=1133$) versus SSRI ($N=689$; fluoxetine, paroxetine, or escitalopram) versus placebo ($N=641$). Duloxetine doses: 40 mg/day (two studies); 60 mg/day (one study); 80 mg/day (four studies); 120 mg/day (four studies). SSRI doses: 10 mg/day (escitalopram), 20 mg/day (fluoxetine and paroxetine).
*Results*: Duloxetine 40–120 mg/day was significantly superior to combined SSRIs (fluoxetine, escitalopram, and paroxetine) on the 17-item Hamilton Depression Rating Scale (HAMD17) total score ($-9.16$ vs. $-8.50$; $P=0.032$). This difference arose from significantly greater efficacy of duloxetine on HAMD17 items: work and activities, psychomotor retardation, sexual functioning, and hypochondriasis. No items in the combined SSRI group were significantly superior to duloxetine; however,

differences approached significance for middle ($P = 0.057$) and late insomnia ($P = 0.06$).
*Conclusion*: This analysis comparing duloxetine to SSRIs fluoxetine, paroxetine, and escitalopram showed a statistically significant advantage on the HAMD17 total score for duloxetine. The differential efficacy was driven by greater improvement for duloxetine-treated patients on work and activities (anhedonia), psychomotor retardation, sexual functioning, and hypochondriasis.

### P 38. Efficacy of duloxetine versus placebo in mild, moderate, and more severely ill patients with major depressive disorder

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*Background*: To determine whether severity of depression affected the efficacy of duloxetine in treating major depressive disorder (MDD).
*Method*: Pooled data from four double-blind, placebo-controlled studies in which patients with MDD were randomized to duloxetine (60 mg/day) or placebo for 8 or 9 weeks. Patients were retrospectively stratified according to baseline HAMD17 total scores: mild = total score $\leq 19$ (duloxetine, $n = 247$; placebo, $n = 184$); moderate = 20–24 (duloxetine, $n = 333$; placebo, $n = 217$); severe = 25+ (duloxetine, $n = 127$; placebo, $n = 87$).
*Results*: Compared with placebo, duloxetine produced significantly greater baseline-to-endpoint mean change in HAMD17 total score, Maier and retardation subscales, HAMD17 Items 1 (depressed mood), 7 (work and activities), and 10 (psychic anxiety) (LOCF analyses; $P \leq 0.05$ for each outcome) in all three patient cohorts. For the severely depressed cohort, superiority of duloxetine over placebo was first observed at Week 1 for the Maier and retardation subscales and for HAMD17 individual Items 1 (depressed mood), 2 (guilt), 3 (suicide), and 9 (agitation); Week 2 for HAMD17 total score; and Week 4 for the anxiety/somatization subscale.
*Conclusion*: As shown here, duloxetine at its recommended therapeutic dose of 60 mg/day demonstrated superior efficacy as compared with placebo in the treatment of MDD, regardless of the baseline severity of depressive symptoms.

### P 39. Quality of life in depressed outpatients with previous psychiatric disorders: Baseline results from FINDER study

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*Objectives*: The Factors INfluencing Depression Endpoints Research (FINDER) study investigates health-related quality of life (HRQOL) in depressed outpatients. The objectives are to describe the frequency of previous selected psychiatric disorders in depressed outpatients, and to assess patients' health-related quality of life (HRQOL) at the enrolment visit.
*Methodology*: FINDER is a 6-month observational study in 12 European countries. Adult patients presenting within the normal course of care for a first or new episode of depression and initiating medication for the treatment of depression were enrolled in the study. HRQOL was measured at enrolment and after 3 and 6 months using patient-administered SF-36 with its Physical and Mental Component Summary (PCS and MCS) scores expressed as population-based norms with a mean of 50 (SD 10). Any values below 50 indicate worse than average scores. Selected psychiatric disorders in the previous 2 years were collected by physician-filled check lists.
*Results*: A total of 3,468 patients were included in the analysis sample, with mean age 46.8 years (SD 14.7). HRQOL as measured by the mean SF-36 scores was below the population norm for both the Mental and Physical Components (MCS 22.2 (SD 10.0); PCS 46.1 (SD 10.3)). A total of 45.1% of patients had at least one other depressive episode in the 2 years preceding study enrolment; 55.6% had other psychiatric disorders, with the most frequent ($>5\%$) being 51.1% anxiety and/or panic disorder, 9% obsessive compulsive disorder, and 6.9% drug and/or alcohol dependence. At the enrolment visit, HRQOL in those with depressive episodes in the previous 2 years was similar to those without (mean PCS 45.2 (SD 10.1) vs. 46.9 (10.6), and mean MCS 22.8 (10.5) vs. 21.6 (9.6), respectively). A similar pattern was observed for those with and without other psychiatric conditions (mean PCS 45.6 (SD 10.1) and 46.8 (SD 10.6) and mean MCS 21.9 (SD 10.0) and 22.6 (SD 10.1), respectively).
*Conclusion*: Reporting of previous psychiatric disorders did not substantially decrease mean SF-36 scores further.

### P 40. Treatment patterns of depression: baseline results from FINDER study

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*Objectives*: The Factors INfluencing Depression Endpoints Research (FINDER) study investigates health-related quality of life (HRQOL) in depressed outpatients, and its association with different demographic and clinical factors. The objectives of this abstract are to describe prior treatment, and treatment prescribed at enrolment for depressed outpatients.
*Methodology*: FINDER is a 6-month observational study in 12 European countries evaluating HRQOL changes of depressed outpatients receiving antidepressant pharmacological treatment. All treatment

decisions were at the discretion of the investigator. HRQOL was measured using patient-administered SF-36 with its Physical and Mental Component Summary (PCS and MCS) scores expressed as population-based norms with mean of 50 (SD10). In addition to medication prescribed at enrolment, information on this was also collected retrospectively for the previous 24 months.

*Results*: A total of 437 investigators enrolled patients into the study, and 3,468 patients were included in the analysis sample, with mean age 46.8 years (SD14.7): 68.2% were female; 32.3% were smokers; 38.2% of patients had received medication for depression in the last 24 months, with this rate being higher for specialists than GPs (42.2 vs. 33.8%). Of those receiving antidepressant (AD) treatment in the last 24 months, 47.6% received SSRIs, 9.9% received TCAs, 14.9% other ADs and 27.7% had combinations of ADs. Additionally, 66.0% of the patients had taken analgesics in the previous 24 months, of which 38.5% were in combination with ADs. At enrolment visit, 63.3% of the patients received SSRIs only, 9.2% TCAs only, 23.5% other ADs only and 4.0% received combination of ADs. HRQOL as measured by the SF-36 scores was below the population norm for both the PCS and MCS across all therapeutic classess with MCS being well below the population norm (MCS: SSRIs 21.6(9.8) TCAs 24.4(10.8) Other 22.9(10.2) and Combination 21.8(11.1)).

*Conclusion*: Mental health scores in the study sample of depressed outpatients were less than half of the population norm. Scores were descriptively very similar between groups of patients prescribed different classes of ADs at the enrolment visit.

## P 41. Escitalopram in the treatment of obsessive-compulsive disorder

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*Purpose*: The efficacy and tolerability of escitalopram in obsessive-compulsive disorder were investigated in a 24-week, randomised, placebo-controlled, active-referenced, double-blind study.

*Methods*: A total of 466 adults with obsessive-compulsive disorder were randomized to escitalopram 10 mg/day ($N=116$), escitalopram 20 mg/day ($N=116$), paroxetine 40 mg/day ($N=119$), or placebo ($N=115$) for 24 weeks. The pre-specified primary efficacy endpoint was the mean change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score from baseline to Week 12 based on the intent-to-treat population and last observation carried forward (LOCF) using analysis of variance (ANCOVA).

*Results*: Escitalopram 20 mg/day was superior to placebo on the primary and almost all secondary outcome endpoints, including remission (Y-BOCS $\leq 10$). After 12 weeks, on the primary efficacy endpoint, there was a statistically significant difference from placebo for 20 mg escitalopram and paroxetine. In the escitalopram 20 mg/day group, the Y-BOCS total score was significantly lower than in the placebo group as early as Week 6. At Week 24, the proportion of remitters (Y-BOCS $\leq 10$, LOCF, pre-defined) was significantly greater ($P<0.05$) for 20 mg escitalopram (41.2%) than placebo (27.4%), but not for 10 mg escitalopram (36.6%) or paroxetine (37.9%). The response rate ($\geq 25$ decrease from baseline Y-BOCS, LOCF, pre-defined) was significantly greater than placebo (50.4%) for 20 mg escitalopram (70.2%) and paroxetine (67.2%). A total of 131 patients (29%) withdrew from the study. There were no significant differences between the treatment groups in the proportion of patients that withdrew. Statistically significantly more patients withdrew from the placebo group (18%) due to lack of efficacy, than in the paroxetine (8%) or escitalopram 20 mg/day group (6%). More paroxetine-treated patients withdrew due to adverse events than escitalopram- or placebo-treated patients. The three adverse events with the highest incidences in the active treatment groups were nausea (19–27%), headache (17–22%) and fatigue (12–19%).

*Conclusion*: Escitalopram was efficacious and well tolerated in the treatment of obsessive-compulsive disorder, with 20 mg escitalopram showing statistically significant superiority at the primary efficacy endpoint.

*Disclosure*: D.J. Stein and N. Fineberg have received consultancy honoraria from H. Lundbeck A/S or Forest Laboratories. B. Tonnoir and E.W. Andersen are full-time employees of H. Lundbeck A/S.

## P 42. Predict: Predicting onset and outcome of depression

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*Backgrounds*: The European Project PREDICT (prediction of future episodes of depression in primary medical care: evaluation of a risk factor profile) is a prospective cohort study which will lead to the development of a multi-factor risk score for prediction of the onset and maintenance of depression in general practice. In an analogous manner as it was done the development of the Framingham cardiovascular risk score.

*Objective*: To develop a reliable and valid risk scale for the onset and maintenance of depression in

primary care attendees across six European and one Latin American country.
*Method*: Consecutive general practice attendees aged 18–75 undertook a detailed interview at their home or the general practice. The interviews included an assessment for (i) depression; (ii) individual-level risk factors (i.e. socio-demography, demands and rewards for paid and unpaid work, debt/financial strain, self-rated physical health problems, long-term disability, alcohol misuse, use of recreational drugs, quality of sexual and emotional relationships, childhood experiences of physical/emotional/sexual abuse, strength of spiritual beliefs, family psychiatric history and anxiety symptoms; and (iii) society-level risk factors: household type and composition, satisfaction with neighbourhood and perception of safety, recent threatening life events, experiences of discrimination, adequacy, availability and sources of social support. Test–retest reliability of the risk assessment tool was assessed in 285 people in the participating countries. All participants completed baseline and follow-up assessments after 6 and 12 months.
*Baseline results*: A total of 15,252 people were approached for the longitudinal study and 10,116 (69%) entered the prospective study. More detailed data on implementing the design in each country and on baseline findings will be presented in subsequent presentations of this seminar.
*Conclusions*: It is possible to design and recruit participants to a prospective study of the onset of depression across a range of cultures, languages and continents.

### P 43. The risk for depression conferred by stressful life-events is modified by variation at the serotonin transporter 5HTTLPR genotype. The Spanish PREDICT-gene cohort

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*Background*: The causal processes underlying depression are yet to be identified but, undoubtedly, comprise both genetic and environmental components. In the present study, we report results from the PREDICT-Gene study, focused on the identification of gene-by-environment interactions as predictors of depression among adult primary-care attendees.
*Sample and Methods*: We tested the potential gene-by-environment interaction between variation at the serotonin transporter gene and previous exposure to threatening life events (TLEs) in depression. A total of 737 consecutively recruited participants from different primary care centres in Malaga (Spain) were genotyped for the 5HTTLPR promoter polymorphism. Additional information was gathered on exposure to TLEs over a 6-month period, socio-demographic data and family history of psychological problems among first-degree relatives. Diagnoses of depression were ascertained using the Composite International Diagnostic Interview (CIDI) by trained interviewers. Two different depressive outcomes were used (ICD-10 depressive episode and ICD-10 severe depressive episode).
*Results*: Both the s/s genotype and exposure to increasing number of TLEs were significantly associated with depression. Moreover, the 5HTTLPR s/s genotype significantly modified the risk conferred by TLEs for both depressive outcomes. Thus, s/s homozygous participants required minimal exposure to TLE (1 TLE) to acquire a level of risk for depression that was only found among l/s or l/l individuals after significantly higher exposure to TLEs (two or more TLEs). The interaction was more apparent when applied to the diagnosis of ICD-10 severe depressive episode and after adjusting by gender, age and family history of psychological problems. Likelihood ratios for the interaction were statistically significant for both depressive outcomes (ICD-10 depressive episode: LR $\times 2 = 4.7$, $P = 0.09$ (crude), LR- $\times 2 = 6.4$, $P = 0.04$ (adjusted); and ICD-10 severe depressive episode: LR $\times 2 = 6.9$, $P = 0.032$; LR- $\times 2 = 8.1$, $P = 0.017$ (adjusted).
*Conclusion*: Our findings add further evidence in favour of an effect modification by the 5HTTLPR genotype on the risk of depression conferred by previous exposure to stressful life events.

### P 44. Long-term treatment with escitalopram and paroxetine in severe major depression

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*Purpose*: This randomised, double-blind fixed-dose study compared the efficacy of escitalopram and paroxetine in the long-term treatment of patients with severe MDD.
*Methods*: Patients with DSM-IV-defined MDD and baseline Montgomery–Åsberg Depression Rating Scale (MADRS $\geq 30$), with or without comorbid anxiety, were randomised in a 1:1 ratio to 24 weeks of double-blind treatment with fixed doses of either escitalopram (20 mg) or paroxetine (40 mg). The primary analysis of efficacy was an analysis of covariance (ANCOVA) of change from baseline to Week 24 in MADRS total score using the last observation carried forward (LOCF) method.
*Results*: At endpoint (24 weeks), the mean change from baseline in total MADRS score was $-25.2$ for patients treated with escitalopram ($n = 228$) and $-23.1$ for patients with paroxetine ($n = 223$), a difference of 2.1 points ($P < 0.05$). The difference

on the MADRS (LOCF) was significantly in favour of escitalopram from Week 8 onwards. The proportion of responders ($\geq$50% decrease in MADRS) after 24 weeks was 82% (escitalopram) and 77% (paroxetine). The corresponding values for remission (MADRS $\leq$12) were 75% (escitalopram) and 67% (paroxetine) ($P < 0.05$). The results on the primary efficacy scale were supported by a significantly greater difference in favour of escitalopram on all secondary efficacy analyses [Hamilton rating scale for Depression (HAM-D), Hamilton rating scale for Anxiety (HAM-A), Clinical Global Impressions scale – Severity and Improvement (CGI-S and CGI-I)]. For very severely depressed patients (baseline MADRS $\geq$35), there was a difference of 3.5 points in favour of escitalopram ($P < 0.05$). The overall withdrawal rate for patients treated with escitalopram (19%) was significantly lower than with paroxetine (32%) ($P < 0.01$). There were no significant differences in the incidences of adverse events (AEs), but the withdrawal rate due to AEs was significantly lower for escitalopram (8%) compared to paroxetine (16%) ($P < 0.05$).
*Conclusion*: Escitalopram was significantly more effective than paroxetine in the treatment of patients with severe MDD.

### P 45. Neural mechanism of dissociation between explicit and implicit memory retrieval in patients with major depressive disorder: Functional MR imaging

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*Objectives*: It is well known that depressed patients have memory retrieval deficits. However, there has been little research about the neural mechanism. The purpose of this study was to identify the cerebral regions and to evaluate the neural mechanism associated with memory deficits in depressive patients using functional MR imaging.
*Methods*: Thirteen depressed patients who met DSM-IV criteria for major depressive disorder and 14 healthy controls matched for sex, age, and educational level underwent a blood-oxygenation level-dependent functional MR imaging using a 1.5T Signa Horizon Echospeed MR system. To activate the cerebral cortices, a series of tasks was performed as follows: encoding of two-syllable words, and explicit (cued recall test) and implicit (word completion test) retrieval of previously learned words under the levels with conceptual and perceptual processing. The activation paradigm consisted of a cycle of alternating periods of 30 s of stimulation and 30 s of rest. Stimulation was accomplished by encoding eight two-syllable words and the retrieval of previously presented words, while the control condition was a white screen with a small fixed cross. During the tasks we acquired 10 slices (6 mm slice thickness, 1 mm gap) parallel to the AC-PC line, and the resulting functional activation maps were reconstructed using a statistical parametric mapping program (SPM 99).
*Results*: Depressive patients were impaired on explicit memory task compared with healthy controls. However, there was no significant difference in implicit memory tasks between two groups. Dissociation between explicit and implicit memory retrieval appeared in depressed patients. During cued recall test, in hippocampus, parahippocampal gyrus, posterior cingulate gyrus, precuneous, and middle temporal gyrus, depressed patients showed significantly less cerebral activation ($P < 0.001$).
*Conclusions*: These results showed the experimental evidence and the neuroanatomical mechanism for explicit memory deficits in depressive patients. Also, our findings indicate that there is neuroanatomical dissociation between explicit and implicit retrieval, suggesting that the performance of implicit and explicit memory-related tasks involves different mechanisms.

### P 46. Effects of modern antidepressants with different mode of action on cardiovascular parameters in patients with major depressive disorder

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*Background/aims*: Current pharmacological treatments of depression include selective serotonin-reuptake inhibitors (SSRIs), agents acting primarily on the noradrenergic system (such as the noradrenalin-reuptake inhibitor (NARI) reboxetine), and dual-acting agents. Cardiovascular side effects like hypo- and hypertension, tachycardia and QTc prolongation due to the antidepressants' peripheral actions, especially on the noradrenergic system, have been reported. It has been claimed that polymorphisms of the norepinephrine transporters (NET) with their respective different activities (peripheral versus central) are responsible for cardiovascular changes and their severity.
*Methods*: Following an overnight fast, blood pressure and heart rate alterations were assessed with a modified Schellong test, and compared between patients who took antidepressants with or without noradrenergic properties. ECGs with QTc-measurement (Bazett) were also performed.
*Results*: Altogether 32 patients with a major depression episode participated: 17 were treated with SSRIs and 15 with an antidepressant with a noradrenergic involvement. No clear cut differences concerning cardiovascular alterations could be detected in the two groups.

*Conclusion*: Cardiovascular changes are not dependent on differently acting antidepressants in our study population. Cardiovascular safety appears to be equal in both groups. However, a higher number of patients is required to confirm these results. A putative exclusive relation between depressive disorder and the above reported outcome has to be established with the examination of a healthy control group. In order to detect NET polymorphisms that entail different cardiovascular phenotypes that could serve as a predictor for response to treatment further genetic examinations will be conducted.