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Speaker Abstracts

Wednesday 9 November

SO 01. Symposium: Suicide overview

SO 0101. Predictors and prevention of suicide

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Background: It is estimated that between 1% and 2% of the world population die by suicide, and suicide is one of the major causes of death in young adults. Risk factors for suicide are a family history of suicidality, a previous history of suicide attempts, persistent suicidal ideation, male sex, aggressive/impulsive personality traits and recent adverse life events. Although most suicides are associated with psychiatric disorders, their role is still unclear. There is, however, no replicated risk factor model for a real prediction of suicides, and there are few lifelong follow-up studies of patient samples on mortality and suicides.

Method: The data presented come from a naturalistic study of 406 patients with major mood disorders, hospitalised between 1959 and 1963 and followed up clinically until 1985; mortality was assessed in 1991, 1997 and 2003. Long-term medication was defined as a minimum of 6 months' treatment after remission from an episode. Suicides in patients with depression and bipolar disorders receiving and not receiving long-term medications were compared by survival analyses and standardised mortality ratios (SMRs).
Results: In our sample 45 of 406 patients (11.1%) committed suicide. Unexpectedly, comorbidity with alcohol use disorders decreased suicide rates but increased general mortality. Long-term medication was mostly given in combination and was strongly anti-suicidal. Compared to other patients, suicide in those receiving long-term medication of lithium, atypical neuroleptics (clozapine, thioridazine) and antidepressants was markedly reduced: the SMR for suicide in untreated patients was 30, that for treated patients 8. Survival analyses of all deaths showed that combined treatment was more effective than monotherapy. In a subsample of patients with both a family history and a personal history of suicide attempts, 45.5% of the untreated group vs. 11.8% of the treated group committed suicide.
Conclusions: Not only lithium but also atypical neuroleptics and antidepressants were strongly anti-suicidal. The study of 45 suicides was too small to allow the applications of Cox proportional hazards models in order to separate the components of combined treatments, and some comparisons were statistically not significant (small Ns), although the survival curves suggest strong anti-suicidal effects.

SO 0102. Abstract unavailable at time of printing.

SO 0103. Toxicity of antidepressants in overdose

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Objective: Depression has been identified as a major risk factor for suicidal ideation and completed suicide. Antidepressants can be used both as a remedy for depression and as a device for suicide attempt. The toxicity of a drug in overdose therefore is a factor when choosing an antidepressant (AD) treatment. The toxicity of an AD can be illustrated in several ways.
Methods: (1) An estimate of a compound's toxicity is its lethal dose 50% (LD50) in animal studies, a measure that is still considered as the best current pre-clinical indicator of fatal toxicity in humans. The ratio between the LD50 and the therapeutically efficient defined daily dose (DDD, defined by the WHO) gives the margin of safety of an AD in overdose.[1] (2) The range of therapeutic and lethal human plasma concentrations of AD are published.[2] The ratio between the lethal (LBC) and the therapeutic blood concentration (ThBC) can be calculated for each AD. The calculations are conducted with respect to the lower margin of the LBC and the upper margin of the ThBC. (3) Case reports on overdoses are important data sources for assessing the toxicity of a substance. The ratios between the highest dose survived and the DDD are presented for different AD. (4) Clinical studies estimated the prevalence of AD intoxications in emergency departments and the severity of AD intoxications (for instance explained by the intubation rate).[3] (5) The fatal toxicity index (FTI) is defined as the number of deaths caused by an AD per million prescriptions of the same AD and is used to describe the toxicity of a drug.[4,5]
Results: Newer ADs are heterogeneous in their pharmacodynamic properties and symptom profile in overdose. The majority of data are available for selective serotonin reuptake inhibitors (SSRIs). Experimental pharmacology (LD 50%), human plasma concentrations (therapeutic, lethal), case reports (highest ingested dose without lethal outcome), clinical studies at emergency departments and forensic post-mortem analyses (FTI) show that new AD are clearly safer than tricyclic AD.
Conclusion: SSRIs can be considered as the current benchmark in terms of safety in overdose.

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SO 0104. Suicidality and mortality in PTSD

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Several studies (e.g. Drescher et al[1]) have found an excess of morbidity and mortality among those who were exposed to traumatic events. They report that causes of death included motor accident, overdose, and alcohol-related disorders. Bullman et al[2] report an excess of mortality, and the causes of this were suicide, poisoning and motor accident. Israeli veterans differ from other veterans in regard to alcoholism and drug abuse – both are significantly lower in Israeli veterans. Moreover, as drafting in Israel is mandatory, there is no socioeconomic bias in the drafting process. We compared more than two thousand veterans with PTSD with an equal number of non-PTSD veterans. Although the initial idea was to compare the suicide rates between veterans with and without PTSD, we realized that the records indicating suicide as the cause of death were partial, probably due to cultural and religious reasons. We therefore looked at the total mortality rate, assuming that this would give a clue in regard to suicide risk as well. The findings were that 77 (3.13%) of the PTSD group had subsequently died, as compared to 93 (3.79%) in the non-PTSD group. As previous studies reported an increased rate of traffic accidents,[1,2] and since criteria D of PTSD might be associated with exaggerated response, we compared the number of traffic reports in more than two thousand veterans with PTSD and an equal number of veterans without PTSD, and found no difference. The implications of these results for PTSD and suicide and stress and morbidity will be discussed.

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SO 02. Symposium: Is there a treatment for recurrent brief depression?

SO 0201. Recurrent brief depression: diagnostic issues

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Recurrent brief depression (RBD) is a disorder meeting the symptomatic criteria for depressive episode (MDE) with the exception that individual episodes last less than two weeks (typically 2–3 days) and do not occur solely in relation to the menstrual cycle.[1] The criteria further require the depressive episodes to have occurred at least once a month over the past year. The frequently reoccurring depressive episodes of RBD may sometimes be misinterpreted as dysthymia. Our own ongoing research on the neuropsychobiology of RBD suggests that a subgroup of patients with pure RBD have epilepsy-like dysrythmia in the temporal lobes indicating an organic affective disorder. A misdiagnosis of dysthymia in such cases may lead to inadequate treatment. Furthermore, in temporal lobe dysrythmia related RBD, suicidal ideation and behavioural disruption may occur. Subsequently a misdiagnosis of borderline personality disorder (BPD) may occur in these instances. Other patients who at first glimpse appear like pure RBD may in fact have additional brief episodes (1–3 days) of unusual over-activity or hypomania, suggesting a bipolar spectrum disorder. Some of these patients may be misdiagnosed as having a narcissistic personality disorder. In other cases the differentiation towards cyclothymia may be difficult. There appears to be a continuum both with respect to frequency and interval for these patients extending to an ultradian rhythm with daily episodes. Anxiety disorders (e.g. panic disorder) and alcohol or other psychoactive substance abuse are well known co-morbidities of bipolar spectrum disorders. In patients with long-term bipolar spectrum associated RBD, such co-morbidities in particular increase the risk of considering a diagnosis of borderline personality disorder. Some cases of RBD may precede or follow MDE.[2] The neurobiological characteristics of those subtypes of RBD compared to pure RBD remains unknown, but the high panic disorder co-morbidity in those cases (OR 5.1) may suggest a relationship to the bipolar spectrum disorder type of RBD in at least some patients. There has also been reported an association between celiac disease and RBD.[3] The implication of that finding is currently unclear.

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SO 0202. Epidemiology of brief and recurrent brief depression

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Objectives: To describe subgroups of brief depression (BD) in terms of prevalence, clinical characteristics, treatment rates and comorbidity with other psychiatric syndromes with special consideration of associations with major depressive episodes (MDE).
Methods: In the epidemiological Zurich cohort study 591 subjects were selected after screening at the age of 19 and studied prospectively by six interviews from the ages of 20/21 to 40/41. All subjects with recurrent brief depression (RBD) met ICD-10 and DSM-IV criteria. RBD was defined as episodes shorter than two weeks with five or more of nine criterial symptoms for depression with work

impairment and about monthly re-occurrence. In addition, an analogous brief depressive group (Infrequent Brief Depression, IBD) was defined tentatively by the lower frequency of one to 11 episodes per year. Weighted annual and cumulative prevalence rates were computed across the study.

Results: Pure RBD without any overlap with MDE or dysthymia was found in 13.2% of the population and pure IBD in another 10.5%. RBD subjects scored higher than IBD subjects in terms of distress, rates of treatment, repeated panic attacks and GAD, but not in terms of suicide attempts (8.4% vs. 10.6%, non-depressed controls 2.3%). On the basis of the suicidality finding, RBD and IBD were tentatively unified as brief depression (BD). Comparisons of pure BD with pure major depressive episodes (MDE) showed that the two groups did not differ in treatment rates, family history of mood and anxiety disorders or comorbidity with bipolar spectrum and anxiety disorders. Subjects with pure BD were more severely ill in terms of work impairment, whereas those with pure MDE tended to show higher suicide attempt rates and distress ratings. The combination of BD with MDE defined a very severe group of MDE, comparable to combined depression (MDE+RBD) and double depression (MDE+dysthymia).

Conclusions: BD is of interest as a diagnostic specifier for severe MDE. RBD is an important independent depressive sub-group, which requires more attention and treatment studies.

SO 0203. Genetic influence on mood circuitries

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Introduction: BDNF and SERT, both of which have been associated with psychopathological states, are important genes in brain development and in functions related to memory and emotion. Genetic variations of the BDNF (val66met) and SERT gene (5-HTTLPR) affect the function of these proteins in neurons and predict variation in human memory and in fear behavior. Our previous work has shown that the S allele of 5-HTTLPR affects the integrity, function and connectivity, and presumably development of a neural circuit linking amygdala and rostral anterior cingulate circuitry,[1] a circuitry related to anxious temperament and depression in the presence of environmental adversity. Additionally, we could show that val66met BDNF affects the development and function of brain circuitries (hippocampus, DLPFC) prominently implicated in aspects cognitive functioning (e.g. working memory).[2,3] Convergent evidence links BDNF to depression, such as data showing association of the functional val66met BDNF polymorphism with increased risk for mood disorders, for temperamental traits related to mood disorders, and associated increases of BDNF expression after electroconvulsive therapy and antidepressive SSRI treatment. These data implicating a biological interaction of BDNF with 5-HTTLPR-dependent signaling suggest a molecular mechanism that could support an epistatic interaction between the functional variants in these genes in risk for depression. This possibility has been explored to a limited degree in animals genetically engineered to be hypomorphic at both genes. We hypothesized that the "insufficient" met BDNF allele does not translate the S allele effect of 5-HTTLPR and therefore protects the subject from significant changes in subgenual cingulate and amygdala volume, which is reflected in functional connectivity data of this brain circuitry.

Methods: We investigated high-resolution anatomical magnetic resonance images (MRI) of 111 normal healthy volunteers (Caucasians of European ancestry) without any psychiatric life-time history using optimized voxel-based morphometry (VBM), a sophisticated fully automated morphological imaging technique, which allows a statistical comparison of gray matter volume on a voxel-by-voxel basis. Furthermore, functional and structural connectivity data were analyzed using SPM2.

Results: Consistent with our initial hypothesis, we found a significant increased 5-HTTLPR S allele volume loss of the subgenual cingulate and amygdala ($p < 0.001$) in val/val BDNF carriers compared to met BDNF genotype. Functional and structural connectivity data reflected merely this relationship ($p < 0.001$).

Conclusion: The met BDNF allele may be a protective genetic factor for depression, because it only insufficiently translates 5-HTTLPR S allele dependent structural and functional changes, which are related to depression.

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SO 0204. Treatment for recurrent brief depression

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Patients with RBD give a history of inadequate response to previous treatments, mostly offered in primary care. Owing to the nature of RBD, with its intermittent bursts of quite severe but short lasting episodes of depression, it is difficult to establish research protocols, which need to be designed for at least 6 months in order to detect group differences. Up to now, knowledge about the treatment of RBD has been limited. Fluoxetine, paroxetine, mirtazapine, moclobemide, and mianserin (in a low dosage) have been tested from the antidepressants which are available on the market. These studies revealed limited efficacy for RBD. However, it is not possible to conclude from these studies that antidepressants do not work in RBD. Further studies are necessary to establish treatment recommendations. As for other indications, exploratory open label studies in carefully selected patient populations are needed before double blind trials are carried out in a confirmatory fashion, a strategy which has not been forwarded for this treatment indication. However, since patients with RBD have a substantial risk of suicide attempts we can already rule out psychotropic agents which have a high toxicity, like tricyclic or tetracyclic antidepressants. Given the

beneficial effects of flupenthixol in one of the earlier studies on RBD by Montgomery et al and the recently published antisuicidal effect of clozapine and other atypical antipsychotics, like quetiapine, this line of research is also worthwhile pursuing as mono- or adjunctive therapy.

Thursday 10 November

SO 03. Symposium: Are there superior antidepressants?

SO 0301. Focus on escitalopram

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Background: In the clinical development program with escitalopram, studies using citalopram as the active reference have indicated that escitalopram is more efficacious than citalopram in the treatment of major depression. A series of preclinical studies demonstrated that R-citalopram counteracts the effect of escitalopram at the neurochemical, functional, and behavioural level. Analysis of data pooled from two clinical trials provided evidence of a superior antidepressive efficacy of escitalopram compared with equivalent doses of citalopram.[1] Direct evidence of a superior effect of escitalopram compared with citalopram was recently reported in patients with severe depression.[2]
Methods: A pooled analysis that included all clinical studies completed as of July 2004, including other SSRIs and venlafaxine.[3]
Results: The efficacy of escitalopram as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) and response rate (at least 50% decrease from baseline MADRS score) was statistically significantly superior to other SSRIs, and equally effective as venlafaxine. Efficacy increased with increasing baseline severity of depression.
Conclusion: The present analysis of the escitalopram clinical database confirms a superior clinical efficacy compared with citalopram and other SSRIs.

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SO 0302. Differences between remission rates in antidepressant treatment

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Initial drug selection has become very important as to whether a depressed patient will achieve remission resulting in full resolution of emotional, physical and functional symptoms of depression. Various meta-analyses have been reported in recent years involving SSRIs (fluoxetine, sertraline, paroxetine, citalopram) versus venlafaxine, mirtazapine, duloxetine and bupropion. Efficacy and some limited safety results of these studies will be discussed. Challenges of the application of the various meta-analytic methods involved with these analyses will addressed. Issues about inadequate agreement about definitions of remission, duration of study period, differing sample sizes and statistical methods applied to these studies will be discussed. Despite some of these shortcomings in depression clinical study research, a growing body of evidence is emerging to a consensus that not all these antidepressants have the same remission rates.

SO 0303. Focus on milnacipran

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Milnacipran inhibits the reuptake of serotonin and noradrenaline with similar potency. This is contrasts with venlafaxine which has about 30-fold greater affinity for the inhibition of serotonin compared to noradrenaline and duloxetine which has a 10-fold greater affinity. In addition, milnacipran has no affinity for the dopamine transporter. A meta-analysis of two randomised double-blind clinical studies comparing milnacipran with the SSRI, fluoxetine and fluvoxamine, showed significantly more responders and a higher remission rate with milnacipran than with the SSRI. Another study, carried out subsequent to this meta-analysis, compared milnacipran to paroxetine in less severely depressed outpatients and reported similar remission rates for the two antidepressants. Although the overall efficacy of the two antidepressants was similar, there was a significantly superior effect of milnacipran compared to paroxetine in the subgroup of patients scoring maximally on item 8 of the HDRS (retardation-slowness of thought and speech; impaired ability to concentrate; decreased motor activity). This gives a rare indication of a subpopulation of depressed patients that may particularly benefit from milnacipran. In addition to its activity in depression, milnacipran seems to have interesting perspectives in various anxiety disorders like generalized anxiety disorder and panic disorder. Recently, milnacipran has also been shown to be active in a number of chronic pain disorders including fibromyalgia syndrome (FMS). In a recent double-blind, placebo-controlled trial, milnacipran produced significantly greater relief from pain compared to placebo. Furthermore, significantly more milnacipran-treated patients reported at least 50% reduction in pain intensity, compared to placebo-treated patients. Milnacipran is generally well tolerated with only a low level of side-effects reflecting its stimulation of both serotonergic and noradrenergic neurotransmission. A comparative study of withdrawal from paroxetine and milnacipran has shown that milnacipran produces only a slight increase in anxiety in some patients in contrast to the classical serotonin withdrawal syndrome seen with paroxetine.

SO 0304. Focus on mirtazapine

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This presentation will discuss the rapid onset of antidepressant effect with mirtazapine compared with

SSRIs.[1] Information comparing the onset of antidepressant effect and tolerability between the FDT formulation of mirtazapine and venlafaxine XR will also be presented.[2] To determine the effect of mirtazapine on the core symptoms of depression, we conducted a meta-analysis comparing the Bech-6 factor score of individual patient data from 10 SSRI-controlled studies of mirtazapine versus SSRIs. In all trials, subjects who met either DSM III or IV criteria for major depression were randomized to treatment for 6 weeks with either mirtazapine (1201; 74.5% completed) or an SSRI (1200; 77.5% completed). The time to first response (50% reduction in Bech-6 score) and time to sustained response (50% reduction on Bech 6 score maintained to endpoint) were compared using fixed and random effects models, and Kaplan–Meier survival analysis. Patients treated with mirtazapine had a significantly greater first response ($p = 0.008$) and sustained response ($p = 0.03$) on the Bech 6 score than subjects treated with SSRIs. The cumulative probability of response was significantly higher for mirtazapine versus SSRIs, and not significantly different for the cumulative probability of sustained response. The results suggest that the early onset of antidepressant effect observed with mirtazapine can be at least partially explained by a direct, rapid alleviation of the core symptoms of depression by mirtazapine. To compare mirtazapine with venlafaxine, a multicenter trial was conducted in Germany. Subjects with a DSM-IV major depressive disorder and a 17-HAMD score ≥ 21, were randomized to mirtazapine FDT 30–45 mg/day ($n = 130$; 91 completed) or venlafaxine XR 75–225 mg/day ($n = 128$; 81 completed), titrated to the highest dose within 6 days. The primary outcome measure was the average of change from baseline HAMD-17 score over days 5, 8, 11 and 15 after treatment initiation. Secondary outcomes included change in HAMD-17 score, response (HAMD-17 score decreased by $>50\%$) and remission (HAMD-17 scores <7) up to day 43. Analyses were performed using the ITT population (LOCF approach). Mirtazapine subjects achieved significantly greater decreases in average HAMD-17 score (-7.48, $n = 127$) than venlafaxine subjects (-5.94, $n = 115$, $p = 0.008$). Response rates were significantly higher ($p < 0.05$) for mirtazapine subjects on days 8 (19.7% vs 6.1%), 11 (31.5% vs 15.7%), and 22 (48.0% vs 33.9%), and remission was significantly higher on day 15 (17.3% vs 7%). The tolerability of the two drugs was similar. Mirtazapine FDT produced a significantly more rapid onset of antidepressant action than venlafaxine XR, extending earlier findings.

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SO 04. Symposium: New antidepressants – how do they work and how effective are they?

SO 0401. What can we learn from pre-clinical studies of antidepressants?

Many antidepressants modulate neurotransmission of serotonin (5-HT) and noradrenaline (NA). The TCAs and the SSRIs are generally held to have comparable efficacy. Selective serotonin reuptake inhibitors (SSRIs) have advantages over their therapeutic predecessors, the TCAs and MAOIs, in that they are better tolerated, safer in overdose, and have fewer unwanted cardiovascular effects. Recently, it has been suggested that antidepressants which simultaneously recruit and engage both serotonin and noradrenaline (SNRI) may be more effective than some SSRIs. One of the most recently-marketed antidepressant is escitalopram, the active enantiomer of the racemic SSRI citalopram. In pre-clinical microdialysis and conditioned fear studies, escitalopram was found to be more efficacious than citalopram indicating a potentially different interaction with the Serotonin Transporter Protein (SERT). The increased efficacy of escitalopram observed in these pharmacological studies could be related to a pronounced binding of escitalopram to an allosteric site of the transporter, which results in a stable and long-lasting binding of escitalopram at the primary site. The latter effect has been shown in radioligand binding studies where the rate of dissociation of [^{3}H]-escitalopram from the serotonin transporter was slower when higher concentrations of escitalopram were added. Against this background, clinical comparisons between escitalopram and SSRIs and non-selective, SNRI agents, such as venlafaxine, are of both theoretical and practical interest.

SO 0402. Escitalopram vs. the SSRI citalopram – results from a randomised head-to-head study

The novel antidepressant, escitalopram, is the S (+) enantiomere of the racemate citalopram. Early in the development pre-clinical studies of escitalopram showed a greater effect than citalopram at comparable escitalopram concentrations. The hypothesis of a potential superior clinical efficacy led to the development of escitalopram as an antidepressant. The hypothesis was confirmed in several controlled clinical trials that revealed better efficacy of escitalopram compared with citalopram, but without reaching statistical significance. In a meta-analysis of four randomized clinical trials comparing escitalopram and citalopram, it was shown that escitalopram was superior to citalopram in terms of magnitude of antidepressant effect and response to treatment and that the benefit of escitalopram over citalopram seemed more evident when a higher Montgomery-Åsberg Depression Rating Scale (MADRS) cut-off score was used. Since then, results obtained from clinical studies using a posteriori and sub-group analyses revealed better efficacy of escitalopram compared with citalopram, in particular in patients with severe MDD. Consequently a head to head trial specifically designed to study the efficacy and tolerability of escitalopram compared with citalopram in French outpatients suffering from major depressive

disorder, under the prior hypothesis that escitalopram would prove superior to citalopram was undertaken. This study confirmed this prior hypothesis, and showed that escitalopram was indeed more than just half of citalopram.

SO 0403. Are antidepressants equally effective in severe depression?

Depression is a disabling illness associated with considerable comorbidity, risk of suicide, and adverse social consequences. The reported lifetime prevalence for Major Depressive Disorder (MDD) in the United States is 16.2%, with rates up to 21.3% in women and 12.7% in men. Although antidepressants are among the most prescribed therapeutic agents worldwide, recent reviews highlight the significant number of depressed patients who fail to achieve a response and the even greater percentage who fail to achieve remission; this is particularly true for patients suffering from severe depression. Several antidepressants have been studied in the treatment of severe depression: these include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenergic reuptake inhibitors (SNRIs). Reported response rates (50% reduction in Hamilton Depression Rating (HAM-D) scale $\geq$50%) for these compounds range from 43% to as high as 70%. Escitalopram is a novel SSRI which is distinguished from conventional SSRIs by displaying almost exclusive selectivity for inhibition of serotonin reuptake. Recent pre-clinical data have indicated that escitalopram in addition may have another interaction with the Serotonin Transporter Protein (SERT) which could result in clinical effects different from what is observed with SSRIs and SNRIs. Recently, a meta-analysis including all studies of escitalopram in which an active comparator was included indicated that escitalopram had significantly better effect than comparators in severe depression. This magnitude of this difference seemed to increase with increasing severity of the depression. This has been further supported by a recent prospectively conducted study in a severe MDD patient population.

SO 0404. Time to antidepressive effect – which antidepressant works best?

Although the development of modern antidepressant medications has led to significant advances, there remains a need for agents that result in rapid response and remission. Available drugs for the treatment of depression generally have a delayed onset of action. The goal of treatment should therefore be to alleviate symptoms as early as possible to reduce the overall burden of depression. Claims for more rapid onset of action are frequently met with scepticism. This is partly because the relevant underlying molecular mechanisms are incompletely understood, and partly because of the lack of carefully designed prospective studies specifically designed to address this issue. There is a case for suggesting that novel mechanisms of action of certain medications elucidated in basic research may be responsible for early onset of action in clinical studies. Basic psychopharmacological data have been used, for example, to argue that this is the case for antidepressants such as mirtazapine and venlafaxine. Furthermore, escitalopram binds to a low-affinity site on the serotonin transporter protein, with consequent strengthening of its own binding to the high-affinity binding site that mediates the inhibition of serotonin reuptake, a property that may account for the more rapid onset of action of escitalopram over citalopram in animal models.

In a meta-analytic approach, the hypothesis of escitalopram having an earlier onset of effect in the treatment of MDD compared to other available antidepressants was tested using data from randomised, double-blind, controlled studies comparing escitalopram with fluoxetine, paroxetine, sertraline or venlafaxine XR.

SO 05. Symposium: Sexuality

SO 0501. Sexual dysfunction with antidepressants

D. Baldwin
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The term sexual dysfunction describes a disturbance in sexual desire and in the psychophysiological changes that characterise the normal sexual response cycle, that causes marked personal distress and interpersonal difficulty. Epidemiological studies indicate that sexual dysfunction is common in the general population, but more common in depressed individuals in community settings and clinical samples. Most antidepressant drugs have adverse effects on sexual function, but accurate identification of the incidence of treatment-emergent dysfunction has proved troublesome, and most investigations of sexual dysfunction associated with antidepressants have one or more methodological flaws. There may be some advantages for bupropion, moclobemide, nefazodone and reboxetine over other antidepressants. Many approaches have been adopted for management of patients with sexual dysfunction associated with antidepressant treatment, including waiting for the problem to resolve; behavioural strategies to modify sexual technique; individual and couple psychotherapy; delaying the intake of antidepressants until after sexual activity; reduction in daily dosage; 'drug holidays', use of adjuvant treatments, and switching to a different antidepressant.

SO 0502. Is there a way to improve sexual dysfunction in depression?

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Sexuality is an elementary need of human life. In this aspect sexual dysfunction has a negative effect on quality of life. Social taboos still make this a difficult subject for people to discuss. The differences of women's and men's sexuality lead to different forms of sexual dysfunction. Sexual dysfunction in men is much more reduced on functional processes; impaired erection can exist without influencing other normal sexual functions. On the other hand, women rarely suffer from isolated sexual dysfunctions. Sexual differences between women and men also play a role in depressive reactions. Up to 90% of the depressive patients are suffering from reduced interests in sexual activity. Because of the complex interaction between psychosocial, biological and pharmacological

aspects, the classification of sexual dysfunction is more difficult. The group of antidepressants with strong serotonergic properties exhibits the highest rates of sexual disturbances. They are missing more or less within substances with postsynaptic Serotonin 2- Receptorblokade or α-adrenolytic Component. Therefore it is very important to identify whether the reduced sexuality is primary based on the depressive symptomatology or may be a side-effect of medication. In general, psychotherapy has a good rate of success in improving sexual dysfunction in depression.

SO 0503. Differential impairment of sexual dysfunction with antidepressants

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Current antidepressant medications have comparable effectiveness, but their use is compromised by poor tolerability and low adherence to treatment. Emergence or exacerbation of sexual dysfunction is recognised as a potential side-effect across all classes of antidepressants (MAOIs, TCAs, SSRIs, SNRIs and newer antidepressants).[1,2] Orgasmic, erectile and ejaculatory dysfunction have all been reported with TCAs and MAOIs.[3] The most common symptoms of sexual dysfunction reported by men and women with SSRIs are diminished libido, delayed or absent orgasm, arousal difficulties, erectile and ejaculatory dysfunction.[4] Agomelatine is the first melatonergic antidepressant being a potent agonist of melatonin receptors with 5-HT2C antagonist properties. Agomelatine 25 mg/day has been shown to be effective in Major Depressive Disorder (MDD) with a good safety and tolerability profile.[5] In the course of its development, agomelatine did not appear to be associated with sexual dysfunction. The Arizona Sexual Experience scale (ASEX) was used in short-term placebo controlled studies and the pooled analysis over a 6-week period showed that agomelatine-treated patients experienced little sexual dysfunction (3%) in comparison with patients treated by placebo (8.6%). The effect of agomelatine 50 mg on sexual function was compared with venlafaxine 150 mg in a specific study using the Sex Effects (SEX-FX) scale in remitted MDD patients after 12 weeks of treatment. The study outcomes showed a comparable antidepressant efficacy between agomelatine and venlafaxine with 78 of 137 (57%) agomelatine and 83 of 140 (59%) venlafaxine treated patients who achieved remission. Significantly fewer remitters experienced sexual dysfunction in the agomelatine group than in the venlafaxine group measured on desire-arousal ($p < 0.05$) and orgasm ($p < 0.01$) dimensions. Overall, agomelatine offers a very favourable profile of sexual function.

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SO 0504. Drug treatment of premature ejaculation

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Until the 1990s, a major problem of drug treatment studies of premature ejaculation was the absence of well-controlled studies. However, in recent years methodology has been improved by introduction of the intravaginal ejaculation latency time (IELT) as a standardized measure of the ejaculation time, the use of a stopwatch, a baseline period, and a quantified definition of premature ejaculation. The introduction of the selective serotonin reuptake inhibitors (SSRIs) meant a revolutionary change in the neurobiological understanding of and drug treatment of lifelong premature ejaculation. A meta-analysis of 35 SSRI and clomipramine studies has shown that daily treatment with paroxetine exerts the strongest ejaculation delay. Interestingly, both animal and human studies have shown that of all SSRIs daily treatment with fluvoxamine has the least ejaculation delaying effect. Sexual psychopharmacological research has provided evidence that premature ejaculation is highly associated with central serotonergic neurotransmission. In addition, neuroanatomical studies have shown that specific centers in the brain mediate the ejaculation process. Moreover, brain imaging studies demonstrated that ejaculation is associated with dopamine release in the meso-diencephalic region. By applying the 0.5 and 2.5 percentiles as medically accepted standards of disease definition on stopwatch data of the IELT values in a multi-national random sample of IELT values, Waldinger et al. have proposed to define premature ejaculation as a neurobiological dysfunction with an unacceptable increase of risk to develop sexual and psychological problems anywhere in lifetime, and showed that IELT values of less than 1 minute may be considered as symptoms of ejaculatory dysfunction.

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SO 06. Symposium: SNRIs – all for one and one for all?

SO 0601. SNRIs – Fruit of a logical evolution of antidepressant action

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Although considerable progress has been made in improving the tolerability of antidepressant drugs, the classical tricyclic antidepressants (TCAs) are still the standard for efficacy. The selective serotonin reuptake inhibitors

(SSRIs) are much better tolerated than the TCAs but their antidepressant efficacy is, at best, equivalent and probably inferior to the TCAs in many situations. The introduction of the SSRIs naturally focused both fundamental and clinical research effort on the role of serotonin in the pharmacogenesis and pharmacotherapy of depression. More recently the probable role of noradrenaline has been 'rediscovered' and increasingly both serotonin and noradrenaline dysfunctions are seen as fundamental to depressive illness. The therapeutic importance of this has been underlined by studies showing the increased antidepressant efficacy obtained when selective serotonergic drugs have been used in conjunction with selective noradrenergic drugs. The development of the new class of serotonin and noradrenaline reuptake inhibitors (SNRIs) was a logical extension of these ideas. Compounds of this class, which currently comprises venlafaxine, milnacipran and duloxetine, act to inhibit the reuptake of both monoamines with no direct actions at postsynaptic receptors. Comparative studies against SSRIs with each of the SNRIs as well as large meta-analyses show that SNRIs have an efficacy which is generally superior to that of the SSRIs and equivalent to the TCAs with a distinctly improved tolerability compared to these latter drugs. By definition, all three members of the SNRI class have actions on both serotonin and noradrenaline. The three compounds do not all have equal potency for both transmitters. Venlafaxine has a 30-fold higher affinity for serotonin than noradrenaline while duloxetine has a 10-fold selectivity for serotonin. Only milnacipran is balanced between the two neurotransmitters with an approximately equal potency for the inhibition of reuptake of serotonin and noradrenaline, both in vitro and in vivo.

SO 0602 SNRIs – A new generation of treatment for anxiety disorders

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A variety of agents are currently used to treat the different anxiety disorders. Benzodiazepines, such as diazepam, are still preferred by some for the treatment of acute anxiety, with the advantage of a rapid onset of action, but they are less suitable for long-term treatment owing to their potential for memory disturbances, sleepiness, lethargy, physical dependence and withdrawal. Compounds acting on monoamine neurotransmission are more suitable in the treatment of long-term or chronic anxiety disorders. Tricyclic antidepressants, such as imipramine, and monoamine oxidase inhibitors have been shown to be effective anxiolytics, but their side-effects and safety concerns have limited their use. The probable role of disturbed serotonergic neurotransmission in anxiety is widely accepted and is the theoretical basis for the use of serotonergic agents such as the 5-$HT1_A$ receptor partial agonist, buspirone, and the selective serotonin reuptake inhibitors (SSRI), such as sertraline and paroxetine, which have largely replaced the earlier antidepressants.

There is clear evidence for decreased serotonergic function in anxiety as well as in depression. Studies of patients with anxiety disorders show reduced levels of serotonin in cerebrospinal fluid (CSF) as well as reduced serotonin transporter binding. The role of noradrenaline in the control of anxiety is less well understood, although there is considerable evidence to suggest that a disturbance of noradrenergic neurotransmission may also contribute to the symptoms of anxiety. Noradrenaline modulates the activity of brain regions such as the amygdala which are associated with anxiety. In addition, anxiety states are associated with increases in the metabolite of noradrenaline, 3-methoxy-4-hydrophenylglycol (MHPG), and hypersecretion of noradrenaline in plasma and CSF. It appears likely that modulation of both serotonin and noradrenaline systems by dual-reuptake inhibitors may prove to be an advantage in the treatment of anxiety disorders. The serotonin-noradrenaline reuptake inhibitors (SNRIs), venlafaxine, milnacipran and duloxetine, are efficacious in relieving anxiety symptoms within depression, and some have proven efficacy in certain anxiety disorders. Initial studies suggest that dual acting agents may have an advantage over selective reuptake inhibitors in certain anxiety disorders, such as post-traumatic stress disorder (PTSD), and in patients with comorbid anxiety and depression.

SO 0603. SNRIs – New hope in the treatment of chronic pain

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Depression and painful symptoms occur frequently together. Over 75% of depressed patients report painful symptoms such as headache, stomach pain, neck and back pain as well as non-specific generalized pain. In addition, World Health Organisation data have shown that primary care patients with chronic pain have a four-fold greater risk of becoming depressed than pain-free patients. Increasingly, pain is considered as an integral symptom of depression and there is evidence to suggest that pain and depression may arise from a common neurobiological dysfunction.

Serotonergic cell bodies, in the raphe nucleus, and noradrenergic cell bodies in the locus coeruleus send projections to various parts of the brain, where they are involved in the control of mood, movement, cognitive functioning and emotions. In addition both serotonergic and noradrenergic neurons project to the spinal cord. These descending pathways serve to inhibit input from the intestines, skeletal muscles and other sensory inputs. Usually, these inhibitory effects are modest, but in times of stress, in the interest of the survival of the individual, they can completely inhibit the input from painful stimuli. A dysfunction of the serotonergic and noradrenergic neurons can thus affect both the ascending and descending pathways resulting in the psychological symptoms of depression and somatic pain symptoms such as chronic pain, fibromyalgia, non-cardiac chest pain, or irritable bowel syndrome.

In view of this, it is not surprising that tricyclic antidepressants have been a standard treatment of chronic pain for many years. In contrast and in spite of their improved tolerance, SSRIs do not appear to be particularly effective in the treatment of pain. Recently, open and controlled trials with selective serotonin and noradrenaline reuptake inhibitors such as venlafaxine, milnacipran and duloxetine, suggest that these compounds may be more effective in relieving pain than selective inhibitors of serotonin reuptake. Wherever valid comparisons have been made the newer dual action drugs appear to be as effective as the tricyclic and considerably better tolerated. Dual action

antidepressants may thus soon become the new standard treatment of chronic pain whether associated with depression or not. In addition, SNRIs may also have a role in modulating neurogenesis and other neuroplastic changes in the central nervous system, thereby leading to more complete recovery in patients suffering from the symptoms of depression or chronic pain.

SO 0604. SNRIs – Vive la différence!

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The three SNRIs have a common mechanism of action: the inhibition of the reuptake of serotonin and noradrenaline. Evidence available to date suggests that all three have similar potential in the treatment of depression, anxiety and chronic pain, although the extent of the demonstration of this varies considerably between the members of the class. All three differ from the tricyclic antidepressants in as much as they are devoid of interactions at the postsynaptic receptors responsible for many of the side-effects of the older drugs. As with other dual acting antidepressants, there is evidence for each of the SNRIs that they may produce superior antidepressant efficacy, at least in more severely depressed patients. In spite of these similarities, the three compounds differ considerably in their relative affinities for the reuptake transporters of serotonin and noradrenaline. Comparative *in vivo* animal data demonstrate that venlafaxine is predominantly an inhibitor of the reuptake of serotonin at low doses and progressively inhibits the reuptake of noradrenaline as the dose is increased. There is no clear evidence that it blocks dopamine reuptake in vivo. Duloxetine also inhibits preferentially the reuptake of serotonin at low doses and affects noradrenaline reuptake as the dose is increased. Milnacipran inhibits the reuptake of both monoamines at similar potencies in vitro and, in vivo, has a preferential action on the reuptake of noradrenaline. These effects will be described using mainly in vivo electrophysiological studies, but also microdialysis experiments, because in vitro data have been at times misleading. Clinical experience with the three SNRIs is widely different and few clinical studies have compared the SNRIs among themselves. At present, there is no evidence to suggest any difference in effectiveness as antidepressants, anxiolytics or anti-pain agents between the three compounds. There may be differences in their tolerability, but equivalent doses on the inhibition of reuptake of serotonin and noradrenaline remain to be established. This issue will be addressed using whole blood 5-HT content determinations and the tyramine pressor test in humans to evaluate serotonin and noradrenaline reuptake potency of these drugs, respectively. Further comparative studies are required before the differences between members of the SNRI class can be fully evaluated.

SO 07. Symposium: Treatment update in GAD

SO 0701. Escitalopram in the anxiety disorders

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The pharmacological management of the various anxiety disorders has undergone a marked transformation over the past decade. The benzodiazepine tranquillisers have fallen out of favour because of doubts regarding long-term efficacy, a range of unwanted effects such as psychomotor and cognitive impairment, and concern over dependence. In their place, the SSRIs have become established as effective and safe medications for most anxiety disorders. Many SSRIs have been licensed for a variety of indications. Most recently, escitalopram, the active moiety of the older drug, citalopram, has been shown to be both highly effective and well tolerated in depressive disorders. Escitalopram has also been extensively evaluated in several anxiety indications including panic disorder, generalised anxiety disorder and social anxiety disorder, both in comparison to placebo and to active comparators such as paroxetine. Representative examples from this database will be presented. In general escitalopram is effective in these indications, without tolerance of effect, and it has a low incidence of side effects, including discontinuation symptoms. In some studies, it proved superior to the comparator SSRI. In summary, SSRIs are now accepted as the treatment of choice in the treatment of various anxiety disorders, and are replacing the benzodiazepines. Of the SSRIs, the data supporting the favourable risk/benefit ratio of escitalopram are the most comprehensive.

SO 0702. Abstract unavailable at time of printing.

SO 0703. A critical review of CBT in GAD

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Generalized anxiety disorder is characterized, according to DSM-IV, by physical symptoms and apprehensive worry, lasting for at least six months. It follows a chronic course with low rates of remission. There is evidence that, among the anxiety disorders, GAD is likely to be the most resistant to both psychological and medical interventions. Clinical guidelines for anxiety disorders were published in December 2004 by the British National Institute for Clinical Excellence (NICE). They conclude that in the longer-term care of individuals with GAD the interventions which have evidence for the longest duration of effect, in descending order, are: psychological therapy, pharmacological therapy (antidepressant medication), and self-help (bibliotherapy based on CBT principles). However, the NICE guidelines recommend that the preference of the person with GAD should be taken into account. With regard to psychological interventions the guidelines clearly recommend that cognitive behavior therapy (CBT) should be used, with an optimal range of duration from 16 to 20 hours total. There have been about 15 controlled studies on the efficacy of psychotherapy for GAD. Meta-analyses suggest the superiority of CBT to other psychological treatments. More recent and methodologically better CBT studies have shown an improvement on the Hamilton Anxiety Scale (HAM-A) ranging from 38 to 65% with effect sizes ranging from 1.1 to 3.2. The waiting control groups showed only small improvements or even a deterioration. Results also suggest that CBT generally results in maintenance of gains for periods up to one year, whereas response after medication discontinuation is attenuated. Available CBT programs are usually integrated treatment packages, including some version of cognitive

therapy to address worry-related thoughts and beliefs as well as relaxation techniques. More recent programs have included an exposure component that derives from conceptualizations of worry as a negatively reinforcing activity that prevents distressing emotional arousal. The metacognitive model of worry refers to the patient's belief that worry prepares, protects, and prevents bad things from happening. In some cases, exposure is designed to provide opportunities for practicing coping skills and desensitizing anxiety, whereas in other cases it is conducted according to an extinction paradigm.

SO 0704. Is there an algorithm for treatment of generalized anxiety disorder (GAD)?

B. Bandelow
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Generalized anxiety disorder (GAD) can effectively be treated with a number of psychopharmacological drugs and with cognitive behavior therapy (CBT). Recommendations for the pharmacological treatment of GAD are based on available randomized, placebo- or comparator-controlled clinical studies. Selective serotonin reuptake inhibitors (SSRIs) and the selective serotonin reuptake inhibitor (SNRI) venlafaxine are the first-line treatments for GAD. Tricyclic antidepressants (TCAs) such as imipramine are equally effective, but they are less well tolerated than the SSRIs. Buspirone may be an alternative. In treatment-resistant cases, benzodiazepines may be used when the patient does not have a history of dependency and tolerance. A new option for the treatment of GAD is pregabalin, a novel compound acting at the alpha-2-delta subunit of the voltage-dependent calcium channels. This drug has been shown to be effective in a number of clinical trials in GAD. There have been no systematic investigations of treatment-refractory patients with generalized anxiety disorder; however, an algorithm for the treatment of non-responders to conventional therapy will be presented.

Friday 11 November

SO 08. Symposium: Antidepressants and pain

SO 0801. Fibromyalgia and antidepressants

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Fibromyalgia syndrome (FMS) is a chronic disease of widespread and debilitating pain, the cause of which is unknown and whose risk factors are poorly understood. It occurs frequently in the general population where it is often co-morbid with other rheumatoid and pain disorders as well as psychiatric disorders such as anxiety and depression. Several types of drugs, including antiepileptics and antidepressants, are used to treat FMS, but none are specifically approved for this indication. The strong comorbidity of FMS with depression led to the early use of tricyclic antidepressants (TCAs), particularly amitriptyline, which have become one of the most common treatment strategies. It is only relatively recently, however, that their efficacy has been demonstrated in controlled trials. Interestingly the effectiveness of antidepressants appears to be independent of the presence of co-morbid depression. Because of the poor tolerability of the tricyclics, the newer antidepressants have been widely tested in FMS. The selective serotonin reuptake inhibitors (SSRIs) and the reversible monoamine oxidase inhibitors (RIMA) do not seem, in general, to be particularly helpful. The serotonin and noradrenaline reuptake inhibitors (SNRIs), however, appear to offer hope of a treatment as effective as the TCAs accompanied with a better tolerability. Duloxetine and milnacipran have been shown in placebo-controlled trials to offer significant relief to patients suffering from FMS. The effectiveness of the SNRIs as well as other dual acting antidepressants, such as mirtazapine, but not the SSRIs implies that a dysfunction of both serotonergic and more particularly noradrenergic neurotransmission probably exists in FMS. Thus, not for the first time, a new class of drugs may not only bring relief to patients but may also be helpful to psychopharmacologists trying to untangle the causes of FMS.

SO 0802. Duloxetine and the control of pain

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Background/Aims: Serotonin (5-HT) and norepinephrine (NE) have been implicated in the etiology and treatment of depression. However, these two monoamines are present in descending pathways in the spinal cord that are involved in the perception of pain, particularly chronic pain, that may be the result of central sensitization. Painful physical symptoms are also associated with depression in 40%–50% of the depressed patients. Duloxetine, a potent and selective dual 5-HT and NE reuptake inhibitor (SNRI), has been approved in both the European Union and the United States for the treatment of major depressive disorder (MDD) and diabetic peripheral neuropathic pain (DPNP). The aim of this presentation is to review the data from all randomized placebo-controlled clinical studies on duloxetine in MDD with a focus on pain symptoms as well as on pain disorders, including both DPNP and fibromyalgia syndrome (FMS), and to elucidate its therapeutic potential in the control of pain.
Methods: Review of data from ten clinical trials in patients with MDD, three trials in DPNP and two trials in FMS. The primary outcome measure for MDD was the $HAMD_{17}$ total score and primary pain measures were used for most of the other studies.
Results: Duloxetine was superior to placebo on the a priori primary outcome measure(s) in six of ten MDD studies, three of three DPNP studies, and one of two FMS studies. Outcomes on multiple secondary measures were positive in three of four remaining MDD studies and the other FMS study.
Conclusions: Duloxetine is effective for the treatment of MDD, including painful physical symptoms, and for the treatment of DPNP and FMS. Efficacy in these pain disorders further reinforces that the effect of duloxetine in painful physical symptoms of depression is independent of its effects on emotional symptoms of MDD. This is consistent with its mechanism of action as an SNRI, presumably working on emotional symptoms within forebrain regions and pain symptoms within the spinal cord.
Conflict of Interest/Disclosure: The studies were funded by, and the authors are employees of, Eli Lilly & Co.

SO 0803. Abstract unavailable at time of printing.

SO 0804. Pregabalin and the treatment of neuropathic pain

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Pregabalin is a novel compound approved for the treatment of peripheral neuropathic pain (NeP) in adults by the EMEA in 2004. The drug acts by binding to the α2δ subunit of voltage gated calcium channels, reducing neurotransmitter release from hyperexcited neurons. The results of ten placebo-controlled trials have demonstrated that pregabalin provides significant pain reduction in patients with painful diabetic neuropathy and post-herpetic neuralgia. There is a clear dose response for the pain reduction over the range of 150 mg/day to 600 mg/day. Significant benefits have also been seen in secondary endpoints such as pain-related sleep interference and patient global impression of change. Open label extension studies have demonstrated the maintenance of the effect for periods up to two years. In one open label study, pregabalin has been shown to be effective in refractory patients who had failed to obtain adequate pain relief from other NeP treatments including gabapentin. Pregabalin has also demonstrated efficacy in the treatment of central neuropathic pain due to spinal cord injury. The most commonly observed side effects of pregabalin include dizziness and somnolence, which are typically mild-to-moderate in severity and tend to resolve with continued treatment. In addition to the robust efficacy demonstrated in the treatment of neuropathic pain, pregabalin has also demonstrated efficacy in the treatment of anxiety and also as adjunctive therapy for partial seizures. The presentation will review the data on the efficacy and tolerability of pregabalin in the treatment of NeP, as well as discuss how the α2δ activity in hyperexcited neurons may contribute to its effectiveness across a number of indications.

SO 09. Symposium: Diagnosis and treatment of dementia

SO 0901. Brain-imaging diagnostic and outcome markers in Alzheimer's disease – ready as surrogate parameters?

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Markers of disease regression or progression or detection of therapeutic effects are used extensively in medical research and patient care. However, in neurodegenerative disorders, such as dementia of Alzheimer's type, structural neuroimaging has until recently been seen solely as a tool to exclude treatable causes of dementia. Now, there is evidence that structural brain imaging as magnetic resonance imaging allows a more accurate diagnosis of different forms in established dementia, and may enhance the possibility to detect patients at risk for Alzheimer's disease or preclinical stages of Alzheimer's disease. To be accepted as a surrogate endpoint in clinical trials with antidementia drugs, links have to be established to show that imaging parameters, e.g. magnetic resonance imaging, are related to the desired clinical outcome and disease modification of the underlying pathogenetic process. The requirements for results from brain imaging studies to be accepted as surrogate endpoints will be presented and discussed from a regulatory point of view.

SO 0902. Designs for demonstrating efficacy in age-associated memory impairment (AAMI)

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Age-associated memory impairment (AAMI) is universal, being present in species that range from Man to fruit fly. This given, what are the issues that have hindered development of new therapies for this indication? Among those to be considered are: (1) How can the condition be defined in a widely accepted, reliable and valid manner? (2) What should the clinical trials look like? (3) How best to measure cognition (especially memory and learning), that can define the severity of the condition and accurately measure change? (4) What instruments can be used to demonstrate clinical relevance (the "so what" question)? (5) Is it socially and medically acceptable to treat a normal aging process? Since the bottom line for all these issues is in the affirmative, the author will suggest AAMI is an entity that should be enshrined in our nosology (DSM V and ICD11) and that regulatory authorities should be prepared to grant labeling for this indication.

SO 0903. Obstacles in demonstrating efficacy in minimal cognitive impairment (MCI)

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The aim of this presentation is to discuss why it is so difficult to find a useful therapeutic intervention for MCI. Several reasons will be put forward and discussed.
The well established Peterson criteria generated a consensus for a while, but that was challenged by the proposition of a number of variants to the concept: amnesic MCI dysexecutive MCI, vascular MCI, among others. The first obstacle to the establishment of the efficacy of a therapeutic intervention is the absence of a well-characterized, relatively homogeneous, widely accepted clinical entity. The second difficulty is the lack of a clear definition of what is a desirable outcome. The outcome more frequently pursued has been "conversion to dementia". Conceptually this is a very interesting target but there are a number of practical caveats in it, namely the operational definition of conversion, the use of supportive/complementary outcomes like imaging and their validation. An alternative to "conversion to dementia" is the symptomatic improvement of MCI itself. Here, issues such as clinical relevance and sensitivity of the measurement tools take precedence. Finally, but of utmost importance, interventions should be more than "biochemical toys". They should be able to produce a beneficial clinical change. The absence of such interventions is the current most serious obstacle. Three main obstacles will be discussed: the characterization of the clinical entity, the potential interventions and the therapeutic goals.

SO 0904. New strategies in the treatment of BPSD in dementia

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Background: Half of patients with severe Alzheimer disease (AD) develop behavioural and psychological symptoms of dementia (BPSD). In fact, BPSD are the number one cause of long-term hospitalisation in patients who suffer from AD. Current treatment options are of limited benefit, sometimes accompanied by serious side-effects. The aim of our studies was to test new treatment options.
Methods: In two open-label pilot studies, six in-patients and seven out-patients who met the NINCDS-ADRDA criteria for probable AD (late stages) and suffering from BPSD, were treated with either 2.5 mg dronabinol for two weeks or 3 mg melatonin for three weeks, respectively. Patient motor activity was objectively measured over the whole study period using wrist-worn actigraphy (Actiwatch, Cambridge Neurotechnology).
Results: Compared to baseline, donabinol led to a rapid reduction in nocturnal motor activity ($p = 0.028$). The findings were corrobarated by improvements in neuropsychiatric inventory (NPI) total score ($p = 0.027$) as well as in subscores for agitation, aberrant motor, and night-time behaviours ($p < 0.05$). Again, compared to baseline, melatonin led to a gradual reduction in nocturnal motor activity ($p = 0.018$). Before the study, full hospitalisation was planned for five of the seven out-patients, but was no longer necessary in three patients after melatonin treatment. In both of the studies, no side-effects were observed.
Conclusions: Both treatment options – melatonin and dronabinol – could become safe new treatment options for behavioural and psychological symptoms of dementia (BPSD).

SO 10. Symposium: New insights in treatment resistant depression (TRD)

SO 1001. The role of physical symptoms in depression and in achieving remission

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The proportion of depressed patients treated according to guidelines is very low, ranging from 12% to 25% in various studies. One of the reasons is a low recognition rate, due in large part to a somatic presentation of depressed patients to their doctor. Indeed the number of somatic symptoms present in depressed patients, when systematically asked by an interviewer, is even higher (4.8) than in patients consulting for physical reasons (2.8). This figure could be explained by the high comorbidity (about one third) observed between physical diseases and depression; however, when assessing depressed patients without physical diagnosis the number of somatic symptoms remains 4.6. It has been suggested that patient may deny the existence of a psychological condition, or may express their symptoms physically as a consequence of difficulty express them psychologically. In fact, only 10% spontaneously consult for psychological reasons while one third do so because of painful symptoms and 40% because of other physical symptoms. Contrarily to the expectations of the different theories, the proportion who deny the psychological nature of their disorder is low (about 10%). Even more interesting, the tendency of patients to complain physically is not correlated with a low psychological expression, but on the contrary both psychological and physical complaints are low or high depending on cultural and personal characteristics. Therefore, it becomes very clear that the unexplained physical symptoms are just part of depression. This is of great importance since it has to be taken into account for diagnosis and treatment. In addition, numerous data show that for a long term remission the absence of residual symptoms is necessary, even if these symptoms are mild. Since these symptoms are typically of a depressive nature, it is necessary to take into account the full range of the symptomatology, including physical symptoms, in order to achieve the best possible treatment.

SO 1002. European program on TRD

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Outcome studies have demonstrated that approximately one third of patients treated for major depression do not respond to antidepressant pharmacotherapy, and has led to the concept of Treatment Resistant Depression (TRD). In an effort to clarify this concept, Thase and Rush[1] proposed a model of staging the various levels of resistance in TRD. An alternative definition has been proposed by Fava et al.[2] In the European Union's Committee for Proprietary Medicinal Products (CPMP) guidelines, TRD is defined as follows: "a patient is considered therapy resistant when consecutive treatment with two products of different classes, used for a sufficient length of time at an adequate dose, fail to induce an acceptable effect".[3]
Beyond the issue of definition and treatment guidelines, the identification of predictors of treatment resistance to antidepressants remains open and needs further investigation. To our knowledge, very few studies has primarily investigated specific clinical predictors of resistance, meaning factors associated with *multiple failures* to respond to adequate antidepressant treatments during the same depressive episode. In an attempt to investigate potential clinical predictors of resistance, we collected within a European multicentre study a large cohort of depressed patients systematically screened for all antidepressant treatments received during their last depressive episode. The depressive episode was considered as *resistant* in case of nonresponse to at least two adequate consecutive antidepressant trials administred during the last episode.
702 subjects were considered for analysis, including 356 patients considered as resistant and 346 considered as non resistant. Diagnoses were obtained using the MINI. A HAMD 17 items was obtained for each patient at inclusion. In addition, each patient was evaluated using a questionnaire investigating demographic and psychosocial characteristics, data on the current major depressive episode, including psychiatric and somatic comorbidities, personal and family history of psychiatric disorders and data on current and past antidepressant treatments. A specific questionnaire on treatment history was developed for the study.

A two-step logistic regression model was applied for the analysis of predictive factors of resistance. This analysis allowed for the identification of predictive variables, using resistance/non resistance as dichotomic dependent variable. A backward elimination logistic regression was applied, eliminating terms with $p < 0.05$ and allowing for the selection of the most discriminative predictive factors, according to p-values and odd ratios (OR). Among the clinical features investigated, using a two-step logistic regression model, five predictive factors were identified: *comorbid anxiety disorder* ($p < 0.001$, $OR = 5.2$), *current suicidal risk* ($p = 0.05$, $OR = 2$), *severe intensity of the episode* ($p = 0.04$, $OR = 2.1$), *melancholic features* ($p = 0.03$, $OR = 2.5$) and n*onresponse or unsatisfying response to first antidepressant treatment lifetime* ($p = 0.003$, $OR = 4.4$).
In conclusion, our findings provide a set of important and reliable predictive variables for treatment resistance which can be easily applied at the clinical level. The nature of these variables should carefully be identified for each patient treated with an antidepressant for a major depressive episode.

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SO 1003. Molecular basis of treatment resistant depression (TRD)

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Treatment modalities for depressive disorders include e.g. phamacological, psychotherapeutic, psychosocial and other (biological) strategies (e.g. electro-convulsive therapy). With respect to the pharmacological approaches, the molecular basis of favourable treatment response is studied more intensively in recent years. The response to antidepressant drug therapy is determined by the interplay of various pharmacokinetic and pharmacodynamic mechanisms, influenced by several genes.
This presentation will give an overview on pharmacogenetic studies focused on drug targets (not so much on drug-metabolizing enzymes, drug transporters or post-target events). We currently know little of the molecular basis of TRD. A computerized literature search on the molecular basis of TRD performed in summer 2005 did not reveal major results. On the other hand the European Program on TRD described in the present symposium is one first major step foreward to understand the molecular basis of treatment resistance. First results of the study will be available shortly and will be presented during the symposium. The studies reporting on pharmacogenetic markers that affect antidepressant pharmacodynamics will be reviewed. With respect to the serotonin transporter gene we have some results showing that an insertion/deletion polymorphism in the promotor region of the gene (short and long allele forms) shows association to response to some antidepressants (SSRIs). But the interpretation of results is difficult, because in different populations the effect was divergent. Other studies focused e.g. on the norepinephrine transporter gene, the tryptophan hydroxylase gene, the serotonin 1A, 1B and 2A receptor genes, the catechol-O-methyltransferase gene, the monoamine oxidase A gene, the brain-derived neurotrophic factor and downstream effector molecules, like guanine nucleotide binding proteins (G proteins). New developments in biological techniques are ongoing and hopefully it will be possible to predict treatment resistance or favourable treatment response before starting a specific treatment regimen in the near future. By doing this, the duration of the course of illnesses will be shorter and the suffering of our patients will be reduced.

SO 1004. Brain mechanisms of TRD

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Treatment resistant depression (TRD) is considered if two or more adequate monotherapies fail to produce clinical antidepressant response. Among other reasons, the clinical and biological heterogeneity this definition of TRD encompasses makes a uniform characterization of the biological basis of TRD difficult and maybe impossible. In addition, a purely clinical definition of depression per se comprises a heterogenous set of neurobiological underpinnings of the same nosological entity. For example, recent work shows that early adverse events during development can contribute to the risk for depression, modulate the neurobiological underlying changes of depression and have a role in response to appropriate treatment. One option to better characterize the neurobiology of TRD might be a more comprehensive classification of depression, which includes endophenotype information. It is is suggested that this will help employing a more specific differential indication of antidepressant therapy. This is particularly relevant considering recent neuroimaging work, which suggests that clinical response to antidepressant treatment is accompanied by converging changes in brain activity – independent of whether pharmacotherapy or psychotherapy was used.

SO 11. Symposium: Long-term treatment of bipolar disorder

SO 1101. Are atypicals mood stabilisers?

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Traditionally, to be called a mood stabiliser a medication had to show both acute and prophylactic efficacy in mania as well as bipolar depression. Applying this restrictive definition lithium may be the only substance that could claim to fulfil such criteria. However, this definition would neglect that there are several useful medications that work very well on one pole of the illness and therefore may be a favourable choice for those patients who – for example – predominately suffer only from recurrent manic episodes or recurrent depressed episodes. A new concept distinguishes between mood stabilisers "from above" (Class A) meaning antimanic and mania- prophylactic properties

and mood stabilisers stabilising "from below" (Class B) which are more helpful in treating and preventing depression.[1] At least class A criteria for mood stabilisation appear to be satisfied by several atypical antipsychotics. Controlled studies with olanzapine and aripiprazole support both acute antimanic and mania- prophylactic properties of these substances.[2] Deducing from clinical experience and open studies this is likely to be true also for other atypical antipsychotics. However, in addition some atypical antipsychotics as olanzapine[3] and quetiapine[4] appear to have at least acute antidepressant efficacy. Prophylactic efficacy against depression has been demonstrated so far only for olanzapine in patients who were prior responsive to this substance against acute mania. Thus, atypical antipsychotics may not yet fulfil such a broad definition of mood stabiliser as lithium does; however, with more controlled data accumulating it appears justified to assume that they show promise beyond the acute treatment of mania.

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SO 1102. Antidepressants in bipolar depression

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Bipolar depression has the reputation of being difficult to treat, because it tends to be resistant to drug therapy, and because antidepressant medication may trigger manic episodes or rapid cycling. Consequently, some guidelines encourage clinicians to avoid prescribing antidepressant drugs to patients with bipolar disorder. There is a lack of consensus in the guidelines regarding treatment of bipolar depression. This presentation demonstrates that conventional antidepressant drugs do improve bipolar depression, and that the risk of triggering mania has been systematically exaggerated particularly in the North American literature. Selective serotonin re-uptake inhibitors (SSRIs) carry a smaller risk than broader-acting drugs, such as most tricyclic antidepressants and the serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine. Lithium and lamotrigine may also have antidepressant efficacy in bipolar depression. In addition certain antipsychotic drugs (olanzapine and quetiapine) have antidepressant efficacy in bipolar depression. Furthermore the combined use of an antidepressant with an anti-manic drug, such as lithium or an atypical antipsychotic, can improve depression with only a small risk of triggering mania. In prophylaxis, lithium, lamotrigine and olanzapine may all be useful in preventing recurrences of bipolar depression; certain patients may also require long-term treatment with an antidepressant. Psychoeducation, while being most important in preventing recurrences of mania, may also be of value in preventing recurrences of bipolar depression.

SO 1103. Brain stimulation for depression – New methods of brain stimulation with potential in the treatment of refractory major depression

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The awareness of an urgent need for the treatment of patients with severe depression that are treatment refractory is growing in the field of psychiatry. Electroconvulsive treatment, while being highly efficacious, is tainted with an undeserved public stigma, access to it is generally difficult and associated with cognitive side-effects. Therefore, novel methods of brain stimulation have been developed over the past decade. Transcranial magnetic stimulation is a non-invasive method of brain stimulation which is being evaluated for the treatment of major depression for the past decade.[1] Only recently clinically useful parameters seem to have been established.[2] A novel form of this treatment, magnetic seizure treatment (MST) – in which stimulation parameters are reached that can reliably and reproducibly induce therapeutic seizures in the same setting as the one used for electroconvulsive therapy (ECT) – has been developed.[3] Results of a recent randomized, within-subject, double-masked trial comparing ECT and MST in 10 patients indicate that MST appears to have less subjective and objective side-effects, is associated with faster recovery of orientation and is superior to ECT on measures of attention, retrograde amnesia and category fluency.[4] Although ECT has an unparalleled and well-documented efficacy in severe depression, it is associated with cognitive side-effects.[5] MST is currently under study in several centres with respect to its antidepressant efficacy; while its more benign side-effect profile has been established already. Vagus nerve stimulation is an established treatment for refractory partial-complex seizures. Recent data from an open label multi-center pilot study (D01) suggest also a potential clinical usefulness in acute and maintenance treatment of drug resistant major depression. In this study, one third of the 60 patients included reached a reduction of depressive symptoms of 50% or more after 3 months of chronic stimulation.[6] Deep brain stimulation is the stereotaxic placement of unilateral or bilateral electrodes connected to a permanently implanted neurostimulator. Although the mode of action is unknown, the hypothesis is that chronic high frequency (130–185 Hz) stimulation reduces neural transmission through inactivation of voltage-dependent ion channels. Recently, the results of deep brain stimulation close to the subgenual cingulate region cg25 (Brodmann area 25) in six patients with refractory major depressive disorder were reported by Mayberg and colleagues.[7] Although only data from small uncontrolled studies are available, the overall outlook on deep brain stimulation in treatment-refractory patients seems promising.[8] We will review in this paper the current data on brain stimulation therapies for depression and provide an outlook on future developments.

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SO 1104. Abstract unavailable at time of printing.

Poster Abstracts

P 01. MCMI-II personality profile of depressive patients

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Background: Clinicians have for a long time been interested in the relationship between depression and personality disorders. The comorbidity of depressive disorders (major depression and dysthymia) and personality disorders has been well-documented in the literature but to our knowledge few studies have investigated the problem of comorbidity with the relatively new self-report instruments.
Methods: 120 patients who had received a preliminary diagnosis of Major Depression or Dysthymia were recruited from two psychiatric centers and the Structured Clinical Interview for DSM-III-R(SCID) and MCMI-II were used to assess their axis I and axis II disorders.
Results: The majority of depressive patients obtained the 1-2-3-6-8 codetypes on MCMI-II that reflect a blend of schizoid, avoidant, dependent, aggressive and passive-aggressive personality traits or disorders which except for scales 6 (Aggressive personalities) is a similar finding, reported in most studies.
Conclusion: The personality profile of depressive patients reflect an individual with strong needs for dependency, social withdrawal, hypersensitivity to rejection and feelings of anger which are expressed directly or indirectly and against the self or others. The relationship between the 1-2-3-6-8 codetype and depression will allow for greater insight into the need for integrating more specific and comprehensive treatments for dually diagnosed patients.

P 02. Escitalopram for relapse prevention in generalised anxiety disorder

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Background: Escitalopram is efficacious in the acute treatment of generalised anxiety disorder (GAD). The present study investigated the effect of escitalopram in the long-term prevention of relapse in patients who had responded to acute treatment with escitalopram.
Methods: A total of 491 adult patients with a primary diagnosis of GAD (according to DSM-IV criteria) and a Hamilton Anxiety (HAM-A) total score of 20 or more, received 12-week, open-label escitalopram 20mg/day treatment. Of these, 375 patients responded to treatment (HAM-A total score of 10 or less) and were randomly assigned to 24–76 weeks of double-blind treatment with escitalopram 20mg/day (n = 187) or placebo (n = 188). The primary efficacy parameter was the time to relapse, defined as either an increase in HAM-A total score to 15 or more, or lack of efficacy as judged by the investigator.
Results: The results of the primary analysis showed a clear beneficial effect of escitalopram relative to placebo on the time to relapse of GAD (log-rank test, $p < 0.001$). The risk of relapse was 4.04 times higher for placebo- than for escitalopram 20 mg-treated patients ($p < 0.001$). Significantly fewer escitalopram-treated patients relapsed (19%) compared with placebo (56%) ($p < 0.001$). Escitalopram was well tolerated, with placebo levels of withdrawals due to adverse events during the double-blind treatment. The withdrawal rate, excluding relapses, was 21% for both escitalopram and placebo.
Conclusion: Thus, escitalopram was effective in preventing relapse and well tolerated in the long-term treatment of GAD.
Disclosure: C Allgulander has received honoraria from, and has conducted clinical research supported by Lundbeck. I Florea and AKT Huusom are employees of Lundbeck.

P 03. Is nutritional pattern of school children with attention deficit/hyperactivity disorder different from normal subjects?

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Objective: The main objective of this research was to compare the nutritional pattern of school children with attention deficit hyperactivity disorder (ADHD) with that of normal children.
Subjects and Methods: In this research 400 school children aged 7–9 years (200 male and 200 female) from primary schools in the City of Ahvaz (one of the 5 largest cities which located in south-west of Iran) were randomly selected and their parents and teachers completed socio-economic status, food frequency, anthropometric and psychological scoring questionnaires.
Results: Findings showed that there is a significant relationship between parental literacy and the severity of disorder; mothers with higher education and occupation levels had more normal children ($P < 0.01$). Food allergy history among ADHD children was prevalent 2.5 times more than normal subjects. ($p < 0.05$) Breakfast consumption was significantly correlated with lower severity of ADHD in boys ($P < 0.01$) but not girls. On the other hand, more daily sugar consumption increased the severity of disorder in females ($P < 0.001$) but not in males. Drinking tea more than 3 cups a day was associated with increased severity scores of ADHD in boys ($P < 0.05$). Food additives, colors and natural salicylates in daily food sources were not related to severity and symptoms of ADHD.
Conclusion: it seems that breakfast consumption is a healthy habit in schoolchildren which can lessen the disorder and frequent tea and sugar consumption has negative effect on severity of ADHD. Parents also must pay more attention to their children food allergies.

P 04. A randomised trial of escitalopram and paroxetine in the treatment of GAD

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Background: The efficacy and tolerability of escitalopram were compared in a 12-week, randomised, placebo-controlled, double-blind study in generalised anxiety disorder (GAD), using paroxetine as active reference.
Methods: Adult patients with GAD were randomly assigned to treatment with placebo (n = 139), escitalopram 5mg/day (n = 134), 10mg/day (n = 136), 20mg/day (n = 133), or paroxetine 20mg/day (n = 140).
Results: Baseline mean Hamilton Anxiety Scale (HAMA) total score was 27. 86% of patients completed treatment. A significantly better therapeutic effect, based on mean change from baseline in HAMA total score at Week 12, was seen for both 10mg and 20mg escitalopram than for placebo ($p < 0.05$); escitalopram 10mg was significantly ($p < 0.05$) more efficacious than paroxetine. The proportion of patients in remission (HAMA $< = 7$) at Week 12 was significantly greater for escitalopram 5mg (44%), 10mg (48%), and 20mg (43%) than placebo (30%) ($p < 0.05$), and significantly greater for escitalopram 10mg than for paroxetine 20mg (33%) ($p < 0.05$). The incidence of adverse events (AEs) was similar across treatment groups. The AEs that were reported with an incidence >10% in at least one treatment group were nausea, fatigue, headache, insomnia, and anorgasmia.
Conclusion: Escitalopram was efficacious and well tolerated in the 12-week treatment of GAD. Escitalopram 10mg was significantly more effective than paroxetine 20mg.
Disclosure: D.S. Baldwin has received consultancy honoraria from Lundbeck. E. Mæhlum and A.K.T. Huusom are employees of Lundbeck.

P 05. Sertraline in the treatment patients with depression and psoriasis

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Introduction: Psoriasis is a chronic and often painful skin disease that can be difficult to heal and afflicts approximately 3% of the population. The comorbidity of depressive disorders in patients with chronic skin diseases intensifies the pathological skin condition and traditional treatment difficult.
Objective: The aim of the study was to investigate the efficacy and tolerability of sertraline (stimuloton) in treatment patients with chronic depressive disorders suffering from psoriasis.
Methods: The study was carried out in the skin unit of Moscow General Hospital [1]52. It involved 20 patients, 9 female (45%), 11 male (55%), mean age 32.8 years; all were inpatients, suffering at the same time from psoriasis (an acute condition; the duration of illness 9.5 ± 3 yr.) and chronic depressions (dysthymia and recurrent depressive disorders). Diagnosis of chronic forms of depression was established according to ICD-10 criteria (F 34.1; F 33.0; F 33.1). In the study the following rating scales had been used: the Hamilton Rating Scale for Depression (HAM-D-21) [Hamilton M, 1967] and the Clinical Global Impressions scale-Severety of illness (CGI-S) [Guy W, 1976]. Also PASI index (Psoriatic Area and Severity Index) [Fridriksson-Petersson, 1978] had been used for estimating diffusion and manifestation of skin desease before and after traditional treatment of psoriasis in addition with sertraline. Safety measures included vital signs, clinical laboratory testing, electrocardiography (ECG).
Results: The reduction of depression had been defined in all examined patients: 50% and more from the baseline (HAM-D-21: baseline – 21.3 ± 1.2; endpoint – 8.4 ± 2.1; CGI: 4.2 ± 0.2; 1.9 ± 0.2). At the end of the fourth week of treatment a decreasing of PASI index of 50–75% was observed in 16 (80%) patients that can be discussed like much improvement. No modifications were reported in ECG, clinical laboratory tests.
Conclusions: Sertraline (stimuloton) may be useful and and well-tolerated in the treatment of patients with chronic depression and psoriasis.

P 06. Relationship between self-esteem and anxiety among undergraduate students

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Objective: The purpose of the present study was to examine the relationship between self-esteem and anxiety among undergraduate students.
Method: Participants were 571 undergraduate students (247 men and 324 women) from the Islamic Azad University of Azadshahr in Iran. The mean age of the participants was 22.7 years (SD = 4.58) and ages ranged from 18 to 30 years old. All participants completed a questionnaire booklet containing two self-report measures: The Rosenberg Self-Esteem Scale (RSE) and the Spielberger State-Trait Anxiety Inventory (STAI).
Results: The results of the present study demonstrate that: the correlation between self-esteem and student's anxiety is meaningful and negative ($r = -0.303$, $p < 0.01$); the correlation between female student's self-esteem and anxiety is ($r = -0.464$, $p < 0.01$); the correlation between male student's self-esteem and anxiety is ($r = -0.219$, $p < 0.01$).
Conclusions: The present study revealed that a higher self-esteem is associated with a lower level of self-reported anxiety. This research supported previous reports in the literature that self-esteem is related positively to known psychological health.

P 07. Results of a Spanish nationwide cross-sectional study on Major Depression IV: relationship between somatic symptoms, quality of life and resource utilization

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Background: The assessment of somatic symptoms (SS) and their impact on quality of life (QoL) and health resource utilisation (RU) is relevant to establishing clinical

implications in primary care patients with major depressive disorder (MDD).
Aims: To examine the relationships between SS and QoL and RU in primary care patients with MDD.
Method: Data on SS, QoL (Medical Outcomes Study 12-item Short-Form Health Survey: SF-12) and RU (number of hospitalisations within the last year and visits to a doctor in the previous 2 weeks) from 1150 patients with MDD were collected as part of a cross-sectional, multicenter, nationwide epidemiological study involving 79 primary care centers in Spain. Independent factors contributing to diminished QoL and greater RU were identified by linear and logistic regression analyses.
Results: SS were present in 93.0% of patients with MDD. Independent contributors for both diminished QoL and greater RU included: more numerous SS and greater SS-induced disability. The presence of moderate/severe pain was identified as an independent contributor for diminished QoL. The duration of SS was unrelated to QoL or to RU.
Conclusion: Special attention must be paid to patients with MDD and SS, particularly if they are numerous and/or disabling, given their impact on QoL and RU and, hence, on clinical treatment of MDD.

P 08. Results of a Spanish nationwide cross-sectional study on Major Depression in Primary Care III: relationship between somatic symptoms and severity of depression

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Background: The relationship between somatic symptoms (SS) and major depressive disorder (MDD) has previously been studied in primary care patients; however, the relationship between SS and severity of depression, and the clinical implications, has not been fully explored to date.
Aims: To examine the relationship between SS and depressive severity as measured by the Zung Self-Rating Depression Scale (SDS) in primary care patients with MDD.
Method: Data on SS and severity of depression from 1150 patients with MDD were collected within the framework of a cross-sectional, multicenter, nationwide epidemiological study involving 79 primary care centers in Spain. Independent factors contributing to the severity of depression were identified by linear regression analysis.
Results: SS were present in 93.0% of patients with MDD (CI 95%: 91.2%, 94.5%). Factors associated with greater depression severity were: SS that produce higher levels of disability and SS that are persistent during activities. Other factors were: duration, number and patient attribution of SS (the shorter the duration, the greater the number; and the more attribution to depression, the greater the severity). Conversely, the severity of pain did not contribute to more severe depression.
Conclusion: Special attention must be paid to patients with MDD and SS, especially if they produce disability and are persistent since these factors relate to depression severity and therefore to the prognosis of MDD.
Supported by funding from Eli Lilly and Company.

P 09. Results of a Spanish nationwide cross-sectional study on Major Depression in Primary Care II: prevalence and factors related to somatization disorder

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Background: Evaluation and characterization of somatization disorder is relevant to better understanding primary care patients with MDD.
Aims: To determine the prevalence of somatization disorder defined in terms of the Abridged Somatization Symptoms Cluster (ASSC) and the factors associated with it in patients with MDD.
Method: ASSC was investigated in 1150 patients with MDD as part of a cross-sectional, multicentre, nationwide epidemiological study involving 79 primary care sites in Spain. ASSC criteria consist of a minimum number of symptoms having no identifiable organic cause and lasting for at least 6 months. Independent factors associated with ASSC were identified by logistic regression analysis.
Results: Of the 1150 patients with MDD, 954 (93.0%; CI 95%: 91.2%, 94.5%) had at least one SS and 350 (30.4%; CI 95%: 27.8%, 33.1%) met ASSC criteria. The adjusted analysis revealed that the risk of having an ASSC-defined somatization disorder increases with age and with the severity of depression; it is also greater in females and in patients who have visited a physician recently and in individuals taking analgesics or antidepressants.
Conclusion: One in three patients diagnosed with MDD in the primary care setting meet ASSC diagnostic criteria for a somatization disorder. Independent factors were described that contribute to identifying patients at risk.
Supported by funding from Eli Lilly and Company.

P 10. Results of a Spanish nationwide cross-sectional study on Major Depression in Primary Care I: prevalence and characteristics of somatic symptoms

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Background: An adequate description of the characteristics and clinical implications of somatic symptoms (SS) in major depressive disorder (MDD) is highly relevant to primary care.
Aims: To determine the prevalence and characteristics of SS in patients with MDD in the primary care setting.
Method: Data on SS from 1150 patients with MDD within the framework of a cross-sectional, multicenter, nationwide epidemiological study involving 79 primary care sites in Spain were analyzed.

Results: Depressed mood and MDD were detected in 1998 and 1150 of 8687 selected patients respectively. SS were both common and numerous in the 1150 MDD patients; 954 patients (93.0%; CI 95%: 91.2%, 94.5%) had at least one SS and 588 (57.3%; CI 95%: 54.2%, 60.4%) had four or more SS. The most commonly reported SS included pain (in 85.5%; CI 95%: 83.3%, 87.5%), cardiopulmonary (80.6%; CI 95%: 78.2%, 82.9%) and gastrointestinal symptoms (69.4%; CI 95%: 66.6%, 72.1%). Back pain was the most commonly reported symptom. Treating physicians mainly attributed cardiopulmonary and gastrointestinal symptoms to depression, whereas pain was attributed less to depression.
Conclusion: SS are common and numerous in patients with MDD in the primary care setting and pain is the most common. The lower attribution rate of pain to depression suggests that primary care physicians usually exclude pain from the spectrum of depressive symptoms.
Supported by funding from Eli Lilly and Company.

P 11. Pilot study of clonazepam and milnacipran in the treatment of patients with panic disorder with comorbid major depression

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Background/Aims: Panic disorder is often co-morbid with major depression. Although antidepressants can effectively treat both disorders, it can be preferable to treat panic attacks with a rapidly acting therapy and to switch to antidepressants once the panic attacks are under control. The aim of this study was to assess the efficacy, safety and tolerability of a treatment strategy of initial clonazepam monotherapy, switching progressively to milnacipran.
Methods: Seventy-four outpatients, with a diagnosis of panic disorder with or without agoraphobia and co-morbid unipolar major depression were recruited. Patients had a minimum of 4 panic attacks in the three weeks prior to recruitment and a baseline MADRS of 16 or more. After a drug-free period of at least 14 days, patients were administered clonazepam, 0.5 mg to 2 mg/day, according to clinical response, during 28 days and then tapered off over the next 2 weeks (ending on day 42). From day 14, patients were administered milnacipran 50 mg/day (25 mg bid) increasing to 100 mg/day (50 mg bid) on day 21 and maintained at this dose for 7 weeks. Milnacipran was then discontinued without tapering. From day 42 to 70 patients received milnacipran as monotherapy. Patients were assessed at baseline, after 14 days and weekly thereafter for the 70 days of treatment. A final assessment was made one week after treatment discontinuation.
Results: At endpoint, 86.7% of the 60 patients who completed the study showed a good antidepressant response (MADRS reduction $>50\%$) and 70.0% were free from full panic attacks with 91.7% classified as global treatment responders (CGI-improvement of 1 or 2 for panic and depression). The treatment was well tolerated, only 4 patients (5.4%) discontinued due to adverse events.
Conclusions: In this open study, the combined sequential treatment with clonazepam and milnacipran was safe and effective in patients suffering from co-morbid panic disorder and major depressive disorder.

P 12. Effectiveness and tolerability of amisulpride in Bipolar Disorder I, treatment of bipolar mania: results of a 24-week open study

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Background: Amisulpride (Solian), a substituted benzamide derivative, is a second-generation antipsychotic that preferentially binds to dopamine D2/D3 receptors in limbic rather than striatal structures. High dosages preferentially antagonise postsynaptic D2/D3 receptors, resulting in reduced dopamine transmission, and low dosages preferentially block presynaptic D2/D3 receptors, resulting in enhanced dopamine transmission. Amisulpride has been reported to be effective in the treatment of schizophrenia and major depressive disorder.
Method: This was a single-blind clinical trial involving 41 subjects suffering from Bipolar Disorder I, manic phase, given a 24-week treatment with Amisulpride (600 mg/day increased to 800 mg after 7 days of treatment). The sample consisted of 13 females (F = 31%; mean age 32.4 y $\pm$1.2) and 28 males (M = 69%; mean age 39.1y $\pm$2.2) consecutively admitted in the Center for the Study of Mood Disorders, recruited in an Emergency Psychiatric Hospital with a DSM-IV TR diagnosis of Bipolar Disorder I, manic phase. The sample was assessed using the Young Mania Rating Scale (YMRS) total score d 20. Assessments were made at Baseline; T1: end of the first week treatment; T2: end 4-week treatment;T3: end 8-week treatment; T4: end 12-week treatment; T5: end 18-week treatment,T6: end 24-week treatment and included, besides the YMRS, the Psychiatric Rating Scale (BPRS), the Hamilton Rating Scale for Depression (HAM-D+ atypical symptoms), the Clinical Global Impressions Scale for Bipolar Disorder, Modified (CGI-BP-M), MADRS and the systematic report of adverse events. Amisulpride was added to other medications, but other antipsychotics.
Results: 36 (88%) patients were responders, 4 (12%) were non responders. Amisulpride turned out to be effective and reasonably safe in the treatment of bipolar mania. At the end of the first week (T1) of treatment in responders (reduction of Young Mania Rating Scale $>50\%$); at endpoint 24-week (T6) treatment amisulpride produced significant improvements (Total Score) on the YMRS ($p = 0.002$), the HAM-D+atypical symptoms ($p = 0.003$), mania ($p = 0.002$), and depression ($p = 0.001$) subscales of the CGI-BP-M, MADRS ($p = 0.004$). The following assessments confirmed the efficacy of this drug for manic bipolar. The most common side effect was sedation (n = 4; 12%), four females (all non responders) had galactorrhea; in the responders group some reported extrapyramidal symptoms and insomnia.
Conclusions: Amisulpride is a suitable drug for the treatment of Manic Bipolar, well tolerated and efficacious in the acute treatment of Bipolar Disorder I, manic phase. This study on amisulpride confirms that the drug, D(2) and D(3) antagonism, may be involved in the mechanisms of the therapeutic response to antipsychotics in mania.

P 13. The treatment benefits of duloxetine in major depressive disorder as assessed by number needed to treat

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Background: The efficacy of an antidepressant is typically assessed by comparing it with placebo using validated rating scales. However, this type of analysis does not translate well to the clinical settings. For clinicians, a more meaningful measure is the number needed to treat (NNT). The objective of this analysis is to demonstrate the efficacy of duloxetine in terms of NNT.
Methods: Data were obtained from nine clinical trials designed to assess the efficacy and safety of duloxetine as a treatment for major depressive disorder (MDD). These studies examined 8–9 weeks of acute treatment with duloxetine in patients with MDD. NNT estimates were determined for duloxetine at 60 mg/day, for duloxetine and selective serotonin reuptake inhibitor (SSRI)-comparators (paroxetine and fluoxetine, 20 mg/day) from six multi-dose studies, and in patients $\geq$65 years of age. NNTs based on Hamilton Depression Rating Scale (HAMD17)-defined response and remission and Clinical Global Impression (CGI) improvement were estimated and compared.
Results: NNTs for duloxetine at 60 mg/day were 6 for response, 9 for remission, and 7 for CGI improvement. In the six SSRI-controlled studies, NNTs for response, remission, and CGI improvement were 6, 7, and 8 for duloxetine, respectively, and 7, 11, and 7 for the SSRIs, respectively. In the study of elderly patients with MDD, NNTs for response, remission, and CGI improvement were 6, 8, and 7 for duloxetine, respectively, at 60 mg/day. The median time to HAMD17-defined response for duloxetine was 39 days as compared with 63 days in patients receiving placebo (log rank $p < .001$). The median time to remission for duloxetine in the same population was 63 days, while median time to remission was not achieved in patients receiving placebo (log rank $p < 0.01$).
Conclusions: The NNTs presented here demonstrate the efficacy of duloxetine over placebo and two established SSRIs, particularly in regards to remission. These values provide a more useful estimate of treatment impact in depressed populations compared with scale-based evaluations often used in clinical trials.

P 14. Why is self-help neglected in the treatment of emotional disorders? A meta-analysis

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Background/aims: Although the burden of emotional disorders is very high, mental health care is available to only a minority of patients. The literature suggests that self-help strategies, both bibliotherapy and self-help groups alike, are effective for various, less serious complaints but it is unclear whether available data support a role for self-help in treatment protocols for patients with clinically significant emotional disorders.
Methods: We searched the literature with a focus on anxiety and/or depressive disorder. Standardised assessment of diagnosis or symptoms and randomised controlled trials were inclusion criteria for a meta-analysis.
Results: The mean effect size of self-help (mainly bibliotherapy) versus control conditions is 0.84, and 0.76 for follow-up; the effect sizes of self-help versus treatment are -0.03 and -0.07 respectively. A longer treatment period is more effective.
Conclusions: Bibliotherapy for clinically significant emotional disorders is more effective than waiting list or no treatment conditions. The dearth of studies on self-help groups for emotional disorders does not permit an evidence-based conclusion concerning the effects of self-help groups. No difference was found between bibliotherapy and psychiatric treatment of relatively short duration.
Declaration of interest: None.
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P 15. Cognitive self-therapy in the treatment of chronic and remittent emotional disorders. A multi-centre randomised controlled trial

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Background/aims: Alternative treatments might counteract the extensive need for care of chronic and remittent depression and anxiety disorders. The study aims to investigate the effectiveness of cognitive self-therapy (CST) in the treatment of depression or generalised anxiety disorder.
Method: Patients ($n = 151$) were randomised to receive CST or treatment as usual (TAU) in a trial lasting for 18 months. Outcome measures were symptoms, social functions, quality of life and utilisation of care, and analysed using mixed models, a repeated measurement analysis.
Results: Patients in both conditions improved significantly. Reduction of symptoms, improvement of social functions and medical utilisation were maintained at the end of the 18 months. Medical care utilisation (therapist contact and hospitalisation) was lower for CST than for TAU. No suicides occurred.
Conclusions: CST reduced medical care utilisation, while no other differences could be found between the conditions.
Declaration of interest: The first author was one of the developers of CST. The study was funded by the Health Care Insurance Board (College voor Zorgverzekeringen) and University Medical Center Groningen, and approved by its Medical Ethical Board (MEC 98/12/214c).

P 16. Paraprofessionals for anxiety and depressive disorders. A meta-analysis

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Background/aims: Presuming that paraprofessionals may relieve the extensive need for care of those with anxiety and depressive disorders, the study aims to investigate the effectiveness of any kind of psychological treatment for anxiety and depressive disorders performed by paraprofessionals.
Methods: Search strategy included CCDANCTR-Studies, electronic databases, citation lists, and correspondence with authors. Included were RCTs using symptom measures, comparing paraprofessionals versus professionals,

and waiting list or placebo condition. Standard mean difference, odds, and generic inverse variance method were used when appropriate, using a random effects model. Sensitivity analysis on quality of studies and self-rated/observer-rated measures, and subgroup analyses for depression/anxiety, paraprofessionals with/without professional background, group/individual intervention, length of follow-up and gender (post-hoc subgroup analysis) were performed.

Results: No differences were found between paraprofessionals and professionals in five studies (n = 1060; SMD = 0.09, 95% CI −0.23 to 0.40, p = 0.58), and no significant heterogeneity. Five studies (n = 220) comparing paraprofessionals versus control showed a significant effect in favour of paraprofessionals (OR = 0.34, 95% CI 0.13 to 0.88, p = 0.03), but heterogeneity was indicated (I^2 = 60.9%, Chi^2 = 10.24, df = 4, p = 0.04). After correction for heterogeneity and removing one study of low quality, three studies (n = 128; mixed gender; women) indicated no significant difference in effect between paraprofessionals and professionals (SMD = 0.13, 95% CI −0.39 to 0.64; p = 0.63) and a strongly significant pooled effect for three studies (n = 188; women) favouring paraprofessionals over the control condition (OR = 0.30, 95% CI 0.18 to 0.48, p < 0.00001), and homogeneity between studies (I^2 = 0%, Chi^2 = 0.47, df = 2, p = 0.79).

Conclusions: No conclusions were allowed about the effect of paraprofessionals compared to professionals, but three studies indicated a significant effect for paraprofessionals (all volunteers) compared to no treatment.

Declaration of interest: None.

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P 17. Modafinil as an adjunct treatment to sleep deprivation in depression

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Sleep deprivation (SD) is a rapid-acting treatment for depression, but its clinical efficacy is hampered by high relapse rates after recovery sleep and its effectiveness is reduced by the demanding effort for the patient to stay awake. The use of the wake-promoting agent modafinil appears beneficial to patients having this form of therapy. We studied a single case study to assess the ability of modafinil to sustain the antidepressive effect of SD. A 70-year-old bipolar patient with a severe depressive recurrence according to the ICD-10 criteria underwent four partial periods of SD (awakening at 2h00 am) on a twice-weekly basis. On the day after each partial SD, he was prescribed modafinil 100 mg at awakening (2h00 am) and at midday. Observer ratings of mood were performed with the 17-item version of the Hamilton depression rating scale (hdrs). Self ratings used 100-mm visual analog scales of mood (VAS) at 9h00 and 18h30 the day before and the day after each partial SD and the Epworth sleepiness scale (ESS) at 18h30 on these same days. The initial hdrs-17 score was 27. After the partial SDs, the VAS for mood improved on average 52.3 mm (±29.1) in the morning and 20.8 mm (±31.8) at 18h30. the average ESS score slightly decreased (−0.75) at 18h30 after PSD. The patient was discharged two days after the last SD (hdrs-17 = 3). modafinil was continued at 200 mg/day. He was still euthymic 1, 2, 4, 8 and 12 weeks after discharge as shown by an hdrs below 7. This is the first report on the combination of modafinil and SD. It suggests that modafinil may (1) alleviate the difficulty of carrying out sleep deprivations, (2) reinforce the action of SD, possibly by preventing daytime naps and micro-sleep, (3) sustain the antidepressant effect of SD, possibly by stabilizing the resynchronization between the circadian clock and the sleep-wake cycle.

P 18. Treatment of anxious vs. non-anxious depression: a post-hoc analysis of an open-label study of duloxetine

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Background: Anxious depression, defined as Major Depressive Disorder (MDD) with high levels of anxiety symptoms, represents a relatively common depressive subtype, with distinctive clinical features. This post-hoc analysis compared the safety, tolerability and efficacy of open-label treatment with duloxetine in outpatients with anxious vs. non-anxious depression.

Methods: All patients met criteria for MDD as defined in DSM-IV. Patients (n = 249) were treated with duloxetine 30 or 60 mg once-daily (QD) for the first week. During the remaining eleven weeks of therapy, the duloxetine dose could be titrated to efficacy within a range from 60 mg QD to 120 mg QD, with 90 mg QD as an intermediate dose. Efficacy measures included the 17-item Hamilton Depression Rating Scale (HAMD17), Hamilton Anxiety Scale (HAMA), and Clinical Global Impression of Severity (CGI-S) scale. Anxious depression was defined as MDD with HAMD Anxiety/Somatization Factor score ≥7.

Results: Anxious (n = 109) and non-anxious (n = 140) patient groups did not differ significantly in demographic factors, treatment status at study entry, early discontinuation rates, overall rates of treatment-emergent adverse events, and rates of specific treatment-emergent adverse events. At endpoint, open treatment with duloxetine was accompanied by a significantly greater reduction in total HAMD17 and HAMD Anxiety/Somatization scores among patients with anxious depression compared to non-anxious depressives. On the other hand, the differences in CGI-S and HAMA scores at endpoint between these two groups were not statistically significant, with both scales showing trends toward greater improvements in anxious depression. Although remission and response rates were similar at endpoint between anxious and non-anxious depressives, patients with anxious depression had a more rapid improvement, displaying a significantly shorter median time to response than non-anxious depressives.

Conclusions: In this post-hoc subgroup analysis, duloxetine exhibited similar safety and tolerability in anxious and non-anxious depressed patients. However, the efficacy of duloxetine in anxious depression was somewhat superior

to that observed in non-anxious depression. Further study in placebo-controlled studies are needed to replicate these findings.

P 19. Posttraumatic stress disorder and perception of health after 11M attacks in Madrid

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Objective: The purpose of this study was to determine the changes in the perception of the health and the prevalence of PTSD among surviving victims of the terrorist attacks treated at our hospital and their nearest relatives and closest associates, at two time periods: 5 to 8 weeks and six months after the attack. Likewise, we hoped to identify the most decisive variables associated with the presence of PTSD.
Method: Evaluation of PTSD symptoms using the Davidson Trauma Scale in a sample of 56 patients seen in the emergency room of a general hospital and their relatives. The self-administered Goldberg General Health Questionnaire (22, 23) was also used to collect subjective changes in perception of health experienced by each individual.
Results: At Month 1, 41.1% of patients (31.3% of males and 54.2% of females) presented PTSD. At Month 6, this figure was 40.9% (30.4% of males and 52.4% of females). Between Month 1 and Month 6, there was a significant improvement in perception of health. The relatives presented similar Davidson Trauma Scale scores at baseline and at 6 months.
Conclusion: The conclusions of this study are that the prevalence of PTSD scarcely varied between Month 1 and Month 6, that women suffered a greater degree of posttraumatic stress symptoms, both at Month 1 and Month 6, and that subjective perception of health improved greatly between the first and second evaluation.

P 20. Winter seasonal affective disorder and night eating syndrome

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Background: Winter seasonal affective disorder (SAD) is a form of recurrent depressive or bipolar disorder characterised by the predictable onset of depression in the fall/winter months with spontaneous remissions in the spring/summer period. Night Eating Syndrome (NES) is defined by morning anorexia, evening hyperphagia, and insomnia. Winter SAD shares some features with NES such as snacking on high-carbohydrate/high-fat foods with the result of increased weight, emotional distress, circadian rhythm disturbances, and good response to serotoninergic antidepressants (SSRIs) and bright-light therapy.
Aims: To assess the prevalence of NES in a sample of outpatients who met DSM-IV criteria for major depression with a winter seasonal pattern, and to define the socio-demographical and clinical variables associated with NES.
Methods: Sixty-two consecutive depressed outpatients with winter seasonal features (DSM-IV criteria) were recruited. Severity of depression was assessed with the Structured Interview Guide for the Hamilton depression rating scale, Seasonal Affective Disorder version (HDRS and Sigh-SAD-25), and with the Hospital Anxiety and Depression scale (HAD-14). The criteria for NES (morning anorexia, evening hyperphagia, in which at least 50% of the daily energy intake is consumed after the last evening meal [80% after 8pm], awakenings at least once a night, consumption of snacks during awakenings in order to restore sleep, persisting of these criteria for at least 3 months) were collected after a thorough psychiatric examination by a senior psychiatrist and a record of food consumption (energy and macronutriment content). Quantitative data were compared by Mann-Whitney tests.
Results: The prevalence of NES was low (4.8%). Patients suffering from NES were significantly older ($z = -1{,}98$, $p = 0.46$) with a greater duration of the illness ($z = -2{,}13$, $P = 0.03$). NES was not related to depression (HDRS and Sigh SAD-25 score, HAD- depression-7 subscore).
Conclusions: Winter SAD and NES are not overlapped disorders.

P 21. Novel hypothesis for the cause of panic disorder via the neuroepithelial bodies in the lung

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Panic disorder (PD) is a complex condition that is further complicated by its numerous inducers, which include hypercapnia, hypoxia, sodium lactate, caffeine and cholecystokinin. It seems unlikely that there are specific suffocation receptors for each of these inducers in the brain. The pulmonary neuroepithelial bodies (NEBs), which are situated at the bifurcation point of the small bronchi, act as storage cells for 5-hydroxytryptamine (5-HT) and sensors for suffocation. If we suppose that PD might represent an inflammation of the NEBs, bradykinin (BK) – which augments the airway hyperresponse to diverse inducers – might cause these cells to release 5-HT along with peptides and panneuroendcrine markers from their dence-core secretary granules. It was reveald that BK with 5-HT could cross the blood-brain barrier (BBB). When 5-HT released from these cells along with BK cross the BBB, the release of the 5-HT at the axonal terminals in the serotonergic neurons in the brain will be inhibited, since the 5-HT1 autoreceptor have a higher affinity for 5-HT than do the 5-HT2 receptors. The inhibition of 5-HT at the axonal terminal causes to suppress the periaqueductal gray matter, which inhibits flight reactions to impending danger, pain or asphyxia. In short, this serotonergic situation might bring about PD. According to this theory, the type of inducer that the PD patient is exposed to is unimportant as long as it stimulates the NEBs, and through the effect of 5-HT and BK, PD would be revaluated as a somatic disease that directly and reversibly affects the brain.

P 22. Psychological factors involved in the chronification of pain

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Objectives: We aimed to enquire about the relationship between some psychological disorders such as anxiety or depression with the intensity and the quality of the perceived pain. On the other hand, we aimed to explore

the psychological factors involved in the perception and the chronification of pain. In order to fulfil this aim, we studied in depth the relationship between some personality traits and their characteristic reaction to pain.
Method: We opted for a descriptive, transversal study. The people taking part in this study were outpatients of the Pain Unit of the "Rio Hortega" Hospital in Valladolid. Most of them suffered from chronic low back pain. All of them were assessed with the McGill Pain Questionnaire (MPQ-SV), the Visual Analogue Scale (VAS) and the Lettinen Test. They all were also diagnosed according to the DSM-IV-TR criteria.
Results: Our study showed that people who met the criteria of depressive disorder obtained higher scores in the emotional factor of the MPQ-SV and they coped with pain in a passive way. It also showed that people with higher levels of anxiety considered their pain as stronger than people with lower levels. Finally, many participants met the criteria of the histrionic and obsessive-compulsive personality disorder.
Conclusion: Some psychological aspects characteristic of depression, such as the passive way of coping or the feeling of helplessness and hopelessness, could be playing a major role in the chronification of pain. On the other hand, given the high number of participants diagnosed with some personality disorders such as the histrionic and obsessive-compulsive disorder, some personality traits could be involved in the chronification of pain. From our point of view, these psychological factors should be taken into account in the treatment of people suffering from chronic pain.

P 23. Effectiveness of psychoeducation in the treatment of bipolar disorder

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Aims: We aimed to assess the effect of a time-limited psychoeducation program upon perceived quality of life and the course of the illness among patients diagnosed with bipolar disorder. The main target of our psychoeducation program was to improve insight of the patients on their illness and, in this way, to increase their medication adherence, being this an essential factor in order to prevent relapses.
Method: Participants were patients (n = 13) with BD type I or II who were clinically described as euthymic or mildly symptomatic. The experimental group consisted of the seven participants who finally took part in the program. The control group was formed by six patients who were not eventually able to take part in the program. Both groups were assessed with the Quality of Life Scale (QLS), the Global Assessment Scale (GAS), the Young Mania Rating Scale (YMRS) and the Beck Depression Inventory (BDI). The assessment of both group was carried out before and after the standardized twenty session program. The scores obtained by participants of both groups was compared in the end. We also checked the number of relapses in all the participants.
Results: Results showed that attending the psychoeducation program improved significantly the scores of the experimental group in the QLS and the GAS scale and diminished the scores in the YMRS and the BDI in a significant way. In contrast, the scores of the control group in such scales did not change significantly. On the other hand the number of relapses was inferior in the experimental group.
Conclusions: The psychoeducation program proved effective in the improvement of the quality of life perceived by the patients and in the reduction of the scores obtained by them in the clinical scales. From our point of view, the clinical implications of these results should not be overlooked. Psychoeducation together with medication seems to be a vital aspect in the prevention of relapses.

P 24. Escitalopram for relapse prevention in older patients with depression

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Background: 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.
Methods: A total of 405 patients aged 65 years or older with a primary diagnosis of MDD (according to DSM-IV criteria) and a MADRS total score of 22 or more, received 12-week, open-label escitalopram 10 or 20mg/day treatment. Of these, 305 patients achieved remission (MADRS total score of 12 or less) and were then randomly assigned to 24 weeks of double-blind treatment with escitalopram (n = 152) or placebo (n = 153). 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: The results of 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-square test, $p < 0.001$). Significantly fewer escitalopram-treated patients relapsed (9%) compared with placebo (33%) (chi-square test, $p < 0.001$). Escitalopram was well tolerated; with 53 patients (13%) withdrawn due to adverse events during the open-label period and 3 escitalopram-treated patients and 6 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 and was well tolerated as continuation treatment by older depressed patients.
Disclosure: Dr. P Gorwood has received honoraria from H. Lundbeck A/S and Dr. C Katona is a consultant for H. Lundbeck A/S. O Lemming and Dr. E Weiller are full-time employees of H. Lundbeck A/S.

P 25. Neuropsychological correlations of symptom dimensions of obsessive-compulsive disorder

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Obsessive-compulsive disorder (OCD) is now believed to be heterogeneous and the method of subtyping the disorder is becoming of great importance. However, little is known about the neuropsychological functions

of symptom dimensions. The purpose of this study was to identify the cognitive deficits that correlate with specific symptom dimensions. Thirteen categories in the Yale-Brown Obsessive Compulsive Scale symptom checklist from 152 patients with OCD were analyzed by principal component analysis. Neuropsychological tests to examine frontal lobe functions were administered to 98 of 152 patients, and the correlations between identified symptom dimensions and neuropsychological performances were analyzed. The five factors identified were contamination, symmetry/ordering, pure obsessions, hoarding, and repeating/counting dimensions. These accounted for 65.4% of the total variance. The symmetry/ordering dimension was negatively correlated with the verbal fluency assessed by the Controlled Oral Word Association Test, with which the pure obsessions dimension was positively correlated. And the pure obsessions and the hoarding dimensions were significantly correlated with poor performances on the Wisconsin Card Sorting Test. The findings further suggest the heterogeneity of OCD and the usefulness of dimensional approaches in the research of the disorder. The symptom dimensions, in particular, implicated in the current study may manifest the limbic/paralimbic or prefrontal dysfunctions. More studies are needed to clarify underlying neurobiological mechanisms of the symptom dimensions and to advance the individualized treatment strategies.

P 26. Analysis of relation between time management behaviors and occupational stress of medical surgical wards

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Background/Objective: According to the Lakein description of time management, individuals first determine their needs and then rank them in terms of importance. Specific activities include setting goals to achieve the needs or wants and prioritizing the tasks necessary to accomplish them. The tasks of most importance are then matched to the time and resources available by planning, scheduling, and making lists.
Methodology: This study analysed the relation between time management behaviors (setting goal and priorities, mechanics of time management, control of time and organization) and occupational stress (role overload, role ambiguity and role conflict). Thirty nurses (all of those sampled) participated in this research. A questionnaire which had 57 questions was used. For data analysis X2 and Pearson correlation coefficient were used.
Results: The results indicate that in general most of the sample located in good level of time management behaviour (TMB) (63.4%). In addition, most of sample (50%) experienced occupational stress in the normal level. Finally, a significant relationship was seen between TMB and occupational stress ($r = -0.81$, $P < 0.001$).
Conclusion: It is important to distinguish among the different facets of time management. The low correlation among the factors indicate that, for instance, if a person sets a goal it does not necessarily follow that he or she feels in control of time or makes lists. Finally, time management behaviors can reduce occupational stress.

P 27. Onset of action of escitalopram: results of a pooled analysis

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Background: In general, antidepressant drugs are regarded as too slow acting: most patients who benefit from treatment require two or more weeks of therapy to respond to treatment. An efficacious and well-tolerated antidepressant drug with an earlier onset of effect would be of greater interest to clinicians and patients.
Methods: To study onset of effect of escitalopram, a selective serotonin reuptake inhibitor (SSRI), data were pooled from controlled randomised clinical double-blind trials comparing this drug with other antidepressant drugs (SSRIs and venlafaxine XR) in major depressive disorder, with assessments of the primary efficacy parameter (mean change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline, using last observation carried forward).
Results: The mean change in MADRS total scores was significantly higher for escitalopram-treated patients than for patients treated with the comparators on Day 7 (-3.9 versus -3.4, respectively, $p = 0.029$). This difference remained significant and in favour of escitalopram at all subsequent assessments. Using secondary outcomes (Clinical Global Impression of Improvement and Severity scales and early improvement), results consistently showed a statistically significantly faster onset of effect of escitalopram compared with the comparators.
Conclusion: By pooling data from the escitalopram clinical trials in MDD comparing escitalopram with other active antidepressant drugs, escitalopram was shown to have a more rapid onset of effect than the comparators, particularly other SSRIs.
Disclosure: Prof. Kasper has received grant/research support from Lundbeck and has served as a consultant, on the advisory board and on the speakers' bureau for Lundbeck. Dr Spadone is a consultant for Eutherapie. Dr Verpillat is a full-time paid employee of H. Lundbeck A/S, Economics and Pricing Division, Paris, France. Prof Angst has served on the speakers' bureau for the Lundbeck Foundation.

P 28. A pooled analysis of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine

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Background: The hypothesis that escitalopram has at least as good efficacy in the acute treatment of major depressive disorder (MDD) as other available antidepressants was tested. In this analysis, studies comparing escitalopram with the following antidepressant compounds: citalopram, fluoxetine, paroxetine, sertraline and venlafaxine XR were used.
Methods: A total of 2,743 patients were in the ten studies in patients with MDD; 2,687 (98.0%) were included in the ITT analysis of the efficacy of escitalopram ($n = 1,345$), SSRIs ($n = 1,102$) and venlafaxine XR ($n = 240$). The meta-analysis was done by ANCOVA on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score adjusting for baseline value, centre and treatment.

Results: Pooling data from all studies sponsored by H. Lundbeck or Forest Laboratories completed as of 1st July 2004 that directly compared escitalopram with other antidepressants reveals that 8-week escitalopram treatment carries an advantage of about 1.1 MADRS points over other antidepressants. The majority of comparisons were with SSRIs, where the effect was consistently larger than that observed in the comparison versus venlafaxine XR. This advantage was larger in patients with severe depression, with 2.3 MADRS points more than other antidepressant compounds. Escitalopram also had greater efficacy, as assessed by remission and response to treatment.
Conclusion: These results suggest that some heterogeneity exists within the class of SSRIs in terms of magnitude of antidepressant effect.
Disclosure: SH Kennedy and RW Lam have received grant funding and occasional consultancy honoraria from H. Lundbeck A/S. HF Andersen and R Nil are employees of H. Lundbeck A/S.

P 29. Frontal dysfunction underlies depressive syndrome in Alzheimer's disease: a FDG-PET study

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Objective: This study aimed to investigate the regional cerebral dysfunction associated with depressive syndrome in Alzheimer's disease (AD) patients.
Method: 12 AD patients with depressive syndrome (ADD), 12 age-, gender-, and severity- matched AD patients without depressive syndrome (ADND) and 12 normal control subjects (NC) underwent a 18-F-fluorodeoxyglucose (FDG) PET scan. Depressive syndrome was defined according to the provisonal diagnostic criteira for depression of AD, which were recently proposed by the National Institute of Mental Health (NIMH) workgroup. The regional cerebral glucose metabolic rate (rCMRglc) in the two AD groups was compared using a voxel-based method. At the coordinate point of the voxel with the highest Z score within each brain area showing the significant difference of the rCMRglc between the AD groups, the normalized rCMRglc were compared between each of the AD groups and the NC group. Results: The ADD group showed a lower rCMRglc in the right superior frontal gyrus than the ADND. There was no brain area where the ADD group showed increasd rCMRglc. Both ADD and ADND group showed lower rCMRglc in the temporoparietal, posterior cingulate and frontal cortex than NC group. Conclusions: These results indicate that a frontal dysfunction, associated with primary or other secondary depressive syndromes in many previous reports, underlies depressive syndrome of AD patients as well.

P 30. Seasonality associated with the serotonin 2A receptor polymorphism

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This study investigated the relationship between the serotonin 2A receptor −1438 A/G polymorphism and seasonal variation in a young population in Korea. We recruited 297 young Korean medical students in this study. All subjects were free of major medical and psychiatric problems. They were genotyped for the 5HTR2A −1438 A/G SNP and evaluated the seasonal variation in mood and behavior by Seasonality Pattern Assessment Questionnaire (SPAQ). Global Seasonality Score (GSS) of SPAQ between three genotypes were not different. However, the comparison between seasonals (syndromal plus subsyndromal SAD according to Kasper's criteria) and normal subjects showed significant difference in the genotype distribution between seasonal and normal subjects. Winter type seasonals showed significantly higher frequency of 5HTR2A −1438 A allele compared with other subjects (¥ö2 = 6.80, p = 0.009; odds ratio = 1.79; 95% confidence interval 1.15–2.78). These results suggest that the 5HTR2A −1438 A/G polymorphism is related to seasonality in the Korean population.

P 31. Interpersonal group psycotherapy in bipolar out-patients

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Although bipolar patients have been not traditionally been viewed as suitable to participate in therapeutic groups, in our study we attempted to stress the efficacy of combined therapy (group psychotherapy and drug treatment) in bipolar out-patients. We maintained interpersonal group psychotherapy in bipolar out-patients for five years, integrating aspects drawn from the psychoanalytic, cognitivist and behavioral models, measuring the interepisodic functioning, therapeutic compliance, number of relapses and number of hospitalizations, and comparing this with the same period of time prior to the patient's inclusion in the group. Group therapy has been shown to be effective in improving interepisodic functioning, increasing the early recognition of the relapse symptoms, improving stress management, communication difficulties and acquiring a better knowledge of oneself. Combined therapy has led to a decrease in relapses, hospitalizations, better dosage adjustment and better drug compliance, wich means a decrease in the socio-health care costs.

P 32. Anxiety and mood disorders in children with learning disabilities

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Objectives: Previous studies at Penteli Children's Hospital indicated that children with learning disabilities present

secondary psychological problems, for example depression. At the present study we aim to extend and systematize the typology of psychological problems on a larger clinical population of children with learning disabilities. It was expected that children with learning difficulties would present high levels of depressive, anxious, and aggressive symptoms, as well as low self-esteem. Also, it was expected that children with more serious learning or intellectual disabilities would present more elevated psychological symptoms.

Methods: The sample was consisted of 211 children, aged 7 to 14. The children were categorized in three different groups: a) children with slight learning disabilities b) children with dyslexia and c) children with learning and intellectual disabilities. Children were given to complete Beck Youth Inventory and their parents were asked to complete the Achenbach questionnaire. In order to compare the three groups we used the x2 test.

Results: The Beck Youth Inventory indicated that 26% of children have low self-concept, 21% anger, 31% anxiety and 19% depressive feelings. We also found that parents generally underestimate those affective problems and focus on the treatment of the learning disabilities.

Conclusions: Our hypothesis was partially confirmed as we found that children with intellectual and learning disabilities present more depression, anxiety symptoms and anger than children with slight learning difficulties.

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P 33. Escitalopram and suicidality in depression in adults

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Background: To examine the incidence of suicide-related behaviour (reported as adverse events), as well as an efficacy measure linked to suicidality in depressed patients treated with escitalopram.

Methods: All placebo-controlled and relapse prevention trials in the escitalopram clinical trial database within major depressive disorder (MDD), were analysed for specific adverse events (AEs) indicative of suicidal behaviour. AEs were presented as both incidence and rate of events. The effect of escitalopram on suicidal thoughts during the trial period was assessed using item 10 (suicidal thoughts) of the Montgomery-Åsberg Depression Rating Scale (MADRS).

Results: In total, 2277 patients with MDD received controlled, double-blind escitalopram treatment in the placebo-controlled (placebo n = 1814) and relapse prevention trials, respectively. There were no fatal suicides in the first two weeks of treatment, one during the full treatment period on placebo (incidence 0.1%; rate 0.003), and none on escitalopram. None of these figures were significantly different between escitalopram and placebo patients. Analysis of data from patients switched to placebo in relapse prevention studies showed no indication of discontinuation-induced suicidal behaviour. None of the figures for non-fatal self-harm and suicidal thoughts were significantly different between escitalopram and placebo. With regard to suicidal thoughts (n = 1939), the mean value over time demonstrated a significant reduction of suicidal thoughts at all time points. In the analysis of the percentage of patients whose score for suicidal thoughts worsened from baseline to subsequent weeks of treatment during the MDD trials, there was a numerically lower percentage of patients in the escitalopram group than in the placebo group who reported worsening of suicidal thoughts during treatment.

Conclusions: There was no indication that escitalopram provokes suicide-related behaviour compared to placebo in MDD. Based on efficacy rating (MADRS item 10), escitalopram was more efficacious versus placebo in lowering suicidal thoughts from weeks 1 through 8 in the treatment of patients with MDD.

Disclosure: AG Pedersen and KF Overø are employees of Lundbeck.

P 34. Discontinuation-emergent symptoms of duloxetine treatment in patients with major depressive disorder

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Background: Discontinuation symptoms are common following antidepressant treatment. This report characterizes symptoms associated with untapered discontinuation of duloxetine.

Methods: Data were obtained from nine clinical trials that assessed the efficacy and safety of duloxetine in the treatment of major depressive disorder (MDD).

Results: In an integrated analysis of six short-term treatment trials (8–9 weeks duration) assessing fixed doses of 40, 60, 80, and 120 mg/day of duloxetine, discontinuation-emergent adverse events (DEAEs) reported significantly more frequently on abrupt discontinuation of duloxetine in at least 2% of patients compared with placebo were dizziness (12.4%), nausea (5.9%), headache (5.3%), paresthesia (2.9%), vomiting (2.4%), irritability (2.4%), and nightmares (2.0%). Dizziness was also the most frequently reported DEAE in analyses of three long-term duloxetine studies of 34 and 52 weeks duration. Most patients rated the severity of their symptoms as mild or moderate. A higher prevalence of DEAEs was seen with 120 mg/day duloxetine compared with lower doses, but a dose-response relationship was not observed across all doses. Extended treatment with duloxetine beyond 8–9 weeks did not appear to lead to increased severity or prevalence of DEAEs.

Conclusions: Abrupt discontinuation of duloxetine is associated with an adverse event profile similar to that reported with selective serotonin reuptake inhibitor (SSRI) and other selective serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants. It is recommended that, whenever possible, clinicians gradually reduce the dose before discontinuation of duloxetine treatment.

Limitations: The main limitation is the use of spontaneously reported DEAEs.

P 35. Seasonal birth distribution in healthy siblings of melancholic and atypical SAD patients

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Background: We have recently published a study investigating birth seasonality in a cohort of 553 patients suffering from seasonal affective disorder (SAD).[1] Interestingly, patients suffering from melancholic depression showed a markedly different birth distribution than patients with atypical depression. The present study compared the birth distribution of the healthy siblings of melancholic and atypical SAD patients to test the hypothesis of idiosyncratic procreational habits of the parents of these patients (parental conception habits theory).[2]
Methods: We conducted a telephone interview with the patients to obtain information on the birth months of their siblings. We were able to obtain reliable information from 338 cases; 267 patients had at least one sibling. Using the method of chart review to acquire information on the family history of our patients, we were able to exclude those siblings with psychiatric disorders from our evaluation. We compared the birth months and the quarter of birth of 289 siblings of atypical patients with the birth data of 47 siblings of our melancholic SAD patients.
Results: The monthly birth distribution of the healthy siblings of our melancholic and atypical SAD patients was statistically significantly different ($\chi^2 = 20.274$, df = 11, $p = 0.042$). However, this result has to be interpreted with care due to very small expected values in the single cells (37.5% of all cells had an expected frequency of <5). Comparison of birth patterns on a quarterly basis (Jan–Mar, Apr–Jun, Jul–Sep, Oct–Dec) showed differences on a trend level ($\chi^2 = 6.804$, df = 3, $p = 0.078$): Siblings of melancholic patients were rather born in the first and fourth quarter, whereas the sibs of atypical patients had elevated birth rates in the second and third quarter.
Conclusions: Our results, while preliminary and limited by the small number of melancholic patients, show that healthy siblings of melancholic and atypical SAD patients display a similar birth pattern than the index patients. This finding is in line with the parental conception habits hypothesis. Further research should be carried out to replicate our findings in larger samples.

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P 36. Compliance with-weekly fluoxetine vs daily fluoxetine and other selective serotonin re-uptake inhibitors after the maintenance therapy in major depressive disorder

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Background: Lack of antidepressant treatment compliance is a frequent cause of depression relapses. Weekly administration of fluoxetine (fluoxetine 90 mg/once a week), after remission of depressive symptoms, could improve compliance, and therefore contribute to improved treatment outcomes
Aim: Evaluate treatment compliance with weekly fluoxetine compared with daily administration of fluoxetine 20 mg and with other SSRIs during MDD maintenance treatment.
Methods: 1135 primary care patients, diagnosed with MDD (DSM-IV) that at the time of study initiation were in remission (HAMD-17 <9) and who had received treatment with daily SSRIs during a period of 3 to 6 months were included. At baseline, daily fluoxetine-treated patients remained with the same treatment or switched to weekly fluoxetine based on investigators opinion. Patients were followed for 6 months, within the framework of an observational, multicentre and controlled study. The adjusted odds ratio of being compliant by the Morisky-Green Test among weekly fluoxetine- treated patients compared with those receiving daily fluoxetine and with those receiving other daily SSRIs is estimated by means of generalized estimations equations methodology.
Results: 1135 patients were treated with weekly fluoxetine (n = 419), daily fluoxetine (n = 331) and other SSRIs (n = 385), with the mean age being 52.73 (SD 14.49). 825 (72.7%) patients were female and 408 (36%) did not have a previous depressive episode. 472 (41.6%) patients were compliant with the treatment at baseline by Morisky-Green Test. Baseline treatment group differences were non-significant except for concomitant medication. At end point 983 (86.6%) patients remained in the study and 545 (55.5%) were compliant by Morisky-Green Test. Weekly fluoxetine-treated patients had a greater odds ratio of being compliant than daily fluoxetine-treated patients (OR = 1.43; IC = 1.08–1.90) and also than the patients receiving other SSRIs (OR = 1.50; IC = 1.14–1.97).
Conclusion: Weekly fluoxetine treatment could be a valid therapeutic option to improve antidepressant long-term compliance in primary care patients with MDD.
Funding: Supported by funding from Eli Lilly and Company.

P 37. The measurement of anxiety in depression

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Objective: There is systematic and quantitative evidence that anxiety is associated with depression. We compared efficacy of anxiety treatment by antidepressants (SSRI) in depressive disorder.

Methodology: We included 30 outpatients with moderate Major Depressive Disorder (15 females and 15 males, aged

20 to 65). The instruments used for evaluation were instruments for diagnosis of depression according to the ICD 10 classification, Hamilton Depression Rating Scale (HAMD), monitoring vital signs and adverse effects. We compared patients' state before/after 14 and 30 days of antidepressants use. We compared improvement of psychic and somatic anxiety during a treatment.

Results: The comparison of patients' state before (visit 1), 14 (visit 2) and 30 (visit 3) days after the use of antidepressants showed significant statistical improvement. Mean HAMD scores for all of patients were on visit 1: 20.76 (in males 21.08; in females 20.45); on visit 2: 15.15 (in males 15.42; in females 14.89); and on visit 3: 8.49 (in males 9.02; in females 7.97). Mean scores of anxiety-psychic in all patients showed: on visit 1: 3.30 (in males 2.27; in females 2.33); on visit 2: 1.63 (in males 1.60; in females 1.67); and on visit 3: 1.93 (in males 1.00; in females 1.87). Mean scores of anxiety-somatic showed improvement in all patients: on visit 1: 1.43 (in males 1.40; in females 1.46); on visit 2: 0.66 (in males 0.73; in females 0.66) and on visit 3: 0.33 (in males 0.2 and in females 0). All monitored vital signs (blood pressure, heart rate and body weight) were stable. Only five cases of adverse effects three with headache (2 females and 1 male) and two with tension decline (1 female and 1 male) were shown.

Conclusion: Antidepressants are efficient in management of depression. In our study antidepressants has proved as efficient as anxiolytics with significant efficient in somatic anxiety, with minimal adverse effects and with an improvement of patients daily functioning. Low intensity adverse effects with no influence on therapeutic efficiency.

P 38. Escitalopram and GAD: efficacy across different subgroups and outcomes

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Background: Generalized anxiety disorder (GAD) is frequently associated with depressive symptoms. The SSRI antidepressant, escitalopram, was examined for efficacy across different subgroups and outcomes (anxious symptoms, depressive symptoms, and quality of life).

Methods: Three randomised, placebo-controlled 8-week, double-blind, studies of escitalopram (10 to 20mg/day) in GAD have employed a similar design, allowing for pooling of the data. The primary efficacy measure was the Hamilton Anxiety Scale (HAMA). General linear models were used to determine the efficacy of escitalopram across different subgroups and outcomes.

Results: Escitalopram was efficacious for GAD on a range of measures of both anxiety and depression (standardised effect sizes >0.3; $p<0.01$ to 0.001), and improved the associated impairment in quality of life (standardised effect size of 0.378; $p<0.001$). There was no significant interaction of effects on the HAMA with demographic or clinical variables. Furthermore, escitalopram was efficacious (standardised effect sizes >0.3; $p<0.01$ to 0.001) on both primary and secondary scales in the subgroup of subjects with above-median severity of depressive symptoms at baseline (Hamilton Depression Rating Scale score >12).

Conclusions: Escitalopram reduces anxiety and depressive symptoms in GAD, and improves quality of life. It is equally efficacious in GAD patients with an above-median level of depressive symptoms. Further research is needed to determine whether these results can be extrapolated to GAD patients with comorbid major depression.

Disclosure: DJ Stein and WG Goodman have received consultancy honoraria from Lundbeck or Forest. R. Nil and HF Andersen are employees of Lundbeck.

P 39. Onset of action of quetiapine monotherapy in bipolar mania

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Background: Quetiapine has been shown to be effective and well tolerated as monotherapy in bipolar mania in 2 double-blind placebo-controlled studies.[1–3]

Objective: Evaluate the onset of action of quetiapine monotherapy in bipolar mania from large, randomized, placebo-controlled studies.

Methods: Results from randomised, placebo-controlled monotherapy studies of quetiapine[1–3] were examined to determine the first point at which significant improvement is noted with quetiapine vs. placebo in patients with DSM-IV bipolar I disorder experiencing a manic episode. Two 12-week studies of quetiapine monotherapy versus placebo and either lithium or haloperidol internal control were evaluated.[1–3] The first evaluation in each of these studies was Day 4, the primary endpoint being change in Young Mania Rating Scale (YMRS) from baseline to Day 21. Significant improvement in YMRS was considered the main criterion for evidence of onset of action.

Results: A significant difference ($p<0.01$) between quetiapine and placebo was first noted in YMRS improvement from baseline at Day 4 in one monotherapy study[1] and Day 7 in the other.[2] A pooled-data analysis from these two studies indicated an onset of action at Day 4 ($p=0.021$).[3] Analysis of YMRS items in the pooled-data set indicated significant improvement ($p<0.05$) with quetiapine compared with placebo in 3 of 11 (appearance, speech rate/amount and sexual interest) and 6 of 11 items (appearance, speech rate/amount, sexual interest, increased motor activity, sleep and language/thought disorder) by Day 4 and Day 7, respectively. Quetiapine treatment resulted in improvement of all 11 YMRS items by Day 21. Adverse events over the first 4 days of quetiapine treatment (when administered dose was being escalated) included somnolence and dry mouth.

Conclusions: Quetiapine is effective and generally well tolerated in patients with bipolar mania, with an onset of action of 4–7 days as monotherapy.

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P 40. Psychiatric comorbidity of L- and D/L-methadone maintained patients – prevalence, additional intake of drugs, gender, and addictive substance-related behaviour

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Objective: Differentiation of L- and D/L-methadone maintained patients and additional heroin and other substance abuse in relationship to comorbidity and sociodemography have not been studied intensively.

Method: 60 methadone razemate (D/L) or L-methadone treated patients in maintenance therapy were interviewed with a questionnaire based on the EuropASI, and comorbidity was assessed using the Mini-DIPS.

Results: 51.7% of subjects (75% male) had a comorbid axis-I disorder, among these anxiety- (36.7%) and affective disorders (30%) were seen most frequently with a higher prevalence in female addicts ($p = 0.05$). Among the affective disorders dysthymia had the highest prevalence (23.4%). In axis-I-comorbid addicts a trend to earlier onset of regular substance consumption was found ($p = 0.09$). Furthermore, they tended to have a higher abuse of benzodiazepines, alcohol, cannabis, and cocaine, but not of heroin, and received a lower D/L-methadone dose than non-comorbid patients ($p < 0.05$). The duration of maintenance treatment showed an inverse relationship to frequency of additional heroin intake ($p < 0.01$). Patients with additional heroin intake received a lower L- but not D/L-methadone dosage ($p < 0.05$).

Conclusions: Higher intake of additional heroin seems not to be correlated with comorbid anxiety- and depressive disorders. However benzodiazepines, alcohol, and cannabis tended to be abused more frequently in axis-I comorbid individuals. In the lower dosage range L-, but not D/L-methadone seems to be more effective in reducing additional heroin abuse. Higher dosages of D/L- and probably L-methadone seem to decrease axis-I comorbidity.

P 41. Hypersomnia in atypical seasonal depression – a comparison between objective measurements and subjective reports

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Background: Previous research has demonstrated that a major part of SAD patients suffers from atypical depression.[1] Hypersomnia (i.e. excessive sleepiness, as evidenced by prolonged nocturnal sleep) has been reported by over 70% of SAD-patients.[2] However, subjectively experienced sleep patterns are known to differ from observed sleeping behavior in depressed patients. The present study compared the severity of hypersomnia as reported by the patients with objective measurements of sleep.

Methods: 17 drug-free SAD outpatients with prominent atypical depressive symptoms and 17 sex- and age-matched healthy controls were included in this evaluation. The Structured Interview Guide for the Hamilton Depression Rating Scale, SAD version (SIGH-SAD) was administered to the patients. Nocturnal activity levels were measured with wrist actigraphy (Actiwatch Plus by Cambridge Neurotechnology Ltd., Cambridgeshire, UK) for one week.

Results: Patients obtained a mean total SIGH-SAD score of 29.5 ± 4.7 and a mean atypical subscore of 13.8 ± 3.4. Mean score on item A6 was 2.5 ± 1.2 indicating a high degree of subjectively experienced hypersomnia. However, the mean daily sleep duration of SAD patients measured by actigraphy was significantly lower compared to controls (patients: $07{:}06 \pm 01{:}29$, controls: $08{:}57 \pm 01{:}52$; $p = 0.003$). We observed a 5.4% lower sleep efficiency (i.e. actual sleep time divided through total time in bed) in SAD patients compared to the control group ($p = 0.030$). There was no significant linear correlation between the severity of hypersomnia indicated by the patients and sleep duration measured with actigraphy ($r_s = 0.097$, $p = 0.711$).

Conclusions: The results of this study, while preliminary, suggest that SAD patients overestimate their sleep time. Sleepiness in the morning and difficulties getting awake could be the result of reduced sleep quality during the night. Further studies could compare sleep of SAD patients during summer and winter to evaluate changes during the seasons.

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