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Speaker Abstracts

Wednesday 19 November

S01. Symposium: New bipolar antidepressants
Chair: J. Angst, H.N. Aschauer

S0101. Are atypical antipsychotics effective in bipolar depression?

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During the course of bipolar disorder, depression is the major burden for patients. However, in the past, research has focused mainly on treatment of mania and development of mood-stabilizing agents. In contrast to unipolar depression, the controlled evidence of efficacy of drugs in bipolar depression is unimpressive. There is no treatment available with good research-based evidence of efficacy. Atypical antipsychotics are used in acute mania and there are data available to support their role in mood-stabilization. Their efficacy in bipolar depression is to be reviewed here. A computerised literature search was performed and pharmaceutical industry was asked to provide information on the topic.

Olanzapine is the only atypical antipsychotic that has been tested in a randomised controlled trial in acute bipolar depression. The study used placebo and a combination of fluoxetine plus olanzapine as control groups for olanzapine monotherapy. The results showed that olanzapine has efficacy in acute bipolar depression. A double-blind study of acute treatment of mania (olanzapine versus valproate) had a 47-week double-blind extension phase. Olanzapine was equally effective as valproate in prevention of relapse including depressive symptoms. Another study reported that efficacy of olanzapine was similar to lithium in preventing depressive episodes. Furthermore, olanzapine does not appear to have any propensity to induce a manic switch or rapid cycling.

Quetiapine and risperidone were shown to be effective in open-label studies as an antidepressant in bipolar depression. Data on other agents are more limited (e.g. clozapine, ziprasidone), but will also be reviewed.

In conclusion, more studies are needed to establish efficacy as first-line treatment in bipolar depression or to evaluate the utility of atypical antipsychotics in bipolar depression, but data so far are promising.

S0102. Long-term treatment of bipolar depression

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The management and prevention of depressive episodes in bipolar disorder remain among the major clinical challenges in psychiatry. Compared with mania, depressive episodes occur more frequently, last longer and lead to greater functional disability. However, until recently the treatment of mania has been the predominant focus of clinical research.

The use of conventional antidepressants in bipolar depression remains an understudied area, particularly with respect to long-term use. A recent study[1] suggests that, in a highly enriched sample of patients tolerating and responding to antidepressant therapy, patients continuing on antidepressants experienced lower relapse rates than those discontinuing their use. However, there are still no randomized clinical trials on which to reach evidence-based decisions regarding the role of antidepressants in the long-term management of bipolar disorder.

The recent maintenance studies of lamotrigine and lithium provide some of the most rigorous evidence for the role of these two mood stabilizers in the management of bipolar disorder. In two large, placebo-controlled trials enrolling a total of over 1300 patients, lamotrigine (now indicated for bipolar disorder in many markets) significantly reduced the risk of a future depressive episode regardless of mood state (manic or depressed) at study entry. Conversely, lithium significantly reduced the risk of future manic but not depressive episodes, regardless of initial mood state.

Ketter et al have recently proposed a new approach to mood stabilizer nomenclature, suggesting that this drug class should be divided into subgroups consisting of Type A (primarily effective against mood episodes that are Above baseline, i.e. mania and hypomania) and Type B (primarily effective against mood episodes that are Below baseline, i.e. depression).[2] The most recent maintenance data suggest that drugs such as lithium and olanzapine belong to the Type A subgroup, whereas lamotrigine belongs to the Type B subgroup. In many patients, skillful polypharmacy utilizing both types of mood stabilizers may be indicated for the optimal management of both poles of bipolar disorder.

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S0103. The switch from depression to hypomania and mania: fact or fiction?

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Objectives: to review the evidence that antidepressants cause hypomania or mania, comparing the natural history of mood disorders with the rates of switches from depression to hypomania under placebos and drugs.

Findings: At the beginning of the 20th century switches from depression to hypomania were described as reactive or spontaneous events in the natural course. Switches under imipramine were considered to be a sign of the antidepressant's potency (1958). After 1978 (Bunney 1978, Wehr and Goodwin 1987) the switch became controversial as it was considered to be potentially drug-induced and to cause deterioration of the course. Because of lack of power, there is no demonstration by double blind study of a statistical difference between the switch rates under antidepressants and placebos, although in many studies hypomania was more frequent under antidepressants than placebos. No proper meta-analysis has been carried out of the trials, which were often methodologically flawed: drop outs not reported, unequal length of treatments, no distinction between pure depression and bipolar disorder, no measurement of hypomania, publication bias. Moreover, a point consistently overlooked is that a patient can only switch into hypomania after having remitted from depression, making the number of responders or remittors the correct denominators for comparisons. Predictors of switches are: bipolarity (temperament, symptoms, diagnoses), mixed features, early age of onset, first episode, high recurrence, high number of hospitalisations, positive family history for mania, good response to treatment.

Conclusions: The zero hypothesis is that there is no difference in switches under active compounds versus placebos. This hypothesis has not been disproved by any methodologically sound trial or meta-analysis. The burden of proof still lies with the proponents of a drug-induced switch.

S0104. Continuation treatment for mania: what happens to depression?

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Long-term treatment and compliance are crucial issues in the outcome of bipolar disorder, a long-lasting condition with highly recurrent episodes which is associated to high levels of suffering, occupational dysfunction, and impairment of social life and relationships. The length of remission, when the individual is well, is reduced in many cases both with age and the number of previous episodes. More than treating acute episodes, the real challenge are long-term prophylactic strategies which aim to reduce the risks of relapse and improve interepisode function. Therefore, although a substantial number of drugs have been proven to work for the treatment of mania, from the clinicians, researchers, and regulatory bodies point of view, it is equally important to prove that any drug that claims to work for mania is not causing switch to depression. Short term trials (typically 3–4 week trials) are not appropriate to test the safety of an atimanic agent as regards to switch to depression. Recent data from well-designed controlled trials support the view that atypical antipsychotics are safer than conventional antipsychotics as far as switch to depression is concerned. Lithium and valproate would be at least as effective as atypical antipsychotics in the prevention of switch to depression, although the atypicals may be better for mania and prevention of mania. Lithium may also have specific antisuicidal effects. Lamotrigine is not an effective antimanic agent, but is clearly useful for the prevention of switch to depression after a manic episode.

A European Depression Day

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As the world becomes increasingly aware of the massive burden associated with mental disorders and takes steps to improve mental health care, the need for accurate and up-to date information is crucial. Information is required in two distinct areas: the disease burden and the available resources. Mental disorders account for a substantial proportion of disease disability and burden, yet current resources for mental health are not adequate. The burden associated with mental disorders is projected to increase over the coming years. The quality and quantity of mental health resources need to improve to meet the current and future needs.

In the light of these assumptions, the Non Governmental Organization "European Depression Day" (EDD) aims to promote a day dedicated to depression in every European country. This is made possible thanks to the action of local independent groups and the mobilization of the mass media. This initiative targets health professionals, general practitioners, psychiatrists and to the general public and requires their co-operation. One of its goals is to draw greater attention to the impact that depression has on families, society and the economy. EDD in Europe will follow the format of the existing American Depression Day and will make doctors and patients more aware of the importance of early diagnosis. In fact only early diagnosis can reduce the economic and social costs and prevent people from suffering.

S02. Symposium: Monotheraphy, new experience with risperidone in bipolar disease
Chair: S. Montgomery

S0201. The challenge of bipolar disorder for the patient if not properly diagnosed and treated

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Bipolar disorder is a severe and recurrent illness. If left untreated, it can affectalmost every aspect of a patient's psychosocial functioning: marriage, friendships, employment, financial standing and physical health. Over 90% of sufferers experience more than one episode, and 16% show a rapid-cycling course.

Surveys have indicated that the average time for correct diagnosis is 11 years. It appears that a significant proportion of patients are misdiagnosed as having major depression, while another part receives no specific diagnosis. The episodic nature of bipolar disorder, and the variability of its symptoms among patients and across the course of illness, render its diagnosis difficult. Its overlap with symptoms of schizophrenia or personality disorders and its common concurrence with co-morbid psychiatric conditions further complicate the diagnosis. In cases seeking and needing help, delayed and inaccurate diagnosis often leads to no or incorrect treatment. In the case when a patient is misdiagnosed with unipolar major depression, he is likely to be treated with an antidepressant, which might precipitate mania or hypomania or induce rapid cycling.

Under- and misdiagnosis of bipolar, thus, is common and may have serious implications towards treatment and expected outcome. As a consequence there is a need for better strategies. These should aim at detecting bipolar patients better and earlier in order to provide improved management, including treatment of acute episodes, prophylaxis, psycho-education and possibly psychotherapy. Wider recognition of bipolar disorder and thus better educational awareness and information targeted to patients and caregivers will lead to more appropriate treatment.

S0202. The use of atypical antipsychotics as monotherapy: new evidence for efficacy (short-term)

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The treatment options for bipolar disorder are increasing. Novel (atypical) antipsychotic drugs, such as risperidone, offer a number of advantages compared with conventional agents. The efficacy of risperidone (monotherapy or added to a mood stabiliser) has been demonstrated for a broad range of symptoms in mania in several double-blind, controlled trials involving more than 1,250 patients: symptomatic improvement was documented by the use of various assessment scales, including the Young Mania Rating Scale (YMRS), Global Assessment Scale (GAS), Clinical Global Impression (CGI), and Montgomery Asberg Depression Rating Scale (MADRS). Stringent analysis of the YMRS score less than or equal to 8, performed in two of the monotherapy trials and one adjunctive therapy trial, (risperidone plus a mood stabilizer) resulted significantly better remission rates when compared with placebo.

A recent European trial (3-week placebo-controlled, with a haloperidol comparator arm) confirms the efficacy and tolerability of risperidone in bipolar. When compared with placebo, significant improvements with risperidone were documented by the mean YMRS score, both at week 1 and subsequent assessments. Significantly more patients responded (= 50% reduction in YMRS total score). GAS scores and CGI scores were significantly better and MADRS scores decreased significantly more with risperidone than with placebo. In a similar US study, mania (YMRS) scores declined rapidly and significantly with risperidone monotherapy as early as day 3 ($p < 0.001$ when compared with placebo; mean dose 4.1mg). Similarly, CGI- and GAS Scores were significantly improved day 3 onwards, confirming the European observations that risperidone improves disease severity and patient functioning. Twice as many patients responded. MADRS scores decxreased more with risperidone than with placebo at day 3 and week 1. Risperidone was well tolerated (most common side effect: somnolence).

S0203. The use of atypical antipsychotics as monotherapy: new evidence for efficacy (longer-term)

S. Kasper
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Despite recent advances in treatment of bipolar disorder, the need for effective and reliable long-term therapy still exists. There is a high risk of relapse for up to 6 months after remission of an acute episode. Prolonged treatment is commonly required to control persistent symptoms and prevent recurrence. Apart from the common under- and misdiagnosis of bipolar, the limited efficacy of first generation mood stabilizers and non-compliance may affect profoundly the patients' quality of life. Achieving remission should thus be a key objective to ensure relapse prevention. With risperidone, sustained remission rates have been achieved: up to 80% in monotherapy and up to 87% in combination therapy. There is evidence that the anti-manic effect of risperidone is maintained. Sustained reduction in symptoms has been shown with risperidone in a 12-week double-blind study (together with superior tolerability to haloperidol). This is in line with observations from longer-lasting double-

blind, open-label and naturalistic studies, where progressive improvements have been observed, both in symptoms and overall functioning with atypical antipsychotic treatment. Currently, there is preliminary evidence of the efficacy of atypicals in relapse prevention of bipolar disorder. In addition, risperidone is effective in the treatment of refractory depression, anxiety and PTSD symptomatology, all commonly present in the bipolar patient and profoundly affecting long term outcome.

S0204. Clinical trials vs clinical experience: special patient populations, defining the best dosage and the best use of atypical antipsychotics in bipolar disorder

S. Montgomery
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Bipolar disorder is a heterogeneous condition: differences in symptom spectrum and severity, presence of psychotic or depressive symptoms, and co-morbidities affect its presentation. Hence, patients with bipolar may particularly benefit from treatments with broad spectrum efficacy. There is growing evidence that atypicals address a wide range of symptoms and are effective for acute and maintenance therapy of bipolar. For instance, in severe patients with a high baseline YMRS score, risperidone was superior to placebo in reducing the score at weeks 1 and 3 ($p < 0.001$). Risperidone has been documented to exert a broad spectrum activity, superior to placebo in several clinical trials, with rapid onset of action, and effective in both moderately and severely ill patients, with or without psychotic symptoms. Both add-on and monotherapy achieve substantial remission rates. Optimal dose titration deserves attention, as to achieve success.

Risperidone's unique receptor profile also provides a rationale to treat depressive and anxiety symptoms. Various clinical trials prove its efficacy in acute bipolar mania (both monotherapy and combination with mood stabilizers). According to preliminary results, adjunctive risperidone enhances the anti-manic and antidepressant effects of mood stabilizers in rapid cycling patients, and also augments antidepressant response: 76% of patients with major depression on risperidone plus fluvoxamine achieved remission. In depressed patients resistant to standard antidepressants, open-label augmentation of citalopram with risperidone resulted in markedly improved MADRS, HAM-A, and CGI-S scales. Risperidone may potentially also be useful for anxiety disorders, such as PTSD and OCD. The reviewed data are in line with observations reported for other atypicals: they provide evidence that risperidone offers benefits to a range of patients with prominent affective and/or anxiety symptoms.

S03. Plenary lecture

S03. The search for genes of bipolar disorder: treatment implications
Chair: S. Kasper

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Bipolar disorder is a common and complex illness characterized by the alternance of depressive and manic episodes, and a rather high mortality rate mainly due to suicide. The bipolar phenotype is most probably determined by the interaction of susceptibility genes and psychosocial vulnerability factors. Classican studies on human genetics of bipolar illness will be reviewed. These include adoption, twin and family studies of bipolar patients. Modern methods using molecular genetic strategies as they apply to psychiatric genetics will be discussed. Several susceptibility genes have been proposed to be related to the bipolar phenotype, among them candidate genes of interest for the understanding of the pathophysiology of bipolar disorder. Nosological, therapeutic and ethical implications of molecular genetic approaches in affective disorders will be emphasized.

Thursday 20 November

S04. Symposium: Recent advances in treatment of anxiety disorder
Chair: M. Bourin, E. Eriksson

S0401. Atypical antipsychotics in treating anxiety disorders – focus on OCD

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Obsessive compulsive disorder (OCD) is a common disorder with a worldwide prevalence of about 2% and unique with regard to treatment response.[1] As opposed to other psychiatric disorders such as depression, panic disorder, post-traumatic stress disorder, etc, in which monoadrenergic and serotonergic medications were found to be effective, it seems that OCD responds primarily to serotonergic medications.[1] However, there are about 40% of the patients who are not responding, or who respond only partially to appropriate intervention with serotonergic medication. In those resistant patients, the possibility of adding on antipsychotic, and especially the new atypical antipsychotic is often raised.[2]

There are actually four types of situation where intervention with antipsychotics might be considered. Obsessive compulsive patients with poor insight (what was previously called 'psychotic obsession'), schizophrenic patients with OCD, obsessive compulsive patients with tic disorder, and obsessive compulsive patients who did not respond to

intervention with an adequate treatment (in terms of dose and duration) or antiobsessive medication.

The data supporting the role of antipsychotic medication in obsessive compulsives with poor insight are not convincing.[3] However, at times the treatment dilemma (antipsychotic or antiobsessive) actually derives from diagnostic ambiguity; many of the very severe ego-syntonic obsessive compulsive patients may present themselves in such a bizarre way that they might be erroneously diagnosed as schizophrenic and treated accordingly, while careful and knowledgeable examination will discover that this is actually a severe case of OCD that should be treated with antiobsessive medication and not antipsychotic.[4]

The prevalence of OCD amongst schizophrenic patients ranges from 10–25% and has a negative effect on the prognosis for those substantial proportion of schizophrenic patients.[5] Preliminary data imply that for this subset of patient (the schizo-obsessive patients) a combination of antipsychotic and antiobsessive medication might be useful.[6]

It is crucial to screen for tic disorder in patients with OCD as this subset of patients responds (both in terms of obsession and tics) to a combination of typical antipsychotic and antiobsessive medication.[2]

Data in regard to augmentation of OCD patients who did not respond to treatment with SSRI suggest that risperidone might have a specific therapeutic potential in this subset of patients. The role of antipsychotics with 5HT 1D properties like ziprasidone needs to be studied.

Antipsychotics in OCD are indicated in patients with OCD+tic disorder (the data cover typical antipsychotics), and in patients with refractory OCD (current data suggest specific role for risperidone). The 'schizo-obsessive' patients — a combination of antipsychotics (probably the atypical ones) with antiobsessive medication might be preferred as opposed to antipsychotic alone, while in 'psychotic OCD', treatment should probably focus on adequate use of antiobsessive medication.

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S0402. Is PMDD an anxiety disorder?

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Premenstrual dysphoric disorder (PMDD) is a severe variant of premenstrual syndrome that afflicts approximately 5% of all women of fertile age. The hallmark of the condition is the surfacing of symptoms during the luteal phase of the menstrual cycle, and the disappearance of symptoms shortly after the onset of menstruation. Whereas many researchers have emphasized the similarities between PMDD and anxiety disorders, and in particular panic disorder, others have suggested that PMDD should be regarded as a variant of depression. Supporting both these notions, the treatment of choice for PMDD — the serotonin reuptake inhibitors (SRIs) — is also first line of treatment for depression and for most anxiety disorders. In this presentation, the relationship between PMDD on the one hand, and anxiety and depression on the other, will be discussed. The conclusion will be that PMDD is neither a variant of depression nor an anxiety disorder, but a distinct diagnostic entity, with *irritability* and *affect lability* rather than depressed mood or anxiety as most characteristic features. The clinical profile of SRIs when used for PMDD — including a short onset of action-suggests that this effect is mediated by other neuronal circuits than the antidepressant and anti-anxiety effects of these drugs. Notwithstanding the fact that PMDD hence should be regarded as a distinct entity, it however does share certain characteristic traits with panic disorder, including an enhanced respiratory variability, as well as anxiety upon exposure to CO2, lactate or CCK. Possible reasons for these intriguing similarities between panic disorder and PMDD, including a tentative involvement of sex steroids, serotonin, and angiotensin in both conditions, will be discussed.

S0403. Recent advances in panic disorder

M. Bourin
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Panic disorder is an incapacitating condition with long term negative consequences. Lifetime prevalence is estimated between 1.5% and 3%. The comorbidity with other psychiatric illnesses is significant (more than 50%). The more frequent associated disorders are anxious disorders, depression, substances abuse and personality disorders, somatisations and the passage to the suicidal act. It seems that comorbidity of bipolar disorder and panic disorder is associated rapid mood switching (McKinnon et al, 2003). On the other hand cigarette smoking in PD patients is linked with more severe and inter anxiety symptoms compared to PD non smokers (Zvolensky et al, 2003). There appears to be a remarkable similarity between the physiological and behavioural consequences of response to a conditioned fear stimulus and a panic attack. In animals, these responses are

mediated by a "fear network" in the brain that is centered in the amygdala and involves its interaction with the hippocampus and medial prefrontal cortex. Projections from the amygdala to hypothalamic and brainstem sites explain many of the observed signs of conditioned fear responses. It is speculated that a similar network is involved in panic disorder. Medications, particularly those that influence the serotonin system, are hypothesized to desensitize the fear network from the level of the amygdala through its projects to the hypothalamus and the brainstem (Gorman et al, 2000). Other authors found a positive correlation between left hippocampal volume and duration of panic disorder with recent cases showing more reduction than older cases, with a decreased volume of the left temporal lobe (Uchida et al, 2003).

The SSRIs represent the treatment of choice with an equal action on the panic attacks and comorbid problems. Yet there remains a gap between pharmacological treatments guidelines and actual delivery that recommendations to use SSRIs to treat panic disorder are not being followed (Bruce et al, 2003). Benzodiazepines are still used, yet there is no difference of response in the patients presenting with or without respiratory symptoms (Valença et al, 2003) as it was claimed previously (Briggs et al, 1991). The principal risk with benzodiazepines is that of the development of dependence. This risk thus limits their prescriptions to emergency situations where a rapid symptomatic amelioration is required and the onset of action of antidepressant treatment allows the reduction and finally the cessation of benzodiazepine treatment. In therapeutic terms the objective is to obtain a complete disappearance of panic attacks during a period of one month to 2 years which is long term treatment not compatible with benzodiazepine use.

S0404. Recent advances in social phobia

C. Allgulander
Karolinska Institutet, The Neurotec Department, Stockholm, Sweden

This presentation aims to provide an overview of recent published research into social phobia (Social anxiety disorder, SAD) that is relevant to future clinical studies. Since 1984 there have been 1357 PubMed citations. SAD is now recognized as a public health issue with a 1-year prevalence of 2–3%, although it remains underdiagnosed. Screening instruments have been developed. Evidence-based treatment guidelines are established based on cognitive behavioural therapy and serotonergic medications as treatments of choice.

Twin studies document the heritability of fear of negative evaluation. Children with behavioral inhibition at age 2 displayed increased amygdala response to unfamiliar faces at age 22. Taking a test in front of an audience triggered a cortisol response indicative of increased HPA axis reactivity in SAD subjects.

Neuroimaging studies have employed anxiety provocation to document amygdala as the focus of response to perceived social threats. This response is attenuated by CBT or serotonergic medication. The serotonin reuptake transporter (SERT) became highly occupied at therapeutic doses of paroxetine in patients with SAD.

Healthy women recognized happy and fearful faces faster and more accurately when administered citalopram iv. Patients with SAD avoided looking at the eyes of faces in such an experiment. The avoidance of eye contact was also documented in videotape recordings of SAD subjects while conversing. Although shyness is perceived as a typical SAD feature, 82% of shy subjects did not meet with the SAD diagnostic criteria.

A substantial portion of SAD subjects suffer from excessive sweating, and subjects with "shy bladder" or cervical dystonia frequently suffer from SAD. Elective mutism may be considered an early variant of SAD. Alcohol abuse was found to be common in SAD subjects, although one study found alcohol to be no more a social anxiolytic than placebo. Women with SAD more often lacked a sex partner, and more often reported impairment in arousal and satisfaction, and men with SAD more often paid for sex.

Delienating primary SAD from innocuous forms of social anxiety remains an issue, perhaps to be resolved in the DSM-V and using the spectrum concept.

Recent treatment studies include SSRIs, SNRIs, pregabalin, and virtual reality.

S05. Symposium: Depression and anxiety disorders: the importance of fast and effective treatment

Chair: D. Baldwin, W.J. Burke

S0501. Priorities in treating depression

W. J. Burke
Nebraska Medical Center, Omaha, USA

Among the goals of new drug development is improvement of the "therapeutic ratio" (i.e., maintenance or enhancement of efficacy, combined with diminishment or elimination of unwanted effects) relative to other classes of agents. In the case of antidepressants, the selective serotonin reuptake inhibitors (SSRIs) have become first-line treatment. Their increased pharmacological specificity is translated into a favourable efficacy and tolerability profile, with greater safety and tolerability compared with tricyclic antidepressants, monoamine oxidase inhibitors and even some of the newer mixed-mechanism drugs. Other important issues are response and remission rates, which are now starting to show differences between the various antidepressants. The presentation will review the clinical evidence supporting the usefulness of SSRIs and other newer antidepressants for the treatment of depression

S0502. How can the treatment of depression be optimised?

S. Kasper
Professor and Chairman, Department of General Psychiatry, University of Vienna, Vienna, Austria

Since the burden of depression is predicted to increase, there is a continuing need to improve and optimise the treatment of depression. Selective serotonin reuptake inhibitors (SSRIs) and non-selective serotonin noradrenaline reuptake inhibitors (SNRIs) have proved efficacious in treating depression.

Escitalopram, the most selective SSRI available for the treatment of depression, offers new advantages for the treatment of depressive disorders. In two studies comparing escitalopram to venlafaxine XR, both efficacy and tolerability advantages emerged for escitalopram compared to venlafaxine XR and demonstrate that escitalopram has a better risk/benefit profile than venlafaxine XR in the treatment of depression.[1,2] Since long-term treatment is needed in order to reduce the risk of relapse and recurrence of depressive episodes, pharmacological treatments with a good long-term tolerability are needed. Escitalopram has been demonstrated to have a favourable short- and long-term tolerability profile and should be considered for continuation and maintenance treatment of patients with depression.

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S0503. Escitalopram – a unique mechanism of action

C. Sánchez
H. Lundbeck A/S, Copenhagen, Denmark

Citalopram is a selective serotonin reuptake inhibitor (SSRI) antidepressant consisting of a racemic 1:1 mixture of the R(−)- and S(+)-enantiomers. Nonclinical studies have shown that the selective serotonin reuptake inhibitory activity of citalopram is attributable to the S-enantiomer, escitalopram, which has been developed as a new single-enantiomer antidepressant. Initial nonclinical and clinical studies comparing escitalopram and citalopram to placebo found that corresponding doses of these two drugs (that is, containing the same amount of the S-enantiomer), and therefore expected to have the same effect, resulted in a better effect for escitalopram. Although R-citalopram is essentially inactive with regards to SSRI activity, these results suggest that the R-citalopram present in citalopram inhibits the effect of escitalopram.

Escitalopram has greater efficacy and faster time to onset than comparable doses of citalopram in biochemical, functional, and behavioural experiments. The lesser efficacy of citalopram in these nonclinical studies is due to the counteraction of the effect of escitalopram by R-citalopram, possibly via an allosteric effect via its interaction with the serotonin transporter.

Data from controlled clinical trials in patients with major depressive disorder consistently show better efficacy and faster time to symptom relief with escitalopram than with citalopram. Thus, the R-enantiomer present in citalopram counteracts the activity of escitalopram, thereby providing a basis for the pharmacological and clinical differences observed between citalopram and escitalopram.

S0504. Unmet needs in anxiety disorders – how can we improve treatment?

D. Baldwin
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Awareness of the burden of anxiety disorders is increasing, and new treatment approaches are needed. The selective serotonin reuptake inhibitors (SSRIs) have become the first-line choice for treatment of anxiety disorders, but little is known about the comparative efficacy and tolerability of different SSRIs in the treatment of anxiety.

SSRIs are recommended as the initial treatment in most anxiety disorders,[1] having advantages over benzodiazepines and some other compounds on the basis of their efficacy, tolerability, effectiveness in co-morbid conditions, and lack of drug dependency.[2] An SSRI with greater efficacy and a lower incidence of side effects could lead to improved clinical outcomes, across a range of anxiety disorders.

Patients with chronic conditions, such as social phobia, generalized anxiety disorder and panic disorder, need long-term care with efficacious and well-tolerated treatments. Escitalopram, a new SSRI, has proved efficacious and well tolerated both in short- and long-term treatment of patients with social phobia, and has efficacy in panic disorder and generalized anxiety disorder.

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S06. Symposium: New treatments for GAD
Chair: S. Montgomery, R. Nil

S0601. Pregabalin compared with other anxiolytics in GAD

R. Kavoussi
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For the past 40 years, the major treatments for anxiety have been limited to GABA agonists (e.g., benzodiazepines) and agents which act on the serotonergic system (e.g., tricyclics, SSRIs, buspirone). Pregabalin is a novel compound which has demonstrated efficacy in neuropathic pain, epilepsy, and generalized anxiety disorder (GAD). PGB has a novel mechanism of action, different from the above agents, involving potent and selective binding to the alpha-2-delta subunit of voltage-dependent calcium channels, resulting in inhibitory modulation of excitatory neurotransmitters such as glutamate. PGB has no clinically significant effects at GABA-A or B or benzodiazepine receptors. To date, five short-term placebo controlled studies (4–6 weeks in duration) and one long-term relapse prevention study have demonstrated the efficacy of pregabalin in the treatment of GAD.

Of the short term studies noted above, four had active comparators: lorazepam 6 mg/day (two studies), alprazolam 1.5 mg/day, and venlafaxine 75 mg/day. Although not powered for equivalence or superiority, these studies demonstrated that pregabalin has efficacy comparable to these agents and a rapid onset of action.

In this session, comparative data for pregabalin versus these other agents will be presented and potential future comparative trials will be discussed.

S0602. SSRIs in the treatment of generalised anxiety disorder

D. Baldwin
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Selective serotonin re-uptake inhibitors (SSRIs) have proven efficacy in acute, continuation and maintenance treatment of patients with major depression, and in short-term and long-term treatment of a range of anxiety disorders including panic disorder, social anxiety disorder and post-traumatic stress disorder. The efficacy and tolerability of SSRIs in the treatment of patients with generalised anxiety disorder has been studied only recently, but randomised controlled trials indicate that escitalopram, paroxetine, and sertraline are all significantly more efficacious than placebo in reducing the severity of anxiety symptoms in acute treatment.[1,2] Relatively little is known about the efficacy of SSRIs in the prevention of relapse, the comparative efficacy and tolerability of differing SSRIs and other evidence-based treatment approaches. This presentation will review data from relevant randomised placebo-controlled and comparator-controlled studies, and highlight the clinical and research needs that still need to be addressed.

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S0603. Discontinuation symptoms in SAD or GAD or depression

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Abrupt discontinuation of long-term pharmacotherapy for depression and anxiety may be associated with the emergence of adverse events (AEs). This problem has gained further attention as a result of the increasing recognition of the need for long-term treatment in anxiety and depressive disorders. Regulatory guidelines for drug development in this field, therefore, require the investigation of discontinuation symptoms. The present descriptive overview uses data from clinical trials with the new SSRI escitalopram to address the following issues: is the discontinuation profile drug- and/or indication-specific? does it depend on the length of treatment? does it play a role in the process of relapse? and how are discontinuation symptoms assessed?

A comparison of different discontinuation and withdrawal scales revealed that the DESS checklist (discontinuation-emergent signs and symptoms[1]) covers the largest spectrum of potential symptoms. This clinician-rated checklist was, therefore, used in escitalopram studies conducted in depression and in social anxiety disorder (SAD).

This overview presents data from two comparative studies in acute treatment of depresssion (one versus venlafaxine and one versus paroxetine) and from two long-term SAD studies, one of which used paroxetine as the active reference. In addition, AEs were investigated in a paroxetine comparative generalized anxiety disorder (GAD) trial after abrupt discontinuation following a 24-week treatment period.

Although the DESS checklist scale generally leads to a higher incidence of reported discontinuation symptoms, the AE reporting system may also provide an assessment of the clinically relevant symptoms occurring after discontinuation. Compared to the modest discontinuation profile of escitalopram, paroxetine (and venlafaxine in depression) showed a more severe discontinuation profile in depression, SAD (both by DESS) and GAD (spontaneously reported AEs). No apparent differences between indications could be detected in discontinuation profiles after 8, 12 and 24 weeks of treatment. This leads to the conclusion that discontinuation

profiles may differ between drugs of the same class (for example, SSRIs) and that such different profiles remain broadly similar in different indications.

Finally, a SAD relapse prevention study allowed the review of early relapses, during the first two weeks after an abrupt switch from escitalopram 10 or 20 mg to placebo. Relapse occurred with and without the emergence of discontinuation symptoms as assessed by the DESS, leading to the conclusion that early relapse is not necessarily associated with discontinuation symptoms.

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S0604. Fast onset of response in GAD

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Rapid response anxiolytics have an important place in the treatment of GAD. GAD is a serious and potentially dangerous condition with an increased risk of suicide and of concomitant physical illness. The use of rapid response anxiolytics would have a potential advantage for those with GAD as well as their physicians and is therefore an important target of drug development.

Current methods for establishing rapid response, which examine the earliest point at which a significant difference between drug and placebo is seen, indicate that anxiolytics such as pregabalin and possibly lorazepam have an early response in contrast to the rather slower response observed with antidepressants such as imipramine, paroxetine, and venlafaxine. The earliest point of a significant drug placebo difference is observed to be rather variable for antidepressants and depends on a number of factors such as the size of the study and the level of placebo response.

Other methods may prove more useful. A survival analysis method comparing time to achieving a responder status (for example 50% reduction on HAM-A) compared to placebo may prove more useful. The most convincing evidence would depend on demonstrating a significant difference between the new drug and a conventional comparator anxiolytic either in a metanalysis of studies or preferably in a large well-conducted comparator study.

S07. Symposium: Pain in psychiatric disorders
Chair: C. Allgulander, D. Perahia

S0701. Painful physical symptoms in depression

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Pain is both a common symptom of major depression and a common comorbidity with a complex causal relationship. Tricyclic antidepressants (TCAs) have long been known for their efficacy in chronic, especially neuropathic, pain. Their analgesic effects are likely mediated by dual serotonin (5HT) and norepinephrine (NE) reuptake inhibition. Selective serotonin reuptake inhibitors (SSRIs) have also been studied in pain disorders but have been found to be less effective. More recently, novel agents have been developed, which recreate the dual 5HT and NE reuptake inhibition of some of the TCAs but without many of the associated adverse effects which limit their tolerability. These include venlafaxine, milnacipran, and duloxetine.

The prevalence and significance of painful physical symptoms as part of the syndrome of depression will be discussed, as will the limitations of SSRIs in the treatment of these symptoms and pain syndromes in general. Data demonstrating the effectiveness of duloxetine, a novel dual reuptake inhibitor of 5HT and NE, in the treatment of painful physical symptoms of depression will be presented and supplemented by data demonstrating the analgesic effects of duloxetine in other indications.

S0702. Pregabalin and neuropathic pain

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There has been increasing interest in the use of psychotropic agents in the treatment of neuropathic pain (e.g., pain secondary to diabetic peripheral neuropathy, post-herpetic neuralgia, etc). There is a long history of anecdotal evidence suggesting that tricyclics, SSRIs, and SNRIs may be effective in reducing pain in these conditions. However, until recently, there has been a lack of systematic data on the efficacy of compounds to treat these conditions. Gabapentin, an antiepileptic agent, is indicated for the treatment of broad neuropathic pain in a number of countries and specific pain syndromes in others (e.g., post-herpetic neuralgia in the United States and France).

Pregabalin is a novel compound which has demonstrated efficacy in epilepsy and generalized anxiety disorder (GAD). Pregabalin has a novel mechanism of action involving potent and selective binding to the alpha-2-delta subunit of voltage-dependent calcium channels, resulting in inhibitory modulation of excitatory neurotransmitters such as glutamate. Pregabalin has been shown to be effective in the treatment of neuropathic pain arising from diabetic peripheral neuropathy and post-herpetic neuralgia.

In this session, data demonstrating the efficacy of pregabalin for the treatment of neuropathic pain will be discussed.

S0703. Animal models and mechanisms

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Psychiatric illness, such as major depression, is frequently associated with somatic complaints, for example 45–95% of patients with depression only present somatic symptoms at first visit.[1] Depression is also more common in patients with chronic pain conditions than in healthy controls.[2] Overall there is substantial clinical evidence that antidepressants are as effective as anticonvulsants in relieving pain symptoms associated with chronic pain conditions,[3,4,5] e.g. neuropathic pain, lower back pain. However, many clinical studies are hampered by small sample sizes and diagnostic and methodological flaws. Furthermore, most controlled clinical studies have been conducted with tricyclic antidepressants (TCA) and the pharmacological mechanisms by which they mediate pain relief remain unclear. Pharmacological studies indicate that both serotonin (5-HT) and noradreline (NA) are involved in modulation of the pain response. Thus TCAs may mediate their pain relieving effect by inhibition of 5-HT and/or NA reuptake. Relatively few and rather contradictory controlled clinical studies have been conducted with selective 5-HT reuptake inhibitors.[3]

Progress in pain research, especially in recent years, has been aided by the development and validation of animal models. Models of acute nociception and neuropathic pain may help to identify potent and effective drugs and may also help in understanding the mechanism of action of currently used drugs. Formalin induced pain is one of the most widely used and predictive models for novel compounds and is a well- characterised behavioural model of tonic chemogenic pain. It has the advantage of easy assessment of spontaneous nocifensive behaviours, such as paw licking. Animal models for neuropathic pain largely involve the chronic constriction injury models, which utilise the ligation of the sciatic nerve.

The presentation will provide an overview of available animal models of pain conditions with an emphasis on models where antidepressants have been studied. The pharmacological mechanisms involved in these responses will be surveyed.

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S0704. Venlafaxine and the control of pain

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Tricyclic antidepressants have demonstrated efficacy in treating often-severe diabetic neuropathy (DN) pain by enhancing synaptic levels of serotonin and norepinephrine. Venlafaxine extended release (XR) is a newer antidepressant, indicated for treatment of depression and generalized anxiety disorder, that selectively inhibits the reuptake of serotonin and norepinephrine. The current study evaluated the efficacy, safety, and tolerability of venlafaxine XR as a treatment for painful DN. Two hundred and forty-four patients were randomly assigned to treatment with venlafaxine XR 75 mg or 150–225 mg, or placebo, for ≤ 6 weeks. The primary efficacy variables were pain intensity and pain relief scales, and secondary efficacy variables were Patient Global Rating of Pain Relief and Clinical Global Impressions (CGI) scale (Severity of Illness and Global Improvement items).

As measured by the primary efficacy variables, venlafaxine XR 150–225 mg resulted in significantly ($P < 0.05$) lower pain intensity (weeks 4–6) than venlafaxine XR 75 mg and placebo, and significantly ($P < 0.05$) greater pain relief (weeks 2–6) than placebo. Venlafaxine XR 75 mg differed statistically from placebo only on pain relief at weeks 2, 3, and 5. Analgesic response rates on the pain intensity scale at week 6 were 39%, venlafaxine XR 75 mg; 56%, venlafaxine XR 150–225 mg; and 34%, placebo ($P = 0.007$ venlafaxine XR 150–225 mg vs placebo; $P = 0.040$ venlafaxine XR 150–225 mg vs venlafaxine XR 75 mg). On the secondary measures, similar results were obtained on Patient Global Rating of Pain Relief and CGI–Severity of Illness and Global Improvement. On CGI–Global Improvement, statistical superiority ($P < 0.05$) over placebo was also demonstrated for venlafaxine XR 150–225 mg.

Because presence of depression was cause for exclusion, symptom improvement can only be attributed to an analgesic, rather than antidepressant, effect. Consistent with its labeling, the most common adverse event associated with venlafaxine XR was nausea. The demonstrated efficacy and favorable safety-tolerability profile of venlafaxine XR in the amelioration of DN pain suggest that this antidepressant could be considered for the analgesic needs of this patient population.

S08. Symposium: The neurobiology of depression: bridging brain and body to achieve and retain remission

Chair: S. Kasper

S0801. Treating depression: a paradigm shift

S. A. Montgomery
Imperial College, University of London, UK

Despite the high prevalence of depressive symptoms and full major depressive episodes in patients of all ages, depression

is under-diagnosed and under-treated by primary care practitioners, who are, paradoxically, the providers most likely to see these patients initially. Both recognition and diagnosis of depression rest on an awareness of risk factors for depression, as well as elicitation of the key signs, symptoms, and history of illness. Depression may co-occur with non-psychiatric medical disorders or with other psychiatric disorders. Some patients may initially deny the depressed mood, but may identify the somatic symptoms (sleep, appetite, and weight changes). Upon further discussion, the interviewer should return to the issues of mood and interest. Patients may initially complain about sleep, appetite, energy, concentration, or intermittent pain. The clinician should be alert to considering the diagnosis of depressive illness in these patients. Once major depressive disorder is diagnosed, interventions that predictably decrease symptoms and morbidity earlier than would occur naturally in the course of the illness are logically tried first. According to the Agency for Health Care Policy and Research, the key initial objectives of treatment, in order of priority, are 1) to reduce and ultimately to remove all signs and symptoms of the depressive syndrome; 2) to restore occupational and psychosocial function to that of the asymptomatic state; and 3) to reduce the likelihood of relapse and recurrence.

S0802. Is two better than one? Strategies to achieve remission

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Depression and its treatments have long been linked to the neurobiology of monoaminergic neurotransmitter systems, especially serotonin (5-HT) and norepinephrine (NE). Although it is not clear that dysfunction of these monoamine systems is causally linked to the pathophysiology of depression, it is well established that effective treatments enhance either serotonergic neurotransmission, noradrenergic neurotransmission, or both. Specific pathways may be the anatomical substrates of relief of specific symptom clusters of depression. Thus, emotional symptoms (e.g., depressed mood) and cognitive symptoms (e.g., problems concentrating) may be relieved by enhancing 1) monoaminergic output to the frontal cortex; 2) guilt and anxiety from limbic areas; and 3) sleep and vegetative symptoms from the hypothalamus and brainstem. Descending serotonergic and noradrenergic pathways are involved in the perception of painful physical symptoms, normally exerting inhibitory actions on painful input into the CNS. Data from preclinical models, suggest that enhancing monoaminergic output to descending spinal pathways may be responsible for relieving the perception of painful physical symptoms in depression; this is done far more effectively if both serotonergic and noradrenergic neurotransmissions are enhanced than if serotonergic neurotransmission alone is enhanced. These data have implications for the treatment of patients suffering simultaneously from depression and physical symptoms.

S0803. Dual-action antidepressants: the new frontier for treatment for co morbid depression

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Novel agents have been developed recently which recreate the dual serotonin (5-HT) and norepinephrine (NE) reuptake inhibition of some TCAs without the limitations on safety and tolerability. These include venlafaxine, milnacipran, and duloxetine. Along with pain, other physical symptoms including fatigue, sleep disturbances, headaches, and general body aches, are recognized as symptoms of depression. Depression that occurs with accompanying physical symptoms has a significant impact on the patient's quality of life. If these physical symptoms linger after treatment for depression has begun, it can greatly diminish the likelihood of achieving remission. This presentation will review traditional strategies for treating depression with and without prominent physical symptoms, including the integration of pharmacological treatments and behavioural treatments. In addition, it will include new data from recent clinical trials with medications that provide balanced 5-HT and NE enhancement, and the implications of such data for more complete symptom resolution, remission, and treatment selection.

Friday 21 November

S09. Symposium: Controlling placebo
Chair: A. Khan, S. Montgomery

S0901. Placebo trials in depression and anxiety

A. Khan, R. Kolts, W. A. Brown
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Large scale, well conducted, antidepressant and anxiolytic trials fail to show superiority over placebo about half the time with approved and established agents. This phenomenon is linked to variable, unpredictable and increasing placebo response. Based on the meta-analysis of 52 antidepressant trials and 40 anxiolytic trials, we have identified certain patient characteristics as well as trial design features that may affect magnitude of placebo response. Specifically, the data suggest that severity of depressive symptoms, as measured by mean total HAM-D score may lead to a differential response to antidepressant and placebo. Additionally, the male/female distribution may affect antidepressant/placebo differences. Regarding trial design, the data suggest that flexible dosing may reduce magnitude of symptom reduction by almost 20%. Further, higher the number of treatment arms, there is

less likelihood of obtaining a positive trial. Use of MADRS may yield comparable results to HAM-D.

S0902. Rater training, certification and other myths

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Within and across study variability in degree of change either on placebo or active drug continues to be a feature of randomized controlled trials, particularly in the case of antidepressants. In some trials, this variability appears to be a function of site and geography. This observation raises two obvious possibilities — local rater behavior and/or method of patient selection — as major sources of variance.

Over the last several years we and others have focused on rater behavior and whether or not training could be shown to favorably impact on inter-site variance and/or "effect size" (i.e. drug-placebo differences). As reported previously, a fairly elaborate one-day rater training effort carried out at the beginning of large multi-site trials had disappointingly small impact on immediate or subsequent performance. Current data, based on an independent review of audiotapes of the actual HAM-D rating interviews in two different multi-site trials, shows that 60% of interviews are insufficient in duration and detail to support even the most basic level of scoring. Not surprisingly, data from those sites with these inadequate interviews, failed to separate active antidepressant from placebo. Such findings reinforce the need to find some way of ensuring that rater behavior is maintained at a quality level in clinical trials.

But what can be done to improve rater performance under real-life conditions? There is emerging information on at least three alternatives to standard approaches to rater training and/or carrying out ratings during trials of anti-depressants. The first, use of an interactive voice response system to capture self-report versions of the HAM-D, revealed excellent psychometric properties but mixed results in actual clinical trials. As one of the individuals who developed this approach has commented, "We had hoped that the IVR HAM-D would show larger effect sizes than the clinician-administered version, but in fact the results seemed to suggest the opposite. . . .".

The second approach takes on the question of rater training which incorporates newer technologies such as the Internet, CDs and videoconferencing which allow rating to be better standardized and centralized. In collaboration with investigators funded by the National Institute of Mental Health to develop a training paradigm incorporating these technologies, it has been possible to improve rater performance under specified test conditions as well as providing ongoing monitoring of rater performance during the course of a trial. It remains to be seen if such enhanced training is really making a difference in our ability to distinguish active drug from placebo.

The third strategy has just completed a small feasibility study and is to be tested in the field over the next year. This involves utilization of videoconferencing to link subject to centralized interviewers/raters. These are a core group of off-site specialists who are blind to treatment condition and study visit with no investment in enrollment. A consortium of academic investigators and small companies interested in tools to be utilized in clinical trials is being funded by a Lilly/Pfizer method research effort to test the centralized rater approach.

In addition to discussing all of the above, the degree to which rater performance vs. other sources of variability on outcome of antidepressant trials will be addressed.

S0903. Severity increases assay sensitivity

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Over the past few years, more than half of the placebo-controlled trials in depression have failed to differentiate an active comparator of proven efficacy from placebo. Post-hoc analyses of these failed trials have shown that a clear separation of the active comparator from placebo was achieved in the group of the more severely ill patients. Some recent examples with a new class of antidepressants agents have confirmed previous observations. Selecting a more severely depressed patient population using a cut-off score on a severity scale does not, however, seem to solve the problem as exemplified in some studies. Effective alternative approaches do exist and their advantages and disadvantages are discussed.

S0904. Better monitoring, better patients

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Over the past 20 years, drug developers have struggled with inconclusive trials in depression, anxiety and increasingly in other disorders such as bipolar mania. This has contributed to increased costs of programs and has prevented the speeding up of development time, because of the need to repeat trials.

Activities to remedy this issue have often focused on improving the quality of the outcome ratings by intense training and certification. Attempts have also been made to identify patient-related factors that may contribute to failed studies. Investigators were asked to recruit only samples that would be informative for the study, and to exclude mild or borderline cases. While these activities are necessary, they have not been sufficient as the number of inconclusive trials remains high.

One area which may deserve more attention in the future is the monitoring of studies. Currently, monitors often focus on the more administrative parts of the trial and formal aspects of GCP compliance. This presentation will propose that the emphasis is shifted to "medical monitoring",

involving CRAs and physicians, and will present examples of how monitoring can be improved to produce better assessments and clearer results.

S10. Symposium: Controlling mania with antipsychotic treatment
Chair: G.B. Cassano

S1001. Pharmacology of atypical antipsychotics in mania

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In recent years the oversimplified dopamine hypothesis of mania and of the action of antipsychotics has been challenged by more complex receptor affinity models (dopamine D2 receptors fast dissociation and loose binding) and interaction (D2 vs. 5-HT_{2A-C}; α1-2; etc). Since then, several studies have suggested that 5-HT_{2A} antagonism could play a major role in preventing the EPS induced by haloperidol.[1] The therapeutic rationale for the 5-HT_{2A} antagonism derives from a proposed disinhibitory action on nigral dopaminergic neurons,[2] leading to increased striatal DA output and competitive displacement of the neuroleptics from post-synaptic D_2 receptor.[3,4] The search for selective 5-HT_{2A} receptor antagonists able to reduce the undesired effect of a D_2 blockade was actively pursued in the design of mixed serotonin 5-HT_{2A} / D_2 antagonists, such as risperidone, olanzapine or quetiapine, able to improve the therapeutic outcome in the treatment of chronic psychotic states.[5]

Interestingly, and in spite of the type of receptor interaction involved, it is evident that ligand-receptor relationship, occurring over milliseconds, cannot fully account for the clinical effects observed over weeks or months.[6] Recent preclinical and clinical studies have shown that signalling pathways involved in regulating cell survival and cell death are to be considered as long-term targets for the actions of mood stabilizers. Chronic neuroleptic treatment causes structural and morphological changes in striatum, accumbens and prefrontal and limbic cortex that are correlated with sustained changes in the expression of transcription factors, immediate early genes, second messengers and neuropeptides. In addition, these effects of antipsychotics are shared by mood-stabilizers of different structure and pharmacological classes. A variety of targets have been proposed as potential effectors of lithium, carbamazepine and valproate action, including a number of factors involved in cell survival pathways, such as CREB, BDNF, Bcl-2, and MAP kinases, and may thus bring about some of their delayed long term beneficial effects via underappreciated neurotrophic effects.[7] However, before innovative treatments may be developed for the treatment of mania, one should solve the puzzle on why also antidepressant share some of the action of the mood stabilizers. The critical appraisal of these data define the need of a better neurobiological model for the explanation of the pathophysiology and therapy of mood disorders.

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S1002. Mania treatment: use of atypical antipsychotics

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Antipsychotics have been extensively used in the treatment of mania over the past several decades. In recent years, novel atypical antipsychotics, which include clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, have demonstrated antimanic efficacy and rapid onset of action both in monotherapy and in adjunct therapy with mood stabilizers. Atypical antipsychotics are also associated with a reduced incidence of neurological side-effects as compared to typical antipsychotics. Patients treated with these agents at effective doses that do not cause extrapyramidal effects benefit from less dysphoria, less impaired cognition and lower risk of tardive dyskinesia. This presentation will review the available research supporting the efficacy of atypical antypsychotics, as well as guideline- and practice-based literature. The available literature raises the suitability of newer antipsychotic agents as first-line agents in the treatment of acute mania and the efficacy in continuation therapy for bipolar patients, although future studies should evaluate their long-term efficacy and safety.

S11. Symposium: New results in mania
Chair: J. Loftus, E. Vieta

S1101. Risperidone in mania

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Bipolar disorder is a recurrent, severe, and often debilitating illness characterized by episodes of mania and depression, and long-term psychosocial disability.[1,2] It affects an estimated 3.7% of the adult population.[3] For many years, the standard treatments for acute mania in the United States have been lithium and divalproex, administered either alone or in combination with an antipsychotic medication.[4] Despite these advances, problems remain in terms of modest efficacy, onset of action, the need to monitor serum levels, and undesirable side effects.

Risperidone, a second generation antipsychotic, has been shown to be effective in both acute and maintenance treatment of bipolar mania in clinical trials involving more than 1,250 patients. Improvement is rapid, seen within 3 days, is independent of psychotic symptoms, occurs in mixed as well as manic episodes, includes improvement in global functioning, and is sustained. Positive results are seen when risperidone is used as adjunctive treatment and as monotherapy. There is no evidence of switching to a depressive episode and baseline depressive symptoms respond to treatment. Risperidone is well-tolerated, with low rates of dropouts and a benign adverse event profile, with somnolence, GI effects, and hyperkinesia being the most common. When compared with haloperidol, risperidone was much better tolerated and certainly no less effective.

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S1102. Quetiapine in mania

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Quetiapine (Seroquel) was compared to placebo and active control in two 12-week, double blind, placebo controlled trials. Quetiapine was more effective than placebo at 3 and 12 weeks. The effect of quetiapine versus placebo increased from week 3 to week 12 suggesting that 3 weeks is an insufficient period of time to treat a manic episode with quetiapine. The efficacy of quetiapine was similar to that of lithium and haloperidol at 12 weeks. The safety profile of quetiapine was better than that of haloperidol and lithium and was similar to that observed with quetiapine in schizophrenic patients. The placebo like EPS profile of quetiapine in manic patients was similar to that observed in schizophrenic patients.

Quetiapine was compared to placebo in patients treated with concomitant lithium or valproate. In one 3 week trial quetiapine was superior to placebo on all endpoints. In a second 6 week trial, quetiapine showed a non-significant benefit over placebo with statistical significance on secondary endpoints at week 6.

S1103. Olanzapine in mania

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Olanzapine is a novel antipsychotic agent that has been extensively studied in large, well-controlled clinical trials in patients with schizophrenia and related disorders. More recently, it also has been extensively studied in the treatment of bipolar disorder and is the first antipsychotic agent to receive an indication for the treatment of acute mania both in the United States and Europe. This presentation will review the results of six large, double-blind clinical trials that evaluated the efficacy of olanzapine for treatment of acute mania and two large, double-blind clinical trials that evaluated the efficacy of olanzapine for relapse prevention. The acute mania studies compared olanzapine to either placebo, haloperidol, risperidone, or divalproex monotherapies, and also compared olanzapine monotherapy to olanzapine in combination with either lithium or divalproex therapy. The relapse prevention studies compared olanzapine to either placebo or lithium. Taken together, the results of these studies indicate that olanzapine is an effective treatment either alone or in combination with mood stabilizers for patients experiencing acute manic episodes, and that it is also effective for prevention of relapse to bipolar mood episodes.

S1104. Ziprasidone in treatment of mania in bipolar disorder

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Clinical trials have aimed to evaluate the efficacy and tolerability of ziprasidone, in monotherapy and with lithium, in patients with bipolar disorder experiencing mania. In a 21-day, double-blind, randomized trial, the ziprasidone group ($n = 137$) demonstrated greater mean improvement in Mania Rating Scale (MRS) score, the primary efficacy variable, at endpoint (day 21 or early discontinuation) than did the placebo group ($n = 65$) ($P < 0.01$) (LOCF). Improvement in CGI–S score was also greater for ziprasidone ($P < 0.001$), as was mean CGI–I score ($P < 0.001$). Significant improvements versus placebo were noted from day 2 in MRS and CGI–S, and from day 4 in CGI–I, and except for

day 4 for MRS, were maintained throughout the study. Rates of discontinuation due to adverse events were 6.5% for ziprasidone and 1.5% for placebo. The results of this study agree with those of a similar previous trial (*Am J Psychiatry* 2003:160:741–748).

In a second 21-day, randomized, double-blind trial, inpatients received lithium plus ziprasidone (n = 101) or placebo (n = 103). At Day 4, rates of change (mixed effects ANCOVA; observed cases) were greater with ziprasidone than with placebo for MRS ($P < 0.05$), CGI–S ($P < 0.01$), CGI–I ($P < 0.01$), Behavior and Ideation ($P < 0.01$), and Ham–D ($P < 0.05$). LS mean changes were greater for MRS Manic Syndrome ($P < 0.05$). At Day 14, rates of change in efficacy variables were comparable; however, ziprasidone-treated patients demonstrated greater LS mean changes in CGI–S, CGI–I, Behavior and Ideation, and PANSS Total (all $P < 0.05$) at Day 14 (observed cases), and in PANSS Total ($P < 0.01$) and Positive ($P < 0.05$) and Negative ($P < 0.01$) subscales at endpoint (LOCF). Rates of discontinuation for adverse events attributed to study treatment were = 5% in both groups.

These data indicate that ziprasidone, in monotherapy or adjunctive treatment, is efficacious and well tolerated in patients with bipolar mania.

S12. Symposium: New treatment for resistant depression
Chair: J. Scott, J. Tauscher

S1201. Augmentation therapy with psychotherapy in resistant depression

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Background: Although there is good evidence that brief therapies such as cognitive therapy lessen relapse and recurrence in acute unipolar depression, they are largely regarded as second line treatments. However, their use is increasingly advocated as an adjunct to medication in chronic or treatment refractory disorders.

Methods: This paper reviews data from three recent randomized controlled trials of psychotherapy plus medication and support versus medication and support alone. Studies ranged from 12 weeks to 5 years in duration.

Results: The largest study demonstrated that remission was twice as likely with the combined treatment than medication or brief therapy alone. Effects in preventing relapse and recurrence were found in the other main study and this benefit appears to persist, for up to $3\frac{1}{2}$ years after the end of CBT. There was also an effect on residual symptom levels.

Conclusions: The effect of brief evidence based therapy in improving remission rates and reducing relapse and recurrence suggests that combined therapies for treatment refractory depression may be clinically and cost effective.

S1202. Are atypical antipsychotics antidepressants?

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Antidepressants are effective in the management of a spectrum of mood and anxiety disorders e.g., major depressive disorders, obsessive-compulsive disorders and panic disorders. Currently available antidepressants appear to exert their effects through the modulation of one or more monoaminergic neurotransmitter systems. This includes increases in serotonin (5-HT) and norepinephrine (NE) particularly in the prefrontal cortex and the hippocampus. In addition, some antidepressants also increase the availability of dopamine (DA) in the prefrontal cortex. However, no single antidepressant is known to possess all of these properties, and delayed treatment response and partial/ non-response, in particular in patients with severe depression, are important clinical problems.

Atypical (but not conventional) antipsychotics also modulate these monoaminergic neurotransmitter systems and are increasingly used for mood and anxiety disorders. Preclinical data can offer insights on the unique effects of some atypical antipsychotics in mood and anxiety disorders. These agents are known to block 5-$HT_{2a,}$ which increases NE firing by reducing the inhibitory effect of 5-HT on NE neurons.[1] Many atypical antipsychotics also increase DA release in prefrontal cortex,[2,3] another possible mechanism for rapid antidepressant activity.[4]

The atypical antipsychotic risperidone can be differentiated from other atypicals by its ability to increase 5HT output in the prefrontal cortex.[5] This appears to be mediated through a combination of α_2 autoreceptor and 5-$HT_{1b/d}$ heteroreceptor blockades. Increased 5-HT output has also been implicated to be of relevance for the rapid and effective treatment of depressive symptoms.[5,6] This 5HT-augmenting propensity of risperidone, in addition to its effects on DA release, may be responsible for emerging reports for efficacy in inadequate/non-responsive and treatment-resistant depression.[7] Other reports suggest efficacy in major depressive disorders (with and without suicidality[8,9]) and obsessive-compulsive disorder.[10] Some reports are emerging with other atypical antipsychotics, such as olanzapine and ziprasidone, in major depressive disorders.[11–13]

Emerging data indicate that patients with mood and anxiety disorders present with symptoms that are commonly seen with psychotic disorders and vice-versa. Development of new chemical entities for these disorders is contingent on a pattern of modulation of NE, 5HT and DA. Atypical antipsychotics, such as risperidone, by producing alterations in the level of these neurotransmitters, may both mimic the effect of currently available antidepressants but in addition enhance efficacy by increasing DA in the prefrontal cortex. Drugs like risperidone, by having efficacy in a variety of symptoms, may be considered to be used across a diagnostic continuum of mood and anxiety disorders known to exist in different psychiatric conditions.

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S1203. SSRI and atypical antipsychotics in bipolar depression

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Bipolar depression, or the depressive phase of bipolar disorder, represents a difficult-to-treat and disabling form of depression. Treatment of bipolar depression remains an under-studied area as clinicians and researchers have historically focused more on the treatment of mania. While there is a wide range of mood-stabilizing medications available, treatment options for bipolar depression remain more limited, and no medication has been formally approved for this indication. Recently, attention has been given to the combination of SSRIs and atypical antipsychotics as a form of treatment for bipolar depression. In particular, an olanzapine/fluoxetine combination has been studied in a large (n=833) double-blind, placebo controlled clinical trial of bipolar depression. This presentation will focus on the acute and long-term efficacy and safety results of this trial, but other possible combinations will also be discussed.

S1204. Current status of lithium augmentation in resistant depression

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Lithium was introduced to clinical psychiatry more than half a century ago as the first specific psychotropic medication. It started the 'psychopharmacological revolution' in clinical psychiatry and was initially identified as being clinically effective in the treatment of 'psychotic excitement', as described in the seminal paper of John Cade in 1949. Subsequently, lithium salts have been widely used for the treatment of bipolar disorders, in particular for acute treatment of manic episodes and for long-term maintenance treatment and prophylaxis of bipolar disorder, type-I. However, during the past two decades lithium has also become a role as an augmentation strategy in treatment resistant or refractory unipolar depression. The paper will review evidence from a total of 28 prospective studies comprising 10 double-blind, placebo-controlled trials, two randomized, double-blind comparator trials, one randomized, single-blind comparator trial, two randomized, open comparator trials, and 13 open-label trials. Overall, the majority of prospective studies support substantial clinical efficacy of lithium augmentation in patients partially or not responsive to antidepressant treatment. Three meta-analyses concluded that 45% to 60% of previously treatment resistant patients will subsequently respond to lithium augmentation. In summary, lithium augmentation of an ongoing treatment with standard antidepressants is a clinically efficacious and well documented treatment option in resistant or refractory depression and should be considered as a first-line treatment strategy in patients suffering from major depression who do not adequately respond to standard care.

Poster Abstracts

P01. Borna disease virus in mood disorders and benefit of novel antiviral therapy

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Aim of the study: Impact of Borna disease virus (BDV) infection in bipolar patients and response to antiviral (amantadine) therapy in either depressive or manic episodes.

Methods: A triple enzyme immune assay (EIA) separately detecting BDV-specific circulating immune complexes (CICs), major viral proteins and antibodies in patients' blood was used to determine infection and antigen load prior to and during oral treatment by amantadine.

Results: BDV, an unique enveloped RNA virus (*Bornaviridae*) causes behavioural syndromes in animals, similar to mood disorders in man. Blood monitoring of patients with major depression or bipolar disorder indicated a high prevalence of activated infections by presence of BDV-CICs in up to 90%, contrasting with 20–30% dormant infections in healthy people. Oral daily treatment of infected such patients by amantadine (2–4 mg per kg body weight), either in acute depression or mania, revealed improvement of symptoms in approximately 70–80% of the cases (60 depressed German patients, 30 manic Austrian patients), paralleling drop of viral antigenemia. An inhibitory effect of amantadine to BDV activity has been previously shown *in vitro* and *in vivo*.

Conclusions: Activated BDV infections are a frequent risk for patients with mood disorders, but, in turn, offer a novel beneficial therapeutic approach by amantadine, either as monotherapy or in addition to regular antidepressants and mood stabilizing medication. Blood monitoring (BDV-triple-EIA) allows both identification of infected patients and effective controlling of therapy.

P02. Risk factors for posttraumatic stress disorder after a road traffic accident

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In Spain, about 5000 people die every year because of road traffic accidents. Survivors of these accidents often develop posttraumatic stress disorder (PTSD) and other anxious and depressive disorders. Studies involving other traumas like sexual abuse or interpersonal violence show that there are some premorbid risk factors, like female gender or poor social environment, for the development of PTSD. The aim of our study was to see if there are also risk factors for the development of PTSD after a road traffic accident.

Materials and methods: We randomly selected 50 people who developed PTSD after a traffic accident and 50 people who did not have psychiatric morbidity after the accident, and we compared gender and clinical and sociodemographic differences among the two groups. Clinical diagnoses were confirmed by the Davidson self-administered scale and the Clinical Assessment Posttraumatic Scale (CAPS). Logistic regression was performed to compare both groups.

Results: The onset of PTSD after a traffic accident was statistically related to female sex and to previous psychiatric morbidity.

Conclusions: Women and people who have a premorbid psychiatryc diagnose seem to be at higher risk of developing PTSD after a road traffic accident.

P03. Pharmacological difference between escitalopram and citalopram

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Citalopram is a 1:1 mixture of R- and S-enantiomers (R-citalopram and escitalopram, respectively). Recent nonclinical and clinical studies suggest that escitalopram has superior therapeutic activity compared with citalopram at equipotent doses. The current set of experiments was designed to evaluate whether the proposed superior efficacy of escitalopram in clinical and preclinical experiments originated in a differential efficacy of escitalopram and citalopram in modifying central serotonin levels. The present study investigated the effects of citalopram and its enantiomers on extracellular serotonin levels using intracerebral microdialysis in ventral hippocampus of freely moving rats.

Both citalopram and escitalopram dose-dependently enhanced serotonin levels in ventral hippocampus. Citalopram (10 μmol/kg, s.c.) enhanced extracellular serotonin levels about 5 fold, whereas escitalopram (5 μmol/kg s.c. equivalent to the amount of escitalopram contained in citalopram, 10 μmol/kg) enhanced serotonin levels 7–8 fold. Combining escitalopram with the R-enantiomer significantly attentuated the serotonin-enhancing effect of escitalopram.

Escitalopram is more effective in enhancing central serotonin levels than citalopram due to the inhibitory properties of R-citalopram on the effect of escitalopram. Although receptor-binding data reveal no prominent affinities of the R-enantiomer of citalopram, it reduces the effectiveness of escitalopram in enhancing serotonergic neurotransmission. The present observations might help to explain the improved clinical efficacy of escitalopram versus citalopram.

P04. Depletion of serotonin in platelets after sertraline administration

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Aim: When enterochromaffin cells in intestines secrete 5-HT into the bloodstream, it is immediately taken by platelets and stored in the electron dense granules and released after vessel injury causing vasoconstriction. The aim of this study is to demonstrate that sertraline depletes platelets content of serotonin (5-HT).

Method: Five healthy male volunteers aged between 30 and 40 were selected for the study. Blood was collected (EDTA tubes) at day zero. Platelets were isolated from the Buffy coat of the blood after centrifugation. Platelets were adjusted to 500,000 platelets per μl of physiological saline, centrifuged, the pellet was digested with distilled water (causing platelets lysis) so that 5-HT platelets content was released, and determined using enzyme linked immunoassay ELISA (EUROIMMUN) in each of the five samples. Sertraline 50mg was administered by the volunteers for five consecutive days, then blood was collected on day 6. The platelets were isolated, adjusted to 500,000 platelets per μl, and digested with distilled water. 5-HT was determined in the platelet lysate using ELISA in each of the five samples (same method as above).

Results: The mean 5-HT concentration in the samples before sertraline administration was 2804 ng/ml of the platelet digest. It decreased to 15 ng/ml after sertraline administration.

Conclusion and possible practical application: Sertraline administration causes severe depletion of 5-HT in platelets. Blood platelets can serve as a peripheral model for the central serotonin presynaptic nerve terminal because the platelets accumulate and release 5-HT in a manner analogous to the brain serotonergic system (Flachaire et al,1990). The concentration of 5-HT in platelets might serve as an indirect index of central serotonergic function of drugs (sertraline and possibly other SSRIs) interfering with the central neuronal uptake of 5-HT.

P05. Successful treatment of refractory depression by combination of predisone with SSRIs

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Aim: An important role of corticosteroids in severe mood disorders is suggested by the high frequent occurrence of mood disorders in Cushing's syndrome and the induction of pathological mood by the use of medicinal cortisone. In this study we will demonstrate our experience with 19 patients that have used antidepressants (selective serotonin reuptake inhibitors, SSRIs) for more than 3 months without significant improvement of their depressive symptoms but are improved upon the usage of low amount of cortisone that will suppress HPA-axis (hypothalamus-pituitary-adrenal axis) to show the augmentation effect of combining prednisone with SSRIs in treating refractory depression.

Method: The patient was labelled as non responder (refractory) to treatment after 2 months of SSRIs (fluoxetine, paroxetine, or citalopram) administration and after switching to a second SSRI and remaining on it for at least one month without improvement. Prednisone 10mg /day in two divided doses was used on 19 patients with chronic unipolar nonresponder depression. Prednisone was tapered and stopped two months after its introduction.

Results: All cases improved within two weeks of steroid introduction; one patient developed panic attack after steroid introduction to fluoxetine, this attack was resolved after switching to citalopram. Patients sustained their improvement for one year after SSRI discontinuation.

Conclusion: the use of steroids in combination with SSRIs (and probably other types of antidepressants) is useful and has a powerful enhancing effect on the antidepressant action of medication; this is probably mediated via the suppression of the adrenal gland secretion, as the low amount of prednisone would suppress the function of this gland. It seems that suppressing HPA-axis has a beneficial effect on depression.

P06. Comparison of sexual functioning in patients receiving duloxetine or paroxetine: acute- and long-term

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Objectives: Evaluate sexual functioning following acute- and long-term treatment with duloxetine, paroxetine or placebo.

Method: Acute-phase data obtained from four 8-week, double-blind studies, with patients randomized to duloxetine (20–60 mg BID; n = 736), paroxetine (20 mg QD; n = 359), or placebo (n = 371). Long-term data obtained from extension phases, in which acute treatment responders received duloxetine (40 or 60 mg BID; n = 297), paroxetine (20 mg QD; n = 140), or placebo (n = 129) for 26 additional weeks. Sexual function evaluated using the Arizona Sexual Experience Scale (ASEX).

Results: In patients without initial sexual dysfunction, the probability of acute phase sexual dysfunction onset was significantly lower for duloxetine-treated patients compared with those receiving paroxetine (p = .015), although both rates were significantly higher than placebo (p = .007 and < .001, respectively). Long-term data revealed that sexual function improved (ASEX total score reduced) in 70.9% of duloxetine-treated patients between baseline and endpoint, compared with 57.6% for paroxetine (p = .060). For ASEX

Questions 1 and 2, a significantly greater proportion of duloxetine-treated patients reported improvement compared to paroxetine ($p = .050$ and .037, respectively). No significant differences were found in Questions 3, 4, or 5.

Conclusion: In these studies, the incidence of acute phase sexual dysfunction development among patients receiving duloxetine across its dose range (40–120 mg/d) was significantly lower than that of paroxetine at the low end of its dose range (20 mg/d). On certain ASEX questions, a significantly higher percentage of duloxetine-treated patients reported improvement in sexual functioning compared with paroxetine.

P07. Duloxetine vs placebo in the prevention of relapse of major depressive disorder

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Objective: Duloxetine hydrochloride is a balanced and potent reuptake inhibitor of both serotonin (5-HT) and norepinephrine (NE). The efficacy and safety of duloxetine in the acute treatment of the emotional and physical symptoms of depression has been established in several studies. The present study compared duloxetine 60 mg once daily with placebo in time to relapse in patients with Major Depressive Disorder (MDD).

Method: In this randomized, double-blind, multi-site, placebo-controlled study conducted in Europe and the United States, 533 outpatients with MDD received duloxetine 60 mg QD for up to 12 weeks. Responders were randomized to either duloxetine 60 mg QD or placebo for 26 weeks (continuation phase). The primary efficacy analysis compared time to relapse using log-rank test.

Results: During acute treatment, 280 (52.5%) responded, indicating they no longer met criteria for depression, and 278 entered the continuation phase. Time to relapse was significantly longer for patients treated with duloxetine 60mg/d than for those treated with placebo ($p = .004$). Duloxetine treated patients scored better on most secondary efficacy measures, including the assessments of depression, anxiety, painful physical symptoms, and quality of life. 11% and 4% of duloxetine treated patients discontinued due to an adverse event in the acute and continuation phase respectively.

Conclusions: Duloxetine significantly increased time to relapse and performed better than placebo on measures of depression, anxiety, painful physical symptoms, and quality of life. Duloxetine was safe and well tolerated.

P08. Open-label pharmacokinetic study of quetiapine plus divalproex in patients with schizophrenic/schizoaffective disorders or bipolar disorder

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Aim: To characterize the pharmacokinetics of quetiapine and divalproex when used in combination for treatment of psychotic and bipolar disorders.

Methods: This multicenter, open-label study enrolled adults with a diagnosis of schizophrenic/schizoaffective disorders (Cohort A) or bipolar disorders (Cohort B). Both cohorts were required to have ≥ 4 weeks' treatment with quetiapine fumarate (150-500 mg/d, Cohort A) and divalproex sodium (250–2000 mg/d, Cohort B). Cohort A received quetiapine Days 1 to 5 (target dose 150 mg bid); divalproex was added Days 6 to 8 (target dose 500 mg bid). Cohort B received divalproex Days 1 to 8; quetiapine was added Days 9 to 11. Target doses were maintained for both cohorts for the next 6 days, then gradually decreased to prestudy quetiapine or divalproex monotherapy dosages. Pharmacokinetic ratios of C^{ss}_{max} and $AUC^{ss}_{.\tau}$ during combination dosing and monotherapy were compared. Ratios within the mean equivalence interval of 0.70 to 1.43 were considered indicative of no drug-drug interaction.

Results: Cohort A ($n = 18$) data revealed coadministration of divalproex increased steady-state maximum concentration (C^{ss}_{max}) of quetiapine by 17% but without any change in steady-state exposure of quetiapine ($AUC^{ss}_{.\tau}$). In Cohort B ($n = 15$) C^{ss}_{max} and $AUC^{ss}_{.\tau}$ declined 11% for total divalproex during coadministration of quetiapine. For both cohorts, all confidence intervals fell within the reference interval (0.70 to 1.43). Mean amount, renal clearance (CL_R), and percent of divalproex excreted in urine were not statistically significantly higher after coadministration of divalproex and quetiapine compared to divalproex monotherapy in Cohort B. No differences were observed in treatment-related adverse events with either quetiapine or divalproex monotherapy or their combination.

Conclusions: Combination therapy with quetiapine and divalproex does not result in a clinically relevant drug-drug interaction.

P09. Potentiation of antidepressant treatment in resistant depression: a comparative study of seroquel versus lithium

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The aim of this study is to compare the effect of quetiapine (Seroquel) to that of lithium when added to the treatment of patients who have failed a trial of antidepressant treatment at maximal doses. All subjects were adults whose age ranged from 32 to 64 years a Hamilton Depression rating score of 20 or greater after 4 weeks of treatment at maximal antidepressant dose. Subjects are evaluated weekly using various rating scales (HAM-D, MADRS, UKU, AIMS, BARNES, BPRS, Widlocher). Lithium is initiated at 600mg and maintained at this dose for the first two weeks. Lithium is then adjusted

to a plasma level of between 0,8-1,2nm/l as clinically indicated. Quetiapine is titrated to a maximum of 400mg in the first week and subsequently as clinically indicated to a maximum of 800mg/day.

Data from the first 16 subjects (8 in lithium group and 8 in quetiapine group) at week 0 and week 8 were analyzed using a 2x2 factorial Anova. Subjects in both treatment groups improved significantly ($F_{1,28} = 44.70$, $p < 0.001$) but to a greater extent with quetiapine ($F_{1,28} = 9.89$, $p < 0.01$). Similar results were observed in the MADRS evaluation (Figure 1).

These observations were confirmed using initial scores as regressors in a covariance analysis of the final scores 88% improvement was observed with quetiapine as compared to 44% with lithium in both HAM-D ($F'_{1,13} = 5.29$, $p < 0.04$) and MADRS ($F'_{1,13} = 4.36$, $p < 0.06$) scores. In conclusion, this study suggests that quetiapine may provide a valuable alternative in the treatment of resistant depression.

P10. Olanzapine/fluoxetine combination in rapid cycling bipolar disorder

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Background: Rapid cycling occurs in 13–20% of bipolar disorder patients and is associated with a poor response to traditional mood stabilizers. Antidepressant monotherapy has been associated with cycle acceleration and treatment-emergent mania. The present study compares olanzapine/fluoxetine combination (OFC) treatment with olanzapine (OLZ) and placebo (PLA) in patients with rapid-cycling bipolar depression.

Methods: 833 subjects with bipolar depression (baseline MADRS total scores $> = 20$) were enrolled in this 8-week double-blind study and randomized to OFC (6/25, 6/50, or 12/50 mg/day, n = 86), OLZ (5–20 mg/day, n = 370), or PLA (n = 377). In a subset of 315 patients with rapid-cycling histories (n = 37 OFC; n = 140 OLZ; n = 138 PLA), depression and treatment-emergent mania were evaluated using the MADRS and YMRS, respectively.

Results: OFC and OLZ demonstrated significantly greater improvement in MADRS total score than placebo by week 1. OFC showed significantly greater MADRS improvement at endpoint than olanzapine (-15.7 vs. -9.5, $p = .005$) or placebo (-9.8, $p = .007$). OFC also showed significantly higher response rates (OFC 77.8% vs. OLZ 35.7%, $p < .001$; vs. PLA 39.4%, $p < .001$) and remission rates (OFC 77.8% vs. OLZ 54.1%, $p = .029$; vs. PLA 49.5%, $p = .009$). Treatment-emergent mania was similar among groups for the subset of rapid cyclers (OFC 10.7%, OLZ 8.9%, PLA 2.6%, $p = .060$) and for the entire sample (OFC 6.4%, olanzapine 5.7%, placebo 6.7%, $p = .861$).

Conclusion: Rapid-cycling subjects treated with OFC experienced greater improvement in depressive symptoms and higher response and remission rates than olanzapine or placebo subjects. There was no indication of an increased risk of cycle acceleration or mania beyond that seen with placebo.

P11. Adjunctive ziprasidone in treatment-resistant depression: pilot study

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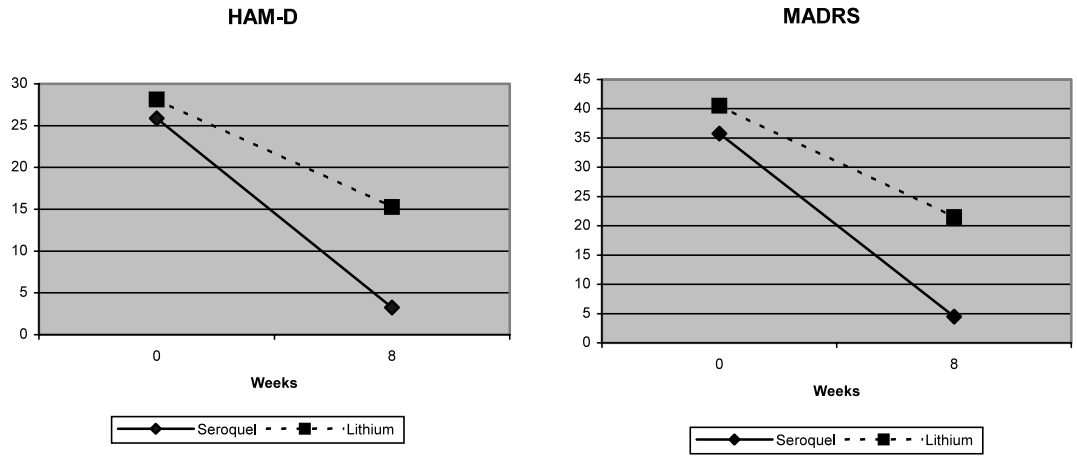
The aim of this study was to evaluate the efficacy of adjunctive ziprasidone with sertraline in treatment-resistant major depression without psychotic features. Patients had a history of failure to respond to at least 4 weeks' adequate antidepressant therapy with ≥ 1 non-SSRI ($\pm$SSRI) or an SSRI only. After a 1-week screening period, 90 patients entered a 6-week open trial of sertraline 100 to 200 mg/day.



P09. Figure 1

Nonresponders (= 30% improvement on MADRS, CGI–S score ≥ 4, and meeting DSM-IV major depression criteria) were randomized to 8 weeks of open treatment with sertraline monotherapy (n = 21) or combination therapy with ziprasidone 40 mg BID (n = 23) or 80 mg BID (n = 20).

At endpoint, patients with a history of non-SSRI (± SSRI) treatment resistance who received combination therapy (n = 26) demonstrated significantly greater improvement versus those patients who received monotherapy (n = 13) in MADRS, the primary efficacy variable ($P = 0.018$), and in HAM–D-17 ($P = 0.022$), CGI–S ($P = 0.005$), and CGI–I ($P = 0.018$). Among patients with a history of SSRI resistance only, improvement with combination therapy (n = 14) did not reach significance versus sertraline monotherapy (n = 7). No specific safety concerns were observed with combination therapy.

In conclusion, in patients with major depression and a history of non-SSRI (± SSRI) treatment failure, augmentation with ziprasidone was associated with significantly greater improvement than continuation of monotherapy in non-responders to high-dose sertraline.

P12. Comprehensive pooled analysis of remission data: venlafaxine vs SSRIs (comparison)

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Objective: Compare antidepressant efficacy of venlafaxine, selective serotonin reuptake inhibitors (SSRIs), and placebo using pooled data from > 7000 patients.

Methods: Original data from a complete set of 33 randomized, double-blind studies from a worldwide search of studies sponsored by Wyeth Pharmaceuticals were pooled to compare outcomes of depressed patients treated with venlafaxine (N = 3410), SSRIs (N = 3355; 1704 fluoxetine, 692 paroxetine, 652 sertraline, 273 citalopram, 34 fluvoxamine), or placebo (N = 932) for less than or equal to 8 weeks. Remission (HAM-D17 score less than or equal to 7) rates and odds ratios (OR) for remission were calculated for venlafaxine versus SSRIs using pooled data from 32/33 studies (1 study did not use the HAM-D scale).

Results: Overall remission rates were venlafaxine, 41% (1375/3337); SSRIs, 35% (1134/3280); and placebo, 24% (223/932). All comparisons were statistically significant for remission and for 9/9 alternate measures of antidepressant efficacy ($P < 0.001$). The overall OR for remission vs SSRIs was 1.307 (95% CI 1.180–1.448), favoring venlafaxine. Individual ORs were 1.401 (95% CI 1.212–1.619) vs fluoxetine; 1.216 (95% CI 0.982–1.506) vs paroxetine; and 1.223 (95% CI 1.005–1.489) vs the other SSRIs. A total of 11.7% of venlafaxine-treated patients discontinued therapy due to adverse events compared to 9.0% on SSRIs and 4.3% on placebo ($P < 0.001$ for all comparisons).

Conclusion: These results confirm prior research suggesting the significantly greater likelihood of achieving remission of depression with venlafaxine versus fluoxetine and other SSRIs.

P13. Meta-analyses of duloxetine in the treatment of MDD

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Objective: To compare the efficacy of duloxetine vs. placebo in the acute treatment of Major Depressive Disorder (MDD).

Method: Data were retrieved from all available, comparable, placebo controlled trials of duloxetine, involving a total of 8 studies, containing 1139 patients. The primary efficacy measure was the 17-item Hamilton scale for depression ($HAMD_{17}$). Secondary efficacy measures included the Montgomery Asberg Depression Rating Scale (MADRS), Clinical Global Impression of Severity (CGI-S), Patient Global Impressions of Improvement (PGI-I) and response and remission rates.

Analyses of the treatment difference between duloxetine and placebo as measured by the $HAMD_{17}$, MADRS, CGI-S and PGI-I were performed based on the mean change from baseline to endpoint. Treatment differences for response and remission rates were analysed by log odds-ratios. Study-specific efficacy differences were analysed and tested for heterogeneity.

Results: Duloxetine was superior to placebo on all conducted analyses. The estimated treatment difference as measured by the $HAMD_{17}$ showed that patients treated with duloxetine were significantly more likely to improve than those given placebo [− 2.20 $CI_{95\%}$ (− 2.73, − 1.66)]. Likewise, treatment differences for the other secondary measures were: MADRS [−2.51 $CI_{95\%}$ (− 3.31, − 1.71)], CGI-S [− 0.36 $CI_{95\%}$ (− 0.45, − 0.26)] and PGI-I [− 0.40 $CI_{95\%}$ (− 0.50, − 0.30)]. The log-odds ratio for the response and remission rates were 0.65 [$CI_{95\%}$ (0.47, 0.82)] and 0.55 [$CI_{95\%}$ (0.37, 0.73)] respectively, showing a statistically significantly improvement for patients on duloxetine. There were no indications of between-study heterogeneities.

Conclusions: Results from these efficacy meta-analyses conducted clearly demonstrate superiority of duloxetine over placebo in the treatment of MDD.

P14. Quetiapine monotherapy for mania associated with bipolar disorder

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Objective: To evaluate the efficacy and safety of quetiapine (QTP) monotherapy for the treatment of mania in a large cohort of patients.

Methods: A total of 604 patients (bipolar I disorder, manic episode) were included in two 12-week, randomized, double-blind, placebo (PBO)-controlled studies to assess the efficacy and safety of QTP (up to 800 mg/d) as monotherapy. Lithium and haloperidol controls were used to assess assay sensitivity. Data from QTP- and PBO-treated patients were pooled for analysis. Assessments included changes from baseline in Young Mania Rating Scale (YMRS), Clinical Global Impression, Clinical Global Impression-Bipolar, Montgomery-Asberg Depression Rating Scale, Positive and Negative Syndrome Scale, Global Assessment Scale, Simpson-Angus Scale, and Barnes Akathisia Rating Scale scores.

Results: A total of 60.8% (127/209) QTP-treated and 38.9% (77/198) PBO-treated patients completed the study. A statistically significant improvement in YMRS total score was observed from Day 4 onward in the QTP group compared with PBO ($p = 0.021$). At Day 21, YMRS scores for QTP and PBO were -13.58 and -7.76, respectively ($p < 0.001$), and this improvement increased by Day 84 ($p < 0.001$). Significantly more QTP patients achieved a response ($> = 50\%$ decrease from baseline in YMRS score) at Day 21 (QTP 48.1% vs PBO 31.3%; $p = 0.001$). Lithium and haloperidol were similar to QTP in all efficacy measures vs PBO by Day 84. Common adverse events for QTP included insomnia, dry mouth, and somnolence. High rates of extrapyramidal symptoms and tremor were observed with haloperidol and lithium, but not with QTP. Mean last week QTP dose in responders at Day 21 was 574 mg/d.

Conclusions: QTP monotherapy is effective, fast-acting, and well tolerated in the treatment of mania associated with bipolar disorder.

P15. Factors of profession deficiency in panic disorder with agoraphobia

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Aim: The aim of this study was to ascertain predictors of profession deficiency in patients with panic disorder with agoraphobia (PDA) that were due to PDA, because PDA is chronic disorder that could disturb work capacity.

Method: Linear regression was used to identify predictors of profession deficiency in a sample of 72 consecutive outpatients (22 men and 50 women) with PDA. Intensity of profession deficiency was ascertained from modified National Institute of Mental Health Panic Questionnaire (NIMH PQ). That represented dependent variable in this regression. Independent variables were demographic data (gender, age and employment), presence of comorbid current major depression episode, presence of comorbid generalized anxiety disorder, presence of any personality disorder and scores on the followed Panic and Agoraphobia Scale (PAS) subscales: panic attacks, agoraphobia (avoidance behavior), anticipatory anxiety and worries about health.

Results: Patients reported severe profession deficiency on all items on NIMH PQ questionnaire. The best predict variable for the profession deficiency in patients with PDA was high score on the PAS dimension of agoraphobia, which relates to frequency of avoidance behavior, number of avoided situations and importance of avoided situations. Demographic data and presence of comorbid Axis I and Axis II disorders and other measures on PAS dimensions did not predict decreased work efficacy in patients with PDA.

Conclusion: Patients generally reported severe effects of PDA on profession deficiency and the results suggested that the impaired work efficacy was associated with avoidance behavior. These results recommend that the treatment of PDA patients should be related to decreasing avoidance behavior in order to establish adequate work performance in patients.

P16. Cognitive impairment in late-onset depression

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The aim of this study is to review the literature concerning cognitive impairment in elderly depressed patients. A review of the literature was performed using medline. The following key words were entered: depression, elderly, neuropsychological deficits, cognitive impairment, executive dysfunction, late-life onset. Several studies have demonstrated impairment on executive function, and verbal and non-verbal memory tasks. This impairment seems to be more severe in late-life onset than in early onset depression, related to treatment resistance and also to neuro-imaging abnormalities on structural MRI scans. Studies have also shown residual cognitive impairment in depressed patients after a follow-up period of 12 months suggesting cognitive impairment to be a trait characteristic of depression in the elderly. Nevertheless, similar neuropsychological deficits have also been found in younger early onset drug free depressed patients. Persistence of cognitive impairment several months after remission of depressive symptoms has also been demonstrated in younger patients. Inclusion of subjects over 80 years also renders interpretation of the significance of cognitive impairment in the elderly due to the possibility of the presence of a degenerative process.

In conclusion, cognitive impairment in late life onset depression has been linked to MRI abnormalities and poor response to treatment. Further research is required to determine if there is a qualitative as opposed to quantitative difference between neuropsychological deficits in late life onset.

P17. Quetiapine combined with lithium or divalproex for the treatment of acute mania associated with bipolar disorder

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Objective: Evaluate the efficacy and safety of quetiapine (QTP) combined with lithium (Li) or divalproex (DVP) for treating bipolar mania.

Methods: Analysis of data from two multicenter trials. Patients with bipolar I disorder experiencing manic episodes were randomized to double-blind, combination therapy with QTP (up to 800 mg/d) plus Li/DVP, or placebo (PBO) plus Li/DVP. The primary endpoint was change from baseline in Young Mania Rating Scale (YMRS) total score at day 21 (QTP + Li/DVP vs PBO + Li/DVP).

Results: 402 (QTP, n = 197; PBO, n = 205) patients were included. The improvement in YMRS at Day 21 with QTP + Li/DVP (− 15.29) was superior to that of PBO + Li/DVP (− 12.19; p = 0.014). A statistically significant difference was observed within the first week ($p < 0.05$). Significantly more QTP + Li/DVP patients achieved a response (≥ 50% decrease in YMRS) at day 21 (QTP + Li/DVP, 55.7%; PBO + Li/DVP, 41.6%; p = 0.009). Improvements in Clinical Global Impression-Bipolar Severity of Illness scores at day 21 were statistically significantly greater with QTP + Li/DVP (− 1.59) compared with PBO + Li/DVP (− 1.19; p = 0.004). Adverse events were generally mild to moderate, the most common (≥ 10%) in the QTP + Li/DVP group being somnolence, dry mouth, and headache. QTP + Li/DVP was not associated with extrapyramidal symptoms, diabetes, or emergent depression. More QTP-treated patients completed the trial, and fewer discontinued due to adverse events, than in the PBO group. QTP had no clinically relevant effect on laboratory, vital sign, and ECG assessments. Most QTP responders (76.7%) at day 21 received doses of 400–800 mg/d. The mean last week QTP dose for responders at day 21 was 492 mg/d.

Conclusions: QTP combined with Li or DVP has superior efficacy to Li or DVP alone in the treatment of mania. The safety profile of this combination is similar to that observed in patients with schizophrenia treated with QTP.

P18. Does age of onset affect the course and severity of major depressive disorder?

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Aim: This paper explores the impact of Age of Onset (AGO) of MDD on the severity of illness and prevalence of co-morbid conditions.

Method: The sample is based on population screening for anxiety and depression in Iceland to recruit participants, age 18–60, for a genome-wide research project. Those fulfilling case-definition criteria were clustered according to family-relatedness in the population-wide deCode Genealogy Database. Further diagnostic work-up was based on the CIDI. All cases of MDD were divided into three AGO groups; below 18, 18–30 and 31+ years. Further analysis was based on MDD severity categories and the frequency and AGO of co-morbid conditions.

Results: The results are based on 945 individuals with MDD, m/f ratio 1:3. Average age on examination was 39.9 years. 24.9% of the sample had a MDD AGO before age 18. The highest male/female ratio was in the youngest group and the highest percentage of severe MDD, a clear trend but did not reach statistical significance.This group also had the highest frequency of anxiety co-morbid disorders ($P < 0.001$). Alcoholism (abuse and dependence) increased with later MDD onset but this was not significant. There was a highly positive correlation between the onset of MDD in each age group and the onset of the co-morbid disorders ($P < 0.01$).

Conclusion: Early onset of MDD shows a trend towards more severity. The frequency of co-morbid affective disorders is significantly increased in early onset.. This cannot be explained by a longer duration of illness in those affected early in their life as the onset of co-morbid disorders is close to the onset of MDD in all age groups. This raises a question about additional genetic vulnerability factors in the youngest group.

P19. Relationship between suicidality and co-morbid disorders

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Aim: To explore the relationship between suicidality and comorbid lifetime psychiatric illness.

Method: The original sample was based on a population-wide screening for anxiety and depression in Iceland, followed by diagnostics with the Composite International Diagnostic Interview (CIDI). The four suicide-related items in the CIDI were given a severity rating (Thoughts of Death = 1, Wish to Die = 2; Suicidal Thoughts = 5, Suicide Attempt = 10; the first three with a time frame of at least two weeks). Four groups were created, with accumulated suicidal severity of 0 (I), 1–4 (II), 5–9 (III) and 9–18 (IV). The anxiety mean was based on eight lifetime disorders, depression on two and alcohol/substance abuse/dependence on two disorders.

Results: 2.236 individuals underwent the CIDI; 1.274 with an anxiety disorder, 1.053 with depression, with much overlap. 1.260 scored 1–18 on the suicidality item score; f/m ratio = 2.2:1; 976 scored zero, f/m ratio 1.7:1. There were 976 in group I, 567 in group II, 518 in group III and 166 in group IV. The mean rate of anxiety disorders increased according to suicidal severity from 0.8 to 2.2; that of depressive disorders from 0.3 to 1.1; and that of alcohol/substance abuse from 0.2 to 0.6. These increases are highly significant ($P < 0.001$) across categories and disorders.

Conclusion: These results show a significant linear relationship between the severity of lifetime morbidity of anxiety, depressive disorders and substance abuse/dependence, and suicide risk.

P20. Escitalopram and venlafaxine XR in the treatment of major depressive disorder (MDD) in a randomized, double-blind, fixed-dose study

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In a previous study in general practice, escitalopram (10–20 mg) was at least as effective as venlafaxine (75–150 mg), with a significantly superior side effect profile.[1] In the present study, comparing escitalopram and venlafaxine at the highest recommended doses in depressed outpatients in the US, it was our aim to see if this efficacy/tolerability profile remained unchanged. In this randomized study, patients presenting with MDD (screening HAMD-24 ≥ 20) received one week of single-blind placebo treatment. If their HAMD-24 remained $= 20$ at baseline (after the single-blind period), they received 8 weeks of treatment with either escitalopram or venlafaxine XR (titrated to 20 mg/day and 225 mg/day, respectively, in accordance with prescribing information). The primary efficacy variable was mean change from baseline in MADRS scores. Mean baseline MADRS scores for the escitalopram ($N = 97$) and venlafaxine ($N = 98$) groups were 30.7 and 30.0, respectively. Escitalopram appeared to be more effective than venlafaxine, with mean changes in MADRS scores from baseline to endpoint of -15.9 and -13.6, respectively, a clinically meaningful difference of 2.3 points. Remission (MADRS ≤ 12) rates at endpoint were 51% for escitalopram and 42% for venlafaxine. The response criterion (MADRS reduction from baseline $\geq 50\%$) was met by 59% of escitalopram- and 48% of venlafaxine-treated patients. In severely depressed patients (MADRS ≥ 30, $N = 121$), escitalopram was more effective than venlafaxine. In these patients, the mean change in MADRS scores was -17.6 vs -14.1 ($p < 0.05$). The proportion of these patients responding to treatment at endpoint was higher for escitalopram than for venlafaxine (60% vs 44%). The proportion of patients in remission was 47% vs 29% ($p < 0.05$). The venlafaxine group had a higher overall incidence of treatment-emergent adverse events than the escitalopram group (85% vs. 68%), and more patients withdrew due to adverse events from the venlafaxine group than from the escitalopram group (16% vs. 4%; $p < 0.01$). These results demonstrate that escitalopram has a better risk/benefit profile than venlafaxine in the treatment of depression.

Reference

1. Montgomery SA, Huusom AKT, Bothmer J (2002) Escitalopram is at least as effective as venlafaxine xr in the treatment of depression and better tolerated (abstr). *Int J Psych Clin Pract* **6:** 250.

P21. Psychiatric effects of three different interferon subtypes in chronic hepatitis patients: a comparison

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The aim of our study was to identify the existence and extent of psychiatric alterations in patients affected by chronic viral hepatitis treated with 3 different IFN sub-types (IFNa2a, PegIntron®, Pegasys®) and to compare these alterations with symptoms presented by a group of MDD patients. Twenty-six patients treated with IFNa2a, 20 patients with PegIntron®, 8 patients with Pegasys® and 15 patients affected by primary MDD were assessed by 17-item HDRDS and BDI at baseline and after 2 months of treatment. The BDI items were divided in three dimensions (somatic, cognitive and affective) (Morley at al, 2002). HDRDS items in two dimensions (thymic and somatic).

Results: After 2 months, patients on IFNa2a exhibited a significant increase in depressive symptoms on the HDRDS; patients with PegIntron® increased their scores on either scales; patients with Pegasys® did not show any significant changes; both IFNa2a and PegIntron® produced a significant increase in somatic scores on the HDRDS and BDI; while primary depressive patients presented higher scores in both affective and somatic scores, above all in the affective one, in the other groups, somatic aspects were prevalent.

Our data indicate that Pegasys® has less psychiatric side effects compared to IFNs with different pharmacokinetic profile, in agreement with preliminary data published in literature. Longer periods (e.g. six or twelve months) of psychiatric observation and a population with more patients receiving Pegasys® are needed to confirm these data.

P22. Prazosin effects on specific symptoms in chronic combat trauma PTSD

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Purpose: Prazosin is a generically available alpha-1 adrenergic antagonist. We recently reported a placebo-controlled crossover study demonstrating that prazosin significantly reduces trauma-related nightmares, sleep disturbance and overall PTSD severity in Vietnam War combat veterans with chronic PTSD (*Am J Psychiatry* 2003; **160**: 371–373). Here we report the effects of prazosin in these subjects on specific PTSD symptoms as described by the Clinician Administered PTSD Scale (CAPS).

Methods: Ten Vietnam combat veterans with chronic PTSD and frequent treatment resistant nightmares (CAPS recurrent distressing dream item score equal to or greater than 6) participated in a double blind, placebo-controlled crossover study. They were randomized to prazosin or placebo for a three-week drug titration period followed by six weeks on maximum effective dose. Following a two-week

washout period, they were then crossed over to the other medication (prazosin or placebo) and treated with a similar titration and treatment phase. Maintenance psychotropic drugs were kept constant throughout. Change scores were compared between prazosin and placebo conditions by paired t test.

Results: Prazosin was significantly more effective than placebo on the following CAPS items: intrusive memories ($p = 0.03$); recurrent distressing dreams ($p < 0.01$); physiologic distress on exposure ($p < 0.01$); decreased interest ($p = 0.03$); numbing ($p = 0.3$); sleep disturbance ($p = 0.02$); irritability/anger ($p = 0.01$).

Conclusions: Prazosin significantly reduces severity of multiple PTSD symptoms across the accepted cluster of PTSD symptoms.

P23. The role of the R- and S-enantiomers in the efficacy of citalopram versus escitalopram

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The pharmacological and nonclinical literature describing the counteraction of the effect of escitalopram by R-citalopram is reviewed, as well as the implications of this counteraction for the clinical efficacy of escitalopram compared to citalopram. The data in this review was gathered from published articles, poster presentations, and abstracts. Citalopram is a selective serotonin reuptake inhibitor (SSRI) antidepressant consisting of a racemic 1:1 mixture of R(−)- and S(+)-enantiomers. Nonclinical studies have shown that the selective serotonin reuptake inhibitory activity of citalopram is attributable to the S-enantiomer, escitalopram, which has has been developed as a new single-enantiomer drug. Initial nonclinical and clinical studies comparing escitalopram and citalopram to placebo found that corresponding doses of these two drugs (that is, containing the same amount of the S-enantiomer) and therefore expected to have the same effect, resulted in a better effect for escitalopram. Although essentially inactive with regards to SSRI activity, these results suggest that the R-citalopram in citalopram counteracts the effect of escitalopram. Escitalopram has greater efficacy and faster time to symptom relief than comparable doses of citalopram in biochemical, functional, and behavioural experiments. The lower efficacy of citalopram in these nonclinical studies is due to the counteraction of the effect of escitalopram by R-citalopram, possibly via an allosteric interaction with the serotonin transporter. Data from controlled clinical trials in patients with major depressive disorder consistently show better efficacy, higher rates of response and remission, and faster time to symptom relief with escitalopram than with citalopram. Thus, the R-enantiomer present in citalopram counteracts the activity of escitalopram, thereby providing a basis for the pharmacological and clinical differences observed between citalopram and escitalopram.

P24. Clinical and neurobiological hypothesis in two cases of Cotard syndrome

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Since Jules Cotard described the délire de négation, about 100 cases have been reported in literature. Regional cerebral blood flow (rCBF) changes have been reported, identified lesions appear unspecific and no studies on brain receptors have been performed. The aims of this study were to investigate the rCBF and the D2 receptorial pattern by 99m Tc-Hexa-Methylpropilene-Amine-Oxime (HMPAO) and 123 I-Iodobenzamide (IBZM) SPET in two cases of Cotard syndrome, a 43 year-old male and a 16 year-old female, and correlate neuroimaging pattern to psychopathological features. Three sections with the best visualization of frontal cortex (FC) and striatum (ST) were selected and summed for semiquantitative analysis. Two symmetrical regions of interests (ROIs) were drawn on right and left areas. FC ROIs were chosen as reference region (FCR) and ST/FCR ratios were bilaterally calculated. After SPET imaging, pharmachotherapy was started. Delusional symptoms completely remitted in the first week of treatment while depressive symptomatology remitted more gradually. A second SPET analysis was performed 3 and 6 months later, respectively in the male and the female patient.

Results: No perfusion abnormalities were found in both patients at visual reporting and, at semiquantitative analysis, no differences were observed in all ratios. At 123IBZM-SPET, ST/FCR ratios appeared decreased with a right vs. left percentage decrement. Visual evaluation confirmed this pattern. The second SPET analysis showed a further bilateral decrease in specific striatal D2 receptor with a right vs. left decrement less than previously.

Conclusions: A high striatal dopaminergic activity with a right/left asymmetry improved after treatment have been found in two cases of Cotard syndrome and we propose a hypothesis reconsidering psychosis as the primary psychopathology in these patients, like in schizophrenia.

P25. Bibliotherapy – cognitive-behavioral self-help in patients with partially remitted depression

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Background: Cognitive-behavioral psychotherapy in combination with pharmacotherapy was shown to be superior over each treatment strategy alone. Above that, recent investigations indicate that Bibliotherapy — a guided self help manual, which uses cognitive-behavioral intervention strate-

gies — significantly reduces both the scores of the Hamilton Rating Scale for Depression (HAMD) and of the Beck Depression Inventory (BDI) in depressed patients compared to controls.

Methods: The inclusion criterion for participation in the study was presence of the diagnosis partially remitted Major Depressive Disorder or Dysthymia (despite sufficient pharmacotherapy) diagnosed by the Mini International Neuropsychiatric Interview (DSM-IV) and patient history. Diagnoses were made in consensus of two experienced psychiatrists. Patients were randomly allocated to two groups starting reading the book immediately (treatment group) or remained in observation for another 6 weeks (waiting group). Pharmacotherapy remained unchanged. Fifty-six patients (male, 17; female, 39; age, 47 yrs) have either completed the Bibliotherapy and read the German version of the self help book "Feeling good" by D. Burns or completed the 6 weeks waiting time. We tested if patients with partially remitted depression or dysthymia having received Bibliotherapy show improvements in scores of the HAMD and BDI rating scale compared to waiting group.

Results: In our preliminary results we include all patients who had completed the study ($N = 56$). The results show a significant reduction of HAMD ($p = 0.049$) in the treatment group in comparison to the waiting group, but not in BDI ($p = 0.06$).

Conclusion: This is preliminary evidence that patients show lower HAMD and BDI scores after having received Bibliotherapy. However, the impact of Bibliotherapy is to be investigated further and the number of patients has to be increased.

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P26. Respiratory and autonomic panic disorder subtypes: clinical correlates and response to alprazolam-XR

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Background: Research suggests that there may be at least two clinically relevant subtypes of panic disorder, a respiratory subtype and an autonomic subtype, each associated with different clinical characteristics.

Methods: Data were combined from two flexible-dose studies in which patients meeting DSM-III criteria for panic disorder were randomized, double-blind, to six weeks of treatment with either alprazolam-XR (ALP-XR; $N = 172$; 59.9% female) or placebo (PBO; $N = 162$; 59.3% female). A Sheehan Patient-Rated Anxiety Scale (SPRAS)-factor score > 8 was required to qualify a patient for either the respiratory or autonomic subtype (equivalent to moderate severity on 4 out of 5 symptoms). Response was defined as much or very much improved on the CGI-I.

Results: 213 patients (64%) had the respiratory subtype (26% with agoraphobia, baseline mean weekly spontaneous vs. situational attacks: 3.7 vs. 4.1); and 195 patients (58%) had the autonomic subtype (26% with agoraphobia, baseline mean weekly spontaneous vs. situational attacks: 3.8 vs. 4.5). For the respiratory subtype, treatment with ALP-XR resulted in significantly greater improvement than placebo in total panic frequency at LOCF endpoint (minus $5.1 + 0.66$ vs. minus $2.4 + 0.65$; $p < 0.01$), and significantly higher CGI-I responder rates at LOCF endpoint (74% vs. 45%; $p < 0.01$). For the autonomic subgroup, treatment with ALP-XR resulted in significantly greater improvement than placebo in total panic frequency at LOCF endpoint (minus $5.4 + 0.67$ vs. minus $3.0 + 0.66$; $p = 0.01$), and significantly higher CGI-I responder rates at LOCF endpoint (72% vs. 40%; $p < 0.01$). Additional data will be presented regarding these two panic subtypes, as well as the efficacy of ALP-XR in improving respiratory and autonomic symptomatology.

Conclusion: ALP-XR demonstrates significant efficacy in both the autonomic and respiratory subtypes of panic disorder.

P27. Ziprasidone in mania: 21-day randomized, placebo-controlled trial

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The aim of this study was to compare the efficacy and tolerability of ziprasidone and placebo in patients with bipolar mania. In a 21-day, double-blind, parallel group trial, patients with bipolar I disorder, current episode manic or mixed, were randomized to ziprasidone (40 to 80 mg BID) or placebo in a 2:1 ratio. Assessments were performed at baseline and days 2, 4, 7, 14, and 21 or early discontinuation. The primary efficacy variable was Mania Rating Scale (MRS); secondary measures included Clinical Global Impression–Severity (CGI–S) and CGI–Improvement (CGI–I). The primary analysis was mean change from baseline to endpoint (day 21 or early discontinuation) using last observation carried forward.

The ziprasidone group ($n = 137$) had a mean change in MRS score of -11.12 versus -5.62 for the placebo group ($n = 65$) ($P < 0.01$). Mean changes in CGI–S were -1.09 for ziprasidone and -0.43 for placebo ($P < 0.001$). Mean CGI–I scores were 2.71 and 3.46, respectively ($P < 0.001$). Significant improvements versus placebo were noted from day 2 in MRS and CGI–S, and from day 4 in CGI–I, and except for day 4 for MRS, were maintained throughout the study. Most treatment-emergent adverse events (AEs) were mild to moderate in severity; 6.5% of ziprasidone-treated and

1.5% of placebo-treated patients discontinued because of AEs.

Thus, in this 21-day study, ziprasidone demonstrated superiority to placebo in improving symptoms and global illness severity in bipolar mania. Significant improvement was noted within two days. Ziprasidone was well tolerated. These data are in accord with results of a similar trial of ziprasidone in acute mania (*Am J Psychiatry* 2003: **160**: 741–748).

P28. The speed of onset of action of alprazolam-XR compared to alprazolam-CT in panic disorder

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Aim: The aim of the study was to compare the speed of onset of action of the extended release (XR) formulation of alprazolam with that of the compressed tablet (CT) formulation in a sample of outpatients with DSM-IV panic disorder.

Data source: Diary records of hourly antianxiety benefit from a 9-week open label switch study, in which 30 patients with DSM-IV diagnoses of panic disorder were stabilized on alprazolam-CT for 3 weeks and then switched to an equivalent milligram dose of alprazolam-XR, were used to examine the timing and magnitude of benefit on both formulations.

Results: The magnitude of benefit at the first hour after the first morning dose was similar before and after the switch to alprazolam-XR. The peak benefit, measured over the hours after the first morning dose, was also similar and 90% of peak benefit was achieved in the first hour on both formulations. In addition, mean time to peak benefit was similar (1.5 hours for alprazolam-CT versus 1.6 hours for alprazolam-XR) and the percent of patients achieving peak benefit in the first hour was also similar: 64% on alprazolam-CT and 71% on alprazolam-XR. Additional analyses indicate that the mean benefit achieved in the first hour on the compressed tablet formulation was not sustained beyond 5.1 (SD 1.7) hours while that on the extended release formulation was sustained for 11.3 (SD 4.2) hours. The results, together with previous findings of equivalent efficacy on the two formulations but a clinically and statistically longer duration of therapeutic action on alprazolam-XR, are discussed.

Conclusion: The results suggest that the speed of onset on alprazolam-XR is similar to that on alprazolam-CT. These results must be viewed in the context of the study limitations including its small size, the lack of independence of groups in a switch study, and the limitations of the diary records used.

P29. Panic cognitions and response to pharmacotherapy of panic disorder with agoraphobia

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Objective: To compare panic cognitions before and after pharmacological treatment of panic disorder with agoraphobia (PDA) and relate them to response to such treatment.

Methods: 111 PDA outpatients were treated with fluoxetine (median dose 20 mg/day) for 12 weeks. The Agoraphobic Cognitions Questionnaire (ACQ) was administered before and after treatment to ascertain changes in panic cognitions that occurred in the course of such treatment. Patients were divided into two groups on the basis of their response to treatment, as measured by the Clinical Global Impressions (CGI) Improvement Scale: one group consisted of patients who were much or very much improved on CGI (treatment responders), while the other comprised of patients who showed little or no improvement after treatment (non-responders). The scores on ACQ were compared between treatment responders and non-responders.

Results: 68 (61.2%) PDA patients were classified as treatment responders, whereas 43 (38.8%) did not respond to treatment. While there were no statistically significant differences in the scores on the ACQ and its subscales between treatment responders and non-responders before treatment, responders had significantly lower scores ($p < 0.001$) on the ACQ and its subscales than non-responders after treatment.

Conclusions: Compared to PDA patients who showed little or no improvement after a 12-week pharmacological treatment, panic-related cognitions were significantly more decreased in patients who were judged to be much or very much improved, although the treatment did not specifically address these cognitions. This finding suggests that treatment response may be associated with significant changes in panic-related cognitions; if so, treatment response might be augmented by specific interventions that would target panic-related cognitions (e.g., cognitive therapy techniques).

P30. Anxiety and the prevalence of major depressive disorders

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Anxiety disorders and major depressive disorders (MDD) are both conditions which are highly prevalent and of common concurrence. It continues to be of interest to clarify their relationship.The sample is based on population screening for anxiety and depression in Iceland to recruit participants, age 18–60, in a genome-wide research project. Those fulfilling case-definition criteria were clustered according to family-relatedness with the help of the population-wide deCode Genealogy Database. Those who met the selection criteria for anxiety, depression and family relatedness were then called

up on for further diagnostic work-up, using a computerized version of the CIDI (version 1.1) administered by trained lay-interviewers.

The results are based on 2232 consecutive CIDI interviews, 1479 women and 753 men. The groups mean age was 41.7 years. The lifetime prevalence of MDD, single episode was 21.4% and for MDD, recurrent it was 11.7%. Both these prevalence figures are three times higher than the population prevalence. The prevalence of anxiety disorders was similarly increased. Of the 2232 persons, 545 had one anxiety disorder diagnosis and 446 two or more anxiety diagnoses. With increasing number of anxiety diagnoses the lifetime prevalence of MDD, single episode, increased, being 59.6% in the group with four anxiety diagnoses. This was not the case for MDD, recurrent where the prevalence did not increase with increasing number of anxiety disorders.

The group studied is selected to include increased number of persons with anxiety and depression. As expected the comorbidity of depression and anxiety is found to be high but the relationship is strongest for multiple anxiety disorders and single episode MDD.

P31. Milnacipran in adolescents suffering from major depression and/or dysthymia

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Objective: We assessed safety and efficacy of the serotonin and norepinephrine reuptake inhibitor (SNRI) milnacipran in depressed adolescents, which is approved for the treatment of depression from age 15 in Austria.

Methods: We conducted an open and naturalistic 12-week trial with the SNRI milnacipran in 15 adolescents aged 15–18 years suffering from major depression (DSM-IV: 296.2) or dysthymia (DSM-IV: 300.4), who received milnacipran in a mean dose of 133 mg daily. Clinical symptoms and side-effects were rated according to Clinical Global Impressions Scale (CGI), Montgomery-Asberg (MADRAS) and Hamilton Depression (HAM-D) Scale.

Results: HAM-D scores at baseline were 22.9 (SD = 0.5) and 3.8 (SD = 5.3) at endpoint. MADRAS scores declined from 30.9 (SD = 5.6) at baseline to 5.3 (SD = 3.0) after 12 weeks. Patients showed a reduction in CGI severity scores from 4.5 at baseline to 1.7 after 12 weeks which was statistically significant ($p < 0.001$) HAM-D scores as well as MADRAS scores declined significantly ($p < 0.001$). Approximately 92% of the 12 patients who finished 12 weeks of treatment showed a CGI-R score of 2 (much improved). Mild and transient side-effects were observed, the most frequent were headache in 21% and nausea in 14% within the first tw weeks.

Conclusions: Data from this 12-week open trial with the SNRI milnacipran suggest a favorable safety profile, comparable to that seen in SSRI treated patients, and good clinical efficacy in depressed adolescents.

P32. Remission in placebo-controlled trials of duloxetine with an SSRI comparator

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Objective: Remission is increasingly recognized as the optimal outcome of the acute phase of antidepressant therapy. Evidence suggests that therapy with dual (5-HT and NE) reuptake inhibitors may bring about higher rates of remission than SSRIs. Duloxetine is a dual reuptake inhibitor that has well-established efficacy and safety in clinical trials. Here we examine the remission rates in controlled studies of duloxetine.

Method: Pooled data from all six randomized, double-blind, placebo controlled clinical trials comparing duloxetine with an SSRI in the treatment of depression were analyzed. The primary definition of remission was a score of ≤ 7 on the 17-item Hamilton Rating Scale for Depression (HAMD17). Because the threshold for entry into these studies was lower than traditionally employed thresholds (HAMD17 ≥ 15), a subset of patients with baseline HAMD17 ≥ 19 was also examined.

Results: Remission rates were 43% (300/697) for duloxetine, 38% (162/423) for SSRIs and 28% (144/507) for placebo ($p < 0.001$). Odds ratios were 1.22 (95% confidence interval, CI: 0.95, 1.56) for duloxetine/SSRI and 1.90 (95% CI: 1.49, 2.43) for duloxetine/placebo. In patients with baseline HAMD17 scores $> = 19$, remission rates were 38% (163/429) for duloxetine, 29% (70/245) for SSRI and 18% (51/289) for placebo ($p < 0.001$). Odds ratios were 1.53 (95% CI: 1.09, 2.15) for duloxetine/SSRI and 2.86 (95% CI: 2.00, 4.10) for duloxetine/placebo.

Conclusion: Remission rates for duloxetine were statistically significantly greater than placebo and numerically greater than SSRI in controlled clinical trials. In patients with baseline HAMD17 scores $= 19$, remission rates for duloxetine were statistically significantly greater than both SSRI and placebo.

P33. Olanzapine versus placebo for relapse prevention in bipolar depression

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Purpose: Placebo-controlled trials have shown olanzapines efficacy for treating acute bipolar mania and acute bipolar

depression; olanzapines efficacy in relapse prevention was suggested by a recent year-long lithium-controlled study. Efficacy for relapse prevention is further tested in this placebo-controlled study.

Methods: Patients in acute manic or mixed episodes of bipolar I disorder were treated openly with olanzapine for 6–12 weeks. Patients achieving symptomatic remission (defined as YMRS total score ≤ 12 and HAMD-21 total score ≤ 8) were randomized to olanzapine (N = 225) (5–20 mg/d) or placebo treatment (N = 136) for 52 weeks of double-blind treatment.

Results: Time to relapse to an affective (manic, depressive, or mixed) episode, defined as YMRS total score ≥ 15 and/or HAMD-21 total score ≥ 15 and/or psychiatric hospitalization, was significantly prolonged by olanzapine treatment ($P < 0.001$, mean olanzapine dose = 12.5 mg). Relapse to an affective episode occurred in 46.7% of olanzapine-treated and 80.1% of placebo-treated patients ($P < 0.001$). Compared with the placebo group, olanzapine-treated patients had a statistically significantly lower rate of relapse into a manic episode (16.4% vs 41.2%, $P < 0.001$), or a depressive episode (34.7% vs 47.8%, $P = 0.015$). Common (> 5%) and significant adverse events occurring in the olanzapine group compared to placebo were weight gain, fatigue, and akathisia. Significantly more olanzapine-treated patients (23.6%) completed the 52-week trial than those on placebo (9.6%, $P = 0.001$) with approximately twice as many placebo-treated patients discontinuing due to lack of efficacy (57.4% vs 28.4%, $P = 0.001$).

Conclusion: Olanzapine delays relapse in bipolar disorder. This year-long, placebo-controlled study found that olanzapine treatment significantly reduced rates of both manic and depressive episodes.

P34. Olanzapine versus lithium in relapse prevention in bipolar disorder

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Purpose: This is the first randomized double-blind comparison of the efficacy and safety of olanzapine and lithium in the prevention of relapse into a manic, mixed, or depressed bipolar episode.

Methods: 543 patients with a diagnosis of bipolar I disorder, manic or mixed type, with a history of at least 2 manic or mixed episodes within 6 years, and a YMRS total score $= 20$ entered the study and received open label combination therapy of olanzapine and lithium for 6–12 weeks. Of these, 431 patients met symptomatic remission criteria (YMRS total score ≤ 12 and HAMD-21 total score ≤ 8) and were randomized to monotherapy with either olanzapine (N = 217) (5–20 mg/d) or lithium (N = 214) (serum level of 0.6 to 1.2 mEq/L in a dose range of 300–1800 mg/d) for 52 weeks of double-blind treatment.

Results: Significantly more olanzapine-treated patients (46.5%) completed the 52-week trial than those on lithium (32.7%; $P = 0.004$). Relapse to an affective episode, defined as YMRS total score ≥ 15 and/or HAMD-21 total score ≥ 15, occurred in 30.0% of olanzapine-treated and 38.8% of lithium-treated patients ($P = 0.055$). Olanzapine-treated patients had a statistically significantly lower incidence of relapse into a manic episode than lithium-treated patients (14.3% vs. 28.0%, respectively, $P < 0.001$), and both groups had similar incidences of relapse into a depressive episode (16.1% vs. 15.4%, respectively, $P = 0.895$). The rates of discontinuation due to adverse events were 18.9% for the olanzapine group and 25.7% for the lithium group ($P = 0.105$). Weight gain across open-label and double-blind therapy phases was statistically significantly greater in the olanzapine group compared to the lithium group (1.79 kg vs −1.38 kg, respectively, $P < 0.001$).

Conclusion: Olanzapine and lithium both appear to effectively and safely prolong remission in bipolar disorder, yet more patients remained on olanzapine throughout this year-long study and it was more effective than lithium in preventing relapse into mania.

P35. Quetiapine treatment of borderline personality disorder

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Introduction: Among the Axis-II disorders, borderline personality disorder (BPD) is considered the most critical to treat due to a high propensity for self-destructiveness. BPD includes four main symptom domains (affective, micropsychotic, impulsive behaviors, and interpersonal problems), of which the first three may be amenable to treatment with pharmacotherapy. Results from studies in patients with schizophrenia suggest that quetiapine will improve these three domains in addition to improving the attentiveness of patients with BPD.

Objective: To evaluate the impact of quetiapine on BPD symptomatology in outpatients with BPD. It is intended to recruit a total of 24 patients who will complete 12 weeks of treatment.

Methods: Outpatients with BPD (DSM-IV criteria; Diagnostic Interview for Borderlines, Revised score $= 7$) entered a 12-week open-label study with quetiapine. The clinical efficacy of quetiapine was evaluated using the following measures: Hamilton Depression and Anxiety Rating Scales, Beck's Hopelessness Scale, Brief Psychiatric Rating Scale (BPRS), Barratt Impulsivity Rating Scale, Buss-Durkey Hostility Inventory, Temperament and Character Inventory, and Global Assessment of Functioning. Attentiveness was examined using a computerized battery evaluating different

attention components (selective attention, divided attention, working memory, executive functions).

Results: We present preliminary data from 19/24 patients who completed 12 weeks of treatment. The mean dose of quetiapine was 258±51 mg/day (range 200–400 mg/day). Depression, anxiety, impulsivity, hostility, and character dimensions were significantly reduced ($p < 0.05$), while social functioning was significantly improved ($p < 0.05$). There were no changes in the psychotic dimension of the BPRS as patients did not present with psychotic symptoms. Selective attention (Stroop test) and divided attention (Dual task) both showed significant improvements ($p < 0.05$).

Conclusions: Quetiapine is effective in reducing many clinical and attentional deficits in patients with BPD.

P36. Anxiolytic activity of proproten: involvement of GABA in this effect

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The aim of this study was to assess anxiolytic activity of proproten (P) and reveal the possible involvement of GABA-ergic system in this effect. Experiments were carried out on white outbred male rats (230–250 g). Vogel's conflict assay, elevated plus-maze, open-field, passive avoidance and rotarod tests were used. In elevated plus-maze P (ultra-low doses of antibodies to S100 protein, 2.5 ml/kg, i.p.) increased the number of entries (1.9 times) and time spent (5.4 times) in the open arms, and decreased both the number of entries and time spent in the closed ones. Diazepam (2 mg/kg, i.p.) produced similar, but more pronounced effect in this test. In the open-field the rats receiving P or diazepam showed reduced anxiety and freely migrated in the open centre area. P and diazepam increased the number of punished responses in Vogel's conflict test. Bicuculline and picrotoxin decreased anticonflict effect of P (Table). P differs greatly from benzodiazepine tranquillizers in lack of sedative, amnestic, myorelaxant activity and withdrawal syndrome. Thus, P possesses a marked anxiolytic profile without sedative, amnestic and muscle relaxant action. GABA system is probably involved in realisation of anxiolytic action of P.

Table. *Anxiolytic activity of proproten in Vogel's conflict test*

	Dose	*Number of punished responses*
Control	–	528.1±73.4
Proproten	2.5 ml/kg, i.p.	740.0±108.4, $p < 0.05$ vs. control
Diazepam	2 mg/kg, i.p.	721±84.3, $p < 0.05$ vs. control
Bicuculline	1 mg/kg, i.p.	327.3±115.4, $p < 0.05$ vs. control
Proproten + bicuculline	2.5 ml/kg+1 mg/kg	419.6±107.4, $p < 0.05$ vs. proproten
Diazepam + bicuculline	2 mg/kg+1 mg/kg	353.6±74.1, $p < 0.05$ vs. diazepam
Picrotoxin	1 mg/kg, i.p.	296.9±125.1, $p < 0.05$ vs. control
Proproten + picrotoxin	2.5 ml/kg+1 mg/kg	469.3±85.5, $p < 0.05$ vs. proproten
Diazepam + picrotoxin	2 mg/kg+1 mg/kg	304.8±95.4, $p < 0.05$ vs. diazepam

P37. Adjunctive ziprasidone for acute bipolar mania: randomized, placebo-controlled trial

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This study aimed to evaluate the efficacy and tolerability of ziprasidone versus placebo in patients with bipolar mania who were receiving lithium concomitantly. In this 21-day, randomized, double-blind trial, inpatients with bipolar I disorder, most recent episode manic or mixed, received ziprasidone (40 mg BID on day 1, 80 mg BID on day 2, and 80 to 160 mg/day thereafter) or placebo. Lithium dosage was adjusted after day 1 to maintain serum levels of 0.8 to 1.2 mEq/L. Primary efficacy variables were the Mania Rating Scale (MRS) and CGI–S. Secondary variables included MRS Manic Syndrome and Behavior and Ideation subscales, Hamilton Depression Scale (Ham–D), CGI–I, and PANSS Total and Positive and Negative subscales.

A total of 101 patients received ziprasidone and 103 placebo. At day 4, rates of change (mixed effects ANCOVA; observed cases) were greater with ziprasidone than with placebo for MRS ($P < 0.05$), CGI–S ($P < 0.01$), CGI–I ($P < 0.01$), Behavior and Ideation ($P < 0.01$), and Ham–D ($P < 0.05$). LS mean changes were greater for MRS Manic Syndrome ($P < 0.05$). At day 14, rates of change in efficacy variables were comparable; however, ziprasidone-treated patients demonstrated greater LS mean changes in CGI–S, CGI–I, Behavior and Ideation, and PANSS Total (all $P < 0.05$) at day 14 (observed cases), and in PANSS Total ($P < 0.01$) and Positive ($P < 0.05$) and Negative ($P < 0.01$) subscales at day 21 or early discontinuation (LOCF). Ziprasidone with lithium was well tolerated; rates of discontinuation for adverse events attributed to study treatment were $= 5\%$ in both groups.

These data suggest that lithium plus ziprasidone may effect earlier onset of improvement than lithium alone and that these agents in combination are well tolerated.

P38. Onset of improvement in emotional and painful physical symptoms of depression with duloxetine treatment

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Objectives: Duloxetine, a new potent and balanced reuptake inhibitor of serotonin (5-HT) and norepinephrine (NE), is expected to show robust and rapid efficacy in treating the emotional symptoms associated with depression. Since 5-HT and NE play an important role in modulation of pain via descending inhibitory pain pathways, it was hypothesized that duloxetine may also demonstrate efficacy in painful physical symptoms, which are commonly associated with depression. We examined the temporal pattern of efficacy of duloxetine 60 mg QD in both the emotional and painful physical symptoms associated with major depression.

Method: Data were pooled from two, 9-week randomized, double-blind, clinical trials of duloxetine 60 mg QD (N = 244) and placebo (N = 251). Emotional symptom outcomes included the 17-item Hamilton Rating Scale for Depression (HAMD17) total score and its subfactors and items, as well as the Clinical Global Impression of Severity (CGI-S), and Patient Global Impression of Improvement (PGI-I) scales. Painful physical symptom outcomes included Visual Analog Scales (VAS) for pain.

Results: For all emotional symptom outcomes, meaningful and significant advantages of duloxetine over placebo were observed at week 1 or 2, and continued to increase throughout the trial. In physical symptom outcomes, meaningful and significant advantages were again observed at week 1 or 2; however, maximal improvement was observed by week 3. For example, at weeks 1 and 9 the advantage of duloxetine over placebo in mean change on HAMD17 item 1 was 0.19 and 0.57, respectively.

Conclusion: In these studies, duloxetine (60 mg QD) demonstrated rapid onset of robust and sustained antidepressant efficacy across a wide range of emotional and physical symptom outcomes.

P39. Bright light therapy in seasonal affective disorder – does it suffice?

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Objectives: Seasonal affective disorder (SAD) is defined as a form of recurrent depressive or bipolar affective disorder characterized by recurrent affective episodes that occur annually at the same time of the year.[1] Guidelines for SAD have proposed bright light therapy (BLT) as the treatment of choice.[2] However conventional antidepressant treatment has also been found to be effective in this condition.[3] The aim of this investigation was to assess the importance of drug treatment in a clinical sample of SAD patients.

Methods: We examined the psychopharmacologic treatment of 578 outpatients (446 females, 132 males) suffering from SAD (unipolar depression: 77.9%, bipolar-II disorder: 19.6%, bipolar-I disorder: 2.2%) that had been treated with BLT at the Department of General Psychiatry (University of Vienna).

Results: 47.9% of all patients received psychopharmacologic treatment in addition to BLT: 34.6% were treated with antidepressants (24.9% SSRI*, 6.6% NaSSA*, 5.2% tricyclic antidepressants, 3.3% tetracyclic antidepressants, 1.4% SNRI*, 1.2% RIMA*, 0.2% NARI*), 5.2% received phase prophylaxis with lithium or antiepileptics, 9.0% were treated with anxiolytic substances (mostly benzodiazepines), 7.6% with phytopharmaceutical medication (7.4% hypericum extract, 0.5% valerian extract), 3.3% with typical neuroleptics, 1.0% with atypical neuroleptics, 3.3% with other medication. No significant differences in medication were observed in regard to gender, age, duration of hospitalization or number of affective episodes. Patients suffering from bipolar disorder received phase prophylactic medication more frequently (bipolar-I: 38.5%, bipolar-II: 8.0%) than patients with unipolar depression (3.6%; Likelihood ratio $\chi^2 = 17.591$, df = 3, p = 0.0005).

Conclusions: A substantial part (about one third) of our patients was treated with antidepressant medication concomitant to BLT. Obviously BLT does not suffice as only antidepressant regimen for all SAD patients. Opposed to the guidelines for the treatment of depression patients with several depressive episodes did not receive antidepressant long-term medication or phase prophylaxis more often than patients with only a few episodes. Our results also show that the majority of patients with bipolar disorder still do not receive any phase prophylactic medication, which could indicate the need for further treatment.

*SSRI, selective serotonin reuptake inhibitors; NaSSA, noradrenergic and specific serotonergic antidepressants; SNRI, serotonin and noradrenalin reuptake inhibitors; RIMA, reversible inhibitors of monoaminoxydase A; NARI, noradrenalin reuptake inhibitors

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P40. Seasonality of birth in seasonal affective disorder

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Background: Seasonal affective disorder (SAD) is defined as a form of recurrent depressive or bipolar affective disorder, characterized by recurrent affective episodes that occur annually at the same time of the year.[1] Season of birth is a putative etiological factor for several psychiatric illnesses. An excess of late winter and early spring births has been demonstrated repeatedly for schizophrenia, which has been hypothesized as the result of a prenatal infection adversely affecting the maturation of critical brain structural and functional components.[2] The aim of this investigation was to examine seasonal differences in the frequency of birth in a clinical sample of SAD patients.

Methods: 578 outpatients (446 females, 132 males) suffering from SAD, winter type, according to the DSM-IV, who had visited the outpatient-clinic for seasonal affective disorder at the Department of General Psychiatry at the University of Vienna, Austria, between 1994 and 2003 were included in this evaluation. We compared the observed number of births in our sample with expected values calculated from a representative sample of 649.842 births between 1951 and 1991 in Vienna. Statistical analysis was performed with the Chi-Square test (two-tailed) on the $p = 0.050$ level of significance.

Results: The analysis of our data indicates that there was a significant deviation of the observed number of births from the expected values calculated on a monthly basis ($\chi^2 = 23.127$, $df = 11$, $p = 0.017$). Furthermore when comparing quarters (periods of 3 months: Jan–Mar, Apr–Jun, Jul–Sep, Oct–Dec) we found less births than expected in the first quarter of the year and a slight excess of births in the second and third quarter ($\chi^2 = 8.416$, $df = 3$, $p = 0.038$). There were also more births in the spring-summer season (calculated from Apr to Sep) and less than expected in fall and winter (Oct to Mar; $\chi^2 = 4.872$, $df = 1$, $p = 0.027$). Interestingly, patients, who had been diagnosed as suffering from melancholic depression ($n = 73$; feature specifier according to DSM-IV) exhibited a different pattern of birth than patients with atypical depression ($n = 385$): melancholic patients had significantly higher birth rates in the first quarter and lower rates in the third quarter ($\chi^2 = 9.849$, $df = 3$, $p = 0.020$). Also melancholic patients were more frequently born in fall/winter and less often in spring/summer compared to patients with atypical depression ($\chi^2 = 5.959$, $df = 1$, $p = 0.015$).

Conclusions: Beside genetic factors, which have been discussed in the pathogenesis of SAD, also environmental factors such as seasonality of birth seem to be of etiological significance. Possibly environmental light shortly after birth (as it has been discussed in schizophrenia by McGrath et al[3]) has a formative influence on the individual vulnerability for the development of seasonal depression in later life. In addition, birth effects seem to be dependent on the symptom profile of the patients, but further studies are needed to elucidate the underlying mechanisms of these observations.

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P41. The preliminary report of an outpatient, double-blind, placebo-controlled study comparing 30 mg and 45 mg of nemifitide versus placebo in major depression

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Aim: This presentation is a preliminary summary of a new proof of principle clinical trial with nemifitide for the treatment of major depression.

Method: This is a double blind, placebo-controlled, multicenter study (principal investigators: Drs. Cunningham, Kiev and Shrivastava, USA) with two doses of nemifitide (30 and 45 mg) versus placebo in the outpatient treatment of major depression ($N = 78$). Ten subcutaneous doses of nemifitide were given once daily (Monday–Friday) over 2 consecutive weeks. The follow-up period was 4 weeks with the total length of the study being 6 weeks. The primary efficacy variable was MADRS (change from baseline). The secondary efficacy variables were HAMD-17, Carroll Self-Rating Depression Scale and CGI. The inclusion criteria were diagnosis of major depressive disorder according to DSM-IV, baseline MADRS ≥ 25 and CGI (severity of illness) ≥ 4. The exclusion criteria were standard for a clinical trial for major depression.

Results: This proof of principal study demonstrated the statistical superiority of the 45 mg/day dose versus placebo at numerous time-points through the study. The dose of 45 mg/day of nemifitide was more effective than 30 mg/day, with indications of a dose response curve. The strata analysis for patients with baseline HAMD > 22 strengthened a statistical separation on all psychometric scales for both 30 and 45 mg of nemifitide from placebo at many time-points. Nemifitide showed a good tolerability and safety profile. No dropouts occurred because of side effects at both doses. The percentage of incidences for side effects with nemifitide was comparable with placebo.

Conclusion: Nemifitide, in this proof of principle study, demonstrated a promising clinical effect in the treatment of major depression with statistical separation from placebo, especially for 45 mg dose.