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Abstracts

SO 01. Will GAD Strengthen or vanish?

SO 0101. Is Generalized Anxiety Disorder Associated with Pain and Somatoform Disorder?

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Background: The reciprocal relationships between symptoms of pain, anxiety, and depression has been well recognized over the past decade. Although recent research confirmed strong links between pain and depression on the diagnostic level, a paucity of research exists regarding the relationship between pain, DSM-IV somatoform and anxiety disorders and GAD respectively. The paper reviews these relationship with particular emphasis on GAD from a clinical epidemiological perspective.
*Methods: N*ationally representative community data of N = 4,181 participants aged 18–65 years and data from primary care are used to explore these associations. Diagnostic assessment is based on standardized diagnostic interview (DSM-IV/M-CIDI). Several thresholds defined pain (no pain, pain symptoms, somatoform pain symptoms, somatoform pain disorder).
Results: Pain is associated with both specific anxiety and depressive disorders, with increasing significant odds ratios (OR) from non-somatoform pain symptoms (OR range: 1.9 to 2.0), to somatoform pain symptoms (OR range: 2.4 to 7.3), to somatoform pain disorder (OR range: 3.3 to 14.8). Somatoform pain symptoms and pain disorder persistently showed associations after adjusting for comorbid other anxiety and depressive disorders and physical illnesses. Highest associations were revealed for Generalized Anxiety Disorder (GAD): all individuals with GAD reported any significant pain with the majority suffering from somatoform pain disorder. Further, GAD patients have also increased odds for a range of mostly chronic and painful conditions. The patterns of associations are unique to GAD and quantitatively and qualitatively different from patterns seen for depression.
Discussion: The known relationship between symptoms of pain, depression and anxiety was confirmed on the DSM-IV diagnostic level for various depressive and anxiety disorders. Particularly the somatoform subtype (medically unexplained pain) of pain appears relevant for these associations and GAD. The close pain-GAD association cannot be explained simply by age and comorbid depression. Closer experimental examination of underlying mechanisms of these associations is needed.

SO 0102. Case against merging Generalized Anxiety Disorder with major depression

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Background: Both DSM-IV and ICD-10 require an episode duration of 6 months for a diagnosis of generalized anxiety disorder (GAD); in DSM-III the duration was 1 month and was increased mainly in order to reduce the association between GAD and major depressive disorder (MDD). This radical change was not supported by the findings of several epidemiological studies.
Method: in the Zurich Study GAD was assessed from age 20/21 to 40/41 by a total of six interviews applied in combination with the SCL-90-R. DSM-III, DSM-III-R and DSM-IV criteria for GAD were applied. MDD was defined by DSM-III-R and bipolar-II disorder (BP-II) by broader (Zurich) criteria. The probands' family history for anxiety, depression and mania was taken at the age of 28.
Results: 91% of subjects treated for GAD remained undiagnosed by the 6-month criterion. GAD was more associated with BP-II than with MDD. The psychiatric comorbidity patterns of GAD and BP-II were very similar and both differed markedly from that of MDD. The prospective course data showed no significant diagnostic cross-over from GAD to depression or vice versa. An elevated FH+ of GAD/panic was present in both GAD and BP-II. In contrast to that, MDD subjects did not show an elevated FH+ for GAD. A FH+ for mania occurred only in bipolars. An elevated FH+ for depression was unspecific and found equally in all three diagnostic groups.
Conclusions: validators such as family history, comorbidity patterns and prospective course over 20 years on diagnostic changes argue against merging GAD with MDD.

SO 0103. Pharmacological treatment in Generalized Anxiety Disorder

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Generalized anxiety disorder (GAD) is common in community and clinical settings. The individual and societal burden associated with GAD is substantial, but many of those who could benefit from treatment are not recognised or treated (Tyrer and Baldwin, 2006). Recent evidence-based guidelines for the pharmacological management of patients with GAD have recommended initial treatment with either a selective serotonin reuptake inhibitor (SSRI) or a serotonin-noradrenaline reuptake inhibitor (SNRI), on the basis of their proven efficacy and reasonable tolerability in randomised placebo-controlled trials (Baldwin et al, 2005; Canadian Psychiatric Association, 2006).

However, there is much room for improvement in both the efficacy and tolerability of treatment. Response rates to first-line treatment can be disappointing and it is hard to predict reliably which patients will respond well and which will have only a limited treatment response. Many patients worry about becoming dependent on medication, a substantial proportion experience troublesome adverse effects, and these problems limit the effectiveness of pharmacological treatments in clinical practice.

The relative lack of longitudinal studies of clinical outcomes in GAD and the small number of placebo-controlled relapse prevention studies lead to uncertainty about the optimal duration of treatment after a satisfactory initial response. There have been few investigations of the further management of patients who have not responded to first-line treatment and there is a pressing need for further augmentation studies, in patients who have not responded to an SSRI or SNRI, or to other initial pharmacological approaches.

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SO 02. What is new in depression?

SO 0201. Desvenlafaxine – A new antidepressant

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Introduction: Desvenlafaxine succinate (desvenlafaxine) is a serotonin-norepinephrine reuptake inhibitor (SNRI)[1] with demonstrated efficacy for the treatment of major depressive disorder (MDD).[2]
Methods: Two identically designed, randomized, double-blind, placebo-controlled studies were conducted: one in the European Union (EU) and one in the United States (US). Patients met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for MDD with a 17-item Hamilton Depression Rating Scale (HAM-D_{17}) total score ≥ 20 at screening and baseline. Two fixed daily doses of desvenlafaxine (50 mg or 100 mg) or placebo were administered for 8 weeks (including a 1 week, 50 mg titration period for the patients receiving 100 mg). The primary efficacy variable, change from baseline on the HAM-D_{17}, was analyzed using analysis of covariance. For all efficacy analyses, the final on-therapy evaluation was the primary end point and the primary population was the intent-to-treat (ITT) population.
Results: The ITT population in these studies were: EU: desvenlafaxine 50 mg (n = 164), desvenlafaxine 100 mg (n = 158), and placebo (n = 161); US: desvenlafaxine 50 mg (n = 150), desvenlafaxine 100 mg (n = 147), and placebo (n = 150). Mean baseline HAM-D_{17} scores ranged from 23.0 to 24.4. Adjusted mean change from baseline scores on the HAM-D_{17} in the EU study were significantly greater for both desvenlafaxine groups (50 mg: -13.2 vs -10.7, $P = 0.002$; 100 mg: -13.7 vs -10.7, $P < 0.001$) compared with placebo. In the US study the 50 mg desvenlafaxine group separated significantly from placebo (-11.5 vs -9.5; $P = 0.018$) but the 100 mg group did not (-11.0 vs -9.5; $P = 0.065$). In both studies, both doses of desvenlafaxine were generally well tolerated and adverse events were consistent with those of the SNRI class.
Conclusions: These results generally support the efficacy of desvenlafaxine 100 mg/d for improving the symptoms of MDD and establish efficacy of the 50 mg/d dose.

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SO 0202. Agomelatine: Sleep and Depression

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Agomelatine represents a distinct paradigm shift in targeted antidepressant pharmacotherapy. MT_1 and MT_2 agonism combined with $5HT_{2C}$ antagonism result in circadian phase advance with resynchronization of disrupted rhythms, while $5HT_{2C}$ antagonism appears to facilitate prefrontal dopamine and norepinephrine release. Positive findings that agomelatine is effective in preclinical models of depression and circadian rhythm disturbance provided justification for a clinical program. An overview of acute agomelatine versus placebo and active comparators; relapse prevention; tolerability and safety; and discontinuation studies will be presented. In addition specific clinical end points relating to sleep restoration, sexual function, depression severity and anxiety symptoms will be reviewed. Future indications for agomelatine including anxiety disorder and bipolar disorder.

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SO 0203. An Update on Psychotic and Refractory Depression

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Although the vast majority of depressed patients respond to antidepressant treatment about 15–20% of nonpsychotic depressives fail to respond to one or more trials of antidepressants. Moreover, 15–18% of major depressives demonstrate psychotic features and data from a number of studies indicate that these patients often require the addition of antipsychotic agents to their antidepressant regimen or electroconvulsive therapy to improve from their disorders. This presentation will review recent studies in psychotic major depression as well as the status of electrical stimulation strategies for refractory depression.

Psychotic major depression is a severe but relatively common subtype of major depression. It is characterized by delusions or hallucinations and although often severe, delusional symptoms are not uncommon in patients with fewer depressive symptoms. Thus, severity and delusions are somewhat independent dimensions for assessing major depression. Patients with the disorder demonstrate marked impairments in attention and working memory, executive function and response inhibition, as well as verbal and visual memory. These functions are mediated by activity in the prefrontal cortex, anterior cingulate, and the hippocampus/medial temporal lobes. Patients with the disorder demonstrate increased activity of the hypothalamic-pituitary-adrenal (HPA) axis as evidenced in increased levels of various cortisol measures. In regard to treatment, patients with the disorder generally are treated with the combination of antipsychotics and antidepressants or electroconvulsive therapy. Recent data from a multicenter trial comparing olanzapine, olanzapine plus fluoxetine and placebo are presented. We also will review recent data on ECT for the disorder. Last, recent research data on the glucocorticoid antagonist, mifepristone, in psychotic depression will also be presented.

In the past few years, there has been extensive study of vagal nerve stimulation (VNS) and rapid transmagnetic brain stimulation (r-TMS) in refractory nonpsychotic major depression. The results to date have been somewhat controversial and the basis for this will be reviewed. Clinical implications are discussed.

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SO 03. Better treatment outcomes from biology to compliance

SO 0301. The biology of incomplete response and non-compliance in mood disorders

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The extent of knowledge relating to the impact of mood disorders on the structural and functional processes of the brain has grown significantly in recent years. Although physicians have long been aware of the clinical implications of incomplete response and non-compliance, there still remains a lack of emphasis upon the importance of the underlying neurobiology and *its* role in the prognosis of mood disorders.

The neurobiology of mood disorders is complex, and its interplay with antidepressants is still being elucidated. This presentation will review some of the current leading theories in this area, with a focus upon neural circuitry and the monoamine, neuropeptide and neurotrophic theories of depression and anxiety. The way in which these systems become dysregulated, as is the case following an episodic or incomplete treatment intervention, will be examined.

One topic of central interest is the hippocampus. In a meta-analysis of 12 studies, hippocampal volume was found to be consistently and significantly reduced in patients with major depressive disorder compared with controls.[1] It has further been shown that the degree of hippocampal reduction is directly proportional to the number and duration of untreated depressive episodes.[2] Improving compliance levels with medication and ensuring appropriate treatment duration may therefore help to minimise the risk of hippocampal atrophy and thereby avoid a prolonged and possibly permanent neuroendocrine dysfunction.

The exact mechanisms behind hippocampal atrophy are not yet fully understood, however there is growing evidence to suggest that the dysregulation of brain-derived neurotropic factor (BDNF) may be an important factor. Study evidence suggests that levels of BDNF, the neurotropin primarily responsible for the function and survival of hippocampal neurons, are normalised through the administration of antidepressants.[3] Aydemir et al. 2006, for example, showed that BDNF levels were lower in antidepressant naïve patients than in healthy controls and that they increased during treatment with escitalopram at 10mg per day. These results are indicative of the effect of antidepressant drugs, including escitalopram, on neuroplasticity and depression, suggesting that BDNF might have an important role in depression. These human studies, as well as translational animal models of stress, depression and neuroplasticity, will be discussed in relation to the biology of mood disorders and treatment response.

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SO 0302. Why is compliance still an issue and is there anything we can do?

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In healthcare, compliance is a patient's behaviour relating to taking medication, following diets, or executing life style changes in accordance with their healthcare provider's health and medical recommendations. Therapeutic non-compliance occurs when an individual's health seeking or maintenance behaviour lacks congruence with the recommendations given by their healthcare provider.[1]

It is estimated that the compliance rate associated with long-term medication therapy is 40–50%. The compliance rate for short-term therapy is estimated, however, to be much higher, at 70–80%, while the rate with lifestyle changes is estimated to be the lowest, at 20–30%.[1]

Improving compliance is generally recognised as a major unmet need in the treatment of mood disorders. Depression itself has been shown to impact upon compliance levels. In every 100 non-compliant patients, an average of 63.5 will be depressed, compared with 36.5 who will not be depressed.[2] Similar problems have been seen in the treatment of bipolar disorder, where it was found that nearly one in two individuals did not take their medications as prescribed.[3]

We require a better understanding of why patients discontinue treatment at different stages, and which strategies would be most effective in improving the situation. For example, studies suggest that the antidepressant compliance questionnaire could help to improve compliance.[4]

Psychosocial factors such as patients' beliefs, attitudes towards therapy and degree of motivation regarding therapy are classified as "soft factors".[1] In contrast with the "hard factors" of non-compliance (e.g. simplicity of dosing regimen, tolerability of medication), the effects of these are much more difficult to measure and counter. A failure to address the soft factors may in fact negate all the efforts spent in countering the effects of the hard factors.

The concept of concordance is now replacing compliance. Concordance ensures that the patient is a decision maker in the process and emphasises agreement and harmony between patient and prescriber – something that has sometimes been ignored in past times.

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SO 0303. How to improve treatment outcomes in mood disorders?

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Patients are often most vulnerable during the early stages of antidepressant treatment. At this time point, attention to detail, on behalf of the clinician, is an important means of improving overall treatment outcome. Attention to detail takes different forms. In addition to choosing the most appropriate antidepressant from the now large selection available, it is essential that a patient accepts and understands his/her treatment regimen and that any changes to this regimen are managed in a timely and evidence-based way.

Avoiding a delayed therapeutic effect can have a number of positive implications for patient acceptance and therefore treatment outcome. The physical, psychological and social impairment associated with mood disorders can be minimised by using an antidepressant with a faster onset of action. This further reduces the risk of premature treatment discontinuation and poor compliance, which in turn are associated with a significant economic impact. In a study by Kasper et al. (2006), the onset of effect of escitalopram compared to other antidepressants was examined by pooling data from controlled randomised double-blind clinical trials. Using the primary efficacy parameter of mean change in the Montgomery-Åsberg Depression Rating Scale, as well as secondary outcomes, there was a consistent and statistically significant advantage for escitalopram in terms of onset of effect.

The careful management of patients who show an early, inadequate response to treatment is also a determinant of treatment outcome. Asnis et al. (2008) compared the efficacy and safety of escitalopram 20 mg/day to duloxetine 60 mg/day following initial non-response to escitalopram 10 mg/day in patients with severe depression. It was suggested that non-responders to escitalopram 10 mg/day did better on an 8-week course of escitalopram 20 mg/day than those switched to duloxetine 60 mg/day in terms of improvement in MADRS scores. This improvement was clinically significant as early as week one of randomised treatment.

Ensuring that patients are kept well informed about treatment expectations, such as time to efficacy, aspects of tolerability and recommended duration of treatment is a key component of the therapeutic process.

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SO 05. Sexual function in depression

SO 0501. Importance of sexual function in depression and how to assess

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Sexual dysfunction occurs in 30 − 70% of patients taking selective serotonin reuptake inhibitors (SSRIs) serotonergic tricyclic antidepressant and in substantial proportions of patients treated with the serotonin-noradrenaline reuptake inhibitors (SNRIs) venlafaxine and duloxetine

There is a high frequency of under communication due to several factors like shame, anxiety, lack of confidence, lack of time or finally deficit of specific learning for psychiatrists. No more than 20% of patients do communicate spontaneously this adverse event while between 50–75% show sexual difficulties using specific questionnaires. Near to 40% of patients are very concerned about sexual problems and they are in risk to dropout the treatment. To avoid lack of compliance, to interview patients with a scale or the use of validated and clinically reliable Sexual Dysfunction Questionnaires is needed. The questionnaires should include questions about the following items: decreased libido, delayed orgasm or anorgasmia, delayed ejaculation, inability to ejaculation, erectile dysfunction and general sexual satisfaction. The best approach to the patient could be to talk openly about their sexual difficulties after the onset of an antidepressant treatment and also to know the sexual functioning from the beginning of the depressive episode in order to discover changes. The ideal questionnaire should be brief, clear, and non-intrusive, hetero applied using a brief interview to avoid misunderstandings and accordingly validated. Existing and validated Sexual Dysfunction Questionnaires like PRSexDQ-SALSEX (Psychotropic Sexual Dysfunction Questionnaire- Salamanca Sex, Montejo AL), CSFQ (Changes in Sexual Functioning Questionnaire, Clayton A.), ASEX (Arizona Sexual Experiences Scale McGhee C.A.) and SEXFX (Sexual Adverse Events Scale, Kennedy S.) have been widely employed to discover this frequent and adverse event. Sexual dysfunction secondary to antidepressant therapy may be managed with a number of approaches. Perhaps the best

option could be to start with a treatment without sexual adverse events in sexually active patients.

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SO 0502. Antidepressant drugs and sexual function

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Adequate sexual expression is an essential part of many human relationships, enhancing quality of life and providing a sense of physical and emotional well-being. Depression is associated with impairments in sexual function and satisfaction, and most classes of antidepressant drug can exert adverse effects on sexual function (Baldwin, 2004; Williams et al, 2006).

Growing awareness of the prevalence of sexual problems in community and health-care settings, and the availability of new treatments for certain forms of sexual dysfunction, have together increased interest in the interrelationships between depression, sexual dysfunction, and antidepressant treatment.

This talk reviews the prevalence of sexual dysfunction in the community and in samples of depressed individuals, and summarises recent investigations of the beneficial and deleterious effects of antidepressant drugs on sexual function (Baldwin et al, 2006; Baldwin et al, 2008).

Further reading

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SO 0503. Reversing Sexual Dysfunction in Depression

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The relationship between sexual dysfunction in untreated depressed patients and the subsequent effects of various antidepressant medications on sexual function is complex. Primary prevention of sexual dysfunction during antidepressant treatment is the optimal approach. Previous presentations will have reviewed preferred monotherapies including agomelatine, bupropion, mirtazapine and moclobemide. However, other tolerability and safety issues may arise with these antidepressants. Several investigators have examined sexual dysfunction during combination antidepressant therapy, particularly in the presence of a partial response. The potential mitigating effect of combining bupropion or mirtazapine with antidepressant agents that cause sexual dysfunction will be reviewed. Other adjunctive agents including phospodiesterase-5-inhibitors, some dopaminergic agents and hormonal therapies will be discussed. Recent data on the effect of sildenafil to improve symptoms of depression in men with erectile dysfunction who did not receive antidepressant therapy will be presented.

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SO 06. Debate: "Is bipolar disorder overdiagnosed?"

PRO:

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Bipolar disorder is a common mental illness, affecting, depending on its definition, between 0.8 and 5% of the general population. Restricted to typical bipolar-I-disorder, the estimated life-time prevalence is between 0.8 and 1.5% worldwide (1). Taking also the so-called "bipolar spectrum" into account this estimate rises up to 5% (2). Besides bipolar-I-disorder, the bipolar spectrum covers classical bipolar-II-disorder and cyclothymic disorder with superimposed major depression (bipolar–II-b), and also rare manifestations as chronic hypomania or mania. However, bipolar disorder is certainly underdiagnosed and, by this, undertreated. It had been estimated than less than 50% of even typical bipolar-I-disorder patients receive a qualified treatment; especially the rate of misdiagnosis is high. Bipolar disorder is often confused with unipolar depression, anxiety disorders, substance abuse and, in younger patients, with ADHD and schizophrenia. Epidemiological figures show that the incidence of bipolar disorder is still rising; thus, there is an obvious need for more education both of the general public and amongst physicians to recognise bipolar disorder early in order to initiate appropriate treatment.

However, in the recent past also question were raised, whether bipolar disorders are diagnosed and whether there are special tendencies to misinterpret certain subtypes of unipolar depression, like agitated depression in the sense of bipolar disorder. Additionally, in some clinical inpatient samples the proportion of bipolar patients was lower than expected, although fully standardised prognostic approaches were used. Finally it is a question whether under clinical conditions one should speak about a false diagnosis, if it turns out that a patient develops signs of a bipolar depression several years.

CONTRA:

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Background: In the available large epidemiological studies, 10% to 20% of patients with Major Depressive Episodes received the diagnosis of bipolar disorders (BP). In recent years the proportion of bipolars has tended to increase, and the question is whether this is due to an over-diagnosis of BP.
Method: The diagnosis of bipolarity is usually based on DSM-IV criteria, requiring an episode of hypomania, defined by euphoria/irritability, the presence of 3 of 7 criterial symptoms, and a minimum duration of 4 days. New research questions these criteria and suggests the use of a diagnostic specifier for bipolarity in order to identify hidden bipolar subjects (D(m)), who have received a diagnosis of major depressive disorder (D). The data come from studies in psychiatric practice, a long-term follow-up of hospital admissions and prospective community studies (Zurich Study, EDPS Munich).
Results: Several studies demonstrate that MDD is heavily over-diagnosed and BP heavily under-diagnosed. There is evidence that between 40% and 60% of MDD subjects are hidden bipolars (D(m)). Prospective data show that D(m) predicts a diagnostic conversion to BP and that the risk of a diagnostic conversion from MDD to BP does not diminish over lifetime; the diagnosis MDD is always uncertain. D(m) also differs in many validators from MDD, which is clearly heterogeneous.
Conclusions: Rather than being over-diagnosed bipolar disorder is heavily under-diagnosed. The increase of BP is real and a consequence of better prospective data and the use of a better diagnostic specifier.

SO 07. Treatment of childhood mood disorders

SO 0701. Suicide and attempted suicide

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Although suicide attempt, and particularly completed suicide are relatively rare events in the community, they are quite common among psychiatric patients who contact different levels of health care system, particularly some weeks or months before the suicide event. More than one third of suicide victims have at least one prior suicide attempt, which significantly increases the risk of further suicide attempts and completed suicide. However, as about two-thirds of suicide victims die in their first attempt early prediction of suicidal behaviour and to intervene prior the first suicidal act is very important. Suicide is very complex, multifactorial behaviour with several biological as well as psychosocial components. It is also associated with a number of 1/Psychiatric (e.g., major mental disorders), 2/Psycho-social (e.g., adverse life situations), and 3/ Demographic (e.g., male gender) suicide risk factors. Since more than 90% of suicide victims and attempters have one or more current Axis I major mental disorder (major depressive episode: 56–87 =, substance-use disorders: 26–55%, schizophrenia: 6–13%), psychiatric risk factors are the clinically most useful predictors, especially if psycho-social and demographic risk factors are also pesent. As suicidal behaviour in major mood disorder patients is a state- and severity dependent phenomenon, to recognize and treat acute mood episodes effectively is a key element in suicide prevention. The most alarming suicide risk factors in patients with current depressive disorders include past suicide attempt, recent suicide attempt/suicidal ideation, severe symptomatology (hopelessness, psychotic features), agitation,

depressive mixed state, and insomnia, particularly in cases when adverse life situations are also present. Recent stidies consistently show that succesful acute and long-term treatment of major mental (particularly mood) disorders markedly reduces the risk of attempted and completed suicide even in this high-risk population.

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SO 0702. Depression in children and adolescents

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The prevalence of MDD is estimated to be approximately 2% in children and 4% to 8% in adolescents, with a male-to-female ratio of 1:1 during childhood and 1:2 during adolescence. The risk of depression increases by a factor of 2 to 4 after puberty, particularly in females, and the cumulative incidence by age 18 is approximately 20% in community samples. Approximately 5% to 10% of children and adolescents have subsyndromal symptoms of MDD. These youths have considerable psychosocial impairment, high family loading for depression, and an increased risk of suicide and developing MDD. Overall, the clinical picture of MDD in children and adolescents is similar to the clinical picture in adults, but there are some differences that can be attributed to the child's physical, emotional, cognitive, and social developmental stages.

Each phase of treatment should include psychoeducation, supportive management, and family and school involvement. For children and adolescents who do not respond to supportive psychotherapy or who have more complicated depressions, a psychological intervention or treatment with antidepressants is indicated. Moderate depression may respond to CBT or IPT alone. More severe depressive episodes will generally require treatment with antidepressants. A recent rigorous meta-analysis of 35 RCTs for depressed youths showed that although some studies demonstrated large effects, overall the effects of psychotherapy for the acute treatment of depressed youths are modest (Weisz et al., 2006). Depressed children and adolescents treated with SSRIs have a relatively good response rate (40%–70%), but the placebo response rate is also high (30%–60%), resulting in an overall NNT of 10 (95% confidence interval [CI] 7–14; Bridge et al., 2007). With the exception of the fluoxetine studies (e.g., Emslie et al., 1997), due to the high placebo responses, significant differences between SSRIs and placebo were only found in depressed adolescents (Bridge et al., 2007). Results of the NIMH multicenter study, the Treatment of Resistant Depression in Adolescents (TORDIA), showed that in depressed adolescents who have failed to respond to an adequate trial with a SSRI, a switch to another antidepressant plus CBT resulted in a better response than a switch to another antidepressant without additional psychotherapy (Brent et al., 2007).

SO 0703. Suicide and depression in childhood

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Suicide in children is rare, although rates increase significantly during adolescents. However, the true rates may be higher as many deaths are be classified under other verdicts, and countries vary in the degree of probability required to give a verdict of suicide. Recent data from the United States suggests that suicide rates in young people have started to increase again after a decade of decline. The risk factors for suicide in children and adolescents are less well understood than they are in adults, but developmental age, degree of agency, family dynamics, access to means and psychopathology all play a role. The ratio of acts of suicidal behaviour to completed suicide is also much greater in adolescents than in adults, suggesting a different aetiological pathway.

The role of antidepressants in the provocation of suicidal behaviour in young people has been the source of much debate in recent years. Pharmacoepidemiological studies of age related anti-depressant prescribing and suicide rates have given mixed results, and secondary analysis of trial data is limited by sample exclusion criteria. However, a recent investigation of data from coroners' records of the deaths of children aged 8–18 years showed that the vast majority had not sought any professional help for their difficulties, and those that did were primarily driven by social care or criminal justice agencies.

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SO 08. The gap between evidence base and experience base in the treatment of affective disorders

SO 0801. Minimal design requirement for efficacy and effectiveness

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To establish efficacy it is still necessary to adopt the well known randomised double-blind placebo-controlled design where both physicians and patients remain blind to treatment. This is to counter the well established biases of uncontrolled and open studies. The widely used last observation carried forward (LOCF) analysis which keeps the score at dropout in the final total allows an estimate of effectiveness under blinded conditions. It is time to apply the rigorous scientific standards of the double-blind RCT to future studies of effectiveness and discount the biased results of uncontrolled studies.

SO 0803. Practical recommendations for efficacy studies in depression

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In the last years it was expressed by several experts of clinical psychopharmacology that their might be need for 'effectiveness' ('real-world',' pragmatic') trials to overcome the limitations of the 'efficacy-studies' (phase III trials) and to prove, that the results of phase III studies are transferable to the 'real-world' conditions. Although it seems principally meaningful to take into account not only 'internal validity', but also 'external validity' as important criteria for the value clinical trials, possibly this issue was overestimated in the recent years. For example there are data upcoming from our own research group showing that apparently in terms of outcome the restrictions to wide rigid inclusion/exclusion criteria in phase III trials does not have that much impact on the efficacy outcome as it is currently believed. But this argument should not fully reject the position, that it might be meaningful to perform studies on patient samples, which are not recruited following the restrictive criteria of phase III trials. However, the much more important questions is, whether these 'pragmatic trials' on less restrictively selected groups of patients should use other outcome criteria, such as non-discontinuation, quality of life, self-rated psychopathological dimensions, etc. as primary outcome criteria than classical efficacy trials. The choice of these other outcome criteria which are apparently now are in fashion for 'effectiveness trials' involves a lot of principal methodological questions, which have to be seriously considered.

The principal question is, whether we should avoid the differentiation between efficacy trials and effectiveness trials and instead should rather use another terminology, e.g. 'efficacy trials of phase III' versus 'efficacy trials of phase IV'. This seems to be not only a semantic problem but would also have methodological consequences in the sense. that also 'efficacy trials of phase IV' should principally follow the same design and outcome criteria as phase III studies, but with the possibility to soften several of the rigid criteria concerning inclusion and exclusion criteria and trial design etc. For phase III trials to get a licence for a drug it is necessary for most indications to form placebo controlled studies or further more 3 arm trials. For 'efficacy studies of phase IV', apart from softening the inclusion and exclusion criteria, active comparator controlled trials (without placebo control) in an adequate statistical design (equivalence design) are satisfying. At least for the methodologically less sound studies, randomised trials should be performed. Important is also that the same statistical methodology and logic is used for these kinds of more practical trials.

SO 09. Recent Developments

SO 0901. SNRI drugs and their place in daily treatment of depression: An exploratory study evaluating milnacipran and venlafaxine in the treatment of adult patients with major depression.

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The antidepressant class of serotonin (5-HT) and noradrenaline (NA) reuptake inhibitors (SNRIs) is comprised of three compounds: venlafaxine (Effexor®), milnacipran (Ixel®), and duloxetine (Cymbalta®).
The present study explored the effects of milnacipran and venlafaxine 100–200 mg/day for the treatment of adults meeting DSM IV-TR criteria for Major depressive Disorder with MADRS total score ≥ 23 at selection and inclusion visits.

Patients were randomly assigned in a 24-week, multicentre, randomized, double-blind study of milnacipran ($n = 97$) or venlafaxine ($n = 98$). After a progressive titration over the first 4 weeks, patients were exposed to 150 or 200 mg/day of treatment during 20 weeks, based on tolerability. At any time during the study, doses could be lowered to 100 mg/day for tolerability concerns.

At baseline, the mean MADRS total score was 31.4 in Milnacipran group and 30.7 in Venlafaxine group,

the mean HAMD17 total score 25.3 and 25.2 respectively.

At 8 weeks, response rates (defined by a decrease of 50% or more of the total score of MADRS between inclusion and last visit) were 64.4% and 65.5% respectively (LOCF). MADRS total scores decrease were similar in both groups (-16.8 vs -16.8). Furthermore, remission rates (MADRS $\leq$ 10) were similar between milnacipran (42.2%) and venlafaxine (42.5%) groups (LOCF).

After 24 week-treatment period, response rates and decrease of the total MADRS score were comparable between milnacipran and venlafaxine groups. A higher MADRS remission rate was observed in the venlafaxine group (62.1% vs 52.2% LOCF) even though HAMD remission rate (defined by HAMD ≤ 7) was similar in the two groups (45.3% in venlafaxine group vs 42.7% in Milnacipran group).

Finally, in the present exploratory analysis, milnacipran exhibited a similar efficacy and tolerance profile compared with venlafaxine for the treatment of adults with major depression.

SO 0902 Imaging Genetics: Lessons for Depression

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Despite extensive research efforts over the last decade, are the genetic mechanisms of depression largely unknown, which have intensively been investigated because of its potential use for diagnostics and drug development. Recently several risk genes for depression have been identified by genome-wide association GWA studies and provide an excellent basis for molecular genetic studies on and animal and neuroimaging studies on a human level. However, only a few functional polymorphisms such as 5-HTTLPR and val66met BDNF have shown so far in vivo effects onto the human brain by the use of neuroimaging technology. Such Imaging Genetics studies, which are in line with many other levels of evidence, highlight the importance of the genetic make-up of the *serotonin transporter* as well as the *BDNF gene* in the context of depression. Furthermore, those studies reflect the genetic complexity of depression by showing epistatic effects as well as providing further evidence for the neuroplasticity hypothesis of depression. Studies utilizing such an approach will further facilitate the understanding of brain effects of depression risk-genes within the next decade of brain research.

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SO 0903 Seasonal rhythm in serotonin availability

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It is a common experience in temperate zones that one feels happier and more energetic on bright and sunny days, and many experience a decline in mood and energy during the dark winter season (Kasper et al 1989). Brain serotonin is involved in the regulation of many physiological functions that vary with season, such as mating, feeding, energy balance, and sleep. Seasonal variations in peripheral serotonergic markers have been demonstrated in several studies in clinical and nonclinical populations. A postmortem study shows seasonal differences in serotonin concentration in the human hypothalamus; another study suggests that sunlight alters serotonin turnover in the human brain. The molecular background of seasonal changes in serotonin function is entirely unknown. The serotonin transporter (5-HTT) is a key element in regulating intensity and spread of the serotonin signal. In a recent study in drug-free patients with seasonal affective disorder (SAD) we aimed at detecting state-related alterations in the efficiency of 5-HTT-mediated inward and outward transport in platelets (Willeit et al 2008). We showed that the 5-HTT is in a hyperfunctional state during winter depression and normalizes after light therapy and in natural summer remission. The aim of another study in healthy subjects was to detect seasonal variations in 5-HTT binding in the living human brain, and to detect correlations between 5-HTT binding and duration of daily sunshine using [^{11}C]DASB positron emission tomography (Praschak-Rieder et al 2008). Regional 5-HTT binding potential values (5-HTT BP), an index of 5-HTT density, were assessed throughout the year in a consecutive sample of 88 drug-naïve healthy volunteers, and were related to meteorological and astronomical data. 5-HTT BP were higher in autumn/winter as compared to spring/summer in all investigated brain regions. Moreover,

regional 5-HTT BP showed negative correlations with the average duration of daily sunshine, such that higher values occurred at times of lesser light. Since higher 5-HTT density is associated with lower synaptic serotonin levels, regulation of 5-HTT density and 5-HTT function by season is a thus far undescribed physiological mechanism that has the potential to explain seasonal changes in normal and pathologic behaviours.

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SO 10. Obsessive and impulsive disorders

SO 1001. Is there an impulsive-obsessive spectrum?

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Although obsessive-compulsive disorder (OCD) is classified as an anxiety disorder in the DSM-IV, recent considerations for a reclassification into an obsessive-compulsive spectrum disorders (OCSDs) cluster are gaining prominence. Similarities in symptomatology, course of illness, patient population, and neurocircuitry of OCD and OCSD are supported by comorbidity, family and neurological studies, which also offer a critical re-evaluation of the relationship between OCD and anxiety disorders. The review examines potential classifications of OCD among the wider spectrum of affective disorders and at the interface between affective disorders and addiction. In addition, it has been suggested that the categorical diagnostic approach would be enhanced by an additional dimensional approach, including parameters such as stability of mood and ability to sustain attention. With further studies, it is ultimately the goal to define OCD and related disorders based on endophenotypes. Despite efforts in this field, there are several fundamental unresolved issues, including the question of which disorders should be grouped together in this category and which characteristics to include as their shared common features, if and how can be defined a impulsive-compulsive spectrum of disorders or if is should— some of the addictive behaviour. A reclassification of OCD among the OCSDs would allow for better scrutiny of distinct obsessive-compulsive symptoms, as currently this disorder often goes undetected in patients who complain of a broad symptom of anxiety. Advantages and disadvantages of establishing OCSDs and its implications for diagnosis, treatment, and research are discussed.

SO 1003. Update on pharmacotherapy of resistant OCD.

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Background. Though first-line treatment with serotonin-reuptake inhibitors (SSRIs or clomipramine) or cognitive behaviour therapy (CBT) is effective for most individuals with obsessive-compulsive disorders (OCDs), a substantial proportion of cases do not respond well. The psychosocial morbidity associated with refractory OCD is high. Certain subtypes of OCD have been associated with a poorer treatment-response, including those with early onset illness, tics, hoarding behaviour and sleep-cycle disturbance.
Aims. This paper reviews new pharmacological strategies for SSRI-resistant OCD.
Results. Randomised trials support the effectiveness of adjunctive antipsychotics and raising SSRI dosage above formulary levels for patients failing SSRI. Roughly one third of such cases respond. In contrast, adding agents that increase serotonergic transmission eg. buspirone, lithium, pindolol, inositol, mirtazepine has not been found consistently effective in small trials. A minority of cases responded to switching from SSRI to venlafaxine or duloxetine. Adjunctive morphine was effective in a small placebo-controlled trial, whereas naltrexone was ineffective in two randomised trials and made some patients worse. Small uncontrolled trials of glutamate receptor modulators eg. riluzole, memantine, N-acetyl cysteine produced positive outcomes. However, d-cycloserine in combination with CBT showed no long-term benefit in three placebo-trials. Preliminary studies with topiramate and pregabalin produced promising results. Research has identified abnormally high levels of circulating anti-basal ganglia antibodies in some cases of childhood onset OCD. Trials of antimicrobial prophylaxis are under way.
Conclusions. New treatment – targets for resistant OCD are required and may direct novel pharmacological strategies for this chronic, debilitating illness.

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SO 11. Dopamine and depression

SO 1101. Bupropion-a dopamine/ noradrenaline antidepressant

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Serotonin and noradrenaline are considered to be the main neurotransmitter systems associated with depression. Their role has been extensively studied and the antidepressant efficacy of drugs involved in these pathways has been established. On the other hand, there is evidence that dopamine is also involved in the pathogenesis of depression, and that it is particularly associated with the disturbance of motivation, pleasure and, to a lesser extend of attention, interest and mood. Bupropion is a noradrenaline and dopamine re-uptake inhibitor (NDRI) and, currently, is the only antidepressant with a dopaminergic action. Its clinical efficacy in depression is equivalent to that of other antidepressants, such as SSRIs, SNRI,s NaSSAs, etc. Its side-effect profile is favourable, since bupropion has a low likelihood to induce somnolence, sexual dysfunction and weight gain. Common side-effects are generally mild and include insomnia, anxiety and an increase of the risk for seizures; seizures, however are particularly rare with the use of the extended-release preparation. For reasons associated with is pharmacological and side-effects profile, clinically, bupropion is more often used in depressive patients who present with hypersomnia, hyperphagia and fatigue. The efficacy of bupropion for the treatment of depression, as well as its safety and tolerablility, have been shown in double-blind randomised controlled trials and have been meta-analytically evaluated.

SO 1102. Second generation antipsychotics in treatment resistant depression

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Although antipsychotics are used mainly in schizophrenia and bipolar disorder it soon emerged that they are helpful also for treatment of depression. Typical neuroleptics have been used in clinical practice as an add-on therapy for unipolar depression. However, the emergence of extrapyramidal symptoms (EPS) and subsequently tardive dyskinesia (TD) during this treatment indicated them as a problematic choice. With the introduction of the so-called atypical antipsychotics (second generation antipsychotics, SGA) it soon was apparent that they are also helpful for treatment refractory depression. On a pharmacodynamic level, this clinical observation is backed up by the notion that SGA excert also an antidepressant mechanisms of action like the 5-HT_{2C} blocking properties and some of them additionally also serotonin or norepinephrine reuptake mechanisms. The few studies carried out in this field indicated that the addition of an SGA, like risperidone or olanzapine, results in a significantly higher proportion of treatment responders. A number of studies also documented the therapeutic properties of the combination therapy of antipsychotics and antidepressants in unipolar depression with psychotic features. Interestingly similar dosages as have been used for treatment of schizophrenia should be used fort his indication. Antidepressant properties of SGA are recently also substantiated by the findings that these compounds (like quetiapine and olanzapine) are of therapeutic benefit in bipolar depression. Altogether, atypical SGA can be considered as a valuable addition for treatment refractory and psychotic unipolar depression

SO 1103. Antipsychotics and Depression

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Patients with major depressive disorder (MDD) require effective treatment to reduce symptoms and improve functional disability. Regardless of the initial choice of antidepressant, about 30% to 50% of depressions will not respond sufficiently to treatment. Various alternative treatment strategies have been proposed for these non- or partially responsive depressions. However, achieving an adequate response in patients with MDD continues to be a challenge.

Possible treatment strategies for patients with MDD who are non-responsive to an adequate trial of a standard antidepressant include switching, combination with another antidepressant with a different mechanism of action, or augmentation with a non-antidepressant drug. Augmentation options include lithium, benzodiazepines, and, recently, attention has turned to the atypical antipsychotics, e.g. aripiprazole, olanzapine, risperidone and quetiapine. Several open studies and case series show favourable outcomes with combination and augmentation treatment with these antipsychotics. A 8-week double blind controlled trial showed significantly greater improvement with the combination of olanzapine and fluoxetin than with either

drug alone. Quetiapine has also been shown to have antidepressant effects in two double-blind, randomized, placebo-controlled trials (RCT); quetiapine was effective as a monotherapy in the acute treatment of patients with depression associated with bipolar I or II disorder. In addition, one RCT suggested that quetiapine was effective as an adjunct to antidepressants for the treatment of MDD. In summary, increasing evidence has emerged that some atypical antipsychotics may be of great value in the treatment of patients with depressive disorders.

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P 01. Relapse prevention and residual symptoms; further analyses of clinical studies with Escitalopram in MDD GAD SAD AND OCD

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Objective: Analyses of data from four published, similarly designed relapse prevention studies with escitalopram in order to compare patients with and without residual symptoms as regards relapse rates and global illness (CGI-S scores) during double-blind, 24-week continuation period.
Methods: The studies, one each in major depressive disorder, generalised anxiety disorder, social anxiety disorder, and obsessive-compulsive disorder, were analysed using ANCOVA (LOCF) or MMRM statistical models.
Results: All studies showed a statistically significant standardised effect size of about 0.7 for escitalopram versus placebo with number-needed-to-treat (NNT) values of about 4. Patients with (score above 0) and without (score = 0) residual symptoms at the start of continuation treatment were defined as to how patients scored on two core items of the MADRS: depressed mood (observed) and inner or psychic tension. At randomisation patients with a residual symptom were globally more ill than patients without such a symptom. Patients who did not continue active treatment worsened, even if they were initially free of a residual symptom. In contrast, patients who continued on escitalopram remained stable or further improved, regardless of residual symptoms or diagnosis. No clear picture emerged regarding whether patients with residual symptoms had a higher relapse rate. The greatest difference in all of the studies was between escitalopram-treated patients (relapse rates of about 20%) and placebo-treated patients (relapse rates of about 50%).
Conclusion: It was not possible from the present analyses to identify patients in particular need of continuation treatment or patients that could safely manage without continuation treatment of these disorders on the basis of residual symptoms.

P 02. Autonomic regulation and coping style in panic disorder

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Background: Panic Disorder has been widely hypothesized to be associated with dysfunction of the autonomic nervous system. A number of studies have reported a condition of increased sympathetic activity on the exposure of provocative stimuli. The aim of the present study was to compare physiological measures of autonomic activation between drug-free panic disordered patients with agoraphobia and controls in terms of tonic level and reactivity to mental stress.
Methods: 15 drug free agoraphobic patients and 25 controls underwent mental stress test (backwards digit recall).

The patients were diagnosed by using the Structural Clinical Interview for DSM-IV. Psychological assessments were done by the Mini International Neuropsychiatric Interview (MINI), the Symptoms Distress Scale (SDS) the Self-Rating Anxiety Scale (SAS), the State-Trait Anxiety Inventory (STAI), the COPE Inventory and the Personality Factor Questionnaire (16PF). Galvanic skin response (GSR), skin temperature, photoplethysmograph amplitude (PLA), pneumogram amplitude, ECG and changes in the mean duration of R-R intervals were measured both at rest and during the mental stress.
Results: Agoraphobic patients showed mental (COPE, item 2) and behavioural disengagement (COPE, item 9) styles of copying and had higher anxiety levels as measured by STAI Y-2 and SAS than controls. The sympathetic activity at rest was significantly higher in agoraphobic patients than in controls. The sympathetic reactivity to stress was very low in PD patients. Correlations between low reactivity to stress and mental and behavioural disengagement were significant.
Conclusion: These findings are consistent with recent evidence for low sympathetic responses to stress in agoraphobic patients (1) Our results suggest that

disengagement coping responses might be directly related to low reactivity to stress.

Reference

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P 03. Association between generalized anxiety disorder and somatic symptoms: a Spanish descriptive study

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Objective: To describe the co-morbidity (especially focus in somatic symptoms), health care use and economical impact in Generalized Anxiety Disorder (GAD) patients, among Primary Care Setting (PCS).
Method: A retrospective multicenter population-based study; data were collect (during year 2006) in six Primary Care clinics, of Badalona Serveis Assistencials S.A. management. All medical records of outpatients over 20 years were included. Main measures: general (age, gender, etc.), co-morbidities, Charlson-index (patient severity) and cost model. The general morbidity burden was measured using Adjusted-Clinical Groups (http://www.acg.jhph.edu). An analysis of logistical regression and the covariance (ANCOVA) was affected for the correction of the models (procedure: Bonferroni), according to the recommendations of Thompson-Barber. Program SPSSWIN; $p < 0.05$.
Results: Observed incidence of GAD in female study population: of the 63,525 patients, 4.7% (95% CI: 4.5% to 4.9%) had GAD; the average episode/year was 6.1 and attendance/year was 10.1 medical assistances. GAD was associated with women (odds ratio [OR] = 1.7; CI 1.5–1.9), dyslipidemia (OR = 1.1; CI 1.0–1.3), smoking (OR = 1.3; CI 1.2–1.4) and somatic symptoms like irritable bowel [3.0%; OR = 1.9 (CI 1.5–2.4)], migraine [6.7%; OR = 1.5 (CI 1.2–1.7)], gastritis [19.1%; OR = 1.4 (CI 1.3–1.5)] or fibromyalgia (3.0%, CI 2.4–3.6). The average of direct cost /year adjusted by age, gender and morbidity burden was 640€ (CI 613.78–666.18€). Patients with GAD took many medications out off regular treatment: muscles-relaxants (10%) or analgesics (39.9%).
Conclusions: Patients with GAD have greater comorbidity and higher direct costs in PCS. Plus, these patients consult about many somatic symptoms and take different somatic's medications.

P 04. Atypical antipsychotic therapy in mood disorders: a cross-sectional assessment of a primary health care database in Spain.

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Objective: To evaluate the use of atypical antipsychotic therapy in mood disorders (depressive or bipolar) outpatients treated in a six primary health centres.
Methods: A cross-sectional observational study assessing an administrative claim database of adult (>20 years) outpatients from six primary health centres during year 2006, was carried-out. Male and female patients on atypical antipsychotic therapy for more than 3 month and with mood disorder were included. Patients with depression and bipolar disorder were compared. Main measures: general (age, gender, etc.), cardiovascular co-morbidities, Charlson-index (patient severity) and cost model. The general morbidity charge was measured using Adjusted-Clinical Groups (http://www.acg.jhph.edu). An analysis of logistical regression and the covariance (ANCOVA) was affected for the correction of the models (procedure: Bonferroni), according to the recommendations of Thompson-Barber. Program SPSSWIN; $p < 0.05$.
Results: A total of 158 patients (48.7% women; 52.6 ± 18.9 years old, mean + SD) treated with atypical antipsychotics (57.6% olanzapine; 27.8% risperidone; 9.5% quetiapine; 3.2% zipresidone and 1.9% amisulpride) during 24.6 ± 19.4 months were identified. Depressive patients were older (55.1 ± 17.7 versus 48.7 ± 20.2 years old; $p = 0.037$), with lower duration of treatment (20.7 ± 16.5 moths versus 30.8 ± 21.9 moths; $p = 0.001$) and higher co-morbidities: diabetes mellitus (13.5% versus 4.8%; $p = 0.043$), dyslipidemia (38.5% versus 22.6%; $p = 0.034$) but not differences in Charlson index or health resources utilization (visits, diagnostic / therapeutic measures and referrals).

The mean adjusted monetary costs per patient per year were 1,847.60€ versus 1,930.16€; so adjusted cost were similar.
Conclusions: Compared with depressive outpatient population, bipolars were younger but longer disease duration; plus, depressive outpatient population show higher cardiovascular co-morbitities.

P 05. Minor Mixed Depression in Forensic Psychiatry

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Working in General Mental Health Services I was struck by the concept of Minor Mixed Depression, formerly called mixed affective state (1). In an outpatient clinic (2006) about 70% of the patients, referred because of depressive states by the general physician, appeared to have mixed states during the use, often for years, of antidepressants. Changing the antidepressant for a mood stabilizer brought substantial relief in the majority of these cases. One might suppose, by the way, that only those patients had been referred who had the most intense complaints of irritable mood, mood swings, early insomnia and racing thougts and that other patients had not been referred, yet, developing so far undetected mixed states.

In an Outpatient Forensic setting (2008) this clinical picture seemed to repeat itself, but now in patients who often were not using antidepressants. They were referred because of violent crimes and referred with alleged borderline personality disorders in combination with antisocial personality disorder and/or Intermittent Explosive Disorder. Again about 70% of these patients could be treated effectively with a mood stabiliser.

Mutatis mutandis the same principle holds for clinical Court-ordered patients.

Reference

(1) A. Koukopoulos et al. in: Bipolar Disorders. Mixed states, rapid cycling and atypical forms. A. Marneros and F.K. Goodwin, ed. Cambridge university press (2005)

P 06. Psychiatric comorbidity, hospitalization and medication use in bipolar children and adolescents with and without rapid cycling

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Background: Despite the growing evidence that the consequences of BD arising during childhood can be devastating, with high rates of mixed and rapid cycling presentations, substance abuse, suicidal risk, legal problems and academic impairment, rapid-cycling in children and adolescents has been insufficiently studied.
Aims: To describe demographic characteristics, medication use and hospitalization in bipolar children and adolescents with and without rapid cycling.
Methods: Analysis was conducted on a cohort of 8,129 children and adolescents patients (¡Ü18 y.o.) with Bipolar disorder (BD), from the Integrated Healthcare Information Services (IHCIS) Identified from June 30, 2000 to July 1, 2003. Demographics variables, type of hospitalization and psychotropic medication used in the year of follow-up were compared between rapid and non rapid cycling bipolar children and adolescents.
Results: Included were 58 patients with rapid cycles (defined as: more than 4 episodes per year) and 8,071 without rapid cycles. Children and adolescents with rapid cycles versus those without rapid cycles were differentiated in their hospitalization and treatment as follows: higher rate of hospital admission for depression (12% vs. 2%, $p < 0.0001$); for other psychiatric conditions (48% vs. 11%, $p < 0.0001$) and for medical conditions (22% vs. 4%, $p < 0.0001$). Patients with rapid cycling were more likely than those without rapid cycling to be given mood stabilizers (91% vs. 60%, $p < 0.0001$), antidepressants (79% vs. 59%, $p = 0.0003$), and antipsychotics (90% vs. 46%, $p < 0.0001$). Although the use of stimulants did not differ between the two groups (24% rapid cycles vs. 23% without rapid cycles, $p = 0.96$), an overall comorbidiy rate of 80% for ADHD was also identified in children and adolescents with rapid cycles.
Conclusions: Our findings support that children and adolescents with rapid cycles require more hospitalizations and pharmacological treatment than those with non-rapid cycles.

In the diagnosis and treatment of children and adolescents with BD will have to take into account the high comorbidity of ADHD mainly in children and adolescents with rapid cycles.

P 07. Treatment delay and outcome in obsessive-compulsive disorder: a naturalistic study

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Background/aims: The Duration of Untreated Illness (DUI), defined as the time elapsing between the onset of a disorder and the beginning of an adequate pharmacological treatment, has been increasingly investigated as a predictor of outcome and course across different psychiatric disorders. This naturalistic study evaluated the influence of clinical and demographic variables, with particular emphasis on the DUI, on the clinical course and outcome of obsessive-compulsive disorder (OCD).
Methods: A sample of 63 outpatients with OCD, diagnosed by means of SCID-I, were enrolled and their main demographic and clinical features

collected. Patients received, according to their clinical conditions and psychiatrists' clinical impression, an open pharmacological treatment of 12 weeks and were evaluated by the administration of CGIs and Y-BOCS at baseline and endpoint. Clinical variables were analyzed dividing the sample into two groups according to DUI (DUI <24 months or >24 months) using chi-square tests for dichotomous variables and independent samples Student's t-tests for continuous ones. Treatment response was evaluated through repeated measure ANOVAs on YBOCS and CGIs scores.
Results: The two groups were not different regarding age ($t=1.93$, $p=0.057$), age at onset ($t=1.71$, $p=0.092$), gender ($\chi^2=0.016$, $p=1.000$), comorbidity with psychiatric disorders before ($\chi^2=5.619$, $p=0.803$) and after ($\chi^2=8.170$, p:0.579) the onset of OCD, comorbidity with substance abuse ($\chi^2=.162$, $p=1.000$), psychiatric family history ($\chi^2=9.604$, $p=0.286$). However, patients with a longer DUI had a longer duration of illness ($t=-5.522$, $p<0.0001$) and more often received a polytherapy as first treated ($\chi^2=13.322$, p:0.008). Of clinical interests, a greater improvement on CGIs (time*effect: $F=84.119$, $p=0.000$; time*GROUP: $F=7.221$, $p=.009$) and YBOCS (time*effect $F=25.591$, $p=.000$; time*-GROUP: $F=4.530$, $p=0.037$) scores was showed in the group with shorter DUI after treatment.
Conclusions: Results from the present naturalistic study suggest a negative role of a longer DUI on the clinical course of OCD and remark the importance of an early intervention in OCD patients. Further prospective research with larger samples is warranted to confirm these results.

P 08. Satisfaction with Medication and Response to Treatment with Escitalopram Compared to Placebo and SNRIs

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Aims: To test whether satisfaction with taking medication, assessed at baseline using item 15 of the Q-LES-Q (satisfaction with medication) predicts outcome or time to withdrawal.
Methods: Four placebo-controlled studies of MDD patients treated with escitalopram assessed the Q-LES-Q (650 patients on escitalopram and 534 on placebo), together with two comparisons of escitalopram versus venlafaxine, or duloxetine (235 patients on escitalopram and 233 on an SNRI). The Q-LES-Q was assessed at baseline and week-8.
Results: At baseline, mean age was 40.1 ± 10.1 years, mean MADRS total score was 30.0 ± 4.5, and the mean Q-LES-Q item 15 score was 2.9 ± 0.9. At week 8, the mean MADRS score of placebo-treated patients with low satisfaction with medication at baseline decreased 9.9 points, versus 11.4 points for patients with moderate satisfaction and 13.6 points for patients with high satisfaction (MMRM). This differentiating effect of baseline satisfaction with medication on the continuous endpoint variable (MADRS) was not found in the active treatment group. In escitalopram-treated patients in the placebo-controlled studies, the improvement for patients with a low, moderate, or high satisfaction at baseline was 14.8, 14.9, and 15.2, respectively.

Remission rates (LOCF) were higher in patients with high baseline satisfaction with medication than with low baseline satisfaction [placebo remission rates of 42% versus 19% ($p<0.01$), 48% versus 37% for escitalopram; SNRI remission rates of 51% versus 43%, and 66% versus 40% ($p<0.01$) for escitalopram in the head-to-head studies]. The change in satisfaction with medication from baseline to endpoint was significantly correlated with symptomatic improvement.

Baseline satisfaction with medication was not significantly correlated with time to withdrawal (all reasons) for escitalopram versus placebo. There was a significant difference ($p<0.001$) in the time to withdrawal and withdrawal due to adverse events between escitalopram and SNRIs ($p<0.001$), in favour of escitalopram.
Conclusion: A higher baseline Q-LES-Q item 15 score appears to be correlated with a higher patient response to placebo, but not to influence overall or AE withdrawal rates, or response to active treatment.

P 09. Adolescents-psychiatric comorbidity among substance abusing

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Aim: We are looking to compare all behaviour problems scores for included adolescents admitted for detoxification treatment for alcohol and narcotic abuse and compare them with general population, in accordance with the Youth Self Report/YSR/. Also, to present their psychosocial functioning and their psychiatric comorbidity.
Method: 31 adolescents, aged 15–18 years, competed the YSR after 7-1o -day stay at Department of Psychiatry. Their psychiatric comorbidity and psychosocial functioning were diagnosed according DSM-IV.
Results: The BPS for the 7 treated young women was significantly higher than for general population, and higher than 24 treated young men, with 2 standard

deviations above tne norm for the population. Psychiatric comorbidity was presented in 8o,64% adolescents. The findings support the discriminative validity of the YRS as part of structured global assessment of adolescence abusing substances, in particular to identify the frequently present psychiatric comorbidity in substance abuse.
Conclusion: We must able to provide both -prevention and intervention for adolescents problems, and also promote discussion of the issues before a child reaches adolescence and the age of risk.
Key words: adolescent, psychiatric comorbidity, substance abusing, prevention

P 10. Double-blind study of the efficacy and tolerability of extended release Quetiapine Fumarate (Quetiapine XR) monotherapy in patients with major depressive disorder (MDD)

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Aim: Assess efficacy and tolerability of quetiapine XR once-daily monotherapy in patients with MDD.
Methods: 8-week, active treatment, randomised double-blind, placebo- and active-controlled study, with a 2-week post-treatment phase (D1448C0004; Amber). Patients were randomised to quetiapine XR 150mg/day, escitalopram 10mg/day or placebo. After 2 weeks patients were assessed for response ($>/=$ 20% improvement in MADRS). Patients with adequate response remained on their initial randomised dose, patients with inadequate response had their dose doubled. Investigators were blinded to criterion for response and presence/absence of dose increase. Primary endpoint: change from randomisation to Week 8 in MADRS total score. Secondary endpoints: change from randomisation to: each assessment in MADRS total score; MADRS response ($>/=$50% reduction in total score); and Week 8 in HAM-D, CGI-S, CGI-I and PSQI global scores. AEs were recorded throughout.
Results: 471 patients were randomised: 157 quetiapine XR, 157 escitalopram, 157 placebo. Baseline MADRS scores: 32.2, 32.0 and 31.6, respectively. At Week 2, 13.0%, 23.7% and 26.1% of patients receiving quetiapine XR, escitalopram and placebo, respectively, required dose increase.

Quetiapine XR (-17.21) and escitalopram (-16.73) showed greater improvements in change from randomisation to Week 8 in MADRS total score, however differences were not significant versus placebo (-15.61). Week 8 response rates were not significantly different for quetiapine XR (60.4%) and escitalopram (59.9%) versus placebo (51.0%). Significant improvements in PSQI global score were observed at Week 8 for quetiapine XR (-4.96) but not escitalopram (-3.32) versus placebo (-3.37). No other secondary endpoints demonstrated significant improvement for quetiapine XR or escitalopram versus placebo.

The most common AEs ($>15\%$) were dry mouth, somnolence, dizziness, headache and nausea in the quetiapine XR group, and headache, nausea and dizziness in the escitalopram group.
Conclusions: In this adequately controlled study, neither quetiapine XR 150/300mg/day or escitalopram 10/20mg/day showed significant separation from placebo in the treatment of MDD. Possible causes include a large placebo response and a high proportion of patients with first episode of MDD (23.7%).

P 11. Double-blind, randomised study of extended release Quetiapine Fumarate (Quetiapine XR) monotherapy in elderly patients with generalized anxiety disorder (GAD)

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Aims: To assess efficacy and tolerability of quetiapine XR in elderly patients with GAD.
Methods: 11-week (9-week randomised, 2-week, post-treatment phase), double-blind, placebo-controlled study (D1448C00015; Chromium). Patients (DSM-IV diagnosis of GAD; $>/=$66 years of age) were randomised to quetiapine XR (flexible dosing 50–300mg/day) or placebo. Primary endpoint: HAM-A total score change from randomisation to Week 9. Secondary endpoints: HAM-A total score change at Week 1; HAM-A response ($>/=$50% reduction in total score) and remission (total score $</=7$) at Week 9; change from randomisation to Week 9 in HAM-A psychic and somatic cluster, PSQI global, VAS pain, Q-LES-Q% maximum total scores and proportion of patients with CGI-I total score $</=2$ at Week 9. AEs were recorded throughout the study.
Results: 450 patients were randomised (mean age 70.4 years): 223 quetiapine XR (mean dose 167.6mg/day) and 227 placebo. At Week 9, quetiapine XR (-14.97, $p<0.001$) significantly reduced mean HAM-A total score from randomisation versus placebo (-7.21). At Week 1, significant reductions in HAM-A total scores were seen with quetiapine XR (-4.18; $p<0.001$) versus placebo (-2.35).

At Week 9, HAM-A response and remission rates were 68.5% and 40.1% with quetiapine XR (both $p<0.001$) versus placebo (23.9% and 12.8%).

HAM-A psychic (8.88; $p < 0.001$) and somatic (-6.05; $p < 0.001$) cluster scores were significantly greater with quetiapine XR than placebo (-3.81 and -3.37). 73.4% ($p < 0.001$) patients had a CGI-I score $</=2$ with quetiapine XR versus placebo (24.3%) and quetiapine XR significantly improved Q-LES-Q SF percent maximum total score (14.82 vs 4.94; $p < 0.001$), PSQI global score (-6.25 vs -2.09; $p < 0.001$) and VAS pain score (-17.95 vs -6.18; $p < 0.001$) versus placebo.

The most common AEs (>10% patients in either group) with quetiapine XR and placebo were somnolence (26.0, 8.4%), dry mouth (16.6, 7.0%), dizziness (13.5, 7.0%) and headache (11.7, 12.8%).
Conclusion: In elderly patients with GAD, quetiapine XR monotherapy (50–300mg/day flexibly dosed) is effective and generally well tolerated, with symptom improvement observed as early as Week 1.

P 12. Speed of processing in patients who suffer from depression and anxiety.

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Background: Patients suffering from depression and anxiety usually are concerned about their cognitive abilities. One of the most frequent complaints is their slowing down situation. The aim of this study is to analyze, in naïve patients suffering from depression and anxiety, abnormalities in their processing speed and its relationship with the anxiodepressive symptomatology and cognitive complaints. method: we examined a group of 20 naïve patients with a DSM-IV-R diagnosis of adaptive disorder, MDD, panic disorder, GAD using the following tools: Madrs and Hars scales were used to assess psychiatric symptomatology. We used MTS from the cantab to asses processing speed. A selection of items from cognitive component of bads was used to measure the subjective assessment of cognitive impairment.
Results: The data reveal that 57% of patients has noticed changes to cognitive level of prefrontal type since the onset of affective symptoms. Up to 25% present alteration on MTS performance and up to 25% present alteration on MTS latency in the tests of major cognitive demand compared with those of minor demands. No correlation was found between severity of depression or anxiety and MTS performance or between the number of repeated episodes and MTS performance. Subjective assessment of the own cognitive performance correlates with MTS mean latency 8 choices ($r = 0{,}509$; $p < 0.05$) and MTS mean latency 2–8 ($r = 0{,}494$; $p < 0.05$).
Conclusions: More than 50% of the patients refer to have cognitive complaints related to prefrontal functions. Up to 25% of the patients present problems in the execution and in tasks with certain cognitive demand in the speed of processing. MTS performance and latency don't correlate with the severity of anxious and depressive symptomatology but they do correlate with the severity of the cognitive complaints. These findings suggest that complaints about executive capacity are related to actual impairment in speed of processing. A good chance for assessment is when a patient that performs an intellectual job is discharged.

P 13. SNRI drugs and their place treatment of depression: an exploratory study evaluating Milnacipran and Venlafaxine in the treatment of adult patients with MDD

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The antidepressant class of serotonin (5-HT) and noradrenaline (NA) reuptake inhibitors (SNRIs) is comprised of three compounds: venlafaxine (Effexor®), milnacipran (Ixel®), and duloxetine (Cymbalta®).

The present study explored the effects of milnacipran and venlafaxine 100–200 mg/day for the treatment of adults meeting DSM IV-TR criteria for Major depressive Disorder with MADRS total score higher than 23 at selection and inclusion visits.

Patients were randomly assigned in a 24-week, multicentre, randomized, double-blind study of milnacipran ($n = 97$) or venlafaxine ($n = 98$). After a progressive titration over the first 4 weeks, patients were exposed to 150 or 200 mg/day of treatment during 20 weeks, based on tolerability. At any time during the study, doses could be lowered to 100 mg/day for tolerability concerns.

At baseline, the mean MADRS total score was 31.4 in Milnacipran group and 30.7 in Venlafaxine group, the mean HAMD17 total score 25.3 and 25.2 respectively.At 8 weeks, response rates (defined by a decrease of 50% or more of the total score of MADRS between inclusion and last visit) were 64.4% and 65.5% respectively (LOCF). MADRS total scores decrease were similar in both groups (-16.8 vs -16.8). Furthermore, remission rates (MADRS lower than 10) were similar between milnacipran (42.2%) and venlafaxine (42.5%) groups (LOCF).

After 24 week-treatment period, response rates and decrease of the total MADRS score were comparable between milnacipran and venlafaxine

groups. A higher MADRS remission rate was observed in the venlafaxine group (62.1% vs 52.2% LOCF) even though HAMD remission rate (defined by HAMD lower than 7) was similar in the two groups (45.3% in venlafaxine group vs 42.7% in Milnacipran group).

Finally, in the present exploratory analysis, milnacipran exhibited a similar efficacy and tolerance profile compared with venlafaxine for the treatment of adults with major depression.

P 14. Leptin modukates orexin-mediated functions at the behavioural and cellular level in mice.

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The two orexin hypothalamic neuropeptides play an important role in arousal and narcolepsy in addition to energy homeostasis. Leptin is putatively involved in the regulation of orexin neuronal activity. Using neurochemical, behavioral and histological methods the in vivo and in vitro interactions between the leptin and orexin systems were studied. Results indicate that there is increased locomotor activity during the active period of the light-dark cycle in female as compared to male mice. Locomotion was decreased following subchronic exposure to a physiological dose of leptin (100 ìg/kg/day, sc, minipump) in female mice. In addition, stereological brain analysis revealed that leptin reduced the number of orexin immunoreactive neurons in the lateral hypothalamus of female but not male mice. Leptin also reduced the activation of these neurons in both genders as measured by c-fos activation. Further mechanistic studies in a mouse hypothalamic cell line revealed that AMPK, a kinase involved in metabolic regulation, could be the transducer of this leptin control of orexin neurons. In summary, these data support the notion that the leptin and orexin systems interact centrally, and indicate how leptin could modulate the orexin-mediated regulation of vigilance states.

P 15. Subtypes of depression in Alzheimer's disease and other dementias.

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Objective: To explore the prevalence and subtypes of depression in patients with Alzheimer's disease (AD), vascular dementia (VaD), or undifferentiated dementia (UD).

Methods: Analysis of subtypes of depression was conducted on 6,440 patients 60 years or older with dementia (2,947 AD, 725 VaD and 2768 with UD) from the Integrated Healthcare Information Services (IHCIS), a National Managed Care Benchmark Database database, identified from January 1, 2001 to December 31, 2001. Sub-types of depression, AD, VaD and UD were diagnosed using ICD-9 criteria.

Results: The prevalence rate of depressive disorders was 27.41% in all patients with dementia independent of the dementia subgroup. The prevalence of depressive disorders was much higher in the VaD group (44.14%) and UD group (32.48%) compared to AD group (18.53%). Compare with AD and UD, VaD patients had significantly higher prevalence in artherosclerotic dementia, depressive disorder NOS, major depressive disorder single and recurrent episodes and neurotic depression ($p < 0.01$). Adjustment disorder, presenil and dementia senile with depression were significantly more common in UD patients, whereas depressive psychosis was similar in all dementias types. AD patients had the lowest prevalence in all subtypes of depression.

Conclusions: This study supports that depression is more prevalent in VaD compared to UD and AD and also provide indicators to the clinician for further evaluation of depression in different dementia subtypes

P 16. Functional and structural alterations of Midcingulate Cortex reflect depression vulnerability.

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Introduction: Depression is among the leading causes of disease burden, diagnosed by emotional and cognitive psychopathological symptoms. Today it is unclear whether resulting differences between acutely depressed patients and normal controls are reflecting the current psychopathological state or neurobiological alterations making patients vulnerable to depression. Since studies on currently remitted subjects suffering from Major Depressive Disorder are sparse we initiated an imaging study aiming for the assessment of functional and structural correlates of vulnerability on a local and

systems level in a large cohort of healthy and remitted subjects. Our analyses focused on cortical and subcortical regions, which have been investigated in the context of depression in animal and human studies. Of particular interest is the cingulate cortex due to its functionally specialized subdivisions such as the midcingulate cortex (MCC).
Methods: Functional and structural MRI scans were obtained from a preliminary data set of 25 healthy controls without any life-time history of psychiatric illness and 25 age and gender-matched remitted depressed patients. During fMRI assessment subjects underwent a paradigm in block design fashion comprising an emotional and a neutral control matching task. Preprocessing of fMRI data was done within AFNI as well as an a priori-based region of interest analysis. Structural images were analyzed utilizing voxel-based morphometry (VBM) as implemented in SPM5.
Results: Preliminary VBM results indicate gray matter volume reduction of the left MCC in remitted patients compared to controls. Our preliminary fMRI results indicate decreased bilateral activity in the MCC and insula in remitted patients compared to controls. All results are corrected for multiple comparisons.
Discussion: Preliminary data suggest that alterations of MCC function and structure reflect vulnerability towards depression. Additionally, brain activity of the insula was found to differentiate patients and controls. Our data suggest a dysregulation of cognitive-emotional network interactions.

P 18. Emotion-related bottom-up regulation of frontal cortical memory networks

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Introduction: Emotion and memory networks are closely linked but mechanisms by which emotional brain circuits impact cognitive circuits are relatively unexplored. While a pure top-down hierarchical model has been in favor for many years, recent data indicate also the importance of bottom-up regulation. In order to untangle effects of emotion networks on cognitive networks, we applied a mixed fMRI paradigm engaging working memory as well as emotion networks to a large sample of healthy controls.
Methods: Eighty-two normal volunteers recruited at NIMH, NIH underwent a two-back working memory task as well as a low-level control task (labeling). Stimuli were taken from the International Affective Picture System (IAPS) containing stimuli with positive, neutral, and negative valence. Stimuli were arranged in within a mixed design in order to optimize for estimation and detection efficacy. Statistics were done within a mixed effects model (4-way ANOVA, with task, valence, and gender as fixed factors, and subjects as random factor). All results are corrected for multiple comparisons.
Results: As hypothesized, emotional stimuli, which activated limbic regions such as bilateral amygdalae (less for pleasant than unpleasant stimuli) and hippocampus, showed a significantly higher activation during the 2-back task in bilateral dorsolateral prefrontal regions adjacent to BA 46/9, indicating a possible bottom-up regulation of neural activity fundamental to working memory. Also in accordance with our hypothesis we found that during the resting condition the BOLD signal within several frontal regions such as DLPFC, medial PFC and subgenual cingulate was negatively correlated with deeper limbic structures such as hippocampus, parahippocampal gyrus and amygdalae indicating a top-down regulation.
Discussion: Our results support the conclusion that the generally favored top-down regulation principle can be overrun in the presence of emotion-laden stimuli mediated by limbic structures such as hippocampus and amygdala. These data provide insights into the mechanisms of emotional modulation of cognitive processes.

P 19. "Subjective Mania Scale" (SMS). What are the drug effects which bipolar patients really want?

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Objective: The purpose of the present study was to develop a questionnaire based on the subjective experiences of patients with previous manic episodes. This questionnaire should be feasible for the clinical investigation of antipsychotics among manic patients.
Methods: In-depth interviews and focus groups were used to assess the subjective experiences of patients during earlier manic episodes. Content analyses of

the transcriptions were used to develop a first draft of the questionnaire. 50 patients from university and non university units were interviewed to investigate the content validity. Another sample of 50 patients was used for investigating sensitivity to change by comparing the patients' responses after a period of 5 weeks. For analysing if the SMS captures symptoms consistent with usual research instruments, the SMS sum-scores were correlated with the sum-scores of Young Mania Rating Scale and Positive and Negative Syndrome Scale.
Results: Content validity: All SMS items were considered as "quite important" or "very important" by at least 55% of the interviewees. Many SMS items were considered as "quite important" or "very important" by more than 90% of the sample. This indicates that the content validity seems to be sufficient.

Concurrent validity: Significant positive associations of the SMS were found at all investigations with the YMRS and the PANSS positive subscale.

Sensitivity to change: All differences between timepoints were significant for the SMS as well as the YMRS. Differences between timepoints of SMS were significantly correlated with the differences between timepoints of YMRS.

Reliability: Exploratory Factor Analysis yielded a one-factor solution. Cronbach's alpha was sufficiently high at all timepoints.
Conclusion: Overall, this new instrument seems to be feasible, reliable and valid. The SMS seems to be a useful measure for clinical trials among patients with mania, considering the subjective view and wishes of the patients themselves.

P 20. Subcortical alterations of brain morphology in healthy and remitted depressed subjects

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Introduction: Available evidence suggests the existence of volumetric abnormalities in subcortical structures evolving during brain development that reflect vulnerability markers of Major Depressive Disorder (MDD). Anatomical magnetic resonance imaging (MRI) is a promising in vivo research method to study the morphology of brain systems related to depression. In the last years a number of neuroimaging studies on depression has focused on the detection of morphometric changes in subcortical structures comparing acute depressed patients and healthy controls. Meta-Analyses of these studies suggest reduced bilateral hippocampal volumes in patients with unipolar depression, whereas studies on amygdala and basal ganglia volumes have been contradictory. Very few studies focused on volumetric alterations comparing acute depressed and remitted depressed patients. The results indicate smaller hippocampal volumes bilaterally in acute depressed patients compared to remitted patients.

Currently there is no available evidence on the question whether there exist volumetric alterations in subcortical structures between remitted depressed patients and healthy controls.
Method: Structural MRI scans were obtained from a preliminary data set of healthy controls without any life-time history of psychiatric illness and remitted depressed patients. MRI data were processed via Freesurfer including a set of automated tools where subcortical segmentation and cortical parcellation are based on both a subject independent probabilistic atlas and subject specific measured values. Volumetric differences were assessed with an ANCOVA design using age, gender and total grey matter as covariate of no interest.
Results: Preliminary data indicate significant increased bilateral hippocampus, amygdala and putamen in remitted depressed patients compared to controls.
Discussion: Our preliminary results support the idea that remitted depression is associated with volumetric alterations in regions involved in emotional and cognitive processing.

P 21. Effective connectivity as a depression vulnerability marker

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Introduction: Converging evidence suggests that dysfunctions within networks of certain brain regions may be major causes of symptoms encountered in patients suffering from psychiatric diseases such as depression. It has also been shown that genetic

factors can influence functional and structural coupling between amygdala and the cingulate cortex, two regions critically involved in emotional processing. However, functional and structural connectivity are correlative measures and hence do not allow for inferences about causal interactions between different regions of the brain. Causal interactions can only be inferred by modeling effective connectivity where connectivities between brain regions are estimated using statistical models based on anatomically motivated assumptions related to the basic structure of the network. Effective connectivity thus requires a significant amount of a-priori knowledge.
Methods: In functional magnetic resonance imaging (fMRI) neural activity is measured indirectly via changes in blood oxygenation after neural activity (blood oxygen level dependent or BOLD signal). However, dynamic causal modeling (DCM) is currently the only effective connectivity method that models activity at the neuronal level separately from activation at the BOLD level allowing for interactions between brain regions at the neuronal level only. In addition to intrinsic regional connectivity DCM also enables stimulus-induced changes in connectivity allowing for important insights on the functional integration between different brain regions.
Outlook: In order to produce valid models of brain connectivity we will base our network definition and connectivity hypotheses partly on published data but also on our own results based on functional as well as structural connectivity analysis. First we will assess differences in functional covariance between remitted depressed subjects vs. healthy controls. With a large enough sample we will also be able to analyze changes in connectivity strengths related to genetic factors thereby providing new depression vulnerability markers. We are planning to present preliminary data demonstrating the feasibility of a DCM approach in depression vulnerability research.

P 22. Superiority of Escitalopram over Paroxetine in the treatment of Major Depressive Disorder (MDD)

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Aims: To compare escitalopram (10–20 mg/day) with paroxetine (20–40 mg/day) for the treatment of major depressive disorder (MDD).
Methods: Pooled data were analysed from two randomised, controlled, 6-month trials comparing escitalopram (n = 394) with paroxetine (n = 383) in patients with MDD. The primary endpoint was the mean change in MADRS score from baseline to last assessment.
Results: Escitalopram-treated patients showed a significant improvement from baseline in MADRS total score after 6 months compared to paroxetine (estimated mean difference 2.0 points, $p < 0.01$). Further significant differences were seen for the CGI-S (mean improvement of 2.1 for escitalopram versus 2.4 for paroxetine, $p < 0.001$) and the CGI-I (mean improvement of 1.8 for escitalopram and 2.0 for paroxetine, $p < 0.01$). In severely depressed patients (MADRS greater or equal to 30), escitalopram-treated patients showed improved efficacy in all scales relative to paroxetine at last assessment. Significantly higher remission rates (MADRS less or equal to 12, $p < 0.05$) were seen with escitalopram and this difference extended to complete remission (MADRS less or equal to 5, $p < 0.01$). Escitalopram demonstrated superior tolerability with significantly fewer withdrawals (17%) compared with the paroxetine group (28%, $p < 0.001$) and significantly fewer withdrawals due to adverse events (7% vs. 12%, $p < 0.01$). Response at week 8 was a strong indicator of the likelihood of completing 6-month treatment and of achieving complete remission.
Conclusion: This study demonstrates increased efficacy and tolerability for escitalopram over longer-term treatment periods when compared with paroxetine. For long-term or maintenance therapy of MDD and particularly in the treatment of severely depressed patients escitalopram improves therapeutic outcomes.

P 23. Efficacy and tolerability of once-daily extended release Quetiapine Fumarate (Quetiapine XR) monotherapy in elderly patients with major depressive disorder (MDD)

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Aim: Assess efficacy and tolerability of quetiapine XR monotherapy in elderly patients with MDD.
Methods: 11-week (9-week randomised; 2-week post-treatment phase), double-blind, placebo-controlled study (D1448C00014; Sapphire). Patients (DSM-IV diagnosis of MDD; >/=66 years) were randomised to quetiapine XR (flexible dosing 50–300mg/day) or placebo. Primary endpoint: MADRS total score change from randomisation to Week 9. Secondary endpoints: MADRS total score change from randomisation to each assessment; MADRS response (>/=50% decrease in total score) and

remission (total score </=8) at Week 9; change from randomisation in HAM-D, HAM-A, CGI-I, PSQI global, VAS pain and Q-LES-Q SF percent maximum total scores. AEs were recorded throughout.
Results: 338 patients were randomised (mean age 71.3 years): 166 quetiapine XR (mean dose 159.9mg/day) and 172 placebo. At Week 9, quetiapine XR significantly reduced MADRS total score from randomisation vs placebo (−16.33 vs −8.79; $p < 0.001$). At Week 1, MADRS total score was significantly reduced with quetiapine XR (−4.65; $p < 0.001$) vs placebo (−2.56).

At Week 9, HAM-D total and item 1 scores were significantly reduced with quetiapine XR (−15.66 and −1.84; both $p < 0.001$) versus placebo (−8.62 and 1.13, respectively). MADRS response rate for quetiapine XR was 64% ($p < 0.001$) vs placebo 30.4% and remission rate was quetiapine XR 45.1% ($p < 0.001$) vs placebo 17.0%.

At Week 9, quetiapine XR significantly reduced HAM-A total scores (−10.51; $p < 0.001$) versus placebo (−5.20) and significantly improved Q-LES-Q percent maximum total score (16.86 vs 9.17; $p < 0.001$), PSQI global score (−6.42 vs 2.89; $p < 0.001$) and VAS pain scores (−18.75 vs −9.01; $p < 0.001$) versus placebo. At Week 9, 71.3% ($p < 0.001$) patients had a CGI-I score </=2 with quetiapine XR vs placebo (39.2%).

Most common AEs (>10% patients in either group) with quetiapine XR and placebo were somnolence (33.1, 8.1%) headache (21.1, 16.3%), dry mouth (20.5, 10.5%) and dizziness (19.3, 15.1%).
Conclusion: In elderly patients with MDD, quetiapine XR monotherapy (50–300mg/day flexibly dosed) is effective and generally well tolerated, with symptom improvement observed as early as Week 1.

P 24. The role of biochemical and immunological markers in antidepressant treatment

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Background: Responsivity rate at the first treatment option of the depressive disorder is appreciated to be 30% of the cases, 30% do not responde, 40% having a partial responce. In contrast with the DSM IV TR and ICD-10 diagnostic criteria and the scores of the HDS scale, the efficacy of the treatment depends on the neurobiochemical model of depression. There is a tendency to overestimate the imporance of serotonine deficit in depression.
Methods: A correlation between the clincial model of depression and the biochemical indicators was tried. The clinical model divided depression in depression with anxiety (deficit of serotonine), inhibated depression (deficit of noradrenaline), depression with emotional demodulation (deficit of dopamine).

For each of these forms, were used biochemical and immunological indicators:
1. for depression through NA deficit:

- the increase in MHPG and the urinary cortizol;
- the decrease of free or sulpho-conjugate DOPEG;
- fast therapeutic answer to amphetamines;
- normal or lightly increase of the T and CD4 lymphocytes.

2. for depression through 5-HT deficit:

- the decrease of 5-HIAA in urine;
- the decrease in the level of plaketary serotonine;
- the significant decrease in the T, CD4 lymphocytes and NK cells.

3. for depression through DA deficit:

- the decrease of HVA in CRL and urine;
- therapeutic answer to DA activators-penbedil or bromcriptine;
- normal level of the T and CD4 lymphocytes.

Results: The main goal was the correlation between the clinical and the biochemical indicators, the selection of the treatment being made on this basis (N1 = 30 cases), compared to a control lot (N2 = 30 cases), to whom the treatment option was free. The evaluation of the treatment responsivity was made on the 6th and the 9th week, the responsivity rate being 70% for N1 and 43% for N2.
Conclusions: The compared statistical data between the two lots sustain the therapeutical evaluation based on clinical and biochemical indicators.

P 25. Caffeine challenge in patients with panic disorder: baseline differences between panickers and non-panickers

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Background/Aims: A proportion of patients with Panic Disorder (PD) display an increased sensitivity to the anxiogenic/panicogenic properties of caffeine. The aim of this study is to identify probable baseline differences between PD patients who panic and those who do not, after caffeine administration.
Methods: In a randomized, double-blind, cross-over experiment performed in two occasions of 3–7 days apart, 200 and 400 mg caffeine, respectively, were administered in a coffee form to 23 drug-free patients with PD with or without Agoraphobia. Evaluations included the State-Trait Anxiety Inventory, the DSM-IV 'panic attack' symptoms (visual

analogue scale form), the Symptom Checklist-90-Revised (SCL-90-R), as well as Breath-Holding (BH) duration, heartbeat perception accuracy and heart rate.
Results: Only those patients who did not present a panic attack after both challenges ('no panic group', N = 14, 66,7%), and those who presented a panic attack after at least one challenge ('panic group', n = 7, 33,3%) were included in the analysis. The panickers, compared to the non-panickers, presented at baseline: significantly higher total score of the SCL-90-R; significantly higher scores on all the SCL-90-R clusters of symptoms, except that of 'paranoid ideation'; significantly lower BH duration.
Conclusions: The present preliminary findings indicate that PD patients who panic after a 200 mg or a 400 mg caffeine challenge, compared to the PD patients who do not panic after both of these challenges, may present at baseline significantly higher non-specific general psychopathology -as reflected in the SCL-90-R- and significantly shorter BH duration.

P 26. A GPRD-based comparison of second-line antidepressant therapy with escitalopram and venlafaxine

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Background/aims: British guidelines recommend escitalopram and venlafaxine as second-line treatments in major depressive disorder (MDD). Clinical trials demonstrated similar efficacy and better tolerability of escitalopram vs. venlafaxine. To assess how these results translate into real-life, this study compared second-line treatment strategies with escitalopram or venlafaxine after failure of first-line generic SSRI, based on drug utilisation and economic outcomes in patients with MDD in the UK.
Methods: This cohort study using the General Practitioners Research Database (GPRD) included adults with a diagnosis of MDD, who had switched from a first-line generic SSRI to escitalopram or venlafaxine between 01-01-2003 and 30-06-2005. 6-month drug utilisation outcomes were dose-adjustments, mean treatment duration (TD), and successful treatment stop (no subsequent need for treatment) after switch. 6-month economic outcomes were healthcare resource use and total healthcare costs, calculated by adding up unit costs applied to resources. Appropriate multivariate models were built, using propensity scoring to control on baseline characteristics.
Results: 535 patients were switched to escitalopram, 1284 to venlafaxine. In the escitalopram cohort compared with the venlafaxine cohort, there were fewer males (32% vs. 38%, $p = 0.02$) and patients had a shorter median time to switch (50 vs. 59 days, $p = 0.005$).

Fewer drug adjustments were needed with escitalopram (27% vs. 44%, $p < 0.001$), consequently, a shorter second-line treatment duration (106 vs. 123 days, $p = 0.003$), numerically more successful stops (37% vs. 32%, $p = 0.25$), and fewer GP visits (12.3 vs. 13.4 visits/patient, $p = 0.06$) were observed in escitalopram-treated patients. 6-month total healthcare costs were significantly lower with escitalopram (£629 vs £749, $p = 0.028$), and were similar in both cohorts without treatment costs (£567 vs. £589, $p = 0.73$).
Conclusion: After failure of a first generic SSRI, second-line treatment with escitalopram was associated with easier management, shorter second-line treatment duration and earlier success, with no increase in healthcare cost, compared with venlafaxine.

P 27. Comparison of real-world observed persistence for patients treated with escitalopram and other antidepressants in a french setting: a database study

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Background: Continued persistence with medication is a key factor for patients to achieve optimal outcomes in most therapeutic areas. Mental health patients exhibit low compliance with medication, although recently published treatment guidelines recommend continuing treatment for a minimum of 6 months after remission.
Methods: 5,637 patients were retrospectively selected from an observational electronic database (IMS® Disease Analyzer France, a patient database based on 1,059 active GPs). Patients were selected if they had a diagnosis of depression and had received an antidepressant during the recruitment window (01/Sep/05 to 31/Jan/06), but not during the previous 6-month period. Patients were followed up for at least 12 months after initial antidepressant treatment to determine continuation of the initial therapy. Patients' baseline characteristics were reported and analyses conducted to assess the effect of baseline characteristics on antidepressant persistence at 3 and 6 months using Cox regression.
Results: Patients treated with escitalopram exhibited significantly greater persistence than patients treated with other antidepressants (fluoxetine, citalopram, sertraline, venlafaxine, and paroxetine). Unadjusted median time to non-persistence was 53 days for escitalopram versus 31 days for other antidepressants ($p < 0.0001$). Patients' age, number of concomitant medications and anxiety statistically

influenced persistence (Cox regression, chi-square test). The adjusted hazard ratio (time-dependant risk of stopping therapy) for escitalopram against others was 0.84 ($p < 0.0001$).
Conclusions: Treatment persistence is a key element of depression recovery. Observational data in France show that depressed patients treated with escitalopram persist with their initial therapy for a longer duration than with other antidepressant therapies, even after having taken into account external factors.

P 28. Surface-based analysis of cortical thickness in healthy subjects and remitted depressed patients

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Introduction: Depression is among the leading causes of disease burden and is associated with significant medical morbidity across the lifespan. Previous findings of structural changes in depression-related brain regions mainly reported relative volumetric alterations in patients suffering from major depression, whereas in other disorders such as schizophrenia or multiple sclerosis also cortical thickness has successfully been used. It is noteworthy that relative cortical volume comprises a voxel-based fraction of the product between total surface area and cortical thickness, two measures, which have shown to be biologically independent. Furthermore, given the significant different registration techniques (surface-based vs. 3D-volume-based) it is not surprising that cortical volume has been reported to be independent of cortical thickness, which underlines the importance of such studies in depression. Since no data are present today on cortical thickness in remitted depressed patients, we initiated a study with the goal to evaluate depression-relevant cortical structures such as the cingulate gyrus in remitted depressed patients.
Methods: Structural magnetic resonance imaging scans were obtained from a preliminary data set of healthy controls without any life-time history of psychiatric illness and remitted depressed patients. Cortical surface models have been created and analyzed with Freesurfer and AFNI/SUMA. While volume-based techniques are lacking topological accuracy, surface-based models preserve the topological folding patterns of the cortex, and hence reduce anatomical variability. Data have been normalized with mean cortical thickness and correction for multiple comparisons applied within an ANCOVA model.
Results: Since this is an ongoing study, we will present preliminary data on differences in cortical thickness within the cingulate gyrus, ventromedial prefrontal and orbitofrontal cortex between remitted depressed patients and healthy controls.
Discussion: Our findings will be discussed in the light of preclinical findings in primates as well as compared to imaging data acquired with other modalities in those regions.

P 29. Penile amputation after trazodone induced priapism

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Introduction: Painful persisting penile erection (priapism) is a rare but very serious side effect that can occur under antidepressants in general and under trazodone in particular. Trazodone is a very commonly prescribed antidepressant. Despite clear evidence, trazodone is often administered in clinical practice, to treat disordered sleep as in insomnia. We describe, the first case of a recurrent priapism occurring under trazodone that finally led to penile amputation.
Case report: A 35-year-old, white male was admitted at the emergency ward with priapism lasting for 15 hours. Clinical interview did not reveal previous events of priapism, substance abuse or genital trauma. Registered medication was acenocumarol. Besides priapism, physical examination, blood sample and toxicological analyses were normal. Corpus cavernosum aspiration showed an ischemic priapism. After resolution by Winter-shunting the patient was discharged. 10 days later he was re-admitted for a recurrent episode. This time interview revealed the introduction of trazodone 150mg per day, by a psychiatrist three weeks ago, for a disordered sleep complaint. Ultrasonography showed venous thrombosis of the penis. Despite anticoagulant therapy with an international normalized ratio (INR) at 12, the patient had an unfavourable outcome with persistent thrombosis. 48 hours later, a dry necrosis of the glans appeared. After three weeks of conservative treatment, amputation of the penis with perineostomy had to be realized.

Discussion: Besides a history of deep venous thrombosis and alcohol abuse, genotype investigation in the present case showed a heterozygote mutation R506Q for the Leiden V factor. Nevertheless we cannot explain thrombosis with an INR at 12 and normal levels of antithrombin III, protein C and S. Trazodone is a widespread antidepressant mostly used in clinical practice for its hypnotic properties. Prescription of antidepressants and probably of trazodone in particular should be carefully administered and closely monitored in patients with history of coagulopathy or clotting disorders.

P 30. Demographic and clinical features and axis I comorbidity in conversion disorder patients in Turkey

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Aims: The incidence of DSM-IV conversion disorder in outpatients is 4.5–32%, with childhood trauma being an important etiological factor. This study aims at investigating other Axis I comorbidity, childhood trauma, and conversion symptom pattern in this patient group
Method: Outpatients who were diagnosed as DSM-IV Conversion Disorder were included in the study except those with a neurological disorder, mental retardation, alcohol and substance abuse/dependency, bipolar, schizophrenic and other psychotic disorders and tardive dyskinesia. The assessment instruments are demographic and clinical questionnaire, Childhood Trauma Questionnaire (CTQ-28) and Hamilton Anxiety and Depression Rating Scales (HARS-HDRS).
Results: 25 female outpatients' mean age were 34.48 (SD + 10,21). 76% were married, 24% had no formel education. 48% (n = 12) were physically, 28% (n = 7) were sexually abused. 36% (n = 9) of the patients attempted suicide at least once. Comorbid depressive disorder prevalence was 40%. Mean HDRS score was 7,88 (SD: 4,43) and mean HARS score was 13,56 (SD: 7,42). There was a significant relationship between HARS scores and suicide attempt (p:0,037). CTQ-28 subgroup mean scores were: emotional neglect 2,86 (SD:1,32), physical neglect 2,04 (SD:0,52), emotional abuse 2,25 (SD:1,26), physical abuse 1,98 (SD:1,56), overall 10, 98 (SD:4,15).
Conclusion: Conversion disorder is a neglected clinical picture in health care system. Past traumatic experiences, high comorbidity rate and suicidality have to be addressed in assessment and treatment for a better prognosis.

P 31. Place of fluvoxamine treatment in prolonged earth-eating (PICA) accompanied with migraine: a case report

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Objective: The compulsive ingestion of unsuitable substances that have little or no nutritional value is referred to as pica. the frequency of pica-the compulsive intake of non-nutritive substances such as earth, clay, chalk, soap, and ice-during pregnancy is underestimated. Its prevalence during pregnancy is generally underestimated. Published data reveal a prevalence of between 8% and 65%. We report a case of a woman eating earth (geophagia) prolonged since 22 years with migraine headache.
Case Report: A forty–eight years old, twenty-four years married woman admitted to outpatient clinic for migraine since thirty-four years. Because of obsessive personality and psychosomatic complains we started fluvoxamine 100 mg/day. In first month migraine symptoms were remitted while pica disappeared.
Conclusion: SSRI can take place in pica treatment, according to the case fluvoxamine, successfully use in obsessive compulsive treatment, may an appropriate choice in pica.

P 32. A double-blind, placebo-controlled study with acute and continuation phase of quetiapine in adults with bipolar depression (EMBOLDEN II)

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Background/aim: To evaluate the efficacy and tolerability of quetiapine and paroxetine monotherapy for major depression in bipolar disorder.
Methods: 740 patients (478 bipolar I, 262 bipolar II) with episodes of major depression (DSM-IV) were randomized to quetiapine 300 mg/d (n = 245), quetiapine 600 mg/d (n = 247), paroxetine 20 mg/d (n = 122), or placebo (n = 126) for 8 weeks (acute treatment phase). In the acute phase, the primary

endpoint was the change from baseline to 8 weeks in MADRS total score. Secondary outcome measures included rates of MADRS response and remission, and HAM-D, CGI-BP-S, and HAM-A scores. After 8 weeks, patients with MADRS and YMRS scores $<$ or $=12$ were randomized to 26- to 52-weeks of continued treatment with quetiapine (300 mg/d or 600 mg/d) or placebo.
Results: At 8 weeks, the mean MADRS score change from baseline was -16.19 (quetiapine 300 mg/d), -16.31 (quetiapine 600 mg/d), -13.76 (paroxetine), and -12.60 (placebo) ($P<0.001$ for both quetiapine doses, $P=0.313$ for paroxetine, vs placebo). Quetiapine (both doses)-treated patients, but not paroxetine-treated patients showed significantly greater improvements ($P<$ or $=0.05$) in most secondary outcome measures at Week 8 versus placebo. Paroxetine significantly improved HAM-A scores ($P<0.05$) but not MADRS or HAM-D scores versus placebo. Both quetiapine doses were associated with greater improvements than paroxetine for MADRS and HAM-D scores. At Week 8, most common adverse events included dry mouth, somnolence, sedation, and dizziness with quetiapine (both doses); and dry mouth, sedation, headache, insomnia, and nausea with paroxetine. For patients previously treated with quetiapine, continued treatment with quetiapine beyond 8 weeks increased the time to recurrence of a mood event and a depression event significantly compared with placebo. Tolerability during the continuation phase mirrored that during the acute phase.
Conclusions: Quetiapine (300 mg/d or 600 mg/d), but not paroxetine, was more effective than placebo for treating acute episodes of depression in bipolar I and II disorder. Quetiapine treatment was generally well tolerated.

P 33. Efficacy and safety of quetiapine in combination with lithium/divalproex as maintenance treatment for bipolar I disorder (TRIAL 126)

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Background/aim: To determine the efficacy and safety of quetiapine in combination with lithium (Li) or divalproex (DVP) compared with placebo plus Li/DVP in the prevention of recurrent mood events (mania, depression, or mixed) in patients with bipolar I disorder in an international, randomized, double-blind, parallel-group study.
Methods: Patients with bipolar I disorder (DSM-IV, most recent episode mania, depression, or mixed) received open-label quetiapine (400–800 mg/d; flexible, divided doses) with either Li or DVP (target serum concentrations 0.5–1.2 mEq/L and 50–125 μg/mL, respectively) for $<$ or $=36$ weeks to achieve $>$ or $=12$ weeks of clinical stability. Patients were subsequently randomized to double-blind treatment with quetiapine (400–800 mg/d) plus Li/DVP or placebo + Li/DVP for up to 104 weeks. The primary endpoint was time to recurrence of any mood event defined by medication initiation, hospitalization, Young Mania Rating Scale or Montgomery-Åsberg Depression Rating Scale score $>$ or $=20$ at 2 consecutive assessments or at final assessment if the patient discontinued, or study discontinuation due to a mood event.
Results: A total of 1461 patients entered the prerandomization phase; 703 (48%) were randomized to receive $>$ or $=1$ dose of double-blind study treatment (ITT population). A markedly lower proportion of patients had a mood event in the quetiapine + Li/DVP group versus the placebo + Li/DVP group (18.5% vs 49.0%, respectively), with a risk reduction of 72% (HR, 0.28; $P<0.0001$). The incidence of adverse events was similar between the 2 treatment groups. The incidence and incidence density of a single-emergent fasting blood glucose value $>$ or $=126$ mg/dL was higher with quetiapine than with placebo (9.3% vs 4.1%; 17.64 vs 9.50 patients per 100 patient-years).
Conclusions: Maintenance treatment with quetiapine in combination with lithium or divalproex significantly increased the time to recurrence of any mood event (mania, depression, or mixed) compared with placebo plus lithium or divalproex irrespective of the polarity of the index episode. Long-term treatment with quetiapine was generally well-tolerated.

P 34. Maintenance treatment in bipolar I disorder with quetiapine concomitant with lithium or divalproex: a North American placebo-controlled, randomized trial (TRIAL 127)

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Background/aims: To examine the long-term efficacy and safety of quetiapine combined with lithium (Li) or divalproex (DVP) in the prevention of recurrent mood events (mania, mixed, or depression) in patients with stabilized bipolar I disorder.

Methods: Pre-randomization, patients with bipolar I disorder (DSM-IV) received open-label quetiapine (400–800 mg/d; flexible, divided doses) with either Li or DVP (target serum concentrations 0.5–1.2 mEq/L and 50–125 μg/mL) for a mania, mixed, or depression event to achieve clinical stability (YMRS and MADRS $<$ or $=12$) for at least 12 weeks. Thereafter, patients were randomized to double-blind maintenance treatment with quetiapine (400–800 mg/d, flexibly dosed)+Li/DVP, or placebo+Li/DVP for up to 104 weeks. Primary endpoint was time to recurrence of a mood episode, defined by medication initiation, hospitalization, YMRS/MADRS scores $>$ or $=20$ (at 2 consecutive assessments), or study discontinuation due to a mood event.
Results: Of 1953 patients who entered the pre-randomization phase, 623 received at least 1 dose of randomized study medication (ITT population). The quetiapine+Li/DVP combination was significantly more effective than placebo+Li/DVP ($P <$ 0.0001). The proportion of patients having a mood event was 20.3% (63/310) for quetiapine+Li/DVP and 52.1% (163/313) for placebo+Li/DVP. The HR for time to recurrence of a mood event was 0.32 (quetiapine+Li/DVP versus placebo+Li/DVP; $P <$ 0.0001), with similar HRs observed for mania and depression events (0.30 and 0.33, respectively; $P <$ 0.0001). Combined safety data from this study and the companion study (Trial 126) were consistent with the recognized safety profile of quetiapine. Combined incidence and incidence density of a single-emergent fasting blood glucose value $>$ or $=$ 126 mg/dL was higher in patients randomized to quetiapine+Li/DVP (10.7%, 18.03 patients per 100 patient-years) than in patients randomized to placebo+Li/DVP (4.6%, 9.53 patients per 100 patient-years).
Conclusions: Quetiapine+Li/DVP was significantly more effective than placebo+Li/DVP in increasing the time to recurrence of a mood event in stable patients with bipolar I disorder.

P 35. Placebo-controlled study with acute and continuation phase of quetiapine in adults with bipolar depression (EMBOLDEN I)

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Background/aim: To evaluate the efficacy and tolerability of quetiapine and lithium monotherapy for major depression in bipolar disorder.
Methods: 802 patients (499 bipolar I and 303 bipolar II), experiencing a recent major depression episode, were randomized to quetiapine 300 mg/d (n $=$265), quetiapine 600 mg/d (n $=$268), lithium 600-1800 mg/d (n $=$136), or placebo (n $=$133) for 8 weeks. Lithium was dosed at 600–1800 mg/d to maintain a serum concentration of 0.6–1.2 mEq/L. The primary endpoint of the acute phase was the change from baseline to Week 8 in MADRS total score. Secondary endpoints included MADRS response and remission rates, HAM-D, CGI-BP-S and HAM-A scores. Patients with MADRS and YMRS scores $<$ or $=12$ were randomized to 26- to 52-weeks of continued treatment with quetiapine (300 mg/d or 600 mg/d) or placebo.
Results: The mean change from baseline to Week 8 in MADRS total score was -15.36 for quetiapine 300 mg/d, -16.10 for quetiapine 600 mg/d, -13.60 for lithium, and -11.81 for placebo ($P <0.001$ for both quetiapine doses, $P =0.123$ for lithium, vs placebo). Quetiapine (both doses)-treated patients, but not lithium-treated patients showed significantly greater improvements ($P <$ or $=0.05$) in most secondary outcome measures at Week 8 versus placebo. Quetiapine 600 mg/d demonstrated significantly greater improvements over lithium for MADRS and HAM-D total scores. The most common adverse events in the acute phase included somnolence, dry mouth, and dizziness with quetiapine (both doses), and nausea with lithium. In patients previously treated with quetiapine, continued treatment with quetiapine beyond 8 weeks significantly increased time to recurrence of a mood event and depression event compared with placebo. Treatment-emergent adverse events were generally in line with those observed in the acute phase.
Conclusions: Quetiapine (300 or 600 mg/d), but not lithium, was more effective than placebo for the treatment of acute depression episodes in bipolar I and bipolar II disorder. Quetiapine treatment was generally well tolerated.

P 36. Quetiapine in the maintenance treatment of bipolar I disorder: combined data from two long-term phase III studies

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Background/aims: Data are presented from 2 long-term studies (D1447C00126; D1447C00127) that examined the efficacy and safety of quetiapine (QTP) in combination with lithium (Li) or divalproex (DVP) in the prevention of mood events (manic, mixed, or depressed) in bipolar I disorder.

Methods: The studies consisted of pre-randomization and randomized phases. Pre-randomization, patients received open-label QTP (400–800 mg/d; flexible, divided doses) with Li or DVP (target serum concentrations 0.5–1.2 mEq/L and 50–125 μg/mL, respectively) for a manic, mixed, or depressed event to achieve > or = 12 weeks of clinical stability. Thereafter, patients were randomized to double-blind treatment with QTP (400–800 mg/d; flexibly dosed) + Li/DVP, or placebo + Li/DVP for up to 104 weeks. The primary endpoint was the time to recurrence of any mood event; defined by medication initiation, hospitalization, Young Mania Rating Scale (YMRS) or Montgomery-Åsberg Depression Rating Scale (MADRS) scores > or = 20 at 2 consecutive assessments, or study discontinuation due to a mood event.
Results: 3414 patients entered the pre-randomization phase and 1326 were randomized and received at least 1 dose of study medication. Rates of recurrence were 19.3% versus 50.4% for QTP and placebo groups, respectively. The risk of recurrence of a mood event was significantly reduced in the QTP + Li/DVP group relative to the placebo + Li/DVP group (hazard ratio [HR], 0.30, $P < 0.001$). The same effect was observed for recurrence of depressed and manic events (HRs, 0.30, $P < 0.001$). Safety data were consistent with the recognized profile of QTP. The incidence density of a single-emergent fasting blood glucose value > or = 126 mg/dL was higher in patients randomized to QTP + Li/DVP (10.7%, 18.03 patients per 100 patient-years) than in patients randomized to placebo + Li/DVP (4.6%, 9.53 patients per 100 patient-years).
Conclusions: QTP + Li/DVP is significantly more effective than placebo + Li/DVP alone in increasing the time to recurrence of any mood event in patients with bipolar I disorder.

P 37. Quetiapine monotherapy up to 52 weeks in patients with bipolar depression: continuation phase data from the embolden I and II studies

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Background/aim: The aim of this analysis was to determine whether the acute findings of the Efficacy of Monotherapy Seroquel in BipOLar DEpressioN (EMBOLDEN) studies extend long-term by examining the continuation efficacy of quetiapine monotherapy in a preplanned pooling of data from EMBOLDEN I and II.
Methods: Following completion of the 8-week acute phases of EMBOLDEN I and II, patients who had received quetiapine (300 mg/d or 600 mg/d) and achieved remission (MADRS and YMRS scores < or = 12) at Week 8, were randomized to the same dose of quetiapine (double-blind) or placebo for at least 26 weeks and up to 52 weeks, or until mood event recurrence. The primary outcome variable was time from randomization (Week 8) to recurrence of any predefined mood event.
Results: 584 patients were included in the continuation phase. Risk for recurrence of a mood event was significantly lower in the quetiapine group relative to placebo (HR, 0.51 [95% CI, 0.38–0.69]; $P < 0.001$). A lower risk for recurrence of depressive (HR, 0.43 [95% CI, 0.30–0.62]; $P < 0.001$) and manic events (HR, 0.75 [95% CI, 0.45–1.24]) was also seen for quetiapine but statistical significance was achieved only for depressive events. Individually, both doses significantly delayed mood event recurrence (HRs, 0.59 [95% CI, 0.41–0.84] and 0.45 [95% CI, 0.30–0.67] for 300 and 600 mg/d, respectively), with a numerical advantage for the 600 mg/d dose. A similar advantage was apparent for recurrence of depressive (HRs, 0.48 [95% CI, 0.30–0.75] and 0.39 [95% CI, 0.24–0.63]) and manic events (HRs, 0.89 [95% CI, 0.49–1.63] and 0.62 [95% CI, 0.32–1.21]. Safety data were consistent with the recognized profile of quetiapine.
Conclusions: The acute efficacy of quetiapine in bipolar depression is maintained in continuation treatment for at least 26 and up to 52 weeks compared with placebo among patients responding to acute treatment. Quetiapine was generally well tolerated.

P 38. Despair beyond repair?: severity of hopelessness in depressed psychiatric inpatients

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Background: Hopelessness is associated with the current diagnosis and future risk of developing depression. Feeling hopeless plays a critical role in suicide ideation, attempts, and completion (Kuo, 2004). When overwhelmed with hopelessness, patients give up their coping efforts (Haeffel, 2008), and become less responsive to psychotherapy and pharmacological treatments (Papakostas, 2007). Unfortunately, prior research has not examined the potential impact of different severity levels of hopelessness.
Methods: 155 adult psychiatric inpatients were assessed. All participants met criteria for a depressive disorder (Major Depression or Dysthymia) based on the Structured Clinical Interview for DSM-IV Axis I

Disorders (SCID: First, 1995). Patients completed the Beck Hopelessness Scale (Beck, 1974), the Beck Depression Inventory (Beck, 1961), the Beck Scale for Suicidal Ideation (Beck, 1979), and the Daily Emotion Report (Nolen-Hoeksema, 1993). Patients were classified as displaying minimal, mild, moderate, or severe levels of hopelessness based on their scores from the BHS.

Results: Although they represented different levels of hopelessness, the four groups of depressed patients did not display any significant differences in age, race, gender, or educational level. However, the moderate and severely hopeless patients reported more severe levels of depression ($F = 27.86$, $p < .0001$), and more frequent suicidal ideation ($F = 22.26$, $p < .0001$). Furthermore, moderate and severely hopeless patients were significantly more likely to rely on rumination ($F = 2.94$, $p < .05$) and less likely to use distraction ($F = 8.97$, $p < .001$) when struggling with difficult interpersonal problems. Additional analyses will examine the impact of hopelessness on the chronic or recurrent nature of the depression.

Conclusions: Hopelessness plays a critical role in the pathway from depression to suicide risk. Higher levels of hopelessness were related to more severe depression, more frequent suicidal thoughts, and tendencies for ineffective coping strategies when struggling with difficult life problems. Clinicians should go beyond the reduction of depressive symptoms and develop strategies for monitoring and reducing hopeless attitudes.

P 39. Clinical and neurocognitive changes with Modafinil in obsessive-compulsive disorder: a case report

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Aim: To investigate modafinil as a cognitive enhancer and wakefulness- promoting agent for excessive day time sleepiness (EDS) in obsessive compulsive disorder (OCD).

Background: OCD involves failures in key neurocognitive domains and commonly co-exists with sleep disorders. We postulated that Modafinil (Provigil)-[2-{(diphenylmethyl) sulfinyl acetamide}], a non-amphetamine wakefulness-promoting agent, may improve somnolence in OCD. Recent studies also report an emerging role for modafinil as a cognitive enhancer in neuropsychiatric disorders [Minzenberg M.J, Carter C.S Neuropsychopharmacology (2008) 33, 1477–1502]. In this context, we considered modafinil may offer a new approach to treating cognitive impairments in OCD.

Method: A single case report of a 34 year old male patient with SSRI-resistant, DSM-IV OCD comorbid with panic disorder, dysthymia and EDS. Modafinil was initiated at 100mgs, increased after seven days to 200mg in divided doses, and after 14 days to 400mg.

Clinical assessments were performed at baseline (immediately before modafinil) and at weekly intervals using the Epworth Sleepiness Scale (ESS), Yale-Brown Obsessive Compulsive Scale (Y-BOCS), Montgomery and Åsberg Depression Rating scale (MÅDRS), Sheehan Disability Scale (SDS), Clinical Global Impression Severity Scale (CGIs), State-Trait Anxiety Inventory, and the Locus of Control Scale. Neuro-cognitive assessment was performed at baseline and on day 14 using the National Adult Reading Test (NART) and selected executive tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Data were analysed using the non-parametric Wilcoxon test.

Results: Clinical measures of OCD, excessive sleepiness and social disability showed small, but not significant, improvement from baseline. However, state anxiety significantly increased and became intolerable when the dose increased to 400mg. Cognitive performance improved in six tested domains; attentional set shifting, inhibitory control, decision-making, planning and motor control, spatial recognition and working memory.

Conclusion: Objective improvement in neuro-cognitive performance observed in our case suggests modafinil (100–200mg) may have a role as a treatment in OCD. Substantiation of clinical and neurocognitive effects in larger case series and randomised placebo-controlled trials is warranted.

P 40. Adjunctive use of Amisulpride in elderly patients with psychotic depression treated with antidepressants

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Background/Aims: Since elderly psychotic patients are more sensitive to extrapyramidal side-effects, atypical antipsychotics seem to be a safer choice of treatment compared to classical antipsychotics. In addition, these patients may be more susceptible to drug interactions and changes in metabolism. The atypical antipsychotic amisulpride (Leucht, 2004) is not metabolised by the liver and is therefore a good candidate for treatment of the elderly. We have evaluated combination treatment for 5 weeks with

amisulpride and antidepressants in non-demented elderly patients with psychotic depression.
Methods: Eleven patients were treated with either citalopram 20–40 mg/day (n = 5) or mirtazapine 30–60 mg/day (n = 6), and amisulpride 75–100 mg/day for 5 weeks. Clinical status was evaluated at baseline and after 3 and 5 weeks using the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale—17 items (HDRS) and the Clinical Global Impression Scale (CGI-S).
Results: In 5 of the 11 patients there was remission of depression, while in another 5 patients there was partial remission of depression and in one patient there was no remission.

Finally, there was resolution of psychotic symptoms in all the patients involved. One patient developed tremor and rigidity but insisted on continuing with the drug since her psychopathology was considerably improved after the addition of amisulpride to antidepressant treatment.
Conclusions: Some elderly patients with psychotic depression may benefit from the combination of amisulpride and antidepressant pharmacotherapy.

Reference

Leucht S (2004). Amisulpride- a selective dopamine antagonist and atypical antipsychotic: results of a meta-analysis of randomized controlled trials. Int J Neuropsychopharmacol 7(Suppl 1):15–20.

P 41. Treating depression in a patient with anorexia nervosa using Bupropion

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Background: Anorexia nervosa is quite often comorbid with depression. Among antidepressants bupropion is an agent with specific contraindication for anorexia nervosa due to its risk of causing epileptic seizures. In this case study there is a 26 -year old female patient with anorexia nervosa whose comorbid depression was successfully treated with bupropion.
Method: A 26 -year old female with a ten-years anorexic history of the binge eating/purging type (with binge eating and self vomiting) came up with a major depressive episode with melancholic features after her father's death. She was administered bupropion 150mg daily for the first month and 300 mg from the second month and so on.
Results: The patient was significantly improved not only concerning her depressive symptoms but also about her eating disorder. She diminished binge eating and self vomiting, her mood and her energy got better and she was able to treat with a lot of activities. She did not report any side effect. In fact she expressed her satisfaction for having a feeling of well being.
Conclusions: Bupropion may be an efficient and safe antidepressant for the treatment of the comorbid depression in cases of anorexia nervosa.

P 42. Atypical depressive symptoms of seasonal affective disorders in women suffering from overweight

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Increase of depressive disorders and prevalence of atypical depression (AD) (according DSM-IV) are relevant problem of contemporary psychiatry. Depressive symptoms of seasonal affective disorder very often have atypical signs among which weight gain and appetite increase can be distinguished.*Objective*: To analyze prevalence and correlation of AD with SAD among outpatients with overweight who sought for psychological correction of overweight.
Material and method: Typical and atypical depressive symptoms were estimated by SIGH-SAD (Williams J. et al., 1991). The Seasonal Pattern Assessment Questionnaire (SPAQ) was used for estimation of seasonality (Rosenthal N. et al., 1984). In compliance with the object, 35 women at the age 37.4 ± 7 years were estimated. Patients whose score of typical symptoms was more than 7 points and who had score of atypical symptoms 7 points or more by SIGH-SAD were considered as patients who had depressive episode with atypical signs.
Results: 62.9% of patients (22) had condition which corresponded to mild depressive episode. In 63.6% (14) of cases atypical signs were observed. In most cases depressive symptoms were accompanied by dysmorphophobia. The average point of typical depressive symptoms among the patients without atypical signs was 11.5 ± 2.9 and patients with atypical signs of depressive symptoms had 14.4 ± 5.7. In group with atypical depressive symptoms the body-weight index was 33.7 ± 6.8 and the total point by SIGH-SAD was 26.9 ± 8.8. In the group with typical depressive symptoms the body-weight index was 29.2 ± 5 and the total point by SIGH-SAD was 17.6 ± 4.3. The reliable differences in age and body-weight index in these groups were not found. Among all the patients 25.7% had a seasonal pattern of disorder. In the group of women with depressive atypical signs the seasonality was found in 21.4% cases. In the group without atypical symptoms the seasonality was observed in 37.5% cases.

Conclusion: Following the showed sampling, the frequency of AD was 40%. The SAD dominated among women with overweight and without atypical signs.

P 43. Comparative study of generalized anxiety disorder patients in a Spanish population setting

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Aims. To evaluate the comorbidity (especially focus in somatic symptoms) and resource use in Generalized Anxiety Disorder (GAD) patients, among Primary Care setting (PCS).
Method. A retrospective multicenter population-based study; data were collected (during year 2006) in six Primary Care Settings (clinics), of Badalona Serveis Assistencials S.A. management. All medical records of outpatients over 20 years were included. Patients with and without GAD were compared. Main measures: general (age, gender, etc.), co-morbidities, Charlson-index (patient severity) and cost model. The general morbidity burden was measured using Adjusted-Clinical Groups (http://www.acg.jhph.edu). An analysis of logistical regression and the covariance (ANCOVA) was affected for the correction of the models (procedure: Bonferroni), according to the recommendations of Thompson-Barber. Program SPSSWIN; $p < 0.05$.
Results. Of the 63,525 patients, 4.7% (95% CI: 4.5% to 4.9%) had GAD. Patients with/without GAD, the average episode/year was 6.1 versus 4.7 and attendance/year 10.1 versus 7.6; $p < 0.001$. GAD was associated with women (odds ratio [OR] = 1.7; CI 1.5–1.9), dyslipidemia (OR = 1.1; CI 1.0–1.3) and smoking (OR = 1.3; CI 1.2–1.4), $p < 0.001$. Plus, GAD group shown a variety of somatic symptoms: irritable bowel [3.0%; OR = 1.9 (CI 1.5–2.4)], migraine [6.7%; OR = 1.5 (CI 1.2–1.7)], gastritis [19.1%; OR = 1.4 (CI 1.3–1.5)] or fibromyalgia (3.0%, CI 2.4–3.6), $p < 0.001$. The average of direct cost /year adjusted by age, gender and morbidity burden was 640€ (CI 613.78–666.18€) versus 576€ (CI 570.86–586.70€); $p < 0.001$. GAD was associated with higher directs costs. Patients with GAD took many medications out off regular treatment: muscles-relaxants (OR = 1.2, CI 1.0–1.3) or analgesics (39.9% in GAD versus 33.5% in population group, $p < 0.001$).
Conclusions. Patients with GAD have greater co-morbidity and higher direct costs in PCS. Plus, these patients consult about many somatic symptoms and take different somatic's medications.

P 44. Influence of obesity in co-morbidity and cost among depressive Spanish outpatients

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Objectives. To measure the economic impact of Depressive Disorders (DD) and associated obesity in a population treated in the Primary Care Setting (PCS) under usual clinical practice conditions.
Methods. All medical records of outpatients over 20 years managed at six PCSs during year 2006. Patients with and without DD or obesity were compared. Four groups were established for comparison: population, obesity, depression and both. Main measures: general (age, gender, etc.), co-morbidities, Charlson-index (patient severity) and cost model. The general morbidity burden was measured using from Adjusted-Clinical Groups (http://www.acg.jhph.edu). An analysis of logistical regression and the covariance (ANCOVA) was affected for the correction of the models (procedure: Bonferroni), according to the recommendations of Thompson-Barber. Program SPSSWIN; $p < 0.05$.
Results. A total of 65.769 subjects were assessed; 12,229 patients with obesity [18.6% (CI: 18.3%–18.9%); 55.6% (CI: 54.7%–56.5%) women]; 3,506 patients with DD [5.3% (CI: 5.1%–5.5%), 72.4% (CI: 70.9%–73.9%) women]; 2,249 patients with both [3.4% (CI: 3.3%–3.5%), 81.2% (CI: 79.6%–82.8%) women] and 47,785 patients in population group [72.7% (CI: 72.4%–73.9%), 51.1% (CI: 50.7%–51.5%) women].

Depressive with obesity patients showed more episodes of co-morbidities/year (14.3 vs 6.3, $p < 0.001$) and higher Charlson index (0.5 vs 0.2. $p < 0.001$) Main co-morbidities episodes associated to DD with obesity were fibromyalgia syndrome [Odd ratio (95% CI); 3.2 (CI: 2.6–3.8), $p < 0.001$], hypertension [2.0 (CI: 1.8–2.3), $p < 0.001$], thyroid disturbances [1.7 (CI: 1.4–1.9), $p < 0.001$] and asthma [1.6 (CI: 1.3–1.9), $p < 0.001$].

DD with obesity were associated with significant higher adjusted total costs: €1,040.94 vs €627.76 (depressive), €627.76 (obesity) and €513.77 (population group), $p < 0.001$. Sixty-nine percent of total cost was drug-derived.

Conclusions. Patient with depressive disorder and obesity showed higher comorbidities and cost than others comparison groups.

P 45. Multinational observational study on factors affecting recovery from mania in bipolar disorder in patients treated with atypical antipsychotics: acute phase results

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Background: Limited evidence supports clinical decisions in relation to prognosis when initiating patients on antipsychotic treatment for bipolar mania. Identifying factors affecting recovery in bipolar mania would have clinical utility.
Methods: Males and females aged 18 years or older initiating or changing oral atypical antipsychotic for the treatment of mania in DSM-IV-TR-diagnosed bipolar disorder were eligible for enrolment. Observations regarding potential prognostic factors and treatment outcomes were recorded at baseline and over the initial acute study phase of 12 weeks. Factors influencing prognosis were analysed using logistic regression.
Results: A total of 933 patients were recruited into the study from China, Egypt, Greece, Hungary, Mexico, Romania, Saudi Arabia and Slovenia, of whom 96.5% completed the first 12 weeks (acute phase) and 872 patients (those meeting the selection criteria) were included in the analyses. At baseline, on average, patients were moderately to markedly ill (overall CGI-BP-S 4.7 ± 1.1; YMRS 31.3 ± 11.1). At the end of 12 weeks, 89.0% of patients had responded based on having a reduction in YMRS score of at least 40% and 73.1% had achieved symptomatic remission defined by a YMRS score of less than or equal to 12 (excluding patents with baseline score $<=12$, $n=42$). For the purpose of analysis, patients were stratified to one of the following treatment groups: 1. olanzapine alone ($n=266$), 2. olanzapine in combination with other non-antipsychotic treatment(s) ($n=296$), 3. quetiapine, alone or in combination ($n=87$), 4. risperidone, alone or in combination ($n=66$) and 5. other atypical antipsychotics and antipsychotic polytherapy ($n=157$). From a logistic regression model, the following baseline factors were found to be simultaneously associated with achieving symptomatic remission ($p<.05$): age when first contacted psychiatric services, YMRS score, race, number of social activities, work status, satisfaction with life, relapse in 4 weeks before baseline and rapid cycling (though not baseline treatment).

P 46. Once-daily extended release quetiapine fumarate (quetiapine xr) monotherapy in major depressive disorder (mdd): analysis in a subgroup of patients with anxious depression

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Aim: This analysis evaluated the efficacy of quetiapine XR monotherapy in patients with anxious depression. This is an important study population and the STAR*D study found that lower response and remission rates were observed in patients with anxious depression.
Methods: Data were analysed from two similar 6-week, double-blind, placebo-controlled studies of quetiapine XR monotherapy (D1448C00001 and D1448C00002), which were prospectively designed to be pooled. Patient subgroups: HAM-D anxiety/somatic factor score $>/=7$ (anxious depression) or <7. Primary endpoint: change from randomisation at Week 6 in MADRS total score. Secondary endpoints: change in MADRS total scores at Week 1, MADRS response ($>/=50\%$ decrease in total score) and remission (total score $</=8$) at Week 6; change at Week 6 in HAM-A total score.
Results: 788 (81%) patients had anxious depression at randomisation: 251 quetiapine XR 150mg/day, 267 quetiapine XR 300mg/day, 270 placebo. At Week 6, MADRS total scores were significantly reduced with quetiapine XR 150 (-14.8; $p<0.001$) and 300mg/day (-15.1; $p<0.001$) versus placebo (11.5). At Week 1, quetiapine XR 150 and 300mg/day reduced MADRS total scores (-8.5 [$p<0.001$], 8.4 [$p<0.001$]) vs placebo (6.2). MADRS response rates at Week 6 were 53.8% and 50.6% (both $p<0.001$) with quetiapine XR 150 and 300mg/day versus placebo (34.1%). MADRS remission rates were significantly greater than placebo (20.0%) with quetiapine XR 300mg/day (28.1%; $p<0.05$) but not QTP XR 150mg/day (23.5%; $p=$

0.313). At Week 6, quetiapine XR (150 and 300mg/day) significantly improved HAM-A total score versus placebo (-8.4 [$p < 0.001$] and -8.1 [$p < 0.01$] vs -6.4).
180 (19%) patients had lower levels of anxiety at randomisation: 64 quetiapine XR 150mg/day; 56 quetiapine XR 300mg/day, 60 placebo. Quetiapine XR was also effective among this subset of study participants.

Conclusion: Quetiapine XR (150 and 300mg/day) monotherapy is effective in patients with anxious depression, with symptom improvement observed as early as Week 1.

Reference

Fava M. et al. *Am J Psychiatry* 2008;165:342–351.