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SO 01. How can we overcome the stigma against treatment?

SO 0101. How can we neutralize the stigma of the treatment of depression?

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Reducing stigma is one of the major policy approaches proposed to reduce levels of unmet need for mental health services. Unfortunately, the stigma that the public associates with mental illness has remained persistent, with no apparent improvements over the past ten years. Depression has been designated a major public health problem by the WHO. It is common, increasing in prevalence, treatable, but under recognized and undertreated with profound negative consequences. There are several barriers to care: stigma of mental illness, attitudes towards mental health providers and mental health treatments and practical barriers impeding access to services. Most individuals with depression are visiting primary care physicians. Majority of patients with depression are missed at their first visit. Substantial part of them remained undetected at 1 year. Few of those who receive a diagnosis of depression receive adequate treatment. Several factors are affecting the early (non)-recognition of depression in primary care: inadequate medical education on mental disorders, stigma, time constraint, somatization, masked depression, co morbid medical illness, tacit collusion. There are some strategies trying to improve the early recognition and treatment of depression. Let us mention targeting education campaigns to the general public, mental health skills training and education for primary care professionals, screening and clinical guidelines use and stepped care model. Introducing of adequate curricula for pre-gradual as well as post-gradual training of physicians and functioning and accessible mental health care system are prerequisites of decisive importance. Complex programs involving policy-makers, NGO's, mental health professionals, carers and families, patients, media, corporate sector, schools and universities organized on international, national and local level may contribute to the improvement of the early recognition and treatment of people suffering from depression.

SO 0102. The need for early onset treatments in depression and anxiety

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Over the last years, psychiatric community has shifted away from acute treatment to focus on early intervention. In this perspective, the Duration of Untreated Illness (DUI), defined as the interval between the onset of a psychiatric disorder and the administration of the first adequate pharmacological treatment [1] and expressing the latency to pharmacological treatments, has received growing interest. A converging body of evidence suggests that the longer the disease remains untreated, the worse is the outcome [2]. Even though most studies assessed the role of the DUI in major psychoses, the parameter has been increasingly investigated in mood and anxiety disorders, which represent highly prevalent conditions. In fact, recent studies have shown the relationship between a long DUI in major depression and an earlier age at onset, longer duration of illness, higher number of relapses and rates of comorbidity. In addition, a relationship between a long DUI in bipolar disorder and a more severe clinical course, higher suicidal risk and number of hospitalization, in particular, has been pointed out [3]. Finally, an association between a long DUI and higher comorbidity rates and worse response to pharmacological treatment was found in anxiety disorders, such as obsessive-compulsive disorder, panic disorder and generalized anxiety disorder. Given that DUI is a potentially modifiable prognostic factor, the assessment of the latency to treatment is one of the first steps in order to plan early interventions. From this prospective, early onset treatments are aimed to delay or prevent the onset of the disorder in people with prodromal symptoms and to provide effective treatment in the early stages of the disorder. Such interventions are now widespread in America, Europe and Australia and focused mainly on major psychoses. Only few studies analyze the effect of early interventions in anxiety and mood disorder and, in these fields, are mostly based on cognitive behavioral therapy (CBT). Nonetheless, programs based on CBT appeared to be effective in panic disorder, in acute traumatic stress disorder and in anxious children. Finally, school and community-based prevention

and early intervention programs have produced positive results, in particular for CBT, exercise and stress management [4].

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SO 0103. Stigma against premenstrual dysphoria caused by the influence of ideologically rooted argumentation on the actions of regulatory authorities

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While a scientifically based questioning of current psychiatric diagnoses and treatments is obviously important for progress, argumentation rooted in anti-psychiatric ideology has proven less helpful, and caused considerable harm, both by depriving patients of effective treatment, and by enhancing the stigma and burden of psychiatric morbidity. In this presentation, the case of premenstrual dysphoria (PMD) will be discussed to illustrate how psychiatry, more than other medical disciplines, is at risk of being influenced by ideology and non-scientific arguments. The existence of PMD was recognized already by Hippocrates, and has been confirmed in a vast number of studies conducted in different cultures. It is well established that premenstrual complaints cause a marked reduction in life quality, and some studies suggest that they also enhance the risk for suicide. Luckily, however, PMD is a highly treatable condition: many controlled studies thus unanimously confirm that selective serotonin reuptake inhibitors (SSRIs) markedly reduce the symptoms in a vast majority of patients, and that the onset of action is short enough to permit the treatment to be restricted to the symptomatic phase of the cycle. While it may hence seem as a reasonable stance that women having large parts of their lives ruined by the burden of PMD should be offered the opportunity to test this safe and well-tried treatment, many debaters

have found reasons to fiercely oppose this idea, by claiming, for example, that PMD is a non-existing condition, or a social construct (in spite of the fact that it has a very robust and well-established biological basis, i.e. the cyclical influence of sex steroids on the brain). As will be discussed in this presentation, this arguing, which seems to be rooted in an unhealthy mixture of anti-psychiatry and an extreme variant of feminism, has contributed both to the reluctance of including PMD among the established diagnoses in DSM, and to the fact that no SSRI is approved for this indication in Europe.

SO 02. GAD as an obstacle to successful management of other psychiatric conditions

SO 0201. Preclinical work in anxiety: Latest insights

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The understanding of the neurobiology of anxiety disorders, including GAD continues to evolve. So too does the development of new treatments and insights into the mechanisms of action of older and newer pharmacological treatments. Basic science and imaging techniques are working towards clarifying the pathophysiological profiles of patients with anxiety conditions and the potential impact of different pharmacological interventions. In the process, they are further defining these conditions that may require treatment but not all be responsive to the same therapeutic interventions, including in patients where they are present as a comorbid condition. Through increased understanding of both neurobiology and psychopharmacology practicing psychiatrists should be able to improve the management of patients with anxiety disorders, with and without comorbid disorders, to achieve optimal outcome with minimal adverse effects.

SO 0202. Concurrent anxiety: Increasing the burden of other psychiatric disorders

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Anxiety disorders such as Generalized Anxiety Disorder (GAD) often occur in patients who have previously or currently experience other anxiety disorders and other psychiatric disorders who present in the psychiatry clinic. Comorbid GAD can have substantial impact not only upon the patients functioning

and wellbeing, but also on the success of treating their primary complaint. The co-occurrence of anxiety with depression has been associated with an increased burden of depressive and anxiety symptoms compared with having depression alone as well as greater functional impairment and decreased response to treatment. Co-occurring anxiety disorders are both prevalent and problematic in bipolar disorder and psychotic disorders such as schizophrenia. Outcome in these serious mental disorders is worse when a comorbid anxiety disorder is present. Both bipolar disorder and psychotic disorders are associated with high rates of completed suicide and functional disability and anxiety can increase the risk of suicide and reduce the chances of functional recovery. Appreciation of how commonly anxiety disorders such as GAD can occur concurrently with other psychiatric disorders such as depression, bipolar disorder and schizophrenia and the potential adverse impact such disorders may have, may help physicians improve management and outcome for these patients.

SO 0203. Optimizing treatment in the presence of anxiety

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Successful management of comorbid anxiety symptoms and disorders, such as Generalized Anxiety Disorder (GAD), in patients in the psychiatry setting can be challenging. The challenges encountered include suboptimal response to SSRIs and SNRIs, the need to use such agents with caution in patients with bipolar disorder, and adherence issues linked to side-effects. Benzodiazepines should only be used short-term and with great caution in patients with a history of substance abuse, a problem commonly encountered in the psychiatric clinic. Pregabalin has been well studied in patients with “primary” GAD, but less is known about its role as a treatment for GAD concurrent with other psychiatric disorders. Polypharmacy among patients with multiple disorders, including anxiety disorders such as GAD, is commonplace and factors such as hepatic metabolism and the potential for pharmacokinetic drug-drug interactions are also important considerations for optimizing treatment. The challenge is even greater when the complexities of concurrent medical conditions are part of the equation. There are a variety of agents at our disposal that can be employed to successfully manage patients in the psychiatric setting who have comorbid anxiety disorders, but success depends on knowing how best to use these agents in conjunction with other

psychotropics and what strategies can be employed to maximize treatment success.

SO 03. Examining opportunities for increasing treatment success in depression and anxiety disorders

SO 0301. Therapeutic drug monitoring of antidepressants: controversies and possibilities

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Significant advancements in the field of therapeutic drug monitoring (TDM) over the recent years now empower the clinician to cost-effectively optimise pharmacotherapy in the individual patient. TDM is best known for its contributions to patient safety, as is the case when administering a drug with both a narrow therapeutic index and a high potential for inter-patient pharmacokinetic variability. The benefits of TDM, however, extend well beyond patient safety.

Antidepressant dose alone has considerable limitations as a predictor of clinical response. For all antidepressants and antipsychotics investigated so far, plasma levels at one and the same dose can vary up to 20-fold among individuals. For both the serotonin transporter and the D₂ subtype of the dopamine receptor, drug plasma levels correlate with target structure occupancy – and therefore clinical response – to a much greater extent than the dose of the drug. TDM can thus assist clinicians in clarifying whether inadequate response is due to abnormalities in drug metabolism or poor adherence (compliance). Further, when levels are at or above the orienting therapeutic level and in the expected range with respect to drug dosage, “true medication refractoriness” may be suspected, justifying a switch in the medication. With the availability of up-to-date guidelines ([1] for routine psychiatric use, [2] for guidelines on the interpretation of plasma levels in court proceedings) and target ranges of the serum/plasma concentrations that are normally observed at therapeutic doses, TDM represents a valuable and increasingly accessible opportunity for improving treatment outcome in patients with mood disorders. TDM has been demonstrated to be cost-effective. The field continues to develop as investigators examine the combination of TDM with genotyping of cytochrome P450 2D6, the key enzyme involved in the polymorphic metabolism of the majority of antidepressants [3].

A better understanding of the complex relationship between antidepressant plasma levels and

clinical response is required, and there is also a clear need for education of clinicians on TDM strategy, as evidenced by recent studies suggesting that TDM is commonly used inappropriately [4].

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SO 0302. Prioritising safety and efficacy in the treatment of depressed elderly patients

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Antidepressants are widely prescribed to depressed persons in later life. Despite this, relatively few controlled comparative trials of these compounds have been conducted in this population. Elderly patients, somewhat contentiously classified as those of 65 years of age and above, are often systematically excluded from randomised controlled trials because of the presence of confounders such as comorbid illness, concomitant medications and general frailty.

The implications of this trend are such that treatment recommendations are often still extrapolated from younger patients. Some headway has been made over the past decade in identifying whether or not there are indeed key differences between younger and older adults. Antidepressant efficacy, for example, has been shown in several studies to be similar across age groups [1]. On other domains, however, such extrapolations do not appear to be appropriate. Antidepressant safety and tolerability are two such examples.

The prioritisation of safety when treating the elderly is important given that aging is associated with changes to both the pharmacodynamics and pharmacokinetics of therapeutic compounds, which, in turn, are further complicated by deteriorating

physiological mechanisms, dietary changes, other diseases and polypharmacy. Elderly patients tend to be more sensitive than younger patients to the adverse effects of psychotropic medications. Of special relevance are the central and peripheral anticholinergic side effects of older antidepressants: memory and concentration impairment, sedation and delirium, arrhythmia, constipation, urinary retention and visual impairment. As a result, tricyclic antidepressants are regarded as “inappropriate medication” for the treatment of elderly patients. While weight gain, sexual dysfunction and sedation are side effects of concern in younger patients, physicians treating elderly patients should consider the potential risks for falls and fractures, cardiovascular complications (orthostatic hypotension, antiplatelet effects, dyslipidaemia), hyponatraemia, and changes to bone mineral density.

Therefore, when choosing between efficacious pharmacological treatments, current best practice dictates that a physician’s primary consideration should be to avoid unnecessary antidepressant-related adverse drug events.

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SO 0303. Is the choice of antidepressant a major factor in attaining the treatment goal?

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Clinicians are faced with a broad and expanding range of pharmacological treatments for depression. Transparency or rationing authorities, whose main motive is to save money, tell clinicians that there is little or no difference in efficacy between different treatments. The evidence from an increasing number of studies and analyses contradicts this assumption. The strongest scientific evidence comes from unbiased double-blind randomised head-to-head studies which have found a significant advantage in favour of one or more antidepressants under conditions of fair comparison. The criteria established for a superior antidepressant that at least two studies demonstrate a significant advantage on the pivotal measure is in line with the regulator agencies which use the same criteria to establish efficacy compared to placebo [1,2]. The alternative method is to demonstrate a significant advantage using a meta-analysis

of responder rates from multiple studies. This has the disadvantage of being a post hoc analysis of studies which have different designs, different pivotal endpoints and include different populations. Nevertheless, despite the potential bias, hypothesis-generating results also find again that some antidepressants are associated with significantly superior efficacy [3].

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SO 04. Treatment of depression with comorbidity

SO 0401. Treatment of depression Parkinson's disease

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Recent reviews show that depression is a common and potentially debilitating aspect of Parkinson's disease, affecting 40–50% of patients. Its aetiology in Parkinson's disease is unclear (biochemical changes, psychosocial factors, and situational stressors have all been implicated), it has an adverse effect on the quality of patients' lives.

The establishment of the most appropriate treatment for PD patients with depression is still lacking a good evidence basis. Either it assumed that PD and depression are two independent diseases and the data available to inform the treatment of depression can be used in PD patients as if they did not have PD what does not seem a very adequate solution because there many data suggesting that PD and depression are not two independent diseases. Or we need dedicated studies, mostly RCTs and long term controlled data to inform the treatment of PD patients with depression. Most of the data need is

lacking. Nevertheless in 2009–2010 three new RCT were published in PD depression that worth discussion, namely Atomoxetine versus placebo; Pramipexole versus placebo and Paroxetine versus nortriptyline versus placebo.

The large gaps still remaining in the field will be highlighted.

SO 0402. Influence of comorbid anxiety disorders on outcome in major depression

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Coexisting anxiety symptoms and comorbid anxiety disorders are common in patients with major depressive disorder – anxiety symptoms are reported by approximately 60% of patients, and comorbid anxiety disorders are seen in around 50% of patients. Early studies encouraged the widespread consensus that patients with comorbid mood and anxiety disorders had more severe symptoms. Similarly, comorbidity of anxiety disorders with major depression has usually been thought to be associated with a less favourable long-term outcome, with longer persistence of symptoms and a greater risk of continuing social and occupational impairment. In addition, the presence of prominent anxiety symptoms in depressed patients is generally considered to be associated with a lower overall response rate to treatment.

This review will examine four aspects of the relationship between major depressive disorder and comorbid anxiety disorders: the pattern of coexisting anxiety and depressive symptoms in occupational and clinical samples; whether the comorbid condition is indeed more severe than 'pure' major depression: whether comorbidity is associated with worse clinical outcomes than are seen in major depressive disorder alone; and whether the response to antidepressant treatment differs, between depressed patients with or without comorbid anxiety disorders.

Although not all evidence is consistent, in general terms the presence of comorbid anxiety disorders in patients with major depressive disorder is associated with greater severity of symptoms and more pronounced impairment; the course of illness is less favourable in patients with the comorbid condition; and relatively fewer depressed patients respond to antidepressant treatment and achieve remission of symptoms, if affected by comorbid anxiety disorders. There is a need for randomised placebo-controlled studies specifically

in patients with comorbid major depressive disorder and anxiety disorders, in order to determine whether this patient group differs from those with 'pure' major depression, in its responsiveness to pharmacological or psychological interventions, as this group comprises the probable majority of depressed individuals seen within routine clinical practice settings.

SO 0403. Pharmacotherapy of neuropsychiatric manifestations of HIV/AIDS

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HIV is an RNA retrovirus causing AIDS, that includes opportunistic infections including the CNS. HIV penetrates the CNS quickly, causing inflammatory and neurotoxic reactions. Neurons do not seem to be infected. Encephalitis and impaired neurogenesis result, as well as myelopathy with spastic paraparesis and sensory ataxia. Most damage occurs in areas involved with movement, memory, and planning. Clinically, the symptoms involve cognitive impairment and psychomotor slowing, but also mania, impulsivity, paranoia, impaired judgement, delirium and hypersomnia. The average survival time for untreated HIV encephalitis is 6–9 months.

HIV-associated dementia occurs in 15–30 per cent of untreated cases, and may be the only presenting symptom of AIDS, and very responsive to HAART (Highly Active AntiRetroviral Therapy).

Other concurrent psychiatric issues are substance use disorders, personality disorders, maladjustment, depression, and psychosis including visual hallucinations and delusions of grandeur. Mania occurs in 4–8 per cent of AIDS patients, and may involve promiscuity and needle sharing that spread the virus.

There is no evidence basis for recommending pharmacotherapy to ameliorate the neuropsychiatric manifestations of HIV/AIDS. Pharmacodynamics and pharmacokinetics of commonly used medications may be altered, and there are multiple confounders, including ethnic interpretations of symptoms, as well as HAART that also may cause CNS adverse effects. Cases have been reported of dramatic and rapid improvement in psychiatric symptomatology and overall health status if HAART is instituted.

Controlled trials are needed in well-defined patient populations that take into account confounders, and employ multiple assessment instruments.

SO 05. Is bipolar depression different from unipolar depression?

SO 0501. Symptoms and course of unipolar and bipolar depression

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Background: To date, there is no prospective information on longitudinal symptom profiles of unipolar (UP) and bipolar (BP) depression in the normal population.

Methods: The Zurich epidemiological study provides diagnoses of UP and BP disorders from seven interviews from age 20/21 to 49/50 (1979 to 2008). The presence of symptoms and treatment was assessed annually in retrospect across thirty years (1978 to 2008); five of the seven interviews (1986 to 2008) assessed the occurrence of 27 depressive and 18 manic symptoms in the past 12 months.

Results: The profiles of the 27 depressive symptoms were almost identical for major UP and BP-II depression; only psychomotor retardation (slow speech and movements) was significantly more frequent in BP-II depression. The onset of depressive symptoms was slightly earlier in BP than in UP depression. In both groups depression recurred in 79%; in another 18% and 15%, respectively, it became chronic, assessed by graphic course patterns. The annual information from ages 20 to 50 showed a more severe course in BP subjects: higher annual presence of symptoms and treatment rates, higher suicide attempt rates (especially in subjects' twenties and forties), higher comorbidity with symptoms of and treatment for anxiety. At age 50 (2008) the outcome of subjects diagnosed from 1979 to 1999: 37% UP and 31% BP received a diagnosis of MDE again and 20% UP 26% BP had been treated for depression; 60% had been symptom-free over the past three years.

Conclusions: the course of BP depression was more severe than UP depression but the outcome was very similar and symptom profiles were almost identical. Suicidality and associated anxiety (panic attacks, GAD etc.) were important in BP depression and increased overall treatment seeking.

SO 0502. A review of the evidence for monotherapy in bipolar depression

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The importance of reaching an accurate diagnosis and the efficacy of available treatment options in patients with bipolar depression are crucial for an appropriate treatment plan. Antidepressants are poorly evidence based for the treatment of bipolar depression. Drugs such as lithium, lamotrigine, the combination of olanzapine with fluoxetine and especially quetiapine have positive data and may be more appropriate as first-line.

The mechanisms of action of atypical antipsychotics that have demonstrated some evidence to support their efficacy in both bipolar mania and bipolar depression, have not been fully elucidated; however, antagonism of dopamine D₂ receptors is believed to underlie their antipsychotic and anti-manic activity. The mechanisms by which atypical antipsychotics improve symptoms in bipolar depression is likely to be multifactorial, comprise several neurological pathways and involve dopamine D₂ receptors, 5-HT receptors, α 2-adrenergic receptors and the noradrenaline transporter (NET). In contrast to other classes of medication, including conventional antipsychotics and serotonin noradrenaline reuptake inhibitors (SNRIs), individual atypical antipsychotics differ considerably in their mechanisms of action and binding affinities for several neuroreceptors.

The potential mechanistic explanations of the clinical antidepressant effects shown with quetiapine have been forwarded following the characterisation of its active human metabolite, norquetiapine (N-desalkylquetiapine). Unlike individual atypicals, norquetiapine is also a potent inhibitor of the noradrenaline transporter (NET). The clinical implications of this attribute are supported by positron emission tomography imaging of NET occupancy in patients treated with quetiapine. Although NET inhibition is believed to contribute to the antidepressant effect of traditional antidepressant therapies, such as tricyclic antidepressants and SNRIs, no other atypical antipsychotic has demonstrated NET inhibition at clinically relevant doses.

A pivotal step in our goal of improving patient outcomes in bipolar disorder is understanding the range of clinical benefits that can be achieved with different therapeutic options.

SO 0503. Augmentation strategies for bipolar and unipolar depression

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Patients with bipolar and unipolar depression require effective treatment to reduce depressive symptoms and improve functional disability. 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. There are similarities on how to treat depressive episodes of bipolar and unipolar depression, but also significant differences that are important in daily clinical practice. The use of antidepressants and mood stabilizers are the most common strategies. Depression dominates the course of bipolar disorder and is associated with significant morbidity and mortality. Nonetheless, the treatment of acute depressive episodes in bipolar disorder remains understudied and controversial. Most treatment guidelines for bipolar disorder advocate first-line monotherapy with conventional "mood stabilizers," especially lithium, for mild to moderate episodes of depression. For more severely depressed patients, the combination of an antidepressant with lithium is recommended first line.

Possible treatment strategies for patients with a depressive episode who are non-responsive to an adequate trial of any antidepressant treatment strategy include switching, combination with another antidepressant with a different mechanism of action, or augmentation with a non-antidepressant drug. Augmentation options include lithium, anticonvulsants benzodiazepines, thyroid hormones and, recently, attention has turned to the atypical antipsychotics, e.g. aripiprazole, olanzapine, risperidone and quetiapine. Several controlled studies show favourable outcomes with combination and augmentation treatment with these antipsychotics in unipolar and bipolar depression.

In unipolar depression lithium as the first-choice augmentation strategy in treating patients with resistant depression is currently the most well-documented augmentation strategy, with more than 30 open-label studies and 10 placebo-controlled studies in the acute treatment of depressive episodes, and has been shown to augment the therapeutic effects of a broad spectrum of antidepressants.

SO 06. Debate: Do the suicide restrictions on antidepressants do more harm than good?

PRO: Do the suicide restrictions on antidepressants do more harm than good?

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In spite of the fact that around two-thirds of suicide victims have current (mostly untreated) major depressive episode, and up-to half of them contact different levels of health-care during the last 4 weeks of their life, over 80% of depressed suicides are untreated or inadequately treated. The most frequent source of medical contact in depression is the suicidality and untreated depression is the major cause of suicide. However, several studies show that successful acute and long-term treatment of unipolar major depression (with antidepressants) and bipolar disorders (with mood stabilizers, antidepressants and/or antipsychotics) markedly reduces the risk of attempted and completed suicide. Given the high prevalence of major depression it is not surprising that the widespread use of antidepressants in the “new SSRI era” appear to have actually lead to a marked decline in suicide rates in most countries with traditionally high baseline suicide rates [3,4]. However, the recently decreased use of antidepressants in children and adolescents seen in USA, The Netherlands and Canada after the FDA black box warnings might be the main cause of a concurrent marked increase in suicide rates in those age-groups [1,2].

On the other hand, however, the meta-analysis of Phase II/III randomized controlled clinical trials on antidepressant monotherapy in unipolar major depression (from which studies the most severe and acutely suicidal patients are excluded therefore no detectable antisuicidal effect could be expected) show a nonsignificant increase of suicidal behaviour in patients taking antidepressants compared to those who are taking placebo. Recent findings show that this small increase in suicidality relates to depression-worsening potential of antidepressant monotherapy (unprotected by mood stabilizers) in subthreshold bipolar depressives (in clinical trials on unipolar depression) and in unrecognized bipolar depressives (in real life situation) [4]. This rarely occurring “suicide-inducing” effect of (some) antidepressants must be small enough to be masked by currently favorable trends in suicide mortality of depressed patients suggesting that the marked suicide restrictions on antidepressants do more harm than good.

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CONTRA: Do the suicide restrictions on antidepressants do more harm than good? NO!

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Reporting and informing professionals and patients on potential risks with the use of medicinal products and to balance these risks versus its proven benefits is one of the key responsibilities of regulatory bodies. Particularly with regard to use of antidepressants regulators have been at the center of a controversy among some medical professionals, the media and the public over two key questions [3]: 1) whether there is a link between antidepressant drug use and the emergence of suicidal ideation and behavior (as well as a rare reports of suicide) in adolescents and young adults, and, if there is such a risk, why the regulatory bodies in the EU and US failed to detect and warn about this risk earlier; and 2) whether the warnings on antidepressants drugs about the risk of treatment emergent “suicidality” in pediatric and younger adult patients resulted in a decrease in diagnosing major depression and prescribing for this population, which would mean an increased risk of undertreatment and reversal in the decline in the annual suicide rate among adolescents and young adults.

For psychiatrists it has been common knowledge that antidepressants might have an early “activating effect” that gives patients the energy to follow through on suicidal impulses before the mood improvement also provided by antidepressants takes effect [2]. It’s still unclear, whether antidepressants only may amplify already existing suicidal thoughts and behaviour or they truly may precipitate them as undesirable effects [1,2]. Therefore warnings in SPC and package leaflet have been intended to make aware professionals and patients, to foster careful diagnosis and to intensify screening for suicidal risks and close monitoring after start of antidepressant treatment. In general regulators strongly believe that approved antidepressants are efficacious, and as a net effect still may reduce risk and rate of actual suicide in the general population over a longer period of time based on their beneficial effects on key symptoms of depression. There was no intention to hamper diagnosis of major depression or to hinder use of antidepressants in patients, who deserve treatment of their serious condition.

The relationship between prescription rate of antidepressants and suicide rates from ecological studies seem to support more a positive net effect with use of antidepressant medication, however, not all studies have shown this.

We therefore recommend a strong cooperation between regulators, professionals and learned societies to inform as good as possible to the best of our patients on these complex issues.

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SO 07. The noradrenergic symptom cluster in depression

SO 0702. The increasing burden of depressive disorder

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In the past years, several epidemiological surveys conducted in general populations and using quite similar sampling and assessment methods have found that the lifetime prevalence of depression is in the range of 10 to 15%. More recently, new epidemiologic surveys conducted in different countries worldwide in the framework of the World Mental Health (WMH) Surveys and using the Composite International Diagnostic Interview as an assessment of mental disorders have provide prevalence rates referring to the DSM-IV classification. As part of this study, a large European study (ESEMED) has reported a 14% lifetime prevalence of mood disorders and a 4.3% annual prevalence, results which are close to the US prevalence rates reported in the NCS Replication study respectively 17.9 and 7.6%. Twelve month prevalence of mood disorders have been found in the WMH Surveys to vary between the countries (0.8 up to 9.6%) with the lowest rates in Nigeria and China and the highest rates in the US, France and Ukraine.

All the studies conducted in depressive disorders have stressed the importance of the mortality and morbidity associated with depression. In fact, the mortality risk and more importantly the suicide risk, must be underlined and its reduction should remain a main target and objective of treatment. Apart from this risk, recent studies have also stress the importance of cardiovascular deaths in depressed patients and, in cardiac patients a higher risk of mortality after myocardial infarction has been reported. Furthermore, the risk of mortality in people suffering from depression seems to be increased with a higher risk in case of comorbid physical illness.

In addition to mortality, impairment and disability associated with depression has been consistently reported in all the epidemiologic studies. Worldwide projections by the WHO for the year 2020 identify

unipolar major depression as the second greatest cause of burden and even the leading cause in developing countries.

Depression affects the life of the subject and is also a huge burden for both the family of the depressed patient and the society.

As a consequence and taking into account the growing impact of depression as a leading cause of burden worldwide in the future, intensive programs and continuous efforts for improving recognition and treatment of depression represent a top rank priority in public health.

SO 0703. The noradrenergic symptom cluster - clinical expression and neuropharmacology

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Signs and symptoms of depression can be linked to one or more monoaminergic systems, specifically the noradrenaline (NA), the dopamine (DA), and the serotonin (5-HT) systems. In particular, the modulation of energy, vigilance, and arousal can be directly linked to the NA system. There is, however, a great deal of overlap in the modulation of the symptoms of depression between these monoaminergic systems. For instance, cognition and motivation are classically considered to be modulated by both the NA and the DA systems. Perturbations in such functions carry a large burden in the ability of depressed patients to deal with their environment, whether it is familial, social, or professional. In the work force, while absenteeism is readily quantifiable and of major importance, it is estimated that presenteeism carries a much larger financial burden.

While it seems logical to use antidepressant medications targeting the NA system in the presence of marked NA symptoms, this approach has not lead to more predictable response. Part of the explanation may derive from the reciprocal interactions between the NA, DA, and the 5-HT systems. For instance when using a selective serotonin reuptake inhibitor (SSRI), 5-HT transmission is enhanced, but at the same time there is a dampening of the activity of NA and DA neurons through inhibitory 5-HT_{2A} and 5-HT_{2C} receptors, respectively. This could explain the remaining fatigue, anergia, anhedonia that are often seen after patients present an overall response to a SSRI. Adding a NA reuptake inhibitor, or switching to a dual 5-HT and NA reuptake inhibitor, may produce additional benefits. In addition, inhibiting NA reuptake increases DA availability in the frontal cortex since DA is mainly cleared by the NA transporters in several brain regions. This could explain

in part the efficacy of the NA reuptake inhibitor atomoxetine in attention deficit disorder.

SO 0704. Improvement of the noradrenergic symptom cluster following treatment with milnacipran

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Depression has a major impact on social functioning and a profound effect on workplace performance resulting in high rates of absenteeism and presenteeism (lost productivity of a worker who is able to work but not to perform optimally). Decreased concentration, mental and physical slowing, loss of energy, lassitude, tiredness, reduced self-care (hygiene) are all symptoms related to reduced noradrenergic activity while depressed mood, loss of interest or pleasure, sleep disturbances, feeling of worthlessness, pessimism and anxiety are symptoms related to the activity of both serotonergic and noradrenergic activity. Social dysfunction thus appears to be related to largely to a noradrenergic dysfunction.

The importance of noradrenergic neurotransmission in social functioning is supported by studies with the specific noradrenaline reuptake inhibitor, reboxetine. In healthy volunteers reboxetine increased cooperative social behavior and social drive. A placebo-controlled study comparing reboxetine with the SSRI, fluoxetine in depressed patients showed significantly greater improvement in social adaptation with reboxetine.

If social adaptation is related to increased noradrenergic activity, SNRIs should be effective in reducing social dysfunction in depressed patients. Two recent studies have examined the effect of milnacipran on social adaptation. A study in 45 depressed patients found that, at the end of the 8 week treatment with milnacipran, 42.2% patients were in remission on the Social Adaptation Self-Evaluation Scale (SASS). In another study in 113 depressed workers or homemakers found mean depression scores were significantly reduced ($p < 0.01$) after 2 weeks whereas the SASS was significantly improved ($p < 0.01$) only after 4 weeks. A preliminary study comparing depressed patients treated by milnacipran (mean 83 mg/d) or paroxetine (mean 35 mg/d) ($n = 15/\text{group}$) showed that milnacipran treatment resulted in a greater number of patients in social remission.

From the limited data available, milnacipran appears to significantly improve social functioning. There is also a first indication that milnacipran may produce a greater effect on social adaptation than the

SSRI, paroxetine. It is hoped that these preliminary data will encourage investigators to measure social dysfunction in future trials of milnacipran.

SO 08. Controversies in resistant depression

SO 0801. Resistant depression state or trait: genetic and clinical evidence?

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The response to antidepressant treatment is still unsatisfactory: about 40–50% of depressed patients do not respond to first antidepressant and about 60% do not reach remission at all leading to the status of resistant depression. Several reasons have been proposed to explain the low rate of response, such as comorbid conditions and psychological and social modulators, nevertheless in the last years a role of genetics has also been reported.

Several clinical factors and gene variants have been reported in association with short term antidepressant response. Age, duration of illness, personality disorders, cognitive status, comorbidities are the strongest clinical factors associated with resistance. Recently a growing number of evidence has been reported also for specific genetic factors: the functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), particularly l allele has been associated with a better response in Caucasian. A significant number of replications are present also for 5-HT_{2a}, 5-HT_{1a}, BDNF, COMT, MAOA, NET, Gbeta3, FKBP5, Pgp, TPH, ACE and GSK-3 β variants, although an high number of failures of replication is reported for these genes. Furthermore new candidate genes have been recently identify through the genome-wide scan approach and multi-sites projects like STAR*D and GENDEP. Among these the more promising are GRIK4, GRIK2 and DTNBP1.

Until now, both clinical and genetic factors have not been univocally linked to resistance, some of them are state dependent but many are trait factors. Probably both clinical and genetic factors are interacting on treatment resistance, like 5-HTTLPR with personality and social modulators. Therefore the possibility to achieve an individualized therapy for resistant depression on the basis of clinical and genetic profile is getting closer, although further study with rigorous methodology and very large samples are clearly required in order to reach this relevant aim.

SO 0802. Do current guidelines interfere with identifying and treating resistant depression?

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The definitions of resistant depression have evolved from a failure to respond to two different antidepressants from different pharmacological classes (CPMP) to a failure to respond to a single antidepressant. The evidence to support the view that switching non-responding patients to treatment with an antidepressant from a different class is useful was never strong and has now been overwhelmed by specific studies carried out by the TRD group. These studies have shown that a definition of failure to respond to two antidepressants of different classes is not soundly based. Waiting for a failure to respond to two antidepressants is slow and potentially dangerous. The evidence suggests that resistant depression should be diagnosed as early as possible and appropriate treatment instituted.

SO 0803. Advances on the treatment of resistant depressionD. Souery^{1,2}, A. Serretti², S. Montgomery², S. Kasper², J. Zohar², J. Mendlewicz²

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It has been estimated that 30 to 45% of adequately treated major depressive disorder episodes fail to achieve an adequate response. The evidence in favour of the strategy of switching to another class of antidepressant in treatment resistant depression has not been adequately tested, consequently a prospective study was undertaken to evaluate the impact of switching strategies.

One hundred ninety patients who failed to respond to a previous antidepressant treatment were randomised to receive either citalopram or desipramine for a period of 4 weeks. Those who failed to respond to these treatments were then treated for a further period of 4 weeks with either maintained on the same antidepressant (citalopram-citalopram and desipramine-desipramine) or switched (citalopram-desipramine and desipramine-citalopram).

Patients receiving citalopram versus desipramine in the first trial were not different for Hamilton Rating Scale for Depression (HRSD), Montgomery Asberg Depression Rating Scale (MADRS), and Clinical Global Impression (CGI) scores while patients assigned to the four different

arms of the second trial were different: in particular non-switched patients reported lower scores in HRSD.

In conclusion this study support the thesis that the switch one antidepressant class to another was not associated with improved response, result that goes in the opposite direction to that predicted by current guidelines.

SO 09. First line treatments post Cipriani**SO 0901. Multiple treatments meta-analysis of antidepressants for major depression: strengths and weakness?**

A. Cipriani

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Multiple treatment meta-analysis is a statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been directly compared. In other words, it is a generalisation of standard pair-wise meta-analysis for A vs B trials, to data structures that include, for example, A vs B, B vs C, and A vs C trials. Multiple treatment meta-analysis (also known as *network meta-analysis*) can summarise RCTs of several different treatments providing point estimates (together with 95% CIs) for their association with a given endpoint, as well as an estimate of incoherence (that is, a measure of how well the entire network fits together, with small values suggesting better internal agreement of the model). Two fruitful roles for MTM have been identified: (i) to strengthen inferences concerning the relative efficacy of two treatments, by including both direct and indirect comparisons to increase precision and combine both direct and indirect evidence; (ii) to facilitate simultaneous inference regarding all treatments in order for example to select the best treatment. Considering how important comparative efficacy could be for clinical practice and policy making, it is useful to use all the available evidence to estimate potential differences in efficacy among treatments. Multiple treatment meta-analyses rely on a strong assumption that studies of different comparisons are similar in all ways other than the interventions being compared. The indirect comparisons involved are not randomized comparisons, and may suffer the biases of observational studies, for example due to

confounding. In situations when both direct and indirect comparisons are available in a review, any use of multiple-treatments meta-analyses should be to supplement, rather than to replace, the direct comparisons. Expert statistical support, as well as subject expertise, is required for carrying out and interpreting multiple-treatments meta-analyses. Multiple treatment meta-analysis has already been used successfully in many fields of medicine and the example of a MTM on antidepressants for major depression will be illustrated and discussed.

SO 0902. Mixed-treatments comparison meta-analysis of antidepressants: implications for everyday clinical practice

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To keep abreast of scientific evidence, physicians need reliable tools for summarizing primary research findings to provide a trustworthy overview of current evidence. The terms review, systematic review, overview, meta-review, meta-analysis and pooled-analysis, although often used interchangeably, refer to different ways of summarizing primary studies' results, with strengths and limitations that should be borne in mind when searching the literature. In addition to these standard methodologies for data pooling, in recent years new statistical techniques have been developed to take into consideration both direct and indirect comparisons among a network of treatments, even when two of the treatments have not been directly compared. Ideally, physicians should combine their own clinical expertise and training with high quality systematic reviews of scientific evidence in order to make optimal decisions about therapeutic interventions. In the field of clinical psychopharmacology, these decisions produce prescriptions issued by physicians, and use of medicines by individuals with psychiatric disorders. The aim of the present talk is to illustrate how the flow connecting evidence to practice deserves careful consideration, as the production of evidence makes little sense if it is not translated into action. Mental health systems that set as a policy priority a commitment to evidence-based practice should try to develop programs to transfer evidence-based treatment recommendations into everyday practice on a continuous basis.

SO 0903. Are direct double-blind comparison the best tests of superiority?

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In the time of EBM meta-analysis has become the preferred method to combine the outcomes of all informative, putatively conflicting studies on the question, whether a certain drug A is superior to a drug B or to placebo. However, it has to be understood that meta-analysis, depending on the applied methodology and depending on the inclusion or exclusion of certain studies can come to inconsistent results, although principally focussing on the same data base. For these and other limitations meta-analysis should primarily be seen as a method to generate hypotheses through an a posteriori analysis of treatment effects but not as the only correct answer to a question of superiority between two treatments.

Considering the traditional experimental methodology of clinical psychopharmacology the only way to test the superior efficacy of a certain drug to another one or to placebo is the direct double-blind comparison. Of course, such a trial has to be performed in the best methodological approach possible, avoiding all kinds of bias and confounders, avoiding especially statistical errors of different kinds etc.

Of course, never can the final result of a trial be seen as a final answer. The empirical methodology of clinical psychopharmacology demands confirmation by at least one other trial. Even then, the empirical process is not finished and e.g. the second trial might generate a negative result, thus conflicting with the two other positive results. This induces questions as to what might be the background for the inconsistent results and then possibly lead again to one or two other studies trying to support the former positive evidence. This is a way of empirical thinking in the sense of falsifications or confirmations.

SO 10. Augmentation in major depressive disorder: Reviewing the role for atypical antipsychotics

SO 1001. When treatment fails – a review of the evidence for atypical antipsychotics as an augmentation strategy in major depression

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Although there are many drugs available for the treatment of major depressive episodes, the overall

treatment outcome of depressed patients is usually far from optimal. Regardless of the initial choice of antidepressant, about 30% to 50% of patients with a major depressive episode will not respond sufficiently to adequately performed first-line treatment. Numerous treatment strategies have been described for use in antidepressant non-responder and treatment-resistant depression. Augmentation treatment strategies involve adding a second drug other than an antidepressant to the treatment regimen when no response or only partial response has been achieved, with the goal of enhancing treatment. Augmentation agents that have been studied include almost all classes of psychotropic medications, and include lithium salts, thyroid hormones, antipsychotics, benzodiazepines, anticonvulsants, psychostimulants and buspirone. One advantage of augmentation is that it eliminates the period of transition between one antidepressant to another and builds on the partial response. Consequently, when they work, augmentation strategies can have a rapid effect. Secondly, augmentation is of benefit for patients who have had some response and may be reluctant to risk losing that improvement. In this presentation, the current available evidence for the efficacy of atypical antipsychotics will be reviewed.

SO 1002. Symptom control – an important outcome for depressed patients

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The efficacy of antidepressant monotherapy is limited to partial response in a significant number of patients with major depressive disorder (MDD). Although rapid resolution of core depressive symptoms is important, the presence of residual symptoms is problematic and associated with greater illness severity, increased risk of relapse and suicide, and greater functional and occupational impairment [1–4]. Residual anxiety symptoms may reduce daily functioning and sleep quality and increase symptom severity and risk of relapse [3]. The recent STAR*D report of a secondary data analysis to compare antidepressant treatment outcomes for patients with anxious and non-anxious depression concluded that anxious depression is associated with poorer acute outcomes, including slower remission and response to treatment, than non-anxious depression [5]. Recently the effect of aripiprazole and quetiapine on the symptoms of anxiety in MDD has been investigated. Aripiprazole, adjunctive to antidepressants, has shown efficacy in patients with MDD with anxious features [6]. Adjunctive extended release

quetiapine fumarate (quetiapine XR) has demonstrated efficacy in MDD and has also been shown to improve symptoms of anxiety in MDD patients [7]. Another important symptom of depression is sleep disturbance which can significantly impact the quality of life of patients with MDD and is a risk factor for recurrence and suicide [1]. Adjunctive quetiapine XR has shown significant restoration of sleep and improvement of sleep quality in patients with MDD [8]. This presentation will look at the symptoms of depression, the impact of residual symptoms on outcomes and review the evidence for atypical antipsychotic augmentation as a treatment strategy for managing incomplete response.

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SO 11. Treatment mechanism in obsessive compulsive disorders (OCD)

SO 1101. Augmentation strategies in resistant obsessive-compulsive disorders (OCD)

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Treatment resistance is a very frequent situation in Obsessive Compulsive Disorder, which may occur at different stages during all the course of illness, having a strong impact on the long-term prognosis of the disease. Epidemiologic studies indicate a prevalence of treatment-resistant patients around 40–60%. Augmentation strategies for treatment-resistant patients are numerous, ranging from cognitive-behavioural therapy to dopaminergic (both agonists and antagonists), serotonergic (intravenous serotonergic agents, 5-HT₃ antagonists etc.) and glutamatergic agents (topiramate, memantine etc.), and a number of them seem to have a quite good efficacy [1,3,7,8]. In front of all these possibilities how can the clinician choose the best one for any individual patient? Current research on animal and human models suggests that the discovery of more precise and distinctive

neurofunctional targets is possible and that may successfully lead to a patient-tailored treatment algorithm. For example, a treatment based on atypical antipsychotics could in the future be reserved for patients with a dysfunction of the anterior cingulate networks [2], as well as ondansetron for those with an impairment of pre-pulse inhibition startle reflex [5,6] and dextroamphetamine for those with deficits in working memory functioning [4]. Categorizing the patients and basing the treatment on reliable and easily detectable neurodysfunctional targets, in order to offer an evidence based high specific therapy is one of the most desirable and exciting goals that in the next future may be achieved.

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SO 1102. Cognitive dimensions of obsessive-compulsive disorders; any relevance for treatment?

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Obsessive-compulsive disorders are characterised by the irresistible urge to perform a narrow repertoire

of compulsive behaviours. In obsessive compulsive disorder (OCD), recurrent intrusive thoughts (obsessions) and repetitive unwanted acts (compulsions) are focussed around key themes such as aggression, cleanliness, order and completeness. Of the putative OCD ‘subtypes’, early onset illness, hoarding/symmetry compulsions and comorbid motor tics appear to predict the greatest resistance to conventional treatment with serotonin reuptake inhibitors (SRIs).

A growing body of evidence implicates failure in top-down cortical inhibition of striatally mediated habitual activity in the pathogenesis of OCD and related disorders (Chamberlain S et al 2008). Neuropsychological and brain imaging studies in OCD patients and their unaffected first degree relatives revealed performance and/or neural processing deficits in [1] reversal learning, [2] extradimensional attentional set-shifting and [3] motor impulsivity; behaviours that are normally modulated by [1] serotonin, [2] dopamine and [3] noradrenaline, respectively. These impairments are thought to contribute toward the development of ‘cognitive inflexibility’ and ‘motor impulsivity’ as endophenotypic traits within OCD families.

The influence of these neurocognitive dimensions on treatment response remains inconclusive. O-C disorders such body dysmorphic disorder, schizophrenia with OCD (Patel DD et al 2010) and obsessive compulsive personality disorder share hallmark cognitive inflexibility with OCD and also appear somewhat responsive to SSRI treatment. In contrast, trichotillomania and pathological skin picking show motor impulsivity and may respond less well to SRIs. A subgroup of pathological skin pickers with cognitive inflexibility was identified that selectively responded positively to treatment with lamotrigine [3].

These results suggest that neurocognitive endophenotypes such as cognitive inflexibility and motor impulsivity, that reflect functional changes within the relevant cortico-striatal circuitry, are differentially expressed across the spectrum of O-C disorders. Further investigation of ‘cross-cutting’ neurocognitive dimensions may be of value in identifying factors associated with treatment outcome in O-C disorders.

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SO 1103. Do imaging studies improve treatment strategies in obsessive-compulsive disorders (OCD)?

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Neuroimaging studies have clearly demonstrated that obsessive-compulsive disorder (OCD) is related to pathology of various brain circuits within the cortico-striato-thalamic network. The anxiety

symptoms and inadequate fear responses pathognomonic for OCD may result from inadequate dorsal prefrontal-striatal control of the amygdala. Cognitive and behavioral inflexibility in OCD is reflected by impairments in response inhibition and attentional set-shifting due to dysfunctional frontal-striatal circuitry. Alternatively, OCD can be conceptualized as a disorder of behavioral addiction with a dependency on repetitious, self-defeating behavior and defective processing of natural rewards. Reward processing is critically dependent on dopaminergic (DA) neurotransmission in ventral striatal-orbitofrontal circuitry. Imaging studies in OCD have consistently shown abnormal activation within this circuitry. In this lecture, a review of neuroimaging studies in OCD, including our own imaging data on reward processing and the DA system will be presented. Modulation of DA reward circuitry may be an important new avenue for OCD treatment.

P 01. The effects of typical and atypical anti-psychotics on inducing obsessive-compulsive symptoms in patients with schizophrenia

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Objective: The impact of typical and atypical anti-psychotics on developing obsessive-compulsive symptoms in schizophrenic patients were investigated in this study.

Materials and methods: 64 schizophrenic patients (32 cases in typical anti-psychotics group and 32 in atypical anti-psychotics group) participated in the study. All the patients first interviewed by SCID and then Yale Brown Obsessive-Compulsive Scale (Y-BOCS) and Brief psychiatric Rating Scale were administered in the beginning, 3 weeks and 6 weeks after treatment. The Data then transferred to SPSS program. for analysis.

Results: In typical group the mean scores of Y-BOCS were 2.40, 2.30 and 2.18 in the beginning, 3 weeks and 6 weeks after treatment. In atypical group the mean scores of Y-BOCS were 4.12, 4.46 and 4.53 in three trials. There were no significant differences in the mean scores of Y-BOCS of two group in the beginning of the trial although a trend toward significance was observed but the differences between scores were significant in trial 2 (3 weeks) and trial 3 (6 weeks).

Discussion: based on this study and in line with previous studies, atypical anti-psychotics may induce obsessive compulsive symptoms (although mild) in patients with schizophrenia. Despite the importance of family history of OCD in clinical manifestations of obsessive-compulsive symptoms, the impact of this factor on reduction or induction of those symptoms was weak.

P 03. The many faces of anxiety in later life

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Background: Anxiety disorders in late life are often underestimated and unrecognized. Some epidemiologic studies have found lower rate of anxiety disorders in elderly. In fact, anxiety is common in this age. Generalized anxiety disorder (GAD), mixed anxiety-depressive disorder, panic disorder, depression with anxiety symptoms (anxious depression) and nonspecific anxiety symptoms that do not fall under a

specific anxiety disorders are some of the many faces of anxiety in elderly.

Aim and method: We examined 80 patients, aged across 55–84 years in acute psychiatric setting for the presence of a current anxiety disorder. All subjects underwent clinical psychiatric examination and evaluation according to ICD-10 criteria for depression and anxiety disorder. Hamilton Depression Rating Scale (HAM-D-17) and Hamilton Anxiety Rating Scale (HAM-A) were applied to evaluate the severity of depression and anxiety. The patients were examined also for a physical comorbidity.

Results: Anxiety was common found in adults with depression both as a symptom and as a coexisting disorder. The largest group consisted of depressed patients experiencing mild to moderate anxiety symptoms (53.75%). Next were the patients with coexisting anxiety and depressive disorder (36.25%). Solitary GAD was less seen (6.25%). Most difficulties arouse in differentiation between GAD and anxious depression in advanced age, while in older age anxiety was less present. Principally, there is a substantial symptom overlap between depression and anxiety. The careful eliciting of depression core symptoms helps diagnosis in such cases. We found out high physical comorbidity in terms of cardiovascular, endocrine, gastrointestinal and neurological issues.

Conclusions: In our study we found out a relatively high rate of anxiety among elderly. Older adults tend to somatize psychiatric problems, have multiple psychiatric medical and medication issues. Anxiety is often but not invariably secondary to depression. Anxiety disorders and anxious depression were generally associated with high physical comorbidity. Additional research is needed to identify more clearly patterns of anxiety variation in advanced age.

P 04. Effects of cholinergic system of medial prefrontal cortex on anxiety-related behaviors

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Medial prefrontal cortex is a brain region that plays an important role in anxiety. In the present study, we investigated possible influence of cholinergic system of medial prefrontal cortex (MPC) on anxiety-like behaviors. Elevated plus maze which is one of the methods used for testing of anxiety is used in our present study. Rats were anaesthetized with ketamine and xylazine and special cannulas were inserted stereotaxically into the MPC. After 1 week recovery,

the effects of intra-MPC administration of physotigmine (5, 10 and 50 ng/rat) and atropine (1, 2 and 4 µg/rat) on percentage open arm time (OAT%) and percentage open arm entries (OAE%) were determined.

Bilateral administration of physotigmine into MPC decreases the OAT% OAE%, indicating anxiogenic-like effect. Intra-MPC injection of atropine, a cholinergic receptor antagonist increased the both OAT% and OAE%, parameters of anxiolytic-like behavior.

Results of the present study, demonstrate that activation cholinergic system in this area produce an anxiogenic-like response while inhibition of metabotropic cholinergic receptors produce an anxiolytic-like response.

P 05. A double-blind, placebo-controlled study of augmentation with LY2216684 for major depressive disorder patients who are partial responders to selective serotonin reuptake inhibitors

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Background/Aims: Many patients treated with selective serotonin reuptake inhibitors (SSRIs) for major depressive disorder (MDD) achieve clinically meaningful benefit, but experience residual symptoms and impairment. LY2216684 HCl (2-Morpholinemethanol, α -[(5-fluoro-2-methoxyphenyl) methyl]- α -(tetrahydro-2H-pyran-4-yl)-, hydrochloride, (α R, 2S)) is a selective norepinephrine reuptake inhibitor. This study examined whether adjunctive treatment with LY2216684 improved outcomes in patients with MDD who were partial responders to SSRIs.

Methods: This was a double-blind, placebo-controlled, 11-week trial with adjunctive flexibly dosed LY2216684 6–18 mg once daily or placebo. Key inclusion criteria were SSRI treatment for \geq 6 weeks, partial response by investigator's opinion, and GRID 17-item Hamilton Depression Rating Scale total score \geq 16. The primary outcome measure was mean change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score. The prespecified primary evaluable sample was patients who improved $<$ 25% on the Quick Inventory for Depression Scale Self-Report 16 items total score during a 2-week double-blind placebo lead-in period. Secondary measures included remission rate (MADRS \leq 10), Sheehan Disability Scale global functioning impairment score, and Fatigue Associated with

Depression scale scores. Tolerability and safety outcomes were assessed.

Results: Of 227 patients (placebo, N = 111; LY2216684, N = 116), 69.6% were female; mean age = 45.4 years. LY2216684-treated patients had numerically greater improvement in MADRS total score ($p = 0.18$), greater rates of remission ($p = 0.044$), greater improvement in overall role functioning ($p = 0.039$), and greater reduction of functional impact of fatigue ($p = 0.012$) compared with placebo-treated patients. In the LY2216684 group, the most frequent treatment-emergent adverse events were hyperhidrosis (7.2%, $p = 0.017$), nausea (7.2%, $p = 0.129$), dizziness (4.5%, $p = 0.113$), and erectile dysfunction and testicular pain in males (6.3% for both events, $p = 0.211$). LY2216684-treated patients significantly differed from placebo-treated patients in the mean changes in standing pulse rate (placebo = 0.51 bpm [SE = 1.05], LY2216684 = 7.18 [SE = 1.04]; $p \leq 0.001$) and diastolic blood pressure (placebo = -0.60 mmHg [SE = 0.74], LY2216684 = 1.99 [SE = 0.74]; $p = 0.012$).

Conclusions: Adjunctive treatment with LY2216684 for patients with MDD who had a partial response to SSRIs was associated with higher remission rates and improved functioning compared with placebo; it was well-tolerated.

P 06. Pooled analysis of the efficacy of adjunctive quetiapine XR in patients with major depressive disorder and high or low levels of baseline anxiety

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Background: Patients with MDD and high anxiety levels typically experience more severe depression and functional impairment than patients with low anxiety. Effects of once-daily extended release quetiapine fumarate (quetiapine XR) adjunct to antidepressants (AD) in patients with MDD and high or low baseline anxiety levels were investigated.

Methods: Pooled data from two (D1448C00006/D1448C00007) 6-week, double-blind, randomised, placebo-controlled trials in patients with inadequate response to AD were analysed. Patients received

adjunctive quetiapine XR (150mg/day or 300mg/day) or placebo + AD. Primary endpoint (both studies): change in MADRS total score versus placebo + AD. Secondary endpoints included: Week 6 change in MADRS, HAM-A and CGI-S total scores in patients with high or low baseline anxiety levels, defined as HAM-A total score ≥ 20 or < 20 , respectively.

Results: For patients with high baseline anxiety levels ($n = 433$), adjunctive quetiapine XR 300mg/day (-15.92 , $p < 0.05$) but not 150mg/day (-15.20 , $p = 0.122$) significantly reduced MADRS total scores versus placebo + AD (-13.49) at Week 6. Adjunctive quetiapine XR 300mg/day significantly improved HAM-A total score (-12.19 , $p < 0.05$) and CGI-S total score (-1.68 , $p < 0.05$) versus placebo + AD (-10.18 , -1.37 , respectively) at Week 6; reductions with adjunctive quetiapine XR 150mg/day at Week 6 were -11.70 ($p = 0.082$) and -1.60 ($p = 0.131$) for HAM-A and CGI-S total scores, respectively.

For patients with low baseline anxiety levels ($n = 486$), adjunctive quetiapine XR 150mg/day (-13.99 , $p < 0.001$) and 300mg/day (-13.98 , $p < 0.001$) significantly improved MADRS total scores versus placebo + AD (-10.83) at Week 6. Adjunctive quetiapine XR 150mg/day and 300mg/day significantly improved HAM-A total score (-6.59 , $p < 0.01$; -6.48 , $p < 0.05$) and CGI-S total score (-1.63 , $p < 0.001$; -1.52 , $p < 0.01$) at Week 6 versus placebo + AD (-4.93 , -1.16 , respectively).

Reported adverse events were similar in both cohorts and were consistent with the known tolerability profile of quetiapine.

Conclusions: In patients with MDD and inadequate response to prior AD, adjunctive quetiapine XR was effective at reducing depressive and anxiety symptoms in patients with high (quetiapine XR 300mg/day) and low (quetiapine XR 150 and 300mg/day) baseline anxiety levels.

Research funded by AstraZeneca Pharmaceuticals.

P 07. Predictive factors of remission for treatment-resistant major depressive disorder (MDD) during treatment with extended-release quetiapine fumarate (quetiapine XR)

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Aim: To explore predictors of remission for patients with treatment-resistant MDD receiving quetiapine XR.

Methods: Post-hoc analysis of data from a 6-week, randomised, open-label, rater-blinded study (NCT00789854) in adults with treatment-resistant MDD (non-responders to 1 or 2 adequate trials of major classes of antidepressant [AD], MADRS total score ≥ 25). Treatment: add-on quetiapine XR (300 mg/day) to ongoing AD therapy, quetiapine XR monotherapy (300 mg/day) or add-on lithium (0.6–1.2 mmol/L). Primary efficacy evaluation: change in MADRS total score from randomisation to Week 6 (pre-specified non-inferiority limit 3 points). Remission definition: MADRS total score ≤ 10 points; a univariate logistic regression approach was used to determine variables predictive for remission.

Results: 688 patients randomised (add-on quetiapine XR [$n = 231$], quetiapine XR monotherapy [$n = 228$], add-on lithium [$n = 229$]). At Week 6, add-on quetiapine XR and quetiapine XR monotherapy were non-inferior to add-on lithium; least squares mean differences in MADRS total score changes: -2.32 (95% confidence interval [CI]: -4.6 , -0.05), which is above the 2 points judged to be clinically relevant, and -0.97 (95% CI: -3.24 , 1.31), respectively. MADRS remission rates: 31.9%, 23.6% and 27.1% for add-on quetiapine XR, quetiapine XR monotherapy and add-on lithium, respectively (no significant differences between groups). The post-hoc analysis identified 22/127 variables that had predictive value for remission including time since first known psychiatric disorder ($p < 0.0001$), time since first known depressed episode ($p = 0.0001$), time since first MDD diagnosis ($p = 0.0016$), time in present episode ($p < 0.0001$), state anxiety ($p = 0.0438$), trait anxiety ($p = 0.0245$) and low anxiety. Plasma lithium concentration (add-on lithium group) within the therapeutic window (0.6–1.2 mmol/L) at end-of-study was also predictive for remission ($p = 0.0239$), while the absolute lithium concentration was not. Sensitivity analyses showed response ($> 50\%$ improvement in MADRS total score) was predicted by the same variables as for remission.

Conclusions: Time and anxiety variables offered the greatest predictive value, with longer time or

higher anxiety associated with a lower likelihood of attaining symptomatic remission or response.

Analysis funded by AstraZeneca Pharmaceuticals.

P 08. Adjunctive quetiapine XR and its effects on sleep disturbance and quality: a pooled analysis from two acute studies in MDD

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Background: Disrupted sleep is common in depression. Effects of once-daily extended release quetiapine fumarate (quetiapine XR) adjunct to ongoing antidepressant (AD) on restoration of sleep and sleep quality in patients with MDD and an inadequate response to prior AD were investigated.

Methods: Pooled data from two (D1448C00006/D1448C00007) 6-week, double-blind, randomised, placebo (placebo + AD)-controlled studies of adjunctive quetiapine XR (150mg/day and 300mg/day) were analysed. Primary endpoint (both studies): change in MADRS total score versus placebo + AD. This post hoc analysis was based on the following secondary endpoints: change from randomisation in MADRS item 4 (reduced sleep), HAM-D items 4, 5 and 6 (insomnia-early, -middle and -late, respectively), sleep disturbance factor (HAM-D items 4 + 5 + 6) and sleep quality (PSQI global score). Change in MADRS total score in patients with baseline HAM-D sleep disturbance factor score ≥ 4 or < 4 , (high and low sleep disturbance, respectively), was evaluated.

Results: 939 patients randomised; MITT population included 919 patients: adjunctive quetiapine XR 150mg/day (n = 309), 300mg/day (n = 307), placebo + AD (n = 303). At Week 6, adjunctive quetiapine XR reduced MADRS item 4, HAM-D sleep disturbance factor, HAM-D items 4, 5 and 6 and PSQI global scores from baseline ($p < 0.001$, both doses versus placebo + AD). In patients with high baseline sleep disturbance (n = 226, adjunctive quetiapine XR 150mg/day; n = 215, 300mg/day; n = 210, placebo + AD), adjunctive quetiapine XR improved ($p < 0.01$) MADRS total score versus placebo + AD from Week 1. In patients with low baseline sleep disturbance (n = 83, adjunctive quetiapine XR 150mg/day; n = 92, 300mg/day; n = 93, placebo + AD), adjunctive quetiapine XR (both doses) improved MADRS total score versus

placebo + AD at Weeks 1 ($p < 0.01$) and 2 ($p < 0.05$) only.

Conclusions: Adjunctive quetiapine XR significantly restored sleep and improved sleep quality in patients with MDD and an inadequate response to prior AD. In patients with high baseline sleep disturbance, adjunctive quetiapine XR improved depressive symptoms from Week 1. For patients with low sleep disturbance, a smaller sample size limited the statistical power; however, adjunctive quetiapine XR was effective in these patients.

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P 10. Improvement of sexual function in depressed outpatients treated with milnacipran

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Impaired sexual function and enjoyment is a symptom of depression which usually improves in parallel with other depressive symptoms. Many classes of antidepressant, however, can exert adverse effects on sexual function and enjoyment. It is thus often difficult to determine the effect of an antidepressant on sexual function (improved sexual function through an improvement of depressive symptoms but drug-induced sexual dysfunction through adverse effects). In addition, variation in the willingness to discuss sexual function complicates any analysis.

The sexual function and enjoyment questionnaire (SFEQ) has been developed to assess sexual function in depressed men and women. Five questions ask the patient to compare the level of various aspects of their sexual activity with their normal levels (before the depressive episode). For each question patients can reply that the levels were “reduced a lot”, “reduced a little”, were “the same”, were “increased a little”, or “increased a lot”.

A 12-week open study evaluated the effects of the serotonin-noradrenaline reuptake inhibitor, milnacipran, in the treatment of 80 (64 women and 16 men) outpatients with major depression in Brazil. In addition the SFEQ was used to assess sexual functioning.

The mean Hamilton Depression Rating (HAMD) scores decreased progressively throughout the study. At end-point 61% of patients were responders ($> 50\%$ reduction of baseline HAMD score), and 17.5% were in remission (HAMD < 8 for at least 2 weeks). At baseline, for all five questions, over 60%

of patients replied “reduced a lot” or “reduced a little”. All SFEQ items improved throughout the study and the differences between the values at baseline and the 12 week end-point was all highly significant ($p < 0.001$) with the exception of the specific questions to men due to the small number of men in the study population. At end-point 60% of patients said their sexual desire was as great as or better than it had been before their depressive episode.

Milnacipran appears to improve sexual function in parallel with other symptoms of depression with no tendency to aggravate any aspects of sexual dysfunction at any time point.

P 11. Is poor insight in obsessive-compulsive disorder a distinct subtype?

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Background: Poor insight in Obsessive Compulsive Disorder (OCD) has been found to be associated with higher disease severity, co-morbidity and poorer treatment outcome. The aim of the study was to explore the phenotypic differences of good and poor insight OCD in a large sample of adult patients with DSM IV OCD.

Methodology: We reviewed the clinical records of all patients evaluated in a specialty OCD clinic in India from 2004–2009. Subjects had been evaluated using the specially devised topical OCD evaluation proforma, the Yale-Brown Obsessive Compulsive Scale (YBOCS), the Mini International Neuropsychiatric Interview (MINI) and the Clinical Global Impression (CGI) scale. A diagnosis of OCD was made according to the DSM-IV criteria. Insight was measured using the Y-BOCS item 11; those with a score of 0 (excellent insight) and 1 (good insight) were considered to have “good insight” and those with ratings 2 to 4 (fair to delusional) were considered to have “poor insight”.

Results: Among 545 subjects, 395 patients (72.5%) had good insight and 150 patients (27.5%) had poor insight. The poor insight group compared to good insight group had higher score on YBOCS compulsions (12.33 ± 4.41 Vs 10.30 ± 5.58 , $p < 0.01$) and total score (25.14 ± 6.51 Vs 22.61 ± 8.65 , $p = 0.01$). Poor insight group was overrepresented by obsessions pertaining to contamination (68.0% Vs 53.4%, $p = 0.003$), need for symmetry (38.0% Vs 26.6%, $p = 0.009$) and compulsions of washing (69.3% Vs 51.1%, <0.001), ordering (40.0% Vs 30.4%, $p = 0.033$), collecting (16.7% Vs 9.4%, $p =$

0.017) and pathological slowness (22.7% Vs 13.7%, $p = 0.011$). However, poor insight OCD had a lower frequency of aggressive (24.0% Vs 38.2%, $p = 0.002$) & sexual obsessions (21.3% Vs 29.9%, $p = 0.002$). There were significantly less number of subjects with “predominantly” obsessions in poor insight group (6.0% Vs 14.2%, $p = 0.004$). In regression analysis, higher score on compulsions, less frequent aggressive obsessions and presence of washing compulsions and pathological slowness predicted poor Insight OCD and explained 73.2% variance.

Conclusions: Poor insight OCD may represent a distinct subtype with greater severity and difference in the clinical profile. Future studies should examine the neurobiological substrates of poor insight by employing neuropsychological and neuroimaging techniques.

P 12. Plasma serotonin level of vietnam war veterans with posttraumatic stress disorder and symptom severity

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Objective: This study was conducted to examine the relationship between plasma serotonin levels and post traumatic stress disorder(PTSD) symptoms in chronic PTSD patients with long term pharmacological treatment.

Methods: Fourteen Vietnam War veterans with chronic PTSD and 28 non-PTSD patients were recruited consecutively. Combat exposure scale(CES), Mississippi scale for combat-related posttraumatic stress disorder (M-PTSD), clinician administered PTSD scale (CAPS), Hamilton rating scale for depression (HAMD), and Hamilton anxiety scale (HAMA) were used to evaluate PTSD symptom severity. We measured plasma serotonin levels by high performance liquid chromatography (HPLC).

Results: The plasma serotonin levels were significantly higher in PTSD group than control group (1st $p = 0.036$, 2nd $p = 0.006$). The score of M-PTSD ($p < 0.001$), CAPS($p < 0.001$), HAMD ($p < 0.001$), and HAMA ($p < 0.001$) were significantly higher in PTSD group than control group. There were no significant relationships between plasma serotonin and PTSD symptoms.

Conclusion: Though the level of plasma serotonin were higher in chronic PTSD patients with long-term pharmacological treatment than non-PTSD patients, the core symptoms of PTSD appeared partially in

PTSD patients. It might be related with various neurotransmitter systems. Therefore further research is needed for other neurotransmitters, a neuroendocrine system and so on to improve treatment of PTSD.

P 13. Demographic, clinical and treatment-related resistance features of Treatment Resistant Depression subjects: preliminary results

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Background: Treatment resistance is relatively common among patients with Major Depressive Disorders and accounts for an important part of human suffering and social burden caused by depression. A systematic assessment of Treatment Resistant Depression (TRD) population is still needed to reduce important cause of resistance.

Aims. The study aimed to detect clinical demographic and treatment-related resistance features of a TRD sample.

Method: Fortyseven inpatients with a Bipolar or Unipolar Depression diagnosis according with DSM-IV-TR criteria, Thase and Rush criteria for TRD at least stage I, Montgomery-Asberg Depression Scale (MADRAS) score > 21 were included in the study. Diagnosis was conducted according Structured Clinical Interviews. Thase and Rush and Massachusetts General Hospital criteria have been used to assess treatment resistance.

Results: TRD sample, MADRAS mean score 32 + 10 was mainly composed by middle aged female, (78.7%), mainly housewives (25.5%), employees (23.4%), or retired (21.3%). Bipolar depression I and II have been the most frequent diagnosis (68.2% and 38.3% respectively). First onset episode was 100% depressive. Most frequent depressive subtype was melancholic (70.2 %), and the majority of the sample (70,2%) show an anxiety disorders axis I co-morbidity. Forty six percent of the sample show a personal history of on-treatment relapse: mainly an augmentation therapy resistance (61.7%: Lamotrigine, 89.6% Dopamine-agonists, 62%, Aripiprazole 55%) and antidepressant combination resistance (53.2%) while 46.8% show a mono-therapy resistance.

Conclusions: Female middle aged subjects with a bipolar diathesis and a bipolar melancholic depression first onset depressive episode, a history of on-treatment relapse with axis I anxiety co-morbidity should be considered a treatment resistant depression population. Treatment-related resistance interested

TCA- SSRI combination, SSRI or SRNI antidepressant mono-therapy and augmentation strategies with lamotrigine, Dopamine-agonists, and Aripiprazole.

P 14. Antipsychotics in treatment-resistant obsessive-compulsive disorder – a systematic review

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Introduction: Since only about 40–60% of all patients with obsessive-compulsive disorder (OCD) respond to treatment with serotonin reuptake inhibitors (SRIs), the evaluation of alternative approaches in the therapy of treatment-resistant OCD has high clinical relevance. Based on the hypothesis of dopaminergic hyperactivation in OCD, many studies have examined additive medication with antipsychotics.

Method: Double-blind randomised controlled studies (DBRCTs) that evaluated the efficacy of a combination therapy of antipsychotics and SRIs in treatment-resistant OCD were covered by systematic literature searches.

Results: A total of ten DBRCTs were identified (four for quetiapine, three for risperidone, two for olanzapine and one for haloperidol) with a participant collective comprising in total 312 OCD-patients. In the augmentation group (antipsychotic + SRI), significantly more subjects fulfilled the response criterion (reduction in the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) greater than 35%) than in the control group (placebo + SRI) (relative risk (RR) = 2.08; 95% CI: 1.3 – 3.32). The standardised mean difference (SMD) of the Y-BOCS reduction between the antipsychotics group and the placebo group also revealed an efficacy in favour of the additional antipsychotic medication (SMD = 0.62, 95% CI: 0.31 – 0.94). The sub-group analysis showed significant efficacy for risperidone only, but not for quetiapine and olanzapine.

Conclusion/Discussion: Based on the favourable relation between efficacy and undesirable effects, risperidone can be regarded as the agent of first choice for augmentation treatment with an SRI. Overall, about one third of patients benefit from this therapy option. However, further scientific studies, mainly with a larger dose of the antipsychotics, are needed before sufficiently empirically secured pharmacological treatment recommendations can be expressed. At the present time it appears unclear as to whether the therapeutic effects of the atypical antipsychotics in therapy-resistant OCD are primarily attributable to antagonism on the dopamine D2 receptor or on the serotonin 5-HT_{2A} receptor.

P 15. The role of the 5-HT_{2C} receptor sub-type in preclinical models of obsessive compulsive disorder

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The involvement of serotonergic function in the pathogenesis of OCD was founded on the efficacy of serotonin reuptake inhibitors (SRIs) in its treatment. Selective serotonin reuptake inhibitors (SSRIs) are now well established in the therapeutic arsenal for obsessive-compulsive disorder. However their effect is imperfect with 40–60% of treated patients failing to respond to an adequate dose or duration of treatment and side effects are common. It is important that new, more effective treatments with fewer side effects be identified. The efficacy of the new antidepressant agomelatine has been investigated in depression and given its selectivity for 5-HT_{2C} antagonism has been researched in animal models approximating to OCD; its efficacy in OCD remains to be established in clinical trials.

Aim: To integrate published findings relating to the involvement of the 5-HT_{2C} receptor in preclinical (animal and human) models of obsessive-compulsive disorder.

Method: A PubMed literature search was performed using the terms: obsessive-compulsive disorder; obsessive; compulsive; serotonin 2c; serotonin 2c receptor; 5-HT_{2C} and 5-HT_{2C} receptor. Research papers on the investigation of the 5-HT_{2C} receptor in animal models of OCD and in humans with OCD were identified.

Results: In rats, binding of serotonin to the 5-HT_{2C} receptor results in the inhibition of dopamine (DA) and noradrenaline (NA) release in the striatum, prefrontal cortex, nucleus accumbens, hippocampus, hypothalamus and amygdala. Antagonism of the receptor leads to an increase of DA and NA in the prefrontal cortex [1]. Excessive self-grooming in animal models of obsessive-compulsive disorder (OCD) is a possible equivalent of compulsive behaviour in OCD patients. Activation of the serotonin_{2c} (5-HT_{2C}) receptor induces self-grooming in rats, which result supports the hypothesis that selective stimulation of central 5-HT_{2C} receptors exacerbates symptoms in OCD [3]. Obsessive-like behaviours are also observed in 5-HT_{2C} receptor knockout mice [2] and in rats administered the potent non-selective 5-HT_{2C} receptor agonist m-chlorophenylpiperazine (mCPP) that can be abolished by pre-treatment with an SSRI [5]. In

addition, patients with OCD experienced an exacerbation of O-C symptoms when mCPP was administered. This effect was prevented in patients first treated with clomipramine [6]. Agomelatine, but not its constituent components, suppressed stress induced glutamate release in the pre-frontal and frontal cortex of stressed rats, suggesting a possible role in anxiety and OCD [5].

Conclusions: Altered 5-HT_{2C} activity has been identified in plausible animal and human models of OCD and may be implicated in the pathogenesis and treatment of OCD.

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P 16. Treating depression in Parkinson's disease with electroconvulsive therapy

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The association between depression and Parkinson's disease is common, as is the difficulty to treat it with tricyclic antidepressants due to the anticholinergic effects or with ineffective selective reuptake inhibitors.

23 patients, with Parkinson's disease and severe and persistent depression resistant to antidepressant

medication, were submitted to electroconvulsive therapy:

Frequency: three times a week

Number of treatment: 12 sessions

Parameters: 100 Hz; 800 mA; 1152 milli-Coulombs

Stimulus electrode placement: bifrontal

During phase-out: 1 treatment every 15 days for 2 months was prescribed followed by 1 treatment per month for 4 months.

The following results were found:

Remission of symptoms of depression, improvement of motor impairment in 19 patients with maintenance of benefits for 20 months without the need to restart electroconvulsive therapy. The patients did not present delirium or cognitive impairment.

4 patients showed remission of symptoms of depression and of motor impairment, but the symptoms reappeared after 3 months. However they also did not present delirium or cognitive impairment.

The results obtained in 19 of the 23 patients suggest that electroconvulsive therapy is an excellent treatment for depression in Parkinson's disease, under the conditions in which it was administered.

P 17. Identifying CYP2D6 intermediate and poor metabolizers among schizophrenic patients with respect to therapeutic response

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Background: CYP2D6 is highly polymorphic enzyme which plays a pivot role in metabolism of xenobiotics, especially psychotropic drugs. Predicting its metabolic activity in patients may help to personalize pharmacotherapy. The aim of the study was to investigate relationship between CYP2D6 genotype and treatment response assessed as PANSS score decrease.

Methods: 22 patients with first episodes of schizophrenia treated with risperidone were included in the study. PANSS score was assessed weekly; reduction of the severity of symptoms in items P1, P2, P3, G5, G9, N1, N4, N6 of PANSS to ≤ 3 was considered as remission; CYP2D6 genotype was assessed by automatic sequencing of DNA isolated from peripheral leucocytes. Experimental procedures were approved by local Ethical Committee.

Results: Based on the genotype analysis, 10 extensive metabolizers (EM), 8 intermediate metabolizers (IM) and 4 poor metabolizers (PM) were identified among 22 patients. Among EM, remission was achieved only in 4 of 10 patients, contrary to 5 of totally 8 patients among IM and 2 of totally 4 patients among PM.

Conclusion: With respect to our results in limited number of patients, poor and intermediate metabolizer status seems to be positive predictive factor for therapeutic response in first episodes of schizophrenia. CYP2D6 genotyping could help to predict therapeutic response to risperidone treatment and therefore to individualize pharmacotherapy of schizophrenia.

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P 18. How well do randomized controlled trial data generalize to real world clinical practice settings? Comparison of two generalized anxiety disorder (GAD) studies

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Background/Aims: It is uncertain how well results from placebo-controlled trials (RCTs) generalize to real world clinical practice settings. The objective of this post hoc analysis is to compare efficacy and safety results from two GAD studies: a placebo-controlled RCT and a study conducted in the clinical practice setting.

Methods: In the clinical practice study (CPS) outpatients with GAD (N = 578) were treated with 4 weeks of pregabalin (PGB) in the dosing range of 150-600 mg/day. In the double-blind, placebo-controlled RCT, outpatients with GAD were randomized to 8-weeks of PGB (300-600 mg/d), or placebo (PBO; only the first 4 weeks are included in the current analysis). Efficacy was evaluated using the Hospital Anxiety and Depression Scale-Anxiety (HADS-A), a visual analogue anxiety scale (VAS-Anxiety), and the Medical Outcomes Study Sleep Scale (MOS-Sleep).

Results: The CPS and RCT studies had similar anxiety severity at baseline (HADS-A, 15.4 vs. 14.0). In the RCT, treatment with pregabalin resulted in significantly greater change versus placebo by Week

4 in the HADS-A (-5.2 vs. -3.5; $P < 0.01$), the VAS-Anxiety (-24.0 vs. -13.3; $P < 0.05$), in the MOS-Sleep scale (-19.0 vs. -9.5; $P < 0.01$), and in the HADS-D (-2.7 vs. -1.4; $P < 0.05$). The magnitude of Week 4 improvement on pregabalin in the CPS study versus the RCT study were comparable or larger on the HADS-A (-5.9), the VAS-Anxiety (-36.0), MOS-Sleep (-22.7) and the HADS-D (-5.1). However, dosing in the CPS was markedly less aggressive, with only 12.2% of patients taking a dose greater than 300 mg. In contrast, 66.1% of patients in the RCT took a maximum daily dose of either 450 mg or 600 mg. 1.2% of patients discontinued the CPS due to an adverse event compared to 12.3% in the RCT.

Conclusions: These results suggest that in clinical practice patients with GAD may achieve comparable efficacy and superior tolerability on lower doses of PGB than tested in RCTs, despite having similar anxiety severity at baseline.

Funded by Pfizer Inc.

P 19. Is silexan an anxiolytic drug?

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Introduction: Preparations from lavender have been known for their relaxing and mood alleviating effects for centuries. Silexan¹ is a novel defined preparation from *Lavandula angustifolia* for oral use that is being investigated for use as an anxiolytic drug.

Methods: We review the results of 4 clinical trials investigating the efficacy of silexan in anxiety disorders and related conditions. All trials assessed the participants' anxiety levels using the Hamilton Anxiety Scale (HAMA) or the State Trait Anxiety Inventory (STAI) as well as measures of co-morbidity and clinical global impressions.

Results: Across all trials 283 patients were exposed to silexan 80 mg/day, 37 were treated with lorazepam 0.5 mg/day and 193 received placebo for 6 or 10 weeks. Average within-group HAMA total scores at baseline ranged between 24.7 and 27.1 points. Patients treated with silexan showed average HAMA total score decreases of between 10.4 ± 7.1 and 12.0 ± 7.2 points at week 6 and of 9.5 ± 9.1 and 16.0 ± 8.3 points at week 10. In subthreshold generalized anxiety disorder (GAD) silexan was superior to placebo from treatment week 2 on, with a mean value difference of at least 4 points (lower bound of 95% confidence interval (CI)) after 10 weeks. In threshold GAD silexan and lorazepam showed comparable

HAMA total score reductions (90% CI for mean value difference: -2.3; 2.8 points). The decrease of anxiety levels was accompanied by a reduction of restlessness and co-morbidity, and by improvements in general well-being.

Conclusions: The results support the efficacy of silexan in subsyndromal anxiety disorder and in GAD. The novel drug may offer interesting perspectives as an anxiolytic particularly in subthreshold GAD.

¹Silexan[®] is the active substance of LASEA[®] (W. Spitzner Arzneimittelfabrik GmbH, Ettlingen).

P 20. The efficacy of agomelatine in previously treated depressed patients

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Background: Agomelatine is a melatonergic (MT1/MT2) receptor agonist and a 5HT_{2C} receptor antagonist whose antidepressant efficacy and safety as first-line treatment have been shown in several clinical studies either versus placebo or versus comparators [1].

Aim of the analysis: To evaluate the antidepressant efficacy of agomelatine in previously treated patients (defined as patients who had been treated with antidepressants at least once during the year before the inclusion) versus the general study population.

Methods: Analysis of two 6-week randomized controlled trials were performed: study 1 [2], placebo-controlled and study 2, a randomized, double blind comparison with sertraline [3].

Results: 40% of the 235 enrolled patients in study 1 ($n = 94$), and 58% of the 307 enrolled patients in study 2 ($n = 177$) had been previously treated with SSRIs or other classes of antidepressants. Baseline characteristics of both the full analysis set (FAS) as well as the subgroup of previously treated patients (subFAS) were comparable in both studies.

In study 1, after 6 weeks, the magnitude of the incremental HAM-D response rate in the subFAS was 31% (46.3% versus 15% an uncommon low placebo responder rate, $p = 0.001$), and in the FAS 19% (54.3% versus 35.3%, $p = 0.003$). The delta between treatment groups on HAMD score in the subFAS-population was 4.43 ($p = 0.005$) and 3.44 ($p < 0.001$) in the FAS. Response rates according to the CGI-I score were 55.6% in the agomelatine-group and 27.5% in the placebo group in the subFAS population.

In study 2, after six weeks in the subFAS the overall HAM-D response rate with agomelatine was 67.5%, and 55.2% ($p=0.096$) with sertraline. The delta between treatment groups in the HAMD score was of 1.63 ($p = 0.124$) (In the FAS population the delta was 1.68, $p = 0.03$) in favour of agomelatine. Response rates in the subFAS population according to the CGI-I score were 80% in the agomelatine-group and 75% in the sertraline-group.

Agomelatine's tolerability was similar to that of placebo and better than that of sertraline.

Conclusion: The data of the subset of previously treated depressed patients, which can be considered to be more difficult to treat, indicates that agomelatine is at least as effective as it is in the treatment of the general study population (FAS).

Overall, due to its different mode of action and its favourable side effect profile, agomelatine – with proven benefits for first-line treatment – is an effective candidate for major depressive disorders who demonstrate less than adequate response to treatment.

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P 21. Prevalence and symptom characteristics of depression in schizophrenia patients

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Background/aims: Early detection of depressive symptoms during treatment of schizophrenia is very important because depressive symptoms are commonly associated with negative results such as long period of admission, failure of social adaptation, high recurrence rate, and frequent suicidal attempts. However, in many cases, it is not easy to evaluate depressive symptoms early in schizophrenia. Therefore, we investigated the prevalence and symptom characteristics of depression in schizophrenia patients regarding whether they had been taking antidepressant or not.

Methods: We recruited 56 schizophrenia outpatients who visited Bongseng Memorial Hospital. We investigated demographic and clinical information, and applied the Beck Depression Inventory (BDI) as a measure of existence and severity of depression.

Results: 1. 14 of 56 patients have depression, so 25% of the subjects were at least mildly depressed.

2. Those diagnosed with depression among the schizophrenia patients showed a high score in order of item 6–feeling of being punished, 15–difficulty in working, 10–crying, 14–feeling of not being attractive to themselves, 19–weight loss, and a low score in items 7–disappointment in themselves, 17–fatigue, 4–dissatisfaction in daily life, 5–guilt, 1–sorrow. Such findings look somewhat different from depressive symptom of Major depression.

3. Among the 14 patients who have depression, half of the patients took antidepressant but the other 7 did not. 12 of the 42 not-depressed patients (28.6%) were also taking antidepressant. Most of them complained about the depression-related symptom when they began the antidepressant medication. It can mean that antidepressants are useful to prevent and treat depression in schizophrenia.

Conclusions: Our study indicates that 25% of schizophrenia patients have depression, which is not a small portion in the whole patient group. Because the depressive symptoms of schizophrenia are somewhat different from those of Major depression, it makes the clinicians overlook the depressive symptoms. Usage of antidepressants is helpful to control the depressive symptoms in schizophrenia patients.

P 22. Trauma induced major depression: associated disability

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Introduction: A data base of more than 3,500 personal injury claimants has been compiled over a 25 year period. The data base was searched for individuals who fulfilled criteria for major depression (DSM III R or DSM IV) to ascertain their disability and functioning.

Method: All subjects had undergone detailed clinical psychiatric assessment (HML or MGL), as well as interview of an informant and a search of their medical records.

Results: Of 223 subjects suffering from major depression 131 were male and 92 female. They were aged between 19 and 69 (mean age = 42.56, SD = +/– 11.11). 50.2% had been off work for longer than 12 months. Almost 2/3, 63.7% had sustained soft tissue injuries. Road traffic accidents predominated (52%). 38.1% had experienced an accident at work. 44.4% had a past history of a mental health problem. 91.5% received treatment, either medication, psychological intervention, or both. More men had been absent from work for 12 months or more (55.72% v 41.93%), but fewer had a past history of depression,

compared with the women (31.3 v 63.04%). The numbers of men and women receiving treatment did not differ significantly, being 90.08% for the men and 93.48% for the women.

Conclusions: Possible reasons for the lengthy period of disability in this group are protracted litigation, a sense of grievance in the injured party, or the failure of conventional treatments in a population often suffering from both physical and mental health problems resulting in a lack of fitness for work. Men do worse possibly because they had experienced more severe trauma than the women. Closer links in orthopaedic departments and accident and emergency units with clinical psychology would be beneficial in coordinating ongoing care for trauma victims.

P 23. Brain neuropeptide Y (NPY) is a marker of PTSD in an animal model

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Background: Posttraumatic Stress Disorder (PTSD) is a major and growing health problem. Since only a small proportion of subjects exposed to stress develop the disorder, it has been hypothesized that a failure to recover homeostasis will result in PTSD. However, the PTSD pathophysiology is not well understood.

Converging evidence implicates NPY, a regulatory peptide widely distributed in the CNS, in anxiety- and stress-related behaviors. Transgenic rats over-expressing NPY show stress resilience, while an increased susceptibility to stress/anxiety is observed in NPY knockout mice.

Aim: To elucidate the underlying mechanisms in adaptive/maladaptive changes in brain we investigated the relationship between NPY expression and behavioral disruption in an animal model of PTSD.

Methods: Animals were exposed to predator scent stress. The outcome measures included behavior in elevated plus-maze and acoustic startle response. Preset cut-off criteria classified animals according to their behavioral responses into 'extreme' (EBR), 'minimal' (MBR), or 'partial' (PBR) response groups. Unexposed rats were controls. Following tests, brains were harvested and dissected into anterior cortex (AC), posterior cortex (PC), amygdala (AMY), hippocampus (HIP), periaqueductal gray (PAG). Peptides were extracted and assayed.

Results: The highest NPY concentrations were found in the PAG followed by AC, PC, HIP, AMY. Two way ANOVA: brain regions: $p < 0.0001$; groups: $p < 0.0001$; brain regions x groups: $p < 0.0001$. Experimental procedures reduced NPY; animals exhibiting largest behavioral changes showed largest regional NPY decrease.

Conclusion: There is a clear-cut association between extreme behavioral disruption and NPY down-regulation. The findings imply an association between the molecular findings and psychopathological processes which result in altered behavior. Studies in humans are necessary to ascertain whether NPY is also changed in subjects suffering from PTSD. The results strengthen our hypothesis and previous findings that NPY plays an important role in regulation of anxiety and depression.

P 24. Comorbid mood and anxiety disorders in adult ADHD patients

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ADHD is a highly heritable neurodevelopmental syndrome with significant lifetime risk for psychiatric comorbidities. Several psychiatric conditions are significantly more common in patients with ADHD than in control subjects, especially in adult ADHD patients.

To evaluate the incidence of comorbid affective disorders, patients with adult ADHD who were first seen at the outpatient clinic of the Department of Psychiatry and Psychotherapy were evaluated for symptoms of major depression, brief recurrent depression, bipolar depression and anxiety disorders. Patients aged between 18 and 75 years were included into the study. Both ADHD symptoms and symptoms of comorbid psychiatric conditions were evaluated according to DSM IVTR criteria. So far, from February 2007 until May 2010, 330 patients (192 males and 138 females) were included into the study.

The mean age of the patients at diagnosis was 33, 7 years for males (range: 18–75) and 35, 9 years for females (range: 18–64). Most of the patients were diagnosed first at the outpatient clinic of the Department of Psychiatry and Psychotherapy. Only 17 (5,2%) patients in our sample were diagnosed with AD(H)D during childhood.

Affective disorders were most frequently diagnosed as comorbid conditions in our patients and occurred in 26% of the patients in our sample. 13% had a minor depressive episode, 7% a major

depressive episode and 6% were diagnosed with bipolar disorder. 21% of our patients were diagnosed with one or several comorbid anxiety disorders, such as GAD, panic disorder and social phobia.

Until now, most adults with ADHD are not diagnosed properly and therefore remain untreated although they are usually diagnosed and treated for comorbid psychiatric disorders. Furthermore, the presence of psychiatric comorbidities may be one factor that influences the persistence of ADHD symptoms into adulthood. In the present study, we systematically analyzed comorbid anxiety and depression in a sample of adult ADHD outpatients in order to estimate the incidence of these disorders in an undiagnosed and not properly treated patient population.

P 25. Anxiety and depression symptoms in children-comorbidity with learning disabilities

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Previous studies at General Children's Hospital of Penteli have indicated that children in primary school with learning difficulties often present secondary psychological problems (e.g. anxiety, depression, anger). This study aimed to systemise the typology of these psychological problems, to confirm the same hypothesis to adolescents and finally to explore the role of children's sex.

The sample consisted of 421 children (292 boys, 129 girls) aged 7 to 14 years old. Children were categorised into 3 groups: children with a) slight learning difficulties, b) dyslexia and c) mental disabilities. Children completed Beck Youth Inventory, while their parents were invited to fill Aschenbach's questionnaire. To compare the 3 groups, we used the t-test, as well as ANOVA.

According to Beck Youth Inventory, 29% of children mentioned low self-esteem, 32,3% presented anxiety, 22,1% depression symptoms, 21,6% anger and 20,9% disruptive behaviour. According to Aschenbach's questionnaire, 21,4% of parents mentioned that their children presented anxiety, 21,4% depression symptoms, 18,5% aggressiveness and 16,2% delinquent behaviour. Based upon these results, it could be argued that parents tend to underestimate these secondary psychoemotional symptoms and mainly focus on the treatment of learning difficulties.

As it was expected, children with dyslexia presented higher levels of anxiety, regardless of their age. Nevertheless, children's self-esteem seemed to be aggravated by age, as adolescents often present lower

self-esteem. Furthermore, children's sex was found to be an important factor, as girls with dyslexia had lower self-esteem and more anxiety and depression symptoms, whereas boys presented disruptive and delinquent behaviour more regularly.

P 26. Efficacy of pregabalin in elderly patients with generalized anxiety disorder (GAD) and with high levels of insomnia

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Background/Aims: An estimated 20%–40% of elderly individuals suffer from insomnia, which is frequently secondary to anxiety, and is associated with increased cognitive impairment and reduced quality of life. The objective of this study was to assess the impact of high levels of insomnia on response to pregabalin (PGB) in elderly patients with GAD.

Methods: This is a post hoc analysis of a double-blind, placebo-controlled, 8-week trial of PGB, in elderly patients (N = 266), age 65 and over, who met DSM-IV criteria for GAD. A high-insomnia subgroup was defined by a baseline HAM-D insomnia factor score ≥ 3 (maximum = 6). Insomnia response was defined as reduction in the HAM-D insomnia factor to a score ≤ 2 . Full remission was a score of 0 on individual HAM-D insomnia items.

Results: At baseline, 65.7% of patients met criteria for the high insomnia subgroup, with 57.9% reporting severe early insomnia, 40.4% severe middle insomnia, and 26.4% severe early morning awakening. Treatment with PGB resulted in a significant reduction in the HAM-A total score compared to placebo on an LOCF-endpoint analysis (-13.8 vs. -10.7 ; $P < 0.05$). The PGB vs. placebo effect size was similar on HAM-A change for both the total patient sample (Cohen's $d = 0.28$) and for the high-insomnia subgroup ($d = 0.31$). Compared to placebo, treatment with PGB resulted in a significantly higher proportion of patients in the high-insomnia subgroup achieving insomnia responder status at LOCF-endpoint (64.2% vs. 44.1%; $P < 0.05$); complete remission was achieved by 43.3% of patients with severe early insomnia, 40.4% of patients with severe middle insomnia, and 42.2% of patients with severe late insomnia. Patients in the high-insomnia subgroup were less

likely than low insomnia patients to discontinue prematurely due to adverse events (7.8% vs. 15.0%).

Conclusions: These results suggest that PGB is an effective and well-tolerated treatment of anxiety in elderly GAD patients who present with high levels of insomnia.

Funded by Pfizer Inc.

P 27. Personality and antidepressant adherence: a pilot study

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Background/aims: Major Depressive Disorder (MDD) is frequently associated with high rates of treatment nonadherence, which represent a major barrier to effective pharmacological treatment. The study of factors influencing medication adherence has been mainly focused on sociodemographic characteristics. Conversely, the relation between personality characteristics and compliance has been relatively understudied. The present study aims to explore the relation between personality characteristics and compliance with antidepressant medication in patients with a first depressive episode or recurrent MDD.

Methods: In this pilot study adherence to antidepressant treatment was evaluated by means of the Simplified Medication Adherence Questionnaire (SMAQ) during 8 weeks in a sample of 23 MDD patients. Personality characteristics were assessed with the NEO Personality Inventory-Revised (NEO-PI-R). Sociodemographic and clinical data (including depression severity) were collected as well.

Results: Sample characteristics: 80 % of the sample were female patients. The mean age was 46,96 years (SD = 14,06). HRSD mean score at baseline was 23,56 (SD = 5,1). 52% of the sample presented a first-episode depression.

Adherence rates: According to SMAQ criteria, adherence rates gradually decreased throughout time: 82.6% patients could be considered adherent

after 4 weeks; in week 8 only 75% of the sample fulfilled SMAQ adherence criteria.

Personality: There were no significant differences between adherent and non-adherent patients in any of the NEO-PI-R subscales.

Depression severity: Adherent patients showed higher scores in the HDRS. However, these differences were not significant.

Conclusions: Despite the demonstrated efficacy of antidepressants, the effectiveness of pharmacotherapy is often limited by treatment nonadherence. According to previous research, correlates of personality might be important predictors of compliance with antidepressant medication. Although in our study no significant differences were found, it is important to notice that the small size of the sample in this pilot investigation may account for these nonsignificant results. Thus, further investigation on this issue is required.

P 28. Are there phenotypic differences in adults with early and late onset obsessive compulsive disorder (OCD)?

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Background: Juvenile OCD is considered to be a subtype of OCD with distinct clinical characteristics, patterns of comorbidity, familiarity, and course. In this study, we examined phenotypic differences between early onset (≤ 18 years) and late onset OCD (> 18 years) in a large sample of adult patients with DSM-IV OCD.

Methods: 545 consecutive patients who consulted the specialty OCD Clinic during the period 1999 to 2009 at NIMHANS formed the sample. They were evaluated with the Yale-Brown Obsessive-Compulsive Scale (YBOCS), the Mini International Neuropsychiatric Interview (MINI) and the Clinical Global Impression scale (CGI)-severity (S) and improvement (I) subscales.

Results: Among 545 subjects, 225 (41%) had early onset and 320 (59%) had late onset OCD. The early onset group compared to the late onset group was overrepresented by males (73% vs. 53%, $p < 0.001$), was less likely to be drug naïve at first consultation (28% vs. 41.6%, $p = 0.001$), had longer duration of illness (9.64 ± 7.58 vs. 6.08 ± 6.28 years, $p < 0.001$) and greater duration of untreated illness was (6.38 ± 6.35 vs. 4.15 ± 5.10 years, $p < 0.001$). Early onset OCD had significantly higher sexual obsessions (36.0% vs. 21.6%, $p < 0.001$), repeating rituals (52.4% vs. 31.6%, $p < 0.001$) and need to

touch (14.2% vs. 6.3%, $p = 0.003$). In addition, early onset OCD was associated with a higher familial loading for OCD (25.8% vs. 12.5%, $p < 0.001$) and showed a higher prevalence of tic disorders (6.7% vs. 1.9%, $p = 0.006$). In regression analysis, presence of family history of OCD, sexual obsessions, repeating rituals and greater duration of illness predicted early onset OCD and explained 69.1% of the variance.

Conclusions: Early onset OCD appears to be different from late onset OCD in its clinical profile and familial occurrence suggesting that early onset is possibly a distinct subtype. Whether early onset OCD is also associated with distinct treatment response needs to be assessed in longitudinal studies.

P 29. Plasma biomarkers to diagnose major depressive disorder

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Despite significant research efforts aimed at understanding the neurobiological underpinnings of psychiatric disorders, the diagnosis of these disorders are still based solely on relatively subjective assessment of symptoms. Therefore, molecular markers which could improve the current classification of psychiatry disorders, and in perspective stratify patients on a biological basis into more homogeneous clinically distinct subgroups, are highly needed. In order to identify novel molecular markers for major depression, we have harnessed a global metabolite profiling (metabolomics). Patients were diagnosed according to DSM criteria and a number of additional clinical variables were assessed. Plasma samples from 34 depressed patients and 38 controls were submitted to metabolomic profiling by capillary electrophoresis mass spectrometry (CE-MS) allowing the quantitative evaluation of up to 538 metabolites, including a series of neurotransmitters and their metabolic intermediates previously suggested to be involved in the pathophysiology of depression. Statistical analysis highlighted several metabolites belonging to pathways or mechanisms previously unsuspected to be involved in the pathophysiology of major depression. The results illustrate the potential of plasma metabolomics for psychiatric disorders, and highlighted multiple metabolites as candidate biomarkers for major depressive disorder, warrant-

ing further investigation in larger independent collections.

P 30. Designing a comparative study of escitalopram versus risperidone for the treatment of behavioral and psychological symptoms in Alzheimer's disease

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Objective: Dementia is a multidimensional disease characterized by progressive cognitive impairment, behavioral symptoms and decline in activities of daily living. The behavioral and psychological symptoms of dementia (BPSD) have an adverse impact on patients' quality of life and create severe stress for caregivers, complicating effective management and precluding the decision to institutionalize patients. Most patients with dementia ultimately require pharmacological interventions to manage BPSD. Agents used include: antipsychotics, anxiolytics, antidepressants, beta-blockers and anticonvulsants. Second generation antipsychotic (SGA) drugs are widely used to treat psychosis, aggression and agitation in patients with Alzheimer's disease, but their benefits are uncertain and adverse effects offset advantages in their efficacy. Recently, in response to a meta-analysis reflecting prospective data, the FDA issued a black-box warning stating that SGAs increase mortality among elderly patients due to increased risk of cerebrovascular events.

We have thus devised a study to compare escitalopram and risperidone for the treatment of psychosis and agitation associated with dementia of the Alzheimer's type.

Methods: A 6-week randomized, controlled trial of BPSD in patients with Alzheimer's disease hospitalized due to these behavioral symptoms was designed by the psychogeriatric department, Abarbanel Mental Health Center, Israel. Participants will be consecutively recruited if they had at least one moderate to severe target symptom (aggression, agitation, hostility, suspiciousness, hallucinations, delusions).

Sample size calculation: In order to record at least a 25% improvement in Neuropsychiatric Inventory (NPI) total score a minimal number of 40 patients equally divided in two arms would give an 85% power with a standard deviation of 0.70.

The primary outcome measure is the change in the NPI total score. Planned pre-post and mixed

model analyses of the main outcome measures of MMSE at base line, NPI and side effects reporting at baseline and at weekly intervals will be carried out.

Hypothesis: Our a-priori hypotheses was that risperidone would be more efficacious for psychosis and escitalopram for agitation and that these compounds will differ in tolerability.

P 31. Prescription of antipsychotics in inpatients with major depressive disorder (MDD) 2000 and 2007 – results from the AMSP International Pharmacovigilance Project

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Background: Monotherapy with antidepressants is advised by international experts and guidelines as the treatment of option for major depressive disorder¹, while use of antipsychotics (AP) is recommended only for patients with additional psychotic features. In the light of recent publications showing putative augmenting effects of AP in depressed patients², we investigated the changes in the prescription pattern of AP in depressive inpatients over a time period of 7 years.

Methods: On two reference days in 2000 (32 psychiatric institutions, N = 1078) and 2007 (54 psychiatric institutions, N = 1826), the following data were recorded for all patients on the wards under surveillance by AMSP (Arzneimittelsicherheit in der Psychiatrie) 3: all drugs prescribed on that day, ICD-10 diagnosis, age and sex. We defined our sample as patients having received one of the following ICD-10 diagnoses: F32.0, F32.00, F32.01, F32.1, F32.10, F32.11, F32.2, F33.0, F33.00, F33.01, F33.1, F33.10, F33.11 and F33.2.

Results: Comparing 2000 to 2007, we found a significant increase in the percentage of inpatients receiving AP (37.9% to 45.8%, $\chi^2:17.257$, $p < 0.001$). The prescription of atypical AP increased from 12.8% to 28.3% ($\chi^2:93.37$, $p < 0.001$), while the percentage of patients receiving typical AP decreased from 30.2% to 24.1%. When limiting the sample to inpatients with severe depression only, the increase in AP prescriptions was not statistically sig-

nificant (44.4% to 48.1%, $\chi^2:2.047$, $p = 0.15$), while in the subsample with mild to moderate depression we found a significant raise in the percentage of inpatients on AP (31.96% to 41.02%, $\chi^2:10,146$; $df:1$, $p < 0.001$).

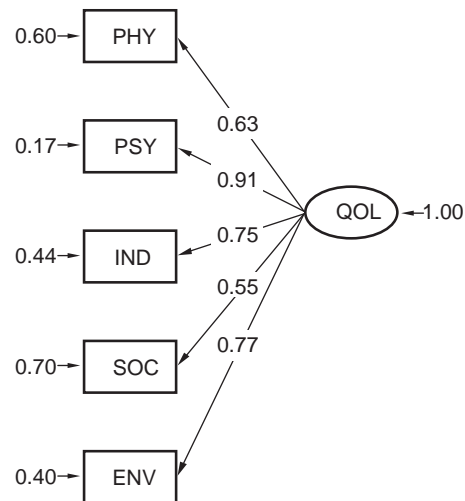
Conclusions: In this prescription study covering a time span of seven years and a sample of up to 1826 patients, we found a significant increase in the percentage of MDD inpatients on antipsychotics and atypical antipsychotics. This phenomenon can be attributed to the increase of inpatients with mild to moderate depression receiving antipsychotic medication. Further trials are needed in order to define the adequate dosage and duration of antipsychotic treatment in depression.

P 32. The reliability and validity of WHOQOL in patients with breast cancer: physical domain and depression

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Background/aims: This study was designed to investigate the reliability and validity of WHOQOL (World Health Organization Quality of Life Assessment



N=64, CFI=0.935, GFI= 0.906

Figure 1. A CFA (confirmatory factor analysis) model in patients with breast cancer without depression. PHY, PSY, IND, SOC, and ENV refer to physical domain, psychological domain, independence domain, social domain, and environment domain, respectively. The standardized validity coefficients are shown on the arrows. The error variances are showed at the left side to the domains. CFI and GFI refer to comparative fit index and goodness-of-fit index, respectively.

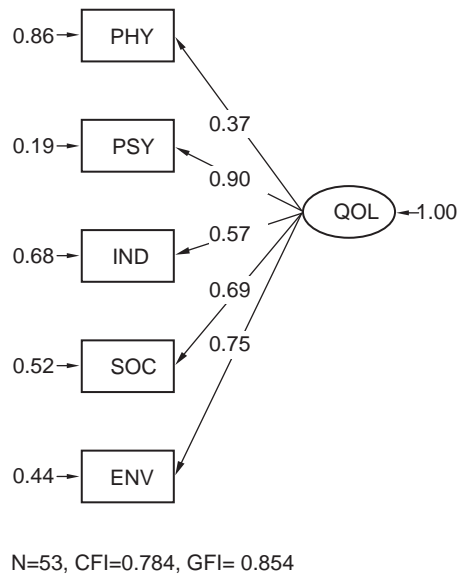


Figure 2. A CFA (confirmatory factor analysis) model in patients with breast cancer with depression. PHY, PSY, IND, SOC, and ENV refer to physical domain, psychological domain, independence domain, social domain, and environment domain, respectively. The standardized validity coefficients are shown on the arrows. The error variances are showed at the left side to the domains. CFI and GFI refer to comparative fit index and goodness-of-fit index, respectively.

Instrument) and the effect of depression in patients with breast cancer.

Methods: One hundred seventeen patients with breast cancer who underwent curative surgery at the department of surgery, Incheon St. Mary's Hospital, the Catholic University of Korea. Depressive symptoms were assessed with the 17-item Hamilton Rating Scale for Depression (HRSD) and quality of life measured with the Korean version of WHOQOL (physical, psychological, independence, social, and environment domain). Fifty three patients had depressive symptoms. Reliability and validity was measured by using the confirmatory factor analysis. Data were analyzed using Statistica (version 6.0) and LISREL (version 8.0). Significance is indicated by a P value of less than 0.05.

Results: The scores of WHOQOL in all domains were lower in depressed patients than in patients without depression ($t = 14$, $df = 115$, $p < 0.001$). Reliability of all domains was more than 30% and validity is also more than 55% in patients without depression by the confirmatory factor analysis (Figure 1). But reliability of physical domain was 14% and validity of physical domain is 37% in depressed patients (Figure 2).

Conclusions: In breast cancer patients with depression, depression affected the physical health of QOL. Therefore, physical health was assessed by

WHOQOL but also by depressive symptom scales.

P 33. Public attitudes towards depression and psychiatric medication: barriers to treatment

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Background: Stigma is regarded as the main barrier to seeking and receiving treatment for psychiatric disorders in general and depression in particular. Only one in two people who suffer from depression are treated for their condition, while the average delay for seeking help is 8 years. Furthermore, attitudes to psychiatric treatments have also been shown to influence help seeking intentions.

Aims: The present study aimed at exploring public attitudes towards depression and psychiatric medication as well as their link to help seeking intentions.

Methods: Telephone interviews were conducted on a random sample of 613 people living in a representative borough of Athens. The interview entailed open-ended questions about the core symptomatology of depression, a standardized questionnaire on public attitudes towards depression and psychiatric medication as well as close-ended questions about help seeking intentions. The statistical analysis employed t-tests for independent samples, ANOVA, correlation and regression methods.

Results: Most of the respondents were capable of spontaneously citing the main symptoms of depression. Nonetheless, the majority of them believed that people with depression are weak (61,7%), unpredictable (53,9%) and could snap out of the disorder if they wanted to (82,2%). Contrary to expectations, they regarded depression as a real medical illness (66,3%). Concerning their attitudes towards medication, the majority endorsed the belief that they are addictive (67,4%), less effective than natural herbs and homeopathy (42,2%) and capable of altering one's personality (56,9%). Nonetheless, most of them reported that they would contact a health professional in case they manifested persistent symptoms of depression (71%). Various factors were found to influence these attitudes, which in turn affected help seeking intentions.

Conclusions: The negative stereotypes and prejudice surrounding depression and psychiatric treatment impinge on patients' willingness to seek timely professional help for their condition and to adhere to

it. Any anti-stigma intervention aiming to dispel these forms of stigma should target specific beliefs and take into consideration the characteristics of the people it addresses.

P 34. Early vs. delayed switch to duloxetine in patients with major depressive disorder not exhibiting early improvement with escitalopram: a double-blind randomized study

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Aims: To compare the efficacy and safety between two treatment strategies: early vs. delayed switch to duloxetine, in MDD patients who do not experience improvement after 4 weeks of escitalopram treatment.

Methods: MDD patients without improvement (< 30% baseline score reduction in the 17-item Hamilton Depression Rating Scale [HAMD17]) after 4 weeks on escitalopram (10 mg/day) were randomized to an early switch to duloxetine strategy (Arm A: duloxetine 60–120 mg/day for 12 weeks) or to a delayed switch strategy (Arm B: continue with escitalopram 10–20 mg/day for 4 additional weeks; then, in case of non-response [response: ≥50% reduction in HAMD17] switch to duloxetine 60–120 mg/day for 8 weeks, or continue with escitalopram in patients with response). Co-primary endpoints were time to confirmed response (at least maintained for 2 consecutive weekly visits) and time to confirmed remission (HAMD17 ≤7). Kaplan-Meier (KM), logistic regression, and repeated measures analyses with associated tests were performed to evaluate differences between strategies (Arm A vs Arm B). Adverse events and vital signs were assessed for safety.

Results: 67% (566/840) of enrolled patients showed no improvement on escitalopram and were randomized to Arm A (282 patients) or Arm B (284 patients). Four weeks after randomization, 165 of the randomized 284 patients in Arm B were switched to duloxetine based on the investigators assessment of non-response in HAMD17. No differences between strategies in co-primary endpoints were found (time to confirmed response: 25% KM estimates: 3.9 vs 4.0 weeks, $p = 0.213$; time to confirmed remission: 6.0 vs 7.9 weeks, $p = 0.075$). Rate of confirmed responders was similar (Arm A: 64.9%; Arm B: 64.1%); how-

ever, more patients randomized to early switch to duloxetine achieved confirmed remission (43.3% vs 35.6%; odds ratio: 1.43; $p = 0.048$). Safety analyses did not raise any concern for either strategy.

Conclusions: No differences between strategies in time to confirmed response and remission were found. However, non-improving patients could benefit from an early switch strategy since greater remission rates were observed.

P 35. Efficacy and safety of zolpidem tartrate sublingual tablet for as-needed treatment of middle-of-the-night (MOTN) insomnia

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Background/aims: Currently no drug is approved for treatment of middle-of-the-night (MOTN) awakening with difficulty returning to sleep. Zolpidem tartrate sublingual tablet 3.5-mg (ZST), with buffers, was developed for treatment of MOTN awakening with difficulty returning to sleep. The buffers hasten onset of “therapeutic blood levels” enabling rapid return to sleep.

Methods: Data from two double-blind, placebo-controlled studies in patients with chronic MOTN insomnia are presented – a polysomnographic (PSG) study ($n = 82$) with ZST (1.75 or 3.5-mg) or placebo being administered 10 minutes after a scheduled MOTN awakening and a 4-week outpatient study ($n = 294$) with patients being instructed to dose (ZST 3.5-mg or placebo) only when they experienced a prolonged awakening and still had 4 hours of bedtime remaining. The primary endpoint for both studies was sleep induction post-MOTN awakening: latency to persistent sleep (LPSMOTN) in the PSG study and latency to sleep onset (LSOMOTN) in the outpatient study. The secondary outcomes were total sleep time (TSTMOTN), number of awakenings (NAWMOTN) and wake after sleep onset (WASOMOTN). Sleep quality and residual effects were assessed in the morning. Statistical significance was determined by ANCOVA, and non-parametric tests were used for data not normally distributed.

Results: ZST 3.5-mg significantly reduced LPSMOTN ($p < 0.001$) in the PSG study and LSOMOTN ($p < 0.0001$) in the outpatient study, also significantly improving maintenance aspects of sleep following MOTN awakening, including TSTMOTN in the sleep-laboratory study ($p < 0.001$) and during week 1 ($p < 0.0107$) and week 2 ($p < 0.0469$) in the outpatient study, reduced NAWMOTN ($p < 0.001$)

and WASOMOTN ($p < 0.006$) in the outpatient study, and improved sleep quality in both studies. In the outpatient study, number of tablets taken per week averaged 4.5 for both ZST and placebo groups. In both groups there was a significant decline in usage across weeks. There were no next-day residual effects.

Conclusions: ZST is safe and effective in prn treatment of insomnia when taken after difficulty returning to sleep after MOTN awakening.

P 36. Treatment of middle of the night insomnia: current therapeutic approaches

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Background/aims: Epidemiology studies indicate that middle-of-the-night (MOTN) awakening with difficulty resuming sleep affects 15% of the U.S. population. Patients with MOTN have significantly less total sleep time and suffer greater daytime impairment versus other insomnia patients. Risk factors include: age, gender, psychiatric disorders and pain. As there are no medications currently indicated for as-needed treatment in the middle of the night (after MOTN awakening), the purpose of this study was to assess current therapeutic practices adopted by physicians for this clinically important population.

Methods: 45 psychiatrists and 133 primary care physicians (PCPs) each provided 1 MOTN case, and 4 general insomnia cases. This resulted in 240 MOTN cases (178 preselected and 62 from general insomnia cases) of the 890 cases. Participating physicians practiced an average of 13.2 years and treated an average of 137 insomnia patients each month.

Results: Review indicated that 87% of the MOTN cases were on pharmacotherapy; physicians instructed 14% of these patients to dose prn at the time of MOTN awakening and 61% of the treatments were with zolpidem IR/CR and eszopiclone, medications requiring 7-8 hours of bedtime post dosing. There were no differences between psychiatrists and PCPs in the frequency of giving MOTN dosing instructions to patients. The less frequent the MOTN awakenings, the more frequently middle of the night dosing was prescribed. Instructions for MOTN dosing increased from 2% to 17% when awakenings decreased from 7 nights to less than 4 nights/week, and to 27% with less than 3 nights/week. 44% of all MOTN patients awakened 4 or less nights per week; 22% awakened every night.

Conclusion: Results are consistent with epidemiologic findings and also indicate that MOTN awakenings are currently being managed with off-label MOTN use of hypnotics intended for bedtime dosing and requiring 7-8 hours time in bed. There is a medical need for a prn medication that, when dosed in the MOTN, rapidly induces sleep without morning residual effects.

P 37. Intra-peritoneal injection of salmonella typhimurium LPS affects anxiety behaviors and serum corticosterone level in pregnant mice and its male offspring

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Background: Maternal infection during pregnancy is associated with an increased risk of neurodevelopmental damage in offspring.

Objectives: In the present study, we have investigated the effects of bacterial LPS on anxiety behaviors and hypothalamus-pituitary-adrenal (HPA) axis reactivity in pregnant mice and male offspring.

Methods: LPS was extracted from *Salmonella typhimurium* with the method proposed by Westphal and Jann (1965) [1]. Pregnant NMRI mice were treated with intra-peritoneal administration of LPS (30, 60, and 120 $\mu\text{g}/\text{kg}$) at the 10th gestational day (s10) [2,3]. Anxiety behavior of pregnant mice and its male offspring (at 7 weeks old) investigated using elevated plus maze test of anxiety [4]. Serum corticosterone were measured using ELISA kits.

Results: Result shows that LPS administration has anxiogenic effects on pregnant females and increases serum concentration of corticosterone. Male offspring shows decreased anxiety behaviors and decreased serum level of corticosterone. The results suggest that prenatal LPS infection may reduce anxiety behaviors and reactivity of HPA axis in adult male offspring versus their mothers.

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P 38. Multitracer PET imaging of the serotonergic system

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The serotonergic neurotransmission is mainly regulated by the major inhibitory (5-HT_{1A}) and excitatory (5-HT_{2A}) serotonergic receptor subtypes and the serotonin transporter (5-HTT). Based on evidences in molecular neuroimaging, postmortem and genetic studies, impaired serotonergic neurotransmission has been implicated with affective disorders. Moreover, a growing number of evidences showed strong interrelations within the serotonergic system suggesting a common mechanism in the modulation of receptor and transporter densities. Here we investigated directly the regional expression of the 5-HT_{1A}, 5-HT_{2A} and 5-HTT using PET and the three highly selective and specific radioligands [carbonyl-¹¹C] WAY-100635, [18F] Altanserin and [11C] DASB in healthy subjects. Binding potential (BPND) values were quantified according to the AAL parcellation scheme. BPND values averaged over both hemispheres ranged from 0.40–6.35 for the 5-HT_{1A} receptor; 0.0–2.01 for the 5-HT_{2A} receptor and 0.09–2.05 for the 5-HTT, respectively. While the 5-HT_{1A} receptor varied several fold, in contrast, the 5-HT_{2A} receptor displayed a more homogeneous distribution throughout cortical regions. As hypothesized, the 5-HT_{1A} receptor showed its highest availability in the parahippocampal cortex, the 5-HT_{2A} receptor in the primary visual cortex and temporal gyrus. Subcortical areas were almost devoid of both receptors, except for the amygdala, the hippocampus and the raphe nucleus. Conversely, high values for the 5-HTT were found in subcortical

areas only. There was a specific topological pattern according to the ratio between the 5-HT_{1A}, 5-HT_{2A} receptors and 5-HTT (“fingerprints”). Such information can be essential for detecting potential local alterations in the ratio between different binding proteins on a network level in pathological conditions. Moreover, these data might provide further insight in area-specific effects of frequently prescribed selective serotonin re-uptake inhibitors (SSRI): 1) due to the distinct local receptor and transporter availability; 2) SSRI application alters the postsynaptic receptor expression and thus; 3) leads to a modified interaction of inhibitory and excitatory receptors.

P 39. 3D brain SPECT imaging as an aid in the management of resistant depression

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Brain SPECT (single photon emission computed tomography) scans indirectly show functional (metabolic) activity via measurement of regional cerebral blood flow (rCBF). What we term 3D SPECT combines the scanning data via thresholding functions to synthesize a 3D model of the brain as follows: pixels representing the top 45% of tracer activity are used in the outside cortical 3D surface view of the brain, and the top 8%, 15% and 45% pixels create the 3D view of the functional interior of the patient’s brain.

70 community-based psychiatric patients with varying degrees of resistant depressive symptoms underwent 3D brain SPECT scans. The following patterns were observed:

- i. Thalamic hyperactivity
- ii. Thalamic hyperactivity plus prefrontal cortical hypoactivity
- iii. Global overactivity suggestive of a bipolar spectrum disorder
- iv. Thalamic hyperactivity plus scattered regions of cortical hypoactivity
- v. Thalamic hyperactivity plus basal ganglia hyperactivity
- vi. Thalamic hyperactivity plus anteromedial temporal lobe(s) hypoactivity
- vii. Thalamic hyperactivity plus anterior cingulate hyperactivity

Directing treatment towards the functional defects proved successful in achieving a response to

treatment in many cases and remission in some cases. For example, in a patient with treatment-resistant depression of longstanding duration, a 3D SPECT scan revealed thalamic hyperactivity plus prefrontal cortical hypoactivity. To better target the prefrontal dysfunction, more aggressive usage of a dopaminergic agent was made to the existing psychopharmacological management with the patient's depression improving as a result of this intervention.

Case studies including the actual 3D brain SPECT scans, pre-scan treatment, post-scan treatment, and outcome, are presented for treatment-resistant depression patients with a variety of the above scan patterns.

All Authors: Sources of funding/Conflicts of interest: None.

P 40. Genome wide association scan of co-morbid anxiety in major depressive disorder (MDD)

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Co-morbidity between depression and anxiety disorders is common. We investigated a broad phenotype of co-morbid anxiety in cases of major depressive disorder (MDD), and performed a genome-wide association (GWA) study in 1,621 subjects with DSM-IV and/or ICD-10 diagnosis of MDD, derived from three studies: DeCC (Depression Case Control, N = 648), GENDEP (Genome-based Therapeutic Drugs for Depression, N = 413), DeNt (Depression Network, N = 306), and a sample from Bonn and Lausanne (N = 254). Depression and anxiety were assessed using the SCAN interview, and a new variable was created named **SUM**mary **AN**xiety (SUX) score, defined as the sum of scores for the following items: SCAN items 4.001 (general rating of anxiety), 4.002 (general rating of phobia), 4.023 (free-floating anxiety) and 4.024 (anxious foreboding with autonomic symptoms). All subjects therefore had a score between 0 and 8 for the worst and 2nd worst episode, or current episode in GENDEP.

SCAN item 1.002 (an anxiety screening item) was used to confirm subjects with no anxiety.

We performed genome-wide analysis of the quantitative SUX phenotype and a discrete trait (SUX = 0 vs SUX ≥ 1), correcting for the Europe-wide ascertainment of cases. Five SNPs attained p-values of < 5 × 10⁻⁶, suggesting evidence of association with anxiety: rs17221829 in the *UBTF2* gene with the quantitative SUX phenotype, rs9980603 and rs1040315 in *DSCAM*, rs10238623 in *CREB5* and rs7867155 in *NCRNA0092* with the discrete SUX phenotype.

In conclusion, we found no SNP conferring a major contribution to co-morbid anxiety in MDD, analysed either as a continuous or discrete trait. Although this study highlighted several genes which may play a role in co-morbid anxiety, each will require replication in further studies to confirm or refute their role.

P 42. Prevalence of depression in cancer patients: cultural influence

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Aim: Depression is the commonest psychological sequelae in cancer patients. It is not only challenging to diagnose but its presentation is also influenced by the patients' cultures. This review aims to determine the prevalence of depression in cancer patients across regions of different cultures.

Methods: A literature search using Pubmed electronic database was conducted. Studies were included if they (a) examined the prevalence of depression in cancer patients and (b) were published in English peer-review journal between 2000 and 2009.

Results: 59 studies from 21 countries were reviewed. These studies were conducted in China (5.1%, n = 3), Japan (10.1%, n = 6), Korea (1.7%, n = 1), India (1.7%, n = 1), Pakistan (1.7%, n = 1), Iran (3.4%, n = 2), Jordan (1.7%, n = 1), UK (8.5%, n = 5), Denmark (3.4%, n = 2), Germany (1.7%, n = 1), Netherlands (3.4%, n = 2), Turkey (3.4%, n = 2), Scotland (3.4%, n = 2), Finland (1.7%, n = 1), Norway (1.7%, n = 1), Slovenia (1.7%, n = 1), Ireland (1.7%, n = 1), Italy (3.4%, n = 2), USA (25.4%, n = 15), Canada (5.1%, n = 3) and Australia (8.5%, n = 5).

Prevalence of depression in cancer patients ranged from 3% to 72%. Asia reported the lowest prevalence 3–39% while Europe had the highest prevalence 7–72%. Middle East 0–57%, North America 6–51% and Australia 4–43%.

Conclusion: Cultural influences contribute to the varying prevalence of depression in cancer patients. Somatization and stigmatization are the possible reasons of lower prevalence in Asia. The biopsychiatric model of mental illness and western psychologization explain the higher prevalence in Western regions. The different conceptual model of mental illness in the Western as compared to the East is another important factor influencing the willingness to express emotion or seek professional treatment. Future research on the cross-cultural variability in the presentation of depression in cancer patients is recommended.

No funding was obtained for this article.

P 43. Altered quality of life in epilepsy: significance of interictal depression

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Background: Depressive disorders in people with epilepsy are a frequently encountered psychiatric comorbidity with prevalence rates of 10-60% of the patients depending on the type of the selected patient populations or differences in methodology for detecting psychiatric symptomatology. As a part of the burden of living with epilepsy they represent an important issue in the management of people with epilepsy being associated with poor quality of life and poor prognosis.

Aim and method: We assessed the frequency and the impact of comorbid depressive disorder on the quality of life of people with epilepsy. The research was conducted on 106 patients with idiopathic epilepsy (41 males and 65 females), aged 18 to 60 years. All subjects underwent the same research protocol applied interictally. Comorbid depressive disorder was diagnosed according to ICD-10 diagnostic criteria for affective and delusional disorders and diagnosis was supported by evaluation on Hamilton Depression Rating Scale (HAM-D-17). Health-related quality of life was measured by Quality of Life in Epilepsy Inventory-31 (QOLIE-31). Statistical analysis included analysis of variance, correlation analysis, T-test analysis.

Results: Comorbid depressive disorder affected 30(28.3%) of all evaluated epilepsy patients. Based on HAM-D-17 scores depression was defined as mild in 24(80%) patients, moderate in 5(17%) patients and severe in 1(3%) patient. There were significant between-group differences for the QOLIE-31 overall score and all scores on QOLIE-31 subscales (seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects and social functioning) which were lower for the patients with comorbid depressive disorder. A

moderate correlation was found between the presence of interictal depressive disorder and lower scores for QOLIE-31 overall score and overall quality of life, emotional well-being, energy/fatigue and social functioning.

Conclusions: Comorbid depressive disorder is relatively common in people with epilepsy resulting in significant reduction of the quality of life of the affected patients. These data clearly highlight the need to better appreciate its importance in the overall treatment plan of these patients.

P 44. Influence of depression, sociodemographic and seizure-related variables on quality of life of adults with epilepsy

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Background: Quality of life is recognised as an important concept to better understand the distress of living with epilepsy. As it is a multidimensional concept it can be influenced by many and different factors including sociodemographic, disease-specific and psychosocial ones.

Aim of this study was to assess the influence of comorbid depressive disorder, some sociodemographic and seizure-related variables on quality of life of patients with epilepsy. The research was conducted on 106 patients with idiopathic epilepsy (41 males and 65 females), aged 18 to 60 years. All subjects underwent clinical psychiatric examination, including evaluation on Hamilton Depression Rating Scale (HAM-D-17) and completed Quality of Life in Epilepsy Inventory-31 (QOLIE-31). Seizure severity was measured by Seizure Severity Questionnaire (SSQ). A questionnaire for demographic and seizure-related variables was also completed. Comorbid depressive disorder was diagnosed according to ICD-10 diagnostic criteria for affective and delusional disorders and ILAE classification for epilepsies and epileptic syndromes was used. Statistical analysis included correlation analysis, T-test analysis and multivariation analysis.

Results: Employability, higher education and younger age, lower seizure frequency and mild seizure severity were associated with better quality of life scores. Comorbid depressive disorder was associated with low quality of life scores accounting for 32% of the variance in QOLIE-31 overall score and was a strong predictor for the variance in overall quality of life, emotional well-being, energy/fatigue and cognitive functioning scores. Seizure severity influenced most the variance in seizure-worry score. Seizure frequency accounted most for social functioning and

medication effects scores. Gender, marital status, seizure type, age at seizure onset, duration of seizures and antiepileptic medication intake had no significant association with QOLIE-31 scores in this study.

Conclusions: Multiple factors determine the quality of life experienced by patients with epilepsy. Detection and treatment of comorbid depressive disorder, being the most frequent psychiatric comorbidity in epilepsy, is a challenge for improving the quality of life of these patients and future research should give priority to this issue.

P 45. Improving compliance and treatment outcome in bipolar and schizophrenic patients by using short message text service (SMS)

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Improving adherence to treatment is a major challenge in bipolar I disorder and schizophrenia.

Aim: To investigate the effect of daily treatment reminders, delivered via a short message service (SMS text) message service [1], on adherence to treatment by assessment of the Medication Adherence Rating Scale (MARS) after 12 weeks treatment with quetiapine.

Methods: Included were bipolar and schizophrenic patients in the SMS cohort patients and in 'without' SMS cohort. The last was decided through their doctor on the same demographic data.

SMS text messages were sent twice daily to remind patients to take medication and obtain replies about their health.

After 4 and 12 week treatment assessments were done; for MARS, the prescription receipt at the pharmacy and the Clinical Global Impression Scale (CGI). For the SMS group also satisfaction of the SMS.

Results: In total 128 patients were included in the study, of which 121 patients were included in the efficacy analysis.

The SMS group was less of Caucasian origin and had longer illness duration.

The mean change from baseline in MARS scores for the SMS cohort 4 and 12 weeks was significantly different from the one without SMS cohort. Respectively 1.4 (0.1 without SMS) and 1.6 (0.3 without SMS).

The prescription rate was not different but only half of this could be traced.

The change in the CGI scale was not different between cohorts.

Satisfaction with the SMS was high: patients 89 and 75% , doctors 94 and 96%.

Discussion: Absence of difference on most assessment items could be the effect of a not blind random study and the relative short duration of the study.

Conclusion: The SMS seemed to be effective in improving adherence. It must be proved in a random trial.

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P 46. Psychiatrists' awareness of adherence to antipsychotic medication in bipolar disorder: results from a survey conducted across eight European countries

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Background/aims: Partial/non-adherence to medication by patients with bipolar disorder has a major influence on rates of relapse and hospitalization [1,2]. Moreover, non-adherence is associated with exacerbation of symptoms, neurocognitive decline [3] and increased risk of suicide [4]. Understanding psychiatrists' views on the causes and management of non-adherence are vital to address adherence problems effectively.

Methods: We conducted a survey in eight European countries of over 2000 psychiatrists treating patients with bipolar disorder. The 15-question survey was developed to ascertain psychiatrists' perceptions of the level and causes of non-adherence, and their preferred methods of assessing adherence.

Results: Psychiatrists estimated that more than half of their patients (57%) were partially/non-adherent during the previous 3 months. Three in four psychiatrists responded that most patients who

deteriorated after stopping medication were unable to attribute this to non-adherence and 59% of psychiatrists perceived that less than half of their patients accepted there was a risk of relapse if they didn't take their medication regularly. Amongst the possible reasons for discontinuing medication, 66% of psychiatrists replied that more than one in five of their patients had an irregular daily routine or lived in circumstances that may have affected their adherence to treatment. Only 4% of psychiatrists deemed that intolerable side effects had led to most of their patients stopping their medication while 11% responded that drug and alcohol consumption may have impacted on adherence to medication for most of their patients.

Conclusions: This survey suggests that partial/non-adherence remains a considerable problem amongst patients with bipolar disorder and there is a need for increased knowledge concerning partial/non-adherence at the level of the clinician-patient interaction, in order to reduce its impact and bring about improved clinical outcomes.

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