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CONCEPT 01

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SO 01. Treatment of alcohol dependence

SO 0101. Which target: prevention of relapse in abstinence or reduction of alcohol intake?

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The issue of controlled drinking has been controversial in many countries over the years. Some alcohol specialists have been slow and mostly unwilling to even consider reduced drinking as a treatment objective for anyone with an alcohol problem, especially when an alcohol dependence syndrome has been diagnosed. This attitude finds its roots in concepts that first became popular through Alcoholics Anonymous and subsequently became commonplace. Viewed from this perspective, the rationale for strong resistance to any moderation alternative is that it supports “denial” and therefore interferes with “alcoholics” taking the “first step” towards recovery. Epidemiological and clinical research has however shown that a substantial proportion of alcohol dependent individuals can actually be successful when aiming low-risk drinking. Many treatment settings promote abstinence as the only acceptable treatment goal for patients with an alcohol use disorder. However, many problem drinkers decline treatment programs aimed at abstinence. Offering both abstinence and non-abstinence treatment goals to clients, permits a client-centered approach that contributes to alleviate client’s resistance to change. The forthcoming DSM-5 introduces a diagnostic shift from the binary diagnostic criteria of alcohol dependence and alcohol abuse, to a single continuum of alcohol use disorders introducing a clear measure of severity such that treatment goals can be tailored accordingly. In this sense, reduction strategies offer a clear opportunity to address patient heterogeneity and lower the treatment barrier by bringing patients into treatment that would otherwise not be treated.

SO 0202. Alcohol dependence and depression

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Alcohol dependency and depression frequently co-occur, resulting in poorer outcomes for both conditions. Management is complicated by service delivery

variables and a relatively sparse evidence-base. Systematic reviews have concluded that antidepressant treatment may improve mood but not necessarily alcohol outcomes (Nunes & Levin, 2004; Torrens et al., 2005). Guidelines advise treatment of the alcohol use disorder first and reassessing depressive symptoms once abstinent. However this is not always possible and more recent evidence suggests that there may be some benefit for combining antidepressants with the opioid receptor antagonist naltrexone (Pettinati et al., 2010; Krystal et al., 2008).

Given the frequent co-occurrence of these disorders, as well as the difficulty in determining which is the primary condition; the need remains for understanding the underlying cognitive and emotional processes involved in the aetiology and maintenance of the co-morbid condition.

Cognitive models have been extensively investigated, with biases in attention and interpretation being the most researched. In alcohol dependency and depression (in the non-comorbid state), biases in selective attention to disorder specific cues are considered key cognitive vulnerability factors in their development and maintenance (Field and Cox, 2008).

However, despite the high prevalence of comorbidity across these disorders, there is much less evidence on how attentional biases to disorder-specific cues interact with each other and the impact that this may have on understanding the natural history of the disorder; and on the potential mechanisms of action of novel psychological and pharmacological treatments (Sinclair et al., 2010).

Recent data from a study of 123 patients presenting for alcohol treatment demonstrated attentional bias towards alcohol related words (on a visual probe task), which reduced with abstinence. It also confirmed previous findings of a significant reduction in depressive symptoms following abstinence. However, unrelated to depressive symptoms or diagnosis patients demonstrated an avoidance of depression related words which increased significantly with abstinence (Sinclair et al 2010). The potential implications for this counter-intuitive finding require further exploration.

SO 0103. A potential new treatment for alcohol dependence

Hannu Alho

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In longitudinal studies on general health a clear correlation between the amount of alcohol consumed and mental and physical consequences such as depression, anxiety, some cancers, fatty liver and liver cirrhosis has been established. In recent years the strategy of “harm reduction” proved very successful in patients addicted to alcohol, both in psychotherapy as well as in pharmacotherapy showed a significant proportion of patients with a considerable reduction in alcohol consumption. These findings indicate that it is timely to open a new discussion on reduced drinking as a treatment goal and ways to achieve this goal. Recent studies have shown that nalmefene is effective to achieve this goal.

The consumption of alcohol stimulates the production and release of endogenous opioid peptides, which mediate the rewarding and reinforcing effects of alcohol. Opioid antagonists (e.g., nalmefene, naloxone, naltrexone) block endogenous opioid activity, thereby, blocking alcohol-induced reinforcement. Evidence from animal studies has shown that the reinforcing actions of ethanol are attenuated by the opioid antagonist. Clinical evidence to further substantiate the use of opioid antagonists in the treatment of alcohol dependence comes from several clinical studies of nalmefene and naltrexone. For example, new clinical data show that the targeted use of nalmefene (preliminary data, nature reviews Drug Discovery, 10,566, 2011) reduces heavy drinking in alcohol-dependent patients without prior detoxification.

SO 02. Depression and Anxiety: Treating the difficult patient

SYMPOSIUM OUTLINE

Via an interactive format, this symposium will explore two specific patient scenarios in which clinicians typically encounter difficulties. The first is the shy, anxious patient with symptoms of both social anxiety disorder and major depressive disorder; the second is the poor responder to antidepressant therapy. Each scenario will be explored from different angles. To begin with, prevalence, diagnosis and controversies will be examined. Using voting pads, audience members will then have the opportunity to challenge the information presented and share opinions on individual patient cases. To complete the discussion on each scenario, the speakers will provide an overview of the available evidence-based treatment approaches, focusing on the most recently published research. Throughout

the symposium, the consequences of inadequately treating “difficult patients” will be addressed, and special emphasis will be placed on the topic of antidepressants and suicide.

SO 03. Advances in Treatment of MDD and GAD

SO 0301. Depression in schizophrenia

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Depression has been historically described as one of the symptoms in schizophrenia, however little attention has been paid to its diagnosis and treatment. In cross-sectional studies 25–30% of the patients with schizophrenia are identified as being depressed. More severe psychopathology, impaired functioning and suicidality are related to depression in schizophrenia (DiS). The prognostic and functional correlates of DiS are different in the acute phase and the chronic phase.

The Calgary Depression Scale has been developed for the identification and measurement of depression in schizophrenia. The scale is available in a large number of languages.

Most studies highlight the correlation between depression and negative symptoms, however good treatment response of positive symptoms in the acute phase is associated with improvement of depressive symptoms. DiS and anhedonia in schizophrenia may overlap, and it could therefore be difficult to differentiate them, especially in acute phase. In the chronic phase the differentiation of depression, negative symptoms and extrapyramidal side effects of antipsychotics may be difficult. Depression after the acute phase is related to higher levels of negative symptoms.

DiS is a major risk factor of suicide attempts and completed suicide in schizophrenia. While data differ, about 10% of patients with schizophrenia die by suicide. Antipsychotic treatment decreases the risk of suicide and clozapine has been identified as an antipsychotic with proven efficacy in preventing suicide in schizophrenia. The use of antidepressants in schizophrenia has been a neglected area of research and the available data are controversial. Since affective changes may be related to a progressive decrease in social interaction and loss of reinforcement of social behaviors psychosocial interventions may be efficacious, such as cognitive therapy and aggressive community treatment.

SO 0302. Risks and Benefits of Atypical Antipsychotics in the Treatment of Generalized Anxiety Disorder (GAD)

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Current treatments for Generalized Anxiety Disorder (GAD) include the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenalin reuptake inhibitors (SNRIs), the calcium channel modulator pregabalin, tricyclic antidepressants (TCAs), benzodiazepines and a number of other medications [1]. There is no ideal drug for the treatment of this disorder. The disadvantages of antidepressants include the late onset of effect (usually after 2–4 weeks) and side effects such as initial jitteriness, nausea or insomnia. Benzodiazepines are associated with the risk of developing addiction. In the recent years, some randomized controlled studies have been conducted with atypical antipsychotics such as quetiapine – either as monotherapy or as adjunctive medication to antidepressant treatment. One advantage of atypical antipsychotic treatment for anxiety disorders is the faster onset of action, while side effects such as the metabolic syndrome have to be taken into account. The risks and benefits of atypical antipsychotics in the treatment in GAD are discussed.

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SO 0303. Atypicals in the treatment of MDD - advantages and risks

Hans-Jürgen Möller

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Placebo-controlled studies performed in recent years have shown that some second generation antipsychotics have antidepressive effects. The positive results from some studies in bipolar depression are especially impressive and underline the antidepressive potencies of novel antipsychotics beyond the spectrum of schizophrenia. The antidepressive effect of second generation antipsychotics was recently also demonstrated in MDD, both as monotherapy as well as augmentation.

The antidepressive potential of second generation antipsychotics is presumably related to their pharmacological mechanisms, which differ from those of traditional neuroleptics. Among others, 5-HT_{2A} antagonism is of special relevance for most of the new antipsychotics in this respect. But also special interactions with the dopaminergic system, as is the case with amisulpride and aripiprazole, or noradrenalin- and/or serotonin-reuptake-inhibition, as with quetiapine and ziprasidone, should be considered. The presentation will present the recent data on efficacy and tolerability.

SO 04. Why are there so few new Psychotropics

SO 0401. Has the demand for evidence in psychiatry become counterproductive?

Elias Eriksson

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Psychologist Irving Kirsch has attracted attention by claiming that antidepressants do not work, and that the larger effect nevertheless sometimes noted in patients receiving active treatment in placebo-controlled trials can be explained entirely by side effects augmenting the placebo effect exerted by the antidepressant. In this presentation, the arguments of Kirsch will be analyzed and rebutted, but it will also be pointed out that bodies such as NICE in UK and SBU in Sweden also have grossly misinterpreted the literature on treatment efficacy, doing partly the same mistakes as Kirsch (e.g., over-relying on meta-analyses, and ignoring methodological errors often leading to type-II errors). Also, such bodies, illogically, usually do not apply the same demands on psychotherapy studies as on drug trials (e.g. with respect to the necessity of an appropriate control group), hence overrating the efficacy of, e.g., CBT, one example being that the Swedish National Board of Health and Welfare recently concluded (groundlessly) that internet-CBT is as effective as antidepressants for the treatment of depression (and more cost effective). Also, it will be pointed out that numerous clinical observations regarding pros and cons of various drugs for various subgroups of patients will, for commercial reasons, never be formally tested in large controlled trials, and hence never become “evidence-based”, notwithstanding the fact that they may be both accurate and relevant. Attempts to make clinicians adhere to recommendations based on such a pseudo-scientific fundament as that presented by

bodies like NICE or SBU, and/or to prevent them from taking non-evidence-based observations into consideration when selecting treatment for the individual patient, by implementing mandatory guidelines, or by denying certain drugs reimbursement, can not be in the interest of the patients or of society; moreover, such a policy may augment the reluctance of many drug companies to invest in the field of psychiatry, hence reducing the likelihood that new and better drugs will be developed.

SO 0402. Economic barriers to developing new treatments

Anders Gersel Pedersen
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Diseases of the central nervous system (CNS) such as depression and alcohol abuse are among the most expensive to society and will continue to be a burden into the next decades. The value of the CNS pharmaceuticals market is close to \$100bill, and it is characterised by substantial unmet medical needs as the majority of available treatments are palliative only or with unwanted side-effects. Unfortunately, drug development in CNS faces more challenges than that of other disease areas. For instance, in CNS there is a higher failure rate in phase III due to lack of efficacy and the overall probability for a new drug to reach market of about 14% is lower than that of other disease areas 17–18%. Increasing regulatory hurdles add to the cost of bringing new CNS drugs to market and price setting is becoming more and more complex. In addition, regulatory studies are designed to show pharmacological effect, not broad public utility. For the pharmaceutical companies this increases the need for investments in health economic studies, and in turn the financial risk, in the pre-approval phase. Also, regulatory authorities are raising the bar for approving new drugs. The reason being that at the time of marketing authorisation the risk-benefit assessment and the value description for the next 5–10 years rely on a ‘snapshot’ in time of available data obtained in the trial context. Thus, a better value description would be achieved through a post-approval assessment based on “everyday” use with predefined metrics. This would also allow for faster regulatory approval, thereby contributing to reduce zero value-creation time. One solution is a higher degree of sharing of the risk – and of the benefit – between pharmaceutical companies and society. Furthermore, with increasing safety hurdles and additional pre-approval costs – extension of exclusivity could be considered. In summary, there is a need for a new economic risk

sharing model to facilitate innovation with limited excessive cost.

SO 0403. Sunset on New Psychotropics in Europe

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Those with psychiatric disorders have long suffered from prejudice. Their illnesses and suffering are often trivialised by journalists in their columns and by government agencies. Tougher regulations appear to be imposed on the licensing of new treatments in psychiatry and harsher criteria for their reimbursement by government agencies compared with other therapeutic areas despite clear evidence that these disorders are associated with the highest levels of suffering and disability according to the WHO.

For a new treatment for a psychiatric disorder to be licensed in the EU more studies meeting stricter conditions are required than is the case with equivalent licensing authorities such as the FDA. For example, in the EU a comparator arm is required in clinical trials in addition to the more scientific placebo control. There is no adequate justification for this demand which appears to confound the demonstration of efficacy and safety versus placebo with pricing issues. A further hurdle in the EU is the requirement that long term efficacy compared to placebo at the minimum effective dose is established before a treatment can be licensed. This causes delay in bringing the drug to the market and adds considerably to the cost of development. The process might be eased if access to specialist advice by the licensing agencies, strictly limited in the European Medicines Agency in contrast to other agencies, were improved.

Difficulties in the licensing process and delays following the granting of a licence inevitably have a negative effect on the viability of developing new treatments. Even when a licence is granted transparency/pricing commissions are the source of serious delays before clinicians are allowed to prescribe the treatment. Delays in allowing access to treatment by EU citizens can be so long that medications become available only after they have come off patent. These issues have led some pharmaceutical companies to withdraw from the development of treatments in psychiatry for the EU market and to close their neuroscience laboratories. The resulting loss of expertise in neuroscience will not be easily reversed. Psychiatric patients in the EU will find that the options for new treatments of their serious disorders are declining compared with other countries.

SO O05. Advances in the therapy of treatment resistance

SO 0501. Is personalised gene targeted therapy in resistant depression possible?

Alessandro Serretti, Chiara Fabbri
Institute of Psychiatry, University of Bologna, Bologna, Italy

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. Evidence suggests that genetic factors contribute for about 50% of the antidepressant response therefore the knowledge of the patient genetic profile may lead to an individualized therapy in the next years in resistant depressed subjects.

Several gene variants have been reported in association with antidepressant response. A growing number of evidence has been reported for the functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), particularly 1 allele has been associated with a better response in Caucasian. A significant number of replication findings are present in literature also for 5-HT2a, 5-HT1a, BDNF, COMT, MAOA, NET, Gbeta3, FKBP5, Pgp, TPH, ACE and GSK-3 β variants, although an high number of failure 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. We also performed a pathway analysis on STAR*D dataset to investigate possible pathways involved in resistant depression.

Until now genetics was not able to predict the overall response to antidepressant. However there are increasing evidences of a genetic modulation on treatment response in resistant depression, both directly and through a modulation or an interaction with clinical variables that could influence the response to antidepressant, like personality and social modulators.

SO 0502. Recent advances in treatment-resistant generalized anxiety disorder

David Baldwin^{1,2}

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Generalized anxiety disorder (GAD) is common in community settings and in primary and secondary medical care. The associated societal burden is considerable, and although some patients receive unnecessary or inappropriate interventions, many of those who might benefit from pharmacological or psychological treatment are not recognised or treated. Evidence-based guidelines for pharmacological management tend to recommend initial treatment with either a selective serotonin reuptake inhibitor (SSRI), a serotonin-noradrenaline reuptake inhibitor (SNRI) or the novel anxiolytic drug pregabalin [1].

Current evidence does not permit reliable conclusions about which treatment approaches might have superior efficacy or tolerability [2]. Response rates can be disappointing in routine practice, and it is not possible to predict reliably which patients will respond well and which will show only a limited response to treatment. However an eventual response to treatment is unlikely if a patient derives no clear benefit within the first four weeks of treatment [3].

There have been few studies of the further management of patients who do not respond to initial treatment and there is a pressing need for further randomised controlled trials, in patients who do not respond to an SSRI, SNRI or other treatment. Current strategies include continuing with the same dose, increasing the dosage, combining with another psychotropic compound (for example an antipsychotic drug or pregabalin), or switching to another drug. The combination of pharmacological with psychological treatments is common in clinical practice, but without proven efficacy.

Future treatment guidelines will be influenced by emerging data with both established and novel pharmacological interventions and through better identification of patient sub-groups that are likely to respond preferentially to particular interventions.

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SO 0503. Novel treatment of resistant depression

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The definitions of treatment resistant depression (TRD) vary from non-response to a single antidepressant given at an adequate dose for sufficient duration to the more complicated failure to respond to two separate courses of treatment with antidepressants from two different classes for an adequate duration (CPMP 2002).¹

Various treatment strategies have been proposed and the evidence in favour of using antidepressants from two different classes is weak and has not been adequately tested.

The primary objective of this multicenter study is to evaluate the efficacy of escitalopram in TRD, assessed by 2 consecutive, failed antidepressant treatments from different classes. The last treatment received being a 4 to 6 week prospective trial with venlafaxine.

To date, 392 MDD patients considered as non responders to at least one adequate antidepressant trial (baseline MADRS score: 31.58) have been openly treated 4 to 6 weeks with venlafaxine. Patients with persisting MDD and with less than 50% reduction on MADRS scores were then switched to escitalopram for an additional 6 weeks prospective trial.

Response rate to venlafaxine (mean maximal dose: 186.73 mg) was 45,60% (140 patients). Remission, defined by MADRS score <12 was observed in 23,8% of venlafaxine treated patients. From the 167 non responders to venlafaxine, 158 TRD patients continued the study and entered an additional 6 weeks treatment with escitalopram (mean maximal dose: 26,55 mg). Response to treatment was observed in 48,3% of patients after 6 weeks with remission rate of 26,2%.

Escitalopram produced a higher than expected response in the treatment of resistant patients who had failed to respond to at least 2 antidepressants including most recently venlafaxine.

The study is supported by an unrestricted grant from Lundbeck S/A.

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SO 06. Debate: the amine hypothesis is a dead end for drug development**PRO: Monoamine Debate**

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For over half a century the pharmaceutical industry has largely focused on antidepressant development by targeting the monoaminergic system. Both the noradrenergic neuronal network, largely centred on the nucleus locus coeruleus and the serotonergic raphe nuclei have been the object of attention. This approach led to the development of the SSRIs which reduced the side-effects burden on patients but no significant improvement has taken place in terms of efficacy. At this point it must be obvious to all that the line of research is in a *cul-de-sac* and that further investment of resources in such a strategy is futile.

One of the major deficits in the monoamine hypothesis of depression which has led to a search for monoamine acting drugs, lies in the fact that far too much credence has been given to data acquired from studies in rodents. Proportionately, there are far more monoamine neurones in a rat than a human brain. The result is that the role of monoamines in psychiatric illnesses has been greatly exaggerated. At this point almost every diagnosis in DSM-IV has been linked to monoamine malfunction. Given the relatively small number of monoamine neurones in the human brain this situation is ridiculous. A simple monoamine hypothesis is far too simplistic to explain the complexity of major depression.

The industry faces the challenge of exiting the intellectual current *cul-de-sac* or exiting antidepressant research altogether. Sadly many companies have taken the latter route.

Far more sophisticated psychobiological models need to be used in drug development, which take on board the full complexity of the depressive syndrome. It is obvious that in the overwhelming majority of patients that stress plays a major role, we need therefore to focus on stress mechanisms. Furthermore, it is beyond doubt that most depressed patients have a pro-inflammatory phenotype characterised by elevations in pro-inflammatory cytokines. This inflammatory component offers a potential drug-development target as do a variety of other biological processes associated with depression such as changes in trophic factors and in pivotal microRNAs.

Surely the time has come to forego our obsession with monoamines?

CONTRA: The amine hypothesis is a dead end for drug development. No way !

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The amine hypothesis of depression was developed to help understand the mechanism of action of the early tricyclic antidepressants that were discovered through clinical serendipity. From its simplistic early form, “the activity of one or more of the monoamine systems needs to be enhanced to achieve an antidepressant effect”, the hypothesis has evolved to a more general notion, “an antidepressant effect is achieved by *modulation* of one or more of the monoamine systems”.

For decades no one has seriously proposed that monoamine modulation is the only step in antidepressant action. It does however appear to be an integral part of (virtually) all forms of antidepressant therapy that have been shown to be effective so far. In addition, modulation of monoamine systems has proven to be a relatively benign way of achieving an antidepressant effect.

The monoamine hypothesis is compatible with all antidepressants that have been approved to date. In addition virtually all putative antidepressants with so-called “new” mechanisms of action seem to involve, at least indirectly, the modulation of one or more monoamine system. Neurogenesis and central inflammatory reactions, for example, which have been suggested to provide new directions in antidepressant research, are both closely associated with monoamine modulation. Similarly light therapy, exercise, St John’s Wort and other “soft” antidepressant therapies all influence monoamine neurotransmission.

As long as the monoamine hypothesis is seen as a construct describing one (although not necessarily the only) easily accessible and relatively benign entry into the labyrinthine path that leads to an antidepressant effect it is far from “a dead-end”. Indeed investigation of the changes brought about in the brain by treatment with the monoaminergic antidepressants has already unearthed an impressive number of mechanisms that may be involved in the antidepressant process and it is likely in the future to lead to new entry points into the labyrinth.

SO 07. Multidimensional Interactions in Depression

SO 0701. The challenges posed by ethnic and cultural diversity in the treatment of depressed patients

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The world is diverse ethnically and culturally. More than ever before in human history, countries are becoming ethnic and cultural melting pots. This is because of migration, both intra-national and international, as well as of the huge development of media with its impact on the “mental globalization”.

This evolution has an impact on the diagnosis and treatment of mental patients. For example, there is a progressive evolution from traditional ways of expressing depression, such as possession and persecution forms, to more “modern” ones, such as guilt depression, evolving towards “post-modern” expression. In most countries of the world, this evolution is taking place, with its corollary, an increase of incidence of suicide. The wide spread of Internet everywhere in the world will dramatically change the information about mental disorders and their treatment in the general population, through direct access to information. This will impact also on the compliance in the future, as patients will be more and more aware of the necessity of continuing the treatment till the doctor decides to stop it.

Concerning traditional healing, it is prevalent in all countries with “traditional” cultures, but it also exists in more modern societies through “soft medicine” practices.

A number of studies have shown differences in pharmacokinetics and pharmacodynamics of antidepressant medications in various ethnic groups. Nothing definitive has been found so far that has a practical significance. The “Cytochrome P450 medicine”, adapting prescription to each patient, whatever is his/her ethnic background, is one solution to this diversity.

SO 0702. Drug-Drug interactions in polymedicated depressed patients

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Based on two recently completed pharmacoepidemiology studies by the author, more than 75% of patients on an antidepressant in clinical practice are taking at least one medication in addition to their antidepressant. Mean and median number of additional medications is 3 and 2, respectively, and extreme is more than 20 additional medications. Thus, the vast majority of patients being treated with antidepressants are at risk of having one or more drug-drug interaction (DDI). There are two major types of DDIs: pharmacodynamic (PD) and pharmacokinetic (PK). PD interactions are where the mechanism of

action of the co-prescribed drugs either potentiate or diminish their respective effects on the body. PK interactions are where one drug affects the absorption, distribution, metabolism, or elimination of the other drug. PD DDI interactions are most common with the oldest antidepressants (i.e., tricyclic antidepressants, TCAs, and monoamine oxidase inhibitors, MAOIs) whereas PK DDIs are more common with newer antidepressants. The most common mechanism involved in PK DDIs is alteration in the activity of cytochrome P450 (CYP) enzymes which are responsible for metabolism of many drugs. Pharmaceutical science has progressed to the point that CYP enzymes mediated DDIs can be minimized, if not completely eliminated when designing and developing new medications. As that has happened, attention has shifted to PK DDIs mediated by effect on drug transporter proteins such as P-glycoprotein. This lecture will provide a brief overview of the pharmacological principles underlying DDIs and the history of DDIs as they relate to antidepressants and then will review all of the currently marketed antidepressants in terms of their potential for either causing or being a victim of DDIs both those which are PD and PK. The presentation will also review the myriad of ways that DDIs can present clinically.

SO 0703. The clinical importance of monoamine interactions in antidepressant therapy

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Noradrenaline (NA), serotonin (5-HT), and dopamine (DA) neurons send projections to each other giving rise to physiologically important reciprocal interactions. 5-HT neurons exert an inhibitory action on both NA and DA neurons. Consequently, when 5-HT transmission is enhanced by some antidepressants, the activity of NA and DA system is dampened. In contrast, NA and DA exert an excitatory effect on 5-HT neurons through α_1 -adrenergic and D2 receptors, respectively, that are located on the cell bodies of 5-HT neurons. Finally at the nerve terminals, 5-HT neurons have inhibitory α_2 -adrenergic receptors and in several forebrain regions DA is removed from synapses by NA reuptake transporters. The implication of these reciprocal interactions is that when interfering with a single neuronal element, there can be repercussions in the other two systems that can have a positive or negative impact.

Milnacipran is both a NA and a 5-HT reuptake inhibitor. Contrary to venlafaxine, duloxetine, and desvenlafaxine, it is more potent *in vivo* to inhibit the

reuptake of NA than that of 5-HT. This lower potency of milnacipran to inhibit 5-HT reuptake in humans is indicated, for instance, by its lesser capacity to decrease platelet 5-HT, occurring through 5-HT reuptake, than venlafaxine or duloxetine. In contrast, milnacipran exerts a potent action on the firing activity of NA neurons through inhibition of NA reuptake.

There are several clinical implications for the preferential action of milnacipran on the NA neurons than on 5-HT neurons. Upon treatment initiation, nausea is less commonly encountered with milnacipran, than with other potent 5-HT reuptake inhibitors (SRIs). As for nausea, sexual dysfunctions can also occur with potent SRIs because enhancing 5-HT levels through blockade of 5-HT transporters may trigger these two side effects. Potently inhibiting NE reuptake will produce an antidepressant effect, but may also improve energy levels, concentration, and possibly cognition through an enhanced NA and DA function in areas such as the frontal cortex. Nevertheless, the capacity of milnacipran to still inhibit to a certain extent 5-HT reuptake but also NA reuptake to a marked degree would explain its therapeutic effect in fibromyalgia. Finally, upon cessation of a milnacipran regimen, 5-HT discontinuation symptoms rarely occur because of its lower occupancy of 5-HT transporters than SRIs, including venlafaxine and duloxetine.

SO 08. Treatment of resistant disorders

SO 0801. Antidepressant-resistance in unipolar and bipolar depression

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Antidepressant-resistant major depression (AD-RD) is a great clinical challenge for the treating clinician. In spite of the fact that there are several causes of AD-RD in general, there is a growing body of evidence that one of the most common source of it is the unrecognized bipolar nature of the “unipolar” major depressive episode, when the patients receive antidepressant monotherapy – unprotected by mood stabilizers/atypical antipsychotics. While it is well documented that the optimal clinical response to antidepressants is much rare in bipolar I and II than in unipolar major depression, only the most recent clinical studies have focused on the boundaries between treatment-resistant unipolar major depressive disorder and bipolar disorder. The most widely noted conclusion of the prior studies on AD-RD is

that if noncompliance, hypothyreosis, use of “depressogenic” drugs and pharmacokinetic causes (e.g. fast metabolization) etc, can be excluded, antidepressant-resistance reflects the heterogeneity of depressive disorders and different subgroups of depressed patients respond (or do not respond) to different drugs. However, current psychopathological research on the complex relationship between unipolar depression and bipolar disorders show that the most common source of antidepressant-resistance in DSM-IV diagnosed unipolar major depression is the result of the subthreshold or unrecognized bipolar nature of the depressive episode and antidepressant-induced (hypo)manic switches, antidepressant-resistance and “suicide-inducing” potential of antidepressants seem to be related to the underlying bipolarity of the major depressive episode.

SO 0802. Treatment for resistant OCD

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Obsessive-compulsive disorder (OCD) is a chronic, disabling, lifespan, neuropsychiatric disorder that usually responds only partially to existing treatments. In this lecture I shall present a narrative review of the available treatment strategies, from the perspective of ‘research-enhanced healthcare’ including data from translational research. I aim to answer three main questions: (1) How effective are the first-line treatments? (2) How long should treatment continue? (3) What is the management of treatment-resistant OCD? Selective serotonin reuptake inhibitors (SSRIs) and cognitive behaviour therapy (CBT) remain the treatment of choice for most patients. It is unclear how far their combination might improve outcomes. SSRIs are associated with improved health-related quality of life. However, discontinuation is associated with relapse and loss of quality of life, implying treatment should continue long-term. A substantial minority of patients fail to respond to SSRI. Such patients may respond to other strategies such as dose elevation or adjunctive antipsychotic, though long-term trials validating the effectiveness and tolerability of these treatments in this patient-group are relatively lacking. Newer compounds, such as serotonin-receptor ligands or agents targeting other neurotransmitter systems that may be relevant for OCD, such as opiate or glutamate pathways, are undergoing evaluation.

SO 0803. Prevention of PTSD: does a window of opportunity exist?

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The medical concept of golden hours is well-established in situations like CVA and MI. PTSD might benefit from this approach as, like in those disorders, the time of onset is clear [1,2].

To date, several interventions have been explored, including debriefing, and administration of benzodiazepines, propranolol, morphine, cortisol and SSRI (for SSRI the “window” was extended beyond a few days, but within one month).

Several debriefing studies suggest that it might not be helpful, and actually might interfere with the robust and potent process of spontaneous recovery.

Intervention with benzodiazepines was also found to have a potential risk of interfering with spontaneous recovery, and recently some groups have recommended against using them. The underlying mechanism of benzodiazepines – deactivation of the HPA axis – may be linked to its adverse activity in the first few hours after exposure to trauma. Propranolol studies have had mixed results, and although it is theoretically of interest, it does not currently seem to be an interesting clinical tool.

A large multicenter, double-blind study conducted recently in Israel sought to examine the efficacy of SSRI (escitalopram) in preventing PTSD for patients displaying symptoms of acute stress disorder, beginning treatment within one month of the traumatic event. Preliminary results, as well as a discussion of the methodological issues involved in recruitment and follow-up for this type of study, will be presented.

Cortisol – the “stress hormone” is a cornerstone in the normal response to traumatic events. An animal model using rats with hyper-reactive HPA axis (the Fischer strain), or hypo-reactive (the Lewis strain), showed that plasticity of the HPA axis is critical for recovery from a traumatic event. It was also found that the normal hyper-secretion of cortisol following exposure to a traumatic event was associated with a reduction in the amplitude of the memory-fear associated with the exposure [3] This has aroused interest in the potential use of a medium dose (100–140 mg) of intravenous cortisol. A small preliminary study has shown that this approach might have potential benefit.

Changing the focus from treatment once PTSD is already established to secondary prevention of PTSD in the “window of opportunity” – the first few hours after exposure to a traumatic event – has

opened the door to new exciting possibilities in PTSD research and treatment.

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SO 09. Advances with Herbal remedies

SO 0901. Is lavender an anxiolytic?

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Background: In primary care settings patients with core symptoms of anxiety are common. Often they stay untreated while not fulfilling all criteria for diagnosing anxiety disorder. Treatment options for sub-threshold anxiety disorders are important because untreated symptoms result in chronification, deterioration and concomitant disorders.

Methods: We summarized available data on efficacy and safety of Silexan, a patented active substance with an essential oil produced from *Lavandula angustifolia* flowers by steam distillation. Silexan complies with the monograph Lavender oil of the Ph. Eur. and exceeds its quality definition with respect to items important for efficacy and tolerability.

Results: Three randomized, double-blind, controlled clinical studies investigated the efficacy of Silexan in subsyndromal anxiety (vs. placebo; 10 weeks treatment), in generalized anxiety disorder (GAD) (vs. lorazepam; 6 weeks), and in restlessness and agitation (vs. placebo; 10 weeks) according to DSM IV or ICD 10 criteria. The studies assessed the severity of anxiety symptoms using the Hamilton Anxiety Scale (HAMA) as primary outcome variable. 230 patients were treated with Silexan 80 mg/day, 37 with lorazepam 0.5 mg/day and 192 received placebo (full analysis set). Baseline scores of HAMA ranged between 24.7 and 27.1 points. Patients treated with Silexan were superior to placebo after week 2. Comparing Silexan and lorazepam in the initial dosage of 0.5 mg resulted in similar HAMA total

score reductions. The decrease of anxiety levels was accompanied by a reduction of restlessness and comorbidity, and by improvements in general well-being and sleep.

Typical adverse effects were limited to predominantly mild and transient gastrointestinal events like eructation and nausea. Silexan showed no unwanted sedative effects and has no potential for drug abuse.

Conclusions: Silexan is a safe herbal treatment option in patients with sub-threshold anxiety disorders. It was shown to be efficacious in treating symptoms associated with anxiety.

SO 0902. Who benefits from St. John's Wort?

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According to the last Cochrane report about St. John's Wort (SJW) of 2008 the plant extracts studied in the included trials were superior to placebo in patients with Major Depression and similarly effective as standard antidepressant drugs. This has been shown in 18 comparisons with placebo and 17 comparisons with standard antidepressants. In accordance with this the official guidelines of the professional psychiatric associations of Germany, Canada and the United States from the years 2009/2010 as well as the HMPG monograph recommend the use of SJW extracts for the treatment of mild to moderate depressive patients.

Based on these studies the benefits for patients are:

- effective for patients with mild to moderate depression (Cochrane 2008).
- suitable for patients not tolerating SSRI- or SNRI-treatment, i. e. being sensitive to side effects (Kasper et al. 2010).
- clear effects on the typical core symptoms of depression characterised by cluster 1 of HDRS-17 (Kasper and Dienel 2002).

There is a substantial difference between the various SJW preparations (WS 5570, STW 3, LI 160 and Ze 117) as for the members of the SSRI family concerning their biochemical and clinical characteristics.

SO 0903. Mood and Anxiety Symptoms in Dementia: The Effects of Ginkgo biloba Extract EGb 761®

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Background: Findings from earlier and smaller trials suggest that Ginkgo biloba extract EGb 761® might improve behavioral and psychological symptoms of dementia. Further research was undertaken to corroborate these data.

Methods: Three placebo-controlled, double-blind, multi-centric clinical trials were performed, each one involving approximately 400 patients with mild to moderate dementia (Alzheimer's disease, vascular dementia or mixed form) who had clinically significant neuropsychiatric symptoms (total composite score on the Neuropsychiatric Inventory (NPI) higher than 4 and at least one composite symptom rating 4 or higher). Patients were randomly assigned to receive 240 mg per day of EGb 761® or placebo for a period of 22 (one trial) or 24 weeks (two trials). Erzigkeit's SKT cognitive test battery was used as primary outcome for the cognitive domain and the NPI was chosen as main outcome for the behavioral/neuropsychiatric domain.

Results: In all three trials EGb 761® was significantly superior to placebo with regard to all dementia-related outcome measures, including cognitive performance, neuropsychiatric symptoms, activities of daily living, clinical global impression and quality of life. Significant improvement in the NPI total score as well as in the NPI caregiver distress score was found in patients treated with EGb 761®, whereas there was no meaningful effect or even worsening in those receiving placebo. Depression, anxiety, apathy, irritability and aberrant nighttime behavior were the symptoms improved most markedly and most consistently across the three trials. EGb 761® was safe and well tolerated with rates of adverse events at placebo level.

Conclusions: The data are in accordance with former findings demonstrating that Ginkgo biloba extract EGb 761® is effective in the treatment of patients with dementia. In addition to cognitive performance, activities of daily living, global assessment and quality of life it improves the patients' neuropsychiatric symptoms and the caregivers' distress related to such symptoms.

SO 10. Hot Topics

SO 1001. New Directions In Insomnia Therapeutics

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Recently there have been significant advances in understanding insomnia Pathophysiology and

phenotypes resulting in advances in pharmacotherapy in terms delivery systems, therapeutic targets as well as the definition of efficacy. New formulations have (i.e. rapid onset and offset of activity) has allowed for more individualized and prn treatment for insomnia specific phenotypes (i.e. Middle of the Night Insomnia) which had previously been treated indirectly. In terms of therapeutic targets it is important to remember that sleep is controlled by alerting neurotransmitters like histamine, acetylcholine, origin, serotonin, and norepinehrine as well by sleep promoting neurotransmitter like adenosine, galanin, GABA and melatonin. Until recently the only drugs approved for the treatment of insomnia were benzodiazepine receptor agonists. While these drugs are efficacious they possesses broad CNS depressant and hence depending on dose and formulation are associated with risks. The search for new receptor targets has resulted in melatonin agonists for sleep onset insomnia as well as serotonin, orexin and histamine antagonists for sleep maintenance. The most interesting advances have been the development of new therapeutic endpoints. As in the past, there continues to be a reliance on both objective as well as patient report assays to define sleep effects. However there is an increased focus on the other aspect of insomnia in terms of daytime effects. Most importantly as insomnia is comorbid with other conditions 90% of patients the efficacy of sleep agents has targeted improving sleep as well as the comorbid condition. Specifically, hypnotics have been evaluated in terms of their effects on depression, anxiety, pain as well as other disorders. Sleep medicine in general and insomnia management is experiencing rapid evolution. It is important to keep clinicians up to date with this rapidly evolving knowledge base.

SO 1002. Branded and Generic Medications - Are they Interchangeable?

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Globally, the pricing of generic medications has made their use more attractive to both public and private payers. Generic medications are less expensive than their branded product counterparts and therefore commonly present a cost-containment strategy in healthcare. Although encouraging the use of generic drugs is a simple way of reducing medication expenditures, the impact on the overall cost of medical care is more complex than just

looking at the “drug cost”. Other factors such as effectiveness, adherence, symptom exacerbation, adverse events and utilization of other health care services should be considered. The choice of medication is multifactorial and rests with the prescribing physician.

Regulatory authorities have similar requirements for the approval of generic medications which are based on the establishment of bioequivalence. It is unclear whether the current standards ensure that generic medications have equivalent efficacy and safety to branded medications. The issue of interchangeability continues to be controversial.

A review of the literature identifies a number of conflicting reports surrounding the efficacy and safety of a variety of pharmaceutical products across therapeutic areas. Clinicians should be aware of the data and consider potential differences when incorporating generic medications into their practice. Medications with a narrow therapeutic range and those with a modified release formulation require particular consideration.

This program will clarify for participants the current bioequivalence requirements and approval process for generic medications. A review of the published data as well as clinical experience with a broad range of medications will be used to highlight potential issues in the prescribing of generic medications.

The program will address the reality that the process of medications choice is based on many factors and that incorporating generic medication ultimately rests with the prescribing physician. Decisions need to be individualized and the goal is to optimize patient outcomes. Financial considerations cannot be ignored but what does this mean for patient care and the overall health care utilization? Is there really a cost saving?

SO 1003. Why Do Clinical Trials Fail? Learning from Computer Administered Assessments

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Purpose: The high failure rate of randomized controlled trials (RCT) is a well recognized obstacle to drug development, but remains poorly understood [1]. We report exploratory analyses utilizing data collected by interactive computer interviews to examine the impact of protocol specified eligibility criteria and rating reliability on signal detection in a Bipolar Depression RCT.

Methods: These clinical trial methodology (CTM) analyses were undertaken as part of a failed randomized controlled trial. The efficacy study was a double-blind placebo controlled trial designed to test adjunctive ziprasidone as treatment for acute depression in 265 bipolar I subjects. Based on assessments administered by the site-based rater (SBR) subjects met all requirements for randomization including DSM IV diagnostic criteria and baseline HAM-D scores ≥ 20 . In addition to the efficacy study assessments, subjects completed independent computer administered assessments for diagnostic confidence and symptom severity (HAMDCOMP, MADRSCOMP, YMRSCOMP) prior to randomization and at least one postrandomization assessment on the MADRS.

The CTM study compared drug-placebo differences on change from baseline MADRSSBR and MADRSCOMP (primary outcome measure) for subgroups created based on the computer assessments including protocol specified baseline severity criteria (HAMDCOMP ≥ 20 , Diagnostic Confidence, Presence of Mixed episode, Baseline Inflation, and Overzealous subject reporting. Diagnostic confidence was measured using the Bipolarity index [2]. A mixed episode was diagnosed, if at least 3 items on the computer administered YMRS were rated to be of clinically significant severity (defined as a score of ≥ 5 on items 5, 6, 8, and 9 or a score ≥ 3 on the other YMRS items.). Rating reliability was defined as poor and attributed to Baseline inflation by the SBR if (MADRSCOMP - MADRSSBR) ≤ -10 , or attributed to Overzealous Reporting by the Subject if (MADRSCOMP - MADRSSBR) $\geq +10$.

CTM signal detection analyses used Stata version 11.0 statistical software. Since the efficacy study was powered to detect a drug-placebo difference of ≥ 4.0 points on change from baseline MADRS, but was not powered for these exploratory analyses, criteria which resulted in more than 1.0 difference in the drug-placebo signal on both the SBR and Comp ratings were arbitrarily defined as “impactful” prior to the data analysis.

Results: There were no statistically significant differences between adjunctive ziprasidone vs mood stabilizer with adjunctive placebo groups with respect to primary outcome (change from baseline MADRS), based on the SBR scores or the computer-administered assessment. While there were numerical advantages consistent with greater study drug-placebo separation in subjects meeting key eligibility criteria, and having higher diagnostic confidence there was a large effect favoring placebo among subjects meeting the criteria for rater baseline inflation and those meeting criteria as “over-zealous subject.”

Conclusions: The main findings of the exploratory CTM analyses, was the observation of

“Impactful” but nonsignificant trends favoring placebo in the subgroups with mixed episodes rather than bipolar depression and among two subgroups with large discordance between MADRSSBR and MADRSCOMP at baseline. This is consistent with the suggestion that unreliable ratings by subjects as well as SBRs contribute to study failure. These results suggest more stringent subject selection processes may improve RCT signal detection, but do not support the practice of qualifying subjects based on a threshold score obtained on a different depression scale than that used for the primary outcome.

SO 11. Dilemmas in Bipolar Disorder

SO 1101. When is depression bipolar? : implications for treatment

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Bipolar disorder is a common mood disorder that is frequently misdiagnosed as major depressive disorder (MDD). Bipolarity may be underdiagnosed because patients often seek treatment when they are depressed but do not often present with hypomania and instruments based on existing diagnostic criteria may be insufficiently sensitive for detecting hypomania. Support for this view comes from the recent BRIDGE study which found that many patients with a *DSM-IV* diagnosis of MDD meet criteria for subthreshold bipolar disorder (Angst et al, Arch Gen Psychiatry 2011;68 791–798). The bipolar specifier criteria employed in BRIDGE identified more MDE patients as having bipolar I or II disorder than were identified by *DSM-IV*. Furthermore, compared with *DSM-IV*, the specifier criteria distinguished bipolar disorder and MDD much more sharply in terms of validators (family history, course) and resulted in a shift of comorbidity (eg, anxiety, substance use disorders and borderline personality disorder) from MDD to bipolar disorder.

The findings from the BRIDGE study of an increased prevalence of bipolar disorder and a shift in comorbidity away from MDD have implications for the management of patients with bipolar disorder. The efficacy of pharmacotherapy in bipolar depression, the prevailing phase of illness in bipolar II disorder, remains uncertain. Numerous studies of the treatment of bipolar depression have included antidepressants, mood stabilizers and antipsychotics. Generally, the quality of these studies was poor, with open-label studies predominating and/or adequate

statistical power usually lacking. However, there is robust evidence of the efficacy of some antipsychotic agents in the treatment of depressive episodes in bipolar II disorder. Considering tolerability in the context of efficacy outcomes for medications may help guide management of patients with bipolar II disorder.

SO 1102. Epidemiology of bipolar spectrum disorders beyond DSM-IV: new results from the Zurich Study

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Background: With the ongoing revisions of DSM-IV and ICD-10 the classification of mood disorders continues in a state of flux. Unfortunately there is a dearth of good epidemiological and clinical data for such revisions: most studies applied a top-down approach based on current diagnoses, which collected little additional data suitable for questioning the underlying diagnostic criteria. The re-analysis of several large studies suggested that the DSM-IV diagnosis of major depressive disorders (MDD) covers a very heterogeneous group, which includes as many as 40% of subjects with sub-threshold bipolarity. Our purpose is to provide some data from the Zurich Cohort Study which may contribute to more precise definitions.

Methods: The Zurich Cohort Study is based on a screening sample of 4547 persons (aged 19/20) representative of the Canton of Zurich collected in 1978; a stratified interview sample (N = 591) enriched for risk cases was selected (2/3 high and 1/3 low scorers on the SCL-90 R). Weighted back to the normal population, it represents 2600 subjects of the general population. Seven interviews by psychologists/psychiatrists were carried out between 1979 and 2008 (up to age 50). The attrition rate over 30 years was 43%. A bottom-up approach based on a wide variety of symptoms was used for the assessment of 12 functional somatic and 15 psychiatric syndromes. This allows varying definitions of bipolar disorders (BD): DSM-IV, Specifier criteria (developed in the BRIDGE study), Zurich criteria.

Results: The cumulative prevalence rates for the three diagnostic concepts (DSM-IV, Specifier, Zurich) were as follows:

- a) DSM-IV BD 2.7% and MDD were 8-fold higher with 23.6%.
- b) Specifier criteria gave prevalence rates of 5.2% BD and 21.0% MDD.

- c) The even broader Zurich criteria resulted in 13.4% BD and 13.2% MDD. In addition we found 9.4% minor bipolar and 12.2% minor depressive disorders.

The analyses of validators favoured the broader Zurich concepts of bipolarity.

Conclusions: The current diagnostic classification of mood disorder is highly questionable.

The large DSM MDD group includes numerous hidden bipolar subjects, who can be identified with good validity by broader criteria for bipolarity. In the future large epidemiological studies using a bottom-up, more phenomenological approach are required.

SO 1103. Evidence for treatment of Bipolar Spectrum

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Treatment of bipolar spectrum, cyclothymic and related bipolar II depression is surprisingly understudied, especially in comparison to mania and unipolar depression. The lack of adequate research in this area is even more astonishing, considering that depressive episodes and symptoms prevail in most bipolar patients seen in clinical practice and are associated with a significant risk of suicide and high mortality for different causes. Agents such as lithium, antiepileptics and atypical antipsychotics have been studied much more thoroughly in Bipolar I. Similarly, only a few controlled studies focused on the efficacy of antidepressants in monotherapy. The relative risk of

(hypo)manic switches or of rapid cycle induction further complicates the treatment of cyclothymic depression. The presence of comorbidity represents another major problem in the treatment bipolar spectrum patients in everyday practice. In many cases, the concomitant anxiety, impulse control or eating disorders represent the major complaints and require specific treatment. Most of the controlled trials on bipolar disorder exclude patients with comorbid drug abuse, anxiety and impulse control disorders and vice versa; as a consequence, the empirical basis for treating patients with complex co-morbidity are almost exclusively derived from open clinical experience. This is a deplorable situation, because the most common patients treated in everyday clinical practice are cyclothymic-bipolar II with complex comorbidity. The "pure" bipolar spectrum disorder is an abstract concept that is never encountered in real world.

As for non-pharmacological intervention cyclothymia should be considered a distinct form of bipolarity, which requires a specific approach. Most of cyclothymics does not match with the model of the disorder that is proposed in psycho-education group for bipolar I. The classical description of bipolar disorder characterized by manic and depressive episodes followed by period of remission, with different algorithms for the treatment of different episodes, does not apply to cyclothymia, where depression and excitement are strongly related and inter-episodic mood instability is the rule. In this patients free intervals and long-lasting remissions are very rare and for this reason the psycho-educational intervention should start as soon as possible. At the moment the correct evaluation of the role and the effectiveness of this type of non-pharmacological intervention require better-designed prospective observations.

P 01. Anxiety and religiosity: Negative associations among Arab adolescents and young adults

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Background: The last few decades have witnessed a resurgence of interest in religions and their effects on, and correlates of different variables including subjective well-being and psychopathology. Several Western publications have revealed negative associations between anxiety and religiosity. However, Arabic studies in this endeavor are scarce. The aim of this study was to estimate the relations between anxiety and religiosity among five Arab samples.

Methods: Five samples ($N = 9943$) of Kuwaiti Muslim adolescents (school students) and young adults (undergraduates) were recruited (see Table I). They responded to the Kuwait University Anxiety Scale (KUAS) along with a self-rating scale to assess the degree of religiosity. Both scales have good reliability and validity. The administration of the two scales was in small group sessions and in Arabic language.

Results: Pearson product-moment correlation coefficients were computed, separately, in each sample. Table I sets out the correlations. Inspection of this table revealed that all the correlations are statistically significant and ranged between -0.18 and -0.24 . The median was -0.22 .

Conclusions: On the basis of the significant and negative correlation between anxiety and religiosity, it was concluded that those who consider themselves as religious experienced less anxiety. Therefore, the present results provide further evidence for a probable mollifying role of religiosity

in providing a buffering effect on anxiety. Religiosity may have the potential to be integrated in the psychotherapeutic procedures, mainly cognitive behavior therapy.

P 02. Family Constellations in Therapy-Resistant Cases of Patients Suffering From Depression and a Wish to Die

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Background: Family constellation has brought significantly good results in treating therapy-resistant depression. The method can be applied in therapy and serves as a tool in supervision.

Our aim is to call the attention of psychiatrists and psychotherapists to this new treatment modality so that they can include it into their therapeutic repertoire.

Method: 12 psychotherapists and psychiatrists of clients suffering from therapy-resistant depression (drugs and psychotherapy) came to supervision into family constellation groups in summer of 2010.

The method is based on the experience that the members of an extended family create a hidden information system that functions according to the rules observed by Hellinger. Family members unconsciously tend to identify with those who had difficult fate, life, feelings and behavior, as if that difficulty had happened in their own life. This process is unconscious; the clients may have no rational information at all about the person they have identified with. The therapists gained a new perspective on the hidden dynamics that might have elicited and maintained the disease. Also the next therapeutic steps and modalities were planned with an applied form of family constellation.

Results: We have worked with 26 cases for 2 months. Patients were followed up 1 year later. The therapist used the new insights in the subsequent individual therapeutic work. Significant and sudden improvement was seen in 18 cases. Slight but marked improvement, that could be considered as the beginning of a longer process was detected in 4 cases. 3 clients showed zero improvement. 1 patient has left the therapy. No switches were performed in medication.

Conclusion: This new approach of systems\’ thinking gave fresh insights to the therapists and helped in resolving majority of the cases that had seemed to be therapy-resistant.

Table I. Pearson correlation coefficients between anxiety (KUAS) and the self-rating scale of religiosity among 5 Kuwaiti samples.

Scales	Age		N	Correlations
	M	SD		
Adolescents	15.9	1.3	2,453	-0.22**
"	14.6	2.3	6,339	-0.24**
"	16.9	1.4	499	-0.23**
Young Adults	20.9	1.5	192	-0.18*
"	21.9	3.0	460	-0.18**
Median				-0.22**

* $p < 0.05$

** $p < 0.01$

P 04. Continuity of outpatient treatment after discharge of patients with major depressive disorder

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Backgrounds/Aims: This study aims to identify socio-demographic and disease-related variables associated with continuity of outpatient treatment after discharge of patients with major depressive disorder in a university hospital.

Methods: The medical records of patients who were discharged with the diagnosis of major depressive disorder from department of psychiatry, St. Mary's hospital from 2007 to 2010 were reviewed. Data on sociodemographic and disease-related variables were analyzed.

Results: Comparing sociodemographic variables, 4-month follow-up group showed older age ($p = 0.006$), lower rate of being employed ($p = 0.013$) and lower rate of being divorced or separated ($p = 0.006$) than non-follow-up group. Comparing disease-related variables, 4-month follow-up group showed longer duration of illness ($p = 0.048$), higher rate of diagnosis of recurrent major depressive disorder rather than single episode major depressive disorder ($p = 0.039$), older age at onset ($p = 0.049$), longer duration of index hospitalization ($p = 0.007$) and higher GAF score at discharge ($p = 0.015$). The univariate logistic regression analysis revealed that older age, longer duration of index hospitalization, and high GAF score at discharge were significantly related to an increased likelihood of 4-month follow-up visits.

Conclusions: Various sociodemographic and disease-related variables appeared to have influence on continuity of outpatient treatment after discharge.

Acknowledgement: There is no conflict of interest.

P 06. Adjunctive tianeptine for partial or nonresponders to selective serotonin reuptake inhibitor treatment in major depressive disorder

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Backgrounds/Aims: To investigate the effectiveness and safety of the adjunctive tianeptine treatment in treatment-resistant major depression patients.

Methods: In this prospective, 6-week, open-label study, we assessed the effectiveness of the addition of tianeptine to 135 patients with major depressive disorder who had previously shown nonresponse or partial response to selective serotonin reuptake inhibitor (SSRI) monotherapy.

Results: The mean dose of tianeptine during the study period was 29.7 ± 7.8 mg/day. Total score of MADRS was decreased from 27.1 ± 7.2 at baseline to 13.1 ± 7.7 at the endpoint ($p < 0.0001$). HDRS total score was also decreased from 22.4 ± 5.1 at baseline to 10.6 ± 5.9 at the endpoint ($p < 0.0001$). There was significant decrease in MADRS and HDRS total score from week 1. Responders were 66.7% (MADRS) and 63.0% (HAMD). Remission were 39.3% (MADRS) and 34.1% (HDRS). In subgroup analysis, 36 patients treated with high dose tianeptine (≥ 37.5 mg/day) showed significantly higher response rate than low dose (< 37.5 mg/day) group at week 2 (HDRS), week 4 and week 6 (MADRS). The remission rate at week 6 (HDRS) was also significantly higher in high dose group than low dose group. However, there was no significant group difference in MADRS ($p = 0.571$) and HDRS ($p = 0.446$) between high dose group and low dose group based on repeated measure ANOVA. There were 23 patients (17.0%) who discontinued the study: ten patients for lost to follow-up, 4 for ineffectiveness, 1 for adverse event (headache) and 8 for other reason. The 80 cases of adverse events in 27 patients (20.0%) were reported during the study period. Most cases of adverse events (80.0%) were occurred before week 2. Most common adverse events were sedation ($n = 8$), headache ($n = 8$), nausea/vomiting ($n = 6$), dry mouth ($n = 5$), palpitation ($n = 3$), and dizziness ($n = 3$).

Conclusion: Our findings suggest that the adjunctive tianeptine with SSRI was an effective and safe treatment for the SSRI resistant patients with major depressive disorder.

Acknowledgement: There is no conflict of interest.

P 07. Does mirtazapine make diabetes worse in the diabetic patients?

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Backgrounds/Aims: It has been known that mirtazapine could induce weight gain and make diabetes worse. But in a clinical situation, there are many instances where mirtazapine is prescribed for diabetic patients complaining of insomnia and depression. This study aimed to assess that mirtazapine has negative effects on diabetic process. To our knowledge, this is the first study on the influence of mirtazapine in diabetic patients.

Methods: We examined 18 patients under the naturalistic diabetes treatments, who had been diagnosed with depression and prescribed mirtazapine at least for 6 months through the retrospective medical records review. The other 18 diabetic patients who had not taken any antidepressants were matched as a control group. BMI, fasting glucose, HbA1c were reviewed among baseline, 3 months and 6 months.

Results: Both groups were not different in baseline characteristics. BMI has increased more in the mirtazapine-treated group ($p < 0.05$), but the changes of fasting glucose and HbA1c were not different between both groups and they were not worse under naturalistic diabetic treatments.

Conclusions: Mirtazapine can increase weight in diabetic patients. However, mirtazapine-induced weight gain was not linked with worsening of diabetic markers for 6 months. This result suggests that mirtazapine can be applied to diabetic patients suffering from depression if they are under the appropriate diabetic treatments and stable state.

Acknowledgement: There is no conflict of interest.

P 08. Comparison of Atypical Antipsychotics Discontinuation Rate in Acute Phase Hospitalized Patients-Retrospective Chart Review Study

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Backgrounds/Aims: The purpose of this study was to compare the discontinuation rate of widely prescribed atypical antipsychotics when administered to

newly admitted, acutely ill patients with schizophrenia or bipolar mania.

Methods: Medical records of patients admitted to the psychiatric ward of two university hospitals between January 2007 and December 2008 were retrospectively reviewed. Subjects were eligible for inclusion if they were prescribed olanzapine, risperidone or aripiprazole for their psychotic or manic symptom control. Patients groups (olanzapine/risperidone/aripiprazole) were compared for rate of antipsychotics discontinuation and duration of treatment continuation.

Results: There was no statistically significant difference in the rate of discontinuation during hospitalized period between olanzapine, risperidone and aripiprazole. Rates of discontinuation were 14.5% for olanzapine, 18.6% for aripiprazole and 24.0% for risperidone. Predictor of treatment discontinuation was a short titration period and long illness duration.

Conclusions: This study demonstrated that risperidone, olanzapine and aripiprazole were comparable with no difference found on the discontinuation rate in treating acutely ill psychiatric patients. However, the small number of patients who participated in this study made it difficult to establish significance.

Acknowledgement: There is no conflict of interest.

P 09. Brain Tissue Loss in Children with Trichotillomania: Voxel-based Morphometry and Diffusion Tensor Studies

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Background and Aims: Trichotillomania (TTM) is a poorly understood disorder that is characterized by repetitive hair pulling that leads to noticeable hair loss, distress, and functional impairment. Very few neuroimaging studies have been conducted on patients with TTM. To the best of our knowledge, no study has investigated neural correlates, such as grey matter and diffusion alterations, in patients with TTM. The objective of this study, therefore, was to investigate specific brain tissue loss with structural magnetic resonance imaging (MRI) and microstructural changes with diffusion tensor MRI (DT-MRI) in children and adolescents with TTM.

Methods: Pediatric subjects with TTM ($n = 9$) and age-, sex-, handedness-, and intelligence quotient-matched healthy controls (HC) ($n = 10$), ages 9 to

17 years, were recruited. Isotropic-voxel three-dimensional T1-weighted structural MRI (3D T1WI) and DT-MRI scans were obtained for each subject. Fractional anisotropy (FA) and trace maps from DT-MRI were calculated. Voxel-based comparisons of 3D T1WI, FA, and trace maps between the two groups were assessed with a two-sample *t*-test.

Results: In TTM patients, the voxel-based morphometry (VBM) analysis of 3DT1WI showed a significant decrease of grey matter volume density mainly in the middle frontal gyrus, the insula, the lingual gyrus, and the middle temporal gyrus. For DT-MRI, trace values were significantly increased in the middle frontal gyrus and significantly decreased in the precentral gyrus and precuneus. FA values were significantly decreased in the precentral gyrus and inferior frontal gyrus and increased mainly in the cingulate gyrus, the middle frontal gyrus, the inferior temporal gyrus, the fusiform gyrus, and the insula.

Conclusions: Using VBM and DT-MRI, we identified regions of significant brain tissue loss and white matter abnormalities in the middle frontal gyrus in pediatric TTM patients. These findings support the concept that TTM shares some neurobiological mechanisms with obsessive-compulsive spectrum disorders (OCS). Future work should examine the neurobiological overlap between TTM and other OCS using other modalities and a larger sample.

P 10. Effect of amitraz on anxiety-like behaviors of pregnant mice and its male offspring

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Background: Amitraz is a member of the formamidine class chemical family and commonly used as insecticide, for both household and agricultural applications, and have recently been linked to behavioral and physiological disruption. In the present study, we have investigated the effect of amitraz on anxiety-related behaviors of pregnant mice and its male offspring.

Methods: Pregnant NMRI mice were treated with daily oral administration of amitraz (7.5, 15.8 and 30 mg/kg) from the 1st to 20th gestational day. Anxiety behavior of pregnant mice and male offspring (at 5 weeks old) examined using elevated plus maze test of anxiety.

Result: Our result show that continues administration of amitraz to pregnant females induced an anxiogenic-like effect on pregnant mice and its male offspring, shown by specific decreases in the percentage of open arm time and percentage of open arm entries in elevated plus maze.

Conclusion: The results suggest that insecticides such as amitraz may have an effect on the physiological systems of pregnant females and prenatal exposure to these chemicals may increase anxiety-like behaviors in adult male offspring.

P 11. Activity of atypical antipsychotics in elevated plus-maze test in rats

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Aims: The aim of this study was to compare the effect of atypical antipsychotics (clozapine, olanzapine, amisulpride, quetiapine, aripiprazole) with confirmed clinical efficacy in affective disorders with that of risperidone in elevated plus-maze test in rats.

Methods: Male Wistar rats weighing 270–320 g were used in the test. Drugs were administered i.p. 60 minutes before testing. An automated device (Campden Instruments Ltd.) was used. Each rat was placed at the junction of the four arms of the maze, facing a closed arm, immediately after a 5-min adaptation period in a plastic black box. During a 5-min test, automated system recorded number of entries into the closed and open arms, the time spent in and the distance covered by a rat in either type of the arms. An increase in open arm activity (duration and/or entries) reflects anxiolytic activity.

Results: Quetiapine (0.3–30 mg/kg) at a dose of 3 mg/kg significantly increased the percentage of time spent in open arms, clozapine (0.3–3 mg/kg) at a dose of 3 mg/kg significantly increased the percentage of entries and time spent in open arms, amisulpride at doses of 1–10 mg/kg significantly increased number (but not the percentage) of open arms entries, and risperidone (0.03–0.3 mg/kg) at doses of 0.03 and 0.1 mg/kg significantly increased the percentage of open arms entries. Aripiprazole (3.0–3 mg/kg) and olanzapine (0.03–0.3 mg/kg) did not produce any antianxiety-like effect in that test.

Conclusions: Screening of potential antipsychotics for anxiolytic-like properties is considered to be an important part of modern drug development. Our

data suggest that most of the examined atypical antipsychotics, both with and without confirmed clinical activity in affective disorders, revealed anxiolytic-like effects in elevated plus maze test in rats.

P 12. EMD 386088 produces anxiolytic-like activity in rats via stimulation of 5-HT₆ receptors

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Aims: The question still arises whether potential therapeutic indication such anxiety will be best served by agonists or antagonists of 5-HT₆ receptors, since equivalent anxiolytic potency can be delivered in animal models by both kind of 5-HT₆ ligands. Data concerning potential anxiolytic activity of 5-HT₆ agonists are sparse. We examined anxiolytic-like activity of 5-HT₆ agonist EMD 386088 (IC₅₀ = 7.4 nM) presenting also moderate affinity at 5-HT₃ receptors (IC₅₀ = 34 nM) using rat elevated plus-maze (EPM).

Methods: Male Wistar rats weighing 270–320g were used. EMD 386088 and SB-271046, diazepam were administered i.p. 30 and 60 minutes, respectively, before testing. An automated device (Campden Instruments Ltd.) was used. Each rat was placed at the junction of the four arms of the maze, facing a closed arm, immediately after a 5-min adaptation period in a plastic black box. During a 5-min test, automated system recorded number of entries into the closed and open arms, the time spent in and the distance covered by a rat in either type of the arms. An increase in open arm activity (duration and/or entries) reflects anxiolytic activity.

Results: EMD 386088 (2.5 mg/kg) significantly increased number of open-arm entries (190%) and time spent in open arms (175%). Its effect is specific, since EMD 386088 (2.5 mg/kg) did not increase any parameters of general exploratory activity of rats. The efficacy of an investigated compound was similar to diazepam (2.5 mg/kg). The anxiolytic-like effect of EMD 386088 was abolished by a 5-HT₆ receptor antagonist SB-271046 (1 mg/kg, a non-active dose in EPM).

Conclusion: The effect of EMD 386088, assessed in EPM, is likely to reflect specific anxiolytic-like activity connected with its 5-HT₆ receptor agonistic properties.

P 13. Major Depressive Disorder (MDD) Severity and the Frequency of Painful Physical Symptoms (PPS): a Pooled Analysis of Observational Studies

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Background/Aims: PPS are common in patients with MDD, with a higher prevalence reported amongst patients with more severe depression [1,2]. The aim of this study was to estimate the frequency of PPS according to MDD severity in a naturalistic setting.

Methods: Data from company-sponsored observational studies of patients in usual care settings were collated and summary statistics produced. Studies enrolled outpatients with a baseline diagnosis of MDD (irrespective of specific diagnostic criteria). Measures of PPS were based on the original study assessment (Somatic Symptom Inventory and Visual Analogue Scale). Patients were divided into analysis cohorts based on PPS status (presence or absence of PPS). Depressive symptom severity was assessed using the 17-item Hamilton depression scale and categorized as mild (≤ 19), moderate, or severe (≥ 25) [3].

Results: Four observational studies (14 countries and 2932 patients) were identified. Of 2901 eligible patients (28.3% male, mean age 45.4 years), 61.7% were classified as having painful physical symptoms (PPS+). At study entry, 73.1% (957/1309) of patients in the severe category of depression, 56.8% (537/945) of those with moderate depression, and 45.6% (295/647) of those with mild depression were PPS+. Longitudinal analysis, using generalized linear mixed models, showed the likelihood of PPS+ was greater for patients with increasing depression severity (Odds Ratio [95% confidence interval] 1.13 [1.10, 1.16], $p < 0.001$).

Conclusions: For patients treated in usual care settings, PPS were associated with depression severity. However, patients with mild and moderate depression also exhibited PPS. Clinicians should be aware that PPS are present across depression severity and may worsen quality of life [4]; therefore treatments that address both PPS and depression may be indicated for patients with mild or moderate MDD, even if PPS had been unsuspected by the clinician.

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P 15. Prevalence, Medical burden and Quality of life of Anxiety disorders in South Korea

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Background/Aims: Anxiety disorders are high comorbidity disease with depressive disorders. There have been many reports that anxiety disorders are associated with medical conditions and threaten the one's quality of life. However, community survey on prevalence and medical burden of anxiety disorders did not proceed in South Korea.

The aim of this study was to estimate the prevalence and association of anxiety disorder with different medical burden compared with mood disorders, especially depressive disorders in the Korean population.

Method: A nationwide sample of 6,510 Korean adults aged 18–64 was interviewed with the Korean version of Composite International Diagnostic Interview 2.1/DSM-IV (K-CIDI) by face to face. We categorized subjects in two groups, independently: mood disorders without alcohol use and anxiety disorders (n = 116), anxiety disorders without alcohol use and mood disorders (n = 244). Medical burden was evaluated by the Cumulative Illness Rating Scale (CIRS) and Quality of life by Euro-QOL.

Results: The lifetime prevalence of anxiety disorders was 6.9% (S.E 0.5%), 1-year prevalence, 5.3% (S.E 0.4%). In particular, specific phobia and generalized anxiety disorder showed higher Lifetime prevalence among anxiety disorders of 3.8% and 1.6%, respectively.

The mostly frequent organ system affected was the head and neck system of subjects with mood and anxiety disorders (mood: 25.9%, anxiety: 26.3%). Subjects with mood or anxiety disorders showed significant high Odds ratios in 4 types of medical burdens, significantly high Odds ratios of neurologic (OR = 2.4, C.I.: 1.3–4.5) and endocrine system (OR = 1.9, C.I.: 1.1–3.3) in subjects with anxiety disorders. The

comorbidity of medical conditions among subjects with anxiety disorders was highest at the middle-age group (35–44 aged). Finally, quality of life of subjects with anxiety disorders was higher than that of mood disorders.

Conclusion: The prevalence of anxiety disorders in South Korea was lower compared with Western countries. Comorbidities of medical conditions were common in anxiety disorders and significantly different compared with mood disorders. The results suggest that clinicians need to evaluate medical comorbidities with anxiety disorders.

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P 16. Smoking related depression is depended on early life experiences and determines quitting outcomes

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Background: Withdrawal symptoms during smoking cessation is associated with depression but data on the relationship between quitting outcome and depression are contradictory (Michelle et al. 2010). Moreover, this problem has been extended by the new quitting agent, varenicline with depressogenic side effect. The aim of our study was to analyze the role of depressive phenotype in smoking quitting.

Methods: We recruited 255 smokers from 15 Hungarian Quitting Centers who decided to quit smoking. Cessation was supported by varenicline (n = 164) or only by psychoeducation (n = 91) and treatment protocol consisted of 4 consultations within 3 months (0, 2, 4, 12 w). Fagerstrom Test for Nicotine Addiction (FTND), Minnesota Nicotine Withdrawal Scale-Self report (MNWSS) and Zung Self Rating Depression Scale (ZSDS) were completed at each consultations. Quantity of smoking was monitored by breath CO measure as well. Parental Bonding Instrument (PBI) was used for measure of early childhood experiences by questions on mother's behavior.

Results: Quitting outcome depended on depression score and withdrawal symptoms: persons with low ZSDS_{0w} score had 1.6-fold higher chance to quit smoking ($p = 0.038$); while increased MNWSS_{2w} score almost doubled the risk for quitting failure ($p = 0.43$). At the end of therapy ZSDS decreased in total sample ($p = 0.001$) and also in subgroup of patients with successful treatment ($p = 0.005$) but not in those who continued smoking. On the other hand, higher ZSDS score at baseline predicted

consequently higher MNWSS scores at each consultations (all p -values < 0.0001). Furthermore, ZSDS score was determined by 'affectionless control' of mother according to the PBI ($p = 0.004$). These findings were independent from the type of therapy.

Conclusion: Baseline depression, which is influenced by early life experiences, is a stronger determining factor on quitting outcome through influencing withdrawal symptoms than quantity of smoking, level of nicotine dependence or type of therapy. Thus, adequate therapy for depression before smoking cessation can be strongly suggested to avoid repeated failures and inversely, successful treatment of nicotine addiction can help in elimination of depression.

P 19. The Impact of Financial Crisis on Depression and Anxiety: Evidence from a Depression Telephone Helpline

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Background/Aims: Mental health telephone helplines are diverse in nature and can play an integral part in mental health services network. Their significance is substantiated in periods of financial crisis, where the mental health of the population is jeopardized. Media reports have suggested a large increase in calls made to telephone helplines as a corollary to the global economic crisis; however, there is no empirical support to this claim. The present study aims to fill this gap by analyzing data obtained in the context of the Depression Telephone Helpline of the University Mental Health Research Institute.

Method: The data extracted from the content of the calls addressed the socio-demographic and clinical characteristics of people with mental health problems, their previous/current contacts with mental health professionals and their reasons for calling. Two scales (Goldberg et al. 1988), one tapping depression and one anxiety, were incorporated in the extraction form in order to detect the presence of depression and anxiety of clinical significance.

Results: A steep increase in calls with direct/indirect reference to the economic crisis was documented from January of 2010 and onwards. Callers who referred to pertinent issues exhibited depressive symptomatology of clinical significance

to a greater extent than callers who made no such reference. On the contrary, callers who elaborated on issues other than the financial strain demonstrated higher levels of alcohol/substance misuse and hypervigilance. Regarding differences in the clinical manifestations of employed and unemployed callers, people who were unemployed displayed higher rates of depression, whereas people who were employed displayed higher rates of anxiety.

Conclusion: The impact of the financial crisis on the mental health of the Greek population has been pervasive, highlighting in this way the importance of mental health helplines as emotional buffers and guides for timely and appropriate service use in response to growing mental health problems. In this way, they can also operate as preventive measures for suicide in individuals presenting themselves with major depressive symptoms.

P 20. Increased suicidality in Greece linked to depression

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Background/Aims: Greece has entered a prolonged period of economic crisis with adverse effects on various aspects of daily life, including the mental health of its citizens. Recently, The Greek Minister of Health has recently reported that the annual suicide rate has increased by 40%. Nonetheless, an investigation addressing the relation of suicidality with major depressive disorder (MDD) and generalized anxiety disorder (GAD) is still lacking.

Methods: In an endeavour to fill this gap, the Greek University Mental Health Research Institute (UMHRI) implemented a nationwide cross-sectional telephone survey in May 2011. The study adopted the same methodology of an earlier one, conducted in 2009, which explored the links among major depressive symptoms and socio-economic parameters. A representative sample of 2.256 respondents was drawn from the national phone-number database with telephone numbers belonging to businesses/services being excluded. Informed consent was obtained from all participants and the study was approved by the UMHRI Ethics Committee. Recent suicidality was assessed with the SCID-I module.

Results: Among the study findings, the most alarming one pertained to suicidal attempts, with a

36% increase in the one-month prevalence from 2009 (1.1%, n = 24) to 2011 (1.5%, n = 34) being observed. Regarding the interrelation between suicidality and MDD, 24 (70.6%) of the 34 suicide attempters presented with MDD, while three (9.8%) of the 24 presented with comorbid MDD and GAD.

Conclusions: Consequently, an imperative need for intensive screening, follow-up and treatment of people manifesting suicidal ideation and depressive symptoms emerges. Despite the turmoil, Greece is struggling to maintain a social welfare state. Telephone help lines might help in alleviating the stress and despair of individuals with suicide ideation and guide them towards effective treatment of their co-existing depressive and/or anxiety symptoms.

Reference

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P 21. Quetiapine fumarate extended release (XR) in bipolar depression and major depressive disorder

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Background: To review preclinical and clinical trial data on the efficacy and tolerability of quetiapine extended release (XR) in bipolar depression and major depressive disorder (MDD).

Methods: Review of data from published studies on PubMed and data presented at scientific congresses.

Results: Quetiapine has a broad spectrum of efficacy in psychotic and mood disorders, which may be explained by its neuroreceptor binding profile. Quetiapine and its major active metabolite, norquetiapine, have actions on 5-HT_{2A} receptors and D₂ receptors that are considered to contribute to efficacy in psychosis and mania. Norquetiapine, unlike quetiapine and similar atypical antipsychotics at clinically relevant doses, has high affinity at the norepinephrine transporter (NET). Action at NET is a property of established antidepressants and may explain the efficacy seen in the quetiapine depression studies. Quetiapine as the immediate release (IR) formulation has a well-established efficacy and safety profile in bipolar depression. Quetiapine XR was developed to provide once-daily dosing, as well as rapid dose escalation, with the objective of improving

adherence. The intensity of sedation during initial dose escalation in healthy volunteers or adults with bipolar depression was lower with quetiapine XR than with quetiapine IR. Quetiapine XR was more effective than placebo in acute bipolar depression, with significance observed as early as Day 7 (first visit post-randomization). In 7 large, randomized, double-blind, placebo-controlled trials, quetiapine XR demonstrated efficacy as monotherapy and as adjunctive therapy to antidepressants in patients with MDD. In patients with an inadequate response to antidepressant therapy, adjunctive quetiapine XR (150 and 300 mg/day) had efficacy that was independent of the concomitant antidepressant. Quetiapine XR monotherapy (50 mg/day, 150 mg/day, and 300 mg/day) provided rapid and sustained symptom improvement as acute and maintenance treatment for MDD. The safety profile of quetiapine XR from these trials is consistent with that of quetiapine IR.

Conclusions: Quetiapine XR is effective in bipolar depression and MDD and has a safety profile consistent with that of quetiapine IR.

P 22. Influence of cognitive insight on the effectiveness of psychoeducation in bipolar patients

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Introduction: Psychoeducation effectively improved the treatment adherence and the course of illness in bipolar disorder patients. Although it was easy to speculate that the effect of psychoeducation depends on the characteristics of patients, but only a few studies have paid attention to the influence of it on the effect of psychoeducation. In this study, we would investigate the influence of cognitive insight on the effectiveness of psychoeducation program in bipolar patients.

Method: Ten psychoeducational sessions were administered to admitted bipolar disorder patients. Total numbers of patients were 46 (18 males, 10 female). The mean age was 36.8 ± 6.4. Patients were tested with YMRS, MADRS, and CGI-S for evaluation of their manic and depressive symptoms. The Beck Cognitive Insight Scale (BCIS) was administered to testify for the estimation of their cognitive attitude. The Attitude of patients was estimated for the effectiveness of psychoeducation after education. We used the Drug Attitude Inventory (DAI) for the evaluation of medication adherence before and after education.

Result: The YMRS significantly reduced after the psychoeducation (7.9 ± 2.3 to 4.9 ± 4.1). The

MADRS did not change (4.5 ± 3.3 to 4.0 ± 2.3). The changes of CGI-S (2.3 ± 0.4 to 2.05 ± 0.7) had statistically significant. The BCIS had a positive correlation with the effectiveness of psychoeducation ($r = 0.352$). Patients' attitudes toward medication significantly improved through psychoeducation (-0.5 ± 1.6 to 0.3 ± 1.2). The change of negative attitudes toward medication had no statistical significance according to psychoeducation (2.5 ± 0.8 to 2.3 ± 0.8).

Conclusion: In this study, a different psychoeducation effect according to the level of the cognitive insight in bipolar disorder patients was revealed. The patients with higher cognitive insight were related with the more positive attitude toward psychoeducation. The patients with higher cognitive insight had the greater change in attitudes toward medication.

P 23. Transcranial direct current stimulation (tDCS) - a treatment for depression

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Introduction: Transcranial direct current stimulation (tDCS) is a somatic treatment recently proposed for depression. tDCS is a non-invasive, safe technique for focal modulation of the brain that induces persisting excitability changes of the cerebral cortex. This study aimed to assess the effects of changes induced by tDCS in a large group of patients with severe, drug-resistant depression.

Methods: 84 patients (aged 24–78 year) with drug-resistant Major Depressive Episode in major Depressive Disorder (MDD) or in Bipolar Disorder (BD), according to DSM IV-TR, were enrolled. Patients were divided into two groups: 'MDD' (N = 64) and 'BD' (N = 20).

BDI was administered as outcome measure, before and after tDCS to assess treatment response. tDCS was delivered over the dorsolateral prefrontal cortex (anode on the left DLPC and cathode on the contralateral area) at the intensity of 2mA, for twenty minutes, twice a day for 5 consecutive days.

Results: All the patients well tolerated the treatment with no side effects. After five days of tDCS the mood scores improved in both groups, by 28%

in MDD group ([baseline vs post stimulation: mean \pm SE] 26.1 ± 1.3 vs 18.6 ± 1.4 , $p < 0.001$) and by 34% in BD group (22.5 ± 2.6 vs 15.2 ± 2.1 , $p = 0.001$). The improvement after tDCS did not differ between the two groups ($p = 0,5$).

Conclusion: tDCS significantly improves patients with severe major depression after five days of treatment without significantly different effects in MDD and BD patients.

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P 24. The role of birth season in personality and pathology: time of birth is associated with affective temperaments in a general student population

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Background: Season of birth is of peculiar interest when studying the effect of environment in the development of several psychological and psychiatric phenomena, since it can be considered an unspecific environmental factor associated with a complex pattern of varying environmental influences especially in high latitudes, such as temperature, photoperiod, and consequentially behavioural rhythms, nutrition, infections, stress and lifestyle. Besides an association with personality traits, a significant effect of season of birth on such neuropsychiatric disorders as schizophrenia, unipolar and bipolar major depression, epilepsy and brain tumors was consistently reported in studies. Season of birth was also associated with central monoamine and monoamine metabolite levels in several studies.

A relationship between birth season and novelty seeking or reward dependence has been described and confirmed in several studies, however, affective temperaments have not so far been studied with respect to their association with birth season. This would be especially important to investigate because of the well-known patoplastic role of affective

temperaments in bipolar disorders. The aim of our present study was to investigate the possible association between affective temperaments and season of birth in a nonclinical sample.

Methods: 366 university students completed the standardized Hungarian version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-Auto-questionnaire. Ordinary Least Squares regression was applied to explain the relationship between TEMPS-A subscale and birth season of the respondents.

Results: We found a significant association between temperament scores and birth season in case of the Hyperthymic, Cyclothymic, Irritable and Depressive temperaments, while no significant results emerged for the Anxious temperament. The pattern of association also showed unique characteristics.

Discussion: Our results support the evidence that there is a strong association between season of birth and personality, extending the results to affective temperaments as well. Furthermore, our results are in line with clinical observations concerning the seasonal variation of onset and hospitalization due to affective episodes. This is especially important, since affective temperaments are conceived as the subaffective and subclinical manifestations of major and minor affective disorders indicating a risk for the development of these disorders and also exerting a possible pathoplastic effect, thus our results also have clinical significance.

P 25. Treatment response to agomelatine in depressed patients previously treated or not by an antidepressant (d-change study)
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Backgrounds/Aims: Agomelatine is a new treatment for depression acting as an agonist of MT1/MT2 receptors and antagonist of 5HT_{2C} receptors. D-CHANGE assessed in daily practice the efficacy of agomelatine in depressed patients that were either not treated before for this episode (naïve population) versus those previously treated with another antidepressant (switch population).

Methods: In this 6-week prospective study, patients received agomelatine (25–50 mg) once daily at bedtime. The severity of symptoms was evaluated with the QIDS-C (Quick Inventory of Depressive Symptomatology by Clinicians) and CGIs (Clinical Global

Improvement Severity). Response was defined as the decrease of QIDS-C by 50% compared to baseline and CGIs score ≤ 2 .

Results: The 2780 recruited patients typically had a severe episode (CGIs: 4.9 ± 0.6 , QIDS-C: 18.8 ± 2.4), which was improved after 2 weeks of treatment (33% and 24% of responders on CGIs and QIDS-C respectively) and 6 weeks (59% and 55.2% of responders on CGIs and QIDS-C respectively). Naïve and switching populations were non-significantly different for the QIDS-C score at baseline and at week 2. After 6 weeks, the naïve patients achieved a QIDS-C score of 8.9, whereas it was 10.1 for the switch population ($p < 0.01$ between the two populations). Lack of efficacy of the previous antidepressant rather than side-effects were associated with better response on QIDS-C within the switching population (57.0% versus 51.0%, $p < 10^{-3}$). Tolerability was good (elevation of transaminases in 1.14% of patients with a blood test).

Conclusion: this large prospective study confirms the clinical interest of agomelatine either in non-previously or previously treated depressed patients, with a response higher in the naïve population, in accordance with the STAR*D study. The treatment response in switchers could probably be explained by the longer duration of the present episode and/or the selection of more resistant patients.

P 26. Early trauma and platelet brain-derived neurotrophic factor (BDNF) after three month follow-up in patients with major depressive disorder

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Background: A consistent body of evidence supports a role of each early trauma and brain-derived neurotrophic factor (BDNF) in the development of major depressive disorder (MDD). However, few previous studies have investigated both at the same time in MDD. This study is aimed to determine the associated factor with platelet BDNF, and the changes of platelet BDNF after three months of treatment in patients with MDD.

Method: Outpatients with MDD from Department of Psychiatry and Depression Center and healthy controls among volunteers were recruited. The study population consisted of 105 patients with MDD and 50 healthy controls. We evaluated serum, plasma, and platelet BDNF at baseline, 1 month, and

3 month, and the Early Trauma Inventory Self Report-Short Form (ETISR-SF) at baseline.

Results: Early trauma showed a significant association with platelet BDNF after controlling for age, gender, education, body mass index, severity of depression, anxiety, mania, and hypomania, alcohol consumption, and current stress at baseline (beta value 0.22, $p=0.050$) and 3 months (beta value 0.36, $p=0.008$). On the contrary, plasma BDNF showed a significant association with MDD but not with early trauma. The MDD patients revealed significantly higher levels of platelet BDNF with all types of trauma including general trauma, physical abuse, emotional abuse, and sexual abuse than without. However, no significant differences were found in healthy controls according to early trauma. The platelet BDNF showed significant correlation with the severity of early trauma at baseline ($r=0.25$, $p=0.012$) and 3 months ($r=0.38$, $p=0.003$) in MDD.

Conclusions: The severity of early trauma is correlated with the level of platelet BDNF in patients with MDD but not in normal controls.

P 27. Investigation of the absorption profile of Lu AA21004

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Introduction: Lu AA21004 is a novel multimodal compound currently in phase III development as an antidepressant.

Objectives: To investigate the absorption profile of Lu AA21004 using pharmacoscintigraphic methods and to determine if the presence of Lu AA21004 alters the gastric emptying time and transit through the gastrointestinal tract.

Methods: Data from two different single-dose, open label, crossover studies were pooled. Healthy subjects (both sexes) were administered IR (instant release) tablets (20 mg) and/or solutions via an enterion capsule (20 mg or 30 mg), where the content of the capsule was released in the proximal small intestine using scintigraphic methods. The subjects given the 20 mg solution were given an additional single dose of a 20 mg with the enterion capsule, but now in the distal small intestine. In addition, the gastric emptying time and transit through the gastrointestinal tract was assessed in a subset of the subjects at baseline and following a single dose of 20 mg IR tablet using two radioactive markers (^{99m}Tc -DTPA and ^{111}In -DTPA).

Results: The absorption profiles were almost identical between IR tablets and enterion capsules.

The median individual t_{\max} differences between the enterion capsule and the IR tablet were -2 hours and -4 hours for the proximal and distal small intestine, respectively, consistent with the transit times for the enterion capsule prior to activation. The dose-normalised AUC ratios of enterion capsule/IR tablet were close to 100% for both the proximal and distal small intestine, while the dose-normalised C_{\max} ratios were 107% and 110%, respectively. The administration of Lu AA21004 did not have a statistically significant effect on gastric emptying time, but there was a statistically significant pro-kinetic effect on small intestinal transit and subsequent colon arrival.

Conclusions: The localization of absorption has no impact on the absorption profile of Lu AA21004. Lu AA21004 does not affect the gastric emptying time but does decrease small intestinal transit time and subsequent colon arrival.

P 28. The Impact of Religiosity, Spirituality on Depression & Quality of Life in Solitary Elderly in a Korean Area

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Objectives: There are findings that humans become more religious as they get older so religiosity and spirituality play important roles in elderly's lives. This study tried to investigate variables associated with depression and quality of life in solitary elderly people. Especially, we focused on the association of religiosity.

Methods: This study was conducted by randomly selecting 274 solitary elderly people of over 65 years of age living in Chun-Cheon City. Surveyors conducted one-to-one interviews by making visits. While researching the several psychosocial variables, symptoms of depression were evaluated by SGDS-K (Short Geriatric Depression Scale of Korean version) and quality of life were measured by GQOL-D (Geriatric Quality of Life-Dementia). And we used the DUREL scale to assess religiosity and spirituality. The DUREL scale has 3 subscales, organizational religious activity (one item that asks about frequency of attending a meeting), non-organizational religious activity (one item that asks about frequency of spending time in private religious activities), intrinsic religiosity (three items that asks about religious belief or experience).

Results: Among the psychosocial factors, sex, housing environment, income satisfaction, exercise, group activity, family connection level, organizational

religious activity showed significant discriminative scores in SGDS & GQOL-D. There were significant correlations between SGDS-K, GQOL-D and 3 subscales of DUREL. Depressed people had lower score in GQOL-D than non-depressed. Among the depressed, people believing in a religion had a higher score in GQOL-D than non-believers. As a result of the multiple regression analysis, we came to know that religiosity and spirituality had an effect on depression and quality of life in solitary elderly.

Conclusion: Religiosity and spirituality have significant effects on depression and the quality of life in solitary elderly. Awareness of these relationship might improve the quality of life in solitary elderly.

P 29. Agomelatine (Valdoxan) in clinical practice: results from the Russian observational program CHRONOS

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Background: Agomelatine (Valdoxan) constitutes a novel approach to depression (melatonergic agonist and 5HT_{2C} antagonist) of proven clinical efficacy and good tolerability profile. This study assessed the efficacy and clinical benefits of agomelatine in patients with moderate or severe nonpsychotic depression treated in a psychiatric care setting.

Methods: 1910 psychiatrists included 6276 patients (80% outpatients, 20% inpatients) with moderate or severe depressive episodes with no psychotic features (ICD-10) for 8-week agomelatine monotherapy (25-50 mg per day). Efficacy measures: HAM-D17; CGI-I, and CGI-S scales at weeks 1, 2, 4, 6, and 8 (intention-to-treat population). Tolerability and safety were evaluated.

Results: Most patients (82%) suffered from moderate (according to ICD-10 criteria) depressive episodes, either single (44%) or recurrent (38%). The average HAM-D17 total score was reduced from 22.5 ± 6.9 at baseline to 4.7 ± 4.7 at week 8 with a statistically significant difference from week 1 (19.5 ± 7.1 ; $P < 0.00001$) onwards ($P < 0.00001$ at week 8). The main symptoms that improved early were depressive mood and sleep disturbance. After 8 weeks of treatment, the proportion of patients with moderate/severe/very severe illness (CGI-S scale) progressively decreased from 100% at baseline to 75% and 7% at weeks 1 and 8, respectively.

At week 8, 81% of patients were responders (at least 50% reduction in HAM-D17 baseline total

score) and 59% of patients were remitters (HAM-D17 total score ≤ 7).

The most frequent adverse events were nausea (4%), dizziness (3.1%), and headache (2.9%). No serious adverse events were observed.

Conclusions: Agomelatine showed antidepressant efficacy in psychiatric care settings with a very good tolerability/safety profile in out- and inpatients with moderate depression, which is consistent with data from randomized controlled studies.

P 30. Correlations between serum C-reactive protein levels and symptoms of bipolar mania and schizophrenia

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Objectives: Inflammation plays an important role in the pathogenesis of bipolar disorder and schizophrenia. The level of serum C-reactive protein (CRP) increases in response to inflammation. In addition, bipolar mania and schizophrenia also have been associated with an increased serum CRP levels. The aim of this study was to determine the relationships between serum CRP levels and symptoms of mania and schizophrenia.

Methods: Between May and December 2010, 27 inpatients (15 males) met the DSM-IV-TR diagnostic criteria for manic episodes and 42 inpatients (22 males) met diagnostic criteria for schizophrenia were selected from a psychiatric ward at a general hospital in Busan city, South Korea. To analyze the data collected, we measured serum CRP levels and evaluated psychiatric symptoms by using Brief Psychiatric Rating Scale (BPRS).

Results: There were no significant differences between two groups; in terms of their age, duration of illness, BMI, total BPRS score, and consumption of antipsychotics. Bipolar mania group (0.87 ± 0.82 mg/L) had significantly higher levels of serum CRP than schizophrenia group (0.50 ± 0.55 mg/L, $p = 0.0423$). In bipolar mania, the BPRS total score ($\beta = 0.033$, $t = 2.630$, $p = 0.0161$) was associated with the serum CRP levels, while other variables were not. Moreover, the levels of serum CRP were correlated significantly with BPRS item 5 (guilty feelings, $r = 0.408$, $p = 0.0345$), 8 (grandiosity, $r = 0.406$, $p = 0.0356$), 10 (hostility, $r = 0.540$, $p = 0.0037$), 11 (suspiciousness, $r = 0.488$, $p = 0.0098$), and 14 (uncooperativeness, $r = 0.473$, $p = 0.0127$). On the other hand, variables of the schizophrenia group did not show a remarkable relationship with the levels of serum CRP.

Conclusions: The serum CRP levels were much higher in patients with bipolar mania than with schizophrenia. It showed positive correlation with hostility and uncooperativeness in bipolar manic patients. Therefore, these data suggested that inflammation could possibly play more important role in pathogenesis of bipolar disorder than schizophrenia. Moreover, this could be associated with irritability which is one symptom of mood disorders. The results from our data showed similar patterns with previous study which had been reported induced irritability from the interferon- α therapy.

P 31. Influence of eating attitude and being ostracized on depressive symptoms among high school students in Korea

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Objectives: The present study examines the influence of eating attitude and body image distortion on depressive symptoms among high school students in Korea.

Methods: 1055 high school students were evaluated from Sep 2010 to January 2011. Sociodemographic questionnaire included age, sex, religion, marital status, education level, monthly income, subjective sense of socioeconomic status, education level of both parents, marital status of parents, level of subjective sense of social support, etc. The questionnaire for body image includes subjective sense of body image satisfaction, Figure Rating Scale, BMI, past history of pediatric obesity diagnosis, age of appearance of secondary sexual characteristics. The questionnaire for mental health includes presence of suicidal ideation, past history of suicidal attempt and self-harm behavior, past history of psychiatric interview, etc. The questionnaire for health habit included subjective sense of health status, smoking, drinking, Alcohol Use Disorder Identification Test (AUDIT) etc. The Korean version of Beck Depression Inventory (K-BDI) was used to evaluate depression. We also included any abuse history from family or other persons. The Korean version of Eating Attitude Test-26 (KEAT-26) was used to evaluate eating attitude. We defined dependent variable as having depressive symptoms and coded positive depressive

symptoms as '1' no depressive symptoms as '0'. A multiple logistic regression analysis was performed to find influence of eating attitude on depressive symptoms using variables that have been found to be risk factors of depressive symptoms.

Results: A high risk group of eating disorder (KEAT-26 score over 19 among male students, over 22 among female student (OR=7.026 95% CI 4.069–12.131) and group of being ostracized (OR=3.012 95% CI 1.560–4.957) were found to be a significant correlate of depressive symptoms among high school students even after controlling important risk factors of depressive symptoms.

Conclusions: In South Korea, disturbed eating attitude and behaviors were associated with depressive symptoms. Various programs to correct eating attitude and distorted body image from government and education facilities are crucial for them not to have depressive symptoms.

P 32. Transcranial Bright Light Treatment via Ear Canals in Seasonal Affective Disorder (SAD) - a Randomized Controlled Study

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Background/Aims: Bright light has widely proved to be effective treatment for winter type seasonal affective disorder (SAD). However, the mechanisms of action of bright light remain still open. The aim of the present study was to investigate whether the transcranial bright light via ear canal has an antidepressant effect in the treatment of SAD.

Methods: This study consisted of 89 adults suffering from winter SAD according to DSM-IV-TR criteria. During four week study period, subjects received 12 min daily doses of photic energy in both ear canals in three different randomly divided subgroups (1, 4, 9 lumen). The light was produced using light emitting diodes (LEDs). Severity of depressive symptoms was assessed with Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD), Hamilton Anxiety Rating Scale (HAMA) and Beck's Depression Inventory (BDI).

Results: Compared to the baseline, the mean SIGH-SAD total scores decreased significantly 17.6

points (47.4%, $p < .0001$), 17.0 points (45.9%, $p < .0001$) and 15.9 points (43.7%, $p < .0001$) in the three treatment groups (1, 4, 9 lumen), respectively. The corresponding decreases for HAMA were 12.0 (49.9%, $p < .0137$), 11.4 (49.5%, $p < .0056$), 10.1 (46.5%, $p < .0001$), respectively; and for BDI 13.7 (67.3%, $p < .0158$), 13.4 (67.4%, $p < .1282$), 11.9 (63.2%, $p < .0013$), respectively. The response rates (i.e. $\geq 50\%$ decrease in corresponding rating scale) in the three randomized subgroups (1, 4, 9 lumen) assessed with BDI were 74%–79%, while being 35%–45% and 47%–62% for SIGH-SAD and HAMA, respectively. Decreases of SAD symptoms and response rates did not significantly differ according to intensity level of received bright light.

Conclusions: To our knowledge, this is the first controlled clinical trial to show antidepressant and anxiolytic effect of transcranial bright light therapy on symptomatic SAD patients. These results are comparable to the findings of earlier bright light studies with traditional devices. In future, studies on neuroimaging, neurobiology and placebo-controlled trials are called for to further assess the efficacy and mechanism of action for transcranially delivered bright light therapy.

P 33. Changes of Cholesterol Level and Impulsiveness after Pharmacologic treatments in Patients with Bipolar Disorder

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Objective: Many Studies support a significant relationship between low cholesterol levels and poor impulse, aggression and mood control. In this study, we investigated the association between total cholesterol levels and impulsiveness, and evaluated correlation between differences of total cholesterol level after pharmacologic treatments and changes of impulsiveness in patients with bipolar disorder (BD).

Methods: Forty patients with bipolar disorder and 40 healthy normal controls were selected. They were evaluated twice with Korean version of Young Mania Rating Scale (K-YMRS), Clinical Global Impression Scale-severity (CGI-S) and Barratt Impulsiveness Scale (BIS) at admission(pretreatment) and after 6 weeks of treatment (post-treatment). Total cholesterol (TC), triglyceride (TG), low density lipoprotein(LDL) and high density lipoprotein (HDL) levels in the BD were measured, at pretreatment and

posttreatment and were compared to that of healthy normal controls.

Results: Post-treatment YMRS scores were significantly lower than pretreatment YMRS scores in the patients with BD. The TC levels were significantly higher in post-treatment patients with BD than pretreatment subjects. Post-treatment BIS scores were significantly lower than pretreatment scores in the patients with BD. But we could not find correlation between TC levels and BIS scores in measurement over time.

Conclusion: Our results replicate earlier reports of significant increase in the cholesterol levels when BD patients were treated with pharmacotherapy about 6 weeks. Although the results in previous reports and in our study are statistically significant, their clinical significance requires further examination in longer-term studies and with larger subjects.

P 34. Influence of eating attitude and being ostracized on depressive symptoms among elementary and middle school students in Korea

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Objectives: Various biological and psychological factors appear to be associated with child and adolescent depressive symptoms. During this period, being ostracized by peers is becoming a big social problem in Korea nowadays. Body image is also important issue among this group, for example, in case of poor body image satisfaction usually lead for them to have depression. There for this research was to determine influence of eating attitude and being ostracized on depressive symptoms among College students in Korea.

Methods: 1221 elementary and middle school students were evaluated from Sep 2010 to January 2011. The sociodemographic questionnaire included age, sex, religion, marital status, education level, monthly income, subjective sense of socioeconomic status, health habit, abuse history, family relationship, etc. The questionnaire for health habit included subjective sense of health status, smoking, drinking, suicidal ideation, and suicidal attempt, Alcohol Use Disorder Identification Test (AUDIT) etc. The

Korean version of Beck Depression Inventory (K-BDI) was used to evaluate depression. The Korean version of Eating Attitude Test-26 (KEAT-26) was used to evaluate eating attitude. We defined dependent variable as having depressive symptoms and coded positive depressive symptoms as '1' no depressive symptoms as '0'. A multiple logistic regression analysis was performed to find influence of eating attitude on depressive symptoms using variables that have been found to be risk factors of depressive symptoms.

Results: High risk group of eating disorder (KEAT-26 score over 19 among male students, over 22 among female student (OR = 7.026 95% CI 4.069–12.131) and group of being ostracized (OR = 2.022 95% CI 1.230–3.567) were found to be a significant correlate of depressive symptoms among elementary and middle school students even after controlling important risk factors of depressive symptoms.

Conclusions: Programs to correct eating attitude and distorted body image and programs that could deal their experiences of being ostracized from government and University are crucial for them not to have depressive symptoms.

P 35. Development of a Computer Based Symmetry and Arrangement Symptoms Measures in Obsessive-Compulsive Disorder
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Background: Epidemiological studies indicated that compulsive ordering and arranging, and a preoccupation with symmetry are common presentations of obsessive-compulsive disorder (OCD). The goal of the current study was to develop and obtain preliminary psychometric data for an objective and quantitative measurement of symmetry and arrangement symptoms in OCD.

Methods: Twenty eight normal volunteers were administered computer based assessment tasks with 4 different conditions with or without target and distraction. Primary dependent variables included several indices of time and click of arranging behaviors. Construct validity for the task was examined by comparing the novel behavioral measures with standardized measures such as Symmetry, Ordering and Arranging Questionnaire (SOAQ), Obsessive Compulsive Inventory-Revised (OCI-R), Beck depression

Inventory (BDI), Beck Anxiety Inventory (BAI) and Quality of life scale (QOL).

Results: We found significant positive correlation between behavioral parameters and standardized scales for OCD (total time and SOAQ: $r^2 = 0.570$, $P < 0.001$; total number of clicks and OCI-R: $r^2 = 0.479$, $P < 0.01$). There was no significant correlation between behavioral parameters and other scales measuring constructs less relevant to ordering and arranging. A main effect of target only was observed on behavioral parameters.

Conclusion: This study therefore provides preliminary data to support the use of this task as a novel behavioral measure of compulsive symptoms related with symmetry, ordering and arranging.

P 36. Pharmacotherapy of depressive disorder - treatment decision after occurrence of diarrhea

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Aim: This report presents a case of diarrhea during therapy with venlafaxine in a patient with depressive disorder.

Case report: Patient, 38 years old, with diagnosis of depressive disorder, in psychiatric treatment for the past 10 years, was admitted to hospital treatment in our Clinic for Psychiatry because of worsening of depressive symptoms. At admission in our hospital he was anxious, depressed, also he confirmed having insomnia and fatigue, and had concentration problems. Before admission to the hospital he was taking maprotiline in daily dosage of 100 mg. At admission he said that he stopped taking maprotiline because he felt sedated, but then worsening in mental condition occurred and he decided to come to hospital. He requested therapy with another antidepressant. Treatment with venlafaxine was initiated in daily dosage of 37,5 mg, along with lorazepam 2,5 mg in the evening, and after several days the patient reported having diarrhea. The patient was advised to continue taking venlafaxine and diet was introduced. During the next two days the patient had diarrhea and therapy with venlafaxine was discontinued. After initiation of another antidepressant the patient reported cessation of diarrhea and diet was discontinued after that. Gradually, the patient's mental condition stabilized and he was discharged from hospital after four weeks of hospital treatment.

P 37. The loudness dependence of the auditory evoked potential (LDAEP) as a predictor of bipolarity: preliminary study

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Background: The loudness dependence of auditory evoked potentials (LDAEP) is considered a valid indicator of central serotonergic activity in humans. The LDAEP has been identified as being inversely associated with central serotonergic activity, with a weak LDAEP reflecting high serotonergic neurotransmission. Recently, some researchers reported that the LDAEP differed significantly between patients with bipolar disorder and major depressive disorder. This study aimed to test the hypothesis that the LDAEP can be used to predict the bipolarity in patients with major depressive episode.

Method: Fourteen patients with major depressive episode were recruited. All patients were female. They had no history of hypomanic or manic episode. To evaluate the LDAEP, the auditory event-related potential was measured before beginning medication. In addition, the Korean version of Mood Disorder Questionnaire (K-MDQ) was used as a screening tool to help diagnose bipolar spectrum disorder. The patients were divided into two subgroups based on their K-MDQ (positive K-MDQ and negative K-MDQ groups). The Mann-Whitney U test was used to compare LDAEP value between the two groups.

Results: The average LDAEP of positive K-MDQ group was higher than that of negative K-MDQ group in the Mann-Whitney U test ($p = 0.021$). Although there was no correlation between K-MDQ score (criteria 1) and LDAEP value in Spearman's test, the strong LDAEP tended to show high K-MDQ score ($p = 0.073$). However, there was no significant difference in BDI and HAMD score between two groups. Additionally, there was no significant difference in the number of subjects that attempted suicide between two groups.

Conclusion: Our findings showed that patients with positive K-MDQ had higher LDAEP value than those with negative K-MDQ. It means that patients with major depressive episode and bipolarity had lower central serotonergic activity than those with major depressive episode and without bipolarity. Measurement of the LDAEP appears to provide useful clinical information, such as the prediction of bipolarity. However, further investigations should employ larger samples.

P 38. Efficacy of duloxetine vs venlafaxine – an updated non-inferiority analysis in major depressive disorder

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Background/Aims: There is information to suggest that the dual-action serotonin noradrenaline reuptake inhibitors (SNRIs) have increased efficacy compared with the selective serotonin reuptake inhibitors (SSRIs), but there is little data to directly compare the SNRIs duloxetine and venlafaxine. The authors are aware of two direct comparative trials (HMBU and HMBQ) and efficacy results from these were presented as a secondary analysis in 2008 using the traditional Last Observation Carried Forwards (LOCF) analysis. Regulators such as the Food and Drug Administration now recommend the use of the Mixed-Effects Model Repeated Measures (MMRM) as the primary analysis and thus data from the two studies have been re-analysed to assess non-inferiority of duloxetine compared to venlafaxine using MMRM with a focus on integrating all the data across the entire study to calculate the average, overall treatment effect.

Methods: Data were combined from two similarly designed multicentre, double-blind, randomised, parallel-group studies in which patients with major depressive disorder were randomised to either duloxetine 60 mg a day or venlafaxine ER 75 mg per day increasing to 150 mg daily after 2 weeks for a 6-week fixed dosing period followed by an additional 6 weeks of treatment in which the dose could be increased. The primary endpoint of this updated post hoc analysis is efficacy using the HAM-D17 assessing non-inferiority of duloxetine vs venlafaxine with an MMRM analysis.

Results: When the results of the two studies were combined ($n = 667$), duloxetine was found to be non-inferior to venlafaxine using MMRM analysis of HAM-D17 scores over the entire study period. This result was demonstrated for both intention-to-treat and per-protocol populations. Furthermore, the effect sizes of the two drugs were very similar.

Conclusions: In this post hoc analysis, the results suggest that duloxetine is not inferior to venlafaxine in terms of efficacy in major depressive disorder. Considerations other than efficacy such as tolerability, safety, licensed uses and ease of dosing should be considered when choosing either duloxetine or venlafaxine.

P 39. A US retrospective database analysis evaluating characteristics of patients with bipolar disorder prior to initiating treatment with immediate-release (IR) or extended-release (XR) quetiapine fumarate

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Background/Aims: The aim of the study was to compare patient characteristics prior to initiating quetiapine IR (QTP-IR) or XR (QTP-XR) treatment for bipolar disorder, in real-world practice.

Methods: This was an observational, retrospective cohort study utilising administrative claims data from the HealthCore Integrated Research Database. Eligible patients (18 to 64 years) had: ≥ 1 pharmacy claim for QTP-IR or QTP-XR between 1st November 2007 and 31st January 2011; a diagnosis of bipolar disorder on/ before the index date (first pharmacy claim for QTP-IR or QTP-XR). Univariate analyses assessed: patient baseline characteristics at the index date; 12-month pre-index clinical characteristics; type of physician providing initial treatment; 12-month pre-index total healthcare resource utilisation and cost.

Results: Overall, 6,876 patients with bipolar disorder were analysed. Pharmacy claims for 83% of these patients were for QTP-IR. During the 12-month pre-index date period, 3.7% of patients in the QTP-IR cohort (pre-IR; n = 5,701) were prescribed multiple index medications compared with 1.6% of patients in the QTP-XR cohort (pre-XR; n = 1,175) ($p < 0.0001$). Significantly more patients in the pre-IR cohort were prescribed hypnotics/sedatives (31.2% vs 27.5%; $p = 0.0114$), anticonvulsants (60.1% vs 55.7%; $p = 0.0055$) and antidepressants other than SSRIs, SNRIs, MAOIs and tricyclic agents (22.4% vs 19.3%; $p = 0.0207$), compared with the pre-XR cohort; whereas, significantly more patients in the pre-XR cohort were prescribed SNRIs (26.6% vs 21.6%; $p = 0.0002$), compared with the pre-IR cohort. The number of all cause (0.8 vs 0.6; $p < 0.0001$) and mental-health related inpatient visits (0.7 vs 0.5; $p < 0.0001$), and total healthcare costs (\$16,302 vs \$13,929; $p < 0.0001$), were significantly higher in the pre-IR cohort compared with the pre-XR cohort.

Conclusions: Characteristics of patients with bipolar disorder newly treated with QTP-IR may differ to those treated with QTP-XR in real-world practice. Total healthcare costs are significantly increased in the 12 months prior to patients initiating treatment with QTP-IR compared with QTP-XR.

P 40. Atomoxetine influence on aggressive behavior in a mice model of social interaction

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Background: The selective norepinephrine reuptake inhibitor atomoxetine (TMX) is a drug used in therapy of attention-deficit/hyperactivity disorder (ADHD), particularly in present co-morbidity with either anxiety or ticks. Reports of induced aggressive and hypomanic behavior have appeared recently in literature. Although often indicated, not much is known about TMX influence on affective behavior. The aim of our study was to clarify whether and how TMX influences affectivity in animal model.

Methods: The used model of agonistic interaction is based on paired interactions of singly-housed male mice with non-aggressive group-housed partners. We analyzed behavioural changes in 11 acts of 4 categories: sociable, timid, aggressive and locomotor. According to their behavior exhibited in the control interaction we analysed separately aggressive (exhibiting at least one attack) and timid (exhibiting defensive-escape acts, but no attack) individually housed mice. Mice were administered TMX at the doses of 0.2 or 1 or 5 mg/kg, or saline in the equal amount of 1ml/kg, orally, 30 min prior to interactions provided one week apart. Paired interactions were videotaped and ethological analysis was performed using the system Observer (Noldus, Holland).

Results: In aggressive mice, TMX at the doses 1 and 5 mg/kg decreased frequency of tail rattling and aggressive unrest. Rearing was enhanced at the dose of 5 mg/kg. In timid mice, the highest dose of TMX selectively increased frequency of tail rattling and aggressive unrest. Other behavioral acts were not significantly influenced by any tested dose of TMX.

Conclusion: Our results show dose-dependently decreased aggressive behavior in aggressive mice after administration of TMX. Reports of such observation have not been published yet. In contrast, TMX induced increased aggression in timid mice in agreement with clinical reports. Although TMX is considered safe and effective treatment for children and adolescent with ADHD, caution should be used.

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P 41. Zinc deficiency and hyperactivation of HPA axis in treatment resistant depressionK. Mlyniec^{1,3}, B. Budziszewska^{2,3},
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Introduction: It has been repeatedly observed that there is a link between serum zinc levels and mood disorders. Patients with major depression exhibit a significantly lower serum zinc levels compared to the control subjects. Moreover, treatment resistant patients appear to have lower serum zinc levels compared to those responsive to pharmacological treatment. Furthermore, lower serum zinc level may be normalized after successful antidepressant therapy. There are also clinical data suggesting that zinc supplementation may enhance antidepressant therapy in patients with unipolar depression, particularly in those previously nonresponsive. In the past decade it has been also reported that zinc deficiency induced by zinc-deficient diet elicits neuropsychological symptoms and behavioral disturbances in animals.

Objectives: The aim of this study was to determine how zinc deprived animals would respond to antidepressant treatment in the forced swim test (FST) and if this changes correlate with corticosterone concentrations.

Materials and methods: Male CD-1 mice (14-16g) were assigned to one of ten different groups according to diet (control 33.5 mg Zn/kg or zinc deficient 0.2 mg Zn/kg for six weeks) and intraperitoneally drug administration (imipramine, 30 mg/kg; escitalopram, 4 mg/kg; reboxetine, 10 mg/kg or bupropion, 15 mg/kg; for two weeks). To evaluate animal behavior immobility time in the FST and locomotor activity were measured. To evaluate serum zinc level the flame technique (FAAS) was applied, corticosterone level was measured by a radioimmunological method (RIA).

Results: Chronic (two weeks) administration of antidepressants to zinc deprived mice induces lower response compared to mice receiving adequate diet in the FST. There were no changes in locomotor activity in all groups, control and zinc-deficient. There was an increase in zinc level after chronically antidepressant treatment in zinc deficient groups. Zinc deficient animals showed also higher serum corticosterone

after antidepressant with different action compared to control.

Conclusions: Zinc deficiency during hyperactivation of HPA axis may be the cause of treatment resistant depression.

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P 42. Efficacy of once-daily extended release quetiapine fumarate (quetiapine XR) in elderly patients with major depressive disorder (MDD) according to baseline anxiety symptoms, sleep disturbance and pain levelsS. Montgomery¹, A. C. Altamura², H. Katila³,
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Background/Aims: The aim of the study was to evaluate the effect of quetiapine XR (QTP-XR) monotherapy in elderly patients with MDD according to baseline anxiety symptoms and baseline levels of sleep disturbance and pain.

Methods: 11-week (9-week randomised; 2-week post-treatment phase), double-blind, placebo-controlled study (D1448C00014) of QTP-XR (flexible-dosing 50–300 mg/day) in patients ≥ 66 years with MDD. Primary endpoint: Week 9 MADRS total score change from randomisation. Post hoc analyses based on primary and secondary endpoints included: Week 9 MADRS total score change from randomisation and response ($\geq 50\%$ improvement in MADRS total score) rates in patients with: anxious depression or lower levels of anxiety at baseline (HAM-A total score ≥ 20 or < 20 , respectively); high or low levels of baseline sleep disturbance (HAM-D sleep disturbance factor [items 4 + 5 + 6] score ≥ 5 or < 5 , respectively); baseline pain Visual Analog Scale (VAS) total score ≥ 40 mm or < 40 mm.

Results: Week 9 MADRS LSM change: 16.3 ($p < 0.001$) QTP-XR ($n = 164$); 8.8 placebo ($n = 171$). Anxious depression subgroup MADRS LSM change: 17.8 ($p < 0.001$) QTP-XR ($n = 78$); -8.5 placebo ($n = 88$); response rates: 65.4% ($p < 0.001$) versus 27.3%, respectively. Lower baseline anxiety levels subgroup MADRS LSM change: 14.8 ($p < 0.001$) QTP-XR ($n = 86$); -8.8 placebo ($n = 83$); response rates: 62.8% ($p < 0.001$) versus 33.7%, respectively.

High levels of baseline sleep disturbance subgroup MADRS LSM change: 17.6 ($p < 0.001$)

QTP-XR (n = 100); placebo (8.7; n = 109); response rates: 66.0% (p < 0.001) versus 27.5%, respectively. Low levels of baseline sleep disturbance subgroup MADRS LSM change: -14.4 (p < 0.001) QTP-XR (n = 64) versus 9.2 placebo (n = 62); response rates: 60.9% (p < 0.001) versus 35.5%, respectively.

Pain VAS total score \geq 40 mm subgroup MADRS LSM change: 16.6 (p < 0.001) QTP-XR (n = 93) versus 8.9 placebo (n = 93); response rates: 65.6% (p < 0.001) versus 29.0%, respectively. Pain VAS total score < 40 mm subgroup MADRS LSM change: -15.7 (p < 0.001) QTP-XR (n = 71) versus -8.7 placebo (n = 78); response rates: 62.0% (p < 0.001) versus 32.1%, respectively.

Conclusions: QTP-XR (50-300mg/day) monotherapy was significantly more effective than placebo in treating depressive symptoms in elderly patients with MDD irrespective of baseline anxiety symptoms and baseline levels of sleep disturbance and pain.

P 43. The perception of an oral dispersible escitalopram tablet in a comparative bioavailability study

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Introduction: Rapidly dissolving oral dispersible tablets (ODT) have been developed to overcome problems related to swallowing.

Objectives: To establish assumed bioequivalence between ODT and the immediate release (IR) escitalopram tablet and to determine its perception by healthy subjects.

Methods: In a randomized, open-label, cross-over design, 30 healthy men received 20mg escitalopram as ODT tablets (2×10 mg or 1×20 mg) or conventional tablets. Twenty blood samples were collected after each dose administration and pharmacokinetic parameters were determined using non-compartmental methods. Safety was assessed by self-reported adverse events (AE) and vital signs. Subjects completed a questionnaire relating to their perception of the ODT.

Results: Serum concentration-time profiles of escitalopram were similar after intake of the 3 treatments. The 90% CI for the mean treatment ratios of the log-transformed peak serum concentration (C_{max}), area under the serum concentration-time curve (AUC) to the last quantifiable time point, and AUC extrapolated to infinity were all within the predefined equivalence range from 80% to 125%. AE incidence was similar for both

dosage forms and all AEs considered related to escitalopram were mild. There were no serious AEs. Most subjects liked the taste (63% agreed or strongly agreed, 15% disagreed or strongly disagreed). 2 out of 3 subjects (65%) found the ODT more convenient than a conventional tablet. Almost all (95%) thought the ODT was easy to take and 58% thought it would be easier to take the ODT than a conventional tablet. Most subjects thought that the ODT was pleasant to take (87%) and would be willing to take it over a long period of time (83%).

Conclusions: This single-dose study found that 2×10 mg or 1×20 mg ODT and the 2×10 mg conventional IR escitalopram tablet met the regulatory criteria for assumed bioequivalence in fasting healthy male volunteers. Based on the subjects' perception of taste, texture and size ODT escitalopram is a convenient and pleasant alternative to the conventional tablet.

P 44. Agomelatine in depression treatment, a multicentre study in Slovakia

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Background: Agomelatine is a novel antidepressant with different mechanism of effect from other antidepressants. It is a potent agonist at melatonergic MT₁ and MT₂ receptors and an antagonist at 5-HT_{2C} receptors[1].

Purpose: The aim of the study was to evaluate the clinical efficacy and safety of agomelatine in clinical psychiatric practice in Slovakia.

Methods: 111 outpatients (28 men) fulfilled the criteria for MDD were involved in multicenter, open, 8-week study. Patients received agomelatine 25 mg with possibility to increase the dosage to 50 mg after two weeks of treatment in one daily dose. Patients were assessed with MADRS (Montgomery-Åsberg Depression Scale), CGI (Clinical Global Impression) and SDS (Sheehan Disability Scale). Transaminases were assessed at baseline and in week 6.

Results: Mean MADRS total score decreased from the baseline level of 28.70 to the endpoint (week 8) value of 9.79 (p < 0.001). Differences of MADRS total score and SDS sub-scores were statistically significant from the first week of treatment (Table I). Response defined as the reduction of total MADRS score 50% was found in 0.9%, 16.2%, 45% and 63.1% of patients in 1st, 2nd, 4th, and 8th week of treatment. The remission (MADRS Score \leq 7[2]) were identified in 1.8%, 18.9% and 39.6% of patients in 2nd, 4th and 8th week of treatment.

Table I. Change of MADRS total score and SDS sub-scores.

Control/week	MADRS Total Score (mean)	Sheehan Disability Scale Sub-scores (means)		
		Work/School	Social Life	Family Life
Baseline (n = 111)	28.7	7.3	7.7	6.9
Week 1 (n = 110)	24.7*	6.5*	6.9*	6.3*
Week 2 (n = 106)	20.3*	5.7*	6.0*	5.2*
Week 4 (n = 104)	15.0*	4.1*	4.3*	3.6*
Week 8 (n = 94)	9.8*	2.5*	2.4*	2.1*

*p < 0.001 vs. baseline; Observed cases.

Conclusions: This study showed a good short-term efficacy of agomelatine in out-patients with depressive episode. Treatment of patients MDD with agomelatine showed early and constituent response both in symptoms of depression and level of functionality. Agomelatine has also a good tolerability. No clinically important increase of hepatic enzymes was observed.

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P 45. The Viennese psychiatric intensive care unit

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Background: Psychiatric intensive care provides treatment for patients with severe psychiatric illness and for psychiatric patients with somatic illness complicating the case.

Objective: To investigate the diagnostic distribution and treatment modalities in a representative sample of patients at the psychiatric intensive care unit (PICU) of the General Hospital of Vienna.

Methods: This is a chart review of 100 consecutive inpatients (52% females, age: 45.7 ± 17.8 years) treated at the Viennese PICU during the years 2008 and 2009.

Results: The mean duration of stay was 18.9 ± 14.8 days. 52% of patients were admitted involuntarily. 18% suffered from organic mental disorder (12% from delirium), 20% were diagnosed with mental disorders due to psychoactive substance use (9% alcohol dependency, 6% benzodiazepine dependency, 5% multiple drug use), 16% had a diagnosis of schizophrenia, 10% of schizoaffective disorder and 5% of transient psychotic disorder. 20% suffered from recurrent depressive disorder, 15% from bipolar affective disorder and 3% from a single depressive episode. 8% fulfilled diagnostic criteria of a neurotic, stress-related or somatoform disorder. 12% had eating disorders, 9% had personality disorders and 1% was diagnosed with mental retardation. Only 15% of patients had a first episode of psychiatric illness. 4% were admitted after an accident and 21% after a suicide attempt (45% poisoning, 25% jumping from height, 20% cutting/piercing with sharp object, 5% vehicular impact, 5% self-immolation). 87% of patients were treated with antipsychotics, 36% received treatment with mood stabilizers. In 49% of patients antidepressants were prescribed. 84% of patients were treated with benzodiazepines (30.3 ± 22.4mg diazepam equivalents), in 17% the opioid nalbuphin was applied. Intravenous psychopharmacotherapy was used in 31% of cases. 10% of patients received ECT.

Conclusions: The Viennese PICU is a highly specialized ward with a very specific patient population that cannot be dealt with on normal psychiatric wards [1]. Such a facility has to be equipped with a higher number of nursing staff, adequate medical equipment and specific experience at the interface between psychiatry and medicine.

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P 46. Bupropion in Depression

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Background: Depression as a disease of modern times is constantly growing and it is regarded as a global, medical, individual and economic problem. The main goal of this paper is to demonstrate the reliability of using an antidepressant with dual mechanism of action (bupropion).

Materials and methods: This is a case of CMHC Prijedor with a recurrent major depressive episode

from the author's practice with a follow up period of 28 weeks after the first visit of CMHC Prijedor.

Results: After resistance to first-line pharmacotherapy (SSRI antidepressant) we achieved an improvement of the patient's condition with involvement of psycho- and socio-therapy after 4 weeks of use of bupropion in a single daily dose of 150 mg [1] [2].

Conclusions: Bupropion is a drug of choice for the treatment of major depressive episodes, especially for inhibited depression, and as a single daily dose of 150 mg is an antidepressant of choice for the elderly with depression [3].

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P 47. Sedation intensity during dose escalation of quetiapine XR or IR in bipolar depression: a multicenter, double-blind, randomized, phase IV study

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Background/Aims: This study examined the hypothesis that the profile of initial tolerability, including somnolence and sedation, differs between quetiapine extended-release (XR) and immediate-release (IR) formulations in patients with bipolar depression.

Methods: In a double-blind, double-dummy, randomized, parallel-group study, male or female patients aged 18-50 years with a DSM-IV-TR diagnosis of bipolar I or II depression were randomized, after washout, to receive placebo on Day 1 and quetiapine XR or IR at escalating doses of 50, 100, 200, 300, and 300 mg once daily on the evenings of Days 2-6, with discharge on Day 7. Sedation intensity was assessed by a self-reported Modified Bond-Lader Visual Analog Scale (VAS) score.

Results: Of 139 randomized patients, 134 completed the study. Sedation intensity at 1 hour after the 50 mg dose (the primary study measure) was

significantly lower with quetiapine XR than IR (mean [SD] VAS score: 33.4 [26.92] vs 44.0 [31.76]; least-squares mean difference: 12.55, $P=0.009$; modified intent-to-treat population). Sedation intensity was shown in secondary analyses to be significantly lower with quetiapine XR than IR at 1, 2, and 3 hours after each dose on Days 2-6 ($P\leq 0.05$), with similar sedation intensity between treatment groups at 4-14 hours post-dose. Overall tolerability for both formulations was consistent with the known profile of quetiapine.

Conclusions: This study demonstrates that, over the initial dose-escalation period studied, patients with bipolar depression reported significantly lower sedation intensity in the 1-3 hours after taking the quetiapine XR compared to IR formulation.

P 48. Duloxetine: Treatment Of Depressive Patients In A Consulting Department

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Objective: Depressive symptoms are frequent in in-patients in general hospitals with a variety of organic conditions. The main aim of a treatment is to manage the symptoms and prevent them from recurring. New antidepressants such as duloxetine, seem to offer greater effectiveness and tolerability for this type of patient.

The primary endpoint for this study was to assess the effectiveness of treatment with duloxetine in a group of in-patients with depressive symptoms.

Methods: This was an observational study with duloxetine, in which a total of 40 patients were included who presented depressive symptoms while in-patients in a general hospital and who had the established inclusion criteria.

The clinical effectiveness of the treatment was assessed with the Hamilton scale (HAM-17) and the Clinical Global Impression scales (CGI) for severity and change.

During follow-up, the incidence of detected adverse reactions was determined using the UKU scale and a record was made of therapeutic compliance.

Results: A total of 40 patients were treated with duloxetine, 21 women and 19 men, 6 of whom (15%) dropped out of the study. The average maintenance dose administered at the baseline visit was 60 mg/day and at discharge was 75 mg/day. At the end of follow-up, there was a reduction with respect to the baseline values of 13.6 points on the Hamilton scale and 2.4 points on the CGI of severity scale. 63.4% of the patients felt "much better" at the final visit, according to the CGI of change scale.

There were a total of 6 drop-outs during the study (15%), all due to side effects, none for a lack of efficacy.

The most common adverse effects were nausea, dry mouth, dizziness and fatigue.

Conclusions: According to the results, it seems that duloxetine may be a good treatment option for patients admitted to general hospital for different conditions of organic origin who present depressive symptoms while in hospital.

P 49. Early antidepressant switch in MDD with pain symptoms: functional improvement

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Background/Aims: Concomitant painful physical symptoms in depressive patients frequently impair functioning and a failure to treat these symptoms may adversely impact treatment outcomes of depression. An early vs. a switch of antidepressants were compared in patients with major depressive disorder (MDD) and moderate to severe pain.

Methods: Pre-specified subgroup analysis of a 16-week, randomized, double-blind clinical study on MDD patients with > 30 mm overall pain visual analog scale (VAS). Patients not achieving 30% reduction Hamilton Depression Rating Scale (HAM-D) after 4 weeks escitalopram (10 mg/day) were randomized to duloxetine 60-120 mg/day (*early switching*) or continued on escitalopram (*conventional switching*) with non-responders at Week 8 switching to duloxetine. Endpoints were time to confirmed response and remission (in weeks after randomization), VAS pain severity, and Sheehan disability scale (SDS). Switch strategies were compared using Kaplan-Meier, logistic regression, and repeated measures analyses.

Results: Of all 566 patients in the study, 291 had a VAS > 30 mm and were therefore included in this analysis. No differences between early (n = 138) and conventional (n = 153) switching patients were found in time to confirmed response (3.9 vs. 4.1 weeks, p = 0.511) or remission (6.0 vs. 8.0 weeks, p = 0.238). Significantly lower VAS mean pain levels for overall

pain (difference for early vs. conventional switch at Week 6: -9.4 [95%CI; -15.4; -3.3]; p = 0.002), as well as for headache, back pain, shoulder pain, interference with daily activities, and time in pain while awake were found for patients in the early switching group at Week 6 and/or Week 8 but not at later time points. Time to achieving normal functioning (SDS total score < 6) was shorter in the early switching group (p = 0.042; 25 percentile 12.0 vs. 12.9 weeks). Safety results were comparable between switching strategies.

Conclusions: In MDD patients with moderate to severe painful physical symptoms not improving after 4 weeks of treatment with escitalopram, an earlier switch to duloxetine may lead to better pain and functional outcomes.

P 50. A Randomised Controlled Study of Ultra-brief Electroconvulsive Therapy at Eight Times Seizure Threshold

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Background: ECT remains the most effective treatment for psychotic, melancholic and treatment resistant depression. Many patients experience distressing cognitive and memory side effects and there is a critical need to develop modes of application that improve tolerability while preserving its high efficacy. A novel approach in ECT delivery is to reduce the pulse width of the electrical stimulus, "ultra-brief pulse width" ECT at six times seizure threshold. This approach has been shown to reduce cognitive side effects and in the initial study efficacy was preserved [1]. Subsequent research suggests that a course of ECT using ultra-brief may be prolonged and remission rates are reduced [2].

Aim: The aim of this study was to investigate ultra-brief pulse width right unilateral ECT at a higher seizure threshold ie 8 times seizure threshold and to compare efficacy and cognitive side effects to standard brief pulse ECT.

Methods: This was a 2 arm clinical trial of a head to head comparison of ultra-brief pulse width right unilateral ECT to standard "brief" pulse width ECT in a randomized, double-blind, trial. All patients received a detailed evaluation of mood and cognitive outcomes.

Results: 92 patients have been randomised to right unilateral ultra-brief pulsewidth ECT versus standard pulsewidth ECT.

Preliminary evaluation of results indicates that ultra-brief ECT was as effective as standard brief pulse

ECT whilst cognitive outcomes were significantly better. A detailed data analysis will be presented.

Conclusions: Ultrabrief pulse width right unilateral ECT at 8 times seizure threshold is a safe and effective treatment with excellent cognitive outcomes.

References

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P 51. Antidepressant-like activity of EMD 386088, a potent 5-HT₆ receptor agonist, and its positive interaction with imipramine in the rat forced swim test

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Growing evidence indicates that 5-hydroxytryptamine receptors are involved in antidepressant-like activity of many drugs. Among them 5-HT₆ receptors play an important role. Until now mostly antagonists of 5-HT₆ receptors were examined and their potential antidepressant action was confirmed. Recently attention of researches has been focused on agonists of these receptors.

EMD 386088 has been described as a potent agonist with high affinity for 5-HT₆ receptors (IC₅₀ = 7,4 nM)

The aim of the present study was to examine an effect of EMD 386088 in modified forced swim test in rats and to investigate the interaction between 5-HT₆ receptor agonist and antidepressant drugs with different mechanism of action. EMD 386088 was administered intraperitoneally once and three times (24, 5 and 1 h) before the test. The active and inactive doses of imipramine and escitalopram were studied and then the effect of joint administration of EMD 386088 (2,5 mg/kg) and imipramine (15 mg/kg) or escitalopram (10 mg/kg) was examined in that test.

EMD 386088 given at a dose of 5 mg/kg significantly reduced the immobility time and increased climbing time in the FST in rats. EMD 386088 administered three times was active at a dose of 2,5 mg/kg

significantly decreasing the immobility time and increasing the climbing time. None of the administered doses of EMD 386088 influenced significantly swimming behavior. Combined treatment with EMD 386088 (2,5 mg/kg) and imipramine (15 mg/kg), but not escitalopram (10 mg/kg), produced stronger antidepressant-like effect than either of drugs given alone.

The results of the present study demonstrate that the 5-HT₆ agonist, administered once and three times, produces an antidepressant-like effect in rats and indicate that a low dose of imipramine induces anti-immobility activity when used in combination with an inactive dose of EMD 386088. This positive interaction seems to be specific, since EMD 386088 and imipramine, given alone or jointly, do not increase the exploratory activity of rats studied in the open field test.

P 52. Outcomes and unmet needs in bipolar disease in real-life practice: results from a large, multinational longitudinal study (WAVEbd)

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Objectives: WAVE-bd (Wide AmbispectiVE study of the clinical management and burden of bipolar disorder [BD]) was designed to address the limitations of longitudinal studies to-date focused on single disease phases or treatment. An objective of the study is to describe clinical management and clinical outcomes related to BD in real-life settings.

Methods: WAVE-bd is a multinational, multicentre, non-interventional, longitudinal study of patients diagnosed with BD with ≥ 1 mood event in the preceding 12 months (retrospective data collection from index mood event to enrolment, followed by a minimum 9 months' prospective follow-up). Patients were selected from a cross-sectional sample representative

of BD populations in daily clinical practice from Austria, Belgium, Brazil, France, Germany, Portugal, Romania, Turkey, Ukraine and Venezuela.

Results: A total of 2896 patients (1989 BD I, 907 BD II) were recruited March to September 2010. In BD I patients the incidence rate (IR, in person-years, [95% CI]) of mild, moderate and severe manic events after the index mood event across all countries was 0.01 [0.01; 0.02], 0.05 [0.04; 0.06] and 0.08 [0.07; 0.09], respectively (overall IR 0.14 [0.13; 0.16]). The IR for depressive events after the index mood event was 0.35 [0.32; 0.37] for BD I and 0.50 [0.46; 0.54] for BD II patients. Hypomanic events after the index mood event had an IR of 0.15 [0.13; 0.17] in BD I patients and 0.19 [0.16; 0.22] in BD II patients. In terms of mixed events, the IR was 0.03 [0.02; 0.03] for mild events, 0.05 [0.04; 0.06] for moderate events and 0.05 [0.04; 0.05] for severe events.

Conclusions: This real-life study reveals a higher incidence rate of depressive episodes, in both BD I and II, than of other types of episode, and highlights a requirement to address unmet needs and improve patient outcomes, particularly where patients have higher rates of BD-related events.

Study funded by AstraZeneca; Clinical Trials Registry: NCT01062607.

P 53. Rates of bipolar disease relapse/recurrence in real-life practice in WAVEbd study

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Objectives: WAVE-bd (Wide AmbispectiVE study of the clinical management and burden of bipolar disorder [BD]) addresses limitations of longitudinal BD studies to-date focused on single disease phases or treatment. An objective of the study was to assess

factors associated with clinical outcomes and variability between countries.

Methods: WAVE-bd is a multinational, multicentre, non-interventional, longitudinal study of patients diagnosed with BD-I or BD-II with ≥ 1 mood event in the preceding 12 months. Retrospective data were collected from index event to enrolment, followed by 9–14 months of prospective follow-up. Patients were selected from a cross-sectional sample representative of BD populations in daily clinical practice from Austria, Belgium, Brazil, France, Germany, Portugal, Romania, Turkey, Ukraine and Venezuela. Relapse is defined as an event within 8 weeks of offset of last event, with the same polarity as last event based on clinical judgement; recurrence is defined as an event of similar polarity after 8 weeks of offset of last event or an episode of opposite polarity at any time after last episode, based on clinical judgement. Global incidence rate (IR) is defined as number of relapses/recurrences divided by total time (years) of follow up of all patients for each group.

Results: Results are presented from 2896 patients (n = 1989 BD I, n = 907 BD II) recruited March–September 2010. Overall, any relapse occurred in 8.2% of patients (8.0% and 8.5% of patients with BD I and BD II, respectively). The global IR [95% CI] of relapses was 0.11 [0.10; 0.12]. In total, 40.5% of patients experienced a recurrence (39.5% and 42.7% of patients with BD I and BD II, respectively), and the global IR [95% CI] of recurrences was 0.47 [0.45; 0.50]. Future analyses will provide a more detailed view on differences in relapse and recurrence rates between countries.

Conclusions: This real-life study will reveal rates of relapse and recurrence in patients with bipolar disorder in clinical practice, and their variability across participating countries.

Study funded by AstraZeneca; Clinical Trials Registry: NCT01062607.

P 55. The effects of 10 mg Lu AA21004 and 30 mg mirtazapine on actual driving performance in healthy subjects

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Introduction: Lu AA21004 is a novel multimodal compound currently in development as an antidepressant.

Objective: The aim of the study was to compare the effects of single and multiple doses of 10 mg Lu AA21004, 30 mg mirtazapine, and placebo on actual driving performance.

Methods: This was a double blind, randomized 3-way crossover trial. The treatments were orally administered each evening for 15 consecutive days. Treatments were separated by a 14-day washout period. Driving tests were performed on Days 2 and 16, approximately 12–16 h after dosing. Driving performance was assessed using a road tracking test measuring SDLP (standard deviation lateral position). Pharmacodynamic parameters were analyzed by ANOVA using a model including fixed effects for treatment, period and sequence, and a random effect for subjects within sequence for the acute phase (Day 2) and steady-state phase (Day 16) separately. The primary analysis of SDLP was a one-sided non-inferiority test of Lu AA21004 compared to placebo at the 5% level of significance, with an inferiority limit of 2.0 cm.

Results: 24 healthy subjects (11 men, 13 women) with a mean age of 31 ± 8.3 years were recruited. Mean plasma concentrations (ng/mL) on Days 2 and 16 were as expected. Analysis of SDLP for Lu AA21004 *versus* placebo showed a mean difference of -1.03 cm (upper 95% CI=0.05) and -0.23 cm (upper 95% CI=0.80) on Days 2 and 16, respectively. Analysis of SDLP for mirtazapine *versus* placebo resulted in a mean difference of 1.52 cm (lower 95% CI=0.32) and 0.07 cm (lower 95% CI=-1.01) on Days 2 and 16, respectively. Analysis of SDLP for mirtazapine *versus* Lu AA21004 resulted in a mean difference of -2.55 cm (upper 95% CI=-1.48) and -0.30 cm (upper 95% CI=0.64) on Days 2 and 16, respectively.

Conclusions: The effect of Lu AA21004 on driving performance as measured by SDLP was similar to that of placebo after both single and multiple doses. Road driving performance after Lu AA21004 treatment was superior to that seen with mirtazapine.

P 56. Transcranial Brain-Targeted Bright Light Treatment via Ear Canals in Seasonal Affective Disorder (SAD), a Pilot Study

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Background: Bright light therapy (BLT) is widely accepted as first-line treatment of seasonal affective disorder (SAD). However, the mechanism of action of BLT is still widely unknown. Consequently, we have challenged the existing conceptual framework that BLT would only be mediated through the eyes. We aimed to study whether transcranially brain-targeted bright light via ear canals reduces depressive symptoms in SAD.

Methods: The light was produced by using a novel invention, which is a medical-device approved in the European Union. The amount of photic energy was 6.0 – 8.5 lumens in both ear canals, and the length of treatment was 8 or 12 minutes five times a week during a four-week study period. The final patient series consisted of 13 physically healthy indoor workers suffering from winter SAD according to DSM-IV criteria. The severity of depressive symptoms was assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) and Beck Depression Inventory (BDI) -21.

Results: The HAMD-17 mean sum score at screening was 23.1 ± 1.6 . Ten out of 13 patients (76.9%) achieved full remission (i.e., HAMD-17 sum score ≤ 7), and 92.3% (12/13) at least 50% reduction in HAMD-17 sum scores during the study period. By using a mixed regression model of repeated measures (AR-1) controlling for age, gender, and HAMD-17 mean sum score at screening, significant differences were found comparing the HAMD-17 mean sum scores of “Week 0” with the corresponding scores at “Week 3” ($t = -2.05$, $p = 0.045$) and “Week 4” visit ($t = -2.77$, $p = 0.008$). Correspondingly, significant differences were found comparing the BDI-21 mean sum scores (15.2 ± 6.7) of “Week 0” with the corresponding scores at “Week 3” ($t = -2.37$, $p = 0.021$) and “Week 4” visit ($t = -3.65$, $p < 0.001$).

Conclusions: The basic assumptions underlying extraocular photoreception in humans deserve to be reconsidered. Given that a proper placebo treatment can be implemented via ear canals, further investigations with randomized placebo-controlled study designs are called for.

P 57. Nausea during treatment of patient with depressive disorder

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Aim: This report presents a case of nausea during therapy with duloxetine in a patient with depressive disorder.

The patient, 34 years old, with a diagnosis of depressive disorder, in psychiatric treatment for the past 8 years, was taking different antidepressants. For the past one year she was taking only alprazolam (in case of anxiety) and her mental condition was stable. Several days before admission to our Clinic for Psychiatry she had insomnia, and had concentration difficulties which caused difficulties in functioning at work. At admission she was depressed, anxious, tensed, irritable, and confirmed having insomnia and concentration difficulties. Treatment with duloxetine was initiated in a daily dosage of 30 mg along with alprazolam in a daily dosage of 1 mg and zolpidem 5 mg in the evening. On the second day the patient reported having moderate nausea. The next three days the patient reported having mild nausea after taking duloxetine, and after that the nausea ceased. The treatment with duloxetine was continued and daily dosage was increased to 60 mg. After two weeks of continuous treatment the patient's mental condition improved – her mood was stable, she was more relaxed and had less concentration difficulties. She was discharged after 5 weeks of hospital treatment and started working again after that.

P 58. Registry of Frequency of Mixed States in Patients with a Major Depressive Episode; Dutch part

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Mixed states, in which symptoms of depression and mania combine, represent a complex and often confusing aspect of the clinical presentation of bipolar illness. Using DSM-IV criteria, they appear clinically difficult to diagnose; $\pm 69\%$ of bipolar cases are not diagnosed.

Purpose: To provide an estimate of the frequency of depressive mixed states in patients diagnosed with major depressive episode (MDE).

Methods: A multicentre cross-sectional International study in 8 countries, was performed. A depressive mixed state was defined as ≥ 3 (hypo)manic symptoms by clinical investigation, case report forms (CRF) and self-report-questionnaires (SQ). The results present a specified analysis of patients from the Netherlands, completing the study between September and December 2009. Psychiatrists included, consecutively, all consulting adult patients with a MDE diagnosis (DSM-IV-TR criteria). The diagnosis of a bipolar disorder was assigned on the basis of

known bipolar history, and of three diagnostic algorithms: 1) DSM-IV, 2) modified DSM-IV (m DSM-IV) without exclusion criteria, 3) a “diagnostic specifier for bipolarity” including an episode of increased activity under criterion A of DSM-IV.

Results: A total of 198 patients with a MDE were included in the Netherlands (out of 2811 patients recruited in the BRIDGE-MIX study). By means of the CRF, 66 patients (34%) were diagnosed with depressive mixed states. The proportion of patients diagnosed with ‘depression mixed state’, was: in patients with known bipolar history: bipolar in 54% and unipolar in 27%; in DSM IV: bipolar in 58% and unipolar 31%; in Modified DSM IV: bipolar in 55% and unipolar in 27% and in Specifier for Bipolarity: bipolar in 58% and unipolar in 21% ($p < 0.0001$).

Depression mixed state by the SQ showed no differences between the groups.

Conclusions: The CRF gives the best results in recognizing bipolar patients in mixed state depression. This helps to give the adequate treatment.

P 59. A Survey of Patient Preferences for a Placebo Orodispersible Tablet

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Aim: To assess the attitudes and preferences relating to an orodispersible (ODT) formulation of patients currently being treated for depression or anxiety disorders with traditional oral antidepressants.

Methods: This was an open study collecting patient reported outcome data from patients with anxiety or depression before and after receiving a single placebo ODT on Day 0 and on Day 3 or 4 after receiving two further daily doses of placebo ODT. Patients aged 18-80 years currently receiving treatment with oral antidepressants were recruited from General Practice and by advertising. Patients with significant symptoms of anxiety or depression (scoring ≥ 9 on either the depression or anxiety subscales of the Hospital Anxiety and Depression Scale) were included in the study.

Results: 150 patients were enrolled in and completed the study. 37% of the patients had had trouble with swallowing tablets and patients with higher depression scores reported more general swallowing problems than those with lower scores ($p = 0.002$). About half (50.7%) of all patients thought that a tablet that melted in the mouth would make it easier to take regularly. The convenience of being able to take a tablet while out of

the house (93.8%), that it does not need to be swallowed (79.1%), and that it could be taken without work colleagues/acquaintances seeing them taking it (72.3%) were also perceived as advantages. Most patients (75.3%) believed that an ODT might work faster but that it would make no difference to the effectiveness of the medication (63.1%) or the number of side effects (81.3%). 96% of the patients reported experiencing a pleasant taste following the placebo ODT, although 7 patients did not like its taste or aftertaste. 80.7% found that the tablets were easy or very easy to get out of the packaging.

Conclusions: Based on the results of the placebo version of escitalopram ODT, the escitalopram ODT is likely to be well accepted by patients suffering from anxiety or depressive symptoms.

P 60. Activity and the sleep-wake cycle in opioid detoxification with methadone or buprenorphine

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Background: Opioid detoxification in patients suffering from opioid dependence is accompanied by alterations of psychomotor activity and disturbances of sleep. Actigraphy has been used for many years to provide accurate measures of the activity-rest cycle in different psychiatric disorders.

Objective: To measure the differential effects of opioid withdrawal with methadone or buprenorphine on activity, circadian rhythm, and sleep in a naturalistic study.

Methods: 42 consecutive inpatients (16 females and 26 males) with opiate addiction were switched to either methadone or buprenorphine and gradually tapered down over the course of 2 to 3 weeks. Wrist actigraphy (Actiwatch Plus) was performed during detoxification in study participants.

Results: There were no significant differences in comedication (lofexidine, quetiapine, and valproic acid) between the methadone and buprenorphine group. Patients in the methadone group showed 11% lower activity and were 24 minutes phase-delayed as compared to buprenorphine-treated patients, whereas the latter had 2.5% lower sleep efficiency and 9% shorter actual sleep time. These group differences were most pronounced for lowest doses ($\leq 20\%$ of maximum individual daily dose, i.e. at the end of withdrawal representing late withdrawal effects). Furthermore, for the

total sample we found a significant decrease of the relative amplitude of the sleep-wake cycle and worsening of all actigraphic sleep parameters from higher (100–20%) to lowest doses (20–0%). The acrophase of the circadian rhythm displayed a phase advance (–88 minutes) from highest (100–80%) to lower doses (80–0%) in methadone-treated patients.

Conclusions: Changes in actigraphic parameters during the late phase of detoxification consisted of a reduction of the relative amplitude of the circadian rhythm, and difficulties falling and remaining asleep as evident by a decrease of sleep efficiency and actual sleep time, and an increase of sleep latency, mean activity score, and fragmentation index. Actigraphy seems to be an apt tool to detect withdrawal symptoms in patients with opioid dependence.

P 61. Dysfunctional Stress Copying and Maladaptive Interpretation of Bodily Sensation in Patients with Panic Disorder

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Background and Aims: Panic attack is defined as a rapid occurrence and escalation of anxiety in which there are various perceptions of bodily sensations and somatic symptoms. The severity and frequency of panic attack vary. During panic attack, subjective intensity of fear and discomfort of patient was affected by interpretation pattern of bodily sensation and somatic symptom as well as degree of physical response. And, some patients with panic disorder have stressful life events in the months before the onset of panic disorder. The purpose of this study was to investigate stress coping strategies and interpretation pattern of bodily sensation in patients with panic disorder.

Method: One hundred-one patients diagnosed as panic disorder by DSM-IV criteria and normal controls were recruited. We evaluated the subjects by using Somato-Sensory Amplification Scale (SSAS), Symptom Interpretation Questionnaire (SIQ), Way of Stress Coping Questionnaire (SCQ), and Panic Disorder Severity Scale (PDSS). We analyzed the data using by independent t-test and Pearson correlation analysis ($p < 0.05$).

Result: Panic disorder patients had a greater amplification of body sensation in SSAS (28.10 ± 7.94 vs 22.63 ± 7.28 , $p < 0.05$), a significantly higher score in physical interpretation (43.90 ± 10.74 vs 37.33 ± 8.92 , $p < 0.05$), and a lower score in environmental inter-

pretation (22.96 ± 6.42 vs 27.23 ± 6.70 , $p < 0.05$) of SIQ than normal controls. PDSS scores were positively correlated with SSAS score and physical interpretation score of SIQ. In the SCQ rating of panic disorder patients, we observed a significantly lower score in the emotional focused coping (16.21 ± 3.48 vs 17.30 ± 2.36 , $p < 0.05$).

Conclusion: These results show that patients with panic disorder have a greater amplification of

body sensation, physical interpretation tendency on somatic symptoms and poor emotional focused stress copying strategy. Also, these findings give a theoretical basis on the necessity for interoceptive exposure to bodily sensation, correction of maladaptive interpretation, and improvement of dysfunctional stress copying strategy as well as pharmacological therapy in the treatment of panic disorder.