Abstracts of Oral Presentations

[SO-01]
Bacopa monniera: Current trends and future directions

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Objectives: Bacopa monniera (BM) is an Indian herb used for centuries as a memory tonic in Ayurvedic medicine. Preclinical research has shown that BM acts as an antioxidant, improves memory, and reduces amyloid plaque deposition in animal models of Alzheimer’s disease. Human studies suggest that BM provides a fairly robust benefit to performance on certain attention, working memory, and learning tasks. This talk will present a review of BM research through animal models to human clinical trials and what research is currently being undertaken on BM.

Methods: Two studies will be discussed further to the review of BM:
(1) An acute dose-ranging study of healthy young adults where participants were required to complete a multi-tasking framework (MTF) and mood scales at baseline, 1hr and 3hrs post dose. The dosage was 300 or 600mg of BM or a matched placebo.
(2) The study utilized a double blind, placebo controlled crossover design where all participants completed a 90 day course of both Bacopa (300mg daily) and placebo during the study. The participants were aged between 40 and 65 years and in good health. The interventions were separated by a 120 day washout period. The scans were undertaken on a 3T Siemens TRIO magnet before and after each 90 day intervention where participants would complete two runs of the task per scan visit.

Results: (1) There was a significant, dose-dependent effect of treatment on ratings of alertness favouring the 600 mg treatment at both post-dose assessment times. There was a trend for dose-related effects on performance of the MTF, in particular for the Stroop task where there was an advantage for the 300 mg dose.
(2) The data collection is still ongoing. The baseline data show a bilateral increase in BOLD activation in the precentral gyrus and precuneus with activation extending to the left inferior frontal gyrus (n=7, p=.005) when compared with controls using a task greater than baseline mask.

Conclusions: The conclusions are speculative at this point for both studies, one being still in the data collection stage, one being underpowered. However, the methodologies and the future directions of these studies will be discussed.

Key words: Bacopa monniera, human cognition, fMRI, nutraceuticals

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[SO-02]
Association of the DRD2 TaqIA, 5-HT1B A-161T, and CNR1 1359 G/A polymorphisms with alcohol dependence: A single center study in the Denizli Province of Turkey

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Background: Alcohol dependence is associated with genetic variants of alcohol-metabolizing enzymes and genes related to the dopaminergic, gamma-aminobutyric acidergic, glutamatergic, opioid, cholinergic, and serotonergic systems. Genetic variations in the endogenous cannabinoid system are also involved in alcohol dependence.

Objective: The present study was aimed at evaluating the association between three polymorphisms, DRD2 TaqIA, 5-HT1B A-161T and CNR1 1359 G/A (rs1049353), and alcohol dependence.

Methods: One hundred and twenty three patients, who were admitted to the Alcohol and Substance Abuse Center of Denizli State Hospital and diagnosed with alcohol dependence according to the DSM-IV criteria, and 125 healthy volunteers were included in the study.

Results: Of the three polymorphisms investigated, 5-HT1B A-161T was the only one found to be associated with alcohol dependence.

Conclusion: The 5-HT1B receptor A-161T polymorphism might be a promising marker for alcohol dependence; however, future studies are needed to clarify these findings.

Key words: Alcohol dependence, DRD2 TaqIA, 5-HT1B A-161T, CNR1 1359 G/A, polymorphism

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Treating psychotic substance abuse patients with opioid agonist therapy and the atypical antipsychotic olanzapine

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Objectives: The aims of the study were: 1. To evaluate the efficacy of olanzapine in patients on methadone maintenance treatment; 2. To explore the time-course variation of cravings and weight at baseline and every 2 months for the first 6 months and then every 6 months until the end of the study (30 months). 3. To compare the severity of the symptoms between patients on methadone and patients on buprenorphine.

Methods: The patients were enrolled from the Outpatient Addiction Unit in Bologna, Italy. All patients gave written informed consent. We randomized 32 patients to treatment with methadone and 13 to treatment with buprenorphine. Based on inclusion and exclusion criteria, 36 patients were included in the study and they were divided into three treatment groups.

At the baseline and follow-up sessions the following rating scales were administered: The Minnesota Multiphasic Personality Inventory-2 (MMPI-2), the SCID-II (to identify and determine DSM-IV Axis II disorders i.e. personality disorders), Bech-Rafaelsen Mania and Melancholia Scales (BRMAS, BRMES; Bech et al. 1988, to cover severity of manic and depressive symptoms, respectively), and a VAS (Visual Analogic Scale, to quantify craving for drugs).

Also the body weight of the participants was registered and followed.

Results: After six months, no significant difference was found among the three subgroups, even though the olanzapine+methadone group achieved better and quicker results and sustained them for longer periods. There was no significant difference at baseline and at the end of the study in all patients.

Total and partial BRMES and BRMAS scores did not significantly change during the follow-up period (6th-30th month), eventhough the curve displayed a downward trend. The VAS total scores were significantly lower both at the 6th and 30th month (p<0.0001) when compared to the baseline condition. None of the three treatment subgroups showed a significant weight gain, both after 6 months (at this follow up we observed better results in the treatment of mania and melancholia) and at the end of the study (eventhough there was a small peak of weight gain). At the 30th month we considered the BRMAS and BRMES scores corresponding to the maintenance phase. Three patients dropped out from the study just before the 30th month session because they stopped olanzapine due to weight gain (5kg for one patient, and 3 kg for two patients).

Conclusions: We observed good adherence to antipsychotic treatment in this sample and we did not detect metabolic complications. Buprenorphine was prescribed for younger patients and patients with lower severity of symptoms.

According to the results of this study, the use of methadone and olanzapine together in the treatment in psychotic substance abusers improved treatment adherence, even in the presence of subthreshhold psychiatric symptoms.

Key words: Heroin, addiction, therapy, dual diagnosis, psychiatry

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A comparison of the effects of typical and atypical antipsychotics on the basolateral amygdala of rats using deep brain EEG recordings

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Objective: It is clinically known that compared to typical antipsychotics, the atypical antipsychotics are likely more efficient in the treatment of psychosis with negative symptoms and cause fewer extrapyramidal side effects.

In the differentiation of receptors and extrapyramidal system (EPS) side effects, there are some medications which cannot be classified as typical or atypical antipsychotics according to their activity at D2 receptors. There is not a clear method to classify antipsychotics.
**Materials & Methods:** The experiments performed in this study were carried out according to the rules in the Guide for the Care and Use of Laboratory Animals adopted by the National Institutes of Health (U.S.A) and received Ege University Animal Ethics Committee's consent. (Approval number: 2010-081)

In this study, 9 Sprague-Dawley (450-500 g) adult male rats (16-20 weeks old) were used. The rats were maintained under controlled environmental conditions throughout the study: 21-25 °C ambient temperature, 12:12 light-dark cycle (light from 7:00-19:00h), and Standard laboratory food and tap water available ad libitum. Under anesthesia, a small hole was drilled. Then by using the bregma as a reference for the stereotaxic method (coordinates Anteroposterior: - 2.8 mm, Lateral: + 4.8 mm, Ventral: - 8.5 mm) (Paxinos Rat Brain), an exterior insulated bipolar EEG electrode was placed in the basolateral amygdala.

The electrodes were fixed by using a dental acrylic (numerous alloys are used in the making of dental restorations). Rats were anesthetized by using ketamine (40 mg/kg) and xylazine (4 mg/kg) intraperitoneally (IP).

Three days after the electrode was fixed, spontaneous amygdala EEG records were taken from the rats by injecting saline, when they were awake and in their own box. Subsequently at 7 days intervals (5 times more than the half life of the drugs), olanzapine 1 mg/kg, haloperidol 1 mg/kg, chlorpromazine 5 mg/kg or ziprasidone 1 mg/kg doses were IP administered. Before each drug injection amygdalar EEG records were taken to observe the baseline rhythm of the amygdala. These drug doses were chosen after consideration of the hypermetabolism of rats.

EEG recording was started 30 minutes after drug injection and each rat was recorded for 20 minutes. Signals were amplified by 10,000 times and filtered within a range of 1-60 Hz. System records were taken by a Biopac MP30 amplifier system and evaluated with FFT (Fast Fourier Transform) and PSA (Power Spectral Analyses) methods. During this process Delta 1-4 Hz, Theta 4-8 Hz, alpha 8-12 Hz and beta 12-20 Hz waves in the EEG are accepted as the ratio of percentage in PSA (Power Spectral Analyses) methods. We confirmed electrode locations histologically following euthanisation.

**Results:** According to the data obtained, the perceptibly dominant frequency in amygdala spontaneous activity was founded to be 1-4 Hz (Delta).

When we compared the EEG records in the 1-4 Hz (Delta) band of the groups which were given typical and atypical antipsychotic drugs to the control group given isotonic saline, there was significant (p < 0.005) inhibition. On the other hand in the 4-8 Hz (Theta) and the 8-12 Hz (Alpha) (Figure 4) bands, a significant increase (p < 0.005) was observed.

When the EEG records of the group which was given atypical antipsychotics were compared to the typical antipsychotic administered groups, in the 1-4 Hz band a significant increase (p< 0.05) and in the 4-8 Hz and 8-12 Hz bands significant inhibition (p<0.05) was observed. In addition, the EEG records of the atypical antipsychotic groups were nearer to those of the saline administered group.

**Conclusions:** The results showed that there was less change in spontaneous electrical activity of the basolateral amygdala in the atypical antipsychotic groups than in the typical antipsychotic ones. The EEG of deep brain recording may be used as a new method for classifying antipsychotics into different groups.

Improvements in cognitive function in schizophrenia with atypical antipsychotics are known. This effect may be due to the impact of atypical antipsychotics on the amygdala. This effect is probably related to the fast-off theory, meaning that the drug binds and leaves the receptor quickly.

Although mesolimbic dopaminergic hyperactivation is inhibited with antipsychotics, the correction of mesocortical dopaminergic hypoactivation and the recovery of cognitive capacity and normal affect are not completely clarified.

There are extensive connections between the prefrontal cortex and the amygdala. Typical antipsychotics in this study increased the frequency of firing in the amygdala. This effect may be interpreted as being similar to the effects of Parkinsonism caused by the blockade of striatal D2 receptors.

In this study typical antipsychotics increased the amygdalar frequency of the EEG. The breakdown of frequency of the amygdala was more pronounced in chlorpromazine administration. This effect of chlorpromazine may be associated with non-selective blockade of the histaminergic, adrenergic, serotonergic, and dopaminergic systems.

Atypical antipsychotics caused a very small change in the basal rhythm of the amygdala (Delta Frequency). This effect is thought to be related to the recovery of normal cognitive function during use of the atypical antipsychotic drugs. In future studies, the effects of antipsychotics in different brain regions may lead to a better differentiation of the typical and atypical antipsychotics.

**Key words:** EEG, amygdala, typical and atypical antipsychotics
[SO-05]

The effect of cognitive-behavioral therapy in reducing the feeling of emotional pressure and blood sugar control in patients with type 2 diabetes

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Objective: The results of some studies show that diabetes patients experience some psychological problems, such as depression, stress, self-negative labeling, and lack of self confidence. In this study, we investigated the effect of cognitive-behavioral therapy (CBT) in reducing the feeling of emotional pressure and blood sugar control in type 2 diabetes patients, who were referred to the Tonekabon Society of Diabetes.

Methods: This feeling was measured by using Marghan's Measure for Feeling of Emotional Pressure. In addition, the blood sugar levels of all patients were tested and recorded. The 24 patients, who had the highest emotional pressure scores, were selected and randomly divided into two groups, each consisting of 12 patients. They were provided CBT. After the end of CBT, they were tested again. The collected data were tested by SPSS software, 10th edition and ANCOVA covariance statistical test.

Results & Conclusions: There were some meaningful differences between the pre-and post-test levels of emotional pressure. The results of the blood sugar test also indicated a reduction in the level of blood sugar and normalization of blood sugar control in some patients with diabetes type 2.

Key words: Stress, blood sugar, lack of self confidence, CBT

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[SO-06]

Acute effects of nicotine on working and reference memory in rats using a 12-arm radial maze

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Objectives: It has been shown that nicotine plays a significant role in improvement of memory. Based on this finding, nicotinic drugs are being developed for possible use as co-treatments for cognitive impairment in some kinds of mental disorders. However, past studies have mostly emphasized working memory function following acute administration of nicotine and the few studies concerned with reference memory have shown no significant effects. As the 8-Arm Radial Maze, which has been used in most of the studies in this field, provides a lower task difficulty, the present article aims to replicate previous studies with a specific emphasis on reference memory using a 12-Arm Radial Maze which provides a higher level of cognitive task demands.

Methods: Three groups of male Wistar rats were used. The rats were subcutaneously injected with three doses of nicotine 20 min prior to the start of each trial on the Radial- Arm Maze. The first group was injected with 0.1 mg/kg nicotine solution, the second group was injected with 0.4 mg/kg, and the third group was the control which received saline. The spatial memory of the rats was tested on a 12-Arm Radial Maze. The arm choices were recorded when the rat had placed all of its paws beyond the threshold at the proximal end of the arm. Each session of the testing continued until the rat ate all 6 baits or until the maximum time of 6 minutes was over. There was at least 24 hours between drug injections during which time the rats were not tested.

Results: The results of repeated analysis of variance showed a significant difference in working memory errors among the three groups, but there was no significant difference in reference memory errors between the groups. An inverted U-shaped dose-effect curve was seen for reference memory which showed that nicotine first results in increased reference memory errors and then, perhaps because of the effect of training, the number of errors decreased.

Conclusions: The current study suggests a negative correlation between acute consumption of nicotine and long-term spatial performance on a 12-Arm Radial Maze, which contradicts the former assumption on an 8-Arm Radial Maze. This finding also emphasizes the different mechanisms underlying working and reference memory that should be considered in pharmacotherapeutic interventions.
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with nicotinic drugs and other drugs for memory impairments in various mental disorders.

Key words: Nicotine, reference memory, learning, radial-arm maze


[SO-07]
The relationship between personality characteristics and internet addiction in adolescents

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Introduction: Personality has been identified as a significant factor in internet addiction. The purpose of the present research was to investigate the role of personality factors in the prediction of internet addiction in adolescents.

Materials-Methods: The research subjects consisted of 261 (146 females, 115 males) adolescents from the city of Ardabil. They were selected by using the random clustering method. The data of the Young Internet addiction (IAT) test and the NEO-FFI Personality Inventory were used together. The data were analyzed by Pearson's correlation coefficient and multivariate regression analysis.

Results: The result of the Pearson correlation coefficients showed that there were significant relationships in adolescent girls between neuroticism (r=0.42, P<0.01), extraversion (r=-0.19, P<0.05) and conscientiousness (r=-0.24, P<0.05) and internet addiction. In addition in adolescent boys there were significant relationships between neuroticism (r=0.32, P<0.01), extraversion (r=-0.23, P<0.05), agreeableness (r=-0.24, P<0.05), and conscientiousness (r=-0.17, P<0.05) and internet addiction. The result of multiple regression analysis demonstrated that neuroticism, extraversion, agreeableness, and conscientiousness explained 32 percent of variance of internet addiction in adolescents.

Conclusions: The results were similar to findings in other studies and they indicated that low levels of neuroticism and high levels of extraversion, agreeableness, and conscientiousness decrease internet addiction risk in adolescents.

Key words: Personality, addiction, Internet, adolescents

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[SO-08]
The sigma-1 receptor ligand, PRE-084, reduced infarct volume, neurological deficits, pro-inflammatory cytokines, and enhanced anti-inflammatory cytokines after embolic stroke in rats

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Objective: Sigma receptor agonists have been found to provide potent neuroprotection in rats and mice. This neuroprotection is thought to be mediated through anti-excitotoxic mechanisms. Neuroprotective and immune modulatory effects of sigma ligands have not been investigated in embolic stroke.

Methods: In the present study, the rats were subjected to embolic stroke or sham stroke and were treated with the sigma-1 receptor agonist, PRE-084 (5mg/kg i.p.), or saline vehicle 3 and 24th after stroke. The infarct volume and behavioural tests were conducted and cytokine levels (ILs-1α and β, IL-2, IL-4, IL-6, IL-10, GM-CSF and TNF-α) were measured in ischemic and non-ischemic cortices. The axonal damage was determined by using the pNF-H ELISA assay.

Results: The treatment with PRE-084 afforded neuroprotection following embolic stroke as evidenced by significantly reduced infarct volume and improved behavioural outcomes. Remarkably, the treatment with PRE-084 reduced levels of pro-inflammatory cytokines and enhanced anti-inflammatory cytokines. The levels of pNF-H were lower in rats treated with PRE-084 suggesting reduced axonal damage, but this finding did not reach statistical significance.

Conclusions: The findings of the present study suggest that part of the neuroprotective effects of sigma-1 receptor agonists may be mediated through a dual effect on cytokine release following stroke.

Key words: Cerebral ischemia, sigma receptor, neuroprotection

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[SO-09]

Comparison of the effects of bupropion and fluoxetine on reaction time in adults with major depressive disorder in a 4-week, single-blind study

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Objectives: Some studies have shown that adults diagnosed with major depression have longer reaction time compared to the healthy population. Longer reaction time may result in educational and occupational impairment and increased risk of fatal driving incidents. Consequently, any impact on reaction time induced by drug therapy may have either positive or negative effects on treatment outcome and quality of life of patients. Bupropion is an effective antidepressant, which clearly acts via different mechanisms than other antidepressants. Its mechanism of action is thought to be dopamine and/or norepinephrine reuptake inhibition with negligible effects on serotonin.

While bupropion is considered an antidepressant with minimal effects on alertness and cognitive function, the present study was designed to evaluate the effects of bupropion on reaction time in comparison with fluoxetine, in adult patients with major depressive disorder.

Methods: A total of 30 patients who met the DSM-IV criteria for major depression were recruited for this study. Patients were randomly assigned to receive either bupropion (200 mg/day) or fluoxetine (20 mg/day) for 4 weeks. Reaction time was assessed at baseline, 2 and 4 weeks of treatment using validated computer-generated tasks and keyboard tapping tests in which the data was collected and analyzed for auditory and visual stimuli. In addition, the participants were assessed using the Hamilton depression rating scale at baseline, 2 and 4 weeks of treatment. The number of correct responses, omissions, and substitution errors for each stimulus were calculated.

Results: No significant differences were observed between the groups regarding demographic characteristics and Hamilton depression score at baseline.

In both groups, the number of correct responses to the visual stimuli increased significantly after 4 weeks of treatment (P<0.05). However, significant improvement in the endpoint auditory task scores was observed solely in the bupropion group compared to the baseline. Furthermore, the number of correct responses to visual stimuli was significantly greater in the bupropion group compared to the fluoxetine group after 2 and 4 weeks of treatment.

Mean reaction times showed no significant differences between the two groups at the end of the study.

Conclusions: Results of this study showed that bupropion did not seem to change reaction times of the patients more than fluoxetine. However, as the number of correct responses to visual stimuli improved, it may be suggested that bupropion treatment in this population may enhance concentration more than fluoxetine.

Key words: Visual and auditory tasks, reaction time, bupropion, fluoxetine

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[SO-10]

A placebo-controlled double-blind add-on study of Ginseng in opioid withdrawal syndrome

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Objectives: Pharmacological treatment of opiate withdrawal syndrome is used to facilitate a safe transition to a relapse prevention program, while ameliorating signs and symptoms of withdrawal in the opioid-dependant individuals.

Ginseng, the root of the Panax species, is a well-known remedy in traditional medicine. Pharmacological studies have determined the inhibitory effects of Ginseng Total Saponin (GTS) on morphine-induced tolerance and physical dependency. This effect might be due to up-regulation inhibition of the cAMP pathway. Since conclusive human clinical data is missing, we performed this randomized, double-blind, placebo-controlled study to assess the effects of ginseng augmentation therapy on withdrawal symptoms of opioid-dependent patients.
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patients treated with methadone.

Methods: A total of 36 male opioid-dependent patients, aged between 18 and 50 years who met the DSM-IV criteria for opioid dependence, were randomly assigned into two groups of 18 members, to receive either ginseng (two 250 mg capsules daily) or placebo for the first 15 days of detoxification. All patients were treated with a Methadone Maintenance Treatment (MMT) protocol. Opioid withdrawal syndrome severity was measured by the Clinical Opioid Withdrawal Scale (COWS) on days 0, 1, 7, 10, and 15. In addition, the required daily methadone dosage was recorded and compared between the groups. This trial was registered in the Iranian Registry of Clinical trials (IRCT) under ID of IRCT201009063106N4 and was approved by the Ethics Committee of Azad University (approval number: 4115).

Results: Patients in the two treatment groups did not differ significantly in socio-demographic and clinical variables at the baseline. As expected, a statistically significant decrease in the COWS total score and symptoms was observed from the first day to the end of the study in both treatment groups. As shown in figure 1, the required daily methadone dosage was lower in the ginseng group from day 5 to the end of the study (P<0.05). Although no significant difference was observed in the COWS total score between the two groups, these scores were achieved with lower methadone dosages in the ginseng group.

Conclusions: The differences in severity of symptoms were not statistically significant between two groups, but patients receiving ginseng experienced similar withdrawal symptoms with lower methadone dosages.

Key words: Methadone, ginseng augmentation therapy, opioid withdrawal syndrome

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[SO-11]
An in vitro analysis of disintegration times of different formulations of orally disintegrating olanzapine

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Objectives: Orally disintegrating tablet (ODT) forms of medications are sometimes used as alternatives to standard oral tablets for patients who have difficulty swallowing, those who need to have ingestion verified, and those who may resist other drug product forms (e.g. injection). ODTs are a tablet or wafer form of medication that disintegrates in the mouth, aided only by saliva. ODTs can disperse in as little as 1 to 2 seconds or as long as 2 to 3 minutes, depending on the different fast dissolve/disintegration technologies used to manufacture the tablets. Orally disintegrating olanzapine (ODO) is manufactured by several different companies, using different formulations and processes. The objective of this study is to investigate differences in disintegration time of these tablets, which may potentially impact clinical parameters such as patient acceptance and adherence to treatment.

Methods: Six types of ODO, along with Risperdal M-Tab as an external comparator, were evaluated for formulation composition, manufacturing method, disintegration and dissolution characteristics, expiration dates, and packaging and formulation differences in comparison with the freeze-dried Zydis/Velotab formulation of ODO. Automated dissolution test equipment, DISTEK DISBA0045 and DISBA0046 with an Opt-Diss UV fiber optic SPEC0088 attachment, was used to capture the various ODT dissolution rates by measuring real time release of the active ingredient. Additionally, a high speed video camera was used to capture disintegration times of ODO products in simulated saliva held at 37℃.

Results: 5-mg Tablets: Release for all tablets except Zoltrix was around 90% or above with 150 rpm for ten minutes at the end of the analysis. In the first three minutes, Lilly’s Zydis formulation was the first to release with dissolution over 30% in less than 60 seconds. At 20 rpm only Zyprexa Zydis had instant disintegration. Other products required more than 30 seconds to dissolve even 10% of the active ingredient. This is likely a function of formulation and compression vs. a freeze drying processing.

10-mg Tablets: Zydis (Velotab) was the first to show dissolution and showed a steady rate of dissolution. Procaps’ Prolanz FAST formulation also had quick dissolution, but showed a longer delay to catch up to the Zydis formulation, taking 2 minutes before they were equivalent. At a lower agitation rate of 20 rpm, Zydis 10 mg still had the fastest dissolution rate in the first 3 minutes. Zydis dissolution was not significantly affected by dosage strengths (5, 10 mg).

15-mg Tablets and 20-mg Tablets: Lilly’s Zydis (Velotab) again provided the fastest disintegration and dissolution. Tablet mass and formulation might slow the release of active ingredient from generic direct compressed tablets.
**Conclusions:** The in vitro disintegration test is a proxy for the disintegration process in a patient’s mouth. Differences found in the formulation and manufacturing processes of ODO products may be associated with different disintegration times, which may potentially impact their use in clinical practice.

**Key words:** In vitro analysis, orally disintegrating olanzapine

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**[SO-12]**

**Effect of duloxetine on functional outcomes in patients with major depressive disorder**

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**Objective:** Patients with major depressive disorder (MDD) often have a reduced ability to function socially, maintain and enjoy relationships and work. The aim of this analysis was to investigate the efficacy of duloxetine vs. placebo on improvement in functioning after 8 weeks of treatment.

**Methods:** This was a pooled analysis of data from two separate 9-month studies conducted under the same protocol in patients with MDD (DSM-IV-TR) to examine the efficacy of duloxetine 60 mg/day (n = 518) vs. placebo (n = 258) on impairment in functioning. Pooling the data from these studies was specified a priori in the protocol to allow for increased power to detect differences between duloxetine and placebo on secondary and exploratory objectives. The measures included in this analysis were: the Hamilton Depression Rating Scale (HAMD) Item 7 (Work / Activities), the Sheehan Disability Scale (SDS), the Social Adaptation Self-evaluation Scale (SASS) to assess social behavior, the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) and the Profile of Mood States -brief form (BPOMS) subscales Vigor / Activity (VA) and Fatigue / Inertia (FI) used as surrogate measures of function. Mean changes from baseline were analyzed by using a mixed-effects model repeated measures approach (MMRM). An analysis of covariance (ANCOVA) using a last observation carried forward (LOCF) approach was conducted as a sensitivity analysis. The endpoint for this analysis was at week 8.

**Results:** At baseline, patients had moderately severe levels of SDS global functional impairment scores (18.3±6.9). At the endpoint, there was significant improvement from baseline (MMRM) with duloxetine treatment on the HAMD Work / Activities (p<.001), Sheehan Disability Scale global (p<.002), SASS total (p<.001), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (p<.001) and BPOMS Vigor / Activity (p=0.012) and Fatigue / Inertia (p=0.006) subscales. At the endpoint (LOCF imputation), duloxetine-treated versus placebo-treated patients had significantly greater improvement from baseline on the HAMD Work / Activities, SDS global, SASS total, CPFQ total and Profile of Mood States -brief form subscales VA and FI.

**Conclusion:** These results suggest that treatment with duloxetine may improve functional impairment in patients with major depressive disorder.

**Key words:** Duloxetine, major depressive disorder

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**[SO-13]**

**Effect of vitamin D on zinc status, carbohydrate metabolism, and activities of some enzymes in alloxan-diabetic rats fed on a zinc deficient diet**

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**Objective:** This study was carried out to investigate the effect of vitamin D on experimental diabetes in albino (Wistar) rats fed on a zinc deficient diet.

**Methods:** Male alloxan-diabetic albino (Wistar) rats of ten weeks of age were divided into three groups. The first group was fed on a zinc...
adequate diet (AZ containing 5.4 mg zinc/100g). The second group was given a zinc deficient diet (ZD containing 0.12 mg zinc/100g), and the third group received a zinc deficient diet and was treated orally with vitamin D (12.5µg/kg) (ZD + VD). Body weight gain was recorded regularly during the experimental period. After three weeks, the animals were sacrificed and blood glucose, serum cholesterol, serum triglycerides, serum total protein, serum urea, serum zinc, liver zinc, kidney zinc, pancreatic zinc, femur zinc, liver glutathione concentrations, serum glutamic oxalic transaminase (GOT), serum glutamic pyruvic transaminase (GPT) and serum alkaline phosphatase activities were determined.

**Results:** The body weight gain of the zinc deficient diabetic animals at the end of three weeks of dietary manipulation was significantly lower than that of the zinc adequate diabetic animals. The zinc deficient diet significantly increased the blood glucose, serum cholesterol, serum triglycerides, and serum urea of the zinc deficient diabetic rats as compared to their counterparts fed on an adequate zinc diet. Meanwhile serum zinc, femur zinc, pancreatic zinc, liver zinc, kidney zinc, serum total protein, and liver glutathione levels were diminished. The consumption of a zinc deficient diet led also to an increase in GOT and GPT and a decrease of serum alkaline phosphatase activities. However, vitamin D treatment ameliorated all of the previous physiological and biochemical parameters.

**Conclusion:** In conclusion, this study demonstrated that vitamin D reduced the severity of diabetes development caused by zinc deficiency. In other words, vitamin D probably increased zinc absorption which led to insulin synthesis and secretion and improvement of insulin activity.

**Key words:** Zinc deficiency, diabetic rats, alloxan, vitamin D, GOT, GPT, alkaline phosphatase

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** Gabapentin in the treatment of opioid withdrawal

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**Objectives:** To evaluate the efficacy of gabapentin (1600 mg/day) as an adjunct to methadone-assisted detoxification (MAD) in the treatment of opioid withdrawal symptoms.

**Methods:** Design: A 3-week open label study (as the second phase) following a double blind placebo controlled study with 900mg/day of gabapentin (as the first phase of this study). Setting: A specialized outpatient clinic for the treatment of patients with addictive disorders. Participants: Twenty-seven opiate addicts, who met the DSM-IV-TR criteria for opioid dependency, randomly selected among outpatients referred to our clinic. Intervention: The subjects received adjunctive treatment with gabapentin (1600 mg/day) in addition to MAD for three weeks. Measurements: The Subjective Opiate Withdrawal Scale (SOWS) with a total score of 0 to 64 was administered at six time-points during the study.

**Results:** The total SOWS score was significantly decreased after the intervention. Compared with our previous trial, an almost significant difference was observed in total SOWS scores between groups treated with gabapentin 1600 mg/day and 900 mg/day at the end of the intervention period (p = 0.06). Gabapentin at a dose of 1600 mg/day was significantly superior to a dose of 900 mg/day in decreasing the severity of coldness, diarrhea, dysphoria, yawning, and muscle tension.

**Conclusion:** Add-on gabapentin at a dose of 1600 mg/day may be effective in reducing some of the withdrawal symptoms in opiate addicts undergoing methadone-assisted detoxification.

**Key words:** Opium dependence, opioid withdrawal, gabapentin

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[SO-14] Gabapentin in the treatment of opioid withdrawal

Ref. No: 152
The role of transcranial magnetic stimulation in cognitive processes and treatment of psychiatric disorders

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Background and Objectives: Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain. This field can be of sufficient magnitude and density to depolarize neurons. When TMS pulses are applied repetitively they can modulate cortical excitability, increasing or decreasing it depending on the parameters of stimulation, even beyond the duration of the train of stimulation. This effect has behavioral consequences and therapeutic potential. Due to its easy use and relatively minor side effects, transcranial magnetic stimulation is now widely used in neurosciences and medicine. The main areas of transcranial magnetic stimulation application are:
1) the investigation of cortical and spinal excitability,
2) the investigation of neuronal plasticity,
3) the investigation of neuronal connectivity,
4) functional mapping, and
5) the treatment of some neurological and psychiatric disorders.

Transcranial magnetic stimulation alone or in combination with other noninvasive neuroimaging (PET – positron emission topography, MRI – magnetic resonance imaging) and neurofunctional (EEG – electroencephalography, ERP – event-related potentials, FMRI – functional magnetic resonance imaging) methods allows the conduction of research on brain functions. Thus, transcranial magnetic stimulation is suitable as a diagnostic tool in neurological and neuropsychiatric brain investigations.

Method: The method of research in this paper was a review of the literature regarding publications that applied TMS for treatment and investigation goals. A total of 104 relevant papers were identified and reviewed and the results are presented here.

Results: TMS is, through inducement of an electrical field, a useful instrument to visualize regional activities in response to stimulation. The mechanism of effect of TMS is through inducing the depolarization of neurons that in turn activates other neurons and produces behavioral and cognitive outcomes, depending on the stimulated area and its function. For example some of the observable TMS-induced effects are: phosphene by stimulating the occipital cortex, interrupting working memory and speech processes by stimulating the frontal lobe, or improving verbal memory in major depressive disorder through modulating effects on the dopamine system. TMS, unlike electroconvulsive therapy (ECT), does not have any substantial cognitive side effects. TMS has effects on neurochemical and synaptic processes in neurons. There are reports in the literature that depression, mania, schizophrenia, pain disorder, hallucinations, catatonia, post traumatic stress disorder, obsessive compulsive disorder, Parkinson’s disease, epilepsy, neuronal plasticity studies, tick disorders, migraine and dystonia are improved by TMS procedures.

Conclusions: Current published studies and meta-analyses have evaluated the efficacy of rTMS, given in treatment paradigms that were almost certainly suboptimal (e.g. duration of two weeks), and found that TMS is a safe and tolerable intervention. These findings raise the possibility of using TMS as a therapeutic device in psychiatric disorders and neuroscience research. This study summarizes the mechanisms of effect, advantages, and side effects of TMS and reviews studies of the efficacy of transcranial magnetic stimulation on psychiatric disorders.

Key words: Transcranial magnetic stimulation (TMS), neuromodulation, electromagnetic induction

Oxytocin inhibition of pentylenetetrazole-induced convulsions and its identification by behavioral measurement and thalamic EEG in the rats

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Objective: In this study, our aim was to reveal the possible anticonvulsant effects of oxytocin (OX) in high doses, as oxytocin has inhibitory
effects in brain. In addition, these effects were correlated with thalamic EEG recordings. To create the convulsions, pentylentetrazol (PTZ) was used.

**Materials-Methods:** In this study sixty 8-12 weeks old Sprague-Dawley adult male rats, which were separated into 10 groups (n=6), were used. In the first through the fifth groups 10, 20, 40, 80, and 120 U/kg OX was injected intraperitoneally (i.p) in order. In the sixth group (control), saline was injected.

Five minutes after of each injection of OX, 70 mg/kg i.p. PTZ was injected into the all rats and seizures were induced. We evaluated the seizure behaviors with the Racine Convulsion Scale and we determined the threshold seizure dose of PTZ, around 35 mg/kg, and the suppressive dose of OX, around 80 and 120 U/kg.

The rats, which were placed in a Plexiglas cage, were evaluated according to the severity of convulsions from 0 to stage 5. The scale of convulsions was: (0):Normal,(1):Frozen,(2):Nodding,(3):Superficial clonic movements,(4): Bilateral clonus in front extremities (piano play)(5):generalized tonic clonic seizures and falling sideways.

To show the anticonvulsant effects of oxytocin using the EEG, the seventh through the tenth groups were used. Under anesthesia a small hole was drilled. Then by taking the bregma as a reference using the stereotaxic method (coordinates AP:-3.6 mm, L:+2.8 mm, V:-5.0 mm) (Paxinos Rat Brain), an exterior insulated bipolar EEG electrode was placed in the left thalamic nucleus. In the seventh group thalamic EEG records were taken after only saline injection.

The rats in the eighth and ninth groups were injected intraperitoneally (ip) with 80 and 120 U/kg OX, respectively. In the tenth group (control), just saline was injected. Five minutes after each OX injection, 35 mg/kg i.p. PTZ was injected into the all rats. EEG recordings were taken for 20 minutes. The signals were amplified by 10,000 times and filtered with a range of 1-60 Hz. System records were taken by a Biopac MP30 amplifier system and evaluated with the FFT (Fast Fourier Transform) and PSA (Power Spectral Analyses) methods. During this process Delta 1-4 Hz, Theta 4-8 Hz, alpha 8-12 Hz and beta 12-20 Hz waves in the EEG are accepted as the ratio of percentage in PSA methods. We affirmed the electrode location histologically following euthanisation.

**RESULTS:** We observed that oxytocin has a powerful anticonvulsant effect, which appears at 40 U/Kg (Stage 3.14±0.69 ) and 80 U/kg (Stage 3.0±0.57) doses moderately and which shows the maximum effect at 120 U/kg (Stage 1.57±0.53) doses (p<0.005).

After injection of subconvulsive dose of PTZ (35mg/kg) and saline, the thalamic EEG delta frequency percentage was 54.6%±2.16 and after injection of only saline the thalamic delta frequency percentage was 80.5%±3.08. We observed significant (p<0.005) diminution in delta frequency and also augmentation in theta frequency. The augmentation of thalamic EEG frequency is linked to the GABA blocker effects of PTZ.

After injection of a subconvulsive dose PTZ (35mg/kg) and saline, the thalamic EEG Delta frequency percentage was 54.6%±2.16 and in the rats given PTZ and 120 U/kg oxytocin the thalamic delta frequency percentage was 94%±1.41. In comparison there was a significant augmentation in delta frequency (p<0.005), and a diminution in theta frequency was observed.

In PTZ and saline injected rats, the EEG formed spike-wave complexes. In the 120U/kg oxytocin and PTZ injected rats, the spike-wave complexes disappeared.

**Conclusion:** Our results indicate that Oxytocin has therapeutic potential similar to anticonvulsants in epilepsy.

**Key words:** Thalamic EEG, oxytocin (OX), racine scale, absence convulsion, generalized convulsion, pentylenetetrazol (PTZ)

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The effects of metoprolol and diltiazem in the prolonged QTc interval caused by ziprasidone injection in rats

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**Introduction:** Antipsychotic drugs cause prolongation in the QTc interval and may cause sudden cardiac death in patients. The reason for this prolongation in QTc interval is that cardiac repolarisation is made more difficult due to the blockade of potassium channels. Therefore, antipsychotic medications predispose patients to torsades de points and ventricular tachycardia. The purpose of this study was to reveal the effects of metoprolol and diltiazem on drug induced (ziprasidone) prolonged QTc (QT correct) interval.

**Materials-methods:** The experiments performed in this study were carried out according to the rules in the Guide for the Care and Use of Laboratory Animals adopted by the National Institutes of Health (U.S.A) and received consent from Ege University Animal Ethics Committee.

In this study 18 Sprague-Dawley adult male rats were used. Before administration of the anti-psychotic under anesthesia (ketamine (40
mg/kg) and xylazine (4 mg/kg) intraperitoneally (IP), an ECG was taken in derivation (D) I and the normal QTc interval was determined. To calculate the QTc interval, Bazett’s formula was used.

The rats were divided into 3 groups (n=6). For the first group, 3 mg/kg ziprasidone and saline, for the second group, 3 mg/kg ziprasidone and 1 mg/kg metoprolol and for the third group, 3 mg/kg ziprasidone and 2 mg/kg diltiazem were administered intraperitoneally. Two hours later, under anesthesia, the QTc interval was calculated by taking the ECG in derivation I.

**Results:** In the first group of rats, given ziprasidone and saline the QTc interval (0.161±0.01 s) was significantly (p<0.05) prolonged compared to the QTc interval (0.125±0.009 s) before the drug administration.

In the second group of rats, administered ziprasidone and metoprolol, the QTc interval (0.123±0.009 s) was significantly (p<0.05) shorter than that of the group given ziprasidone and saline (the first group, QTc interval = 0.161±0.01 s).

In the third group of rats, injected with ziprasidone and diltiazem, the QTc interval (0.125±0.004 s) was significantly (p<0.05) shorter than that of the group given ziprasidone and saline (the first group, QTc interval = 0.161±0.01 s).

**Discussion:** High dose ziprasidone causes prolongation in the QTc interval. Metoprolol and diltiazem prevent ziprasidone induced elongation of the QTc interval. The prophylactic use of these drugs may be an option for reducing the risk for ventricular arrhythmias and sudden cardiac death in patients taking antipsychotics.

**Key words:** Long QTc, ziprasidone, metoprolol, diltiazem, ventricular arrhythmias, sudden cardiac death

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