was sampled between 18.00 and 08.00 the following morning. The procedures were repeated on the seventh day of treatment. Salivary cortisol and melatonin and urinary 6-sulphatoxymelatonin were measured by specific direct radioimunnoasays.

Results: Both saliva melatonin and urinary 6-sulphatoxymelatonin were not significantly effected by either Jarsin treatment. Whereas, salivary cortisol was significantly increased by the low dose of Jarsin [ANOVA time ($F=7.28$; $df=1,16$; $p<0.0001$), drug ($F=4.48$; $df=1,16$; $p=0.05$) and drug by dose interaction ($F=4.41$; $df=1,16$; $p=0.05$) but not by the higher dose of Jarsin.

Conclusions: Data supports the existence of a U-shaped dose-response curve for SJW but not for any noradrenaline-mediated mode of action. Jarsin may be clinically effective at a reduced daily dose.

P.1.064 Differential response to imipramine in mice lacking D2 or D4 dopamine receptor gene

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The dopaminergic system of the brain is thought to play a major role in the regulation of motor, cognitive, neuroendocrine functions and in the pathogenesis of several pathological conditions, including affective disorders. Recent studies suggest a possible role of D4 dopamine receptor in diseases involving central dopamine systems. In this sense, antagonists with high affinity to D4 dopamine receptor showed antipsychotic and antimanic activities and D4 blockade decreases the firing of dopamine pathways in cortical areas. Moreover, D4 dopamine receptor levels are elevated in mayor depression states. On the other hand, knockout mice lacking D4 dopamine receptors show enhanced reactivity to stimulants. Forced swimming test in mice is the most widely used tool for assessing antidepressant activity preclinically and it has been also used to investigate the mechanism of action of antidepressants. On the other hand, mice with genetically altered expression of a specific protein (i.e. receptor, transporter, etc) are nowadays a new tool in the searching of targets for antidepressant activity. A list of genetically modified mice has been tested in simple tests predictive of antidepressant activity as forced swimming test or tail suspension test. To date, mice lacking D2 or D4 dopamine receptor genes have not tested in order to detect depressive or antidepressant-like behaviours. Only D5 receptor knock out mice have been tested in the forced swimming test and have shown antidepressant-like effects. The aim of this study is to test whether D2 or D4 dopamine receptor-deficient mice have an antidepressant-like behaviour and whether imipramine keeps its effect in these mice.

Methods: Forced swimming test in mice were performed as model of depression. Animals were forced to swimming during six minutes and immobility was recorded during the last four minutes. The immobility observed in this test reflects certain aspects of a highly complex disease state and is reduced by a variety of antidepressants. The classical tricyclic antidepressant imipramine (10 mg/kg) was i.p. administered three times, 24, 12 and 1 hour before test.

Results: D4 knockout mice show an antidepressant-like behaviour compared with wild type mice (91.5 ± 10.25 vs 142.0 ± 15.14, $p< 0.05$). Imipramine does not show any effect compared with saline treated in D4 knock out mice (86.9 ± 16.36 vs 63.4 ± 9.77, n.s.). D2 knock out mice behave as wild type in the forced swimming test (129.8 ± 13.5 vs 107.5 ± 77 16.36, n.s.). In contrast to the lack of effect of imipramine in D4 knock out mice, imipramine keeps its antidepressant properties in D2 knock out mice (61.1 ± 14.43 vs 129.8 ± 13.50, $p< 0.05$).

Conclusion: Mice lacking D4 dopamine receptor gene have an antidepressant-like behaviour in the forced swimming test and were unresponsive to imipramine treatment. However, the responses to imipramine were unaffected in the D2 knockout animals.

P.1.065 Effect of the antidepressant nefazodone on the density of cells expressing mu-opioid receptors in discrete brain areas processing sensory and affective dimensions of pain

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Introduction: Pain results not just from the physical insult but also from a combination of physical, emotional and psychological abnormalities. Thus, in a wide sense, pain can be thought of as having sensory (discriminative) and affective (the 'unpleasantness') dimensions, and can lead to secondary effects such as anxiety and depression. Moreover, there is evidence to indicate that parallel spinal pathways might distribute information to brain circuits that are concerned with either sensory or affective qualities of pain. Antidepressants (ADs) are widely used as co-analgesics. It is not known, however, whether the effectiveness of the antidepressants as co-analgesics is due to a direct effect on nociceptive pathways or results from their solely effect on affectivity. This aspect is very difficult to study in animals, although in man some data point out to an independence of effects. One possibility is that ADs have some effect on the opioid system that is very implicated modulating pain but also affectiviy probaly in different SNC projections or nucleus. For this reasons we explore the possibility that ADs enhance the cellular expression of the opioid system in those discrete areas implicating the sensorial and affective dimensions of pain. The aim of our study was to evaluate the antinociceptive and the antidepressant effects of chronic NFZ and its possible relations with modifications in mu-opioid receptor expression in brain areas related to pain and affectivity.

Materials and Methods: Male albino Wistar rats weighing 200–250 g were used. Rats were chronically treated with NFZ (20 and 50 mg/kg ip, during 14 days) and 24 hours after the last injection, tail flick was performed as nociceptive test. Then, a new dose of NFZ was administered and 24 hours after, Porsolt test was carried out. In other animals, two hours after the last treatment, they were perfused transcardially under deep anaesthesia with saline plus 50 mM phosphate buffer, pH 7.4, followed by 4 % paraformaldehyde. The brains were removed and 50 micrometer sections were cut using a cryostatic microtome with an stereotaxic atlas guide and immunostained for mu-opioid receptor with polyclonal antisera raised in rabbits. Several brain regions were analysed: frontal and cingulate cortex, raphe dorsalis nucleus, and periaqueductal gray.

Results: Chronic NFZ treatment induced a significant increase in tail-flick latency (Dose 20 mg/kg= +27.78% and 50 mg/kg=

+30.28%) and a significant decrease in immobility time (Dose 20 mg/kg= −52.2% and 50 mg/kg= −67.5%) ($p<0.05$). We found a significant increase in the density of neural cells inmunostained for mu-opioid receptor in the frontal cortex (+39.20%), cingulate cortex (+18.6%), raphe dorsalis nucleus (+45.65%) and periaqueductal gray (+32.15%) after chronic nefazodone treatment.

Conclusions: These results show that chronic NFZ induces antinociceptive and antidepressant-like effects in rats and increases mu-opioid receptor expression in brain areas related to pain and affectivity. These results demonstrate that some antidepressants could be effective on sensorial and affective dimensions of pain by means of its action on the opioid system in addition to the action on monoamines.

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P.1.066 The effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients

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Objective: It is widely accepted that the alterations in synaptic level of monoamines underlies the pathophysiology of mood disorders. However, recent studies suggested a possible role of brain-derived neurotrophic factor (BDNF) in depression (1). Recently, Karege et al showed that serum levels of BDNF of drug-free depressed patients were lower than those of controls (2). However, there is no data about the serum levels of BDNF in treated depressed patients.In this study, we want to test the hypothesis that as a peripheral marker of depression, serum BDNF levels which are lower that those of controls during depression will be increased with the antidepressant treatment.

Method: SD was 35.5±8.1; 7 male and 21 female)±Twenty-eight patients (mean age diagnosed as major depressive disorder according to DSM-IV criteria were included in the study. Thirteen of the patients had their first mood episode and were drug-naïve. Other patients were drug-free for at least 4 weeks. The severity of depression was assessed by HAM-D. Blood samples were collected at the baseline and after 8 weeks of antidepressant treatment (during remission). Serum BDNF was kept at −70°C before testing, and assayed with an ELISA Kit (Promega; Madison, WI, USA), after dilution with the Block and Sample solution (provided with the kit).The data were evaluated by t-test, analysis of variance (ANOVA) and Pearson' s correlation coefficient. For t-test,a´was adjusted to 0.016 with Bonferroni correction for preventing the type I error.

Results: At the baseline, mean serum BDNF levels of patients was lower than those of controls ($t=2.47$ $df=44$ $p=0.015$). There was a significant negative correlation between HAM-D scores and BDNF levels ($r=0.49$ $p=0.007$). Analysis of covariance indicated that both the severity of depression and the gender, accounted for the negative correlation between BDNF and depression (F-ratio was 12.24 and 6.83, $P=0.002$ and 0.015, for severity and gender, respectively). Mean BDNF levels of patients increased significantly with the treatment ($t=7.81$ $df=27$ $p<0.001$).

Conclusion: Our results showed that serum BDNF levels of depressed patients which was lower than those of controls increased significantly with the antidepressant treatment. This finding supports the hypothesis that BDNF plays an essential role in pathophysiology of the major depression and its treatment.

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P.1.067 Bipolar disorder: One year follow-up study

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Background: It is a well known fact that bipolar disorder involves multiple relapses, impaired psychosocial functioning and disability. Many longitudinal studies have been carried out in order to elucidate the patterns of course and to determine the issues affecting the course and outcome of the disorder. Most of these studies agree on that bipolar disorder is an episodic and long standing disease, and long term outcome is variable. Its course can be best examined by naturalistic follow-up studies.

Objective: The aim of this study was to investigate the course and outcome of bipolar disorder in a one year naturalistic follow up of interepisode patients.

Method: The outcome data of 48 patients (male=24, female=24) who were evaluated three times, once in every 6 months were analysed. Interepisode bipolar patients were interviewed with the Schedule for Affective Disorders and Schizophrenia (SADS) initially and with SADS-Change version at follow up visits. They both include Global Assessment Scale (GAS). Patients were also asked at every session to complete the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Brief Disability Questionnaire (BDQ) and a form for the treatment follow-up.

Results: There were no statistically significant changes in symptom severity. An improvement in psychosocial functioning which was evaluated by BDQ and GAS was observed. The relapse rate during the follow-up period was 31.2%. We classified the sample as good, medium and bad course groups with respect to GAS scores. Interepisode residual symptom levels (manic, depressive symptoms and delusions) differed significantly between GAS-based groups. Patients with good course were maintained mainly on lithium monotherapy. Presence of interepisode residual depressive symptoms predicted the final GAS score at the end of the follow-up period.

Conclusion: Relapse rate compared to earlier reports was lower in this study. Presence of interepisode depressive symptoms was associated with a less favourable course. On the other hand successful maintenance with lithium monotherapy was related with good course. Our sample size is small and follow-up duration is short. Relatively lower relapse rate may reflect the consequence of these above mentioned limitations.

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