MILD TO MODERATE ALCOHOL WITHDRAWAL
PREGABALIN AND LORAZEPAM IN THE TREATMENT OF

A COMPARISON OF EFFICACY AND SAFETY OF
PREGABALIN AND LORAZEPAM IN THE TREATMENT OF
MILD TO MODERATE ALCOHOL WITHDRAWAL
SYNDROME

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Background: Alcohol withdrawal is a maladaptive behavioral change with accompanying physical and cognitive symptoms with severe morbidity. This study was conducted to compare the efficacy and safety of pregabalin and lorazepam in treatment of mild to moderate alcohol withdrawal syndrome.

Methods: This was a prospective, open label, randomized, comparative and parallel group clinical study. Fifty patients aged 18–45 years fulfilling the ICD-10 criteria for alcohol withdrawal, clinical institute withdrawal assessment for alcohol-revised (CIWA-Ar) score ≥10 and willing to give an informed consent were included in the study. Group I was given oral pregabalin 150 mg twice daily tapered to 75 mg in the night on day 7. Group II was given oral lorazepam 2 mg thrice daily which was reduced to 1 mg in the night by day 7. Efficacy assessment was done by evaluation of CIWA-Ar scores, craving for alcohol on visual analogue scale (VAS), patient global comfort on VAS and relapse rate by breath analysis on day 2, 3, 5 and 7. Safety assessment was done by ADR monitoring, withdrawal from study and laboratory investigations. Categorical data was analyzed by Friedman’s and continuous data by repeated measures ANOVA. Intergroup analysis was done using Mann-Whitney test for categorical data and independent t test for continuous data. Adverse drug reactions were analyzed using Chi-square test.

Results: Pregabalin was found to be as effective as lorazepam in reducing CIWA-Ar scores and craving with the advantage of a faster relief. Pregabalin was superior to lorazepam in in reducing patient global discomfort on VAS. Incidence and severity of ADR’s was comparable in both groups. All ADR’s were mild and reversible. Drowsiness and nausea were found to be more with lorazepam while pain in lower limbs was more with pregabalin. No withdrawal due to ADR’s happened in either of the groups.

Conclusions: Pregabalin can be an effective and safe alternative to gold standard lorazepam in the treatment of mild to moderate alcohol withdrawal.

A CRUDE HYDROETHANOLIC EXTRACT OF BOOPHONE DISTICHA HAS ANXIOLYTIC-LIKE EFFECTS IN BALB/C MICE

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Background: Boophone disticha (BD) is one of the most widely used psychoactive plants in southern Africa. Traditionally, extracts of the bulb and leaves are used for treating various ailments including anxiety like conditions. However, there is a lack of scientific data based on in vivo models to support its use in these conditions. In view of the above, the present study sought to investigate the anxiolytic-like activity of an oral dose of a hydroethanolic extract of BD in BALB/c mice using the Elevated Plus Maze (EPM) test.

Methods: Forty BALB/c mice were randomly placed into five groups of eight (n=8), namely, normal saline vehicle control, diazepam 10 mg/70 kg and Boophone disticha (10, 25 and 40 mg/kg) groups. All treatments were given by oral gavage. The animals were left to explore the EPM for 5 min with video recording in a soundproof room. Parameters recorded in this study included number of open and closed arm entries, time spent in open and closed arms, rearing, stretched attend posture and head dips. Comparisons between groups were performed using an ANOVA test followed by Tukey’s pairwise test. For all analyses a P-value <0.05 was considered to be significant.

Results: Mice treated with Boophone disticha for all study doses showed a significant increase in the amount of time spent in the open arm (P < 0.05), unprotected head dips (P < 0.01) and unprotected stretched attend posture (P < 0.01) when compared to the vehicle control. A notable increase in the number of open arm entries and a reduction in number of close arm rears was also evident. The low dose group (Boophane 10 mg) showed the most activity for all the parameters measured.

Conclusion: The hydroethanolic extract of Boophone disticha at all doses used in this study exhibited anxiolytic-like activity in mice.

A NOVEL ANTIBODY-BASED MEDICINE AMELIORATES LEARNING AND MEMORY DEFICITS IN AMYLOID β RAT MODEL OF ALZHEIMER’S DISEASE

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Background: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by increased amyloid β (Aβ) deposition and neuronal dysfunction. Release-active antibodies to S100 protein (RA anti-S100) were previously known to possess neuroprotective activity in several in vivo models, and release-active antibodies to endothelial NO synthase (RA anti-NO) were acknowledged to exert endothelial protective effects.

Methods: The study was approved by institutional animal ethical committee. Male Wistar rats (16 weeks old, 276 - 299 g) of five experimental groups were injected into the right ventricle with 5 µL Aβ (15 nM) each according to the methods of Paxinos and Watson Atlas (AP=0.8, L=1.5, H=3.8). Rats of two control groups were either injected with saline (n=20) or sham-operated (n=10). RA anti-S100 (10 µL/kg, n=22), RA anti-NO (10 µL/kg, n=27), combination of RA anti-S100 and RA anti-NO (10 µL/kg, n=24), vehicle (distilled water, 10 µL/kg, n=26), memantine hydrochloride (10 mg/kg, n=20) were administered for 21 days starting from the day of Aβ injection. The set of tests was carried out during the study; on day 6–8 after Aβ challenge - the novel object recognition test, on day 9 and 4 days after - passive avoidance test, on day 10–12 - locomotory activity and exploratory behavior in the open field, on days 16, 17, 18, 19, 20 - the rats’ operant learning ability in PhenoMaster system (TSE Systems, Germany). On day 21 five rats of each experimental group and three rats of each control group were sacrificed and brain tissue samples were collected for immunohistochemical analysis. Both parametric and non-parametric (Mann-Whitney, Fisher’s exact test) tests were applied.
Pearsen and Spearman correlation were calculated. A principal factor analysis was also utilized.

**Results:** RA anti-S100 and RA anti-NOS combines the properties of separate components in behavioral tests, which are supported by histological examinations (figure). The combination ameliorated amyloid-induced learning and memory deficits, influenced the emotional state of rats, partially protects neuronal cells from neurodegeneration. The effect of combination drug was comparable to that of memantine hydrochloride.

**Conclusions:** The combination drug comprising RA anti-S100 and RA anti-NOS acting synergically can be a possible treatment option of AD.

**Results:** A 30-min restraint stress significantly activated LH orexin neurons, increased orexin A levels in the VTA, and reinstated extinguished cocaine CPP. This stress-induced cocaine reinstatement was prevented by OX1R (SB 334867), DAGL inhibitors (THL), CB1R (AM 251) antagonists, respectively, and abolished in CB1 receptor-knockout mice. In VTA slices, orexin A presynaptically inhibited GABAergic transmission onto dopaminergic neurons. This effect was antagonized by SB 334867 and AM 251, prevented by internal GDP-ß-S and by PLC and DAGL inhibitors, and potentiated by inhibiting 2AG degradation.

**Conclusion:** These results suggest that acute restraint stress activates hypothalamic orexin neurons to release orexins that induce extinguished cocaine seeking via activating postsynaptic OX1 receptors on VTA dopaminergic neurons through a Gq protein-PLC-DAGL cascade generating 2AG, an endocannabinoid that retrogradely inhibits GABA release through presynaptic CB1 receptors, leading to disinhibition of VTA dopamine neurons.

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**ACID-SENSING ION CHANNELS (ASICs) PROMOTE THE INFLAMMATION AND MIGRATION OF CULTURED RAT MICROGLIA**

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**Background:** Microglia, the main immune cells in central nervous system (CNS), acts as the surveillance and scavenger of immune defense and inflammatory response in central CNS. Some primary studies prompted that, there might be close relationship between acid-sensing ion channels (ASICs) and immune inflammation, however, the exact role of ASICs in microglia during immune inflammation remains elusive.

**Methods:** We identify the expression of ASICs in microglia from mRNA level by RT-PCR. Quantitative real-time PCR experiments were performed to quantitative analysis of mRNA encoding ASIC1, ASIC2a and ASIC3. Western blotting was used to detected protein expression of ASICs. We determine the distribution of ASICs in microglia by The cellular immunofluorescence method. Whole-cell patch clamp was adopted to detect the current properties of microglia.

**Results:** We demonstrated that ASIC1, ASIC2a and ASIC3 were existed in cultured and in situ rat microglia, with a different distribution from neurons. In lipopolysaccharide (LPS)-stimulated microglia, the expression of ASIC1 and ASIC2a were upregulated. ASIC-like currents and acid-induced elevation of intracellular calcium were amplified in LPS-stimulated microglia, which could be inhibited by the non-specific ASICs antagonist amiloride and specific homomeric ASIC1a blocker PcTx1. Amiloride and PcTx1 reduced the expression of inflammatory cytokines, including inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) in LPS-stimulated microglia. Furthermore, we also observed significant increase in the expression of ASIC1 and ASIC2a in scrape-stimulated microglia. Amiloride and PcTx1 inhibited the migration of primary cultured rat microglia by inhibiting ERK phosphorylation.

**Conclusions:** Taken together, these results suggest that ASICs participate in neuroinflammatory response, which provide a novel therapeutic strategy for controlling the inflammation-relevant neuronal disease.

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**ACONITUM COCHILEARE WOROSCHIN-OIL ATTENUATES THE MOLECULAR MARKERS OF EPILEPTOGENESIS IN KINDLED MICE WITH SAFE TOXICITY PROFILE**

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**Background:** Epilepsy is a chronic neurological disorder, characterized by recurrent seizures occurring as a result of synchronized dis-