all patients stayed sober the whole treatment and follow up period (90.2% vs. 84.6 %). The biological markers normalized in both groups significantly without any group differences. Neither cognitive impairment nor adverse events were found more often in one of the groups. Interpretation. sodium oxybate and oxazepam are both effective and safe in treating alcohol withdrawal and in reducing craving for alcohol. Any kind of craving after discontinuation of sodium oxybate or of oxazepam was not an issue. Motivation process could be started early in both groups.

SAT2.2
SODIUM OXYBATE IN THE PREVENTION OF ALCOHOL RELAPSES IN ALCOHOL DEPENDENT PATIENTS (GATE 2 STUDY)
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Background. Maintenance of abstinence from alcohol represents the most important, but also the most challenging objective in the treatment of alcohol dependent patients. We aimed to investigate the long-term safety and efficacy of sodium oxybate in the long-term treatment of recently detoxified alcohol-dependent patients.

Methods. 314 patients with a diagnosis of alcohol dependence according to DSM-IV criteria were randomly enrolled from 11 European sites and allocated to two treatment groups: sodium oxybate (n = 154) and placebo (n = 160). Study duration was of 12 months (6 months of double-blind treatment period and 6 months of untreated follow-up). The primary outcome was the Cumulative Abstinence Duration (CAD).

Findings. Sodium oxybate was superior to placebo in achieving and maintaining abstinence from alcohol (p = 0.05). Specifically, sodium oxybate was particularly effective in Lesch type II patients (p = 0.035), but also in Lesch type III and IV patients (not statistically significant because of a lower sample size). Moreover, the incidence of craving for and abuse of the drug, and of other safety endpoints did not differ between sodium oxybate and placebo groups.

Interpretation. This long-term study confirms the safety and efficacy of sodium oxybate in promoting and maintaining abstinence from alcohol in recently detoxified alcoholics, particularly, but not only, in Lesch Type II alcohol-dependent patients. In addition, we found no evidence of abuse, misuse or dependence for the drug in this large patient population. Funding: Laboratorio Farmaceutico CT S.r.l.

SAT2.3
PHARMACODYNAMIC INTERACTIONS OF A SOLID FORMULATION OF SODIUM OXYBATE AND ALCOHOL IN HEALTHY VOLUNTEERS:
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Background. Sodium oxybate shares some pharmacological effects with alcohol, and has been approved for the treatment of alcohol dependence in Europe. This study evaluated the pharmacodynamic interactions of SMO.IR, a solid formulation of sodium oxybate and alcohol, to assess possible syner- gism, potentiation or antagonism of SMO.IR and alcohol.

Methods. 24 healthy volunteers participated in a double-blind crossover trial. Study participants randomly received: SMO.IR alone, alcohol alone, SMO IRIR + alcohol, and double placebo. Study endpoints were objective and subjective cognitive tests, adverse events, vital signs assessed before, and 15 and 165 minutes after study drug administration, Cognitive tests included: Body Sway Test, Saccadic Eye Movement, Choice Reaction Time, Critical Tracking Test, Digit Vigilance, Numeric and, Spatial Working Memory, Bond & Lader VAS, ARCI 49, and Biphasic Alcohol Effects Scale.

Results. Alcohol produced a significant impairment in cognitive performance and subjective sedation at 15 min. SMO.IR-induced less pronounced objective and subjective sedation 165 min post dose. There was a significant interaction between SMO.IR and alcohol at 15 min, with an increase in alertness and stimulation and a decrease in sedation. An isolated mild decrease in digit vigilance accuracy was observed at 165 minutes post dose with the combination. The combination increased the number of treatment-emergent adverse events: 46 vs 30 with SMO.IR and 34 with alcohol. No significant changes in vital signs, oxygen saturation, and laboratory tests were observed.

Conclusion. SMO.IR and alcohol have a distinct pharmacodynamic profile. Sedative effects of SMO.IR are much less marked than those of alcohol and no reciprocal potentiation was observed.

SAT2.4
A RETROSPECTIVE STUDY ON THE USE OF SODIUM OXYBATE IN NORTHERN ITALY
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Background. The Sodium Oxybate is successfully used in Italy from one to fifteen years for the treatment of both alcohol withdrawal and relapse prevention. The principal aim of this retrospective study, named GUM (GHb use and misuse), was to evaluate the effectiveness and the safety of Sodium Oxybate in the daily clinical practice.

Method. The study analysed 485 individuals (604 treatment cycles), with a diagnosis of alcohol dependence according to DSM-IV criteria, treated with Sodium Oxybate at seven alcoholism rehabilitation centers in northern Italy in the years 2005–2007. The primary outcomes of the study were: the drug anti-withdrawal effects; the drug effects on relapse prevention, the treatment dropout rate; while the secondary outcomes were: the drug side effects and adverse reactions, the appetitive behaviour (“misuse”), the drug abuse and the overdose, intoxication and withdrawal episodes. Finally, the study evaluated, for the first time, in a large cohort of Italian alcoholics, the prevalence of both infection diseases (e.g. hepatitis C, HIV, etc.) and prevalent psychiatric illness (including personality disorders).

Findings. The study confirmed the effectiveness of Sodium Oxybate in suppressing withdrawal syndrome (81% of the subjects treated were successfully rehabilitated) and in maintaining abstinence (76% and 78% of patients were abstinent at six and twelve months after starting treatment). The study showed that the drug is also safe and manageable, especially if used in doses between 50 and 100 mg/kg/die (the average dose was between 78.11 ± 23.30 mg/kg/die). Misuse and abuse were limited (12% of treatments), cases of intoxication an overdose extremely rare. For the first time in Italy, the study helped to identify the main demographics and clinical features of a significant sample of alcoholics subjects treated with Sodium Oxybate and the prevalence of prevalent infections diseases (31% were HBeAb + HBSAg positive, 15% were HCV positive and 4% were HIV positive) and psychiatric illnesses (12% in Axis I and 4% in Axis II).

Interpretation. The GUM study confirms the effectiveness and the safety of Sodium Oxybate in the treatment of subjects undergoing rehabilitation in Italian alcohol treatment centers. Funding: Laboratorio Farmaceutico CT S.r.l.
and small RNA fraction (<200 nt) were isolated and treated with DNase. Concentrations of mature mmu-miR-9, miR-9-5p and miR-9-3p precursors: pre-miR-9-1, -9-2, and -9-3 were determined by qRT-PCR. Preliminary results indicate that exposure to 20 mM but not 50 mM ethanol for 15 min caused an almost 2-fold increase in miR-9 expression. Interestingly, the expression of pre-miR-9-1 was also increased in response to ethanol. We are currently testing ethanol effect on expression of pre-miR-9-2 and -9-3 precursors. We are also trying to understand interplay between genetic (SNPs) and epigenetic (DNA methylation) mechanisms on regulation of expression of mir-9 genes by ethanol. We performed sequencing of promoters of mir-9 genes using human samples and observed presence of several SNPs in these regions. Some of these SNPs could alter binding of transcription factors and/or promoter methylation. Together, these results can provide new understanding of development of alcohol addiction.

O1.2 NEUROINFLAMMATORY PARP PATHWAYS IN ETHANOL-DEPENDENT NEURODEGENERATION: SUPPRESSION BY OMEGA-3 FATTY ACID
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Chronic alcoholism is a significant worldwide reason for brain/synaptic damage and mild-to-moderate cognitive impairment, but the mechanisms are unresolved. In that regard, repetitive, subchronic binge ethanol exposure with adult rats and rat organotypic brain cultures triggers neuroinflammatory routes leading to oxidative stress and regional neurodegeneration. Our results indicate excessive arachidonic acid (AA) mobilization due to increased phospholipase A2 (PLA2) levels/activity, and this appears to related to elevations in astroglial aquaporin-4 (AQP4) and brain edema. Furthermore, inhibiting AQP4 is neuroprotective. A promising sensor for the binge ethanol which could be triggering downstream AQP4 and PLA2 elevations is nuclear poly(ADP-ribose) polymerase-1 (PARP1), also potentiated by ethanol. Indeed, blocking PARP1 activity with PJ34 reduces binge ethanol-induced neurotoxicity, which implies that a component of the process is necroptotic or “parthanatotic” in nature. Furthermore, omega-3 docosahexaenoic acid (DHA 22:6) administration significantly suppresses PARP1, AQP4 and PLA2 elevations, AA release, and neurodamage. Details regarding the PLA2 isoforms involved and insights into DHA’s mechanism of neuroprotection will be presented. Other laboratories have reported that chronic ethanol treatments increase tol-like receptors/ligands, pro-inflammatory cytokines and NADPH oxidase; we suggest that those neuroimmune pathways interact via cross-talk with PARP1-AQP4-PLA2-AA cascades in order to augment oxidative stress as well. Supported by USPHS U01 AA018279 and the Loyola Univ. Alcohol Research Program.

O1.3 BINGE-LIKE DRINKING IN SARDINIAN ALCOHOL-PREFERRING RATS EXPOSED TO AN UNPREDICTABLE SCHEDULE OF LIMITED ACCESS TO MULTIPLE ALCOHOL CONCENTRATIONS
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This paper describes a new experimental procedure of alcohol drinking promoting exceptionally high intakes of alcohol in Sardinian alcohol-preferring (sP) rats (one of the few rat lines selectively bred worldwide for excessive alcohol consumption). sP rats were exposed to the 4-bottle “alcohol (10%, 20%, and 30%, v/v) vs water” choice regimen during one of the 12 hours of the dark phase of the daily light/dark cycle; the time of alcohol exposure was changed daily under a semi-random order and was unpredictable to rats. Alcohol intake was found to be highly positively correlated (n = 24, r = 0.984, P < 0.0001) with the time of alcohol exposure and ranged from an average of 0.86 ± 0.06 g/kg (drinking session occurring during the 1st hour of the dark phase) to an average of 2.00 ± 0.07 g/kg (drinking session occurring during the 12th hour of the dark phase). The difference in alcohol drinking during the 12th hour of the dark phase resulted in (a) blood alcohol levels averaging 101.1 ± 8.1 mg/dl and (b) severe signs of alcohol intoxication (e.g., markedly impaired performance at a Rota-Rod task). These results demonstrate that unpredictable, limited access to multiple alcohol concentrations may result in exceptionally high intakes of alcohol in sP rats. A progressively increasing emotional “distress” associated to the rats’ expectation of alcohol might be the neurobiological basis of this behavior.

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O1.4 REHABILITATION AND NEUROPROTECTION: USE OF EXERCISE AND ENVIRONMENT IN FAS (MODEL)
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Prenatal alcohol exposure in humans can result in a wide range of deficits collectively referred to as Fetal Alcohol Spectrum Disorders (FASD). Impairments vary with degree and timing of alcohol exposure and include anatomical, behavioral and cognitive effects that persist into adulthood and are accompanied by structural changes. In rodent models of FASD, exposure to alcohol during the development produces significant damage to several brain regions, including the hippocampus and prefrontal cortex (PFC). In the adult hippocampal dentate gyrus (DG), the process of generating new neurons is affected. In addition, overall decrease in frontal brain size and reduced medial PFC pyramidal neuron dendritic complexity (Rasmussen, 2005) indicate damage to cortical areas. Using a rodent model of binge drinking during third trimester equivalent, we explored therapeutic effects of exercise alone and exercise followed by exposure to environmental complexity (EC) on neuroanatomical parameters (adult neurogenesis in DG, dendritic complexity of postmitotic doublecortin-positive cells in the DG and dendritic complexity of pyramidal neurons in mPFC) and on behavioral outcomes. Following post-natal alcohol exposure, rats were assigned to cages with running wheel or standard housing from PD30-42, followed by exposure to EC (PD42-72) after wheel-running. Animals were tested on learning behavior and brains were collected for neuroanatomy. Our data indicates that 1) exercise alone is not sufficient to rescue the alcohol-induced deficits; 2) a “super” combination of exercise followed by EC is more effective in promoting new cell survival and dendritic reorganization; and 3) behavioral (learning) deficits could be reversed by the “super” therapy.

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FREE ORAL COMMUNICATIONS 2: PHARMACOLOGICAL TREATMENT OF ALCOHOL DEPENDENCE
O2.1 CONTINUING TREATMENT IN SPITE OF RELAPSES: UTILE? A LONGITUDINAL META-ANALYSIS ON ACAMPROSATE RANDOMIZED CONTROLLED TRIALS
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Background. Rates of continuous abstinence achieved with acamprosate as determined in randomized controlled trials (RCTs) consider patients who returned to drinking during therapy as treatment failures regardless of whether patients continued to drink afterwards or not. Clinical practice suggests that alcohol-dependent patients may achieve stable abstinence in a second or even later attempt following one or more relapses. In this context, our objective is to assess the effectiveness of acamprosate as a function of the previous drinking status.

Material. Based on 6423 patients and 24 RCTs, we conducted a longitudinal generalized mixed meta-analytic model assessing first-order autocorrelation in time for alcohol consumption.

Results. We found three highly significant effects (p < .001): linear deteriorating effect of consumption at time (t-1) of .38 drinks/month 95%CI [.34, .43], overall trend deterioration in time of .11 drink [0.07, .16], an interaction time-treatment of -.19 [-.24, -.15], but no significant interaction treatment-consumption (p = .23).

Conclusion. Drinking status at any time is essentially affected by previous period consumption: At long term, a strict continuous abstinence is much more effective than decreasing alcohol consumption and the effect of acamprosate increases at every period. This compensates the deterioration of drinking outcomes in time, and remains the same, irrespective of relapse occurrence during the previous period. We conclude that, after a patient’s return to drinking, treatment with acamprosate should be continued. Furthermore, due to the high-observed autocorrelation inducing the mediating effects of previous periods, our results suggest that continuing the treatment has a cumulative therapeutic effect likely to exceed effect sizes demonstrated in clinical trials.