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EFFICACY AND TOLERABILITY OF HIGH-DOSE BACLOFEN IN A U.S. COMMUNITY POPULATION: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

C.A. Pedersen, L. Willing, A. Kampov-Polevoi, R. Jordan, R. Casey, J. Tatreau, R. Gallop, K. McCann, M. Stansbury, J.C. Garbutt
Department of Psychiatry and Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, 27599-7160, USA

Introduction: Baclofen, a GABA-B receptor agonist, has been reported to be effective for alcohol use disorders in some but not all clinical trials. Early studies with baclofen utilized a dose of 30 mg/days but open-label experience suggested that higher doses, up to 300 mg/days, may be more effective. Several clinical trials have tested higher doses (90–180 mg/days range) with mixed results. To assess the efficacy and tolerability of "high-dose" baclofen in a U.S. population we completed a randomized, placebo-controlled trial comparing 30 mg/days of baclofen to 90 mg/days (1:1:1).
Methods: 120 subjects (mean age 46.1 ± 10.1 years; 53% male; 86% Caucasian; 8.7 ± 4.5 (F) and 11.4 ± 5.3 (M) baseline drinks/drinking day) were recruited from the community utilizing advertising and social media. Inclusion criteria: DSM-IV alcohol dependence; consumption of >14 drinks/week (women) and >21 drinks/week (men) with an average of 2 heavy drinking days (>3 drinks/day (women); >4 drinks/day (men)) per week in the month prior to screening. Subjects with active medical or psychiatric illness or other substance abuse except for marijuana/nicotine were excluded. Subjects were randomized based on gender and heavy drinking status (10 drinks/drinking day women; 14 drinks/drinking day men). Baclofen was titrated up/down over the 16 week trial. Medical Management was provided. The Time-Line Follow Back, Penn Alcohol Craving Scale and Spielberger Anxiety Scale were utilized. The two primary outcome measures were % days abstinent and % heavy drinking days, which were analyzed through a general linear model.
Results: Unblinding for data analysis is ongoing, therefore aggregate overall trial results are reported. Full results of drinking outcomes, craving, anxiety and tolerability by treatment condition will be presented at the meeting. 61% of subjects completed the trial with drop-outs occurring for: Lost Interest 24; Lost to F/U 9; Side-effects 7; Relapse 2; Other 5. Most commonly reported side-effects were drowsiness/somnolence (76), dizziness (56), nausea (14), and headache (11).
Conclusion: This is the first placebo-controlled trial of high-dose baclofen completed in a U.S. community population. While main outcome measures are still being analyzed the trial is of interest as it had lower than expected retention and a significant number of adverse events including high rates of drowsiness, a known side-effect of baclofen. Implications for the use of baclofen in community populations will be reviewed.

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BACLOFEN REDUCES ALCOHOL CUE-INDUCED FMRI BRAIN ACTIVATION IN TREATMENT-SEEKING ALCOHOL DEPENDENT INDIVIDUALS

W.B. Logge, A.J. Baillie, R.W. Morris, P.S. Haber, K.C. Morley
Drug Health Services, Royal Prince Alfred Hospital, Sydney, NSW, 2050, Australia

Baclofen, a selective $GABA_B$ receptor agonist is emerging as a potential treatment for alcohol dependence. We tested whether baclofen attenuated subjective craving and reduced alcohol cue-induced brain activation during a fMRI visual alcohol cue reactivity task in treatment-seeking alcohol dependent individuals compared to those taking placebo. Participants included 27 alcohol dependent individuals who received baclofen (30–75 mg/day; $n = 17$) or a placebo ($n = 10$) for at least two weeks. They completed a visual fMRI alcohol cue reactivity task, measuring blood oxygen level dependent (BOLD) responses as an index of alcohol cue reactivity. Two sample t-tests were conducted for treatment group (placebo, baclofen) for contrast Alcohol > Control cues to assess whether baclofen reduced brain activation to alcohol cues. Subjective alcohol craving was measured pre- and post-imaging session using the Alcohol Urge Questionnaire, and after each fMRI image block during the cue reactivity task (Alcohol, Control) using a Visual Analogue Scale. Subjective craving scores for alcohol cues increased overall from pre- to post-imaging session ($p = 0.035$), but there were no differences between groups, and there were no differences in craving scores during the fMRI task, either for image blocks or between groups. Reduced BOLD activation to alcohol cues was seen in baclofen group compared to placebo in several regions, including the sensorimotor cortices (bilateral primary sensory cortices), regulatory areas including the middle frontal gyrus, reward-related pathways (left caudate and anterior cingulate cortex) and middle cingulate cortices, the right insula, and extra striate visual region (lingual gyrus). Baclofen-treated participants did not show any regions of increased BOLD activation compared to the placebo group. Results indicate that baclofen may reduce cue-elicited brain activation to alcohol cues in treatment-seeking alcohol dependent individuals.

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BACLOFEN ADMINISTRATION ATTENUATES INSULA RESPONSE DURING ANTICIPATORY ANXIETY IN ALCOHOL DEPENDENT PATIENTS

K.C. Morley, R. Morris, W. Logge, A. Baillie, I. Fraser, P.S. Haber
NHMRC Centre of Research Excellence in Mental Health and Substance Use, Central Clinical School, Sydney Medical School, University of Sydney, NSW, Australia

Background: Alcohol dependent individuals demonstrate atypical brain BOLD responses to anticipatory anxiety. We aimed to investigate the effect of baclofen, a GABAb agonist, on this response in order to explore the mechanism by which baclofen may exert beneficial effects in the treatment of alcohol dependence.
Methods: Participants included 28 alcohol dependent individuals enrolled in a double-blind, placebo controlled, randomised trials. Participants underwent a conditioned cue task to evoke anticipatory anxiety during fMRI prior to treatment initiation (electric pulse). Participants then completed a pleasant and aversive (including threat of electric pulse) picture cued (matched from IAPS) anticipation task during fMRI after taking daily baclofen (30 mg/day BAC: $N = 10$, 75 mg/day BAC: $N = 8$) or placebo (PL = 10) for at least 2 weeks. We also included 11 age and gender matched non drinking healthy controls (HC).
Results: Alcohol dependent subjects demonstrated greater activation in the insula and amygdala during anticipation of aversive stimuli compared to non drinking healthy controls. Baclofen significantly decreased activation in bilateral insula during the anticipation of aversive stimuli.
Conclusion: Reduced insular activation during anticipation of negative events may explain therapeutic efficacy of baclofen demonstrated in some studies.

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MODERATION OF BACLOFEN RESPONSE BY A GABAB RECEPTOR POLYMORPHISM

K.C. Morley, N. Luquin, A. Baillie, I. Fraser, R. Trent, G. Dore, N. Phung, P. Haber
NHMRC Centre of Research Excellence in Mental Health and Substance Use, Central Clinical School, Sydney Medical School, University of Sydney & Drug Health Services, Royal Prince Alfred Hospital, NSW, Australia

Background: Baclofen has been shown to reduce alcohol consumption in alcohol-dependent individuals, but there is marked heterogeneity in response. The present study evaluated whether the response to baclofen is moderated by a single nucleotide polymorphism (rs29220) in the $GABA_B$ receptor subunit 1 gene (*GABABR1*).
Methods: Alcohol dependent patients were treated for 12 weeks with 30 mg/day of baclofen, 75 mg baclofen or placebo. Predefined primary outcomes included survival time to lapse (any drinking) and relapse (>5 drinks per day in men and >4 in women), and the composite outcomes of drinks per drinking day, number of heavy drinking days, and percentage days abstinent.
Results: We observed significant medication x genotype interaction effect for time to relapse (OR: 3.40, 95% CI: 1.01–11.46) and a near significant interaction effect for time to lapse (OR: 3.29, 95% CI: 0.98–11.06). Multivariate analyses revealed an overall genotype x medication effect ($p < 0.05$), with a significant interaction effect for percentage days abstinent. Patients with the CC genotype demonstrated increased percentage days abstinent and a greater time to relapse following baclofen treatment (80% vs. 36%; 50.55 days vs. 9.71 days), while those with the G- genotype showed no medication differences (57% vs. 59%; 27.21 days vs. 28.88 days). Patients with the CC genotype reported significantly less dizziness than the G- carriers (24% vs. 0% for CC and G- respectively, $p < 0.01$).
Conclusion: Our study is the first demonstration that the *GABABR1* rs29220 polymorphism moderates response to baclofen in the treatment of alcohol dependence and may have important implications for treatment selection.

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ASSOCIATION BETWEEN BACLOFEN RECEIPT FOR ANY INDICATION AND CHANGES IN REPORTED DRINKING AMONG CLINICAL SUB-POPULATIONS WITH AND WITHOUT ALCOHOL USE DISORDERS

C.T. Rentsch[1,2], J.P. Tate[1,2], K.J. Bryant[1,2], A.C. Justice[1,2], D.A. Fiellin[1,2]
[1]Yale University School of Medicine, New Haven, CT, 06511, USA and [2]Veterans Aging Cohort Study, VA CT Healthcare System, West Haven, CT, 06516, USA

Purpose: Baclofen, a GABA beta-receptor agonist used for spasticity, has efficacy in treating unhealthy alcohol use. We sought to determine if baclofen prescribed for any indication was associated with changes in reported drinking among clinical subgroups with and without alcohol use disorders (AUD), and by baseline levels of reported drinking and dose of baclofen.
Data: The Veterans Aging Cohort Study (VACS).
Methods: We included patients with AUDIT-C>0 who received baclofen (BACLO+) for ≥90 consecutive days for any indication between 2009 and 2012, and compared them to propensity score (PS)-matched, baclofen unexposed (BACLO-) patients. An index date was defined as prescription release date for BACLO+ patients and a randomly selected outpatient visit date for BACLO-. Pre and post index date AUDIT-C scores were compared between BACLO+ and BACLO- using difference-in-difference analysis. Pre-index date AUDIT-C scores were considered closest value to the index date, and post-index scores were closest value to the last date of follow-up. For BACLO+ we excluded AUDIT-C data obtained >90 days after last prescription refill. We considered a 1-point change in AUDIT-C to be clinically significant. We conducted stratified analyses by baseline AUD (assessed using ICD-9 codes) and AUDIT-C, and average daily dose of baclofen during follow-up.
Results: There were no demographic or clinical differences between 896 BACLO+ and 3,727 BACLO- PS-matched patients (total $n = 4{,}623$), (all $p > 0.4$). Patients in the PS-matched sample were mostly male (97%), 82% HIV-uninfected, 48% African-American, and 44% white. BACLO+ patients had higher pre-index date AUDIT-C scores (3.3 vs. 3.1; $p = 0.41$) but lower post-AUDIT-C scores (2.0 vs. 2.3; $p = 0.08$). Among all patients, the difference-in-difference (DiD) estimate of the additional decrease in AUDIT-C scores between BACLO+ and BACLO- was statistically but not clinically different (DiD 0.39, 95% CI 0.07, 0.72). Among patients with AUD, BACLO+ patients AUDIT-C scores dropped 0.80 points (95% CI 0.23, 1.38) more than BACLO-. The largest DiD estimate was found among patients with a baseline AUDIT-C>6 and an average daily baclofen dose >30 mg (DiD 3.26, 95% CI 1.38, 5.13).
Conclusion: Provision of baclofen for any reason is associated with statistically significant decreases in AUDIT-C scores among general patient populations, and clinically significant decreases among heavy drinkers and those with AUD history.

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PRAZOSIN REDUCES DRINKS PER DAY AND HEAVY DRINKING EPISODES IN DEPENDENT DRINKERS WITH ALCOHOL WITHDRAWAL SYMPTOMS AT TREATMENT ENTRY

S.E. Wemm, V. Milivojevic, R. Hart, G.A. Angarita, H.C. Fox, R. Sinha
Department of Psychiatry, Yale University School of Medicine, New Haven CT, 06519, USA

Purpose: Chronic alcohol abuse increases basal autonomic and biological stress responses that may drive alcohol withdrawal symptoms, craving and risk of relapse. Previous basic science research indicates that Prazosin, an alpha1-antagonist, decreases alcohol withdrawal symptoms and intake in dependent laboratory animals. Here, we assessed whether Prazosin versus Placebo reduced alcohol drinking outcomes, particularly in those reporting alcohol withdrawal symptoms at treatment entry in a 12-week double-blind, randomized controlled trial.
Methods: Treatment-seeking individuals that met current DSM-IV-TR criteria for alcohol dependence ($n = 100$, men = 66, women = 34) were randomized to prazosin ($n = 56$) or placebo ($n = 44$) reaching target dose (16 mg/day, T.I.D. dosing) achieved at day 15 in the trial, and a 5-day medication taper in week 12. Alcohol withdrawal was assessed at treatment initiation before first study dose. Twelve-Step Counseling was provided to all individuals along with contingency management (Fishbowl) for treatment attendance. Participants completed daily assessments of the number of drinks per day (log-transformed) and craving via daily interactive voice recording and the weekly Timeline Followback. Heavy drinking days were dichotomized into heavy drinking days (1) or light/non-drinking days (0). Intent-to-treat analyses using piecewise mixed effects models were used to separate treatment effects before and after full-dose.
Results: Prazosin relative to placebo was efficacious in reducing drinks per drinking day ($b = -0.001$, $p < 0.03$) and likelihood of a heavy drinking day ($b = -0.006$, $p < 0.03$) after reaching target dose, but only in those with greater alcohol withdrawal symptoms at treatment entry. Prazosin reduced daily craving relative to placebo after reaching target dose of the medication ($b = -0.0059$, $p < 0.002$) for all participants. That is, individuals with higher withdrawal at the beginning of treatment experienced the greatest benefit in the reduction of the number of drinks and heavy drinking days. Treatment attrition and compliance were equivalent across groups ($\chi^2[N = 100] = 0.158$, $p = 0.69$).
Conclusion: Acute withdrawal symptoms at treatment entry are a common feature of moderate and severe alcohol use disorders (AUD). Current findings suggest that Prazosin may be most effective in reducing drinking in subgroups of AUD patients experiencing alcohol withdrawal symptoms upon acute alcohol abstinence. Further evaluation of alpha1-antagonists, such as Prazosin, in the treatment of alcohol use disorders for those with positive alcohol withdrawal symptoms at treatment entry is warranted. (Supported by R01-AA020504, K02-023566; T32- DA007238).

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EFFECTS OF PRAZOSIN ON CRAVING, AUTONOMIC AND HPA AXIS RESPONSES TO STRESS IN ALCOHOL DEPENDENT MEN AND WOMEN IN EARLY ABSTINENCE

V. Milivojevic, G.A. Angarita, R. Sinha, H.C. Fox
The Yale Stress Center, Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06519, USA

Purpose: Chronic alcohol abuse results in significant changes to stress biology and autonomic arousal which contribute to acute alcohol withdrawal symptoms, tolerance of the hypothalamic-pituitary adrenal (HPA) axis stress responses, high stress-induced craving and risk of alcohol relapse. Thus, exposure to and recovery from stress during early abstinence may be jeopardized by such stress system dysfunction. Significant preclinical evidence suggests that noradrenergic disruption may contribute to these stress arousal changes and that alpha-1 adrenergic antagonists, such as Prazosin, may normalize these relapse-related stress system adaptations and reduce alcohol intake. On the basis of this previous research, we hypothesized that Prazosin will reduce stress-induced craving, normalize neuroendocrine tolerance and early abstinence autonomic arousal especially in responses to stress provoked in a human laboratory experimental study.
Methods: Forty inpatient treatment-seeking alcohol dependent individuals were randomly assigned to receive either placebo (PLA; $n = 18$) or 16 mg/day, T.I.D., Prazosin ($n = 22$), titrated over 2 weeks. In week 3 after achieving full medication dose, patients were exposed to three 5-minute personalized guided imagery conditions (stress, alcohol cue, neutral/relaxing), one per day, on three consecutive days in a random, counterbalanced order. Alcohol craving, heart rate, and cortisol levels were assessed at baseline, immediately following imagery exposure and at regular recovery time points.
Results: A Treatment X Imagery Condition interaction showed that Prazosin relative to PLA significantly reduced alcohol craving in response to stress and alcohol cue imagery (p's < 0.05). Moreover, a Treatment X Imagery Condition X Time point interaction indicated that Prazosin also decreased basal cortisol and increased cortisol response to stress imagery compared to PLA (p's < 0.05). Finally, a Treatment X Imagery Condition interaction showed that Prazosin relative to PLA increased heart rate responses to the alcohol cue imagery ($p < 0.05$).
Conclusions: Findings show that the alpha-1 adrenergic antagonist Prazosin reduced alcohol craving in response to provoked stress and alcohol cues, and normalized the tonic and phasic HPA axis and heart rate response to stress and alcohol cue exposure in a human laboratory experiment. As such, decreasing craving and normalizing stress responsivity in early abstinence via the adrenergic system may show promise in relapse prevention.
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PRAZOSIN INCREASED BRAIN ACTIVITY IN THE LEFT DORSOLATERAL PREFRONTAL CORTEX AND HYPOTHALAMUS IN PATIENTS WITH ALCOHOL USE DISORDER

D. Seo, R.J. Douglas, C. Lacadie, G. Hermes, R. Sinha
Departments of Psychiatry and Radiology, Yale University School of Medicine, New Haven, CT 06519, USA

Purpose: Chronic alcohol abuse significantly alters stress pathways and noradrenergic signaling, thereby increasing vulnerability to alcohol withdrawal symptoms, neuroendocrine tolerance and high risk of relapse. Prazosin, an alpha1-antagonist that decreases noradrenergic activation, decreased alcohol withdrawal, normalized stress physiology and reduced excessive alcohol intake in preclinical studies. However, the effect of Prazosin on brain activation in humans remains unclear. The current study aims to investigate the effects of chronic Prazosin versus Placebo treatment on brain response to stress, alcohol cue, and neutral stimuli using functional magnetic resonance imaging (fMRI) in patients with alcohol use disorder (AUD).
Methods: Twenty-four treatment-seeking AUD patients were randomized either to Prazosin [$N = 10$ (5 female); Age = 38.7(3.3)], 16 mg/day, T.I.D. dosing), or Placebo group ($N = 14$ (3 female); Age = 39.7(2.8)) in a 12-week double-blind, randomized controlled design, achieving full dose on day 15, and a 5-day medication taper in week 12. To examine the effects of chronic Prazosin or Placebo treatment, participants underwent an fMRI session upon treatment initiation (IT) and a second fMRI session during chronic treatment in week 10 (CT). fMRI sessions assessed brain response to brief sustained exposure to stress, alcohol cue and neutral cue picture stimuli. Participants were exposed to each picture only once, and stimuli with equivalent emotional intensity and content were used for two fMRI sessions.
Results: A significant Session X Group effect ($p < 0.001$, whole-brain corrected) in the left dorsolateral prefrontal cortex (DLPFC) and hypothalamus was observed. Compared to the placebo group, the Prazosin group showed increased overall activity in the left DLPFC activity and hypothalamus with CT vs. IT period. In addition, a significant Session X Group X Task effect ($p < 0.001$, whole-brain corrected) in the left ventromedial prefrontal cortex (VmPFC) showed that prazosin but not the placebo group displayed greater left VmPFC response to stress and alcohol cues in CT vs. IT period.
Conclusions: Prazosin treatment improved prefrontal brain function in regions involved in cognitive control and regulation of craving (left DLPFC), and stress and alcohol cue related responses in the left VmPFC emotion regulation region. Prazosin may exert its positive effects by increasing greater cognitive control over alcohol caving and over emotional/stress reactivity in treatment engaged AUD patients. (Supported by R01-AA013892, R01-AA020504, K08-AA023545).

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NEUROCOGNITIVE DEVELOPMENT, PUBERTAL STATUS, AND SOCIAL EXPECTANCIES PREDICT ADOLESCENT DRINKING BEHAVIORS

R. Tan, C. Lu, I. Li, N. Castro, J. Jacobus
Department of Psychiatry, University of California San Diego, La Jolla, CA 92037, USA

Research has demonstrated a link between cognitive deficits and heavy alcohol use in adolescents and young adults, and studies suggest that poorer neurocognitive performance in early adolescence may increase risk for earlier alcohol use onset. Pubertal onset, social behaviors (e.g., dating) and positive alcohol expectancies are also associated with earlier onset of alcohol use in adolescence and increased risk of weekly alcohol use initiation and heavy drinking. The current study sought to examine whether neurocognitive functioning, alcohol expectancies, and dating behaviors prior to alcohol initiation predicted age of alcohol and binge drinking onset. The study also aimed to determine if neurocognitive functioning was moderated by pubertal status at age 12–14 in predicting drinking outcomes. The sample consisted of 295 healthy 12- to 14-year-olds with little to no prior experience with alcohol or substance use at baseline who were part of an ongoing 15-year longitudinal project examining substance use and neurocognition. Results indicated that visuospatial ability significantly predicted age of first drink, with better performance on visuospatial tasks predicting a later onset of drinking ($p < 0.05$). Processing speed significantly predicted age of first binge, with faster processing speed related to an earlier onset of binge drinking ($p < 0.05$). Baseline positive social expectancies and dating experience, but not pubertal development, was negatively associated with age of alcohol initiation ($p < 0.01$). Notably, interactions between processing speed and pubertal onset ($p = 0.06$), as well as cognitive inhibition and pubertal onset ($p = 0.07$) were marginally significant in predicting age of first drink. The results from the current study suggest that certain aspects of cognitive functioning and social development may predict drinking onset and binge drinking onset in adolescence. These results have important implications for prevention and early intervention efforts of alcohol use disorders. Future studies in our laboratory will more extensively explore relationships between pubertal maturation, neurocognitive functioning, and drinking patterns.

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BACLOFEN DESENSITIZES THE FRONTO-STRIATAL REWARD NETWORK IN ALCOHOL DEPENDENT PATIENTS: A RANDOMIZED, PLACEBO-CONTROLLED PHARMACO FMRI TRIAL

P. Pelz, A. Genauck, T. Gleich, R.C. Lorenz, A. Heinz, C.A. Müller, A. Beck
Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité – Universitätsmedizin Berlin, Berlin, 10117, Germany

Background: In addictive disorders, the fronto-striatal reward network functions seem to be altered during anticipation of monetary gains (gain anticipation) (Luijten et al., 2017). Functional magnetic resonance imaging (fMRI) studies using a slot machine paradigm observed strong signal in striatum and insula during gain anticipation in healthy control subjects (HC) (Lorenz et al., 2014; 2015a). Moreover, there is evidence that HC show reduced fronto-striatal signal during gain anticipation when performing the slot machine task a second time (Lorenz et al., 2015b). Baclofen (Lioresal), a GABA-B receptor agonist, has been suggested to modulate dopaminergic transmission in the striatum (Fadda et al., 2003). We thus hypothesized that it would have an influence on fronto-striatal reward anticipation processes in alcohol dependent patients (ADP).
Methods: We included 13 patients in the baclofen group (mean age: 47.54 (SD = 7.83)) and 15 patients in the placebo group (mean age: 47.00 (SD = 7.26)). Each patient was individually titrated to a maximum of 270 mg daily dosage in a double-blind and randomized pharmaco-fMRI trial with t1 at baseline and t2 after 2 weeks of high-dose intake. We measured fronto-striatal gain anticipation signal by having patients play a slot machine paradigm (three rotating cylinders) during echo-planar imaging. We analyzed the contrast of gain possible (first two cylinders showing congruent symbols while third cylinder still rotating) versus no gain possible (first two cylinders showing incongruent symbols while third cylinder still rotating).
Results: At t1 both groups showed high striatal activations during gain anticipation. At t2 the baclofen group showed significantly decreased activation during gain anticipation in the right insula than the placebo group.
Conclusion: Patients receiving baclofen showed a stronger decrease in insula activation from t1 to t2 compared to the placebo group. This could be evidence that baclofen desensitizes the fronto-striatal reward system in a way that is also seen in HC subjects performing the slot machine task a second time. Consequently, baclofen might prove an additional treatment option for alcohol dependence. Furthermore, our study shows that pharmaco-fMRI studies may be valuable for assessing the neurobiological basis of pharmacological treatment effects in alcohol dependence.

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ALTERED BRAIN CORTICAL MATURATION IS FOUND IN ADOLESCENTS WITH A FAMILY HISTORY OF ALCOHOLISM

B. Holla, R.D. Bharath, G. Venkatasubramanian, V. Benegal
Centre for Addiction Medicine, Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore - 560029, India

Background: Substance-naïve adolescents from high-density Alcohol Use Disorder (AUD) families exhibit altered subcortical brain volumes structurally and altered executive-functioning and emotion-processing functionally, compared to their peers. However, there is a dearth of literature exploring alterations of cortical thickness (CTh) in this population.
Methods: T1-weighted structural brain MRI was acquired in 75 substance-naïve male-offspring of treatment-seeking early-onset (<25 years) AUD patients with high familial-loading of AUDs (≥ 2 affected relatives) (FHP) and 65 age-matched substance-naïve male controls with negative family history (FHN) from the community. Surface-based CTh reconstruction was done using FreeSurfer Software Suite v5.3. Univariate general linear models were implemented at each vertex using SurfStat, controlling for age (linear and quadratic-effects), and head-size, to examine the main effect of familial AUD-risk on CTh and its relationship with Externalising symptom score (ESS).
Results: A nested model comparison (F-test) revealed that the quadratic age model provided a significantly better goodness of fit than the linear model in several spatially distributed clusters across the cortex. A Johnson-Neyman procedure revealed that the main effect of familial AUD-risk on CTh was seen during adolescence, where the FHP group had thicker cortices involving bilateral precentral gyri, left caudal Middle Frontal Gyrus (MFG), bilateral temporo-parietal junction, left inferior-frontal gyrus, and right inferior-temporal gyrus. Thicker cortices in left MFG and inferior-parietal lobule were also associated with greater ESS within both groups.
Conclusions: Taken together, these results suggest that adolescents with a family history of alcoholism possibly have a slower rate or a delay in cortical thinning and maturation in brain regions that are critical for higher order cognition like executive function, emotion regulation and social cognition. More importantly, these group differences diminished with age by young adulthood, indicating that the adolescents and young adults in the FHP group who pass through this risk age without substance misuse, are likely to be resilient and have similar levels of cortical thickness compared to their peers. Early supportive intervention for a delay in alcohol initiation during this critical phase may be crucial for this at-risk population.

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MULTI-MODAL NEUROIMAGING CHARACTERIZATION OF ALCOHOL USE DISORDER AND CO-OCCURRING MILD TRAUMATIC BRAIN INJURY

A.A. Herrold[1,2], N. Jordan[1,2], T. Parrish[1,2], D. Cobia[1,2], X. Wang[1,2], A. Chambers[1,2], A. Sander[1,2], G.L. Karje[1,2], A. Aaronson[1,2], F. Sesso-Osburn[1,2], T.L.B. Pape[1,2]
[1]Research Service and Center for Innovation in Complex Chronic Healthcare, Edward Hines Jr., VA Hospital and [2]Department of Psychiatry and Behavioral Sciences, Northwestern University, Feinberg School of Medicine

Purpose: To characterize the brain state of Veterans with co-occurring alcohol use disorder and mild traumatic brain injury (AUD+mTBI), as these are conditions that commonly co-occur and are understudied.
Methods: The total sample of 11 Veterans were classified into two groups based on the Symptom Attribution and Classification Algorithm (Pape, Herrold, *et al.* 2016) and the Alcohol Use Disorder Identification Test, consumption questions: (1) AUD+mTBI ($n = 5$) and (2) healthy control ($n = 6$).
Data: Veterans completed self-report measures related to addiction including the obsessive subscale of the obsessive-compulsive craving scale (OBS). Veterans were scanned on a Siemens 3T Tim Trio MRI scanner to acquire structural (MPRAGE) and functional (alcohol cue task; Vollstadt-Klein *et al.* 2010). Gray matter density and fMRI task data analysis was conducted using SPM8 and the VBM8 toolbox.
Results: Gray matter density was significantly decreased ($p < 0.01$, small volume correction) among AUD+mTBI relative to healthy control Veterans, mainly in cortical and limbic brain regions (prefrontal cortex, anterior cingulate cortex, insula). Veterans with AUD+mTBI had significantly greater cue-induced activation ($p < 0.01$, small volume correction) in reward-related brain regions involved in habitual behavior (caudate and putamen) and contextual memory (hippocampus) than healthy control Veterans. Among AUD+mTBI Veterans there was a trend for greater cue-induced activation to be positively correlated with alcohol craving ($R^2 = 0.71$, $p = 0.16$).
Conclusions: These results suggest that the brain state of Veterans with co-occurring AUD+mTBI is characterized by gray matter atrophy and hyper- cue-induced activity within reward-related brain regions. Atrophy in cortical regions may lead to less feedback to sub-cortical regions (caudate and putamen) resulting in increased activations to alcohol-related cues. Future research to further characterize the AUD+mTBI brain state in terms of functional and structural connectivity is warranted.

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INTRANASAL OXYTOCIN DOES NOT MODULATE SUBJECTIVE, BEHAVIORAL, OR PHYSIOLOGICAL RESPONSES TO ACUTE ALCOHOL IN HEALTHY SOCIAL DRINKERS

A. Vena, A. King, H. de Wit
Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL 60637, USA

Both preclinical and clinical evidence suggest that the neuropeptide oxytocin may be of value in treating alcohol use disorder. In animals, oxytocin reduces the reinforcing properties of alcohol and in two small clinical studies repeated administrations of oxytocin reduced withdrawal severity and percent heavy drinking days among alcohol dependent individuals. However, the therapeutic mechanism by which oxytocin may reduce alcohol consumption and its potential efficacy in non-dependent alcohol users remain unclear. Therefore, we examined the effect of oxytocin on subjective, behavioral, or physiological responses to alcohol in young adult social drinkers. Participants completed two study sessions at which they consumed alcohol (ALC; 0.8 g/kg) or placebo (NoALC) in combination with intranasal oxytocin (40 IU) or placebo. Subjects ($N = 35$; mean age 26 $\pm$ 4.8 (SD) years; 46% female; avg 12 $\pm$ 6.5 drinks/week; no major psychiatric conditions) received nasal sprays containing oxytocin at one session and placebo at the other session, 20 min before consuming alcohol. Subjective ratings, heart rate and blood pressure, and four behavioral tasks (flanker task, digit span, go/no-go, and pursuit rotor) were the primary outcome measures. ALC produced its expected subjective and behavioral effects, impairing performance on the digit span and go/no-go tasks. Oxytocin did not affect responses to alcohol on any measure. We can conclude that, under these conditions, acute intranasal oxytocin does not alter the behavioral pharmacological effects of acute alcohol in healthy young adult social drinkers, but our findings do not rule out a role for oxytocin in modulating such effects among alcohol dependent populations.

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RESPONSE TO PHARMACOTHERAPY: A COMPARISON OF ENDPOINTS BASED ON ABSTINENCE, NO HEAVY DRINKING AND REDUCTIONS IN WHO DRINKING LEVELS IN THREE TRIALS

S.S. O'Malley, D.E. Falk, R.Z. Litten, K. Witkiewitz, R. Anton, H.R. Kranzler, K. Mann, D.S. Hasin, B. Johnson, D. Meulien, J. Fertig, M. Ryan, M. Slater, and members of the ACTIVE Workgroup
Yale School of Medicine, Psychiatry, New Haven, CT 06517, USA

Purpose: The Food and Drug Administration (FDA), in draft guidance for Phase III alcohol use disorder (AUD) pharmacotherapy trials, recommends that "trials should measure the proportion of patients in each treatment group who attain, and sustain over the observation period, a target drinking pattern that is considered a valid surrogate for clinical benefit" (pg. 10). There are 2 alcohol treatment outcomes currently accepted by the FDA: the proportion of patients who are abstinent, and the proportion of patients with no heavy drinking days. Recently, attention has turned to 2 other endpoints based on reductions in drinking using the World Health Organization (WHO) risk levels of alcohol consumption (grams of ethanol/day) (WHO, 2000). Specifically, reductions in WHO 1 and 2 risk drinking levels were shown to predict clinical benefit and reduced risk of AUD in prior research. In this study, we compared rates of response for these 4 responder outcomes and their sensitivity to medication effects.
Methods: Data were obtained from 3 multi-site randomized controlled pharmacotherapy trials of different medications: naltrexone (Anton, 2006), varenicline (Litten, 2013), and topiramate (Johnson, 2007). Within each study, the proportion of patients in active and placebo conditions that achieved each outcome was computed by month and effect sizes calculated.
Results: The percentage of responders increased from the most conservative outcome, abstinence, to the least conservative outcome, the WHO 1-level shift. In the varenicline study, for example, 9.4% of participants were abstinent, 20.8% had no heavy drinking, 53% had a 2-shift reduction in WHO Risk and 75% had a WHO 1-shift by the last month of treatment. Across studies, the effect sizes for comparisons between active and placebo for the new WHO-2 and WHO-1 shift outcomes compared favorably with the current FDA accepted endpoints, abstinence and no heavy drinking.
Conclusion: These findings suggest that the WHO 2- and 1- shift endpoints may be worthy of further development as outcome measures in alcohol pharmacotherapy trials. In addition, since the WHO shift measures captured improvements experienced by more patients than abstinence and no heavy drinking, these outcomes might be attractive to both patients and providers.

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A DEEPER INSIGHT INTO HOW BACLOFEN MAY AFFECT ALCOHOL CONSUMPTION: BIOBEHAVIORAL RESULTS FROM A HUMAN LABORATORY INVESTIGATION

M. Farokhnia, S. Deschaine, A. Sadighi, F. Akhlaghi, L. Leggio
Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, National Institute on Alcohol Abuse and Alcoholism and National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20892, USA

The selective $GABA_B$ receptor agonist, baclofen, has been studied as a potential pharmacotherapy for alcohol use disorder. Despite promising data from preclinical experiments, human studies with baclofen have shown mixed results. Additional research is needed to understand how this medication works from a biobehavioral standpoint; well-controlled human laboratory studies provide an informative platform to address this question. Here, we analyzed data from a laboratory experiment before which alcohol-dependent individuals ($N = 34$) received baclofen (30 mg/day) or placebo for a week. The experimental session included three consecutive phases: (1) alcohol cue-reactivity (water trial followed by two alcohol trials), (2) fixed-dose alcohol priming (40 min, target blood alcohol concentration: 0.03 g/dL), (3) alcohol self-administration (2 h, up to 8 mini-drinks). Repeated assessments of alcohol craving, subjective responses, mood, and anxiety were conducted throughout the session. Blood samples were also collected for pharmacokinetic measurements. Baclofen, compared to placebo, did not significantly attenuate cue-elicited craving or alcohol self-administration. However, baclofen moderated the relationship between alcohol priming and self-administration as shown by significant interaction effects between drug condition (baclofen versus placebo) and priming variables (alcohol craving: $F_{3,9} = 6.03$, $p = 0.01$; alcohol sedation: $F_{1,6} = 7.16$, $p = 0.01$; breath alcohol concentration: $F_{1,25} = 5.22$, $p = 0.03$) on the total amount of alcohol self-administered. A similar pattern was observed for other alcohol-related subjective responses, but the interaction terms did not reach statistical significance (p's>0.05). Baclofen pharmacokinetic parameters were calculated as follows (mean $\pm$ standard error): maximum plasma concentration (C_{max}) = 84.90 $\pm$ 13.58 ng/mL; time to C_{max} (t_{max}) = 2.47 $\pm$ 0.21 h; apparent plasma clearance at steady state (CL_{ss}/F) = 60866.52 $\pm$ 12641.72 mL/h; half-life ($t_{1/2}$) = 4.42 $\pm$ 0.29 h; area under plasma concentration - time curve (AUC) = 1033.49 $\pm$ 97.77 h*ng/mL. Bivariate correlation analyses between pharmacokinetic parameters and behavioral outcomes showed that baclofen C_{max} was negatively correlated with alcohol craving during cue-reactivity ($r = -0.57$, $p = 0.03$), negatively correlated with ratings of 'like more' during priming phase ($r = -0.59$, $p = 0.02$), and positively correlated with alcohol sedation during priming phase ($r = 0.55$, $p = 0.03$). In conclusion, these data suggest that baclofen may act through dissociating the link between an initial drink (priming) and subsequent alcohol consumption (self-administration). This study also sheds light on how baclofen pharmacokinetic parameters are correlated with behavioral outcomes assessed in a laboratory setting.

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PREDICTING FACTORS OF LONG-TERM FOLLOW-UP IN TREATING ALCOHOLICS WITH NALTREXONE OR ACAMPROSATE IN KOREA

W.-Y. Jumg, S.-Y. Huh, S.-G. Kim
Department of Psychiatry, Pusan National University Yangsan Hospital, Yangsan, ASIIKRIKS011I YANGSAN, Korea

Purpose: Alcohol use disorder is a common disease and its lifetime prevalence is 12.2% in Korea. Despite this high prevalence, alcohol use disorder has a high recurrence rate. One study reveals 82.1% recurrence rate within 3 months after discharge. Another study reveals 80.3% recurrence rate within 6 months after discharge. To prevent recurrence, maintenance treatment is crucial. Especially, medication is critical during maintenance treatment. In Korea naltrexone and acamprosate are authorized medications. But the two medications have different mechanisms and actions. The purpose of this study is to investigate predicting factors of long-term follow-up in treating alcoholics with naltrexone or acamprosate in Korea.
Methods: Retrospective study was conducted by a psychiatrist with more than 3 years of clinical experience. From November 2008-May 2017, we studied patients diagnosed with alcohol abuse or alcohol dependence in the Department of Psychiatry at Pusan National University Yangsan Hospital. We examined prescribed days of naltrexone or acamprosate and among these patients as well as factors of patients that maintained at least 180 days. Throughout the obtained data logistic regression analysis was conducted using SPSS version 22.
Results: In the naltrexone group ($n = 184$), treatment duration was longer for those highly educated ($p = 0.022$), with more medical disease ($p = 0.030$), prescribed more other psychotropics ($p = 0.000$), diagnosed as alcohol abuse than alcohol dependence ($p = 0.020$). In the acamprosate group ($n = 154$), treatment duration was longer for those with less other psychiatric disease ($p = 0.002$).
Conclusions: Predicting factors were different in long-term follow-up patients prescribed naltrexone or acamprosate. A well-designed study will be needed to accurately evaluate predicting factors according to the type of drug.