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SEROTONERGIC AGENTS AND ALCOHOLISM TREATMENT: TESTING THE JOHNSON MODEL BY COMPUTER SIMULATION

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Those with early onset alcoholism may respond better to treatment with ondansetron (a 5-HT3 receptor antagonist) than with selective serotonin reuptake inhibitors (SSRIs), while those with late onset alcoholism may respond better to SSRIs. Alcoholism subtyping may be useful in making treatment decisions, although a patient's genotype at loci that influence the dysfunctional system may be more so. Johnson (ACER 24 1597-1601) proposed a model of serotonin (5-HT) function that focuses on a common genetic variant in the 5-HT transporter regulatory region (5-HTTLPR). The present study formalizes and extends Johnson's descriptive model into a computer-based simulation that uses finite difference equations. Values for variables used in the model were based on empirical findings in the human and animal literature. Data were generated for each condition by 100 simulation runs. Results of the model are consistent with expectations that the LL genotype would have lower mean levels of synaptic 5-HT than the S_ genotype. Reductions in 5-HT transporter function due to chronic alcoholism increased mean 5-HT levels for the LL genotype by 82% and for the S_ genotype by 2%. For those with alcoholism, binge drinking episodes raised mean 5-HT levels by 111% and 54% for LL's and S_s, respectively. SSRI treatment raised mean 5-HT levels by 75% for LL's and 57% for S_s. The simulation results suggest that SSRI treatment may not be effective for individuals with the LL genotype because binge drinking enhances 5-HT function to a greater degree. During binge drinking, ondansetron treatment decreased 5-HT3 receptor mediated dopamine firing by 61% in LLs and by 33% in S_s. Ondansetron treatment is more effective at reducing alcohol's rewarding effects in those with the LL genotype. The results generally support the Johnson model, and the notion that genotypes may become useful for treatment decisions. (NIAAA K01 AA00295)

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PREDICTORS OF RESPONSE TO NALTREXONE IN THE TREATMENT OF ALCOHOL DEPENDENCE IN MEN

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Naltrexone has shown to be effective in the treatment of alcohol dependence. However, its effectiveness varies from patient to patient. Considering the heterogeneity of alcohol dependence, it was of interest to investigate potential predictors of response to treatment. The purpose of this study was to determine which variables are related with a good outcome in alcoholic patients treated with naltrexone. We studied the outcome of 336 patients seen at the outpatient Unit of Problems Related to Alcohol. In a ramdomized way, 168 patients received naltrexone as coadjuvant and usual treament (psychotherapy, referral to self-help groups and support with occasional disulfiram) and 168 patients did not receive naltrexone. We studied the influence of naltrexone on the outcome of patients presenting variables which are potential predictors of prognosis. Globally, the group treated with naltrexone showed the best outcome (p=0.03). The use of naltrexone produced a clear improvement in patients with early onset of problems related with alcohol (p=0.028), those with positive family history (p=0.017) and those presenting history of abuse of other drugs (p<0.001). However, naltrexone did not improve the outcome of patients not presenting these variables. In conclusion, the treatment with naltrexone may result more effective among alcohol dependent patients showing specific characteristics that suggest a greater vulnerability to alcohol addiction (family history, early onset of problems related to alcohol and other drug abuse comorbidity). Supported by Grant from FIS (01/1438 to J. Manzanares).

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GAMMA-HYDROXYBUTYRIC ACID VS NALTREXONE IN MAINTAINING ALCOHOL ABSTINENCE: AN OPEN RANDOMIZED COMPARATIVE PILOT-STUDY

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After the remission of withdrawal syndrome, maintaining abstinence from alcohol is the main goal in alcohol dependence treatment. Many pharmacological agents , have been recently tested in the treatment of alcohol addiction. NTX and GHB have proved able to maintain alcohol abstinence in about 20-60% and 30-80% of treated patients respectively. At present, there are no studies comparing the effect of NTX and GHB in maintaining abstinence from alcohol after a short-term treatment period. The aim of our open randomized pilot-study was to evaluate the efficacy of GHB compared with NTX in maintaining abstinence from alcohol after 3 months of treatment. A total of 35 recently detoxified alcohol dependence outpatients , were randomly enrolled in two groups. -GHB group was composed by 18 patients treated with oral doses of 50 mg/kg of GHB fractionated in three daily doses for three months, -NTX group was composed by 17 patients treated with oral doses of 50 mg/day of NTX for three months. The drugs and its administration has been entrusted to a referred family member. All patients were abstinent at time of admission. Each subject has been checked as an outpatient every week for the duration of the treatment period. At the end of the study a statistically significant difference (p = 0.02) in the number of abstinent patients between GHB group and NTX group was found. In patients who failed to be abstinent , no relapses in heavy drinking were observed in NTX group, while in GHB group, all patients relapsed. Moreover, a significant reduction in alcohol craving and laboratory markers of alcohol abuse were found in both groups. No craving for the drugs was observed in both groups. The results of the present study show that GHB is more efficacious than NTX in maintaining abstinence from alcohol in a short-term treatment period, on the other hand, NTX confirmed its ability in reducing alcohol relapses in heavy drinking.

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COMBINING NALTREXONE AND MEMANTINE TO BLOCK THE REWARDING EFFECTS OF ALCOHOL: AN EXPERIMENTAL PILOT STUDY IN HUMAN SUBJECTS

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The high priority for developing new pharmacotherapy approaches to the treatment of alcoholism has not decreased with recent data indicating the lack of efficacy of naltrexone treatment in alcohol dependent veterans (Krystal et al. 2001). Supported by results from preclinical work (Hölter et al. 1996), we have been collecting data on the capacity of naltrexone (unspecific opioid antagonist), memantine (an uncompetitive NMDA receptor antagonist), and the combination to block the rewarding effects of ethanol intoxication in healthy human subjects. Our experimental study is being conducted in a double blind, placebo controlled, cross-over fashion. Subjects receive 37.5 mg naltrexone or placebo before administration of 30 mg/70kg memantine or placebo. Two hours later a total of 49g/70kg of alcohol is administered in a within-session cumulative-dosing procedure. Stimulating subjective effects are assessed in several measurements, including the BAES (Biphasic Alcohol Effect Scale). Further assessments include cognition (CPT, word recall) and coordination (one leg stand). Results are analyzed using generalized linear mixed models (SAS PROC MIXED, SAS PROC GENMOD). Our pilot data in 8 healthy human subjects indicate that memantine and naltrexone, by themselves, influence the basal level of stimulation (naltrexone is mildly sedating, memantine is mildly stimulating). Of greatest interest, our data suggest that the combination of memantine and naltrexone (but not either drug alone) blocks the dose-related stimulatory effects of ethanol. Similarly, naltrexone blocks the memantine-potentiation of discriminative stimulus effects of ethanol (i.e., blocks the ability of increasing doses of ethanol to be perceived as "more ethanol like"). Together, these data suggest that naltrexone might be a critical therapeutic adjuvant if memantine or other related drugs are developed as pharmacotherapies for alcohol dependence. Krystal JH et al. NEJM 2001;345 1734-1739. Holter SM et al. Eur J Pharamcol 1996; 31 314-315

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NALTREXONE AND ACAMPROSATE: META-ANALYSIS OF TWO MEDICAL TREATMENTS FOR ALCOHOLISM

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A meta-analysis was performed to assess the relative effectiveness of naltrexone and acamprosate in the treatment of alcoholism. Studies identified from the medical literature were collected and reviewed. Databases searched for relevant studies included Medline, PSYCInfo, EMBASE, IPA, and CINAHL. Outcomes common to the majority of studies were chosen for quantitative analysis. For the naltrexone studies, outcomes included relapse to heavy drinking, relapse to any drinking, and percentage of drinking days during the treatment period. For the acamprosate studies, only relapse to any drinking was assessed in all of the trials. Summary risk differences for dichotomous outcomes were calculated within each group of studies. Meta-regression was performed to compare the two drugs directly and to assess the influence of study characteristics on treatment effect.

8 naltrexone studies (N = 1,482) and 15 acamprosate studies (N = 3,979) were included in this analysis. Random effects estimates were reported, due to the high between-study variance for all outcomes in both treatment groups. For naltrexone, the risk difference for relapse to heavy drinking in treatment versus placebo groups was .16 (95% CI: .07, .25; NNT = 6.28). The risk difference for relapse to any drinking was .08 (95% CI: -.02, .17; NNT = 12.95). In the acamprosate studies, the overall risk difference for relapse to any drinking was .12 (95% CI: .08, .17; NNT = 8.15). Meta-regression indicated that prescribing acamprosate versus naltrexone ($p < .1$) and giving some form of required psychotherapy ($p < .05$) were both predictors of treatment effect on abstinence. The evidence of effectiveness of these two medications is considered in the context of this cumulative body of published studies. While more research will be necessary to understand fully the effectiveness of these drugs and the populations in which one or the other may be indicated, these results suggest that acamprosate is more effective than naltrexone at helping weaned alcoholic patients maintain abstinence.

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CONSIDERATIONS FOR SCREENING INSTRUMENTS IN A HOSPITAL TRAUMA SETTING

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Evidence has accumulated over the past ten years that brief interventions can be as effective as more intensive treatments with at-risk or problem drinkers, and there is a growing consensus that screening and brief interventions should be promoted in health care settings. Trauma and emergency department settings in particular are ideal for this type of intervention, when patients in the midst of experiencing physical distress related to their alcohol use may be ready to change their drinking. Because time is extremely limited in these settings, the current study examined various ways of gathering information for use in the feedback component used in many brief interventions. The Alcohol Use Disorders Identification Test (AUDIT), and several Likert-scaled questions regarding alcohol use were administered to 61 patients admitted with a positive blood alcohol concentration to a Level 1 trauma center. Results indicate that patients were more likely to attribute their injury to their alcohol use when using a Likert-scaled question (75%) than a similar question on the AUDIT (38%). In order to implement effective brief interventions with patients hospitalized following an alcohol-related injury, it may be helpful to supplement the AUDIT with additional questions when conducting screening.