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RAPID COMMUNICATION

Combining Ondansetron and Naltrexone Effectively Treats Biologically Predisposed Alcoholics: From Hypotheses to Preliminary Clinical Evidence

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Background: Individuals considered to be early onset alcoholics (EOA) are characterized by an early onset age, a broad range of antisocial behaviors, high familial loading, and presumed biological disease predisposition. Ondansetron, a 5-HT_3 antagonist, improves drinking outcomes and increases abstinence rates among EOA. Individuals with high familial loading for developing alcoholism have lower levels of β-endorphin and demonstrate a more pronounced increase in β-endorphin levels in response to alcohol administration compared with individuals who do not have alcoholic relatives. The propensity for naltrexone (a mu opioid antagonist) to reduce alcohol's rewarding effects and drinking in humans is greatest in individuals with high familial loading. Predicated on the added knowledge that 5-HT_3 receptors may themselves mediate alcohol reward via activation of the endogenous opioid system, we hypothesized that the combination of ondansetron and naltrexone would act synergistically and would be an effective treatment in EOA.

Methods: We conducted an 8-week double-blind placebo controlled clinical trial in which 20 EOA were randomized to receive ondansetron (4 μg/kg twice a day) + naltrexone (25 mg twice a day) or placebo as an adjunct to weekly standardized group Cognitive Behavioral Therapy.

Results: At endpoint, subjects who received ondansetron + naltrexone ($n = 10$), compared with those who received placebo ($n = 10$), had fewer drinks/day (covariate adjusted mean 0.99 ± 0.60 vs. 3.68 ± 0.63; $F1, 16 = 9.35, p = 0.008$; effect size = 1.42), drinks/drinking day (covariate adjusted mean 3.14 ± 0.87 vs. 6.76 ± 0.71; $F1, 13 = 10.45, p = 0.007$; effect size = 1.71), and a trend toward increased percent days abstinent (covariate adjusted mean 69.76 ± 8.64 vs. 48.24 ± 9.12; $F1, 16 = 3.58, p = 0.08$; effect size = 0.88).

Conclusions: Ondansetron plus naltrexone seems to synergistically improve the drinking outcomes of EOA. Larger scale studies that test these medications, both alone and together, among various alcoholic subtypes are needed to establish and extend these promising findings.

Key Words: Serotonin (5-HT), Ondansetron, 5-HT_3 Antagonist, Naltrexone, Opioid Antagonist.

DERANGEMENT OF MULTIPLE neurochemical pathways underlie biological predisposition to the early development of alcoholism. Combining effective therapeutic agents that target these neurochemical abnormalities opens new vistas for developing powerful medicinal interventions, and provides additional clues as to the biological underpinnings of the disease.

Ondansetron [4 μg/kg twice a day (bid)], a 5-HT_3 antagonist, reduces the alcohol consumption and improves abstinence among early onset alcoholics (EOA) but not late onset alcoholics (LOA) (Johnson et al., 1999). EOA, compared with LOA, have high biological disease predisposition that manifests as an earlier onset of problem drinking, increased propensity toward a broad range of antisocial behaviors, and greater familial loading, notably among first degree relatives (Johnson et al., 2000). We have proposed a mechanistic hypothesis by which genotypic polymorphisms at the serotonin transporter may explain at least part of the biological difference between EOA and LOA, how these differences increase an individual's likelihood for an early onset of alcoholism, and how ondansetron normalizes serotonergic function in EOA to reduce drinking (Johnson and Ait-Daoud, 2000).

Naltrexone (50 mg/day), a mu opioid receptor antagonist, improves abstinence rates among treatment-seeking alcoholics (Anton et al., 1999; Johnson and Ait-Daoud, 2000; O'Malley et al., 1992; Volpicelli et al., 1992), although there

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also have been demonstrations of inefficacy (Litten and Allen, 1998). We speculated that one important reason for this discrepancy may be that naltrexone is most effective in alcoholics with high disease predisposition. Although no empirical clinical studies have been conducted that test naltrexone's effectiveness in subtypes of alcoholics, systematic analysis of some pivotal animal and human laboratory data support this prediction. In animals, naltrexone's propensity to reduce ethanol intake is negatively correlated with baseline β-endorphin levels (Gianoulakis et al., 1996). King and colleagues (1997) studied the effects of naltrexone pretreatment in nonalcoholic social drinkers (average consumption 2 drinks/day). Compared with subjects who did not have any alcoholic relatives, subjects with family histories of alcoholism (i.e., high-risk subjects) experienced less of alcohol's stimulant effects but reported increased tension, fatigue, and confusion, and decreased vigor. Individuals at high genetic risk for developing alcoholism have lower levels of β-endorphin and demonstrate a more pronounced increase in β-endorphin levels in response to alcohol administration compared with those who do not have alcoholic relatives. Naltrexone's propensity to reduce alcohol intake in humans is greater in individuals with high β-endorphin levels (Gianoulakis et al., 1996). These data suggest that naltrexone's ability to reduce alcohol's rewarding effects is largest in those with a biological and/or genetic predisposition toward alcoholism.

Increased familial loading is one feature associated with the early development of alcoholism (Babor et al., 1992; Johnson et al., 2000). Thus, it is reasonable to propose that EOA have both serotonergic and opioid abnormalities (Johnson and Ait-Daoud, 2000) and that combined treatment for each of these neurochemical disorders would have an additive, if not a synergistic, effect to improve the drinking outcomes of EOA. Prediction that the mechanistic interaction of the specific serotonergic and opioid medications would result in synergism, rather than being simply additive or even oppositional, required us to analyze further and extrapolate from the findings of recent basic research. Intriguingly, there is preclinical evidence for a synergistic interaction between the 5-HT_3 receptor and endogenous opioids in the mesocorticolimbic dopamine (DA) reward system (Johnson and Ait-Daoud, 2000). Binding studies demonstrate that 5-HT_3 receptors are highly concentrated within the mesocorticolimbic system including the nucleus accumbens (Barnes et al., 1990; Kilpatrick et al., 1987; Perry, 1990) which receives its serotonergic innervation from the dorsal raphe nucleus (Yoshimoto and McBride, 1992). Alcohol's rewarding effects through enhancement of DA release in the nucleus accumbens are mediated through activation of 5-HT_3 receptors (Campbell and McBride, 1995). It is known that alcohol stimulates the release of β-endorphins and enkephalins (Gianoulakis, 1989) which also produce DA release through activation of mu and delta opioid receptors. Importantly, morphine can increase ethanol intake (Hubbell et al., 1986, 1987; Reid and Hunter, 1984), and morphine-induced rises in extracellular DA levels and place preference are attenuated by 5-HT_3 antagonists (Carboni et al., 1988, 1989; Imperato and Angelucci, 1989; Pei et al., 1993). Ondansetron attenuates morphine or TAN-67 (a selective delta opioid agonist)-induced enhancement of alcohol place preference, an effect that seems greater at the mu than delta opioid receptors (Matsuzawa et al., 1999). Alcohol-induced increases in DA levels can be attenuated also by both mu and delta opioid receptor antagonists (Widdowson and Holman, 1992). Taken together, these data suggest that 5-HT_3 receptors may themselves mediate alcohol reward via activation of the endogenous opioid system. In addition, the augmentation of this effect may be due to the fact that the opioid and 5-HT_3 systems also show a distribution that when combined result in more extensive DA modulation by affecting dopaminergic activity at the extremities of the mesocorticolimbic system rather than just at the more centrally located nucleus accumbens. For example, whereas ondansetron has additional anti-DA actions in more rostral structures such as the frontal cortex, DA release may be modulated effectively at the more caudally located ventral tegmental area (VTA) through endogenous opioids. In effect, the net result of combining ondansetron and naltrexone would be to diminish DA function throughout the mesocorticolimbic system, thereby resulting in synergism at attenuating alcohol-induced reward. Indeed, the result of a recent study demonstrates that the combination of ondansetron and naltrexone is more effective than either alone at reducing ethanol intake in animals (Le and Sellers, 1994), thereby solidifying the basis for testing the effectiveness of this medication combination in biologically predisposed alcoholics.

The present preliminary, double-blind, placebo-controlled clinical trial tested the hypothesis that EOA who received the combination of ondansetron (4 μg/kg bid) and naltrexone (25 mg bid) would experience a large reduction in drinking compared with their counterparts who received placebo as an adjunct to standardized manual-driven psychotherapy.

MATERIALS AND METHODS

Subjects

Twenty male and female subjects were enrolled. Subjects were included if they: (1) were between 25 and 65 years old and in good physical health (see exclusion criteria); (2) fulfilled at least 3 of 7 DSM-IV (American Psychiatric Association, 1994) criteria for alcohol dependence; (3) had an age of alcoholism onset < 25 years; (4) scored > 5 on the Michigan Alcoholism Screening Test (Selzer, 1971); (5) reported during the telephone screen that they drank ≥ 3 standard drinks/day; (6) desired to stop alcohol consumption (but abstinence was not a study entry criterion) and had a willingness to participate in psychosocial treatment; and (7) had a negative urine toxicological screen for narcotics, amphetamines, or sedative hypnotics at intake. Subjects were excluded if they: (1) had a current psychiatric history other than alcohol or nicotine dependence; (2) had severe alcohol withdrawal symptoms that necessitated inpatient detoxification; (3) were incarcerated or compelled to receive alcoholism treatment to avoid incarceration or employment loss; (4) were pregnant or lactating; (5) had clinically significant abnormalities on physical examination, electrocardiographic (EKG) recording, hematologic evaluation, or elevated bilirubin levels; (6) had been enrolled in alcoholism treatment within 30 days of screening; or (7) were taking medications with a potential effect on alcohol consumption.

The Institutional Review Board at the University of Texas, Health Science Center at San Antonio, provided ethical approval for the study. Subjects were recruited by advertisement in the San Antonio area.

General Procedures

At intake (visit 0), subjects received the following screening assessments after providing written informed consent: (1) an evaluation of physical health, which included a medical history and physical examination, vital signs (i.e., blood pressure, pulse, and temperature), 12-lead EKG recording, and laboratory studies including a urine pregnancy test; (2) an alcohol breath test; (3) a urine drug and biochemical screen; (4) a psychiatric evaluation using the Structured Clinical Interview (SCID) (Spitzer et al., 1992; Williams et al., 1992) for DSM-IV (American Psychiatric Association, 1994); (5) the determination of the age at which problem drinking began (i.e., age of onset), which was based on detailed responses derived from item B 28 of the Comprehensive Drinking Profile (Miller and Marlatt, 1984); (6) The Michigan Alcoholism Screening Test (Selzer, 1971), which assessed the severity of alcohol-related problems; (7) an evaluation of self-reported alcohol drinking using the Time-Line Follow Back for the previous 90 days (Sobell and Sobell, 1992); and (8) an assessment of alcohol withdrawal symptoms as determined by the Clinical Institute Withdrawal Assessment-Revised (Sullivan et al., 1989). Eligible subjects were invited back to the clinic (i.e., visit 1) where they were given either ondansetron + naltrexone or a placebo and they attended their first Cognitive Behavioral Therapy session.

From visits 1–8 (i.e., the visits with double-blind drug response) subjects' assessment included weekly vital signs, alcohol breath test, Time-Line Follow Back, Clinical Institute Withdrawal Assessment - Revised, adverse event profile, concomitant medications, pill count, and attendance at psychosocial treatments outside the study. At week 4, subjects received a hematologic, biochemical, and urine pregnancy tests. Urine drug screens were conducted weekly. At visit 8 (study end), a physical examination and the hematologic and biochemical checks were repeated to establish health status.

Although efficacy data and blood draws were collected by trained research assistants, both the treatment compliance and the physical health and safety measures were checked by trained research nurses and physicians.

Medication: Supply, Doses, Blinding, and Compliance

Ondansetron was purchased as 8 mg tablets. Procedures for medication compounding and dispensing were approved by the Food and Drug Administration (FDA) under IND # 45,228. Tablets were crushed by a licensed pharmacist, and the ondansetron dose (4 μg/kg bid) was packed into opaque size 1 gelatin capsules (Shinogi Qualicaps, Shinogi Qualicaps SA, Madrid, Spain) with cornstarch filler. Naltrexone, purchased as 25 mg tablets, were over-encapsulated in opaque size 1 gelatin capsules identical to those used for ondansetron. Naltrexone was dispensed at a dose of 25 mg bid. Placebos were opaque gelatin capsules of the same size, shape, and color but contained only cornstarch.

Ondansetron and naltrexone (or their matching placebos) were dispensed in two separate bottles numbered sequentially and labeled with subject identification number, study and visit numbers, and the date. Instructions on each bottle asked subjects to take one tablet in the morning and another in the evening. Subjects returned the medication bottles at each weekly visit so that the pattern of capsule consumption could be recorded.

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy, an integration of cognitive-behavioral and social learning theory, focuses on enabling alcoholics to achieve and maintain abstinence by enhancing their ability to manage "high-risk" situations which can trigger alcohol-seeking behavior (Bandura, 1977; Marlatt and Gordon, 1985). All subjects received weekly standardized Cognitive Behavioral Therapy in groups of up to six individuals using the eight core sessions of the *Cognitive-Behavioral Coping Skills Therapy Manual* (US, 1992), and selected exercises from the handbook *Treating Alcohol Dependence: A Coping Skills Therapy Guide* (Monti et al., 1989). Cognitive Behavioral Therapy was delivered by experienced masters-level therapists.

Statistics

Data Quality Assurance. We complied with FDA guidelines of Good Clinical Practice. An experienced doctoral-level statistician supervised the database management. Database validation was conducted by rechecking all entries on each subject's responses to the experimental measures. Verified data were analyzed using Statistical Analysis Systemô version 6.12 (SAS II, 1997; SAS Institute, Cary, NC).

Efficacy Measures. Efficacy variables were: Self-reported alcohol consumption using the Time-Line Follow Back (Drinks/Day; Drinks/Drinking Day, and Percent Days Abstinent).

Compliance Measures. Treatment compliance measures were: (1) study attendance rate, and (2) medication compliance—pill count.

Physical Health and Safety Measures. Physical health and safety measures were: (1) alcohol breath test at clinic attendance; (2) assessment of alcohol withdrawal symptoms—Clinical Institute Withdrawal Assessment - Revised; (3) vital signs; (4) hematologic, biochemical, and urine drug screens; (5) use of concomitant medications; (6) attendance at psychosocial treatments outside the study, and (7) adverse events profile.

Data Analytic Procedures. Subjects were randomized to treatment after the screening visit (i.e., visit 0) to receive either the medication combination (ondansetron + naltrexone) or placebo. All subjects randomized to double-blind study medication were included in the efficacy analyses for each outcome measure (Meinert, 1986.). Outcome of double-blind treatment was measured for any and all visits from 1 to 8.

Subjects were assigned randomly to one of two groups (placebo, or ondansetron + naltrexone) after stratifying based on the average drinking level (Drinks/Day) at intake. Repeated measures Analysis of Covariance (ANCOVA) was used to examine for main effects of treatment with baseline measures as potential covariates (see below) and summary measures of outcome from visits 1–8. Continuously distributed data were reported as their means ± SE.

For each of the self-reported drinking measures, the values for the past 90 days and of visit 0 were considered as possible baseline covariates. If an Analysis of Variance (ANOVA) for the past 90 days or visit 0 was significant or the baseline measure was significantly related to the outcome measure for the comparison between treatment conditions, then the groups were unequal on that measure or the baseline reduced variance. In either case, the baseline values (i.e., past 90 days or visit 0) were included as a covariate in the efficacy analysis to adjust for these differences. These covariates removed the effects of past drinking history and baseline difference, and increased precision for the double-blind effectiveness response. Any covariate for inclusion in the final model was tested for its interaction with treatment condition. Additionally, covariates were plotted against the residuals to determine their random normal distribution. In all cases, these plots showed significant covariates to be linear and resulted in valid analyses.

As a data reduction technique, the self-reported drinking response was calculated as the mean of visits 1 through 8. This average response analysis preserved sample size because all subjects with at least one outcome measure (i.e., any of visits 1 through 8) were included in the efficacy analysis. As these means have a variance inversely proportional to the number of visits attended (Graybill, 1970), the outcome analysis was weighted by the number of visits. The residuals of this repeated measures ANCOVA, weighted for missing data effects, were checked for normality by computing their skewness and kurtosis and checked for homogeneity of variance by plotting them in a histogram and against the predicted outcome. Log transformation was necessary for normalizing the distribution of the visit 1–8 Drinks/Day data in the ANCOVA.

Additionally, to facilitate easy clinical interpretation of the results, endpoint ANCOVA analyses were conducted on the drinking data that compared the medication combination condition with placebo. Endpoint was defined as the last visit of recorded drinking data in the study for each subject. All inferential statistical tests were two-tailed.

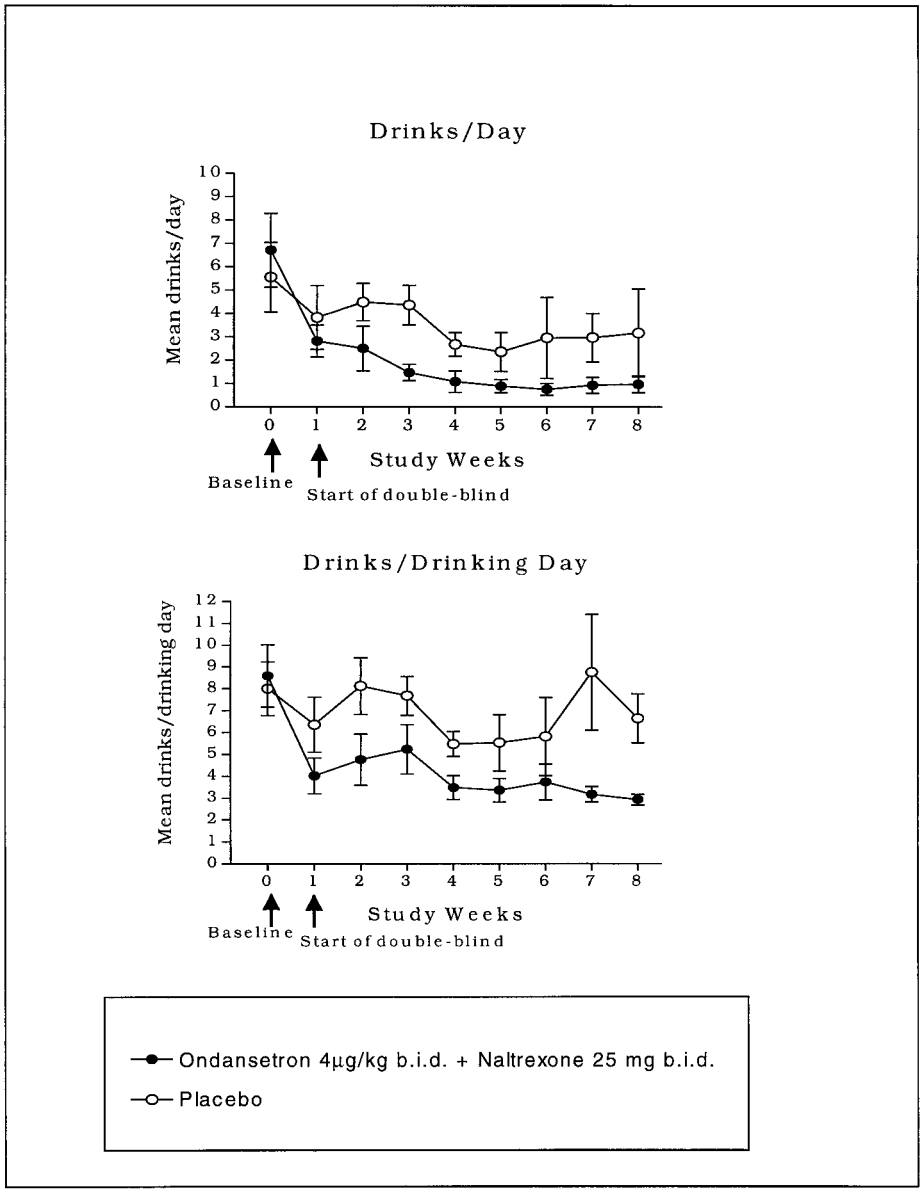

Fig. 1. Mean (± SE) Drinks/Day and Drinks/Drinking Day during the study among Early Onset Alcoholics.

RESULTS

Study Sample

Of the 20 subjects who participated, 10 were randomized to receive ondansetron + naltrexone, and the remaining 10 received placebo. The treatment groups were similar and the cohort had the following demographic characteristics: (a) age (mean age = 38.0 ± 1.78 years); (b) gender (totals: females = 5; males = 15); (c) ethnicity (totals: Caucasian = 12, Hispanics = 8); (d) past 90 days drinking level (mean 7.44 ± 0.79 Drinks/Day), or (e) scores on the Michigan Alcoholism Screening Test (mean 32.94 ± 2.14).

Efficacy Measures

For Drinks/Day, comparing ondansetron + naltrexone versus placebo, there was a significant main treatment effect on the ANCOVA at: (a) visits 1–8 (adjusted mean = 1.31 ± 0.48 vs. 3.61 ± 0.50; $F1, 16 = 10.99$, $p = 0.004$), and (b) at endpoint (adjusted mean 0.99 ± 0.60 vs. 3.68 ± 0.63; $F1, 16 = 9.35$, $p = 0.008$). See Fig. 1.

For Drinks/Drinking Day, comparing ondansetron + naltrexone versus placebo, there was a significant main treatment effect on the ANCOVA at: (a) visits 1–8 (adjusted mean = 3.64 ± 0.76 vs. 6.95 ± 0.67; $F1, 15 = 10.58$, $p = 0.005$), and (b) at endpoint (adjusted mean 3.14 ± 0.87 vs. 6.76 ± 0.71; $F1, 13 = 10.45$, $p = 0.007$). See Fig. 1.

For Percent Days Abstinent, comparing ondansetron + naltrexone versus placebo, there was a significant main treatment effect on the ANCOVA at: (a) visits 1–8 (adjusted mean = 66.45 ± 5.17 vs. 48.83 ± 5.45; $F1, 16 = 5.35$, $p = 0.03$), and (b) a trend at endpoint (adjusted mean 72.06 ± 8.64 vs. 48.24 ± 9.12; $F1, 16 = 3.53$, $p = 0.08$).

Effect sizes of 0.2, 0.5, and 0.8 are defined as small, medium, and large, respectively (Cohen, 1988). Effect sizes based on the visits 1 - 8 versus endpoint analyses for the Drinks/Day, Drinks/Drinking Day, and Percent Days Abstinent data were 0.58 vs.1.42, 0.63 vs. 1.71, and 0.41 vs. 0.88, respectively.

Compliance Measures

No significant difference existed between the ondansetron + naltrexone versus placebo groups in: (a) mean number of visits attended: 8.30 ± 0.60 vs. 8.33 ± 0.55, and (b) percentage of pills taken: 96.57 ± 0.06 vs. 94.74 ± 0.03. One subject who entered the study at visit 0 did not return for any further appointment. No reasons were provided. Thirty percent of subjects failed to attend all 9 study visits with no significant difference between the treatment groups.

Physical Health and Safety Measures

No serious adverse events occurred. Both the medication combination and placebo were well tolerated with few adverse events. Only one subject who was constipated and who received the medication combination reported any side effect attributable to the study medication which was rated above 'minimal'. Minimal nausea and fatigue versus constipation were reported by two versus three subjects, respectively, who received the medication combination. Comparatively, minimal headaches and constipation were reported in four and two subjects on placebo, respectively. No side effect persisted between weekly study visits, or required medical intervention. No subject withdrew from the study due to side effects.

Positive alcohol breath tests were rare. Only one subject had a breath alcohol concentration of greater than 0.08%, and this occurred for two visits (mean = 0.093%). Alcohol withdrawal symptoms were infrequent, did not differ between groups, and the average level on the Clinical Institute Withdrawal Assessment - Revised was 0.51 ± 0.13. Positive test results for at least 1 of 9 agents in the urine drug screen were reported by two subjects who were positive for marijuana on two occasions during the study. Two subjects who received the medication combination and another who received placebo attended Alcoholics Anonymous meetings outside the study. No subject received a physician prescribed concomitant medication for a known side effect of either ondansetron or naltrexone.

DISCUSSION

The combination of ondansetron + naltrexone significantly reduced the alcohol consumption of EOA. This drinking reduction from baseline (i.e., visit 0) to endpoint was striking for the medication combination versus the placebo (85% vs. 34%).

Two limitations of the study results merit consideration. First, the small sample size resulted in only a trend toward statistical significance for the endpoint analysis of Percent Days Abstinent. There was, however, a notable clinical difference in Percent Days Abstinent between the two groups, and the ANCOVA averaging abstinence over the eight treatment weeks was significant. We have, therefore, provided effect size estimates for all the outcome data to enable empirical calculation of power for future large-scale extension studies. Second, we did not directly test the effectiveness of naltrexone alone or ondansetron alone in the present study due to its preliminary nature. Nevertheless, comparisons from the literature would suggest that the effect sizes related to the outcome data in the present study are larger than those seen for either of the medications alone in previous trials. This finding is supportive of a synergistic combination between the two medications, and provides a foundation for the conceptual and mechanistic hypothesis outlined earlier in the text.

Although abstinence at intake was not a study entry requirement, it was the treatment goal of the psychotherapy and clinical milieu. Enrollment of currently drinking alcoholics represented a more naturalistic point related to when help was sought. By not requiring the more usual short abstinence period at enrollment, the potential for post cessation "rebound" into drinking was reduced. Importantly, the drinking reductions seen were not accompanied by any appreciable withdrawal symptoms irrespective of treatment group. Additionally, this experimental model, rather than an abstinence paradigm for this clinical trial, is theoretically more analogous to animal studies where medications are tested for their effectiveness to reduce ethanol consumption in individuals with an established drinking pattern.

Medication compliance rates were high (mean = 95%) for both treatment conditions. Adverse events were infrequent, nonpersistent between study visits, and typically of no greater than "minimal intensity." Strikingly, ondansetron seems to counteract some of naltrexone's important adverse effects, particularly nausea, which has been associated with reduced compliance and subject withdrawal from treatment (Croop et al., 1997). Most subjects attended all sessions, and the attrition rate was modest for a pharmacotherapy trial in alcoholism.

Future studies that test the effectiveness of ondansetron and naltrexone, both alone and combined, in various subtypes of alcoholics, are needed to bolster our proof-of-concept understanding of how mechanistic processes associated with a biological disease predisposition interact with the pharmacological changes produced by the medications.

In summary, it is tempting to speculate that the combination of ondansetron + naltrexone may act synergistically to boost treatment response because the effect sizes seen were much larger than have been reported by investigators who have examined the efficacy of each medication alone. Establishing this prediction would, however, require testing the efficacy of each medication as a treatment for alcoholism, both alone and in combination, within the same clinical trial. Understanding the underlying biology of the disease, and the fundamental pharmacological processes involved in the proposed medication interaction for its treatment, are critical to

exploring this new vista of combined pharmacotherapies for treating alcoholism.

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REFERENCES

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (ed 4th). American Psychiatric Press, Washington, D.C.

Anton RF, Moak D, Waid L, Latham PK, Malcolm RJ, Dias JK (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. Am J Psychiatry 156:1758–1764.

Babor TF, Dolinsky ZS, Meyer RE, Hesselbrock M, Hofmann M, Tennen H (1992) Types of alcoholics: Concurrent and predictive validity of some common classifications schemes. Br J Addiction 87:1415–1431.

Bandura A (1977) Self-efficacy: Toward a unifying theory of behavioral change. Psychol Rev 84:191–215.

Barnes JM, Barnes NM, Champaneria S, Costall B, Naylor RJ (1990) Characterization and autoradiographic localization of 5-HT3 receptor recognition sites identified with [3H]-(S)-zacopride in the forebrain of the rat. Neuropharmacology 29:1037–1045.

Campbell AD, McBride WJ (1995) Serotonin-3 receptor and ethanol-stimulated dopamine release in the nucleus accumbens. Pharmacol Biochem Behav 51:835–842.

Carboni E, Acquas E, Frau R, Di Chiara G (1989) Differential inhibitory effects of a 5-HT3 antagonist on drug-induced stimulation of dopamine release. Eur J Pharmacol 164:515–519.

Carboni E, Acquas E, Leone P, Perezzani L, Di Chiara G (1998) 5-HT3 receptor antagonists block morphine- and nicotine-induced place-preference conditioning. Eur J Pharmacol 151:159–160.

Cohen J (1988) *Statistical Power Analysis for the Behavioral Sciences* (2nd ed). Lawrence Erlbaum Associates, New Jersey.

Croop RS, Faulkner EB, Labriola DF (1997) The safety profile of naltrexone in the treatment of alcoholism: Results from a multicenter usage study. The Naltrexone Usage Study Group Arch Gen Psychiatry 54:1130–1135.

Gianoulakis C (1989) The effect of ethanol on the biosynthesis and regulation of opioid peptides. Experientia 45:428–435.

Gianoulakis C, de Waele JP, Thavundayil J (1996) Implication of the endogenous opioid system in excessive ethanol consumption. Alcohol 13:19–23.

Graybill FA (1970) *Theory and Application of the Linear Model*. Wadsworth Publishing Company, North Scituate, Massachusetts.

Hubbell CL, Czirr SA, Hunter GA, Beaman CM, LeCann NC, Reid LD (1986) Consumption of ethanol solution is potentiated by morphine and attenuated by naloxone persistently across repeated daily administrations. Alcohol 3:39–54.

Hubbell CL, Czirr SA, Reid LD (1987) Persistence and specificity of small doses of morphine on intake of alcoholic beverages. Alcohol 4:149–156.

Imperato A, Angelucci L (1989) 5-HT3 receptors control dopamine release in the nucleus accumbens of freely moving rats. Neurosci Lett 101:214–217.

Johnson BA, Ait-Daoud N (2000) Neuropharmacological treatments for alcoholism: Scientific basis and clinical findings. Psychopharmacology, in press.

Johnson BA, Cloninger CR, Roache JD, Bordnick PS, Ruiz P (2000) Age of onset as a discriminator between alcoholic subtypes in a treatment-seeking outpatient population. Am J Addict 9:17–27.

Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, Burdnick PS, Ait-Daoud N (1999) Ondansetron and alcohol consumption: Preliminary analysis of double-blind trial. Paper presented at the National Institute on Alcohol Abuse and Alcoholism Symposium: Medications Development for Alcoholism, American Society of Addiction Medicine Meeting, New York

Kilpatrick GJ, Jones BJ, Tyers MB (1987) Identification and distribution of 5-HT3 receptors in rat brain using radioligand binding. Nature 330:746–748.

King AC, Volpicelli JR, Frazer A, O'Brien CP (1997) Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence. Psychopharmacology 129:15–22.

Le AD, Sellers EM (1994) Interaction between opiate and 5-HT3 receptor antagonists in the regulation of alcohol intake. Alcohol Alcohol Suppl 2:545–549.

Litten RZ, Allen JP (1998) Advances in development of medications for alcoholism treatment. Psychopharmacology 139:20–33.

Marlatt GA, Gordon JR (1985) *Relapse Prevention*. Guildford Press, New York.

Matsuzawa S, Suzuki T, Misawa M, Nagase H (1999) Roles of 5-HT3 and opioid receptors in the ethanol-induced place preference in rats exposed to conditioned fear stress. Life Sci 64:L241–L249.

Meinert CL(1986) *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York.

Miller WR, Marlatt GA (1984) *Manual for the Comprehensive Drinker Profile*. Psychological Assessment Resources, Odessa, Florida.

Monti PM, Abrams DB, Kadden R, Cooney N (1989) *Treating Alcohol Dependence: A Coping Skills Therapy Guide*. Guildford Press, New York.

O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B (1992) Naltrexone and coping skills therapy for alcohol dependence: A controlled study. Arch Gen Psychiatry 49:881–887.

Pei Q, Zetterstrom T, Leslie RA, Grahame-Smith DG(1993) 5-HT3 receptor antagonists inhibit morphine-induced stimulation of mesolimbic dopamine release and function in the rat. Eur J Pharmacol 230:63–68.

Perry DC (1990) Autoradiography of [3H]quipazine in rodent brain. Eur J Pharmacol 187:75–85.

Reid LD, Hunter GA (1984) Morphine and naloxone modulate intake of ethanol. Alcohol 1:33–37.

SAS II (1997) *SAS Users Guide: Statistics, Version 6.12* (6th ed). SAS Institute Inc., Cary NC.

Selzer ML (1971) The Michigan alcoholism screening test: The quest for a new diagnostic instrument. Am J Psychiatry 127:1653–1658.

Sobell LC, Sobell MB (1992) Timeline follow-back: A technique for assessing self-reported alcohol consumption, in *Measuring Alcohol Consumption*. (Litten R, Allen J eds), pp 41–72, Humana Press Inc., Totowa, New Jersey.

Spitzer RL, Williams JB, Gibbon M, First MB (1992) The structured clinical interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 49:624–629.

Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM (1989) Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment of alcohol scale (CIWA-Ar). Brit J Addict 84:1353–1357.

US Department of Health and Human Services (1992) Cognitive-Behavioral Coping Skills Therapy, vol 3, US Department of Health and Human Services, Washington, D.C.

Volpicelli JR, Alterman AI, Hayasgida M, O'Brien CP (1992) Naltrexone in the treatment of alcohol dependence. Arch Gen Psych 49:876–880.

Widdowson PS, Holman RB (1992) Ethanol-induced increase in endogenous dopamine release may involve endogenous opiates. J Neurochem 59:157–163.

Williams JB, Gibbon M, First MB, Spitzer RL, Davies M, Borus J, Howes MJ, Kane J, Pope HG Jr, Rounsaville B (1992) The Structured Clinical Interview for DSM-III-R (SCID). II. Multisite test-retest reliability. Archives of General Psychiatry 49:630–636.

Yoshimoto K, McBride WJ (1992) Regulation of nucleus accumbens dopamine release by the dorsal raphe nucleus in the rat. Neurochem Res 17:401–407.