Psychopharmacology (1997) 129 : 15–22

ORIGINAL INVESTIGATION

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Effect of naltrexone on subjective alcohol response in subjects at high and low risk for future alcohol dependence

Received: 22 August 1995 / Final version: 25 July 1996

Abstract We investigated specific subjective effects of naltrexone pretreatment or placebo during various intervals on the breath alcohol level (BAL) curve in nonalcoholic volunteers. Fifteen high-risk (social drinkers with an alcoholic father) and 14 low-risk (no alcoholic relatives in at least two generations) subjects were tested in a double-blind, placebo-controlled study of the effects of 50 mg oral naltrexone on response to a moderate dose of alcohol. Dependent measures included subjective stimulation and sedation subscales from the Biphasic Alcohol Effects Scale (BAES) and mood subscales from the Profile of Mood States (POMS). At rising BALs, high-risk subjects showed a naltrexone-related attenuation of BAES stimulation. This effect was not evident in low-risk subjects, who directionally showed the opposite effect, although nonsignificant. For both groups, there were no significant naltrexone-related effects for BAES sedation; however, naltrexone did affect several POMS scales on alcohol response, such as decreased vigor, and increased fatigue, tension, and confusion. Confusion was significantly elevated for the high-risk group during rising BALs of the naltrexone session. The results suggest a differential response to naltrexone, based on paternal history of alcoholism and level of stimulation experienced during alcohol drinking.

Key words Naltrexone · Alcohol · Genetics · Social drinkers · Family history of alcoholism · Biphasic Alcohol Effects Scale

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Introduction

Numerous animal studies have shown that opioid antagonists decrease alcohol preference (Altschuler et al. 1980; Volpicelli et al. 1986; Froehlich et al. 1987, 1990; Hubbell et al. 1991; Hyytiä and Sinclair 1993). In a recent double-blind, placebo-controlled human clinical study, naltrexone significantly reduced relapse rates and alcohol consumption in treated alcoholic patients compared to placebo-treated alcoholics (Volpicelli et al. 1992). These clinical results have been replicated in another study with naltrexone (O'Malley et al. 1992) and in a preliminary study with the opioid antagonist nalmefene (Mason et al. 1994).

The most widely accepted hypothesis for naltrexone's effect is that opioid antagonism blocks alcohol-stimulated increases in endogenous opioid activity, resulting in attenuation of alcohol "high" or euphoria (Volpicelli 1987). Support for an alcohol/endogenous opioid association has been demonstrated in offspring of alcoholics (two- or three-generational) who have shown dose-dependent increases in β-endorphin-related peptides to test doses of alcohol (Gianoulakis et al. 1989, 1996). Additionally, naltrexone-treated alcoholics have indicated a reduced subjective high (Volpicelli et al. 1995) and craving (O'Malley et al. 1996) after an alcohol "slip". However, methodological difficulties with these subjective data, such as the retrospective nature of the reports and the lack of standardization of alcohol beverage type or amount consumed, have limited our further understanding of naltrexone-alcohol interactions.

In a recent well-controlled study of naltrexone and alcohol effects in social drinkers, naltrexone was found to decrease the subjective stimulant effects and increase the sedative effects of alcohol (Swift et al. 1994). However, in another study of light social drinkers, naltrexone pretreatment did not significantly alter subjective alcohol response (Doty and deWit 1995). Both investigations utilized methodologically sound, well-controlled laboratory studies; however, the results

may not extend to mechanisms in clinical samples because subjects were relatively light drinkers (i.e., approximately four drinks weekly) and did not show increases in stimulation from alcohol or loss of control as often observed in alcoholics.

To understand further the mechanisms of opioid antagonist treatment, we examined subjective effects of naltrexone on alcohol drinking in subjects at high and low risk for the future development of alcohol dependence. High-risk individuals (i.e., sons of alcoholics) might represent a closer link to clinical patients, given their reported 3-fold or higher increased risk for the future development of the disorder (Goodwin et al. 1973; Cloninger et al. 1981). High-risk subjects have also shown altered subjective alcohol response (for review, see Pollock 1992) compared to individuals without such a family history, including both tolerance (Schuckit 1994) and sensitization (Newlin et al. 1995) to the effects of alcohol, depending on the phase of the breath alcohol level (BAL) curve and type of assessment instrument used. It has been suggested that high risk individuals show sensitization to the stimulant effects of alcohol during rising BALs and tolerance to the sedative effects during descending BALs (for review, see Newlin and Thomson 1990). Clinical observations in naltrexone-treated patients have implied that naltrexone may block or reduce this stimulation during the first few alcoholic drinks, i.e. during rising BALs.

The specific objective of this study was to determine the effect of naltrexone on self-reported stimulation and sedation from alcohol, as well as general mood states, during discrete intervals on the BAL curve in subjects at high and low-risk for alcoholism. Our hypothesis was that naltrexone pretreatment would result in a decrease in subjective stimulation, especially during rising BALs, and an increase in sedation during decreasing BALs. We predicted that these effects would be especially pronounced for the high-risk compared to the low-risk group. Finally, groups were compared on the ability to distinguish naltrexone from placebo, and on the aversive effects or side effects experienced from naltrexone alone and naltrexone-alcohol interactions.

Materials and methods

Subjects

Participants were healthy nonalcoholic male social drinkers between the ages of 21 and 31 years. Thirty-one subjects entered and completed the study. Therefore, the final sample for data analysis consisted of 29 subjects for the high- (n = 15) and low-risk (n = 14) groups. However, one high risk subject was eliminated from data analyses because he was unable to consume all of the alcohol during either session, and one low risk subject was eliminated because he did not fully meet the family history criteria.

High-risk subjects reported a minimum of a positive biological paternal history for alcohol dependence and low-risk subjects documented a two-generational negative family history for alcohol dependence. In other words, high-risk subjects were those individuals with alcoholic fathers plus any other alcoholic biological relatives and low-risk subjects had no alcoholic relatives in the last two generations.

The high- and low-risk groups were selected to match on age and quantity-frequency index of alcohol consumption. Exclusion criteria for both groups were a history of alcohol or substance dependence or regular heavy use of drugs other than alcohol (>1x/month), psychiatric or medical disorders, clinically significant abnormalities on screening laboratory tests (SGOT, GGTP, bilirubin, etc.), or a positive urine drug screen (amphetamines, barbiturates, opiates, cocaine). The screening questionnaires consisted of the Symptom Checklist (SCL-90; Derogatis 1983), a quantity-frequency index scale (QFI; Cahalan et al. 1969) the CAGE (Mayfield et al. 1974; Ewing, 1984), the Brief Michigan Alcohol Screening Test (B-MAST-10; Pokorny et al. 1972) for self and primary relatives, and a family tree for both primary and secondary biological relatives to assess two generational family history for alcohol dependence (DSM-IIIR criteria). The validity of offspring reports for familial drinking practices has been previously established (O'Malley et al. 1986; Sher and Descutner 1986; Levenson et al. 1987). Subjects were recruited through newspaper advertisement or flyers in the general Philadelphia area and at local universities and were paid $150 for participation. Study procedures met APA ethical standards and were approved by the University of Pennsylvania Institutional Review Board.

Procedure

Subjects meeting the inclusion criteria signed informed consent and were scheduled for two testing sessions, spaced at least 7 days apart (mean = 10.28 ± 4.45; range 7–21 days). Subjects were instructed to refrain from alcohol for at least 24 h prior to testing and from food, caffeine, and nicotine on the morning of testing. Each subject was tested individually.

The subject arrived at 9:00 a.m. and was given a light breakfast (English muffin, jelly or jam, apple juice), a breathalyzer test, and the short version of the Profile of Mood States (POMS; McNair et al. 1971; Schacham 1983) questionnaire to assess baseline mood. At 9:30 a.m. after vital signs were obtained, the subject was given a pill, either 50 mg naltrexone or an identical placebo pill. Both experimenter and subject were blinded as to the content of the pill and the groups were counterbalanced for pill order.

For the next several hours, the subject was allowed to relax and either read magazines or view documentary videotapes provided at the center. After the subject completed a side effects questionnaire, an indwelling Teflon catheter was inserted into the subject's antecubital vein with blood sampling at various points during the afternoon as part of a larger investigation (King 1995). Each subject was given a low-fat light lunch (juice, sandwich, pretzels) at approximately 12:00 p.m., followed by readministration of subjective questionnaires.

The alcohol drinking interval (25 min) commenced at approximately 1:00 p.m., 3½ h post-medication or placebo. This medication-alcohol interval was chosen to reduce nausea and acute physiological effects of naltrexone (Atkinson 1984; Swift et al. 1994) while taking advantage of opioid receptor blockade and oral naltrexone metabolism. The elimination half-life of oral naltrexone has been shown to vary from 1.1 to 10.3 h (Wall et al. 1981; Meyer et al. 1984; Gonzalez and Brogden 1988). During the 25-min drinking interval, the subject was instructed to consume three equal-sized beers, with each drink consumed up to 5 min followed by either a 5-min rest period or completion of subjective questionnaires. The alcoholic beverage was a high alcohol content beer (over 7% v/v ethanol) used in order to minimize volume. Other investigations have employed ethanol-juice mixtures which is problematic for several reasons, including lack of naturalism, taste aversion, and possible nausea. The total amount of alcohol consumed was approximately 0.6 g alcohol/kg body weight (i.e., range 38.2–58.6 g total alcohol, based on each subject's body weight).

After finishing the alcohol beverages, the subject was allowed to read or watch videotapes, with subjective report measured at regular intervals after the onset of drinking, i.e., at 30, 60 and 120 min. Breathalyzers were obtained every 30 min after the drinking interval, commencing at the 60-min reading (the 30-min time point would not have represented a valid breathalyzer reading given that it was only 5 min after the last drink). When the subject's BAL reached 0.02 on the descending limb (at approximately 180 min), he was escorted home. The second session was identical to the first, with the addition of an exit interview at the end of the study.

Subjective scales

The subjective questionnaires given during the testing sessions were the 37-item shortened version of the POMS (McNair et al. 1971; Schacham 1983) and a modified version of the Biphasic Alcohol Effects Scale (BAES; Martin et al. 1993). The POMS (item ratings 0–4) was used to assess general mood states at baseline and during ascending and descending portions of the BAL curve. It is composed of the following six scales: vigor, fatigue, anxiety, depression, anger, and confusion.

The BAES, a 14-item unipolar adjective rating scale with item ratings 0–10, was used to measure both the stimulant and sedative effects of alcohol during rising and falling BALs. The stimulant scale includes the following items: elated, energized, excited, stimulated, talkative, up, and vigorous; the sedative scale includes difficulty concentrating, down, heavy head, inactive, sedated, slow thoughts, and sluggish. The BAES has been validated to yield higher stimulation scores during ascending BALs and higher sedation during descending BALs (Martin et al. 1993); therefore only those time points (30 and 120 min) were used in data analyses. The modification of the BAES was the substitution of instructions, "...circle one number which corresponds to how you are feeling at this moment" rather than the typical instructions of having the subject to describe how these feelings were produced by alcohol.

During each session, prior to drinking and 3 h post-drinking, the subject completed a side effects questionnaire (identical to that administered by Volpicelli et al. 1992), consisting of ratings (0 = absent; 1 = present) for headache, anxiety, nausea, vomiting, sexual desire, and erections. At the completion of both sessions, the subject was given an exit interview and asked to compare the sessions on preference based on the alcohol effect achieved, similarity to usual drinking, taste, and which session he believed he received the medication.

Statistical analyses

The high- and low-risk groups were compared on general demographic and drinking characteristics via Student's *t*-tests. Data on subjective alcohol effects (BAES) and mood states (POMS) were summarized to scale scores from each questionnaire. The stimulation and sedation subscales of the BAES were analyzed in four-way repeated measures analyses of variance (ANOVAs) with Group (high risk, low risk) and Order (naltrexone first, placebo first) as the between-subjects factors and Time (rising BAL, falling BAL) and Medication Condition (naltrexone, placebo) as the within-subject variables. For the short POMS, similar four-way repeated measures ANOVAs were employed comparing scores at baseline and rising and declining BALs. Post-hoc Tukey's HSD test for unequal sample sizes was used for significant main effects or interaction effects terms. Categorical data such as the side effects and the exit interview data were analyzed by Fisher's Exact and Chi Square analyses, respectively.

Results

Demographic variables

The high- and low-risk groups did not differ significantly on general demographic (age, education, SCL-90, etc.) or alcohol consumption patterns (overall QFI, B-MAST-10, etc.; see Table 1). Subjects typically drank four standard drinks (4.31 ± 2.3) twice weekly

Table 1 Demographic and drinking characteristics. Results shown are mean (± SEM). Typical and maximum quantity measures were converted to standard number of drinks (1 drink = 1.5 oz liquor, 12 oz beer, or 6 oz wine). Chi-square analyses were conducted on race

	Low risk (FH−) (n = 14)	High risk (FH+) (n = 15)	$t(27)$, P value
General characteristics			
Age (years)	23.7 (0.85)	24.0 (0.65)	−0.20, ns
Education (years)	16.6 (0.51)	15.3 (0.30)	2.12, $P = 0.04$
Height (cm)	179.2 (1.9)	178.2 (1.7)	0.08, ns
Weight (kg)	76.0 (2.6)	78.1 (2.3)	−0.22, ns
SCL-90	15.2 (3.9)	17.9 (3.6)	−0.51, ns
Race (% Caucasian)	79% (11/14)	87% (13/15)	$\chi^2 = 0.33$, ns
Alcohol drinking patterns			
History			
CAGE	0.71 (0.22)	1.20 (0.31)	−1.26, ns
B-MAST-10	0.07 (0.07)	0.67 (0.34)	−1.64, ns
Age first drink	15.6 (0.58)	13.3 (0.88)	2.10, $P = 0.05$
Age first hangover	17.7 (0.46)	16.0 (0.80)	1.85, ns
Last 6 months			
No. times intoxicated	18.9 (5.8)	24.2 (5.1)	−0.69, ns
QFI (oz.100% EtOH/day)	0.81 (0.17)	1.22 (0.29)	−1.24, ns
Typical quantity (drinks)	4.07 (0.34)	5.13 (0.47)	−1.09, ns
Max. quantity (drinks)	10.7 (0.50)	13.2 (1.50)	−0.87, ns
Typical frequency	0.32 (0.06)	0.29 (0.05)	0.35, ns
Oz beer (avg oz/occasion)	43.7 (6.79)	53.1 (9.7)	−0.78, ns
Oz wine (avg oz/occasion)	7.97 (1.33)	7.65 (1.50)	0.16, ns
Oz liquor (avg oz/occasion)	1.55 (0.42)	4.20 (0.62)	−3.47, $P = 0.002$

(2.13 ± 1.4) and also binged on alcohol (i.e., > 5 drinks in one occasion) on a monthly basis.

Compared to the low-risk group, the high-risk group was significantly lower on education, socioeconomic status, and years raised by biological father, all of which may be consequences of being raised in an alcoholic household (Table 2). They also drank nearly three times the quantity of hard liquor on liquor-drinking days than low-risk subjects, although liquor drinking was infrequent for both groups, approximately 2–3 times monthly. The mean MAST score for fathers of high risk subjects was 6.13 ± 2.1 (range 3–10), with 67% receiving treatment for their addiction, while the MAST scores for the fathers of the low-risk subjects were 0.00 with 0% receiving treatment.

Naltrexone and side effects

There was a trend (for the overall sample) of an increased rate of side effects reported during the naltrexone session compared to the placebo session [$\chi^2(1) = 3.14$, $P < 0.08$]. This was evident for both the post-pill alone (placebo, 24% subjects with side effects, versus naltrexone, 42%) and post-pill and alcohol intervals (placebo and alcohol, 35% subjects with side effects, versus naltrexone and alcohol, 42%). The groups, however, did not significantly differ in rates of specific side effects, such as headache, anxiety, nausea, vomiting, sexual desire, or erections [Fisher's exact (two-tailed), Ps > 0.11]. Three subjects (all high risk) vomited during the alcohol drinking portion of the naltrexone session and an additional two subjects (one high risk, one low risk) vomited shortly after or hours after completion of the naltrexone session. Those subjects ($n = 3$) who vomited during the session showed directionally lower peak BALs (0.045 compared to 0.059 for non-vomiters) and slightly lower stimulation scores (x = 13.0 + 2.33) compared to those who did not vomit (x = 14.7 + 2.26). There was no incidence of vomiting during or after the placebo pill session, or during the naltrexone session prior to drinking the alcohol.

Effect of naltrexone on alcohol response

Naltrexone did not significantly alter ethanol pharmacokinetics, as measured by the BAL curve (see Fig. 1). BALs for both the ascending and descending portions were approximately 0.035–0.045%, with peak BALs approximately 0.05–0.06%.

For BAES stimulation, a significant main effect was observed for Time [$F(1, 25) = 28.33$, $P < 0.0001$], with higher stimulation scores during rising BALs than descending BALs, as expected (Fig. 2). A significant Group × Medication interaction was also evident [$F(1, 25) = 53.58$, $P = 0.01$], with post-hoc comparisons revealing that naltrexone attenuated stimulation scores for the high risk group (Tukey's HSD, $P = 0.05$). Naltrexone-attenuated stimulation was not evident in the low risk group, as they showed a nonsignificant effect in the opposite direction (see Fig. 2).

There was a trend for a main effect of Session Order [$F(1, 25) = 3, 52$, $P = 0.07$] for BAES stimulation, with subjects tending to report higher scores during the first session. However, order did not significantly interact with the other independent variables [Fs(1, 25) ≤ 3.42, Ps = ns] and did not affect the previously reported group differences in stimulation.

No significant main effects or interactions were observed for BAES sedation (Fig. 3). It appears that subjects were able to assess independently the subjective changes from the BAES, as sedation and stimulation did not significantly correlate during either limb of the BAL curve [rs(29) ≤ 0.30, Ps = ns].

For the POMS, main effects of Time were observed for vigor, fatigue, and confusion [Fs(1, 25)>22.32, Ps < 0.001] with vigor showing time-dependent decreased levels, and fatigue and confusion showing increased levels, which were evident during declining BALs. A significant main effect of Medication was

Table 2 Familial characteristics. Results shown are mean (± SEM)

	Low risk (FH−) (n = 14)	High risk (FH+) (n = 15)	t (27), P value
Family history			
Hollingshead index (father)	1.57 (0.23)	2.8 (0.36)	−2.87, P = 0.008
Years education (father)	16.6 (0.65)	13.7 (1.10)	2.26, P = 0.03
Years raised biol. father	16.0 (1.2)	11.7 (1.8)	−2.87, P = 0.06
% Paternal alcoholism	0%	100% (15/15)	–
% 1 + *consequence of drinking in biological male relatives*[a]			
Uncle	0%	47% (7/15)	–
Grandfather	0%	47% (7/15)	–
Full brother	0%	33% (3/9)[b]	–
Self	0%	29% (4/15)	–

[a]Consequences of drinking based on DSM-IIIR criteria and reported in this Table only for male relatives as groups were defined by paternal alcoholism and incidence for female relatives was relatively low

[b]Only 9 FH+ subjects reported having a biological brother

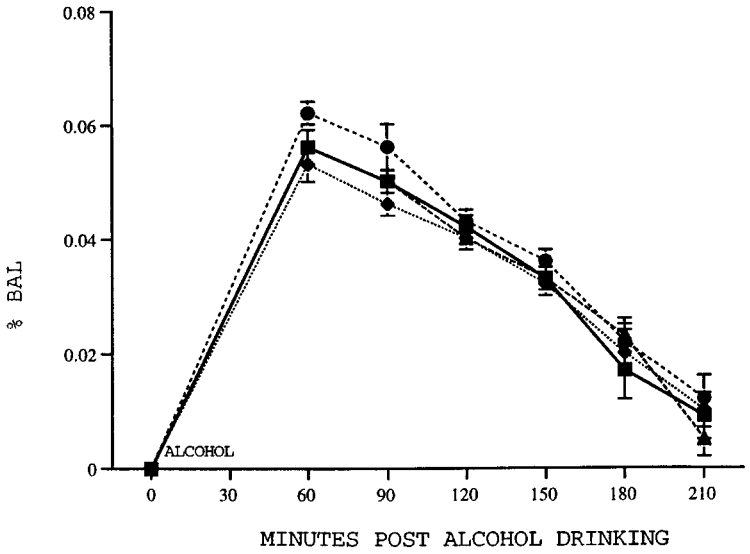

Fig. 1 Breath alcohol levels in subjects before and after drinking approximately 0.6 g/kg alcohol. High risk, $n = 15$; low risk, $n = 14$. *NAL* 50 mg PO naltrexone pretreatment; *PLA* placebo pretreatment. *ALCOHOL* alcohol drinking interval (0–25 min). The first valid breathalyzer reading for our design was taken at 60 min post-onset of drinking. –■– High risk NAL; ...◆ low risk NAL; .... ●... high risk PLA; ---▲--- low risk PLA

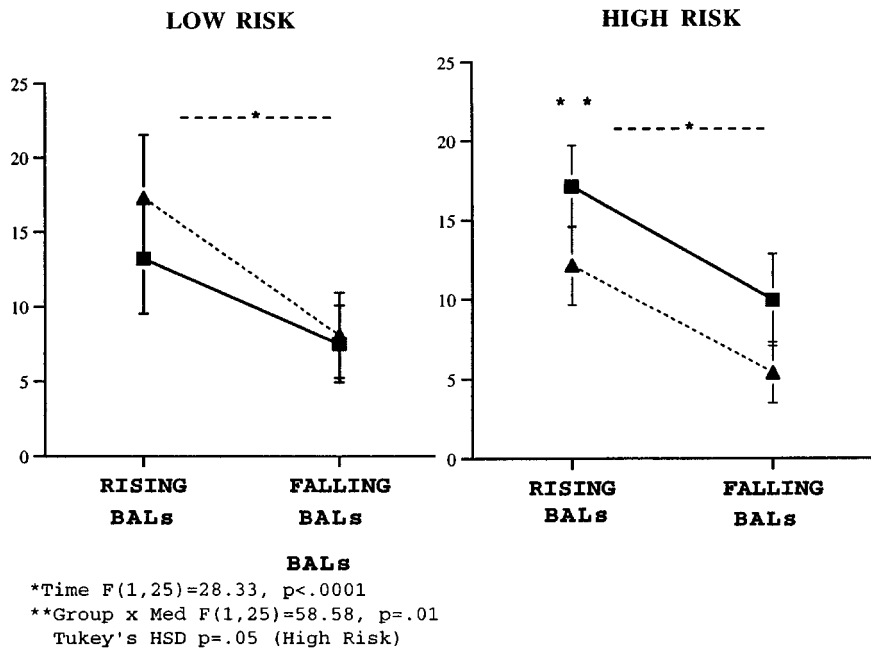

Fig. 2 BAES stimulation scores during the naltrexone and placebo pill sessions for low- and high-risk subjects. Data shown represent means (± SEMs). *RISING BAL* 30 min post-onset of alcohol drinking; *FALLING BAL* 120 min post-onset of alcohol drinking. –■– Placebo pill; ---▲--- naltrexone

found for vigor, fatigue, tension, and confusion [*F*s (1, 25) < 9.61, *P*s < 0.05], with naltrexone decreasing vigor and increasing fatigue, tension, and confusion scores. A significant interaction was found for POMS confusion [Group × Med × Time: $F(2, 50) = 3.73$, $P < 0.05$], with the High Risk group showing naltrexone-induced increased confusion at rising BALs (Tukey's HSD, *P*s < 0.05, all comparisons).

A post-hoc analysis was conducted for all subjects on a median split of placebo pill session stimulation scores (rising BALs), resulting in two new group classifications without regard to family history, those who were "highly stimulated" by alcohol and those who were not. Comparing these groups on stimulation during the naltrexone session, we found that only those "high stimulated" subjects during alcohol showed naltrexone-related reduction in stimulation with the "low stimulated" subjects showing naltrexone-related increased stimulation [$F(1, 27) = 5.31$, $P < 0.05$].

Other associated factors

For the exit interview, 12 out of the 15 high-risk subjects (80%) compared to five out of the 14 low-risk subjects (36%) reported that the effects achieved during the placebo pill session were more like everyday drinking [$\chi^2(1) = 5.85$, $P < 0.05$]. Correct identification of the medication session was directionally higher for the high-risk group, but this was not significant [80%

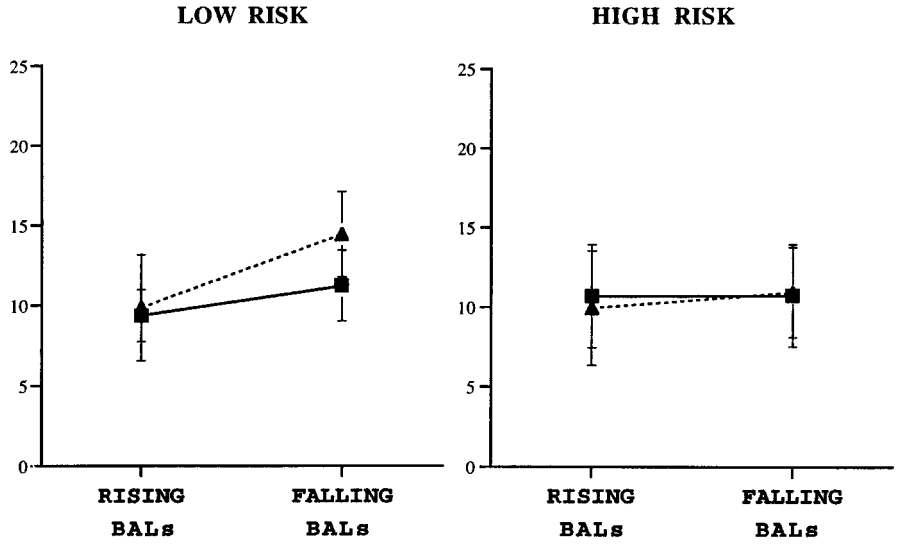

Fig. 3 BAES sedation scores during the naltrexone and placebo pill sessions for low- and high-risk subjects. Data shown represent means (± SEMs). *RISING BAL* 30 min post-onset of alcohol drinking; *FALLING BAL* 120 min post onset of alcohol drinking. No significant effects were found. –■– Placebo pill; ---▲--- naltrexone

high-risk versus 56% low-risk, χ^2 (1) = 1.77, P = ns]. The groups did not differ significantly in taste preference for the sessions.

Discussion

In the present study, those subjects at familial high risk for alcoholism showed attenuated alcohol stimulation after naltrexone pretreatment. This is consistent with retrospective subjective reports in treated alcoholic patients (Volpicelli et al. 1995; O'Malley et al. 1996) and with animal studies showing that opioid antagonists reduce alcohol preference (Altschuler 1980; Volpicelli et al. 1986; Froehlich et al. 1987, 1990; Hubbell et al. 1991; Hyytiä and Sinclair 1993). Results from the present study, in combination with prior human and animal work, suggest that opioid receptor antagonists decrease the reinforcing effects of ethanol among those at high risk for alcoholism.

In addition, high-risk compared to low-risk subjects were better able to distinguish the naltrexone session. The high-risk group reported the alcohol effects during the naltrexone session were unlike those achieved in everyday drinking. Although both groups showed naltrexone-induced changes in some general POMS mood states (fatigue, tension, etc.), we may speculate that the high-risk subjects' increased POMS confusion scores at rising BALs could have resulted from naltrexone-induced alterations in "usual" alcohol stimulation, which was experienced during the placebo pill session (see Fig. 2).

Similar to prior research, we used a within-subjects design so that each subject served as his own control. We did not utilize an alcohol placebo session, given that: 1) there is questionable efficacy of alcohol placebos at the BAL levels achieved in this study (O'Boyle et al. 1994); 2) the taste of a non-alcohol beer would likely have been discriminable from the high-alcohol content beer; and 3) that two prior studies have shown negligible subjective effects of naltrexone with placebo alcohol beverages (Swift et al. 1994; Doty and deWit 1995). In contrast to the majority of alcohol challenge studies, we utilized an afternoon drinking protocol, administered several subjective indices at baseline and during various phases of the BAL curve, and had subjects drink their preferred beverage, beer, (93% were predominant beer drinkers) to provide a more naturalistic and potentially enjoyable drinking experience.

As for subject selection, the question of the validity or meaningfulness of our risk group distinctions may arise, given the relatively small sample sizes and the inherent heterogeneity reported in subjects defined and grouped by family history characteristics (Dawson et al. 1992; Schuckit 1994). In light of this general issue, our re-examination of data by median split of placebo pill session rising BAL stimulation scores revealed that those subjects who were "highly stimulated" during alcohol showed naltrexone-related reduction in stimulation. It should be noted that one-third of those "highly stimulated" subjects had no familial risk for alcoholism (i.e., classified as low risk); therefore, response to test doses of alcohol may be another interesting factor to investigate in subgroup responses to opioid antagonists.

Several caveats and methodological issues should be mentioned to avoid overinterpretation of the results. First, although the groups were counterbalanced for medication order, those subjects who received placebo first had the advantage of experiencing a baseline laboratory drinking session with which to compare the effects of naltrexone and to adapt to the novel environment. Situational novelty has been shown previously to affect alcohol response (Newlin and Pretorius 1991). Therefore, it is suggested that future studies carefully consider the influence of medication/placebo

order on subjects' drinking reports, as a result of either pharmacological (metabolites, receptor changes) or psychological factors (expectancy, conditioning), or both.

Second, several subjects experienced aversive effects, the most severe of which was vomiting. Three subjects (all high risk) vomited during the alcohol drinking portion of the naltrexone session and an additional two subjects (one high risk, one low risk) vomited shortly after or hours after completion of the naltrexone session. Subjects who vomited during the session showed directionally lower peak BALs and stimulation scores; however, statistical analyses were not conducted due to the small number of subjects who experienced vomiting. No subject vomited during or after the placebo pill session, or during the naltrexone session prior to drinking the alcohol. Although the incidence of vomiting or nausea may not have been directly related to stimulation and positive effects, it is no doubt an important associated factor in naltrexone and alcohol consumption and more frequently observed in high-risk subjects (four high-risk subjects vomited versus one low-risk subject).

In sum, the results of the present study suggest that those individuals at high risk due to paternal alcoholism are differentially affected by naltrexone pretreatment compared to their low-risk counterparts. If increased activity of the endogenous opioid system mediates alcohol drinking and excessive consumption, then it would be expected that high-risk individuals could potentially show greater alcohol-related increases in endogenous opioids (Gianoulakis et al. 1989, 1996; de Waele et al. 1992) . Alternatively, differential opioid receptor sensitivity or responsivity (for review see Ulm et al. 1995), or interaction with other potential neurotransmitter systems (i.e., dopamine, serotonin) might also be factors involved in alcohol reinforcement (Weiss et al. 1990; Widdowson and Holman 1992). Alcohol-opioid interactions may also be influenced by either intrinsic or alcohol-induced differences in the metabolism or biotransformation of opioid antagonists (King et al. 1996). As ongoing studies will enable us to understand further the biological mechanisms of opioid antagonist treatment for alcoholism, continued preclinical laboratory studies will aid in both the classification of naltrexone-related mood states and biphasic alcohol effects and in the identification of those individuals most likely to benefit.

Acknowledgements We would like to thank the staffs at The University of Pennsylvania Treatment Research Unit and The Rockefeller University Laboratory on the Biology of Addictive Diseases for assistance in this study. Assistance in medical screening and study procedures was conducted by Louise Epperson, Doug Primavera, Patricia Volpicelli, and Dr. Kyle Kampman. Appreciation is also expressed to Dr. Mary Jeanne Kreek (Rockefeller University), and to Drs. Arthur Alterman and Ronald Ehrman, and to Nathan Watson (University of Pennsylvania) for suggestions on study protocol and implementation. This study was supported in part by the National Institute on Alcoholism and Alcohol Abuse (R0I-AA0 7517) and the National Institute on Drug Abuse (T32-0A7241, P50-DA05186).

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