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## BRIEF REPORT

# TARGETED NALTREXONE TREATMENT OF EARLY PROBLEM DRINKERS

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**Abstract** — Naltrexone is approved for daily use in the treatment of alcohol dependence. We evaluated the feasibility of using targeted naltrexone (i.e., on an "as-needed" basis) to treat early problem drinkers. Twenty-one subjects (52% male) received brief coping skills training weekly for 4 weeks, along with naltrexone (50 mg), which they were instructed to use 2 to 5 times per week in anticipation of high-risk drinking situations. During treatment, statistically and clinically significant declines were observed across a variety of drinking-related outcomes, including the intensity of drinking, the decline in which was correlated with medication use. Beneficial effects of the intervention were still evident during the 3-month posttreatment period. Further research, including a placebo-controlled evaluation of targeted naltrexone, is needed to determine the optimal treatment strategy for early problem drinkers, many of whom are seen in the primary-care medical setting. © 1997 Elsevier Science Ltd

Alcohol consumption occurs along a continuum, with no sharp demarcation between "social" or "moderate" drinking and "problem" or "harmful" drinking (Babor, Kranzler, & Lauerman, 1987). There exists a large subgroup of people who drink heavily, but who are not seriously dependent on alcohol (Hilton & Clark, 1987). Intensive psychosocial interventions that focus on abstinence from alcohol are not well suited to early problem drinkers, who do not readily identify themselves as alcoholics and who may be unwilling or unable to commit the time, effort, and expense required for intensive rehabilitation (Duckert & Johnsen, 1987; Sanchez-Craig, Annis, Bornet, & MacDonald, 1984). Brief intervention strategies have generally been shown to reduce drinking in this patient population (Babor, 1994; Bien, Miller, & Tonigan, 1993), though the size of the treatment effect tends to be small (Babor, 1994).

The use of a medication, such as naltrexone, which is effective in the treatment of alcohol dependence (O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992), may enhance the effects of counseling with early problem drinkers. Bohn, Kranzler, Beazoglou, and Staehler (1994) examined the effect of naltrexone on alcohol consumption in early problem drinkers who received four sessions of brief counseling to reduce drinking during a 6-week study period. They found significant reductions in drinking and alcohol-related problems. Swift, Whelihan, Kuznetsov, Buongiorno, and Hsuing (1994), in a laboratory study, found that naltrexone augmented

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some of the sedative (i.e., aversive) effects and reduced some of the positive effects of alcohol.

Two studies that used alcohol-sensitizing medications (Annis & Peachey, 1992; Duckert & Johnsen, 1987) suggest that a targeted approach to medication administration is potentially useful in reducing heavy drinking. The pharmacokinetics of naltrexone suggest that it may be particularly suitable for targeted administration. Naltrexone is orally available, with peak plasma levels achieved within an hour of oral administration (Crabtree, 1984), at which time there is also blockade of $\mu$ opiate receptors in the brain (Lee et al., 1988). These findings are consistent with the drug's capacity to acutely alter the reinforcing effects of alcohol (Swift et al., 1994).

The purpose of the present open-label study was to evaluate in early problem drinkers the feasibility and potential effectiveness of targeted naltrexone administration to help cope with situations identified by the subject as being high risk for heavy drinking. In this study, the medication was combined with coping skills treatment in an approach intended to be useful for the primary-care management of early problem drinkers.

## METHODS

Subjects were recruited through newspaper advertisements. Following a telephone screening interview, subjects were interviewed in person by a research nurse, gave their informed consent to participate, and then underwent a clinical laboratory evaluation and physical examination. Inclusion criteria were: age 18–60; stable residence; ability to read English; average weekly intake of $\geq$21 standard drinks for males and $\geq$15 standard drinks for females *or* a current DSM-IV (APA, 1994) diagnosis of alcohol abuse or mild alcohol dependence. Women of child-bearing potential were required to practice reliable birth control and to have a negative serum pregnancy test. Subjects were excluded if they met more than four DSM-IV criteria for alcohol dependence; met current criteria for a DSM-IV Drug Use Disorder (other than nicotine); met lifetime criteria for opioid dependence; had used psychoactive drugs in the preceding month; or had a significant psychiatric or medical illness.

### *Subjects*

Of the 79 people who responded to the advertisements, 21 subjects, of whom 11 (52%) were male, were included in the clinical trial. Their mean age was 44 (range = 32–60) years and they had a mean of 15 (range = 12–20) years of education. Twenty (95%) of the subjects were employed. Eleven subjects (52%) met DSM-IV criteria for mild alcohol dependence, 8 subjects (38%) met criteria for alcohol abuse, and 2 subjects (10%) met only heavy drinking criteria.

### *Study procedures*

*Assessments.* Measures of alcohol consumption during the 30 days prior to treatment were obtained using the Time-Line Follow-Back Assessment method (TLFB; Sobell et al., 1980). The Addiction Severity Index (ASI; McLellan et al., 1992) and a questionnaire consisting of 19 items measuring the patient's desire to drink were also administered at this time. Laboratory tests included $\gamma$-glutamyltranspeptidase (GGTP), an objective measure of alcohol intake.

Each evening during the treatment period, subjects were asked to record for that day in a booklet provided for that purpose, their alcohol consumption and desire to

drink. Subjects also indicated whether they used naltrexone that day and, if so, the circumstances under which it was taken. The following assessments were repeated weekly during the 4-week treatment period: breath alcohol testing, a questionnaire that inquired about psychoactive substance use and treatment received outside the study protocol, and a side effects questionnaire. At the end of active treatment, a research assessment was repeated, which consisted of the TLFB, ASI, the alcohol desire questionnaire, and GGTP level. A telephone interview was also conducted with a collateral informant to provide concurrent validation of alcohol use. A comparable follow-up assessment was also conducted 3 months after active treatment ended. Of the 21 subjects enrolled in the study, 18 (85.7%) were interviewed at follow-up, with 3 subjects refusing the follow-up interview. Informant interviews were also conducted at this time.

*Treatment.* Therapy was conducted over four sessions, using a treatment manual that focused on skills training. Each 25-minute session centered on skills to avoid or otherwise cope with high-risk drinking situations. A booklet was provided that summarized the material presented in each session. During the first therapy session, subjects made a choice either to stop drinking or to drink "sensibly," which was defined using the guidelines developed by Sanchez-Craig, Wilkinson, and Davila (1995). Subjects were encouraged to use coping strategies, including naltrexone, to deal with high-risk situations; use of the medication 2 hours before entering a high-risk situation was considered optimal. Only five capsules were distributed for the 7-day period between sessions, and subjects were instructed to take one on each of at least 2 days during the week. Medication was provided in opaque capsules containing riboflavin (25 mg) to facilitate compliance monitoring (Del Boca, Kranzler, Brown, & Korner, 1996).

*Analyses.* Relations between variables were examined using paired *t*-tests and the Spearman correlation coefficient (rho). Continuous data are presented as mean ± standard deviation (*SD*). All *p* values reported are two-tailed.

## RESULTS

### *Medication tolerance and compliance*

Although naltrexone was generally well tolerated, two subjects discontinued the medication due to adverse effects: one complained of nausea, headache, dizziness, and diarrhea, while the second complained of nausea, dyspepsia, and vomiting. Subjects reported taking a mean of 9.1 ($SD = 4.5$, range = 1–17) naltrexone capsules during the 4-week treatment period. This was highly correlated ($n = 19$, rho = .94, $p < .001$) with the results of capsule counts conducted by the research nurse at each visit (mean = 10.0, $SD = 4.9$, range 1–17). Riboflavin testing also revealed a high rate of medication compliance. Of the urine samples collected within 24 hours of the time the subject reported naltrexone ingestion (which is the longest time over which it is reliably detected), 91.2% were positive for riboflavin.

The most commonly reported reason for taking naltrexone was as a general preventive measure, with 95.2% of subjects endorsing that item at least once and 57.9% of all doses of naltrexone having been taken for that reason. The majority of subjects (85.7%) also reported using naltrexone in anticipation of a high-risk drinking situation (with 28.9% of all doses being taken for that reason). Smaller proportions of subjects reported taking the medication during a high-risk drinking situation, with 38.1% en-

dorsing this item on at least one occasion and 5.8% of all doses being taken for this reason. Naltrexone use in situations other than those related to high risk for drinking was the least commonly endorsed reason, with 28.6% of subjects endorsing this item on at least one occasion and 7.4% of all medication use being for this reason.

*Attendance at counseling sessions and other treatment received*

Subjects attended a mean of 3.7 ($SD$ = 0.8) counseling sessions. Eighteen subjects (86%) attended all four counseling sessions. Two subjects each reported participation in two sessions of counseling in addition to that provided as part of the study protocol. In neither case was the counseling related to drinking. No subjects reported attendance at AA meetings.

*Validation of self-reports*

There was a high degree of association between self-reported measures of drinking and reports from collateral informants, during both the treatment and the follow-up periods. Correlations for the number of drinking days and the intensity of drinking all were highly significant (rho $\geq 0.75, p \leq .003$).

*Drinking and related outcomes*

Table 1 shows pretreatment, treatment, and posttreatment values for alcohol-related variables. Significant differences existed between pretreatment and treatment periods on all of these measures [$t(20) = -7.51$ to $-2.19$, $p < .001$ to $< .05$]. Furthermore, many of the improvements persisted over the 3 months following active treatment. Specifically, the number of drinking days, the intensity of drinking, the number of heavy drinking days, and ASI alcohol score remained significantly decreased from pretreatment levels [$t(17) = -6.65$ to $-2.72$, $p < .001$ to $< .015$]. Among the 16 subjects with posttreatment GGTP levels, there was a nonsignificant trend for posttreatment levels to be lower than baseline levels [49.1 ($SD$ = 42.4) vs. 41.2 ($SD$ = 29.2), $t(15) = -1.79$, $p = 0.094$]. At follow-up, desire to drink did not differ from baseline levels [$t(17) = -1.52$, $p = 0.15$].

An examination of the relation between the decrease in these measures from pretreatment to treatment endpoint and the number of naltrexone capsules taken by subjects

Table 1. Alcohol-related measures (Mean ± $SD$) during pretreatment, treatment, and posttreatment periods

| | Pretreatment ($N$ = 21) | Treatment ($N$ = 21) | Posttreatment ($N$ = 18) |
|---|---|---|---|
| Days drinking[a] | 22.6 (8.0) | 11.0 (8.8)*** | 15.0 (11.4)** |
| Drinks/Drinking day[a] | 4.9 (2.4) | 2.5 (1.8)*** | 3.1 (2.5)* |
| Heavy drinking days[b] | 7.5 (10.2) | 0.7 (1.5)** | 2.7 (7.4)* |
| Craving score[c] | 23.0 (19.1) | 12.4 (10.0)* | 18.1 (17.2) |
| GGTP level[d] | 42.9 (38.5) | 34.3 (28.7)* | 41.2 (29.2)[†] |
| ASI[e] alcohol score | 0.58 (0.12) | 0.24 (0.20)*** | 0.27 (0.21)*** |

[a]During the preceding 30-day period.
[b]≥six or more drinks per day.
[c]Modified from Bohn et al. (1995).
[d]Gamma-glutamyltranspeptidase.
[e]Addiction Severity Index (McLellan et al., 1992).
Difference from Pretreatment (paired $t$-test, two-tailed):
[†]$p < .10$ ($n$ = 16).
*$p < .05$.
**$p < .01$.
***$p < .001$.

showed that the number of heavy drinking days ($n = 19$, rho = $-.47$, $p = .044$) and intensity of drinking ($n = 19$, rho = $-.47$, $p = .041$) were both negatively correlated with naltrexone use. The correlation of other change scores with the number of capsules consumed was not significant ($p \geq .14$ for all).

## DISCUSSION

In this study, subjects who received brief skills training, combined with targeted use of naltrexone for 4 weeks, showed clinically significant reductions in drinking from pretreatment levels. The magnitude of these reductions is comparable to those observed by Bohn et al. (1994), who treated early problem drinkers for 6 weeks with brief counseling and daily naltrexone. The large reduction in heavy drinking in these studies is consistent with the results of controlled trials of naltrexone in alcoholics (O'Malley et al. 1992; Volpicelli et al., 1992). In the present study, the reductions in heavy drinking were significantly correlated with the number of capsules that subjects took during treatment and may reflect efficacy of the targeted approach to naltrexone administration. However, a placebo control is necessary to test the alternative interpretation that medication use reflected motivation to reduce drinking.

In a large-scale study of interventions with early-problem drinkers, Wallace, Cutler, & Haines (1988) found that patients receiving 1 to 3 sessions of practitioner advice to reduce their drinking showed a decrease in weekly alcohol consumption of approximately 26%, a change that was measured at 6 months after baseline assessment. In the present study, total alcohol consumption declined 74% during the active treatment period and 49.6% during the 3-month posttreatment follow-up. The greater reduction in drinking in the present study suggests that there may have been an effect of naltrexone to reduce drinking in addition to that attributable to brief counseling.

In summary, a number of studies of early problem drinkers have shown significant reductions in drinking as a consequence of brief interventions (Babor, 1994; Bien et al., 1993). However, these effects are generally of a smaller magnitude than those observed when naltrexone is used in conjunction with brief counseling. Further, the correlation observed in the present study between the number of naltrexone capsules taken by subjects and the reductions observed during treatment suggests that the addition of medication to brief skills training may have enhanced the effect of counseling. Together with the findings reported by Bohn et al. (1994), the findings reported here suggest that naltrexone reduces drinking among early problem drinkers whether it is administered daily or is used on a targeted (i.e., "as-needed") basis to reduce the risk of heavy drinking. A placebo-controlled comparison of these approaches appears warranted.

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