TITLE: Naltrexone for the Treatment of Alcohol Dependence in Individuals with Co-Dependencies: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES:

Poly-drug abuse is common with 55% of individuals admitted for substance abuse treatment in the US reporting abuse of more than one substance.¹ It is associated with an increased risk of adverse effects, medical complications, overdose and death.¹ Treatment of patients with co-dependencies may be more difficult. Concurrent cocaine and alcohol abuse is a strong predictor of relapse and treatment failure.¹

This report reviews the clinical evidence on the use of naltrexone for patients with alcohol and other concurrent drug dependencies.

RESEARCH QUESTION:

What is the clinical effectiveness of naltrexone when used to treat alcohol dependence in individuals with co-dependencies?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID MedLine and OVID Embase, The Cochrane Library (Issue 3, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and September 2009. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), controlled clinical trials, and observational studies. Reference lists of articles were handsearched.
SUMMARY OF FINDINGS:

Two RCTs were identified in the literature search. Two other relevant trials were found that fell outside of the literature search dates. These are listed in the appendix. No health technology assessments, systematic reviews, controlled clinical trials, or observational studies were found that met the inclusion criteria.

Randomized controlled trials

The double blind RCT by Schmitz et al.\(^2\) enrolled 80 patients who met the DSM-IV criteria for dependence on cocaine and alcohol. The study excluded patients with other drug dependencies (except nicotine or cannabis) and those with serious medical conditions or liver disease. After an initial abstinence from cocaine (defined as three concurrent cocaine-negative urine tests over a 10 day period), patients were randomized to one of four treatment groups: naltrexone 50 mg per day plus relapse prevention psychotherapy; naltrexone 50 mg per day plus standard drug counseling; placebo plus relapse prevention psychotherapy; or placebo plus standard drug counseling. Treatment duration was 12 weeks and included 20 individual one-hour therapy sessions.\(^2\)

The average age of participants was 36 years.\(^2\) The majority were male (84%), African American (61%), and unemployed (59%). Life-time use averaged 10.3 years for cocaine and 18.5 years for alcohol. The average number of days of drug use in the past 30 days was 14.6 days for cocaine and 17.9 days for alcohol.\(^2\)

Twenty five participants (33%) completed 12 weeks of treatment.\(^2\) The mean number of therapy sessions attended was 10.3. Retention was similar between groups. Medication compliance was higher in the naltrexone groups (93%) versus the placebo groups (83%, p<0.04). The number of adverse effects reported per week was similar between the naltrexone and placebo groups. The most common adverse effects were headache and nausea.

In the first four weeks the number of cocaine positive urine tests was statistically significantly lower in the patients receiving relapse prevention therapy compared to standard counseling. No other medication or therapy effects were found for cocaine use. No statistically significant medication or therapy effects were noted on the number of drinking days or mean number of drinks per drinking day. The authors concluded that naltrexone 50 mg per day did not reduce cocaine or alcohol use.\(^2\)

The double blind RCT by Pettinati et al.\(^3\) enrolled 164 treatment-seeking patients with dependence on cocaine and alcohol (according to the DSM-IV criteria). Patients were excluded if they had other drug dependencies, serious medical conditions, liver disease, psychiatric symptoms, or were receiving psychiatric medications or opiates. Randomization was stratified by gender so the gender specific treatment effects could be analyzed. Patients were required to abstain from alcohol for three days and have a negative urine drug screen prior to randomization. Patients were randomized to one of four treatment groups: naltrexone 150 mg per day plus traditional cognitive behavioural therapy (CBT); naltrexone 150 mg per day plus low-intensity medical management (known as BRENDA); placebo plus traditional CBT; or placebo plus BRENDA. Treatment duration was 12 weeks. Doses of naltrexone or placebo were titrated up from 50 mg per day to 150 mg per day every three days as tolerated by the
individual. Compliance was monitored with pill counts and patient self-reports. CBT included weekly 45 minute sessions. Weekly sessions with BRENDA were 30 minutes in duration.\(^3\) The average age of participants was 39 years.\(^3\) The majority were male (71%), African American (76%), employed (71%), and of lower socioeconomic status (61%). Participants had used cocaine, on average, for 12.2 years and alcohol for 19.7 years. The average number of days of drug use (in past 30 days) was 12.5 days for cocaine and 17.1 days for alcohol. Patients were similar between treatment groups, however, males reported more years of alcohol abuse, and females had higher cocaine severity scores at baseline. Sixty-four percent of participants completed the 12 week study. Treatment retention was not statistically significantly different between treatment groups or between men and women.\(^3\)

The odds of cocaine use (as measured by positive urine test) increased over time in all four treatment groups.\(^3\) For all groups this increase in use was statistically significant (p<0.001). The authors reported that this observation was not unexpected in a study where abstinence was required for enrollment. Between group differences were not statistically significant except for one comparison. The rate of increase in cocaine use was significantly greater for females treated with naltrexone than in placebo treated males (p=0.03). Males treated with naltrexone were 1.7 times less likely to self-report cocaine use than placebo treated males (p=0.05). Conversely, naltrexone treated females were 2.4 times more likely to report cocaine use than placebo treated females (p=0.05).\(^3\)

Similar increases in alcohol use over time were reported as with cocaine use. No statistically significant medication, therapy, or gender effects were detected for alcohol use.\(^3\)

Adverse effects ranged from mild to severe. Overall, the most frequently reported adverse events were headache (62%), anxiety (61%), and nausea (40%). No patients died during the study and two patients left the study to receive inpatient substance abuse treatment.\(^3\)

The study’s authors concluded that 150 mg per day of naltrexone combined with psychosocial treatment reduced cocaine and alcohol use in men relative to the high rates observed in women. It should be noted that these differences were not statistically significantly different from placebo. The authors also concluded that the type of psychosocial treatment did not affect outcomes.\(^3\)

**Limitations**

Reporting in both studies was of similar quality. Neither report stated the methods used to randomize patients or to conceal their treatment allocation. The study by Pettinati was designed to explore the gender differences in treatment effects. Due to the overall sample size and the small number of women, the study had low power to detect differences between groups.\(^3\) The study by Schmitz also had limited power to detect differences between groups due to small sample size (20 patients per group).\(^2\)

The statistical analysis followed methods used in the social sciences which may not be of the same standard that is expected in the medical literature.
Both studies examined the use of naltrexone as part of an outpatient drug treatment program for patients with cocaine and alcohol dependence. No studies were identified for any other co-dependencies or any other treatment setting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Limited evidence was identified on the use of naltrexone for patients with co-dependencies. Two RCTs were identified, but no clear benefit was detected for naltrexone combined with psychotherapy versus placebo when used in short-term outpatient treatment of cocaine and alcohol dependence. No studies were identified for patients with other drug co-dependencies. The limited available information may be a consideration for decisions about the use of naltrexone for this patient population.

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APPENDIX: Other studies of interest outside the literature search dates
