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The Efficacy of Antabuse, Campral, and Naltrexone in Treating Alcohol Use Disorders with Special Attention to the Sinclair Method and Medication Management

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ABSTRACT

A review of the relevant literature was conducted to determine the relative efficacy of Antabuse (disulfiram), Campral (acamprosate), and naltrexone (Revia) in the treatment of Alcohol Use Disorders (AUDs). It was found that medication compliance with Antabuse--whether oral or implanted--is so poor that some researchers consider it to be completely ineffective. Campral has shown a small effect in treating AUDs in several European studies, but this was not replicated in American studies on Campral. Project COMBINE showed that Medication Management has a large significant effect in reducing heavy drinking and increasing abstinence days even when the medication is a placebo. Project COMBINE showed a small effect for the efficacy of naltrexone over a placebo. Research conducted by Sinclair in Finland shows that naltrexone has a large significant effect when clients are told to take naltrexone only before drinking alcohol, but that naltrexone has no positive effect and may have a negative effect if clients are told to abstain and to take naltrexone daily. Currently American physicians are told to prescribe naltrexone only to people who abstain and are told that naltrexone is to be taken daily. The Sinclair data suggests that prescribing information which American physicians receive concerning naltrexone should be revised to reflect Sinclair's research.

1) Disulfiram (brand name Antabuse)

O'Brien and McKay (2002) and Hughes and Cook (1997) both report that neither oral nor implanted disulfiram produce better results than placebo because of extremely poor medication compliance. Garbutt (2009) reports noncompliance rates of up to 80% with Antabuse. However, he also notes that Antabuse can be effective when used with Community Reinforcement Approaches which increase medication compliance--for example when the disulfiram is administered by a spouse.

2) Acamprosate (brand name Campral)

Garbutt (2009) reports that 20 European studies found that acamprosate had an effect on treatment outcome for AUDs but that the 2 large experiments conducted in the US on the use of acamprosate for AUDs did not show an effect. This discrepancy seems to be due to the fact that the US studies used different measures for determining efficacy or applied them at different times than did the European studies. Paille et al (1995) and Whitworth et al (1996) are representative of the European studies. Paille et al (1995) found the number of abstinence days significant at 6 months ($p \leq 0.02$) but not significant at 12 months ($p = 0.096$) ($n = 538$). Whitworth et al (1996) found a statistically significant difference between the number of subjects taking acamprosate versus those taking a placebo. 41 subjects taking acamprosate ($n = 224$) had

maintained continuous abstinence at day 360 as opposed to 16 subjects taking a placebo (n = 224) (p = 0.007).

The two US studies were Anton et al's (2006) Project COMBINE (acamprosate (n = 608), placebo (n = 618)) and Mason, Goodman, Chabac and Leher (2006) (placebo (n = 260), acamprosate 2 g (n = 258), acamprosate 3 g (n = 83)).

The subjects of the Anton et al (2006) study were given 9 sessions of Medication Management over the course of 16 weeks. Assessments were conducted at each session of Medication Management regardless of whether the subject received medication or placebo/ Additional assessments were conducted at weeks 26, 52, and 68 weeks post-randomization (one year post-treatment). Assessment measures were number of days to first heavy drinking day and percent of days abstinent; no significant differences were found between placebo and acamprosate. Anton et al (2006) also studied the effects of naltrexone versus placebo and found a significant effect of naltrexone on these measures.

Mason et al (2006) measured percent of abstinence days at 24 weeks; no significant difference for general pool of subjects, however a significant effect of acamprosate was found post hoc with subjects motivated for abstinence.

3) Medication Management

All groups in Project COMBINE (Anton et al (2006)) who received pills and Medication Management showed significant reduction in drinking and increased percentage of abstinence days. Percent days abstinent from baseline to end of study tripled from 25.2 to 73.1 (P<.001), and drinks per drinking day declined by 44%, from 12.6 to 7.1 (P<.03), with the net effect that alcohol consumption decreased by 80%, from 66 to 13 drinks per week. One standard drink = 0.5 oz ethanol. Placebo plus medication management showed a highly significant effect in reducing number of drinks per week and increasing percentage of abstinence days.

4) The Opioid Antagonists Naltrexone, Naloxone, and Nalmefene and the Sinclair Method

Table 1 summarizes the properties of the common opioid antagonists. Naltrexone is the only opioid antagonist commonly used to treat AUD in humans. Nalmefene is commonly used in animal experiments on AUD. Naloxone is unsuitable for treating AUD because of its short half life and because it must be given by injection.

TABLE 1 Opioid Antagonists			
Name	Naltrexone	Naloxone	Nalmefene
Brand Name	Revia	Narcan	Revex
Rte of Admin	Oral	Injection	Oral or Injection
Use	Opiate Tx and Alcohol Tx	Opiate OD	Opiate Tx and Opiate OD and Alcohol Tx
FDA Approved	1984 Opiate Tx 1994 Alcohol Tx	1971	1995 Discontinued
Receptor(s)	Mu, Kappa, (Delta)	Mu	Mu, Kappa, Delta
Hepatotoxicity	Medium	Medium	Low
Half-life	4 hours 6-beta-naltrexol 13 hours	1 hour	11 hours

Heinälä et al (2001), Sinclair (2001) and Eskapa (2008) all describe how naltrexone can be used for the Pharmacological Extinction of AUDs--also known as "The Sinclair Method". The Sinclair Method assumes that alcohol addiction is an example of operant conditioning. When a person drinks alcohol, endorphins are released and reinforce the drinking behavior. Drinking is learned behavior. Operant conditioning is normally a good thing because it helps people to learn new behaviors needed for survival. However, in the case of alcohol addiction it leads people to learn a maladaptive behavior

In Pharmacological Extinction, clients take naltrexone one hour before drinking alcohol. The endorphins are still released, but they cannot bind to the mu receptors because these receptors are blocked by the naltrexone. There is no reinforcement for the drinking behavior. In the absence of reinforcement, the drinking behavior becomes extinguished. Naltrexone is to be taken only before drinking and never otherwise. Taking it at other times could lead to the extinction of desirable behaviors. Naltrexone is to be taken before drinking by persons with AUDs for life.

Figure 1 shows the results of Pharmacological Extinction with human subjects. Subjects started at a baseline of 37 standard drinks per week and after 450 days of naltrexone treatment their consumption dropped to an average of 9 standard drinks per week. One standard drink = 0.5 oz ethanol. Figure 2 shows the extinction of craving rated on a scale of 0 to 10.

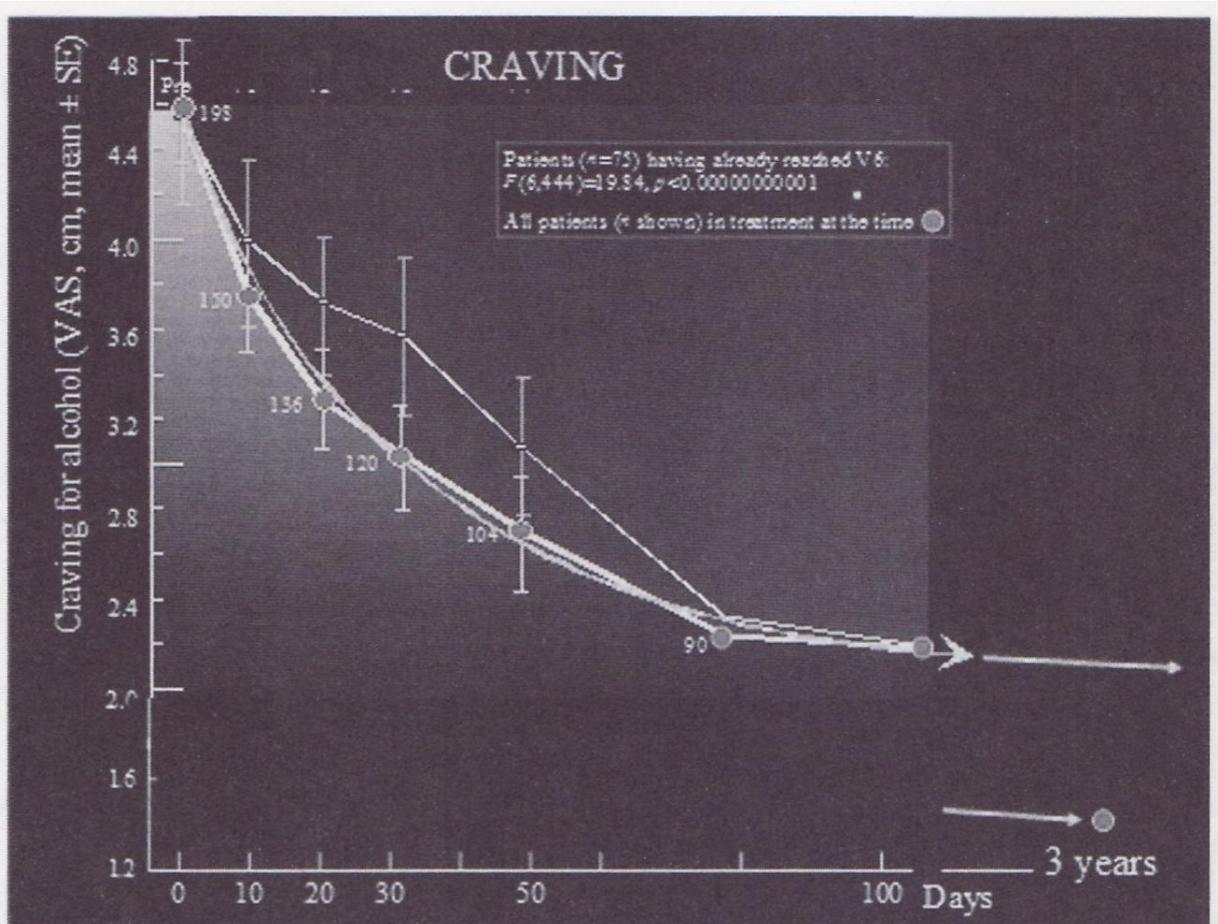


Figure 2) Extinction of Craving in Human Subjects Treated with Naltrexone via the Sinclair Method (from Eskapa 2008). The top line represents the data from the first 75 subjects treated with the Sinclair Method.

Figure 3 shows that naltrexone is only effective when used with controlled drinking and that it is not effective when used with abstinence.

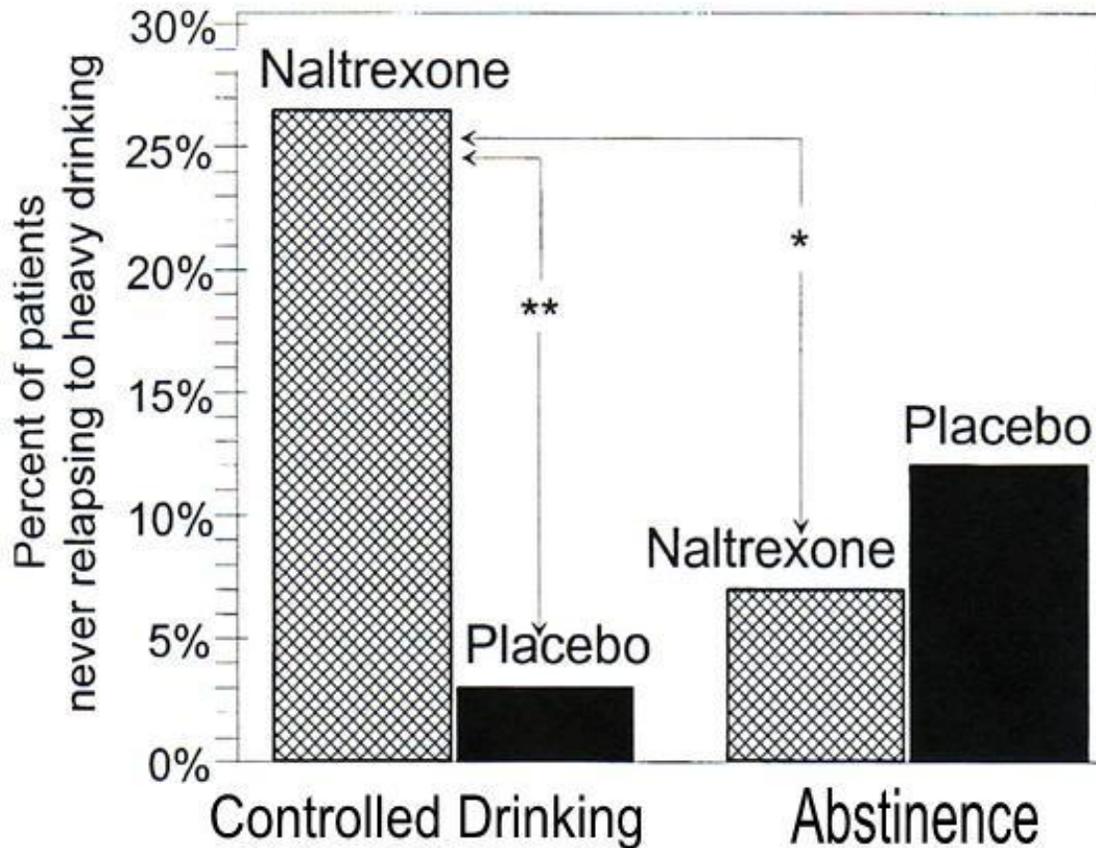


Figure 3) A 32 week study of relapses to heavy drinking

****p = 0.008, *p = 0.041 (Fisher exact test)**

Heavy drinking is defined as 5 or more standard drinks per day. (adapted from Heinälä et al 2001)

Figure 4 shows that opioid antagonists affect the actual behavior of drinking alcohol in rats. That opioid antagonists do not cause a devaluation of alcohol itself is demonstrated by the fact that nalmefene given together with alcohol which is injected or introduced into the stomach via a tube does not decrease alcohol drinking behavior in rats when these rats are again presented with an opportunity to drink. Only the combination of naltrexone and actually drinking the alcohol leads to the extinction of the drinking behavior.

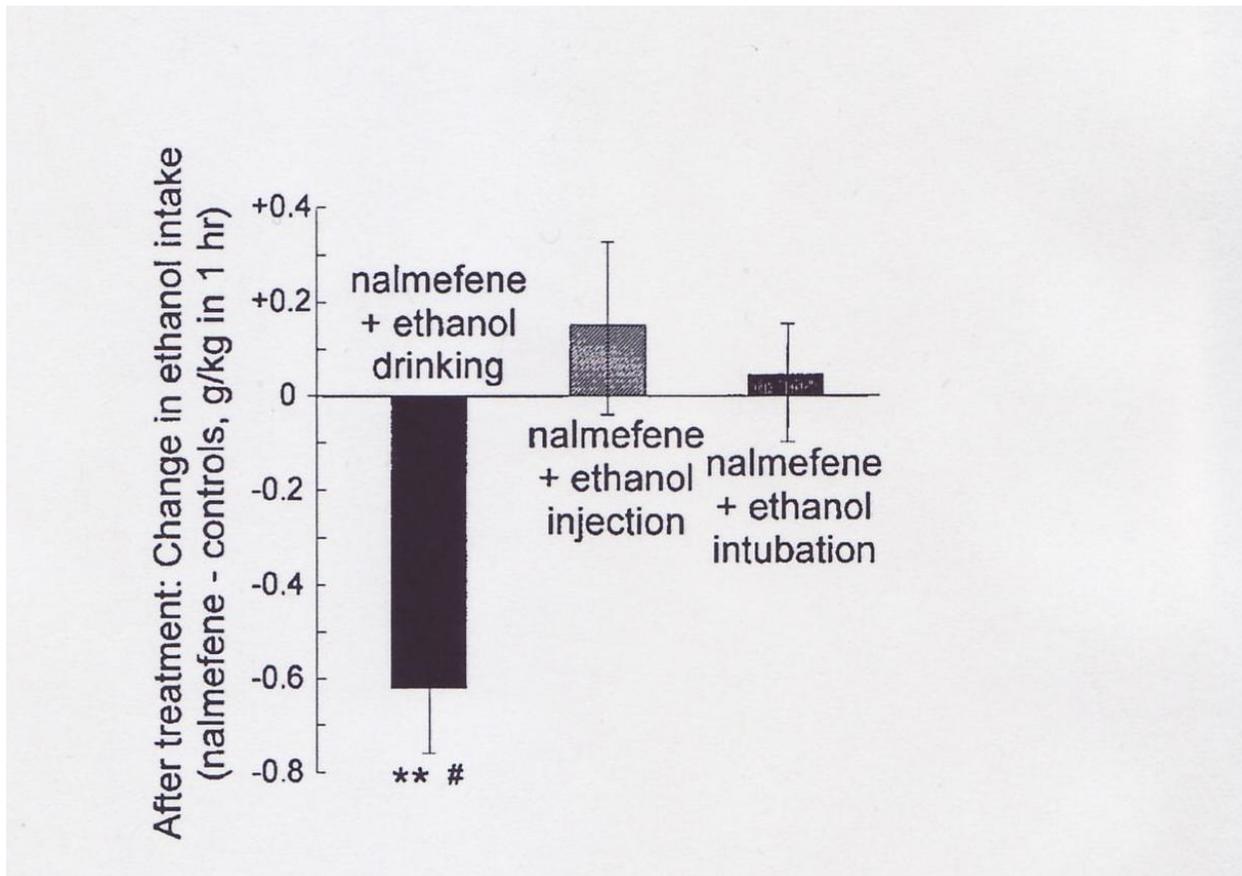


Figure 4) Opioid antagonists lead to extinction of drinking behavior not devaluation of alcohol. (from Sinclair 2001) ($t[10] = 4.11$, $p = 0.002$)**

Figure 5 shows the extinction of drinking behavior in rats treated with the opioid antagonist nalmefene over a period of five days. This also shows a statistically significant increase in drinking behavior in two post-treatment drinking sessions following the discontinuation of the nalmefene. This leads to the conclusion that in humans with AUDs naltrexone should always be taken before drinking for life.

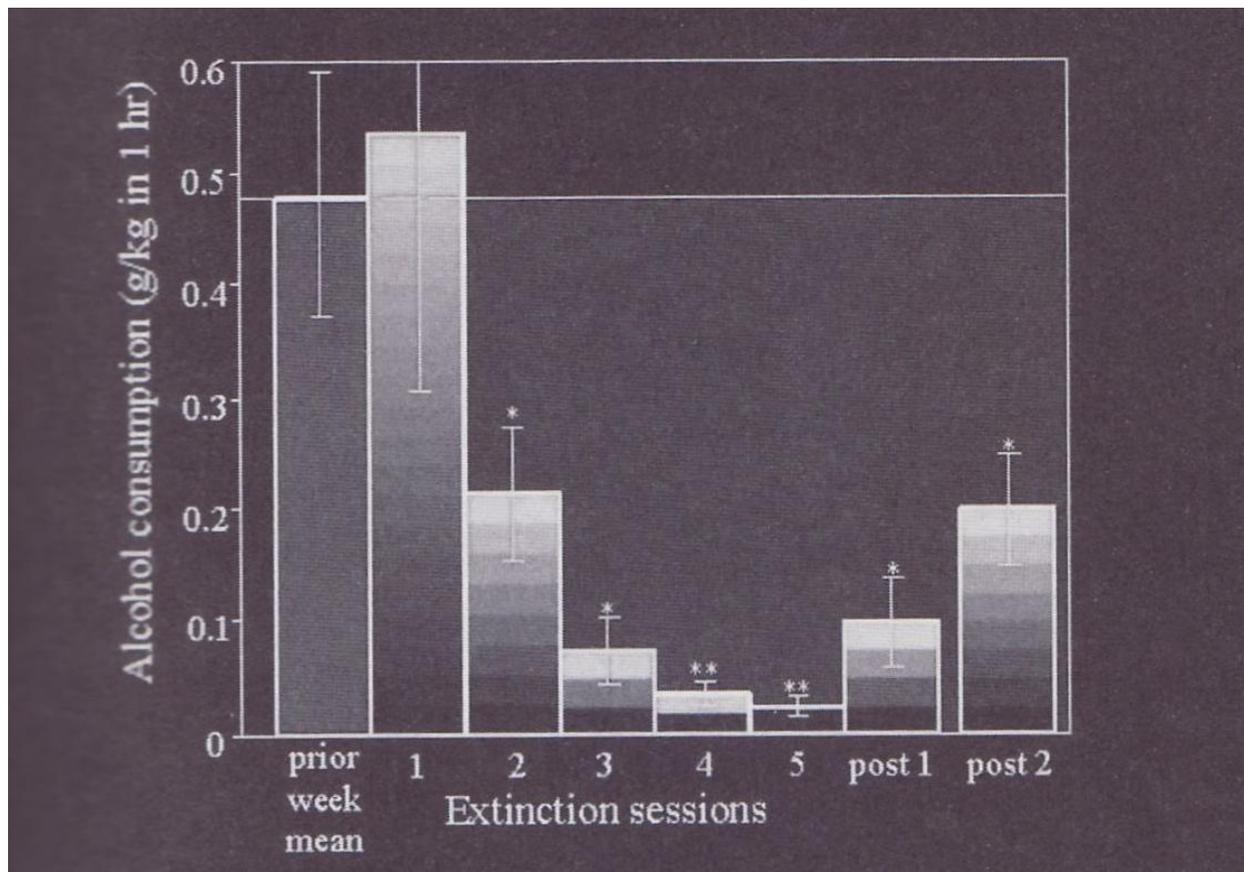


Figure 5) Extinction of drinking in rats treated with nalmefene and post-treatment sessions

***p < 0.05; **p < 0.01**

5) Problems with the Sinclair Method

The Sinclair method was successful with around 80% of subjects. About 10% were not medication compliant. Naltrexone was also ineffective for about 10% of subjects. It is hypothesized that this may be due to a gene for craving sweets or a peculiar form of the opioid receptor (Eskapa, 2008, p.51).

6) Conclusion

The literature reviewed shows us that two highly effective means of reducing alcohol use in subjects are naltrexone used according to the Sinclair Method and Medication Management whether accompanied by medication or a placebo. When reduced drinking rather than total abstinence is used as a measure of effect size then both of these methods show very large effects. A change in labeling of naltrexone is called for so that MDs will no longer mistakenly require patients to abstain when taking it--which can actually negate its effect.

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