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INVITED REVIEW

EVIDENCE ABOUT THE USE OF NALTREXONE AND FOR DIFFERENT WAYS OF USING IT IN THE TREATMENT OF ALCOHOLISM

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Abstract — Eight double-blind placebo-controlled clinical trials in five countries have demonstrated the safety and efficacy of naltrexone as an adjunct in alcoholism treatment. The efficacy depends, however, on how naltrexone is used. Three of the trials tested naltrexone in two ways: (1) with supportive therapy, i.e. support of complete abstinence; (2) with therapy tacitly accepting that relapses may occur and teaching how to cope with them. Although all found benefits from naltrexone with the coping therapy, none of them found any significant benefit of naltrexone over placebo when combined with support for abstinence. These results are consistent with our pre-clinical studies in which naltrexone, naloxone, and nalmefene were effective when paired with drinking but ineffective when given during abstinence. This supported the hypothesis that the primary mechanism involved is extinction (as had been concluded earlier for the effects of naltrexone in opiate addiction treatment), because extinction only weakens responses that are made while reinforcement is blocked. On this basis, it was proposed that: (1) naltrexone should be administered to patients who were still currently drinking; (2) the instructions should be to take naltrexone only when drinking was anticipated; (3) this treatment should continue indefinitely. Subsequently, clinical trials have found that naltrexone used in this manner is safe and effective.

INTRODUCTION

There is general agreement that alcoholism treatment should be based on scientific evidence. The present article reviews the evidence and conclusions about the use of naltrexone: first the evidence about naltrexone in general, then about two opposing ways of using it, and finally about specific features in the protocol.

Pre-clinical studies have shown that naltrexone and other antagonists decreased the animals' alcohol drinking and operant responding for it (e.g. Altshuler *et al*., 1980; Sinden *et al*., 1983; Sinclair, 1989, 1990, 1995, 1996*a*; Kornet *et al*., 1990, 1991; Hyytiä and Sinclair, 1993; Cunningham *et al*., 1994; Kelley-Poole and George, 1994; Sinclair *et al*., 1994; Myers and Lankford, 1996; Davidson and Amit, 1996; Cowen *et al*., 1999; Heyser *et al*., 1999; Holter and Spanagel, 1999; Hyytiä *et al*., 1999; June *et al*., 1999; Overstreet *et al*., 1999; Williams and Woods, 1999).

A double-blind, placebo-controlled (DBPC) trial by Volpicelli *et al*. (1990, 1992) first showed clinically that naltrexone reduced alcohol drinking and especially the relapsing to heavy drinking. It was replicated by O'Malley *et al*. (1990, 1992). A meta-analysis showed the naltrexone plus coping procedure in the latter study to be better at reducing drinking than all other treatments (Agosti, 1995).

First, the American Food and Drug Administration in 1994 and then similar boards in many other countries have approved naltrexone for use within comprehensive alcoholism treatment programmes. The safety of naltrexone was established from the thousands of patients treated with naltrexone for other indications, mainly opiate overdose and addiction, and by several hundred patients treated for alcoholism with naltrexone in open-label trials (Croop *et al*., 1997).

Following the first two clinical trials, there have been six more DBPC clinical trials with naltrexone with positive results: in the UK (Chick in Litten *et al*., 1996); Maryland (McCaul *et al*., 1997), Sweden (Balldin *et al*., 1997; Månsson *et al*., 1999*a*,*b*), South Carolina (Anton, 1999; Anton *et al*., 1999), Finland (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*), and Australia (Morris *et al*., 1999). There also has been a DBPC trial showing the safety and efficacy of nalmefene (Mason *et al*., 1994, 1999).

A World Health Organization (1996) publication concluded that naltrexone was a 'safe and effective treatment for alcohol dependence'. The Agency for Health Care Policy and Research (AHCPR), reviewing the scientific evidence for different pharmaceuticals in treating alcoholism (Garbutt *et al*., 1999; on the Internet at http://www.ahcpr.gov/clinic/alcosumm.htm), supported both naltrexone and acamprosate, but with the evidence for naltrexone being somewhat better. Disulfiram got a moderate rating, and other medicines were given poor ratings for the extent to which their use in alcoholism treatment is justified by the scientific evidence.

In summary, the use of naltrexone in the treatment of alcoholism is well supported by the scientific evidence and accepted by many regulatory agencies. Indeed, there probably is stronger scientific evidence supporting the use of naltrexone than for using any other medication, and probably more conclusive scientific evidence for it than for any other alcoholism treatment of any kind.

MAINTAINING ABSTINENCE OR EXTINGUISHING DRINKING

Although the scientific evidence shows that naltrexone can be effective, it also shows that the efficacy is highly dependent upon the method with which the medicine is used. The clinical results are consistent with what we found in preclinical studies over a decade ago (Sinclair, 1996*a*, 1998*a*), and together present a clear indication about how naltrexone should be used.

Pre-clinical results

We found that opioid antagonists (naloxone, nalmefene, and naltrexone) had to be given in conjunction with alcohol drinking to produce positive results. The animals had to drink alcohol while the opioid receptors were blocked. This progressively decreased drinking and lever pressing for alcohol; furthermore, the benefits persisted after the medicine was gone (Sinclair, 1989, 1990). In contrast, giving naltrexone, naloxone, or nalmefene during abstinence was not useful: it did not reduce subsequent drinking but instead tended to increase it (Sinclair, 1989, 1990; Sinclair *et al*., 1992; Sinclair and Jääskeläinen, 1995).

The dependence upon getting alcohol while on naltrexone is logical, and clear even from the initial DuPont product announcement (Clintron, 1995): 'How does ReVia™ work? It is believed that alcohol causes the release of endogenous opioids. The binding of these opioids to the receptors in the brain may be responsible for the positive reinforcing effects of alcohol. ReVia™, an opioid receptor antagonist, competitively binds to these receptors, blocking the endogenous opioids at these sites.' If there is no alcohol, then there is no alcohol-induced release of endogenous opioids for naltrexone to block, and naltrexone should not work in treatment.

My own hypothesis was more specific (Sinclair, 1989, 1990). My research had already suggested that the binding of the opioids might cause the reinforcement from alcohol (Sinclair *et al*., 1973). Drinking alcohol while an opioid antagonist blocked the reinforcement from ethanol should extinguish alcohol drinking and craving (Sinclair, 1989, 1990).

A similar hypothesis had been proposed for the use of opioid antagonists against opiate addiction (Wikler, 1976), and was supported by pre-clinical (Davis and Smith, 1974) and clinical (Renault, 1980) results. There is also evidence that extinction is the basis for the ability of the antagonists to suppress intracranial self-stimulation (Kelsey *et al*., 1984; Trujillo *et al*., 1989)

We have attempted to test the extinction hypothesis against all other explanations we or others could imagine. For example, at a visit with Volpicelli's group, they suggested that the primary mechanism for the benefits might be devaluation. They suggested an experiment that would distinguish extinction from devaluation. An essential requirement for extinction is that the response be emitted (in the present case, alcohol must be drunk by the rats) while reinforcement is blocked. In contrast, devaluation would be caused also by pairing naltrexone or nalmefene with injected or intubated ethanol. The results of this experiment are shown here. The rats that actively drank alcohol while on nalmefene all decreased their drinking over the four treatment days (Fig. 1), and they continued to drink less alcohol than saline controls on the first post-treatment day (Fig. 2). The rats injected or intubated with the same quantities of alcohol while on nalmefene during the treatment days, however, tended on the post-treatment day to drink more alcohol than their saline controls. Thus, the results are contrary to devaluation, but consistent with extinction.

Implications from pre-clinical studies for clinical treatment

These results and those from several dozen other pre-clinical studies provide strong evidence that the major benefits from naltrexone are produced by the mechanism of extinction (for reviews, see Sinclair, 1987, 1990, 1998*a*). It should be noted

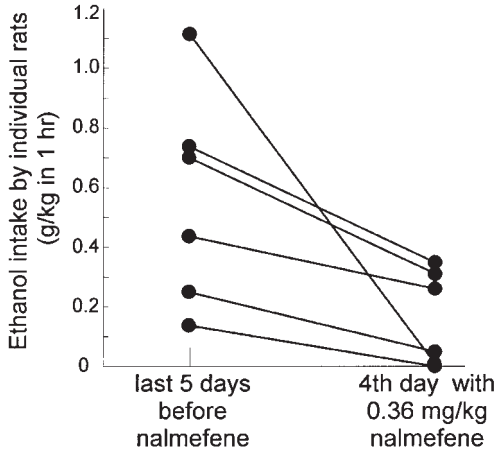

Fig. 1. Reduction of rats' alcohol drinking by nalmefene.

Shown are the individual intakes by six male Wistar rats having access to 10% ethanol solution 1 h daily before nalmefene treatment (mean 4 days) and their intakes on the fourth day of receiving a subcutaneous injection of nalmefene (0.36 mg/kg) 20 min before the beginning of alcohol access hour. Food and water were available at all times. The rats had had 42 days of continual access and 12 days of limited access to alcohol prior to the experiment. Nalmefene reduced the alcohol drinking of every rat and significantly reduced that by the group ($t[5] = 2.70$, $P = 0.04$).

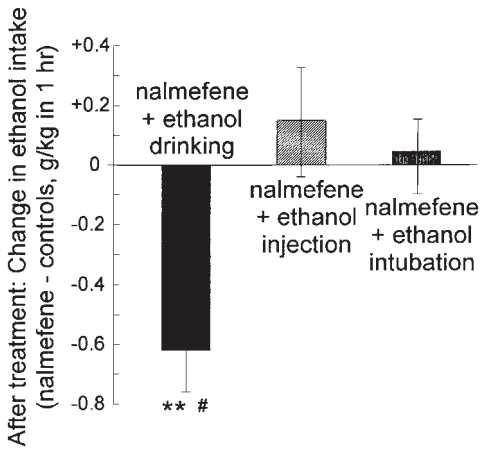

Fig. 2. Post-treatment suppression of alcohol intake occurring only when nalmefene had been paired with alcohol drinking.

The first bar shows the continued suppression in the same rats shown in Fig. 1 on the first day after the 4 days of nalmefene treatment plus alcohol drinking, minus the intake by six matched control rats that received saline injections (**$t[10] = 4.11$, $P = 0.002$). In contrast, littermates given nalmefene and then injected intraperitoneally with the same amounts of alcohol as those consumed voluntarily (middle bar, $n = 6$) or intubated by stomach tube with the same amounts (right bar, $n = 6$) did not show any suppression; instead they tended to drink more alcohol on the first post-treatment day than did their controls given saline and then injected or intubated with the alcohol. The intake by the rats that had previously had nalmefene paired with ethanol drinking was significantly lower than that by the rats having nalmefene paired with ethanol injection (#$t[10] = 2.30$, $P = 0.04$).

that the antagonists probably produce other relevant effects: blocking of the stimulatory effect from ethanol (Kiianmaa *et al*., 1983) may remove an important stimulus involved in the first drink phenomenon; changing the stimuli from those to which alcohol drinking had been learned; causing upregulation of opioid receptors (Pert *et al*., 1973; Zukin *et al*., 1982). The latter is probably detrimental and may be the reason why the rats given antagonists without the opportunity to drink alcohol tend subsequently to drink more alcohol than saline controls.

Conditioned cue extinction hypothetically is one way in which naltrexone might have been beneficial during abstinence. The release of endorphins supposedly becomes conditioned to cues present during alcohol drinking. Thus, naltrexone during abstinence could extinguish the ability of these cues to cause craving. The slightly better results here with intubated alcohol than injected alcohol may be explained by intubation providing the smell and taste of alcohol, i.e. cues that might trigger a conditioned release of endorphins. Although supporting the idea that conditioned cue extinction may exist, the results show that it alone (without extinction of the alcohol drinking) is a weak factor and not strong enough to produce a net positive result.

Proposal for clinical treatment

Previously, the only medications approved for use in the treatment of alcoholism have been alcohol-sensitizing drugs such as disulfiram. They are generally given after detoxification, with the goal of preventing relapse to drinking.

The hypothesis from our animal studies — that opioid antagonists could extinguish alcohol drinking — suggested that naltrexone should be given in a different way and with a different goal. Naltrexone should be given in a way that allowed extinction: 'repeatedly administering to a subject suffering from alcoholism an opiate antagonist' and while it is active 'having the subject drink an alcoholic beverage' (Sinclair, 1989). Commercially, this has been called the 'Sinclair Method'. The technical term is 'pharmacological extinction' (Clarke, 1991; Sinclair, 1996*b*, 1998*c*). It should be noted that the method is pragmatic, rather than theoretical. Giving naltrexone (or naloxone or nalmefene) and then having alcohol drunk is the method that was effective in our rats, regardless of whether the benefits were caused by extinction or not.

According to my proposal, naltrexone should be given to patients who are currently drinking. The purpose for giving naltrexone should be to reduce craving and drinking progressively down to low levels (or on to abstinence if the patient so chooses).

Pharmacological extinction had been clinically demonstrated many years ago in a test of naltrexone for treating opiate addiction (Renault, 1980). A multicentre DBPC study organized by the National Institute of Drug Abuse (NIDA) gave naltrexone or placebo to 1005 patients, with instructions to abstain for opiates. Overall, there were no significant benefits from naltrexone. A small subgroup of patients, however, disobeyed instructions; they took opiates while on medication, and among them there were several significant results favouring naltrexone over placebo. It was concluded that the primary mechanism for naltrexone was extinction. Extinction requires that the patient make the drug-taking response while reinforcement is blocked. Thus, naltrexone only worked well in those patients making the response of taking heroin or methadone while on the medication.

Clinical results with alcoholism

Most earlier DBPC clinical trials detoxified alcoholics before giving them medication. As Mason *et al*. (1994) pointed out, this provides a test of extinction and of whether the antagonists have to be paired with drinking. If the antagonists are effective during abstinence, for example, directly reducing craving, then patients receiving the active medication should be better able to resist alcohol and will take longer before sampling alcohol again than the placebo patients. On the other hand, if the primary benefits from the antagonists are from extinction, or other mechanisms that work only when paired with drinking, there should be no significant difference between groups in the time to relapsing and taking the first drink again.

The latter had already been shown to be true in the first clinical trial of naltrexone for alcoholism (Volpicelli *et al*., 1990, 1992). No significant benefit from naltrexone was found while the patients remained abstinent. In particular, it was no better than placebo in delaying the first sampling of alcohol again. Instead, the authors concluded, 'The primary effect of naltrexone was seen in patients who drank any alcohol while attending outpatient treatment' (p. 876).

Since then, five subsequent DBPC studies of naltrexone (O'Malley *et al*., 1990, 1992, 1996; Chick in Litten *et al*., 1996; Balldin *et al*., 1997; Anton *et al*., 1999) and nalmefene (Mason *et al*., 1994) have obtained the same general result favouring pharmacological extinction. All of the studies have found significant benefits of naltrexone or nalmefene over placebo when the patients drank while on the medication. None of these studies found a significant effect from the antagonist during abstinence in delaying the first drink different from placebo. The only partial exception is a newer trial by Volpicelli *et al*. (1997). When all of the data were used in the analysis, naltrexone was significantly better than placebo only after sampling had begun. When non-complying patients were eliminated, however, a small but significant benefit was found in delaying the first drink, thus suggesting that there may be another mechanism in addition to extinction helping to reduce drinking (or that some of the patients lied when they said they had been abstinent), but the more powerful effects occur when extinction is possible. (See Sinclair, 1998*b*, for a more thorough discussion of these data.)

Instructions to abstain

Two of these trials (O'Malley *et al*., 1992; Balldin *et al*., 1997) and the recent Finnish DBPC trial (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*) tested naltrexone vs placebo with two different types of therapy. In each, one pair of groups received cognitive therapy on how to cope with small relapses (Coping groups), thus in practice generally allowing the patients to drink some alcohol while on the medication (even if the eventual goal of the therapy was abstinence); the other pair were given strong support of complete abstinence, forbidding all drinking from the start (Supportive groups). As might be expected, the rate of complete abstinence was higher in the groups with Support of abstinence than in the ones taught to Cope with slips. This was, however, not beneficial in the long run.

Consistent results were obtained. All three trials found significant benefits of naltrexone over placebo in the Coping

groups (naltrexone plus drinking). None of them found significant benefits from naltrexone over placebo in the Supportive groups (i.e. naltrexone plus abstinence). Indeed, as in the pre-clinical studies, there was a non-significant tendency in the O'Malley *et al*. (1992) trial for naltrexone plus abstinence to increase craving. Also in the Finnish trial, the primary index — relapse to heavy drinking — showed naltrexone tending to be worse than placebo when both were combined with Support of abstinence (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*). In contrast, the benefit of naltrexone over placebo in the Coping groups was strong enough to reach a high level of significance ($P = 0.008$) in all of the material, without having to eliminate patients who did not comply or complete the study. Naltrexone with Coping therapy was also significantly better than naltrexone with Support of abstinence ($P = 0.041$).

Follow-up studies from both the Yale trial (O'Malley *et al*., 1996) and the Swedish trial (Månsson *et al*., 1999*a*,*b*) have both found continued post-treatment benefits of naltrexone over placebo in the Coping groups, but not in the Support of abstinence groups. This seems comparable to the continued post-treatment benefits shown here (Fig. 2) among rats that drank alcohol while on nalmefene.

It should be noted that discussion here of the Swedish trial is based upon the data presented in detailed published abstracts. Several important works in this field have not yet been published as articles. Therefore, in order to make this review more comprehensive, the rule followed in this review has been to cover all the available data; not only those published in papers, but also those in abstracts, plus our own unpublished results. The inclusion of this material that has not been subjected to peer review means that the conclusions derived therefrom must be seen more tentatively. Some trials (e.g. the German one) were not included because sufficient data for analysing them had not yet been published.

One other finding in the Finnish trial should be mentioned, namely that of the poorer results among the placebo patients in those given coping therapy than those given support of abstinence. Controlled drinking was a complete failure among the placebo patients. The best results of all, however, were obtained with controlled drinking plus naltrexone.

In conclusion, there is abundant evidence suggesting that the combination of naltrexone and drinking — thus allowing pharmacological extinction — is an effective tool in alcoholism treatment that eventually allows patients to regain better control over their alcohol consumption. In contrast, there is no pre-clinical evidence that naltrexone given only during abstinence is beneficial and no clinical evidence that naltrexone is significantly better than placebo when given with strong support of abstinence.

THREE SPECIFIC PROTOCOL FEATURES

Our pre-clinical studies, and the idea that the major benefits are produced by extinction, led to specific recommendations about how to use opioid antagonists. Some of them are radically different from the protocol used with disulfiram. The three most important and distinctive features are: (1) prior detoxification and abstinence is not required (Sinclair, 1989); (2) selective extinction: the antagonist is taken only when drinking is expected (Sinclair *et al*., 1992); (3) treatment continues indefinitely (Sinclair *et al*., 1992).

The advantages and scientific support for each of these features will now be considered separately.

No prior detoxification

No dangerous reaction occurs if a patient drinks while on naltrexone or nalmefene; instead (as reviewed above), there is good evidence that the primary benefits from the antagonists are produced when they are paired with drinking. Therefore, it was proposed that 'unlike most treatments, this one does not involve immediately becoming abstinent' (Sinclair, 1989). Instead, the patient starts taking naltrexone while still drinking. The treatment should not be used on patients who have already managed with conventional means to remain abstinent.

Advantages. Eliminating the requirement for prior detoxification increases the percentage of patients who can be treated. There are probably many patients who are unwilling to go through detoxification or unable to remain abstinent long enough to enter other treatments. Retention in naltrexone treatment has been found to be better if the patients did not have to go through detoxification (Maxwell and Shinderman, 1997). Detoxification without medication is unpleasant and potentially dangerous. Consequently, barbiturates, benzodiazepines, or both are generally given to the patients. This, however, produces the risk that these patients, who have already demonstrated their high risk for addictive behaviour with alcohol, will become addicted to these other medications if taken long enough. Inpatient detoxification is also expensive; the average cost according to one American study ranged from $6336 with no medication to $9630 when phenobarbital plus lorazepam were used (Marck *et al*., 1997).

Theoretically, one would expect these problems to be eliminated by using opioid antagonists without prior detoxification, as an alternative to traditional withdrawal methods. Also, withdrawal is safer if the process is done slowly, allowing the body to adjust gradually, and spreading the adverse reactions over a longer period of time. It would be safer if alcoholics gradually decreased their consumption over many weeks, rather than stopped suddenly. This probably is not possible for most patients in conventional treatments, but it happens automatically when naltrexone is given to currently drinking alcoholics (Bohn *et al*., 1994; Sinclair, 1997; Sinclair *et al*., 1998*a*,*b*).

If one were to evaluate the success of, for example, a benzodiazepine programme for ethanol withdrawal, one would look at the safety (how severe were the adverse effects) and the efficacy (what percentage of patients eventually are free of physiological dependence on alcohol). The use of naltrexone in currently drinking patients is an alternative to traditional withdrawal programmes and needs to be evaluated according to the same criteria.

Safety. If opioid antagonists are given to a patient who is dependent upon opiates, a precipitous withdrawal is produced, concentrating the adverse reactions, which in normal withdrawal are distributed over many hours, into a short period. On the basis of the general lack of cross-dependence between opiates and alcohol, however, precipitous withdrawal should not be produced in patients who are physiologically dependent upon alcohol. Consistent with these expectations, no withdrawal signs or adverse effects were seen in any of the preclinical studies in which naloxone, naltrexone, or nalmefene

was given to alcohol-drinking animals without prior detoxification. This included a nalmefene study using a weaning-to-alcohol procedure that resulted in extremely high sustained levels of alcohol intake (Sinclair and Suomela, 1994).

Clinical trials have confirmed that giving naltrexone to patients without prior detoxification is safe. The Finnish study is the first double-blind, placebo-controlled clinical trial to give naltrexone to currently drinking alcoholics (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*). Either naltrexone (50 mg daily) or placebo were given to 121 alcoholics. No severe adverse effects were observed when medication was begun. The medication was well tolerated. The number of patients showing one or more side-effects throughout the 8 months of the study was not significantly higher for naltrexone (39 out of 63) than placebo (28 out of 58) ($P > 0.10$). At no time were there indications of severe ethanol withdrawal.

Although efficacy must be established with such controlled trials, the safety of a procedure can be judged also from open-label tests. The lack of prior detoxification has been used in several such tests, in heavy drinkers (Bohn *et al*., 1994; Kranzler *et al*., 1997) and in alcoholics (Maxwell and Shinderman, 1997; Sinclair, 1997; Sinclair *et al*., 1998*a*,*b*). No safety problems have been found in any of these studies; all have found the medication to be well tolerated.

A surprising finding from the Finnish clinical trial is that naltrexone was better tolerated in therapy aimed at controlled drinking than together with support of abstinence (Heinälä *et al*., 2000). A significantly higher percentage of naltrexone patients, compared to placebo patients, reported side-effects in the Supportive groups (74% vs 40%), but naltrexone had no effect over placebo in the Coping groups (50% vs 49%). Most notably, in the first week on naltrexone there was a significant increase in side-effects among the naltrexone patients told to abstain: 4.9 times higher than in their placebo group that week and 3.5 times higher than their own rate during the week before they received naltrexone. In contrast, there was no increase in side-effects when the Coping group was first given naltrexone, and they had a significantly lower rate than in the Supportive/Naltrexone group.

The risks from alcohol drinking itself need also to be considered. *A priori*, one might expect that these would be minimized in naltrexone treatment by telling patients to abstain. As discussed in the next section (Efficacy and safety), however, telling patients in the Finnish trial to abstain while on naltrexone produced significantly more relapses to heavy drinking and, thus, probably more potential harm from alcohol drinking than did naltrexone plus coping therapy that allowed some drinking.

It should also be noted, however, that opioid antagonists do not block the motor impairment from ethanol, and in some conditions can even increase the intoxication (Sinclair *et al*., 1982). Similarly, there is evidence in humans that naltrexone might increase the difficulty with divided attention caused by ethanol intoxication (Jääskeläinen *et al*., 1998). Patients treated with naltrexone paired with drinking should be given strong warnings about the possibly greater dangers from intoxication, for example, in conjunction with driving.

Efficacy. Nearly all of the controlled pre-clinical studies demonstrating the efficacy of opioid antagonists in reducing alcohol drinking have omitted prior detoxification; they have administered the drugs to animals that were currently drinking or self-administering alcohol every day. This has also been a feature in several open-label clinical trials (Bohn *et al*., 1994; Kranzler *et al*., 1997; Maxwell and Shinderman, 1997; Sinclair, 1997; Sinclair *et al*., 1998*a*,*b*). The studies have universally found significant reductions in drinking. The treatment was considered successful in ~80% of the patients (Maxwell and Shinderman, 1997).

The results from these clinical trials showed that the patients' alcohol craving and drinking slowly diminished over many weeks (Bohn *et al*., 1994; Sinclair, 1997; Sinclair *et al*., 1998*a*,*b*). The decrease has the form of a typical extinction curve.

Figure 3 shows how craving, measured with a visual analogue scale (VAS), progressively declined over 110 days of naltrexone treatment in a Finnish open-label naltrexone trial conducted without prior detoxification (Sinclair, 1997; Sinclair *et al*., 1998*a*,*b*). Craving measured with the Obsessive Compulsive Drinking Scale (OCDS) also decreased significantly. Progressive, highly significant decreases were also found in alcohol

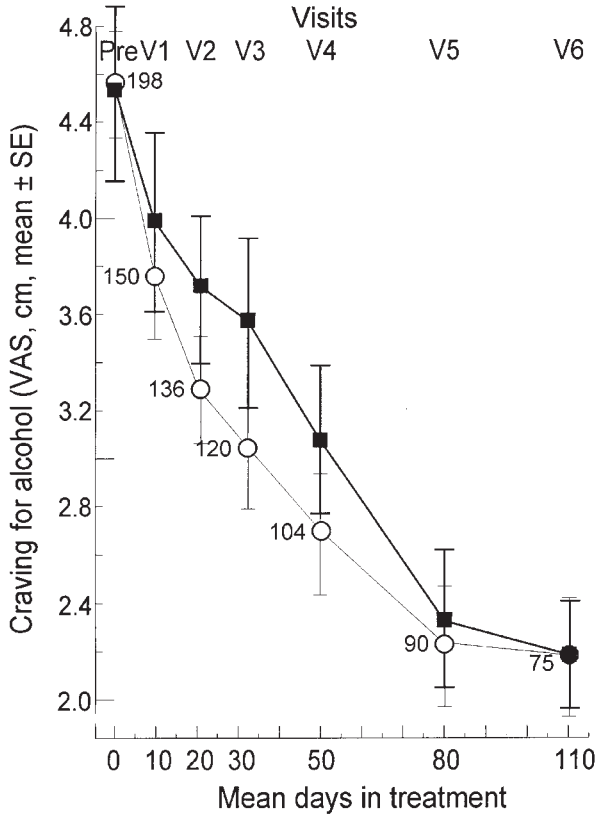

Fig. 3. The progressive decrease in reported craving for alcohol. Craving was recorded prior to the beginning of naltrexone treatment (50 mg, 1 h before drinking) and at the six scheduled counselling visits (V1–V6), using the visual analogue scale. Data are from an open-label trial at two Finnish clinics giving targeted naltrexone without prior detoxification. Solid squares show the mean scores for the first 75 patients who had completed the six visits. Their decrease in craving was highly significant: $F(6,444) = 19.84$, $P < 0.0001$ with a repeated measures analysis of variance. The data are from an on-going expanding programme and at the time that these 75 had completed six visits, many more were in the middle or just starting the programme. The circles show the results from all the subjects in the database at that time (except 14 who reported only zeros), with the number contributing next to the circle.

intake (measured with daily drinking diaries), liver markers, and depression scores. The curve for drinking was similar to that shown in Figure 3 for their craving. Of the 147 patients who had completed enough treatment to be classified, 115 (78%) were considered successful and had a mean (± SEM) final drinking level of 9.4 ± 1.0 drinks weekly; 38 of the patients (26%) reached abstinence, although only 3% listed it as the goal of treatment. Also, consistent with extinction, the reported connections between various stimuli and drinking decreased significantly ($P < 0.001$) regardless of whether the stimuli were pleasurable, unpleasant, or neutral (Sinclair *et al*., 1998*b*).

The efficacy of naltrexone without prior detoxification has now been demonstrated also in DBPC trials. The Finnish DBPC study gave naltrexone (or placebo) to alcoholics who were drinking at the time (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*). It found that naltrexone was highly significantly better than placebo in preventing relapse to heavy drinking in the groups with coping therapy aimed at controlled drinking. An Australian DBPC trial also found positive results and no particular problems when naltrexone was given without prior detoxification (Morris, 1999).

Selective extinction

Most earlier clinical trials have prescribed taking the antagonist every day. Selective extinction, however, is achieved by having patients take it only when they are drinking. In the optimal embodiment of this feature, patients avoid making other responses that are probably reinforced through the opioid system (e.g. eating highly palatable foods, having sex, jogging) while they are on the antagonist. Then when the craving for alcohol is manageable, they have days when no antagonist is taken, no alcohol is drunk, but these other behaviours are now enjoyed. The simpler form of taking naltrexone only when drinking has also been called ‘targeted medication’ (Kranzler *et al*., 1997).

The Finnish DBPC clinical trial included an instruction to take naltrexone only when having a particularly high craving for alcohol (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*). An open-label Finnish trial used instructions to take naltrexone 1 h before drinking: no drinking without taking the naltrexone first, and no naltrexone if no alcohol is drunk that day (Sinclair, 1998*b*; Sinclair *et al*., 1998*a*,*b*). Patients have not reported difficulties in complying with either set of instructions.

Advantages. Some of the clinical trials had found a side-effect of weakening of other behaviours, such as eating sweets and interest in sex, that are believed to be reinforced through the opioid system (Bohn *et al*., 1994; Balldin *et al*., 1997; Månsson *et al*., 1999*a*,*b*). This was expected on theoretical grounds, because any opioidergically reinforced behaviour produced while naltrexone blocked such reinforcement should be extinguished. A pre-clinical study (Sinclair *et al*., 1994) showed that this could be eliminated by limiting the other behaviours to days when no alcohol and no naltrexone were present, thus preventing extinction of these competing actions. In the animal study, the competing behaviour, saccharin drinking, was increased in the same animals in which alcohol drinking was nearly abolished by selective extinction.

Continual blockade of the opioidergic system causes up-regulation of the opiate receptors and supersensitivity (Pert *et al*., 1973; Zukin *et al*., 1982; Hyytiä *et al*., 1999). This is probably detrimental, lessening the effectiveness of the antagonist (Overstreet *et al*., 1999). It may be responsible for rebound increases in drinking (e.g. Fig. 2) after the end of giving antagonists without drinking. Supersensitivity is counteracted by having breaks in the blockade periodically. Therefore, targeted medication, with skipping the antagonist on days when no alcohol is consumed, should produce less opioidergic up-regulation. Taking the antagonists only on drinking days reduces the monthly cost of medication, without decreasing the benefits.

Efficacy and safety. Selective extinction with naltrexone has been used in open-label tests (Kranzler *et al*., 1997; Sinclair *et al*., 1998*a*,*b*) and during the latter 20 weeks in the Finnish DBPC trial, after an initial 12 weeks of daily medication (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*). The results were excellent in all of the studies; naltrexone was shown to be significantly better than placebo in the DBPC study, with targeted naltrexone maintaining and extending the benefits over placebo achieved during continual medication. No problems with safety have been evident.

Selective-extinction treatment continues indefinitely

One advantage of the opioid antagonist treatment of alcoholism is that the benefits persist after the termination of the medication. This is apparently because the benefits are caused by the drug acting not directly but rather by extinction: the behavioural changes produced by extinction persist indefinitely. Follow-up studies consistently have found that the benefits from naltrexone plus coping therapy continued after the end of medication, although eventually weakened over the post-treatment period (O’Malley *et al*., 1996; Anton *et al*., 1999; Månsson *et al*., 1999*b*). Similarly, in my animal studies, drinking was reduced after the end of treatment with naltrexone, naloxone, or nalmefene, but eventually the rats returned to their previous level of alcohol consumption (e.g. Sinclair, 1989, 1990). We believe this is caused by a relearning of the extinguished drinking behaviour. Relearning can, of course, be prevented by always taking naltrexone before drinking.

Comparing the results from the 3 month South Carolina study, the 6-month Swedish one, and the 8-month Finnish DBPC trial clearly indicated that the benefits from naltrexone persist as long as it is used, and the longer the treatment, the better. The benefits over placebo obtained during the first 3 months do not expand much further with additional naltrexone treatment, but are maintained. The benefits are not gradually lost as they are if naltrexone is terminated. To the question, ‘What is the optimal duration of naltrexone treatment in alcoholics?’, one might well respond ‘What is the optimal duration of insulin treatment in diabetics?’

There is no experimental or theoretical justification for terminating naltrexone treatment after a fixed period of time of any duration. The only real justification is financial: taking naltrexone every day for the rest of one’s life would be expensive.

Proposal. The finding that naltrexone is effective only when paired with drinking, however, offers a partial solution to these problems. There should be no end to naltrexone treatment but the medication has to be taken only when drinking. Patients are advised always to carry a pill with them — for the rest of their lives — but to take it only on those occasions when they are likely to drink (Sinclair *et al*., 1992). If they never drink, it costs them nothing. If they do happen to drink, it amounts to

one more treatment (extinction) session, and there will be no loss of benefits.

Efficacy and safety. The Finnish trial demonstrated that the benefits of naltrexone over placebo could be maintained for at least 8 months by taking medication only when there was high craving (Alho *et al*., 1999; Heinälä *et al*., 1999*a*,*b*). No safety problems were found.

Longer data have been obtained for the patients in the Finnish open-label trial (Sinclair, 1997; Sinclair *et al*., 1998*a*,*b*). The protocol in it included all three proposed features: no prior detoxification, targeted medication, and continued treatment. (The initial craving data from this study were shown in Fig. 3.) Some individual drinking records up to 15 months were obtained, with the level of drinking remaining down. More recently, we have collected data from a follow-up study with the first of these patients (Sinclair *et al*., 2000). They were now contacted on the average 31 months after starting naltrexone (range 25–40 months). The 27 responding patients who said they were still complying with the instructions to take naltrexone when drinking all reported that they still were drinking less than before treatment; in contrast, only eight of the 30 who were not complying were still drinking less than before. The complying patients were significantly better than the non-complying ones on craving (VAS and OCDS), drinks per occasion, maximum number of occasions per week, and the laboratory markers mean corpuscular volume, γ-glutamyltransferase and aspartate amino transferase. Compliance was significantly related to pre-treatment measures related to social compliance in general, but not to severity. The results suggest that continued targeted use of naltrexone is safe and effective for at least 3 years.

OTHER PROTOCOL FEATURES

The features discussed so far, for which there is scientific evidence, constitute only the bare bones of a treatment programme with naltrexone. Providing a real treatment for patients means making decisions about many other features about which there is little or no evidence. What type of psychological therapy should be given? By whom? How often? Individually or in groups? Should the treatment be combined with other resources (e.g. Alcoholics Anonymous)? With other medicines?

All of the successful clinical trials have been conducted with naltrexone in conjunction with comprehensive programmes of psychological therapy for treating alcoholism, and approval was given for such usage. There have, however, been no clinical studies testing whether the therapy is needed. The antagonists alone are effective in animals. The possibility should be considered that the antagonists might be used, at least in some patients, with only instructions and a minimum of therapy. Until this is established scientifically, however, naltrexone should be used within a comprehensive programme of alcoholism treatment.

It is unclear whether the programme must be based on cognitive behavioural therapy (CBT). Although most of the successful trials have used CBT, and CBT has been shown to be better than support of abstinence in conjunction with naltrexone, there is no evidence presently that CBT is the best type of therapy to use with naltrexone. Indeed, there may be no single programme that is the best package for naltrexone for all cultures, all alcoholics, and all therapists. Extinction should provide a tool (for reducing craving and drinking) that can be incorporated within a wide variety of different alcoholism treatment programmes. Nevertheless, until scientific evidence has shown other therapies to be effective with naltrexone, clinics should use CBT with it, or better still, specific structured CBT programmes that have been demonstrated to work with naltrexone.

GENERAL CONCLUSIONS AND COMMENTS

There remain many questions about the use of naltrexone in alcoholism treatment that need to be examined scientifically. Nevertheless, although it is important to use evidence-based treatment, it would be wrong to delay the use of naltrexone treatment until all of these questions have been answered conclusively. We have at our disposal a treatment which has been demonstrated to be safe and effective. It should be used now. Where there is scientific evidence, we should follow it. Where there is no evidence, we should use those procedures that were part of the programmes obtaining the positive results: (1) the use of naltrexone is probably the most thoroughly scientifically established adjunct in the alcoholism treatment field; (2) naltrexone should not be used together with supportive therapy enforcing abstinence; (3) naltrexone can be used safely in alcoholics without prior detoxification; (4) naltrexone is effective even if it is taken only when drinking is expected; (5) naltrexone use — when alcohol drinking is expected — should continue indefinitely; (6) the success of the treatment should be evaluated in terms of the health and satisfaction of the patients.

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