New treatment options for substance abuse from a public health viewpoint

John David Sinclair

Naltrexone is the first safe and effective pharmaceutical adjunct for use in the treatment of alcohol abuse. Theoretically it could be effective also as a means for terminating methadone maintenance and in the treatment of other forms of substance abuse. Two general types of protocols have been used with naltrexone. One protocol is similar to the protocol appropriate for use with disulfiram; it is designed to preclude use of the substance while on naltrexone. The other protocol is based on preclinical research showing that opioid antagonists can cause extinction of alcohol drinking; it is designed to maximize the effects from extinction. The results from the clinical trials are consistent with the conclusion that the major benefits from naltrexone treatment, regardless of protocol, are being caused by extinction. The extinction protocol is better from the position of public health, increasing the range of patients who can be treated, reducing the total cost and allowing patients to be treated with dignity. Pharmacological extinction is a new form of medicine, shown to be highly accessible and effective in treating excessive drinking and providing interesting possibilities for the treatment of other learned behavioural disorders.

Key words: alcoholism; extinction; methadone; naltrexone; opiates; public health.


Introduction

A decade ago the feasibility of using psycho-pharmacological agents for treating alcoholism was still an open question (1). Laboratory studies had shown that some drugs altered alcohol drinking in animals and that the model of voluntary alcohol consumption in rats had good predictive ability for screening medicines. The chances of finding a useful medicine were seen as good, and the opioid antagonists seemed particularly promising.

Since then double-blind, placebo-controlled clinical trials have shown that the antagonists, naltrexone (2–7) and nalmefene (8, 9), can indeed be effective in treating alcohol dependence. Extensive open-label tests have confirmed the effectiveness of naltrexone in over a thousand patients (10–14). Meta-analyses have shown that naltrexone, used correctly, was superior to all other procedures for which there was sufficient data for comparison (15, 16). Naltrexone was approved for alcoholism treatment in the USA in 1994 and since then in numerous other countries, including Finland. Nalmefene has the advantages of not being toxic to the liver and having no first-pass metabolism, but it has not been tested as thoroughly and has not yet been approved for general use in the required oral doses.

The efficacy of the opioid antagonists has been shown to be particularly dependent upon the protocol with which they are employed. A Swedish clinical trial showed that naltrexone is not effective without a comprehensive programme of cognitive therapy (7). One study at Yale University showed that naltrexone suppressed craving (4) and helped to prevent relapse.
to heavy drinking 6 months later (17) only in the 'coping skills' groups given counselling about how to prevent a small relapse from becoming a large drinking binge. Naltrexone in the 'supportive' groups giving strong counselling to prevent all drinking was not effective: there it produced about the same relapse rate at 6 months as the placebo and actually tended to increase craving.

The question no longer is whether naltrexone and nalmefene are useful, but rather what protocol will maximize their efficacy. When considering this question, it is important to take a larger, public health perspective. We need to consider what percentage of excessive drinkers would be willing and able to take a treatment, how often the treatment will have to be repeated, and what is the total cost, not per treatment, but over the lifetime of a patient.

Two protocols

The clinical trials of naltrexone and nalmefene have employed two general types of protocols, presented in Figure 1. One is similar to the protocol previously used with disulfiram (a). The other protocol (b) was designed to maximize benefits from the mechanism of extinction.

The 'disulfiram protocol' was used in the first two naltrexone clinical trials (3, 4) upon which the approval of the US Food and Drug Administration (FDA) was based, and consequently similar protocols have been used in many of the subsequent trials (5–9) and in most of the clinical practice with naltrexone. Patients must undergo detoxification and then remain abstinent on their own for an extended period of time (usually 1–3 weeks) prior to treatment. They are then provided with naltrexone (or nalmefene) every day for 3 months (or 6 months in (17)), after which no more medication is given.

The 'extinction protocol' is based on extensive preclinical research showing that naloxone, naltrexone and nalmefene cause extinction of alcohol drinking (13, 18–22) and responding for alcohol (23, 24). A form of the extinction protocol was first tested clinically by Bohn et al (10) in the USA. The specific variety shown in Figure 1 is that employed originally by a chain of private clinics in Finland (13). Other forms have been used by Kranzler et al (11) and Maxwell and Shinderman (12). The most notable distinction of the extinction protocol is that administration of the antagonist is begun without prior detoxification and abstinence. Patients currently drinking alcohol on a regular basis are provided with naltrexone without being told to abstain. The forms used by Kranzler et al (11) and in the Finnish clinics (13) have the additional feature of 'targeted naltrexone': patients are told to take naltrexone only when they are in a situation in which they are likely to drink. The Finnish form shown in Figure 1 gradually switches from continual naltrexone to targeted naltrexone, which then continues indefinitely: patients understand that they are to carry naltrexone with them for the rest of their lives, even if they seldom, if ever, have to take it.

Are prior detoxification and abstinence useful?

The trials with the disulfiram protocol have generally included an analysis of survival to first drink, ie how long the patients on the antagonist or placebo are able to remain abstinent before first sampling alcohol again. If patients taking the antagonist are able to abstain longer than those on placebo, then the medication alone is producing benefits and there is a justification for the prior detoxification and abstinence before giving it. On the other hand, if the antagonists are beneficial only after patients start drinking again, then there is no reason to force them to stop drinking before starting to take the antagonist.

The results from all published clinical trials are summarized in Table 1. All of them have found positive results from the antagonists once patients began drinking. In contrast, the studies generally did not find significant benefits from the naltrexone or nalmefene during the initial abstinence period.

The contrast between the lack of effects while still abstinent and the benefits while drinking was already clear in the first clinical trial, that by Volpicelli et al (3): 'Naltrexone treatment did not appear to prevent subjects from sampling alcohol... (χ² [1] = 1.15, not significant).’ ‘The primary effect of naltrexone was...
Table 1. The significant positive effects from naltrexone and nalmefene generally occur when the antagonists are used together with alcohol drinking.

<table>
<thead>
<tr>
<th>First author, year (ref)</th>
<th>Significant benefits before starting to drink</th>
<th>Significant benefits after drinking (extinction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volpicelli, 1992 (2, 3)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>O’Malley, 1992 (4)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bohn, 1994 (10)</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Mason, 1994 (8)*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chick, 1996 (5)</td>
<td>special analysis†</td>
<td>No</td>
</tr>
<tr>
<td>McCaul, 1996 (5)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mason, 1996 (9)*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kranzler, 1997 (11)</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Volpicelli, 1997 (6)</td>
<td>special analysis†</td>
<td>No</td>
</tr>
<tr>
<td>Volpicelli, 1997 (6)</td>
<td>special analysis†</td>
<td>Yes</td>
</tr>
<tr>
<td>Baldin, 1997 (7)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Maxwell, 1997 (12)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sinclair, 1997 (13)</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Renault, 1980 (25)</td>
<td>(opiate addiction) (without opiate use)</td>
<td>(with opiate use)</td>
</tr>
</tbody>
</table>

* Testing nalmefene; all others tested naltrexone.
† Omitting noncomplying patients.
NA, not applicable: the protocol did not include prior detoxification and abstinence.

seen in patients who drank any alcohol while attending outpatient treatment.’

Similarly, no significant effect was reported in the replication by O’Malley et al (4) on the duration of initial abstinence. There has been some confusion on this point, with some popular reports incorrectly claiming that there was a positive result. In the published article (4), however, the only significant effect was for the naltrexone/supportive group compared to the placebo/coping group. This cross-comparison is inappropriate and has no bearing on naltrexone per se. Moncrieff and Drummond (26) also noted the lack of significant effects in this study (4) on this survival to first drink analysis.

The same pattern can be seen throughout Table 1. The Maxwell and Shinderman trial (12) was different in that the comparison was between a group of alcoholics given strict counselling to abstain while on naltrexone (all dropped out of treatment) and a group of dual-diagnosis alcoholics generally allowed to drink while on naltrexone (good results).

The final entry in Table 1 is not with alcohol but from the 1980 National Institute on Drug Abuse (NIDA) double-blind, placebo-controlled trial of naltrexone for opiate addiction with 1005 subjects (25). They were instructed never to take opiates while on the medication and warned that they might die if they did so. Overall, there were no significant benefits from naltrexone. Good results were obtained, however, within the subgroup that disobeyed instructions and took heroin or methadone while on naltrexone.

Support for extinction

The report on the NIDA trial (25) stated: ‘the theory behind narcotic antagonist treatment involves extinction.’ Furthermore, ‘the concept of extinction implies some use of narcotic drugs.’ In other words, only emitted responses can be extinguished, and thus only patients who disobeyed and took opiates during treatment benefitted from naltrexone. Preclinical studies had earlier demonstrated that opioid antagonists could extinguish opiate self-administration (27). The clinical trial demonstrated that naltrexone could produce extinction in humans also, and that this was the only powerful benefit from the antagonist.

As Mason et al (8) pointed out, the type of results shown in Table 1 also provide a test of the extinction hypothesis in alcoholism treatment: ‘Sinclair [ref (13) here] has proposed a learning theory model of extinction to account for the reduction in alcohol consumption associated with opiate antagonist treatment... This implies that an opiate antagonist may not initially prevent alcohol craving or sampling per se in abstinent alcoholics, but would be expected to reduce craving and relapses to excessive drinking in those patients who sample alcohol while taking the antagonist.’

The results in Table 1 are consistent with the conclusion that extinction is the mechanism underlying the major benefits from opiate antagonists. Most of the other hypotheses for how they work would predict benefits during abstinence. For example, if naltrexone corrected some physiological imbalance and thereby reduced craving for alcohol, it should reduce craving also during abstinence and thus help to prevent the first sampling. Extinction, however, affects only responses that are emitted, and thus weakens drinking only after the response of alcohol drinking has been produced while on naltrexone or nalmefene.

Extinction is also supported by the fact that beneficial effects persist after the termination of naltrexone treatment, as has been found consistently in the clinical trials (7, 10, 17) and in most preclinical studies (18–20, 22, 28).

A weak effect during abstinence

The primary benefits from the antagonists have come after the patients begin drinking alcohol while on the medication. FDA approval obviously was given as a result of these significant effects in the two clinical trials (3, 4). Our animal studies also showed that the
antagonists were effective only when paired with alcohol drinking (13, 18–20, 28). It might seem reasonable, therefore, to omit the prior detoxification and abstinence parts of the protocol, just as supportive therapy or naltrexone without comprehensive cognitive therapy can be dropped because they have not produced benefits in the clinical tests.

The situation is not, however, that simple. There does seem to be some benefit during abstinence. We have seen evidence for it in our preclinical work (28). Most of the trials have found a weak but positive effect from the antagonists prior to drinking. It finally reached significance in the new Volpicelli et al study (6) when using an especially powerful analysis provided by excluding noncomplying and non-completing patients. Because of this weak effect before drinking, the use of prior detoxification and abstinence might still be justified if there were no detrimental effects.

There are, however, several problems. Our animal studies have found a rebound after-effect from taking the antagonists during abstinence, probably related to receptor supersensitivity, causing alcohol drinking to increase (18–20, 28). This needs to be examined further in humans. There is also an ethical dilemma. We cannot tell abstaining alcoholics to start drinking again, but it also seems unethical to tell the patients to abstain while on naltrexone, knowing that they will receive the major benefits only if they obey the instructions. This practice would prevent the most obedient and motivated patients of the most charismatic doctors from having their craving and drinking extinguished. There is no dilemma, however, if prior detoxification is omitted. In this case the doctor is instructing the drinking alcoholic about a slower and safer means of detoxification, a means which also eventually takes away the craving for alcohol. Finally, there are major disadvantages to the disulfiram protocol from a public health viewpoint.

Public health considerations

Currently, only a small percentage of the people with alcohol problems seek help. Regardless of how successful a treatment is in a clinical trial, it will not be successful from a public health standpoint if people are unwilling or unable to receive it.

Fear of detoxification is one of the obstacles preventing alcoholics from getting treatment. Alcohol withdrawal is an extremely unpleasant experience. In rare cases it can be fatal. It also is very expensive: the cost for inpatient detoxification reported in the USA was $6162–9630 (29). Dependence can develop for the barbiturates or benzodiazepines provided during detoxification.

The prior abstinence requirement of the disulfiram protocol is another obstacle. Many patients are unwilling or able to abstain for a week or more before beginning treatment. This restricts the treatment for excessive drinking to the less severely affected patients or to the highly motivated ones who are, in fact, able to refrain from drinking for at least some time.

I have seen no published justifications for the use of prior detoxification and abstinence. It was important with disulfiram to exclude patients who were likely to disobey and drink while on the medication, because it could be fatal. In the case of naltrexone, however, there clearly is no danger from sampling alcohol while on the medication. The empirical evidence suggests instead that the major benefits from naltrexone begin only after drinking.

The initial requirements of the disulfiram protocol are unpleasant, expensive, dangerous, unnecessary, and an obstacle preventing many patients from entering treatment. These disadvantages are far greater than the possible benefit from the weak effect during abstinence. Therefore, it seems reasonable to eliminate prior detoxification and abstinence, as is done in the extinction paradigm.

Final abstinence as a limiting factor

The disulfiram protocol not only begins with abstinence but also ends with abstinence as the only acceptable behaviour once the naltrexone treatment is over. Regardless of how naltrexone is working, we all agree that patients who resume drinking without naltrexone will eventually be back to the alcoholic state they had prior to treatment.

This requirement for abstinence as a goal may stop many people from entering treatment. Only 3% of patients in a survey from the Finnish clinics listed abstinence as their goal. This is undoubtedly a biased sample. Nevertheless, it seems likely that many alcoholics would prefer goals of drinking less or having greater control of their intake. They would like to be able to drink on social or business occasions, as their friends and associates do, but at the same time have enough control over their behaviour to stop drinking when the others do.

The extinction protocol shown in Figure 1 makes this possible primarily because the treatment continues indefinitely. One feature of naltrexone noted both with opiate use and alcohol drinking is that it helps to prevent sampling from turning into a major binge. Those patients who have been through the extinction treatment and thereafter always have naltrexone with them can take a pill and then drink a small amount of alcohol without danger of triggering a relapse. This has been demonstrated in the Finnish clinics. Of the
147 initial patients who could be classified, the 115 (78%) successful ones reduced their consumption to a final level averaging 9.4 ± 1.0 (SE) standard drinks of 12 g per week. 26% reached abstinence, but the other 74% were still drinking on social occasions without falling into a drinking binge. Furthermore, each time they drink while on naltrexone constitutes another extinction trial, with the effect of slightly reducing future craving and drinking still further. The trends for all patients were downward, and none had relapsed back to their previous high level of drinking.

The revolving door of treatment

People may avoid treatment because they understand that the benefits are only temporary and that the procedure will have to be repeated over and over again. This has been generally the case with alcoholism treatments previously.

The follow-up studies with naltrexone treatment have obtained rather good results (7, 17). The extinction protocol, however, should theoretically be still better: indeed it should be effective indefinitely as there is no termination to the treatment. There is so far no evidence to the contrary, but even the longest records are for only a couple of years, and it is too soon to tell whether this theoretical promise will be realized.

Dignity

The stigma associated with being an alcoholic and the indignity with which alcoholics are frequently treated constitute a major obstruction to entering treatment. Much effort has been placed toward removing the stigma, toward seeing alcoholism as a disease without moral implications. These efforts have been limited in the past, however, by the treatment requirements themselves. Let me relate an anecdote that finally made this clear to me, and illustrated how there may now be a solution.

I was lecturing at a hospital in Boston about naltrexone treatment with the extinction protocol. Afterwards the director of the hospital Dr Michael Pearlman was showing me around. One of the patients walked by, and the director said to her, ‘Hello. I would like to introduce you to Dr Sinclair. He has been telling us about a new drug for alcohol problems.’

‘Is that one of those medicines where I can’t drink?’ she questioned bitterly.

‘Well, as a matter of fact,’ I replied, ‘it’s just the opposite!’ I explained to her about alcohol drinking being learned – which felt right to her. I told her about extinction – and she thought it seemed reasonable that there should be a way to weaken behaviours that had got too strong. Indeed, she was ready to agree to start the treatment. But then a bothersome thought occurred to her.

‘Well, O.K. But I don’t want Dr Smith giving it to me. He steps on me for my drinking, what with my having kids and all.’ (Translation: he castigates her, telling her she is not behaving as a proper mother when she drinks.)

I told her, ‘One of our rules with this method is that the patients must be treated with dignity.’ Her eyes brightened at the idea.

The revelation to me, that the extinction protocol makes dignity possible, came from the Dr Pearlman’s reply. ‘Well’, he said to her softly, ‘you see, before the only thing we had to offer you was abstinence. And we had to use whatever “hammer” we had, just to try to make you abstain. But now we have another alternative.’

Conclusions

Naltrexone and nalmefene have great potential for reducing the tremendous suffering and cost to society from excessive drinking. For this to be realized, however, the antagonists must be used with a protocol based not on tradition, hunches or bureaucratic considerations, but rather on the scientific results showing the physiological mechanism.

Opiate antagonists should not be used with prior detoxification. Instead, extinction with the antagonists provides the safest and easiest form of detoxification, gradually reducing the craving and drinking over several months. They should not be used with prior abstinence. Alcoholics in recovery, who are able on their own to remain abistent, do not need this treatment and should be excluded from it. Extinction is specifically for people who are currently drinking. It removes the cause for excessive drinking and eventually the danger from social drinking. Thus it provides the individual with the physiological freedom to decide whether to drink or not. Theoretically, it can provide a permanent solution. Finally, it provides a means for treating alcoholism while allowing the patients to retain their dignity.

The antagonists are not magic bullets. They are not sufficient on their own. They must be combined not only with the proper protocol but also with a comprehensive programme to help people, freed from their addiction, to establish a new life.

Two more ingredients are needed to make the treatment successful from a public health viewpoint. Extinction provides a safe and effective method that is also acceptable to most potential patients. It is still necessary, however, to identify the people in need of treatment, or help them identify themselves. Finally, it is necessary to develop the means for providing the
comprehensive treatment to the millions of people around the world who need it.

Even such grandiose ideas may, however, be only the beginning. Pharmacological extinction is a new form of medicine for treating behaviours that have become too powerful. What other behaviours might be treated? It can stop a rat from taking sweets. Can it control compulsive eating in humans? It can stop a rat from drinking methadone. Can it be used successfully to terminate methadone substitution therapy? Can it extinguish addiction to gambling, sexual obsessions, compulsive thrill-seeking criminal activity?

We will see.

References

19. Sinclair JD. The story in Finland behind the new naltrexone treatment for alcoholism (and how I got the patent for it). Life and Education in Finland 1995; (3): 2–16.