Naltrexone Itself Does Not Reduce Clinically-Relevant Craving

David Sinclair

Draft. March 31, 2009

One of the strongest effects of using naltrexone in the treatment of alcoholism is the progressive decrease in the craving for alcohol. For example, the significance of the effect was p=0.00000000001 when I analyzed the data from the first 210 patients at ContrAl Clinics (Figure 1). Patients themselves often comment after a couple months of treatment that, to their surprise, they no longer are particularly interested in drinking. Previously, alcohol had been the focus of their lives, the main thing they were thinking about. Somehow the treatment had gotten rid of the obsession.
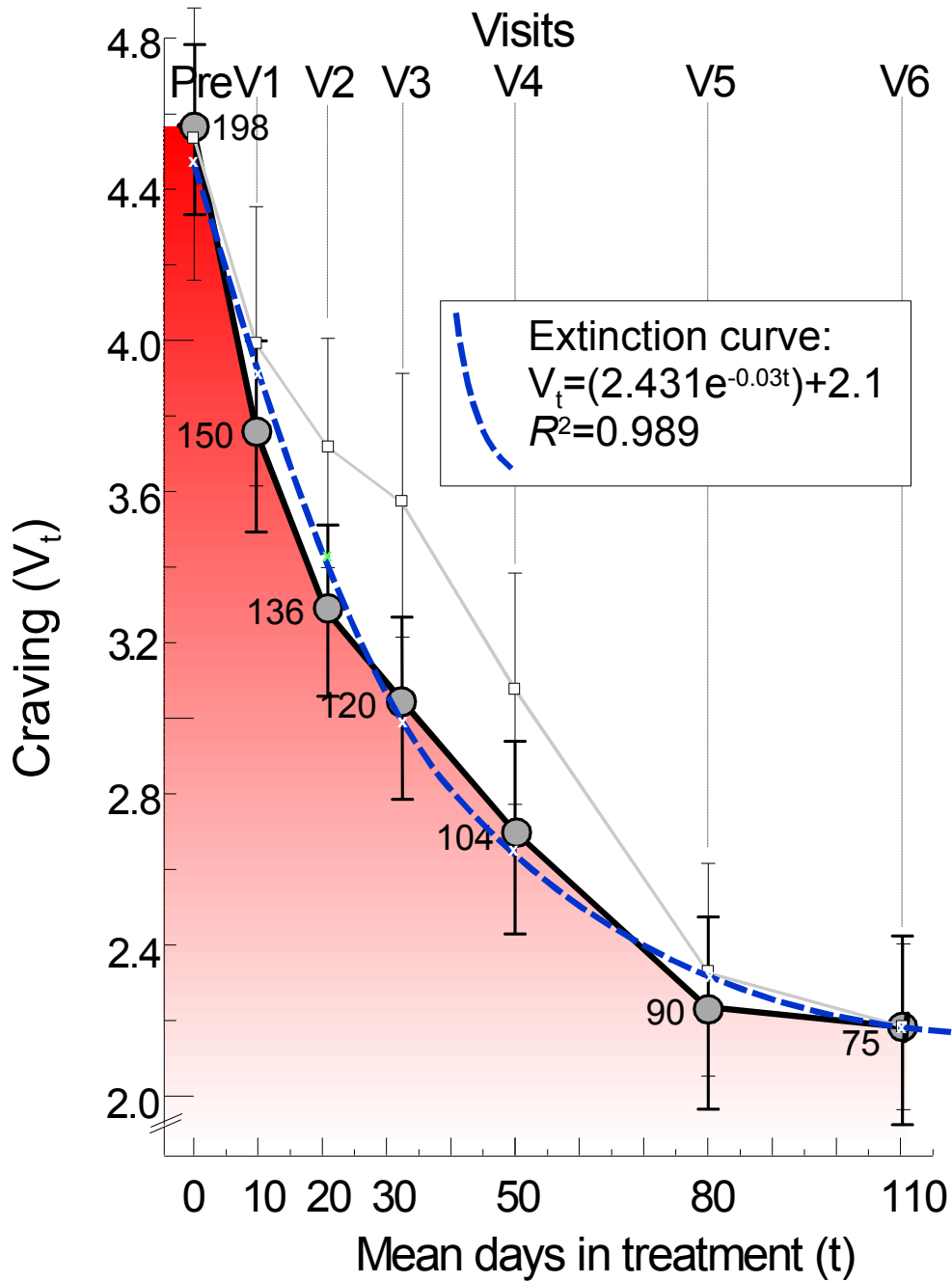
Perhaps because of these results, some people have gotten the mistaken idea that naltrexone itself reduces the craving. Alcoholics are writing in response to Roy Eskapa's book[i], telling that they can only find doctors who will prescribe naltrexone for the purpose of suppressing craving while abstaining. A recent video on UTube, although positive about naltrexone, said that it "blocks the craving and the high". The practice of giving naltrexone in a targeted manner (i.e., taking the medicine only on drinking days) is often described as telling patients to take naltrexone only when they need it to suppress a particularly high craving. Another clinician tells patients to take a double dose of naltrexone on days when they are having very high craving. Most of the theories proposed for how naltrexone works (e.g. that alcoholism is caused by too little[ii] or too much[iii] opioidergic activity), aside from the initial one that it causes extinction[iv],[v], predict that the antagonists directly block craving.

The evidence, however, is very clear on this point, as shown in this review. Naltrexone does not directly suppress craving. Craving is suppressed after drinking alcohol while on naltrexone, that is, after the mechanism of extinction has had an effect. Before the first sampling of alcohol, however, the opioid antagonists produce no significant reduction in craving. The incorrect belief that naltrexone alone blocks craving has probably played a major role in its being used incorrect and thus in the low rate of prescribing the medicine.

Table 1 summarizes the differing predictions from the two hypotheses for how opioid antagonists work. The evidence from preclinical and clinical research relevant to each of the predictions is then presented. The analyses are limited to these two hypotheses. Naturally, it is possible that neither is correct and that some other explanation is correct. Therefore, evidence that one hypothesis is wrong does not automatically imply that the other is true. The possibility that both are correct can also not be excluded *a priori*.

Table 1. The differing predictions of the two hypotheses for how opioid antagonists work.

IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
1. Craving is reduced by the antagonist before the first alcohol drink	1. Craving is not reduced by the antagonist before the first drink
2. The antagonist delays taking the first drink	2. The antagonist has no effect on when drinking resumes
3. The amount of craving is not affected by the experience of drinking while on the antagonist	3. The craving decreases as a function of the amount of experience drinking while on the antagonist.
4. The craving decrease has no particular form	4. The craving decrease follows the form of an extinction curve $V_t = (V_0 * e^{-\lambda * t}) + V_{sum}$
5. The antagonist reduces craving triggered by pleasant (endorphin-releasing) stimuli and not by unpleasant and neutral stimuli	5. The antagonist reduces craving triggered not only by pleasant stimuli but also by unpleasant and neutral stimuli
6. The craving reduction does not continue after the antagonist is no longer present	6. The reduction in craving continues after the antagonist has been removed

Figure 1. The reduction in craving developing as a function of days in treatment with 50 mg naltrexone 1 hr before drinking. Craving was reported at each clinical visit, using a 100 mm visual analog scale. 198 of the first 210 patients provided usable data.

IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
Craving is reduced by the antagonist before the first alcohol drink	Craving is not reduced by the antagonist before the first drink

Pre-clinical studies of voluntary alcohol drinking

I have conducted a large number of experiments (at last count, 47 studies) on the effect of opioid antagonist on voluntary alcohol drinking. Most involved giving placebo or naloxone, nalmefene, or naltrexone to rats just before returning alcohol access to after a period of alcohol deprivation; often this was with "limited access" in which the rats had continual access to food and water but access to the alcohol solution only one hour a day. Rats reliably wake up and start drinking the alcohol solution as soon as it is returned, thus demonstrating high motivation for alcohol. The rate of alcohol drinking during the first 10 minutes is orders of magnitude higher than that seen during continual access. In order to see the direct effect of the opioid antagonists on craving – separate from any effects that develop <u>after</u> drinking while reinforcement is blocked (i.e., extinction effects) – we need to look at the rats' behavior the very first time the antagonist is administered.

I have never in all these studies seen a decrease in the behavior of starting to drink alcohol solution after the first administration of antagonist (e.g.,[vi]). In the experiment shown in Fig 2, all of the rats started drinking immediately when the alcohol bottle was put back on the cage during both the pre-treatment period and on the first nalmefene sessions. On subsequent treatment days, the percentage of rats starting to drink immediately decreases progressively, becoming significantly lower than seen in the rats given placebo, and by the 4th or 5th pairing of drinking with antagonist, almost none of the animals were showing the behavior. The same result is seen in the amount of alcohol consumed in the first 10 minutes: no significant effect on the first day getting the antagonist, but a significant reduction developing on subsequent days

Drinking may decrease slightly later in the first extinction session and the rats' total alcohol intake is often significantly reduced in the first session following injection of naloxone, naltrexone or nalmefene. This can be seen in the operant behavior in Figure 3. However, when the antagonist was given to rats in a stress-free oral manner, similar to how humans take the medicine, there was no decrease in alcohol drinking during the first hour-long alcohol session but rather a slight tendency for an increase in drinking [vii](see Fig. 2).
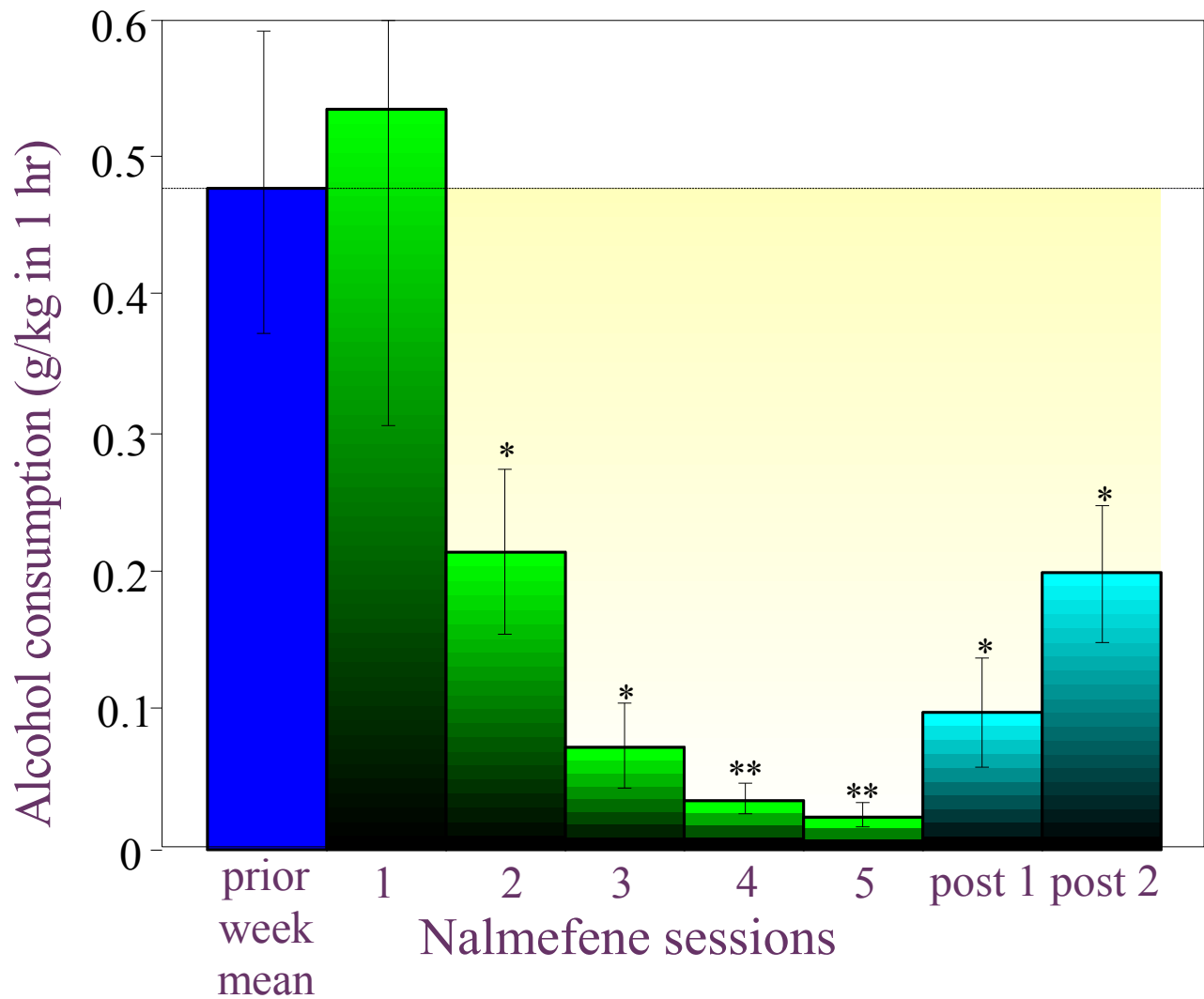
Figure 2. Extinction of voluntary alcohol drinking in male Wistar rats with one hour daily access to 10% alcohol solution and continual access to food and water. Prior to the alcohol sessions the rats ate measured amounts of a cocoa-flavored sucrose paste. These 7 rats then had 10 mg/kg nalmefene in the paste before each of the next 5 sessions. *p<0.05; **p<0.01 relative to 7 controls given only the vehicle.

Lever pressing for alcohol solution

The lack of reduction in motivation for alcohol before the first drink is shown very clearly when opioid antagonists are administered to rats that have learned operant responding for drops of alcohol solution. The graph below (Fig.3, unpublished data from Petri Hyytiä's experiments published in viii) shows the number of lever presses for 10% alcohol solution, recorded automatically every two minutes, in rats having access to alcohol one hour a day.

The important data for the question of craving is the bar showing the responding during the first two minutes of the FIRST NALOXONE session. The rats had been injected with 1 mg/kg naloxone, 30 minutes earlier. The antagonist produced no reduction in responding for alcohol during the first 2 minutes. Naloxone had no direct effect on the motivation for alcohol.

Figure 3. Lever pressing for alcohol by rats during an hour session proceeded by a saline injection (left) and then in three successive sessions proceeded by a naloxone injection. Responding in general was significantly reduced by naloxone, but responding during the first 2 minutes of the first naloxone session – indicative of any direct effect of naloxone on motivation for alcohol – was not reduced.

Responding during the first 2 minutes of the SECOND NALOXONE and THIRD NALOXONE session, however, reduced progressively. The motivation for alcohol was reduced after pairing of naloxone with lever pressing and alcohol drinking, i.e., after triggering extinction.

Published cumulative response patterns from two experiments with different doses of naloxone 30 min before access to lever pressing for alcohol also show that naloxone does not directly reduce motivation for alcohol.[vii] The AA rats began responding immediately for oral ethanol with naloxone having no effect on responding in either experiment during the first 2 minutes and no significant effect during the first 5 minutes. Higher doses of naloxone did, however, suppress responding later in the 1 hr sessions.

Clinical evidence with opiate addicts

The first naltrexone clinical trial was for treatment of opiate addiction.ix Once the patients began self-administering opiates while on naltrexone, the reported craving began decreasing and by the end of the trial, their craving was significantly lower than that reported by the patients receiving the placebo. Among the majority of patients who never self-administered opiates, however, naltrexone had no effect on craving. Naltrexone itself did not reduce craving for opiates.

The explanation given for these results was that naltrexone is thought to work through the mechanism of extinction. Extinction is the mechanism that weakens a learned response after a response is made and then is not followed by reinforcement. In the best known example, Pavlov's dogs, conditioned to salivate to the sound of a bell by having a bell ring before getting food, had the conditioned response extinguished by not getting food after salivating to the bell. Extinction requires that the response first be made – and then not get reinforcement. Consequently, only the patients that made the response of taking opiates while naltrexone blocked the reinforcement had the craving weakened by extinction.

Our clinical results with alcoholics in regular practice

The daily intake of alcohol, reported in the drinking diaries of the first 210 alcoholics treated at the Tapiola and Tampere ContrAl clinics (not previously published), is shown in Figure 4. As in the pre-clinical results, the critical data is the effect on the first day of treatment with naltrexone. If naltrexone itself is able to reduce the patients' craving to the extent that it is clinically relevant for drinking, then there should be a significant reduction in the number of drinks taken on this first day of treatment.

In fact, there was no reduction at all from the mean level of alcohol drinking during the two weeks before treatment. Indeed, the number of drinks consumed on the first day is slightly, although not significantly, higher than the pre-treatment mean. Naltrexone alone did not reduce craving and drinking.

Subsequently, after drinking has been paired with naltrexone and extinction could have an influence, alcohol consumption decreased progressively. The decrease is very highly significant.
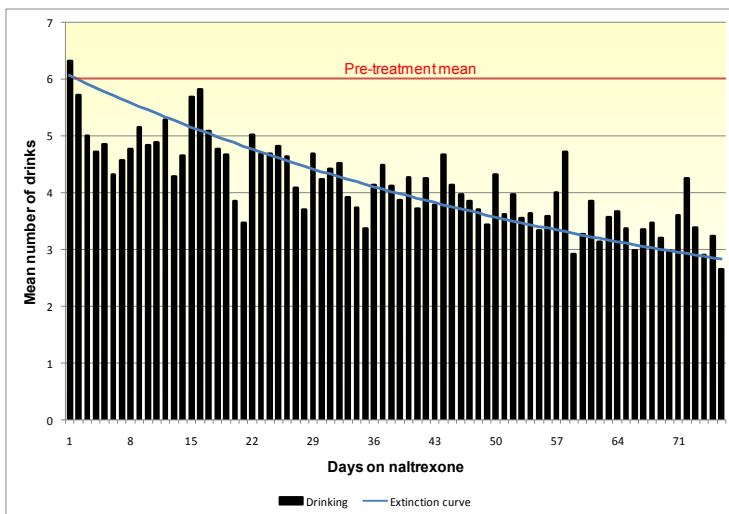

Figure 4. Daily intake of alcohol, reported in drinking diaries, by the first 210 Finnish patients taking 50 mg naltrexone daily. The theoretical extinction curve is from the Rescorla-Wagner equation (see Extinction Curve section below) with V set at the pretreatment mean, 6.07 drinks per day; Vsum set at 1.3 drinks per day, the mean level eventually found after about a year for successful patients; S was set at 0.015. The extinction curve explains 66.4% of the variability in the daily drinking data.

IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
The antagonist delays taking the first drink	The antagonist has no effect on when drinking resumes

9

Other clinical results

The most common protocol used in clinical trials of treating alcoholism with naltrexone has been, first, to detoxify the patients, and then instructing them to abstain completely from alcohol while take either naltrexone or placebo every day. If naltrexone directly reduced craving, the patients getting the antagonist would be able to abstain longer than those getting placebo.

My database has 24 publications using this protocol with either naltrexone or nalmefene. Every one of them found no significant effect of the antagonist on the time to the first drink , i.e., no significant effect of the antagonist on clinically-relevant craving:
x,xi,xii,xiii,xiv,xv,xvi,xvii,xviii,xix,xx,xxi,xxii,xxiii,xxiv,xxv,xxvi,xxvii,xxviii,xxix,xxx,xxxi,xxxii, xxxiii. Reviews also conclude that the evidence for both naltrexone xxxiv and nalmefene xxxv shows the antagonists are effective in preventing patients who are drinking from relapsing to heavy drinking but do not prolong abstinence.

First drink priming from endorphins

In addition to extinction, there is at least one other mechanism through which naltrexone seems to suppress alcohol drinking: blocking of the "first drink effect." The evidence for this is rather weak but one can see possible evidence in Figure 3. The rats in the SALINE Session showed a second bout of lever pressing for alcohol, approximately 20 to 30 minutes into the hour. The second bout is missing in each of the naloxone sessions, including the first, when the responding in the first 2 minutes was not reduced. A likely explanation is that effects from the first bout of drinking were stimuli for the second bout. One of the effects of the first bout was a release of endorphins, and the effects of the endorphins were among the stimuli for the second bout. Naltrexone blocks the effects of the endorphins, and thus removes a stimulus for the second bout of drinking.

There is also anecdotal evidence from clinical practice. Patients frequently report, early in naltrexone treatment, that they are surprised to find that they did not finish the bottle, that they are satisfied by only a few drinks and do not bother taking more. Our explanation has been that naltrexone is blocking the first drink effect. The one thing that also always has been present when the second drink is taken is the effect produced by the first drink. This is generally a stimulatory effect, and it has been shown in animals that the stimulatory effect of alcohol is blocked by opioid antagonists.xxxvi

Direct opioidergic stimulation of drinking

In addition to effects related to learning, there is some evidence that endorphins may have a direct ability to stimulate alcohol drinking prior to any experience with alcohol. Figure 5 shows results obtained with AA rats given a single injection of morphine; the time was distributed throughout the day in order to preclude any circadian influences. A high peak in alcohol drinking was observed 4 hours after the morphine injection, regardless of the time of day when the morphine had been administered. This was followed by a suppression of alcohol drinking, keeping is significantly lower than the rats own prior level of intake for several days.

These results were observed in rats that had had prolonged prior experience with voluntary alcohol drinking.

Almost identical results, however, had previously been seen in naïve Sprague Dawley rats, i.e., ones that had never had alcohol before the large morphine injection (30 mg/kg IP).xxxvii As in the alcohol-experienced rats, there was a very high peak in alcohol drinking during the fourth hour after getting morphine, followed by a significant suppression, relative to controls, for the next 6 days.

These results indicate that opioidergic activation can stimulate alcohol drinking even without prior drinking experience.
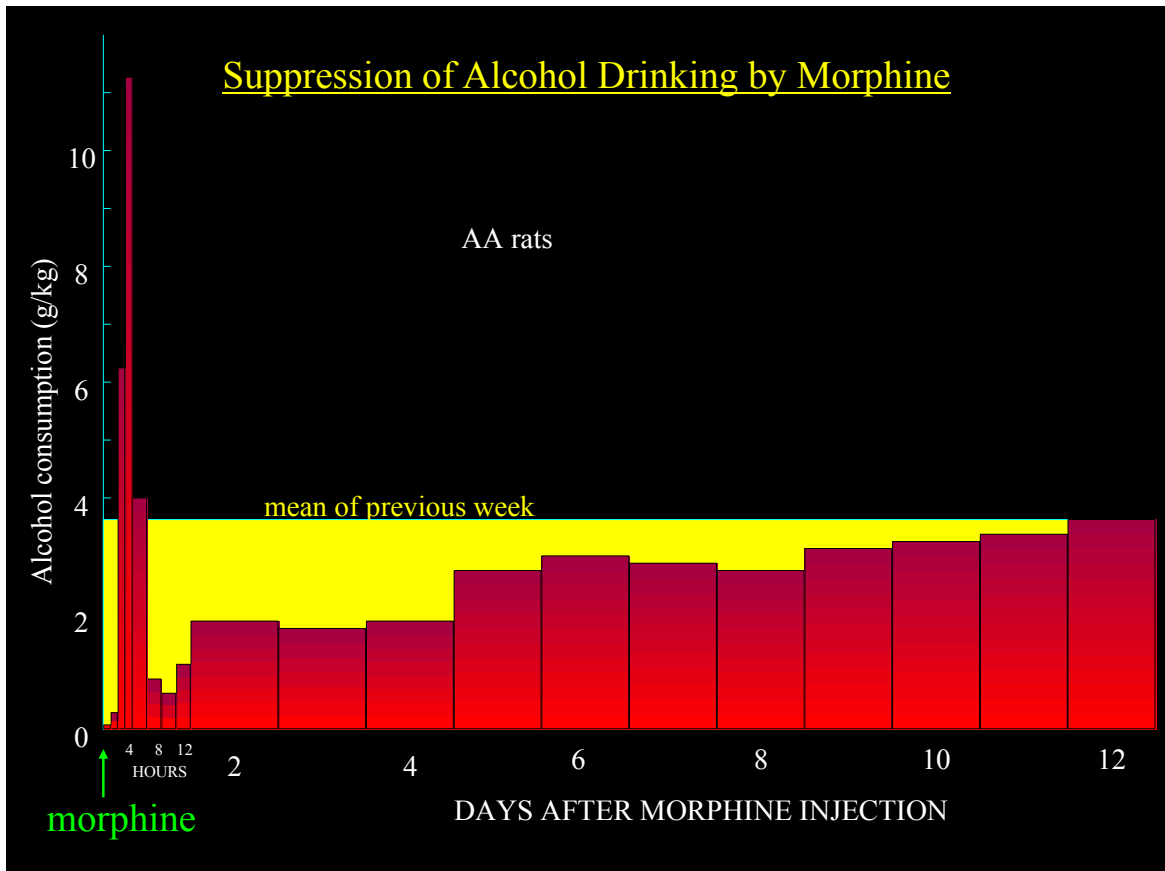

Figure 5. Effects of a single injection of morphine on subsequent alcohol drinking. In both AA rats (here) and Long Evans rats (Sinclair et al., 1982) morphine blocked alcohol drinking while the rats were impaired by the opiate, followed by a short period when drinking of alcohol, but not water, was greatly increased, after which alcohol drinking was significantly suppressed for many days.

Theory for expecting direct blocking of craving

The learned ability of stimuli related to alcohol to elicit feelings of craving is known to be reduced after drinking alcohol while naltrexone is present. The theory proposing, however, that naltrexone alone can block craving starts with the assumption that when alcohol is drunk, and thus endorphins released, the stimuli present at the time would be classically conditioned to cause a release of endorphins by themselves. In analogy with Pavlov's experiment, if you repeated had a bell rung before you drank alcohol, eventually the bell itself would cause endorphins to be released. The binding of these endorphins to their receptors or some effect from it would then be felt as craving and would help to stimulate more alcohol drinking, just as the morphine in Figure 5 did and as the first drink is believed to work. Naturally, if the opioid receptors were block by naltrexone, the craving related to alcohol cues would not be produced and drinking would not be stimulated, just as naltrexone probably blocks the first drink stimulation of subsequent drinking.

The weakest part of the theory is the assumption that alcohol-related cues develop the ability to release endorphins. There is no doubt such cues are able to produce craving and that they help elicit drinking, but to my knowledge there has been no proof that they cause endorphins to be released. If the cues do not cause endorphins to be released, opioid antagonists could not affect whatever effects the cues have: specifically opioid antagonists could not block craving elicited by alcohol-related stimuli.

Against the hypothesis that the cues release endorphins, is the apparent failure of the cues to produce reinforcement. Does watching a bar or seeing advertisements for alcoholic beverages cause reinforcement? Probably not. It does not satisfy the desire for alcohol. In fact, there are other theories claiming such stimuli do not produce pleasant reactions but instead produce unpleasant feelings similar to withdrawal.

IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
The amount of craving is not affected by the experience of drinking while on the antagonist	**The reduction in craving increases as a function of the amount of experience drinking while on the antagonist.**

Effect of experience

There is no doubt that experience with the medication increases the amount of decrease in craving, and drinking (See Figures 1, 2, 3, 4, 9). Thus the prediction of the extinction hypothesis is supported. One might argue however, that some medicines (e.g., Prozac) show benefits only after several days of administration, so the increase in the effect of naltrexone could still be caused by direct actions of the medicine. None of the clinical trials starting with abstinence, however, has reported that power of naltrexone to block craving and drinking increases as a function of the number of days on the medication while abstinent. Instead, patients generally have more ability to remain abstinent early in the trial than after several weeks on naltrexone.

It is far more likely that naltrexone and nalmefene produce tolerance rather than sensitization. Blocking receptors causes a homeostatic increase in the number of receptors – an upregulation, resulting in temporary supersensitivity once the antagonist is gone from the body. Figure 6 shows the upregulation in the number of opioid receptors in AA rats produced specifically when naltrexone was being used to reduce alcohol drinking.[ix]
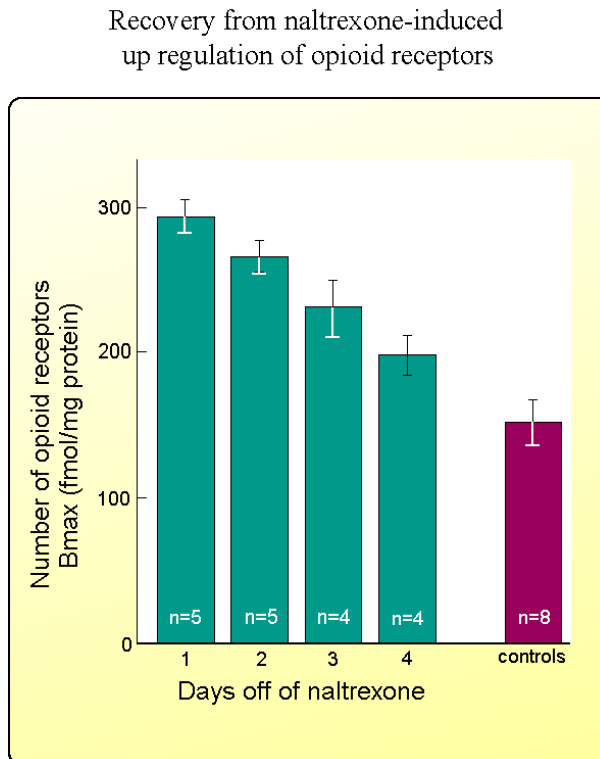

Figure 6. Recovery from upregulation in AA rats caused by prior administration of naltrexone (1mg/kg orally

twice daily for 8 days).xxxviii

Preclinical studies have shown clearly that the antagonists given during abstinence do not develop the ability to decrease subsequent alcohol drinking. Figure 7 shows our results with nalmefene xxxix. Instead, alcohol drinking was reduced less in rats treated on the preceding days with nalmefene than with placebo. Administering naltrexone to rats during abstinence has also been reported to increase their alcohol drinking afterwards.xl
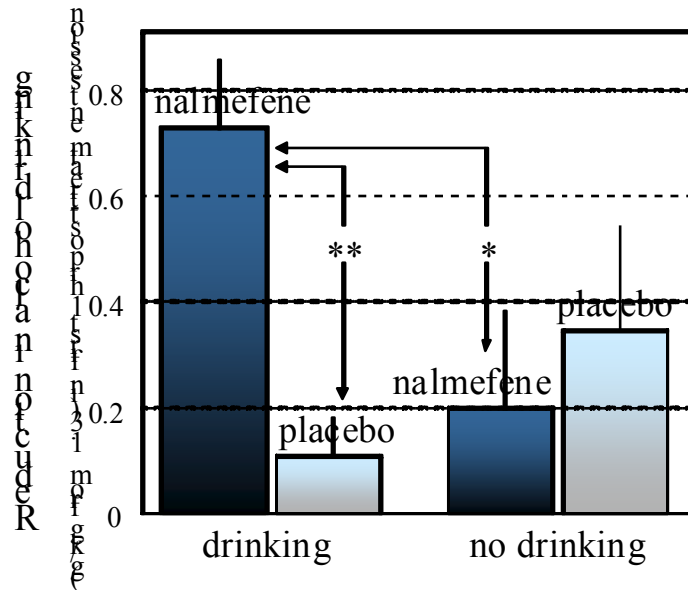

Figure 7. Drinking on the 5th day by rats given nalmefene or placebo on the previous 4 days either paired with alcohol drinking (left columns) or with no drinking (right columns).

Extinction curves: Rescorla-Wagner

IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
The craving decrease has no particular form	The craving decrease follows the form of an extinction curve $V_t=(V_0*e^{-\lambda*t})+V_{sum}$

The previous sections have been tests primarily of whether the antagonists directly suppress craving (left column), with extinction (right column) only providing an alternative explanation. This section, however, deals with a new test for whether the antagonists function through the mechanism of extinction. The direct action hypothesis does not predict any form for the decrease in craving with experience drinking on the medication because it does not predict there should be any such decrease (as covered in the previous section).

The decrease in response strength produced by extinction follows a specific curve, called an extinction curve. The Rescorla-Wagnerxli equation for the extinction curve states that the change in response strength on each extinction session is

$$\Delta V=S[Vmax-(V-Vsum)]$$

where V is strength of the response prior to the session, ΔV is the change in strength produced by the extinction session; S is a constant related to the salience of the situation; Vmax is zero for extinction; Vsum is the strength of the response produced in other ways.

Mathematically, it is simply an exponential curve, similar to that for radioactive decay and many other processes (including patients dropping out of a trial), with the additional terms Vmax and Vsum added. When Vmax is not zero, the formula accounts for learning data. Vsum is not zero when there other stimuli helping to elicit the response, which is usually the case outside of the laboratory. It has the form: $Vt=V0*e^{-\lambda*t}$. For the data in Figure 9, this becomes: $Vt= 0.5*e^{-0.91629*t}$.

(I studied physics before switching to psychology. Much of what we did in physics was testing the goodness of fit of our observed data to a curve produced by a mathematical formula based upon a theory about the mechanism involved. Once in psychology, I never had the opportunity to do this sort of curve fitting because I never was working with mechanisms for which there were well established formulas. Dealing with extinction is, therefore, a pleasant except because the Rescorla-Wagner is an accepted formula for this psychological mechanism.)

Extinction curves: computer simulation of extinction
The Rescorla-Wagner formula is not based on any specific neurological mechanism for how extinction is caused.

Figure 8 shows the results from a computer simulation of extinction [xlii]. An exponential curve with the addition of a Vsum term, i.e., a Rescorla-Wagner extinction curve accounts for 99.7% of the variability in the computer simulation results. Therefore, the two are essentially the same, except the computer simulation also accounted for the spontaneous recovery seen in empirical data (e.g., in Figure 2 here.)

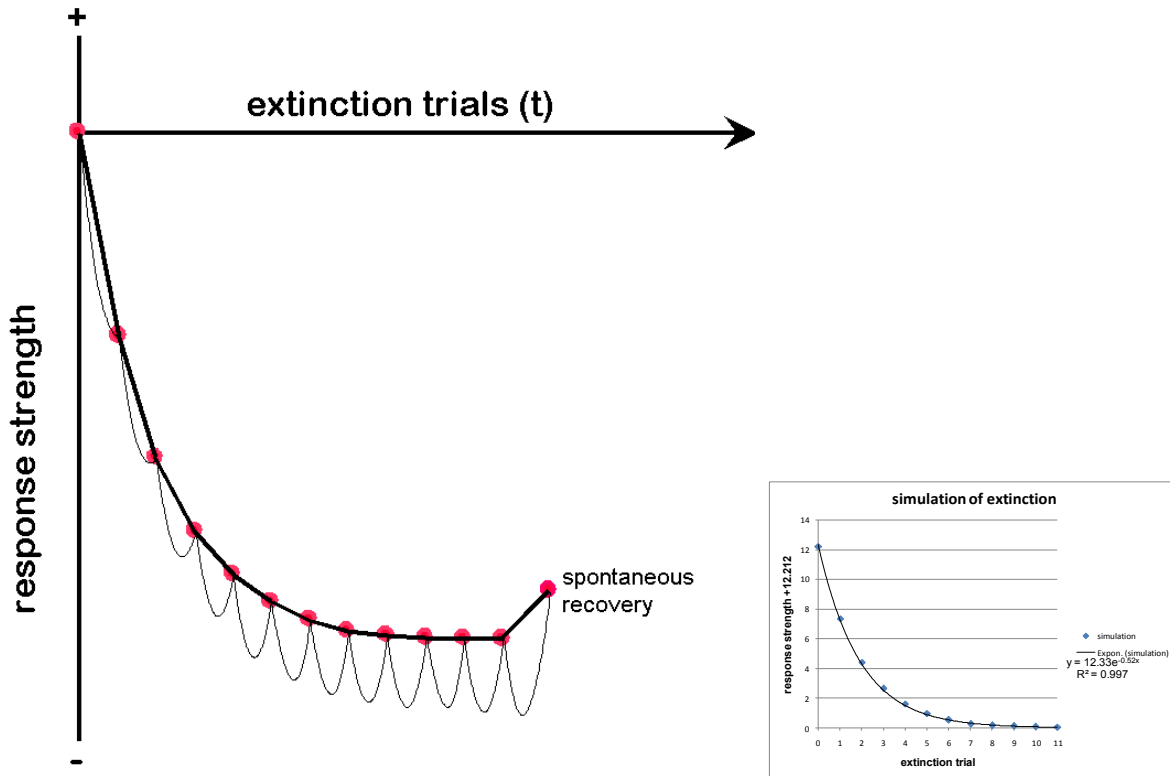Figure 8. Upper: Theoretical extinction curve produced by a computer simulation of extinction in neural networks with the strength of synapses obeying the "rest principle" rule.[xiii]

Lower: The best fitting exponential curve for the all but the last data point accounts for 99.7% of the variability:

$$V = 12.33 * e^{-0.52t} - 12.212$$

The 12.212 is the same as the Vsum constant in the Rescorla-Wagner formula.

Curve fitting to preclinical data

Curve fitting begins by supplying values for the constants in the formula, on the basis of theoretical considerations if possible, or on the basis of what produces the curve that best fits the observed empirical data, i.e., what curve explains the highest percentage of the variability in the data.

Compare the Rescorla-Wagner extinction curve in Figure 8 here with the actual results in Figure 2. It is almost a perfect fit. The formula accounts for 99.3% of the variability in the actual data (R^2 = 0.996), Notice that the Rescorla-Wagner formula does not account for the extinction burst, i.e., the slightly higher responding sometimes seen on the first extinction session or for spontaneous recovery usually seen on the first post-extinction session after a delay.

Theoretical Extinction Curve
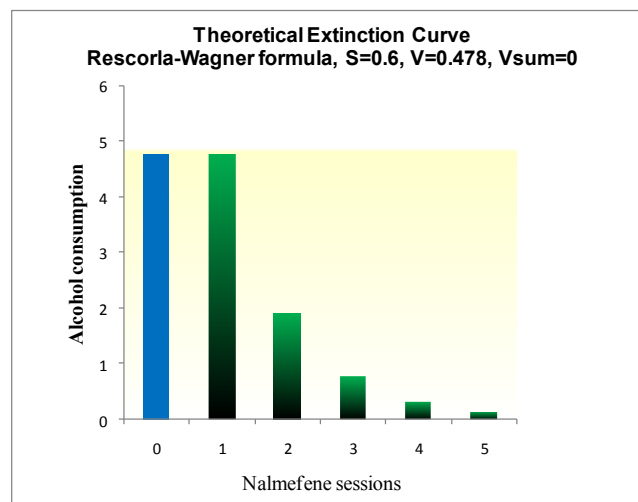**Rescorla-Wagner formula, S=0.6, V=0.478, Vsum=0**

Figure 9. The Extinction Curve according to the Rescorla-Wagner formula, where V was initially set at the pre-treatment level of drinking, 0.478; ΔV is the change in strength produced by the extinction session; S was set at 0.6; Vmax is zero for extinction; Vsum was set at 0. So the formula here shown is ΔV=0.6*[0-(0.5-0)] = 0.6*(-0.5) for the first effect of the first nalmefene session. Compare the theoretical results here with the observed results in Figure 2. The Rescorla-Wagner formula accounts for 99.3% of the variability in these sidata points.

Curve fitting to clinical data

The extinction curves for the clinical data were already shown on the figures. The mean craving data from all patients on naltrexone, shown in Figure 1, is very closely matched by the Rescorla-Wagner formula with Vsum set at 2.10. In exponential form it is $V_t=2.431e^{-0.03t} + 2.10$. It accounted for 98.9% of the variability in the empirical data.

In Figure 4, which showed the daily drinking records of the alcoholics on naltrexone, the theoretical extinction

curve from the Rescorla-Wagner equation with V set at the pretreatment mean, 6.1 drinks per day, Vsum set at 1.6 drinks per day, and S set at 0.018, accounted for 66.4% of the variability. This is far lower than that the preclinical data probably because of the extraneous factors that affect the day-to-day drinking of humans more than the intake by laboratory rats. It also is lower than the clinical craving data, probably because factors in addition to craving that influence human drinking.

The results support the conclusion that extinction is responsible for the decrease in craving produced by naltrexone, and plays a major role in the reduction in drinking.

Direct measure of cue-induced craving

There have been several studies examining the effect of naltrexone on how much craving people report when seeing stimuli related to alcohol.[xliii],[xliv],[xlv]. Each of these experiments, however, used patients who were being treated with naltrexone. Thus they cannot separate the effect of naltrexone itself from the effects of extinction caused by previously having drunk alcohol while on naltrexone, and the data already reviewed indicate that extinction has powerful effect on craving for alcohol in general. Therefore, we cannot conclude from these studies that naltrexone directly was reducing the elicited craving.

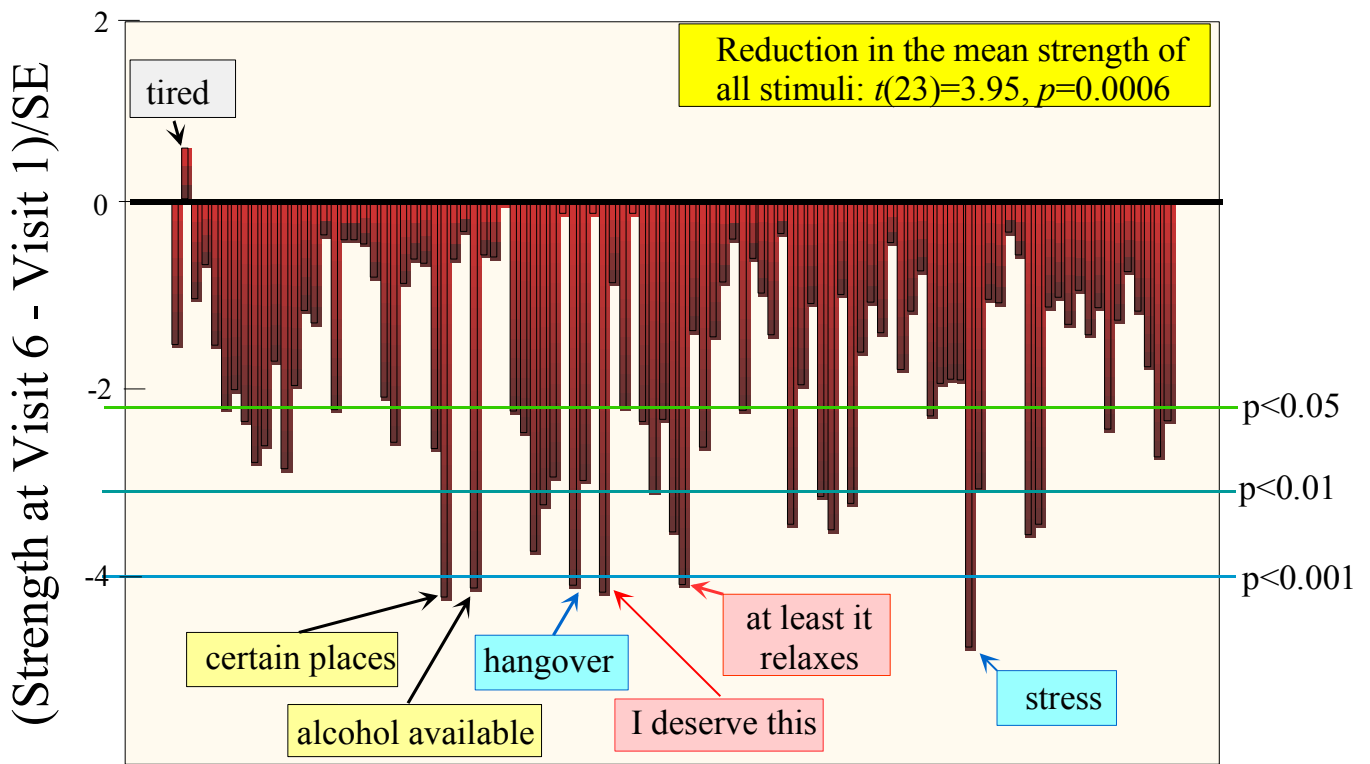| IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
The antagonist reduces craving triggered by pleasant (endorphin-releasing) stimuli and not by unpleasant and neutral stimuli	The antagonist reduces craving triggered not only by pleasant stimuli but also by unpleasant and neutral stimuli

An additional test can be obtained from an experiment we did at ContrAl Clinics.[xlvi] When I first was proposing that alcoholism could be treated with naltrexone, several people stated that they thought it would only help with one type of alcoholic. It was assumed that some people drank because they were stressed, had a hangover, or otherwise unhappy, and they expected alcohol would reduce their pain. Other alcoholics drank because they were in a party mood and expected alcohol to provide euphoria. The pleasure was assumed to be caused by the release of endorphins but the effects against stress, anxiety, hangover, etc., came from other neural systems. Therefore, they predicted that naltrexone would only be effective in the alcoholics who drank to get euphoria. These would also be the people who had stimuli related to the pleasant effects become conditioned to release endorphins that then could produce craving and drinking.

In contrast, the hypothesis that naltrexone worked by extinction predicted that all sorts of stimuli, not just pleasant ones, would have their ability to trigger craving and drinking weakened. It assumes that any stimulus that is frequently present when alcohol is drunk and endorphins released will have it connections to craving and drinking reinforced by the neuronal actions of the endorphins. Reinforcement is independent of pleasure; it is simply the strengthening of synapses and can even occur unconsciously. Extinction is also independent of pleasure. Any stimulus – pleasant, unpleasant, or neutral – which previously had had its connections to craving and drinking reinforced by the presences of endorphins will have the same connections weakened by the mechanism of extinction when the receptors for the endorphins are blocked when alcohol is consumed in response to the stimulus.

In order to test the differing predictions of the two theories for the actions of naltrexone, alcoholics coming for treatment at the first Finnish clinic were twice presented with 101 stimuli that might trigger alcohol drinking. Some of the stimuli were external, others were feelings or thoughts. The patients rated each stimulus as 1 to 5 for how strongly it was connected to their own drinking. Complete data were obtained from 24 patients. The test was given at the Visit 1, after about 10 days on naltrexone, and again at Visit 6, after about 100 days. The differences between the V6 and V1 ratings of a specific stimulus item were calculated for each subject. As shown in Figure 10, nearly all stimuli showed less reported ability to trigger drinking at the later visit, with the mean reduction for all stimuli combined being very highly significant: p=0.0006.

Both tests were conducted with patients taking naltrexone. The difference between the two tests was the intervening 90 days of drinking while on naltrexone. The hypothesis that naltrexone has a direct effect on the ability of stimuli to trigger drinking cannot explain why there was a difference between the two tests. The amount of naltrexone in the body would have been at least as high if not higher during Visit 1, when most patients were using naltrexone daily, than at Visit 6 when most of the subjects were using naltrexone only infrequently. Instead it appears that extinction had produced a powerful and consistent reduction in the reported ability of the stimuli to start drinking.

The results also supported the prediction from the extinction hypothesis that the weakening in the ability of stimuli to trigger drinking should occur for all sorts of stimuli (See Figure 10). The 6 stimuli with the most significant reductions (p< 0.001) included two pleasant ones, two unpleasant ones, and two neutral ones.

Figure 10. The reduction in the strength of the connection between 101 different stimuli and drinking from the first visit, about 10 days after starting naltrexone, to the sixth visit, after about 100 days on naltrexone. Nearly every stimulus had a weaker connection to drinking after the additional 90 days of treatment: 36 showed significant (p<0.05) weakening. Of particular theoretical interest, naltrexone worked not only when alcohol might be causing pleasant effects (e.g., "I deserve this") but also with unpleasant stimuli and neutral ones. This is contrary to the common belief that naltrexone works by blocking the pleasure from alcohol, but it is consistent with the view that extinction weakens the connections from all sorts of stimuli to craving and drinking.

Continued benefits without the medication

IF THE ANTAGONIST DIRECTLY REDUCES CRAVING FOR ALCOHOL	IF EXTINCTION, PRODUCED AFTER DRINKING WHILE THE ANTAGONIST BLOCKS REINFORCEMENT, REDUCES CRAVING
The craving reduction does not continue after the antagonist is no longer present	The reduction in craving continues after the antagonist has been removed

The evidence from both preclinical and clinical studies shows that the suppression of alcohol drinking continues long after the last administration of antagonist. This finding was reported in our first preclinical experimentsxlvii . The rats did eventually return to their previous level of alcohol drinking, apparently because of relearning the behavior now that reinforcement was again obtained, but it took them from 4 days to 2 weeks. In the meantime, drinking was significantly suppressed even though no naloxone remained in the body.

The continued efficacy is shown also in Figure 2 here. Alcohol was still significantly suppressed on both the first and second days after the last nalmefene administration ("Post1" and "Post2"). In an unpublished study ("Continued Efficacy After Nalmefene Treatment" used when applying for FDA approval of nalmefene), the first post-treatment access again to alcohol was a week after the last of 4 daily nalmefene injections (0.18 mg/kg subcutaneously): alcohol drinking was still significantly lower than in the saline-injected control animals. The report concluded "The results indicate that treatment with nalmefene, as well as with naloxone, can have a continued efficacy for suppressing alcohol drinking, persisting after all of the antagonist has been eliminated."

The strong reduction in craving shown in Figure 1 is, after the first month or two of treatment, coming primarily from patients who did not have naltrexone in their systems at the time of being tested. At Visit 6, about a quarter of the patients had stopped drinking completely and thus, according to the instructions, they were not taking any naltrexone. The others were only taking naltrexone on days when they expected to drink, and in most cases they had not been drinking or taking naltrexone on the weekdays when they visited the clinic.

The result was still clearer in the 3 year follow up the first naltrexone patients.xlviii The craving reported at this time was down to 1.4 cm on the VAS scale, which is significantly lower than the mean result of 2.2 cm reported back at Visit 6 after about 110 days of treatment (see Fig. 1). The patients in the follow up reported drinking (and taking naltrexone) at most only 1.4 times a week on average. So nearly all of the craving reports made in the follow up study were made by patients without any naltrexone in their systems.

These results are important for clinical practice. If craving were only reduced when naltrexone was blocking opioid receptors, doctors should try to make sure that their alcoholic patients continue taking naltrexone every day for the rest of their lives. Fortunately this is not true. The craving remains suppressed, once it has been extinguished, so long as the patient does not drink without first taking naltrexone – and thus relearning the addiction. Consequently, doctors can advise patients that they only need to take naltrexone on the days when they are drinking. Since the patients seldom are drinking, they seldom take naltrexone; most of the time they merely have to carry it with them on the off chance that they might change their minds and decide to drink. This is, of course, both safer and less expensive that taking naltrexone every day.

Conclusion

There is no evidence indicating that opioid antagonists have any effect on craving for alcohol in rats or alcoholics prior to the resumption of drinking. We cannot conclude that opioid antagonists have no direct effect (prior to extinction) on the craving for alcohol. That would be proving the null hypothesis. The data show, however, that if there is any such effect, it is too small to have a significant clinical effect on alcohol drinking.

Implications for treatment

The false belief that naltrexone directly blocks craving for alcohol has, I believe, been detrimental for the efficacious use of the medication. Most clinicians have a strong aversion to allowing their patients to drink while on naltrexone. They have throughout their career been telling alcoholics to abstain, and they want to continue telling alcoholics to abstain. Consequently, there is great resistance to the scientific evidence that naltrexone works through extinction because extinction requires the alcoholic to drink alcohol while naltrexone blocks the reinforcement.

Clinicians would like naltrexone to block craving directly. If it did, then they could detoxify alcoholics, then instruct them to abstain, and still give them naltrexone at the same time to block the craving and help them remain abstinent. Maintaining the false belief that this is how naltrexone works has allowed clinicians to prescribe the medication in this manner that is of no benefit – and probably even of some detriment – to their patients.

As a result of its being prescribed incorrectly, it has often not been effective, and the medication has gained a poor reputation. This has contributed to very few alcoholics being prescribed naltrexone.

An additional problem is poor compliance. Patients who are told that naltrexone will block their craving while they remain abstinent soon discover that they are still craving alcohol. They conclude that naltrexone does not work, since it did not produce the effect they were told to expect. Consequently, they are likely to stop using it, without ever having paired it with drinking and benefitted from extinction.

It is difficult to persuade clinicians to adopt a protocol that allows extinction. The belief that naltrexone blocks craving, without ever having to taste alcohol while on the medication, has provided them with justification for prescribing naltrexone the way they want to – with abstinence. Opioid antagonists are unlikely to be used effectively so long as clinicians believe it that the presence of the medicine in the body is an effective tool for blocking the craving for alcohol – or for opiates.

References

i Eskapa, R. (2008) *The Cure for Alcoholism*. Dallas, BenBella Books.

ii Tractenberg MC, Blum K. Alcohol and opioid peptides: Neuropharmacological rational for physical craving of alcohol. Am J Drug Alcohol Abuse 13: 365-372, 1987

iii Reid, L.D. and C.L.Hubbell (1992) Opioids modulate rats' propensities to take alcoholic beverages. In: Naranjo CA and Sellers EM (eds) *Novel Pharmacological Interverntions for Alcoholism*. New York: Springer-Verlag, pp.121-134

iv Wikler A. The theoretical basis of narcotic addiction treatment with narcotic antagonists. In: <u>Narcotic Antagonists: Naltrexone.</u> Julius D & Renault P (Eds.) Rockville: National Institute of Drug Abuse, pp. 119-122, 1976;

v Sinclair, J.D. Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol and Alcoholism*, 36**:** 2-10, 2001

vi Sinclair, J.D.; Iiro P. Jääskeläinen. Continued efficacy after naloxone-induced suppression of alcohol drinking: dependence upon relative timing. *Alcoholism; Clinical and Experimental Research:* **19** *supplement*, 13A, 1995.

vii Sinclair, J.D. From optimal complexity to the naltrexone extinction of alcoholism. In: *Viewing Psychology as a Whole: The Integrative Science of William N. Dember.* R. Hoffman, M.F.Sherrick and J.S.Warm (eds) Washington, D.C.: American Psychological Association, 1998, pp. 491-508.

viii Hyytiä, P. and J.D.Sinclair. Responding for oral ethanol after naloxone treatment by alcohol-preferring AA rats. *Alcoholism: Clinical and Experimental Research* **17**: 631-636, 1993.

ix Renault, P. F. (1978) Treatment of heroin-dependent persons with antagonists: Current status. *Bulletin on Narcotics* **30**: 21-29 ¶ Renault, P. F. (1980) Treatment of heroin-dependent persons with antagonists: Current status. In*: Naltrexone: Research Monograph 28*, Willett, R. E., and Barnett, G., (eds.), Washington, DC: National Institute of Drug Abuse, 11-22.

x Volpicelli, J. R., O'Brien, C. P., Alterman, A. I., and Hayashida, M. (1990) Naltrexone and the treatment of alcohol dependence: Initial observations. In: Reid, L. D., (ed.) *Opioids, bulimia, and alcohol abuse & alcoholism*. New York: Springer-Verlag, 1990; 195-214. *No significant benefits before first drink on Naltrexone.*

xi O'Malley, S., Jaffe, A., Chang, G., Witte, G., Schottenfeld, R.S., and Rounsaville, B.J. Naltrexone in the treatment of alcohol dependence. (1990) In: Reid, L.D., (ed.) *Opioids, bulimia, and alcohol abuse & alcoholism*. New York: Springer-Verlag; pp 149-157. *No significant benefits before the first drink on Naltrexone.*

xii Volpicelli, J. R., Alterman, A. I., Hayashida, M, and O'Brien, C. P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* **49**: 876-880. <u>First DBPC clinical trial for alcoholism. Naltrexone was safe and effective, with the primary effects being found in patients drinking while on medication, as required by extinction.</u> *No significant benefits before first drink on Naltrexone.*

xiii O'Malley, S.S., Jaffe, A.J., Chang, G., Schottenfeld, R.S., Meyer, R.E., and Rounsaville, B. (1992). Naltrexone and coping skills therapy for alcohol dependence. *Archives of General Psychiatry* **49**: 881-887. <u>The other DBPC trial in addition to Volpicelli used for FDA approval of Naltrexone for alcoholism. Naltrexone was safe and effective in gCopingh groups inadvertently encouraged to break abstinence,</u> *but there were no significant benefits in gSupportiveh groups with instructions to abstain. No significant benefits before the first drink on Naltrexone. Significant interactions indicating Naltrexone is better with Coping than Supportive therapy.*

xiv Mason, B.J., Ritvo, E.C., Salvato, F., Zimmer, E. Goldberg, G., and Welch, B. (1993). Nalmefene modification of alcohol dependence: A pilot study. *Proceedings of American Psychiatric Association Annual Meeting*, San Francisco, CA, May 1993, p. 170, abstract NR442

xv Mason, B.J., Ritvo, E.C., Salvato, F.R., Goldberg, G. (1994) Preliminary dose finding for nalmefene treatment of alcoholism. *Alcohol Clin Exp Res* 18: p. 464 (abstract 270)

xvi Mason, B.J., Ritvo, E.C., Morgan, R.O., Salvato, F.R., Goldberg, G., Welch, B., and Mantero-Atienza, E. (1994) A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral Nalmefene HCL for alcohol dependence. *Alcoholism: Clinical and Experimental Research 18:* 1162-1167. Small DBPC trial showing Nalmefene (similar to Naltrexone) is safe and effective in treating alcoholism. *No significant benefits before first drink on Nalmefene; the article says this finding confirms Sinclair□fs hypothesis that the medication is working through extinction*

xvii O'Malley, S.S., Jaffe, A.J., Rode, S., and Rounsaville, B.J. (1996) Experience of a "slip" among alcoholics treated with Naltrexone or placebo. *American Journal of Psychiatry*, **153**(2): 281-283. *Naltrexone patients drink the same as placebo patients on first day of a slip (before extinction),* but the Naltrexone patients subsequently are less likely to relapse into heavy drinking and have lower craving.

xviii Volpicelli, J. R., Rhines, K. C., Rhines, J. S., Volpicelli, L. A., Alterman, A. I., and O□fBrien, C. P. (1997) Naltrexone and alcohol dependence: Role of subject compliance. *Archives of General Psychiatry* **54**: 737-742. Naltrexone was safe and effective, but poor compliance limited results. *No significant benefits before first drink in total population,* but when only compliant patients examined, there was a significant benefit before the reported first drink.

xix Oslin, D., Liberto, J., O'Brien, C.P., Krois, S., and Norbeck J. (1997) Naltrexone as an adjunct treatment for older patients with alcohol dependence. *American Journal of Geriatric Psychiatry* **5**: 324-332. Naltrexone was safe and effective in older patients who drank, *but of no benefit until the first drink on medication*.

xx Kranzler, H. R., Tennen, H., Penta, C., and Bohn, M. J. (1997). Targeted Naltrexone treatment of early problem drinkers. *Addictive Behaviors* **22**: 431-436.

xxi Kranzler, H. R., Tennen, H., Blomqvist et al.. (2001) Targeted naltrexone treatment for early problem drinkers. *Alcohol: Clinical and Experimental Research* **25** (Suppl. 5) 144A. Naltrexone was safe and produced significant benefits, *but no benefits before first drink while on medication*.

xxii Anton, R. F., Moak, D. H., Waid, L. R., Latham, P. K., Malcolm, R.J., and Dias, J. K. (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. *American Journal of Psychiatry* **156**: 1758–1764. DBPC trial showing Naltrexone with coping to be safe and effective. *No benefit before first drink on medication*.

xxiii Mason, B. J., Salvato, F. R., Williams, L. D., Ritvo, E. C., and Cutler, R. B. (1999) A double-blind, placebo-controlled study of oral Nalmefene for alcohol dependence. *Archives of General Psychiatry* **56**:719-725. Second Nalmefene study, DBPC trial showing it to be safe and effective, *but not beneficial until first drink on medication*.

xxiv Rubio, G. (1999) How to use Naltrexone in different alcoholic patient groups. Abstract to "Evidence Based Medicine of Naltrexone in Alcoholism", satellite symposium to the 7th Congress of the European Society for Biomedical Research on Alcoholism. Barcelona, Spain, June 16-19, 1999. Open label but placebo controlled study showing Naltrexone was safe and effective. *No benefit until first drink on medication*.

xxv Knox, P.C., and Donovan, D.M. (1999) Using Naltrexone in inpatient alcoholism treatment. *Journal of Psychoactive Drugs* **31** (4):373-388. *Naltrexone with abstinence (in an inpatient program) was of no benefit; 63 alcoholics, DBPC.*

xxvi Morris, P.L.P., Hopwood, M., Whelan, G., Gardiner, J., and Drummond, E. (2001) Naltrexone for alcohol dependence: A randomised controlled trial. *Addiction* **96**: 1565-1573 Naltrexone was safe and effective with Coping with Drinking protocol. *No benefit until first drink on medication.*

xxvii Chick, J., Anton, R., Checinski, K., Croop, R., Drummond, D.C., Farmer, R., Labriola, D., Marshall, J., Moncrieff, J., Morgan, M.Y., Peters, T., and Ritson, B. (2000) A multicentre, randomized, double-blind, placebo-controlled trial of Naltrexone in the treatment of alcohol dependence or abuse. *Alcohol & Alcoholism* **35**(6):587-593, Nov-Dec. DBPC trial showing naltrexone was safe and effective in complying patients. *No benefit until after first drink*

on medication.

xxviii   Monti, P. M., Rohsenow, D. J., Swift, R. M., Gulliver, S. B., Colby, S. M., Mueller, T. I., Brown, R. A., Gordon, A., Abrams, D. B., Niaura, R. S., and Asher, M. K. (2001)   Naltrexone and cue exposure with coping and communication skills training   for alcoholics: Treatment process and 1-year outcomes   *Alcoholism: Clinical & Experimental Research* **25**(11):1634-1647. Naltrexone plus coping therapy was safe and effective. *No benefit until first drink on medication.*

xxix   Rubio, G., Jiménez-Arriero, A., Ponce, G., and Palomo, T. (2001) Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. *Alcohol and Alcoholism* **36**: 419-425. Naltrexone was safe and effective with Coping with Drinking protocol. *No benefit until first drink on medication.*

xxx   Guardia J, Caso C, Arias F, Gual A, Sanahuja J, Ramirez M, Mengual I, Gonzalvo B, Segura L, Trujols J, and Casas M. (2002) A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial *Alcoholism: Clinical and Experimental Research* 26(9):1381-1387 Naltrexone was safe and effective in 202 patients reducing relapses to heavy drinking. *No benefit until first drink while on medication.*

xxxi   Oslin DW, W Berrettini, HR Kranzler, H Pettinati, J Gelernter, JR Volpicelli, CP O'Brien (2003) A functional polymorphism of the μ-opioid response in alcohol-dependent patients. *Neuropsychopharmacology* 28: 1546-1552. Combination of three previous trials, one published positive (Monterosso et al. 2001), one published negative (Kranzler et al., 2000) and one unpublished found significant benefit of NTX on relapse rate and time to first relapse, with significantly better results in patient with the A/G or G/G allele than the A/A allele at the gene for mu receptors, but no medication by genotype interaction. *No significant effect of NTX on abstinence.*

xxxii   Morley KC, Teesson M , Reid SC, Sannibale C, Thomson C, Phung N, Weltman M, Bell JR, Richardson K & Haber PS (2006) Naltrexone versus acamprosate in the treatment of alcohol dependence: a multi-centre, randomized, double-blind, placebo-controlled trial. *Addiction* 10: 1451-1462. DBPC on 169 Australian alcoholics finds naltrexone significantly delays relapse to heavy drinking *but not time to first drink.*

xxxiii   O'Malley SS, Sinha R, Grilo CM, Capone C, Farren CK, McKee SA, Rounsaville BJ & Wu R (2007) Naltrexone and cognitive behavioural coping skills therapy for the treatment of alcohol drinking and eating disorders features in alcohol-dependent women: A randomized controlled trial. *Alcoholism, Clinical and Experimental Research* 31: 625-634. No effect on abstinence.

xxxiv   Srisurapanont, M. and Jarusuraisin, N. (2005) Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol* 8:267–280

xxxv   Sinclair, J D (2005) The Second Generation of Anti-Relapse Drugs:Opioidergic Compounds: Clinical. In: R Spanagel and K Mann (eds): *Drugs for Relapse Prevention of Alcoholism*, in the series Milestones in Drug Therapy. Basal, Switzerland; Birkhäuser, pages 125-134.

xxxvi   Kiianmaa, K, Hoffman, P.L. and Tabakoff, B. (1983) Antagonism of the behavioral effects of ethanol by naltrexone in BALB/C, C57BL/6, and DBA/2 mice. *Psychopharmacology* 79: 291-294

xxxvii   Sinclair, J.D., M.Rusi, M.M.Airaksinen, and H.L.Altshuler. Relating TIQ's, opiates, and ethanol. *Beta-Carbolines and Tetrahydroisoquinolines, Progress in Clinical Biological Research,* **90**: 365-376, 1982.

XXXviii   Parkes, J. H. and J.D.Sinclair. Reduction of alcohol drinking and upregulation of opioid receptors by oral naltrexone in AA rats. *Alcohol* **21**: 215-221, 2000.

xxxix   Sinclair D., F. Fantozzi, and J. Yanai. **Uso efficace del naltrexone: ciò che non è stato detto a medici e pazienti** (Effective use of naltrexone: What doctors and patients have not been told.) (in Italian) *The Italian Journal of the Addictions* 41: 15-21, 2003.

xl   Jorge Juárez, Barrios De Tomasi Eliana (2007) Alcohol consumption is enhanced after naltrexone treatment. Alcoholism: *Clinical and Experimental Research* 31 (2), 260-264

xli Pierce, WD & Cheney CD (2004) Behavior Analysis and Learning, Lawrence Erlbaum Associates, Hillsdale, NJ. See: p. 74.

xlii   Sinclair, J.D. *The Rest Principle: A Neurophysiological Theory of Behavior*. Hillsdale, N.J.: Lawrence Erlbaum Associates, 1981. Page 35 (redrawn from Fig. 4.4)

xliii   Monti, P.M., Rohsenow, D.J., Swift, R.M., Abrams, D.B., Colby, S.M., Mueller, T.I., Brown, R.A., and Gordon, A. (1996) Effects of Naltrexone on urge to drink during alcohol cue exposure: preliminary results. *Alcoholism: Clinical and Experimental Research* **20**: Supplement, 92A*,* <u>After seeing their own usual alcoholic beverage, Naltrexone patients had significantly smaller urge to drink than did placebo patients.</u>

xliv   Monti, P. M., Rohsenow, D. J., Swift, R. M., Gulliver, S. B., Colby, S. M., Mueller, T. I., Brown, R. A., Gordon, A., Abrams, D. B., Niaura, R. S., and Asher, M. K. (2001)   Naltrexone and cue exposure with coping and communication skills training   for alcoholics: Treatment process and 1-year outcomes *Alcoholism: Clinical & Experimental Research* **25**(11):1634-1647.

xlv   Grüsser SM, Ziegler S, Thalemann C, Partecke L (2006) Naltrexone as anticraving treatment: A psychophysiologicical evaluation. [3rd] Stapleford International Addiction Conference on: Latest developments in effective medical treatments for addiction, Berlin, March 18-19<u>. Naltrexone implants in detoxified opiate addicts produced significantly fewer relapses than levomethadone implants, better psychological results, and subsequently less emotional-motivational involvement when seeing stimuli related to opiate use.</u>

xlvi   Sinclair, J. D., Kymäläinen, O., and Jakobson, B. (1998) Extinction of the association between stimuli and drinking in the clinical treatment of alcoholism with Naltrexone. *Alcoholism: Clinical and Experimental Research* **22:** suppl.: 144A.

xlvii   Sinclair, J.D. Drugs to decrease alcohol drinking. *Annals of Medicine* **22**: 357-362, 1990.

xlviii   Sinclair, J.D., K.Sinclair, and H.Alho. Long-term follow up of continued naltrexone treatment. Alcoholism: Clinical and Experimental Research 24: suppl. 182A. 2000 (S16:4).