3 The Hard Evidence Behind the Cure

Intellectuals solve problems; geniuses prevent them.
—Albert Einstein (1879–1955)

The evidence from clinical trials around the world confirms the findings from research with alcoholic animals completed more than two decades ago. The conclusion is that combining active drinking with naltrexone is the most vital ingredient for success. There are several other essential features:

- No prior detoxification or withdrawal is required before naltrexone is prescribed.
- Naltrexone is taken only when drinking.
- Other behaviors reinforced by the opioid system are avoided while on naltrexone but occur on days when no naltrexone or alcohol is taken.

- Naltrexone is taken before drinking for the rest of the patient's life. A patient does not take naltrexone if he or she is not going to drink.

This approach to treatment has now been shown in clinical trials to be safe and effective. These procedures work without any need to punish or demoralize the patient.

Prior to conducting clinical trials with people, laboratory experiments proved that when alcoholic rats drank alcohol after they had been given opioid antagonists such as naltrexone, nalmefene, or naloxone, their drinking steadily decreased. These medications blocked the effects of endorphins and opiates such as morphine in the brain. By doing this, they prevented the endorphins released each time alcohol is consumed from reinforcing the system in the brain that leads to drinking.

As long as the alcoholic animals always had the medication before drinking, their drinking levels decreased and then remained down indefinitely. But if the medication was stopped and they were given access to alcohol, they gradually relearned the behavior and eventually began drinking heavily again. All of this was exactly as predicted by Sinclair's learning model of addiction and his pharmacological extinction method for treating it. Also as expected, naltrexone, naloxone, or nalmefene were of no benefit if they were given during abstinence—if the addicted rats were given the medication but not allowed to drink alcohol. In fact, giving these opioid antagonist medications *without drinking* tended to increase drinking levels slightly in already addicted laboratory animals because of pharmacologically enhanced learning.

Pharmacologically enhanced learning is produced from increased reinforcement because of a phenomenon called *receptor upregulation*. The body responds to having any particular variety of receptor blocked by producing more of that type of receptor. Consequently, naltrexone administration causes an increase in the number of opioid receptors ("upregulation") and the brain becomes super-sensitive to endorphins or opiates. *The clinical implications are that opioid antagonists such as naltrexone should therefore generally not be prescribed together with abstinence*.

The failure of naltrexone with abstinence was seen in the first clinical trial of its use for treating heroin addiction, as reported by Renault in 1980.[27] Naltrexone was prescribed to heroin addicts with instructions to abstain from taking heroin while on the medication. The overall results showed that naltrexone produced no significant benefits over placebo. It worked very well, however, for those patients who disobeyed the doctor's orders and took heroin (or methadone) while on the medication!

The first clinical trial of naltrexone for alcoholism, reported in 1992 by Volpicelli and associates at the University of Pennsylvania, gave naltrexone to alcoholics who had first been withdrawn from alcohol.[28] As might have been predicted from Sinclair's laboratory experiments, naltrexone was of no benefit so long as the patients took the medication while abstinent. In other words, naltrexone was no better than placebo in keeping them abstinent. However, naltrexone worked well after the patients began drinking together with the medication. The treatment was particularly effective in preventing patients who had sampled alcohol from progressing to a heavy drinking binge. The paper concluded: "the primary effect of naltrexone was seen in patients who drank alcohol while attending outpatient treatment." The study also found that "naltrexone was not associated with mood changes or other psychiatric symptoms."

The second clinical trial, reported in 1992 by O'Malley and associates was, by accident, a direct test of Sinclair's extinction treatment.[29] Two groups of patients were prescribed naltrexone or placebo and received strong instructions to abstain from drinking. Two additional groups were prescribed naltrexone or placebo but given instructions that inadvertently encouraged them to drink while on the medication. (These patients were told that falling off the wagon was not serious—it should almost be expected—but the important thing was to learn to cope with a slip so it did not turn into a binge.)

The results were the same as those Sinclair's team had found with alcoholic rats (shown in Figure 6). Naltrexone had significant benefits over placebo only in the group accidentally encouraged to drink while on the medication, but it was worthless with instruc-

tions to abstain. The most powerful results in the paper were the ones comparing the two naltrexone treatments and showing that it worked better with drinking than with support of abstinence. In addition, on some measures, like craving and number of drinks per occasion, naltrexone with abstinence tended to be even worse than placebo, just as it was in the results of the Finnish clinical trial shown earlier in Figure 6, and as Sinclair had found in rats, because naltrexone plus abstinence produces enhanced learning of alcohol drinking.

An open-label test on people who were not alcoholics but nevertheless were heavy drinkers gave naltrexone without prior detoxification and produced results that look almost identical to those Sinclair had found in rats (see Figure 2): alcohol drinking was reduced progressively along what appears to be an extinction curve, and it remained suppressed a month after the end of naltrexone treatment.[30]

A subsequent Swedish trial also compared naltrexone prescribed with abstinence groups with naltrexone prescribed with drinking groups.[31]Again, the results were the same: naltrexone worked when patients were inadvertently *encouraged to drink while on the medication, but it was worthless with instructions to abstain.*

The Finnish clinical trial by Heinälä (2001) was the first based on an understanding of extinction and thus to use controlled drinking deliberately as the goal for half of the subjects. The result, previously shown in Figure 6, shows that naltrexone was beneficial when combined with drinking but not when given with instructions to abstain.

Similarly, a trial in Chicago by Maxwell and Shinderman found no benefits when naltrexone was given to alcoholics with instructions to abstain, but there were positive results when alcoholics, also suffering from mental illness and usually hard to treat, were given naltrexone but not made to abstain.[32]

In another confirmation of the Sinclair Method, Henry Kranzler of the University of Connecticut's Department of Psychiatry and his colleagues confirmed that the treatment was highly effective when naltrexone was taken on an "as-needed" basis in high-risk drinking situations—always *before* the urge to drink became

overwhelming. The study conforms to Sinclair's Naltrexone + Drinking model of de-addiction and was published in the journal *Addictive Behaviors* in 1997.[33] Beneficial effects were still evident three months after treatment—patients were either not drinking or drinking far less than before treatment combining naltrexone with drinking.

Another team of researchers led by José Guardia in Spain published similar findings in 2002.[34] The multicenter, double-blind, placebo-controlled trial—the gold standard in clinical trials, where neither doctors nor patients know if they are taking an active ingredient—showed lasting benefits from naltrexone in 202 alcoholics. However, *the only patients who showed a significant benefit were those who drank while taking the medication.* The study concluded that naltrexone was well tolerated and reduced relapse to heavy drinking. "The most significant finding of our study," said Guardia, "was that naltrexone-treated alcohol-dependent subjects showed a reduced relapse rate to heavy drinking in comparison with those patients treated with a placebo. We know that alcoholism is a recoverable disease."

A study published in the *American Journal of Psychiatry* in 1997 by Lifrak found that naltrexone was safe and effective in adolescent alcoholics.[35] Oslin reported that naltrexone was effective in older alcoholics who were allowed to drink on the medication, but as with younger subjects, it was of no use during abstinence in delaying the first drink.[36]

All together, successful results have been reported in seventy-two of the seventy-four clinical trials with naltrexone or nalmefene to date that had conditions allowing extinction.* In contrast, thirty-five of the thirty-six trials that had conditions preventing extinction (such as treating hospital inpatients, strong instructions to abstain, or during a period, such as before the first drink, when

* Nalmefene is the "sister" drug. It is not yet fully approved by the FDA, but it is currently approved for human trials in the United States and is expected to be released soon in Europe. Nalmefene, unlike naltrexone, is not metabolized in the liver and so does not stress the liver. Also, nalmefene has a stronger binding affinity for opioid receptors than naltrexone. Naltrexone is now generic (the patents have expired), so it has not been pursued by large pharmaceutical companies because the right to manufacture it is not exclusive. In other words, any legitimate pharmaceutical company could make naltrexone, which has brought the price of the medicine down by virtue of open competition.

extinction could not occur) failed to find any benefits from naltrexone or nalmefene. Most of the successful trials—fifty-eight of them—were in the treatment of alcoholism; the others were for addiction to heroin, cocaine, or amphetamine or for pathological gambling (see Appendix A). This is an amazingly consistent set of findings. The theory, the animal results, the clinical trials with addiction to heroin and other drugs, and the clinical trials with alcoholism show that naltrexone is successful when used according to the Sinclair Method. And they show naltrexone is not useful when used with abstinence.

Unfortunately, many doctors have prescribed naltrexone along with instructions to abstain. This is partly because the manufacturer did not instruct doctors to use naltrexone in combination with active drinking, and also because of the presumption that naltrexone should work with abstinence. Even many doctors in America who worked on the clinical trials showing naltrexone does not produce significant effects with abstinence still say that they prefer having naltrexone being given with instructions to abstain. Acknowledging the role of extinction as the reason naltrexone works, one alcohol researcher was categorical: "it might be true that naltrexone only works with drinking," he said, "but this is only of 'academic interest' because you can't tell an alcoholic to start drinking again and you can't predict when the patient would relapse." Fortunately, most researchers today understand that naltrexone works through pharmacological extinction.

Often, treatment protocols have been based on the assumption that medications can only be given after patients have already been through withdrawal and detoxification and are currently abstaining alcoholics. This is the way disulfiram or Antabuse (the largely ineffective drug that causes nausea or even death if the patient drinks while taking it) is administered. Naltrexone is often prescribed as a *substitute* for Antabuse, which it is not. It is also the way naltrexone must be given to opiate addicts.

Naltrexone can be given in another, more effective and ethical way to alcoholics. This way offers a practical solution for having the patient drink while taking naltrexone, and also benefit from both taking naltrexone and instructions to abstain.

Naltrexone can be given to alcoholics who are still actively drinking. These patients were drinking yesterday and they almost certainly will be drinking tomorrow. They do not need to be told to drink. Indeed, they may be told to try to control their intake. But most important, they are told always to take naltrexone before drinking: "If you feel the urge to drink, take your naltrexone before you do."

This is how naltrexone has been used since 1995 in Finland. It is also how naltrexone was given in the Finnish clinical trial by Heinälä et al. All of the earlier controlled trials with alcoholics had first put the patients through detoxification, which meant that patients had to stop drinking for a period (three weeks) before being allowed into the clinical trial. These alcoholic patients had only inadvertently been encouraged to drink, because one cannot ethically tell an abstinent alcoholic to drink. The Finnish trial, however, moved the onset of naltrexone treatment back in time, before detoxification, when the alcoholics were still drinking.

The safety of starting naltrexone without first getting rid of physiological dependence had, of course, first been checked in rats. The clinical trials not only confirmed that this was a safe procedure, but produced the initially surprising result that naltrexone caused fewer side effects in drinking patients than in patients told to abstain.[24]

Patients treated with the Sinclair Method are, in fact, slowly detoxified over the course of treatment. They start the treatment with a physiological dependence on alcohol, but after several months of gradually reducing their drinking, they are consuming so little that they no longer show withdrawal symptoms. Thus, giving naltrexone to drinking alcoholics can be viewed as a new, improved form of gradual detoxification.

Alcohol withdrawal is a severe condition, sometimes causing hallucinations, tremors, anxiety, depression, and seizures. It can even be fatal. The usual way to deal with severe withdrawal symptoms is to prescribe benzodiazepines like Librium® or Valium®. Although these drugs help with the withdrawal symptoms, there is the very real risk that the patient will become seriously addicted to these drugs. Inpatient detoxification is also very expensive. A study published in 1997 found the cost then ranged from $6,336

with no medication to $9,630 when both lorazepam and phenobarbital were used.[37]

It has always been known that the safest way to withdraw from alcohol would be to reduce gradually the amount of alcohol taken each day. Then the body would have time to adapt. There would be no severe withdrawal reactions, and it would not be necessary to expose the alcoholics to other addictive medicines. The trouble was that alcoholics would not be able to taper off their drinking on their own. After all, the core of the problem is that they cannot control their alcohol intake.

Extinction with naltrexone, however, automatically produces this safer form of detoxification. Thus, the actual amount of alcohol drunk each day while taking naltrexone is reduced automatically, gradually, and rather effortlessly. Naltrexone, unlike benzodiazepines and barbiturates, is not at all addictive. No one ever gets high or develops a craving for naltrexone.*

The Sinclair Method—taking naltrexone before drinking—safely and effectively detoxifies the patient. It gradually removes the physiological dependence on alcohol with less risk than the traditional inpatient or outpatient detoxification programs.

The Sinclair Method is a safe and effective detoxification procedure with one additional benefit: the patient is also cured of alcoholism. The craving for alcohol and the obsessive drinking—the basis for the alcoholism—are also removed.

Seventy-two clinical trials consistently show that naltrexone and nalmefene, when used according to the Sinclair Method, are effective in treating addictions.** This is generally understood to be the most powerful way of treating alcoholism. Again, the trials consistently show naltrexone must be used along with drinking, and the Finnish clinical trial shows the best way of using it in conjunction with drinking.

Finally, the results of Project COMBINE, the largest clinical trial in the history of alcoholism research, consisting of 1,383 diag-

* The litmus test for an "addictive substance" is whether rats or humans will "work" to get it. Will they work to receive reinforcement from alcohol, cocaine, nicotine, or heroin? Yes. But they will not work for naltrexone or nalmefene.

** See Appendix A.

nosed alcoholics and conducted by an assembly of the top American researchers in the field, were published in the *Journal of the American Medical Association* (May 3, 2006).[38] This trial confirmed that naltrexone was effective but did not find significant benefits for another medicine called acamprosate. Most important, Project COMBINE found that naltrexone is effective for compulsive drinking with only basic medical management—no intensive psychotherapy is required. Naltrexone had originally been tested only within comprehensive programs of alcoholism treatment, including intensive counseling and therapy; consequently, the FDA approved it for use as an adjunct within such programs.

Project COMBINE clearly shows that this restriction is not correct. Naltrexone works without counseling. This has also been found in a smaller Australian study[39] with naltrexone and in a Finnish trial[40] with nalmefene. Therefore, the original restriction of prescribing the medication only within the context of highly specialized treatment or rehab has been removed. Now, your family doctor can safely prescribe naltrexone.

The Finnish clinics using the Sinclair Method have found that it is effective in 78 percent of the patients. Clinics using it in Florida report 85 percent efficacy. The first results from CORD,* a nongovernmental organization (NGO) using the Sinclair Method in India, indicate a 75 percent success rate.

About half of the cases in which naltrexone was not effective involve a failure to take the medication or a patient dropping out of treatment. This is a very low rate of noncompliance for alcoholism treatment. There is, however, a small minority of patients—perhaps 10 percent—who, according to their "drinking diaries," are using naltrexone properly but do not benefit from it. One of the hot research areas today is trying to find "markers" to identify these individuals who do not respond to naltrexone. There is evidence that they tend to be people who do not have close relatives who are alcoholics, who do not like very strong sweet solutions, and—according to Project COMBINE—who have a particular form of opioid receptor.

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* Chinmaya Organization for Rural Development, Sidbari, Himachal Pradesh, India.

The positive clinical trials, the results of Project COMBINE, and the reputation of the *Journal of the American Medical Association* mean that the use of naltrexone—and eventually, its sister medication, nalmefene—should increase greatly in the months and years to come. In other words, once the word that Naltrexone + Drinking = Cure gets out, alcoholism's days are numbered.

The American Medical Association usually restricts access to published studies on its Web site, but at the time of publication, it considered the results of Project COMBINE to be so important that it made the study freely available for download.

The Project COMBINE study began in 2001. When its results were published in May 2006, it was immediately recognized—even picked up by the media—as a landmark in alcohol research. Raymond Anton of the Medical University of South Carolina and Stephanie O'Malley of Yale University led the trial in collaboration with twenty other leading alcohol researchers.

Although Project COMBINE did not specifically set out to test the Sinclair Method formally, it concluded that naltrexone is invaluable in the treatment of alcoholism and recommended that the medication should now be prescribed for alcoholism in general medical practice, even without the requirement for intensive counseling or A.A. meetings. Although less than 2 percent of alcoholics in the United States have ever had the opportunity of being prescribed naltrexone, the indications are that it could become the new gold standard for treatment to reach the millions of alcoholics in America, Europe, and beyond who would otherwise be left untreated and unprotected from the ravages of this progressive illness.

Even in the United Kingdom, where naltrexone can—scandalously—only be prescribed for alcohol abuse on a private basis (that is, not subsidized by the government's National Health Service), the treatment now offers a brighter future for alcoholics, heavy drinkers, and those who simply need more control over their drinking.

David Sinclair reported on the lasting benefits of naltrexone three years after the start of treatment, in which patients continued to take naltrexone an hour before drinking.[41] The patients did not take the medication on days when they were not drink-

ing. The patients' craving, drinking levels, and liver damage markers were all way down. Indeed, these patients were drinking and craving alcohol less after three years than they had been after the first five months of treatment. Traditional abstinence-based alcoholism treatments had always found that the results were best at the beginning of treatment, and then gradually, week after week, the patients would relapse and the drinking would increase to the level it had been before treatment. Pharmacological extinction produces exactly the opposite pattern, as shown by this three-year follow-up study. The drinking and craving is highest in the first weeks of treatment, but becomes progressively lower as the weeks on treatment progress because each intervening episode of drinking while on naltrexone was one more extinction trial. In other words, the more often people drink while on naltrexone, the less they will want to drink.

The clinical trials demonstrating the efficacy of naltrexone continue coming out. For example, Morley et al. published an Australian double-blind, placebo-controlled study of 169 alcoholics in 2006.[42] Like the earlier studies, it showed naltrexone was effective in preventing alcoholics who were drinking while on the medication from relapsing to heavy drinking, but taking naltrexone during the initial period of abstinence did not delay the first sampling of alcohol.

The United States now has 1,630 drug courts; they are beginning to use naltrexone for alcoholic defendants who, rather than serving custodial sentences, can be monitored to ensure they take the medication. California Superior Court Judge Stevens was one of the first to institute mandated naltrexone treatment. He was so impressed with the results that he said, "We have had too much success not to use it." Describing himself as conservative, Judge Stevens is emphatic that imprisonment and standard therapies leave addiction intact. In his view, they basically do not work because they cannot prevent alcohol and opiates from "lighting up the brain"—which is why he believes most offenders relapse and find themselves back before the courts. An interview with Judge Stevens can be viewed on the Internet.*

* Naltrexone and the law. See http://youtube.com/watch?v=a88oFbHZS4E.

The Sinclair Method fulfills the cost-effective requirements as "evidence-based medicine"; more detailed scientific and academic references to published journal articles on the clinical trials can be found in Appendix A, the annotated bibliography of the clinical trials published prior to March 2008.

The graph in Figure 7 plots the results from an article by Agosti (1995) comparing the power of different forms of alcoholism treatment to reduce the number of drinks, as measured in various

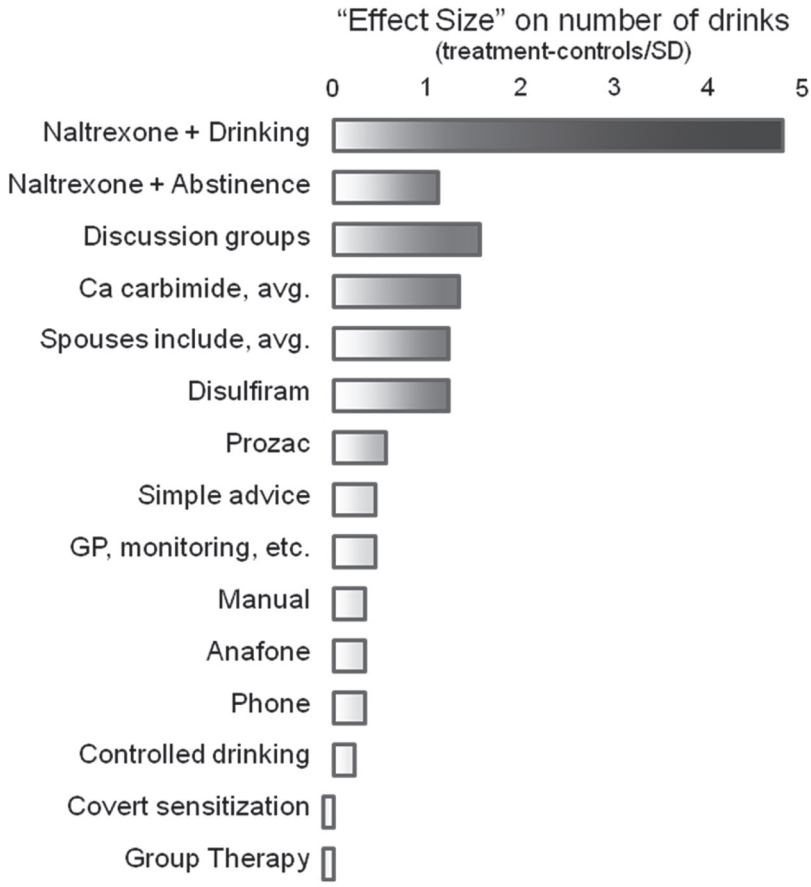

Figure 7. The "Effect Size" on reduction of the number of drinks shows that Naltrexone + Drinking (that is, the Sinclair Method) is more effective than giving Naltrexone + No Drinking Allowed and also that it reduces drinking far more effectively than other medications or other therapies (Agosti, 1995).

clinical trials. The naltrexone data are from the O'Malley et al. 1992 study. The article is rather old—1995—so it does not include data for newer treatments such as the use of the medication acamprosate. There have, however, been no similarly broad analyses made since then, and Agosti's conclusion, that naltrexone used appropriately is the most powerful treatment, is still valid today.