The Science of Naltrexone

When naltrexone first came on the market as a treatment for alcohol use disorder (AUD), I was conducting clinical research on the treatment ward of the National Institute on Alcohol Abuse and Alcoholism at the National Institutes of Health in Bethesda, Maryland. We soon began to prescribe naltrexone daily whenever we discharged someone from detox. Naltrexone did help patients stay abstinent, but most did not take it for long, and they typically resumed excessive drinking when they stopped (Jonas et al., 2014). Naltrexone did not seem to be the alcoholism cure my research colleagues were working for.

My thinking about naltrexone began to change when my friend Mark* asked me for a naltrexone prescription. I was surprised to learn he had a problem with alcohol; he was a successful executive—I had never seen him drink. However, when Mark held a business reception, he would lose control of his drinking and embarrass himself. He said he couldn’t stop after just one drink unless he took naltrexone first. He thought it would help if he always took it before drinking. Now he wanted a refill.

Here was a conundrum: My friend was clearly in danger of developing a serious problem with alcohol. I had seen suffering when people tried but failed to drink moderately. I also had seen the benefits of abstinence, and I admired the personality development of those who worked twelve-step programs. However, if I was adamant that Mark embrace abstinence, I risked ending further discussions with him about treatment. On the other hand, if I wrote Mark a prescription for naltrexone, that would give my tacit approval to keep drinking, and it would be on my conscience if Mark drank and had a bad outcome.

The Sinclair Method Changed My Mind About Naltrexone and Alcohol Recovery

By John C. Umhau, MD, MPH, CPE

*Names have been changed.
The use of naltrexone targeted for use before drinking is popularly credited to John David Sinclair, PhD (1943–2015), whose animal research showed that alcohol’s reinforcing effect could be blocked by naltrexone. Sinclair found that, over time, animals trained to drink alcohol would “extinguish” or unlearn their drinking behavior if alcohol was always preceded by naltrexone (John David Sinclair, 2001). Sinclair also found that the longer alcohol-drinking animals were deprived of alcohol, the more they would press a lever to get it, an effect he attributed to upregulation of opiate receptors. He called this the “alcohol deprivation effect,” a parallel to the increase in alcohol craving experienced by some people with AUD the longer they abstained from drinking. Sinclair reasoned that if a person who craved took naltrexone before they drank alcohol, alcohol drinking would not be reinforced. If this occurred repeatedly, the craving would gradually be “extinguished” by the effect of naltrexone.

Sinclair confirmed his hypothesis with clinical studies in Finland, and found that targeted naltrexone could not only help people drink less, but over time, it could help them lose the desire for alcohol. He called this process pharmacological extinction (Heinälä et al., 2001).

Sinclair recognized that for behavioral adaptation to occur, healthy pleasurable activities must be reinforced, so he encouraged no use of naltrexone on non-drinking days. This allowed endorphins produced by non-drinking behaviors (e.g., taking a walk in the park, enjoying a game) to reinforce those healthy behaviors. Sinclair postulated that this would help “rewire” the brain by replacing the drive to drink alcohol with a drive for healthy activities (John David Sinclair, 2001). Sinclair observed that the process of extinction typically takes four to six months or more, and that 78% of those who completed treatment could reach extinction (John David Sinclair, 2001).

Sinclair patented his proposal for therapy in 1989, and after publishing papers on its success in Finland, worked to commercialize his therapeutic technique (John D Sinclair, 1989). When naltrexone was approved by the U.S. Food and Drug Administration in 1995, the label omitted any reference to targeted use in actively drinking people and therefore did not impinge on Sinclair’s patented method. Also, the method’s unconventional requirement for drinking to continue during treatment conflicts with the tenants of traditional abstinence-based treatment, and is a significant barrier to wider acceptance by the treatment community (Barrio & Gual, 2016). Perhaps for these reasons, Sinclair’s method has remained relatively obscure.

As I reviewed naltrexone research, I found considerable support for Sinclair’s method (Niciu & Arias, 2013). Data shows that patients with AUD can be compliant with as-needed dosing and that taking naltrexone before drinking can reduce craving, consumption, and therefore the harm from alcohol (Volpicelli et al., 1997). Studies suggested that naltrexone was most effective for those who drank alcohol while taking it; this unusual finding was consistent with naltrexone trials showing that therapy promoting abstinence was ineffective compared to therapy which helped people cope with drinking (O’malley et al., 1992; John David Sinclair, 2001). This more successful counseling approach encouraged people who had a “slip” to keep taking naltrexone. Targeted naltrexone can also reduce consumption gradually, thereby eliminating the need for inpatient detoxification (John David Sinclair, 2001).

Long-term daily use of naltrexone can be hard to maintain; it can reduce healthy pleasures and cause a blah, dull feeling about life. Targeted use provides a realistic way to treat a lifelong condition while minimizing cost and the potential for adverse effects (Heinälä et al., 2001). Nalmefene, an opioid antagonist similar to naltrexone, is approved for targeted use in Europe to reduce alcohol consumption (Marazziti et al., 2015; Soyka, 2014).

Talking to Patients About Naltrexone

I first tried the Sinclair Method with Zoe, a very accomplished nurse who had come to realize that consuming a bottle of wine every night was not normal. She had no interest in abstinence or Alcoholics Anonymous, but she was interested in drinking less.

We discussed naltrexone and how it could provide a protective effect, or “wall” against the euphoria that can drive excessive drinking. After watching a TEDx talk given by actress Claudia Christian about the method (available at www.alcoholrecoverymedicine.com/sinclair-method), Zoe was keen to try it. She was hopeful that if she used naltrexone faithfully an hour before drinking, she could be free of obsessive thoughts about alcohol.

Next time I saw her, Zoe related a remarkable story. After she took her first naltrexone pill, she waited the required hour, and then had a drink. The usual “buzz” was gone. One glass of wine was all she wanted. Naltrexone helped “rewire” the brain by replacing the drive to drink alcohol with a drive for healthy activities.

... I am nothing short of amazed at the difference in my attitude towards alcohol. The very first drink I took after my first dosage was vastly different than any other drink I can remember. The intense satisfaction and almost euphoric feeling was simply not there. I really struggled to finish that glass of wine the first time—I just wasn’t terribly interested in drinking it.

After a few months of faithful use, Zoe was drinking only on weekends, and made a point of enjoying the outdoors on alcohol-free days. After 6 months she had reached “extinction” and no longer thought about alcohol. She would go for 6 weeks without drinking anything, but if she did drink, she was careful to take naltrexone and she did not exceed two drinks.

Success with the Sinclair Method is predicated on total compliance. If drinking ever occurs without first taking naltrexone, the resulting...
The Sinclair Method

### Possible Benefits
- Patients unwilling to be abstinent can be engaged in treatment.
- Long-term compliance is enhanced compared with daily use.
- Patients are actively involved in treatment.
- Less risk of adverse effects exists than with daily use of naltrexone.
- Pleasurable endorphins from healthy activities are only blocked when naltrexone is used.
- Gradual reduction of drinking reduces the risk of delirium-tremens.
- Costly and inconvenient inpatient treatment may be avoided.
- Alcohol craving may be permanently eliminated.
- Targeted use costs less than daily use of naltrexone.
- It is low cost and applicable for use in developing countries.

### Possible Harms
- Patients may feel that drinking has been sanctioned by their physician.
- Patients who can remain abstinent may be encouraged to continue drinking.
- The use of medication to reduce drinking may delay someone from seeking psychosocial support for abstinence.
- If driving occurs while intoxicated, naltrexone may further impair coordination.
- Patients may develop a false confidence on their ability to safety drink while taking naltrexone.
- Medication-only treatment may reduce the potential for personal growth derived from following 12-step principles.

The Sinclair method requires a lifelong commitment to take naltrexone before every drink (John David Sinclair, 2001), but finding appropriate long-term support can be difficult. Naltrexone can take away alcohol craving, but it doesn’t remove all reasons to drink (Umhau, 2019). Alcohol has anesthetic and anti-inflammatory properties, and can rapidly relieve physical and emotional pain, as well as boredom. Habits and peer pressure to drink can be hard to resist, especially without an understanding support system. Lifestyle counseling that promotes recovery through socialization, exercise and healthy foods (especially those that contain the omega-3 fatty acids found in seafood) may prove to be critical for long term success with the Sinclair Method.

I didn’t hear from Zoe for more than a year, but when I did, it was because she had relapsed after drinking at a wedding. Although Zoe was faithful to take naltrexone before the wedding, and although naltrexone blocked the “buzz” from her first drink, as the wedding day progressed and she kept drinking, by evening she began to feel the familiar euphoric effect of alcohol. Once she broke through the naltrexone “wall,” drinking alcohol felt too wonderful to stop. The next day she did not bother to take naltrexone at all. Now, she was eager for help from a counselor and peer support. When she reached extinction again, she would choose abstinence.

Once, I pulled one of our alcohol counselors into the exam room to hear Zoe’s story firsthand.

I could feel Zoe’s excitement as she shared her story, but my colleague did not seem to understand extinction or the progress Zoe experienced. The elephant in the room was our programmatic requirement for abstinence. My colleague invited Zoe to join a support group, but was careful to explain that the group would not condone any drinking.

Once the counselor left, and we were alone, Zoe confided that she would never attend such a group – the Sinclair Method had given her hope, and she had no desire to be shamed by her choice of therapy. I remember wishing I had somewhere to send her for support.

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### Understanding the Naltrexone Wall

Sixty minutes after swallowing a tablet, naltrexone blood concentrations are at their maximum, endorphin receptors are blocked, and this “wall” prevents alcohol induced euphoria. Since a “first drink” induces maximum alcohol craving, this is the critical time for naltrexone to have effect (Hendershot, Wardell, Samokhvalov, & Rehm, 2017). The endorphin release induced by subsequent drinks is less than the first, and therefore waning naltrexone concentrations may continue to provide an effective wall. However, four to six hours after taking the pill, naltrexone concentrations have dropped, a stiff drink can break the naltrexone wall, and relapse is possible.

The naltrexone labeling implies that 50 mg of naltrexone can block euphoria from heroin for 24 hours, however the effect on alcohol may not last this long (Umhau, 2019b). For a given dose of naltrexone, different people can have very different blood levels, and only those with the highest levels benefit (Brünen et al., 2018). Because of this variability, some people may require a repeated or higher naltrexone dose. Slowly drinking less concentrated alcoholic drinks may minimize the need for higher doses of naltrexone. Therapy can be informed by the subjective effect of alcohol in relation to the time elapsed since taking naltrexone.

### Side Effects

Naltrexone is well tolerated; common symptoms such as nausea or headache typically resolve over time and can be minimized by taking the pill with food and fluids (Croop, Faulkner, & Labriola, 1997). Suicidal thoughts are a rare side-effect requiring special caution. Naltrexone may also require monitoring of liver function. Naltrexone will also block the effect of opioid pain medications, so people on naltrexone should carry...
a wallet card indicating this fact. Naltrexone can precipitate opiate withdrawal in the chronic opioid user; it is possible that daily drinkers develop a milder but analogous situation when they begin naltrexone and the endorphins produced by heavy drinking are blocked. Naltrexone does not block alcohol intoxication, and may enhance the impairment of peripheral vision and divided attention associated with intoxication.

With daily naltrexone use, opioid receptors up-regulate, and can retain this increased sensitivity if naltrexone is suddenly stopped. Therefore, someone taking naltrexone every workday, but who stops on the weekend, may find that their super-sensitized opiate receptors make drinking especially pleasurable. This increased euphoria with drinking can reverse the previous progress towards extinction and also explain why compliance is critical for those prescribed daily naltrexone (Tempel, Gardner, & Zukin, 1985; Volpicelli et al., 1997).

**The Future of Alcohol Treatment**
Robust scientific evidence supports the use of medication to reduce alcohol consumption. However, less than 9% of patients who could benefit receive these potentially lifesaving drugs (Kranzler & Soyka, 2018). Recently I was talking to a patient who was very happy with the way medication had helped him overcome alcohol craving and allowed him to be abstinent. However, he confided that if he had known such medication existed 14 months earlier, he would not now be facing divorce and the loss of his family.

There is much we need to know about the best use of medication to treat AUD. In addition to naltrexone, FDA approved medications for AUD include acamprosate and disulfiram; other medications are used “off label,” including topiramate, baclofen, prazosin, and ondansetron (Kranzler & Soyka, 2018), but we don’t know if any of these medications can produce extinction. We also don’t know if using a monthly injection of depo naloxone can augment the use of targeted naltrexone when compliance is an issue (Brünen et al., 2018). Critically, there is no published data on therapy for those who reach extinction with naltrexone and later relapse.

Although most physicians are familiar with naltrexone, few are aware of the research literature supporting targeted naltrexone for AUD and even fewer have experience with the Sinclair Method. Sinclair’s method may be particularly effective early in the disease when people first
recognize that they have a problem with alcohol yet retain the resources necessary to maintain compliance with naltrexone.

Part of the reason that medications that reduce drinking are underused may be due to poor communication between members of the health care team. Medication requires considerable psychosocial support for success. For counselors who have a good relationship with a prescriber, discussing patients and sharing information can lead to the best outcome (Oslin et al., 2014). For counselors who lack a close relationship with a prescriber, incorporating medical treatment can be facilitated by the use of telemedicine. Video links allow convenient collaboration between a counselor and a prescriber, and can expand the availability of physicians who specialize in treating AUD. When the telemedicine visit occurs at a counselor’s office, medical treatment can begin with the client’s initial visit.

Regardless of how patients get their medications, they will benefit from skilled counseling support. This can be reimbursed through the collaborative care model, a team-based approach to enhance primary care with behavioral health integration. In this model, an addiction medicine specialist provides consultation to both the primary care team and a behavioral health care manager, (e.g., a Certified Addiction Counselor), who has a collaborative relationship with the health care team (Oslin et al., 2014). Medicaid and private payer reimbursement codes provided for this model can result in a net positive revenue potential (Lee, Scheuter, Rochlin, Platceh, & Kaplan, 2019).

The most effective treatment systems and programs have yet to be developed, and when they are, they may look very different than programs of today. For example, some patients may require a controlled environment that enforces compliance and provides psychosocial and nutritional support, while others with less severe disease and a healthy lifestyle may simply require education and medication follow up.

Many important scientific advances disrupt the status quo, and the use of targeted naltrexone is unlikely to be an exception. Early intervention with targeted naltrexone has enormous public health implications as a treatment option for AUD (Nicu & Arias, 2013). When people first recognize that they have an alcohol problem, Sinclair’s method not only provides hope, but it also engages them with addiction professionals. I am encouraged that this and other new interventions may one day remove both the stigma and the scourge of AUD. In the case of my friend Mark, Sinclair’s method provided a path to abstinence, and freedom from addiction to alcohol.

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**REFERENCES**


