

Perry - With my compliments, Richard

A PRACTITIONER'S EXPERIENCE WITH NALTREXONE

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I appreciate being invited to share my 25 years of experiences with naltrexone, and want to acknowledge Elaine Resnick, M.S.W., my wife, who has been an indispensable collaborator to this presentation and on our naltrexone research -- starting in 1973 with FDA Phase II studies and extending to the present with patients in our private practices.

We have no hesitation in explicitly stating that our experiences with naltrexone have been very positive; it is an extremely useful, but very underutilized medication that has been effective in the treatment of many patients. It has literally been a life-saver for many opioid-dependent people who, without it, would have been unable to escape from a never-ending cycle of detoxifications and relapses. For this group, taking naltrexone has facilitated continued abstinence, which would have been impossible without it.

However, naltrexone is a unique medication – unique in the fact that unlike most medications, it doesn't actually "treat" a disorder, rather it creates the circumstance that allows treatment to take place. Naltrexone does this by creating the equivalent of a "drug-free" environment, in an out-patient setting, so that the patient remains living in his or her home and community. One of the primary benefits of naltrexone is that it permits time for the extinction of classically conditioned craving and conditioned abstinence symptoms. The phenomenon of Pavlovian conditioning is one of the most common contributing causes of relapse – but is a little known and poorly understood phenomenon within the treatment community.

I would like briefly to review the history of how and why naltrexone was developed in the first place.

In the 1950's and 60's, heroin addicts would be arrested in New York City and sent to a Federal Prison in Lexington, KY, where the NIDA Addiction Research Center was then located. This was the place where some of the most fundamental and best addiction research has been conducted and as a result extraordinary contributions were made to our understanding of the mechanisms of heroin addiction and its treatment.

The researchers at Lexington made a common observation that during confinement at the prison hospital (or any other confinement, for that matter) craving for heroin would dissipate gradually. For periods of years, these former addicts had no heroin craving at all. When discharged, however, upon returning to New York, while crossing the George Washington Bridge, for example, suddenly and inexplicably they would be overcome by intense cravings, which would lead to impulsive heroin use and relapse. Often, this reaction occurs on the very first day back, even after having had years of abstinence and no craving or interest in resuming heroin use. At that time relapse rates were in the range of 95% or more. Contrast this with the heroin-addicted soldiers who returned to the United States from Viet Nam, whose relapse rates were only 14%.

So how can these seemingly contradictory phenomenon be understood? It was Drs. Abraham Wikler and William Martin who demonstrated, initially in animals, that Pavlovian conditioning was the primary factor in this process of relapse. Just as Pavlov's dogs salivate when the bell is rung, once it has been paired with the smell of meat, in the former addict innumerable external and internal cues that previously were associated with heroin self-administration, serve as "bells" that produce physiologic changes identical to those that

occur during pharmacologic abstinence – dilated pupils, sweating, cramps – the entire abstinence syndrome! Symptoms of Conditioned Abstinence are the same as those that occur during narcotic withdrawal. In a controlled laboratory setting, at the University of Pennsylvania, Drs. Charles O'Brien and Anna Rose-Childress clearly demonstrated that this phenomenon occurs with human subjects.

Bill Moyers in his recent PBS-TV series on addiction emphasized addiction to be a disease of the brain. Thirty years ago, Wikler described the heroin user as having developed, "*sui generis*," a new condition. Wikler showed addiction becomes a disease of the brain when he demonstrated conditioned abstinence, and recently these findings are being confirmed and refined by using modern brain scan technology.

To extinguish the conditioned response of salivation in Pavlov's dogs, the bell must continue to ring, but never again be associated with meat. However, even with occasional reinforcement, one could maintain conditioned salivation forever.

Conditioning factors are the same for people addicted to heroin. For extinction to occur, there must be exposure to the conditioned stimulus without any reinforcement. Time alone will not do it. Addicts are extremely vulnerable to relapse, unless extinction occurs. Therefore, they need to be protected by naltrexone during exposure to the myriad of conditioned stimuli associated with their heroin use.

Wikler described psychotherapy and psychoanalysis as notorious failures for addiction treatment, because, as he put it: "There were forces at work of which neither the therapist nor the patient were aware." Unfortunately, I do not think many treatment providers today are any more aware of these forces than they were during Wikler's time, thirty years ago.

Wikler and Martin theorized that if a narcotic antagonist medication could be developed that was both orally effective and long lasting, it might have clinical efficacy by allowing all the "bells" to ring for detoxified heroin addicts without heroin reinforcement, thereby enabling or facilitating their conditioned abstinence and craving to become extinguished over time.

It was this new concept of addiction that gave birth to the development of naltrexone. Clinical trials were begun in 1973, which led to subsequent approval by the FDA. As stated in the PDR, it is used "as an adjunct to the maintenance of an opioid-free state in detoxified formerly opioid-dependent individuals."

In our studies, starting under NIDA-funded grants and continuing in private practice, we consistently found that among opioid-dependent patients who request detoxification, 15-20% are able to complete it as out-patients and begin naltrexone and 10-15% of the original group are still taking it at 6 months follow up, while continuing in an aftercare treatment program. These results are comparable to what's been found by other addiction researchers and, by the way, are comparable to success rates in many other areas of medicine. In 1978 we reported that of 267 heroin addicts who started naltrexone, those who continued in treatment for 3-24 months and then stopped treatment – at a follow-up 6 months after stopping – 31% had remained opioid-free. Even better outcomes are found in selected treatment groups, such as addicted professionals and federal probationers, and these will be described by other presentors.

I have a strong aversion to those who use a statistic of 15% overall effectiveness to denigrate the value of naltrexone's usefulness, because this statistic represents the lives of many thousands of individuals. And for each individual protected from relapse, it is a 100% effective treatment for him or her.

It's obvious naltrexone is not appropriate for every heroin addict – but neither is methadone maintenance or entering a therapeutic community an appropriate treatment for every narcotic addict.

So how do we select our patients? In reality, we don't – they select themselves, but they are able to do this only after having been properly informed of all available treatment options. Patients also should be told that switching from naltrexone to another modality is always an option, because it is not uncommon for a patient's medication need to change over time.

SLIDE 1 (page 10)

There is both "good news" and "bad news" regarding naltrexone treatment. The good news is that it is highly effective for relapse-prevention. It can be considered virtually 100% effective in providing the required drug-free environment, although there is a very small sub-group (<10%).who cannot take it due to adverse side-effects. ...

For patients who do take it, naltrexone creates the equivalent of an environment in which heroin is totally unavailable. It eliminates any need for the person to struggle with ambivalence or to rely upon "Will Power." Relying on will power, by itself, is insufficient as a determinant of future behavior. It's highly reassuring for both patients and families to know that the decision to remain drug-free needs to be made only one time each day and it is by making that daily decision to take naltrexone that "will power" comes in – the decision to take the medication. Each day that choice is made, the person is protected from a relapse that inevitably would follow even a single impulsive heroin use. So long as the naltrexone is taken, even if impulsive opioid use occurs, the patient is protected from readdiction and the opioid drug has no more effect than placebo.

SLIDE 2 (page 11)

The "bad news" is that few detoxified heroin addicts are ever even told of its availability. Since naltrexone has been on the market, we have had experience with hundreds of previously detoxified addicts and rarely has anyone been informed that it even exists. In a few cases when a patient has been told about naltrexone, while in a detoxification program or a rehabilitation facility, they are then often given instructions for using it that are totally inadequate and a guaranteed set up for failure. When that happens, the medication usually gets a bad rap, when the fault really lies with the way the physician has provided it.

Innumerable patients have told us that the doctor gave them a prescription for naltrexone, with instructions to "take one daily." This approach is doomed to failure. Treatment providers need to create an optimum context so that the medication will be taken.

SLIDE 3 (page 12)

This context should include three elements: psychoeducation; monitoring medication compliance; and providing ongoing therapeutic contact.

The educational component involves explaining conditioning and extinction and helping patients to learn to identify their own internal and external "triggers." Also, addiction must be reframed from a stigmatized condition to that of a chronic illness. In this context, relapse should be anticipated and if it occurs should not be dealt with as a moral or treatment failure. Treatment with naltrexone should be resumed as quickly as possible.

Patients should be encouraged to stay on naltrexone for at least 12 months and to discontinue it only after conferring with the physician, with input from significant others, if possible.

It is essential to have a responsible person monitor that naltrexone is taken. Left to self-administer it, patients invariably fool themselves into thinking they can skip a dose and use heroin for one day only. As expected, this commonly leads to a full blown relapse. If there was only a single heroin use, naltrexone can be restarted after only 24 hours. In contrast, to begin naltrexone, at least 5 days abstinence is needed after heroin dependence has developed and 10 days abstinence from methadone dependence.

We usually assign monitoring to a person with whom the patient lives. In several cases an employer has been used. The person who monitors the naltrexone can be told he or she no longer needs to be concerned about heroin being used, so long as he or she knows the medication has been taken. The patient is usually relieved to know that heroin can no longer be used "in secret," since refusal to take the naltrexone becomes equivalent to announcing, in advance, that there is an intention to use heroin. Since ambivalence is ubiquitous in addiction, all patients should be encouraged to talk about it, without feeling ashamed. They need to know that there may always be some inner desire to use, even if their predominant desire is to "stay clean."

We characterize naltrexone as "insurance policy," telling them there will be times in the future when craving will occur, particularly if encountering an unanticipated conditioned stimulus, such as being offered heroin at a social gathering. But if naltrexone is taken, the patient is relieved from having to struggle with impulses and is protected from relapse, even if heroin is used. Describing naltrexone as an insurance policy is an easily understood and concrete analogy that can help to motivate compliance.

If there is no appropriate person to monitor the naltrexone, then it is important that the patient receive it at the treating clinic or physician's office, or in some cases a pharmacy. Many patients who live alone have come to my office three times a week, to receive naltrexone directly from me.

I always administer the first dose and use this time as an opportunity to demonstrate to the family how to do it. Early on we learned that the person administering naltrexone can't simply hand the tablet to the patient, because this enables ambivalent patients to simply "cheek it" and then spit it out.

The method I demonstrate on giving the first dose is to put the naltrexone in a cup, crush it with the back of a spoon, then add a liquid to the powder and watch the patient drink it. Doing this guarantees that the medication is swallowed and is preferable to examining the patient's mouth or taking the risk of non-compliance.

Lastly, we believe the outcome is better (and have reported experimental data to support this belief) if all patients are seen by a professional therapist for ongoing support and guidance and for treatment of co-morbid conditions, which are common in the addict population, particularly depressive disorders and marital conflicts.

As you can see, we are still enthusiastic about naltrexone and hope that more efforts are made to educate physicians, addiction counselors and the public about its value in treatment.

END OF TALK

Slide 1

NALTREXONE

- **Highly effective (>90%) for relapse-prevention in a selected group**
- **Eliminates need to struggle with ambivalence or "will power"**
- **Reassuring to patients and families**

Slide 2

NALTREXONE

The Bad News

- **Few detoxified addicts even informed of its availability**
- **Instructions for proper use are often inadequate**
- **Need to create an "optimum context" for its use**

Slide 3

NALTREXONE

Elements of Optimum Treatment Context:

- **Psychoeducational:**
 - Explaining the important role of conditioning**
 - A chronic relapsing illness**
 - Time in treatment 9-12 months or longer**
- **Monitoring medication compliance**
- **Providing ongoing therapeutic contact:**
 - Developing a therapeutic alliance**
 - A non-judgmental approach**
 - Treatment of comorbid conditions**