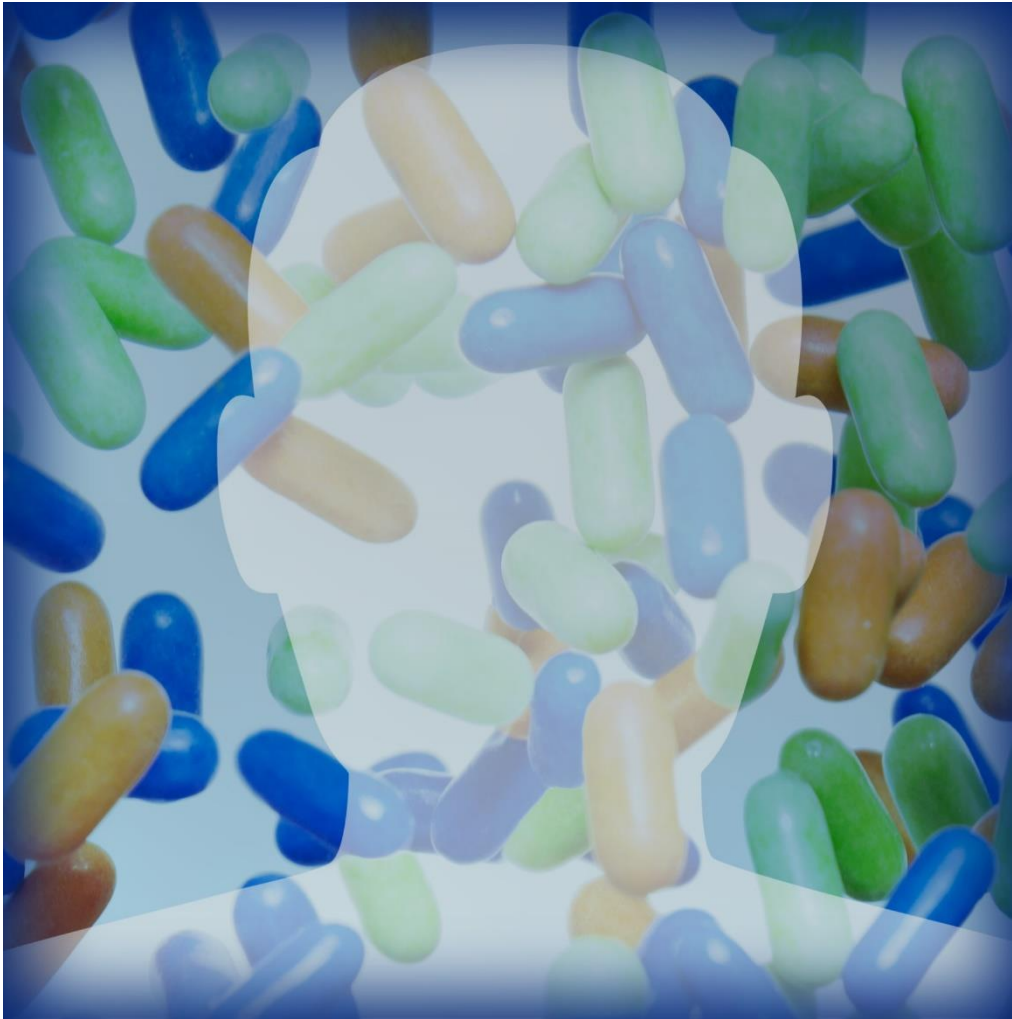


Naltrexone: A History and Future Directions

By Benjamin Srivastava, M.D. and Mark S. Gold, M.D.



Illustration/EGADS

Editor's Note: Trying to kick drug addiction without medicines is said to be like relying on willpower to overcome diabetes or asthma. Enter naltrexone, which has been around since 1984 and reduces the cravings for drugs and alcohol by fine-tuning the brain's chemical reward system. Why has it recently increased in popularity? How does it compare to similar strategies? Has it made a difference? Our authors, who have long studied addiction and the brain, confront a drug and alcohol addiction problem that today kills more Americans each day than gun violence or car accidents.

The opioid epidemic is one of the foremost public health crises in the United States. A recent analysis from Stanford University suggested that without any changes in currently available treatment, prevention, and public health approaches, we should expect to have 510,000 deaths from prescription opioids and street heroin from 2016 to 2025 in the US.¹ Both the lay press and scientific literature are full of proposals, analyses, and potential solutions. Most focus on expanding access to and dissemination of overdose reversal treatment (naloxone), and the medication-assisted treatment (MAT) drugs methadone, buprenorphine, and naltrexone. Obviously, expanding the availability of naloxone and MAT drugs are important steps that can be readily implemented, especially using an approach similar to what was done during the HIV epidemic.^{2,3} But in addition to such efforts, we must invest in research to develop new treatments informed by neuroscientific evidence.

Naltrexone's Evolution

A comprehensive discussion of naltrexone should be understood within the context of naloxone, which is considered its short-acting version based on relative half-lives (three hours for naloxone, 13 hours for oral naltrexone). When first synthesized, naloxone was a novel medication as well as a cornerstone of research into the pharmacology of the opioid system. Naloxone successfully competes against opioids to bind to the “Mu” opioid receptor on neurons, completely blocking the opioid’s downstream effects. As a “Mu opioid receptor (MOR) antagonist,” it reverses the potentially deadly effects of opioid overdose.

Naloxone was first synthesized and subsequently patented in 1961 by Drs. Jack Fischman and Mozez Lewenstein of the Memorial Sloan Kettering Institute for Cancer Research, based on a theory proposed by their colleague, Dr. Harold Blumberg at the Long Island-based Endo Laboratories. Intravenous naloxone (Envizio) was approved by the Food and Drug Administration (FDA) for opioid overdose reversal in 1971 and was shortly adopted as a standard emergency treatment at many of the nation’s premier academic medical centers. At Yale New Haven Hospital’s emergency department, I (MSG) routinely administered the drug nearly 40 years ago.^{4 5}

Until recently, naloxone was only available for intravenous use. In 2014, the FDA approved a subcutaneous/intramuscular autoinjector form that could be administered by an individual. In 2017, they approved a nasal spray form (NARCAN). We have long held that naloxone is similar to CPR or the Epi Pen—it reverses the acute, life threatening consequences of an illness, but it does not address the illness itself. Nevertheless, as physicians who have long labored in psychiatry and in addiction specifically, we absolutely need and want to rescue, resuscitate, and revive the patient and give them another chance to make a change. Allison L. Pitt and her Stanford colleagues correctly point out that none of the current treatment and policy proposals can substantially reduce opioid-induced deaths in the long term, but of the current interventions, naloxone could have the most impact.¹

Like naloxone, the long-acting naltrexone is a MOR antagonist. It was first synthesized in 1963 by Endo Laboratories, which was later purchased in 1969 by DuPont Pharmaceuticals. Though the drug remained essentially dormant for several years, it attracted interest in 1972 when Congress passed the Drug Abuse Office and Treatment Act for the purpose of developing non-addictive (i.e., non-agonist) treatments for heroin addiction. At that time, methadone, a long acting MOR agonist, was the only medication available for opioid addiction. It seemed to quell cravings yet not produce as significant of a “high” or cognitive inhibition of heroin (though still did in some cases).

Practically speaking, heroin-dependent patients, if compliant with methadone, are able to work, have relationships, and lead productive lives. While methadone is an agonist (binds to opioid receptors and is addictive), it seemed to quell cravings. Nevertheless, the drug must be dispensed at a licensed clinic and requires careful monitoring; it is liable to abuse and diversion and, if combined with other sedating drugs (e.g., barbiturates, benzodiazepines, alcohol), can lead to overdose and death. Thus naltrexone, without the sedating, euphoric, and potentially fatal side effects of methadone, had enormous appeal as an office-based, alternative pharmacotherapeutic option for opioid-use disorder.

Naltrexone’s Learning Curve

In 1974, the National Institute on Drug Abuse (NIDA) approached DuPont Pharmaceuticals about rigorously studying naltrexone to facilitate FDA approval.⁶ Though early trials led by Dr. Chuck

O'Brien at the University of Pennsylvania and others were promising, they were plagued by participants' noncompliance. Specifically, since participants needed to make the decision daily to take oral naltrexone instead of heroin, many intermittently chose to use heroin instead. Noncompliance was followed by almost inevitable relapse, which was (and continues to be) a major issue that limits the utility of daily oral naltrexone.^{7,8} Nevertheless, the FDA in 1984 approved naltrexone for treating heroin addiction, noting in the labeling that it does not reinforce medication compliance, and a therapeutic effect is expected only when given under external conditions that support its continued use.

An extended-release form, administered in monthly injections (Vivitrol), demonstrated markedly improved compliance over the oral formulation. Its manufacturer (Alkermes) applied for and received FDA approval in 2006 for alcohol-use disorder and in 2010 for opioid-use disorder.^{9,10} An even longer-acting implantable form of naltrexone has since been developed, although is still being tested and not currently approved for clinical use.¹¹

At Yale in the mid-1970s, we had already done major work on elucidating the neurobiology of opioid withdrawal and the role of noradrenergic discharge in making withdrawal symptoms so difficult to tolerate. We first discovered that symptoms of opioid withdrawal were modulated by excessive discharge of norepinephrine from the locus coeruleus, a nucleus in the pons of the brainstem involved in physiological responses to stress and panic. Then, in a series of landmark papers, we showed that clonidine, by directly inhibiting this discharge, suppresses withdrawal symptoms.¹² We could safely detoxify patients and send them to Alcoholics Anonymous (A.A.) or a residential treatment center, or put them on the oral form of naltrexone. We thought at that time that we had found the perfect MAT. Naltrexone was inexpensive, long-acting (as opposed to naloxone), safe, and effective. Patients did not report major central nervous system side effects, and the drug completely blocked the effects of heroin.

Some patients taking naltrexone tried to overcome the blockade by injecting large amounts of heroin and complained to the physician that they weren't getting high and were wasting their money. Compared with methadone, patients on naltrexone did not experience any euphoria, tolerance, or withdrawal; naltrexone was clearly non-addictive. But as discussed above, few

patients complied with short-acting naltrexone treatment, and most relapsed. These lessons, learned in the late 1970s and early 1980s, are not generally included in today's discussions of naltrexone (or naloxone) implementation.^{4, 13, 14}

In the 1980s, we tested naltrexone in groups that had professional reasons to adhere to prescribed treatments: physicians and businessmen, who are often coerced into following treatment and have strong professional and financial incentives to remain abstinent. Our early results were clear: more patients than in the past took naltrexone, stayed in treatment, and were drug free for a six-month period. We then suggested (at the time, controversially) that for medication-assisted treatment to be effective, patients need to be incentivized and followed longitudinally (on the order of years, not just for several weeks or 90 days) in a structured setting that addressed all medical, psychiatric, and social aspects of their addiction.¹⁵

Our long-time colleague Dr. Robert DuPont, a former US "Drug Czar" (head of the Office of National Drug Control Policy) and the first director of the NIDA, and others continued exhaustive work on programs to help physicians suffering from addiction. They completed a longitudinal study that began in 2008 and followed individuals enrolled in different states' confidential Physician's Health Programs (PHPs) over five years. That study demonstrated that at five years nearly 80 percent of physicians enrolled in PHPs who received comprehensive care, including 90-day structured residential treatment, continuous monitoring through drug testing, support groups (addressing psychiatric and medical comorbidity), and long-term follow up, had remained in treatment, were abstinent, and had returned to work. Of note, very few physicians were prescribed naltrexone and none were prescribed FDA-approved agonist therapy (buprenorphine, which had been approved in 2002, or methadone). Decisions regarding pharmacotherapy were largely left to the treatment centers and treating physicians^{16, 17}

Since then, naltrexone has been found to have considerable utility in the treatment of impaired physicians. As anesthesiologists are particularly notorious for developing intravenous opioid addictions, oftentimes with consequences including overdose and death, the State of Florida's PHP recommended that all anesthesiologists (but not necessarily other specialties) diagnosed with opioid addiction be maintained on naltrexone injections and continue with the other aspects of

their prescribed treatment. PHP data indicates that this practice is successful in maintaining abstinence and retention in treatment.¹⁸ These experiences suggest that patients need help taking treatment as prescribed and for as long as necessary.

Naltrexone and Alcohol

While drug overdoses claimed 63,000 American lives in 2016, it is estimated that excessive alcohol use caused 88,000 deaths during the same year,¹⁹ so obviously alcoholism represents an important public health problem as well. In 1986, Dr. Joseph Volpicelli, a psychiatrist and research fellow at University of Pennsylvania, demonstrated that in an animal model of alcohol consumption, rats drink more when exposed to a foot shock (a painful stimulus). Further, naltrexone blocked post-shock increase of alcohol consumption, implicating a likely mechanism of the endogenous opioid (specifically endorphin) system in alcohol consumption.²⁰ This landmark study prompted the first clinical trial of oral naltrexone in alcohol-use disorder, conducted by Volpicelli and O'Brien. It demonstrated naltrexone's efficacy in preventing relapse in these patients.²¹

A group at Yale replicated their findings in a larger cohort, leading to FDA approval of the drug for the treatment of alcoholism.²² Since then, many clinical trials have demonstrated that naltrexone consistently reduces the overall amount of alcohol consumed and the number of heavy drinking days, albeit with moderate effect sizes.²³ Another study found that alcohol-use disorder and opioid-use disorder frequently co-occur and, if alcohol-use disorder is left untreated, the rate of opioid relapse quadruples.²⁴ Thus, naltrexone may have dual efficacy in the treatment of co-occurring alcohol and opioid-use disorders.

One challenge has emerged because of the small to moderate effect sizes of naltrexone therapy: predicting which patients will respond to naltrexone. Hugh Myrick and colleagues showed that naltrexone reduces craving through reduced activation of the ventral striatum—the brain's reward system—when presented with a salient cue.²⁵ Schacht and colleagues demonstrated that genotype may influence this process, via dopaminergic neurotransmission.²⁶ A later study by the same group failed to show genotypic moderation of these effects, but found that carriers of a candidate gene had an accelerated return to drinking after medication was stopped.²⁷ Thus, genetic and imaging

findings as they relate to patient response to naltrexone have been inconsistent.

This inconsistency raises an important point about brain connectivity. Most task-based functional magnetic resonance imaging (fMRI) studies presuppose that the task reflects an actual neuropsychological construct (i.e., valid description of human behavior with a consistent neurobiological underpinning) and that the signal-to-noise ratio is low.²⁸ Additionally, most such studies focus strictly on anatomical areas, although decades of research in systems neuroscience have demonstrated that the brain is functionally organized into resting state networks (RSNs).^{28, 29} In fact, when scanned for a sufficient amount of time (~100 minutes vs the 5-10 minutes that most resting state studies use), an individualized connectome with topological distinctions in anatomical organization of RSNs from a group average may be produced.^{30, 31}

Recent work from Caterina Gratton and colleagues demonstrated that cortical RSNs within an individual are stable and contribute the largest amount of between subject variability in brain connectivity, even when tasks are superimposed.³² Thus, a novel approach for investigating genotype by fMRI interaction predicting naltrexone response may involve the utilization of resting state functional connectivity using highly sampled subjects.

Agonist Versus Antagonist Treatment

One cannot read news of the addiction field without noting the debate between agonist (methadone or buprenorphine) and antagonist (naltrexone) treatment advocates, often reflecting unclear understanding or biased interpretation of evidence. Each medication has its strengths and weaknesses, and treatments can work differently in different patients. Methadone has proven five-year outcomes with decades of data supporting its use. But it can only be dispensed at licensed clinics, has a very complex pharmacologic profile and, as an MOR agonist, can cause sedation and death when combined with other drugs.²³ Buprenorphine is safer and easier to dose than methadone, but retention in treatment is much lower and, like methadone, it is subject to diversion and abuse.

Naltrexone, as an MOR antagonist, lacks the other drugs' potential for abuse, but has limited data support; its FDA approval was based on a single randomized controlled trial. In the extended-

release form, its efficacy in opioid abstinence was similar to buprenorphine²³ in two short term, 12-week trials; however, failure to initiate naltrexone (because the subjects needed to be opioid free for a period of days) was a significant barrier to naltrexone treatment.^{34, 35} In sum, long term data is scant for naltrexone and weak/inconsistent for buprenorphine. Indeed, clearly the best evidence for long term outcomes is with methadone.³⁷

Ultimately, given their similar efficacy in randomized controlled trials, injectable naltrexone is like buprenorphine, a viable option to be considered in treatment, but it should not be an end in itself. Indeed, Pitt et al comprehensively studied policies aimed at the “demand” side (i.e., treating addiction directly), and most proved to be beneficial without causing harm, but no single policy is predicted to substantially reduce addiction or its consequences in the long term.¹

Looking Ahead

Naltrexone, like methadone and buprenorphine, has demonstrated success, and our experience tells us that all these drugs can help patients. But the science of addiction dictates that we need to push for more sophisticated neuroscience-informed treatment (i.e., in terms of effects on brain circuits).

Addiction is a chronic disease that can cause long lasting changes in the brain. It is a complex illness involving multiple neurotransmitter systems and circuits, and the Stanford group data referenced above challenges the assumption that affecting one neurotransmitter system (either agonist or antagonist) is a panacea and that simple “dissemination” of MAT will solve the opioid epidemic.^{1, 40,}

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We have shown neuropathological, circuit level, and behavioral similarities between traumatic brain injury and chronic methamphetamine use.⁴² The idea that the brain’s reward circuitry, memory, neurotransmitter systems, cell bodies, and higher functions may be the same after addiction as before has been assumed but not demonstrated. Resting state functional connectivity may serve as the ideal tool to study brain changes in vivo, as is proposed by the NIDA ABCD study, a longitudinal study following subjects from childhood to adulthood with the specific intent of examining developmental brain changes associated with substance use disorders.⁴³

Similarly, we need better neuroscience-informed diagnostic and prognostic markers. Every physician who treats patients with substance-use disorders understands the phenomenon of “protracted withdrawal”—symptoms that persist well beyond the immediate context of drug cessation—but this has long been difficult to study and operationalize on the level of symptoms alone.⁴⁴ Here, resting state functional connectivity may provide a useful tool for illuminating the condition from a systems-neuroscience perspective. A landmark paper by Andrew Drysdale and colleagues used resting state functional connectivity to define “biotypes” of Major Depressive Disorder (MDD), and a similar approach may be applied to substance use disorders.⁴⁵

In regard to new interventions, preliminary evidence indicates that vigorous physical exercise on the one hand, and repetitive transcranial magnetic stimulation (rTMS) on the other may be promising post-addiction treatments.⁴⁶⁻⁴⁸ A mechanistically novel family of medications, neurosteroids (positive allosteric modulators of GABA-A receptors), have substantial preclinical data indicating therapeutic effects for a variety of psychiatric illness, including addiction.^{49, 50} Given that the likely therapeutic mechanism of neurosteroids involves network-level changes in brain stress states and demonstrated changes in self administration studies of drugs of abuse with progesterone, one may expect similarly positive results in randomized controlled trials for opioid use disorder.^{49, 51}

In sum, naltrexone can be an extremely helpful medication for opioid and alcohol use disorders. But it is a conceptual error to think that it (or any current FDA-approved medication) should suffice as a standalone treatment for either illness. We emphasize two points: First, the current status of mechanism-based treatments (whether MOR agonist or antagonist) is crude, and we advocate for more resources directed towards the development of biological markers using advanced neuroimaging techniques; novel drug development based on a systems neuroscience rather than neurotransmitter approach; and rigorous studies investigating neuromodulation. Second, addiction should be viewed in the same light as other chronic illnesses, requiring longitudinal comprehensive care, with a focus on prevention, mitigation, and long-term outcome.¹

Addiction is an enduring illness that characteristically develops over time, yet treatment often is administered in time limited settings. Short-term interventions give patients and families the idea that treatment is some sort of quick fix, but in truth abstinence and long-term recovery are the goals of treatment. Only then will we be able to consistently and effectively address not only the opioid epidemic but the broader question of addiction as a whole.

Bios

Mark S. Gold, M.D., is an adjunct professor in the Department of Psychiatry at Washington University and an active member of the advisory council at the Washington University School of Medicine's Public Health Institute. Gold was a professor, eminent scholar, distinguished professor, distinguished alumni professor, chairman, and emeritus eminent scholar during his 25 years at the University of Florida. He is the author of *Wonder Drugs: How They Work* (Simon & Schuster, 1986), and he and co-workers have won a number of awards, including the Foundations Fund Prize (APA). Gold has been recognized by the Drug Enforcement Administration for 30 Years of Service, the National Association of Treatment Professionals for Lifetime Achievement, ASAM's McGovern Award for Lifetime Achievement, National Leadership Award, DARE Lifetime Achievement Award, and PRIDE awards for his career in research and prevention, and the PATH Foundation's Lifetime Achievement Award.

A. Benjamin Srivastava, M.D., is a clinical and research fellow in addiction psychiatry at Columbia University Medical Center and the New York State Psychiatric Institute. He received his undergraduate degree from the University of Michigan-Ann Arbor and M.D. from the University of Florida College of Medicine, completing his residency in psychiatry at Washington University in St. Louis, where he published articles and book chapters on addiction under the mentorship of Mark S. Gold.

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