

A Perspective on Opioid Pharmacotherapy: Where We Are and How We Got Here

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Abstract Four decades of concerted pharmacotherapy research has netted us three medications approved for the treatment of opioid addiction. The clinical pharmacology, safety, efficacy, and clinical use of these medications are familiar to most clinical researchers and clinicians in addiction medicine. Less common is an understanding of the social and political forces behind the choice of these particular agents for their development and how these forces continue to influence how clinicians interact with patients who have opioid use disorder. This review brings into focus those forces and puts into context how we came to have these particular medications. What we know determines our views of the world we live in, including our patients and ourselves, as well as those to whom we give power to govern us. The issues are raised by the author, who does not provide resolutions; answers to the questions of how to address the issues must come from the reader.

Keywords Pharmacotherapy · Opioids · Methadone · Naltrexone · Buprenorphine

Note. After last year's conference, the editors of this special issue asked me to write a historical review of the development of pharmacotherapy for treating opioid addiction. It seemed a reasonable request—after all, I have been part of that medication development effort for most of its history. I was assured that I may tell the story from my own point of view, so this manuscript presents my views about how things appear to me. If reading this bothers you, try taking it with some humor and laughter, still the best medicine.

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Introduction

We have three approved medications to treat opioid addiction: methadone, naltrexone, and buprenorphine. A methadone related compound levo-alpha-acetylmethadol (LAAM), as explained below, was approved in 1994, but is not available because the manufacturer stopped making it. Naltrexone has an oral form and a sustained-release injectable formulation. Buprenorphine comes in a sublingual preparation (as tablet or film). That just about covers what we have to show for 50 years of concerted research efforts supported by the U.S. National Institute on Drug Abuse (NIDA) and its forebears.

Treatment development for opioid addiction can be traced to the synthesis of the potent opioid morphine 60 years before the Civil War. It saved many lives and eased the suffering of many others during that very deadly conflict, but morphine addiction was rampant when the war drew to its close in the spring of 1865; the “soldier’s disease,” or the “army’s disease”, it was called. In the decades that followed, the medical profession’s failure to find a cure for addiction and the prohibitionist fever of the era culminated in the Harrison Narcotic Act of 1914. Its subsequent court rulings effectively took addiction treatment out of the hands of physicians, thus setting the social and medical position regarding addiction, addicts, and addiction treatment. For almost the entire century that followed, addiction was a criminal offense and generations of physicians were accordingly trained to regard addicts as criminals. It was not until the approval of buprenorphine in 2002, literally aided by an act of Congress, before physicians could again prescribe an opioid to treat their patients’ opioid addiction.

The story of modern pharmacotherapy for opioid addiction usually begins with Drs. Vincent P. Dole and Marie E. Nyswander introducing methadone treatment in the mid-1960s (Dole and Nyswander 1965) and ends most recently

with a couple of pharmaceutical companies competing to develop sustained-release forms of buprenorphine (Ling 2012). Such an account, with a bit of clinical pharmacology and reports of clinical trials thrown in, would give us a good picture of what medications we have on our shelves and how to use them to treat patients. Limiting the story that way, however, we would miss some part of the story that may yet help us understand how we come to have these medications and what that really means for us as researchers and clinicians. This article is about the rest of that story. The events recounted here represent things as I saw them occur and as I see them now. Some of my observations may cause mild discomfort, for which I prescribe a sense of humor and a dose of laughter, which is after all the best medicine.

Methadone and LAAM

A synthetic opioid analgesic invented during World War II, methadone is taken by mouth, quickly absorbed, and slowly eliminated, allowing it to be taken once daily. Clinically it prevents symptoms of withdrawal and reduces craving and illicit opioid use. Continued treatment normalizes physiological functions and facilitates social rehabilitation, pragmatically summed up as the “3 Js”—off Junk, out of Jail, on a Job.

By 1970, following the seminal work of Dole and Nyswander (1965), a small number of patients were receiving methadone as an experimental treatment. It was then that mothers of veterans returning from Vietnam and addicted to heroin were calling and writing their Senators and Congressmen demanding something to be done for their sons who had gone to war as nice, clean American boys but had come home as heroin addicts. The United States had a military draft then and mothers lived in the same neighborhood as their political leaders and could reach them. Faced with the seriousness of the problem and the pressure of running for a second term, President Nixon appointed Jerome Jaffe, M.D., to direct the Cabinet-level Special Action Office for Drug Abuse Prevention (SAODAP). Dubbed the first National “Drug Czar,” Dr. Jaffe established throughout the country the network of methadone clinics that would become the model of heroin addiction treatment around the world; that model of specialty clinics dispensing methadone on a daily-dose basis persists to this day.

Although methadone’s safety and efficacy had been long recognized (Gossop et al. 2001; Marsch 1998), its clinical use was not widely embraced. Social skepticism and political resistance resulted in a compromise that set forth stringent regulations for its use to this day. From the very beginning our policy has been: Addicts are sick, they need help; but they also sin and must suffer a little.” So we built treatment programs and put up barriers making it difficult for patients to get into

treatment. The justification was “to prove their motivation.” Many other countries that had adopted the U.S. methadone treatment system have evolved over time to have policies more consistent with their social views of the addicts and addiction. In the U.S., however, methadone treatment remains today one of the most strictly regulated of medical undertakings. Attitudes do not change easily.

Still, under Dr. Jaffe and the leadership of SAODAP, thousands of methadone clinics emerged across the country. Clinicians with direct experience in treating opioid-addicted patients were gratified by positive changes in the lives of those in methadone treatment. Dr. Jaffe indisputably did more for the opioid addicts of this world than any other individual, and his designation to head SAODAP proved to be one of President Nixon’s best appointments. While intended to respond to the heroin crisis associated with the Vietnam war, the government’s effort also benefited many veterans of previous conflicts. A vibrant private methadone treatment industry also emerged, serving non-veterans.

As a pharmacotherapy for opioid addiction, methadone has much to offer, but as an agent that promotes patients’ social and vocational rehabilitation it falls short. Daily clinic attendance hinders educational activities, working, and job seeking. Giving “take-home doses” creates problems of its own—street diversion and accidental poisoning. More important perhaps, we as a society have been uneasy about giving opioid to opioid addicts. Changing regulatory policy to accommodate these shortcomings would seem insurmountable. One potential solution would be to develop other pharmacological agents with longer durations of action that could replace or greatly augment the use of methadone. Dr. Jaffe already was familiar with one such agent, levo-alpha-acetylmethadol (LAAM).

In addition to its own opioid effects, the methadone congener LAAM is metabolized to two potent metabolites, nor-LAAM and Di-nor-LAAM, each more powerful than the parent compound, contributing to prolonging the opioid effects so that LAAM is clinically effective when administered three times a week (Ling et al. 1994). In the 1970s, SAODAP, which was superseded by the National Institute on Drug Abuse (NIDA), sponsored a series of clinical studies showing LAAM’s clinical safety and efficacy (Ling et al. 1978). However, the changing drug scene and the political climate of the 1980s delayed LAAM’s approval until 1994. More disturbing and disappointing was the subsequent failure of its clinical implementation (Ling, Rawson, & Anglin, 2003). Concerns over its potential cardiac effects led to its withdrawal from the European Union market and to FDA’s imposition of a “black box” warning that resulted in the manufacturer’s decision to cease production. Nothing in the sequence of events suggests, however, that Jaffe’s original vision for a longer-acting medication was incorrect.

Naltrexone

The idea of using a narcotic antagonist to treat opioid addiction has its rationale rooted in animal behavioral studies showing that antagonists block the rewarding effects of opioids and over time animals learn to stop drug self-administration, referred to as extinction. It was suggested that humans would do the same. In this scenario naltrexone, a potent opioid antagonist derived from oxymorphone, was almost a perfect agent: it completely blocks the effects of opioids, has no reinforcing properties of its own, and it was relatively safe with few side effects. One of its touted virtues was that when taken, it makes patients feel as if they have taken nothing. No one had apparently bothered to ask the patients for whom the medication was meant whether they wanted to take something that makes them feel nothing. The answer, as time would tell, was quite clearly not. Nevertheless, in 1971, 4 years after its synthesis, Congress designated it a high priority for SAODAP to develop for treating opioid addiction. Congress provided specific funding for it so that, as Dr. Jaffe put it, SAODAP really had no choice in the matter.

Early clinical trials with oral naltrexone formulations proved to have very poor medication adherence (Chalk et al. 2011; Harris et al. 2004; Roozen et al. 2006) and low patient acceptance except among a few special, “highly motivated” groups: physicians, other licensed health care personnel, and attorneys, who shared a common threat of losing their livelihood. Patients who stayed on the medication, as long as they took the medication would benefit from it. Prisoners on work release, who had no other choices, also seemed to do well. When opportunities presented to stop the medication, almost everyone did and relapse was almost uniform. Such findings did not deter governmental encouragement to continue developing an antagonist and, based almost entirely on its pharmacological blockade with little clinical data, the US FDA approved in 1984 an oral naltrexone formulation to treat opioid addiction. Subsequent marketing did not prove a commercial success.

Still, extensive resources were devoted to developing an extended-release formulation that once given would last for 30 days, thus permitting no choice for the patient. Early work with depot formulations indicated the superiority over oral naltrexone (e.g., Colquhoun et al. 2005; Comer et al. 2002, 2006) Eventually the FDA approved a sustained-release formulation of naltrexone for opioid addiction in October 2010. Ironically, the pivotal study (Krupitsky et al. 2010) that provided the data for the FDA approval was conducted in Russia where conditions were like those faced by the select groups who constituted the “successful” patients in the U.S. in earlier trials; these were patients who had no other choices. A product “made in the USA” thus was to prove highly effective in Russia and the data “made as in USA” helped facilitate its approval in the U.S. The open-armed embrace given to

naltrexone can be attributed to our preoccupation with detoxification—addicts should just “get off” and stop drug use, our ambivalence about, if not downright hatred for, methadone, and our desire for a “non-addicting” medication that addicts cannot enjoy. A separate review of the antagonist-based treatment appears in this special issue, with more details on the development of naltrexone for treatment of opioid addiction (Woody et al. 2016).

Buprenorphine

Buprenorphine’s emergence in clinical opioid pharmacotherapy is the most significant event in addiction medicine since the introduction of methadone (Fiellin 2007; Green 2010). A partial opioid agonist, buprenorphine exhibits effects of agonists or antagonists depending on the background opioid activity (Walsh et al. 1995). Recognition of this characteristic led Dr. Donald Jasinski to consider its use to treat opioid addiction. He figured that buprenorphine has properties like those of methadone that patients like and properties like those of naltrexone that patients hate but clinicians like, so maybe it would be just the thing to treat opioid addiction. Patients would take something that acts as an opioid agonist like methadone and in time have something in them that acts like an opioid antagonist without having to actually take naltrexone. He was right. Jasinski conducted a series of studies in the 1970s and published the results in the Archives of General Psychiatry in 1978 (Jasinski et al. 1978). What followed, under a joint development agreement with the drug manufacturer Reckitt Benckiser Pharmaceuticals (Indivior), was a series of NIDA-sponsored trials comparing buprenorphine to methadone, buprenorphine to placebo, and buprenorphine in various doses (Doran et al. 2007; Fudala et al. 2003; West et al. 2000). Data from those studies established buprenorphine to be safe and effective, leading to its approval by the FDA, along with the passage in 2000 of the Drug Addiction Treatment Act (DATA). It became clinically available to clinicians in 2002 with some special requirements of physician training and provision of certain ancillary clinical services. Since that time, the clinical utility of buprenorphine has been well documented (e.g., Mattick et al. 2008). Development of extended-release formulations will likely extend buprenorphine’s clinical usefulness, bringing to a close the full circle of the story. We still have at our disposal three approved medications, with several formulations that are now available and perhaps a couple more for buprenorphine in the near future (Ling 2012).

Observations

Several observations remain on the non-pharmacological factors influencing the development of opioid addiction

medications and what they should mean to us clinical researchers and clinicians.

1. Methadone, naltrexone, and buprenorphine are not three medications in a single opioid addiction treatment system, but are agents in three distinct treatment systems, each with its own peculiar requirements and advantages and disadvantages. There is no rationale, as is often insisted, to compare their relative clinical effectiveness on an artificially created “level playing field” in the name of research vigor that bears no semblance to real-life circumstances. Each must be evaluated on the conditions limiting or favoring its optimal clinical application and benchmarked against appropriate common outcome criteria or measures specific to its own situation. The three medications come with, in addition to their different pharmacological properties, other perceived attributes, such as societal attitudes toward antagonist and agonist approaches. Such aspects cannot be “leveled” and yet can critically influence treatment outcome.
2. The delivery of methadone requires a specialized clinic and has a set of its own regulations; it is the most stringently regulated medical practice on earth. Contrary to beliefs in certain quarters, methadone pharmacotherapy does need the involvement of a competent and compassionate physician. It is important to keep in mind that the regulatory constraints on its clinical use had less to do with its pharmacological properties and more with how we as a society, represented by our policymakers, regard addicts and treatment for them; the strict regulations were put forth as a compromise that doctors and patients must live with forty years ago and have not noticeably changed to this day.
3. Our love of the opioid antagonist—naltrexone—has less to do with its medicinal properties than with what we think of and feel about addicts and addiction. We as a society basically do not like addicts to have something that gets them even a little bit high. We think addicts should just get off drugs and by strenuously hauling up on their own bootstraps should stay off no matter what. Policymakers and some clinicians continue to promote detoxification as ‘treatment,’ even though detoxification does nothing to help people stay off drugs. Naltrexone has few takers and its acceptance requires coercion and lack of free choice—the Al Capone factor. Its lack of clinical success has little to do with its absolute or intrinsic pharmacological efficacy, but is attributable to its lack of relative clinical effectiveness when other treatment choices are available; we must hope that availability of treatment options becomes the case for most if not all addicted patients around the world.
4. For buprenorphine to realize its full clinical potential, we must realize that its true significance is not that we have another medication to treat opioid addiction, but that its availability returns the treatment of opioid addiction to the hands of the physician. For nearly a century, physicians were indoctrinated with the societal attitude that addicts, through their criminal drug use activities, brought upon themselves the suffering they deserve. Even after we began to regard addicts as having a disease, our policies continued to reflect our attitude: addicts are sick, they need help, but they also sin, so do not help them too much. Until the correct mindset is restored in the physician, the mere availability of an effective medication will not make a difference. To put it another way, for buprenorphine to succeed clinically, physicians themselves must first change before they can help patients change their lives. Buprenorphine’s clinical advantage is its high safety profile and its ability to be prescribed for patients in the physician’s place of normal practice. Still, its approval was not without oppositions, some from unexpected quarters. Who would have thought that methadone treatment providers who lived through decades of regulatory hassles would oppose the approval of buprenorphine? They did, to the very end. Thus, even with the help of a congressional act, buprenorphine’s clinical availability came with strings. Physicians can only treat a limited number of patients and must, after undergoing an approved course of training, obtain an official waiver and provide, directly or by referral, psychosocial treatment. No other medication has been approved for use in any other patient population with such requirements. What does that tell you about the attitude of those in control toward these patients and toward the physicians who treat them? It was argued that the reason for the psychosocial support requirement was that psychosocial conditions were part of the reported clinical trials that led to FDA approval. Does anyone really believe that cardiovascular and cancer trials are conducted without “psychosocial support” and therefore no such support is required by stipulation for their use? Several years ago we undertook a study in which all patients received usual medical care and then groups of patients were given additional psychosocial therapy—cognitive behavioral therapy, contingency management, or both. After 6 months, all patients improved but there were otherwise no differences; the added psychosocial treatment had produced no added benefits (Ling et al. 2013). We were told that the usual medical care provided in the trial was too effective to allow the therapeutic benefits of these other treatments, required as a matter of policy, to come through. What are we saying, really? No fundamental change has occurred on the conditions of buprenorphine prescribing since its approval more than a decade ago.

5. We could benefit from Rene Descartes' admonition to "question everything" and reflect on how social and political policies arise and for whose benefits these policies are. Are they in the best interests of those whose lives they affect most? What does "the rest of the story" tell us? Here are a few of my favorites. These questions are from me; their answers, for that matter, must be from you.
- In the beginning there was methadone detoxification and there was methadone maintenance; they were not pretty but a spade was a spade. At some point methadone maintenance treatment became "opioid substitution therapy." Patients did not change that, people in control did. One reason given was that there were other medications available, but that did not explain what it was that we were trying to substitute. The preferred term now is "medication-assisted treatment," MAT. What beneficial "treatment" exactly are these medications assisting? What do those who perform the assisting know about these medications and how often are patients informed of the nature and purpose of these medications or the treatment they mean to assist?
 - Why do we call the people we treat for addiction "clients" instead of patients? Is there a difference? Are the terms equivalents such that if I am a client when I go see my doctor, am I a patient when I go shop for a car? It is sometime said we empower patients by calling them clients, giving them autonomy in decisions making. Really? The terms "patient" and "client" define the relationship between the parties. Traditionally, doctors have patients and merchants have clients. The relationship defined by the terms patient and client could not have been more different. The relationship between a physician and her patient is one of trust based on sincerity, which means no barrier, no deception, nothing to hide between us. The basic relationship between the merchant, the provider of goods, and his client is mutual concealment if not downright deception. You do not want the other party to know everything, not the whole truth in any event. Is that the kind of therapeutic relationship we should have with people who put their lives in our hands? What does that say about us when we let things like that happen or even encourage it?
 - So what's in a name? Does naming matter? Here's what comes to my mind. You decide. "...the Lord formed every beast of the field.... and brought them to Adam....and whatsoever Adam called every living creature that was the name thereof. " *Gen. 2:19*. And Adam exercised dominion over them. To name is to exercise control over something. Throughout history, the first thing explorers did with their discovery was to give it a name. In the 1920s the American Medical Association named 4 types of addicts and their respective recommended treatment:

"correctional cases" were to be sent to internment camps; "mental defectives (degenerates)" were recommended for sterilization; "social misfits" were to be provided vocational guidance; "otherwise normals" were to receive psychoanalysis. So that's what naming can do.

Closing Comments

Today our leaders and policymakers are telling us that our opioid-addicted patient has a chronic brain disease that should be treated like any other chronic disease, like hypertension and diabetes, for example. We like that because it makes life easy for us and we get paid by health insurance. But look around the treatment "industry" and ask whether things have really changed. We have studied addiction as a science for more than 40 years but we treat our patients the way we did 40 years ago. And who is responsible for that?

Here's what Anne Fletcher found in our current treatment system (Inside Rehab, Viking Penguin, 2013) when she visited a bunch of drug treatment facilities, many "upscale" and "state of the art," and talked to people like Tom McLellan, Mark Willenbring (NIAAA), and Dr. Drew Pinsky:

- Treatment is delivered by the least-qualified and least-supervised member of the staff (the counselors).
- Most "treatment" consists of Alcoholics Anonymous (AA) "12-Step"-type groups.
- Physicians have minor roles in treatment, medications are uncommonly used.
- Forty years of research is almost entirely ignored by the treatment industry.

Tom McLellan told her we have no real way to decide where to send which patient and if you have seen one treatment program you'd seen them all. Willenbring said we assess each patient individually but we send them all to the same groups. Drew Pinsky insisted that treatment is all a group process. The executive director of the Betty Ford Center said AA 12-step must be the core program treatment philosophy. In 2012, a big gathering was held at the Betty Ford Center on the topic "Addiction is a chronic brain disease." In attendance were many nationally known addiction researchers and treatment leaders. For an hour the latest research was presented, including the latest neuro-imaging and genetic studies, followed by remarks and testimonies from four people in recovery. Every one of them talked about how the 12-Step programs helped their recovery without mentioning anything else. So who is championing addiction being a brain disease and who benefits from status quo? Past director of NIDA Alan Leshner used to say, "So addiction is a brain disease, where are all the doctors"?

According to James Burke, those in power have throughout history tried to use new knowledge to maintain social order and to control those they governed, not necessarily with ill intent, but they liked being in control and having things their way. For example, the early church had for years used the position of the sun and the moon and the stars to determine the date of Easter, based on a system passed down from Aristotle that put the earth at the center of the universe. But one year Easter could not be found based on the calculations. Obviously that was not good so Copernicus was asked to solve the problem. Copernicus told the church fathers Easter would be right there if, instead of putting the earth at the center of the universe, the church father would put, as Galileo told them, the sun in the center. That would go against the system according to the church so the fathers accepted Copernicus's Easter but called his method a mathematical fiction. It's all right to use it to find Easter but God knew Copernicus was wrong.

If this story does not seem convincing enough, remember that a tenet of Darwin's theory of evolution—survival of the fittest—was once used to justify minimally educating children of the working class, and Sunday school hymnals in the 1860s used to teach children of the poor to accept their “low and poor estate”, to obey and murmur not. (Burke and Orenstein 1997.)

That is how the rich get richer and poor get poorer. Someone had observed that Americans like reality shows because we do not have to face reality when we can put it on TV. We do not like to look ourselves in the mirror because we do not want to see the enemy and find out that they are us. But look we must. It's about time.

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