

# Recent advances in the treatment of opiate addiction<sup>☆</sup>

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## Abstract

Advances in the modern treatment of opiate addiction are the result of an evolutionary process often attributed to the introduction of methadone maintenance in the 1960s. The underpinnings and the forces that shaped these advances, however, date back to the rise of the prohibition movement at the turn of the century, which culminated in passage of the Harrison Narcotic Act, signaling a major shift in US social attitudes towards heroin addicts and their addiction. Subsequent US social and political attitudes have shaped the course of treatment practices in parallel with scientific advances and pharmacological developments, from the establishment of methadone treatment in specialized narcotics treatment clinics to the introduction of buprenorphine and the concomitant legislative mandate that made it available to general physicians, reflecting again the current societal attitude. While pharmacological progress may appear to be related to scientific advancement, the major driving force behind the direction of treatment development and its implementation into the treatment community is deeply ingrained in the concurrent evolution of societal attitudes and political policies. Moreover, the undisputed US dominance in science and politics lends global impetus to these developments.

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## 1. Introduction

The modern era of opiate pharmacotherapy is often attributed to Dole and Nyswander's introduction of methadone maintenance in the 1960s ([1,86]), but the story dates back a century earlier to the close of the Civil War when morphine addiction was rampant ([2]). So many soldiers had become addicted that it came to be known as the 'soldiers' disease' or the 'army's disease'. The medical profession's failure to find a cure and the many false hopes offered by charlatans led to a backlash fueled by the rise of the prohibition movement, and culminated in the 1914 passage of the Harrison Narcotic Act, which effectively removed opiate addiction treatment from the practice of medicine. Over the ensuing decades, opiate addiction came

to be regarded as a social evil that was generally remedied by criminal prosecution ([3,4]). With the growth of US military and economic power during and after the Second World War this social attitude was imposed, with reluctance in some instances, on much of the rest of the world. Advances in opiate addiction treatment must thus be viewed in the context of changes in societal attitudes as well as gains in medical research, and physicians, both as members of society and of the medical community, must utilize these advances in a manner that reflects both roles responsibly. This article aims to highlight some of the more salient events marking the progress of modern opiate pharmacotherapy, beginning with the introduction of methadone and culminating in the approval of buprenorphine, and examining how political and social forces and the mood of society continue to shape these developments.

## 2. Historical developments in opiate pharmacotherapy

While the Harrison Narcotic Act itself did not expressly prohibit physicians from prescribing opioids to opiate

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addicted patients in the normal course of medical practice, such prescriptions could not be for treatment of addiction. Subsequent interpretation of the Act by the court system (i.e. [5,6]) and law enforcement agencies, with the successful prosecution and conviction of physicians, led to the closing of existing narcotic treatment facilities. By the 1920s, the American Medical Association (AMA) itself had condemned prescribing opiates to addicts and their recommendations for treatment of heroin addiction made no reference to pharmacotherapy. The last medical facility to dispense narcotics to opiate addicts closed its door in 1923 ([7]).

Heroin addiction however, did not disappear with prohibition and punishment. By the end of World War II, heroin addiction re-emerged as a serious worldwide problem and governments were forced to reconsider the prevailing policies and measures of control ([8]). In the 1950s, the medical profession revived the idea of addiction as a medical disease (as Alcoholics Anonymous had done 20 years earlier), beginning with alcoholism and eventually extending to other drugs, including opiates. In 1961, the AMA began revising its policy, questioning whether law enforcement was the best strategy to deal with addiction ([9]). Research into opiate addiction and its treatment was again encouraged and clinicians began to utilize short-term opiate substitution for detoxification ([10]).

The watershed event that revitalized opiate pharmacotherapy was Dole and Nyswander's introduction of methadone maintenance in 1964 but adoption of the treatment was slow. While a number of clinics were operating under the Investigational New Drug (IND) applications issued by the Food and Drug Administration (FDA), thus exempting them from the Bureau of Narcotics policies that still held as illegal the prescribing of opiates to addicts, society in general did not embrace this form of treatment; by 1970 only a few thousand patients were being treated at various methadone clinics. Law enforcement agencies remained skeptical and even the treatment community itself continued to embrace the treatment philosophy of traditional therapeutic communities and abstinence. Methadone was viewed as a barrier to recovery and, in some cases, even as a government effort to enslave Blacks ([11]).

With escalation of the Vietnam War, however, renewed societal pressures emerged to address heroin addiction among returning soldiers. In response, President Nixon established the cabinet level Special Action Office for Drug Abuse Prevention (SAODAP) to deal with the problem and appointed Dr Jerome Jaffe to head the office as the first national 'Drug Czar'. A compromise strategy evolved from that effort, leading to the promulgation of a set of regulations that acknowledged the safety and efficacy of methadone maintenance treatment but also imposing specific conditions governing its use, ranging from the qualification of patients to enter treatment to the maximum allowable initial dose ([12,13]). These changes were

groundbreaking nevertheless, and heralded a new era of treatment for opiate addiction.

Interestingly, while the impetus for the movement was the Vietnam War and the returning veterans, many of those who benefited from the government's efforts were in fact veterans of earlier wars. Although heroin abuse was widespread among soldiers in Vietnam, subsequent follow-up showed that only a small minority (less than 5%) ([14,15]) continued to be addicted after returning home. Still, the leadership role that the US took in this effort led to adoption of methadone maintenance treatment in many countries around the world. Some of these countries, notably Canada, Australia and some parts of Europe, eventually devised their own policies, which were often much more pragmatic than those in the US; domestic policies continued to be marked by ambivalence.

Today, methadone maintenance treatment in the US remains one of the most regulated of all medical practices and has kept methadone treatment out of mainstream medicine ([11,16–18]). Prevailing social attitudes and public policies continue to perpetuate the stigmatization of addicts and create barriers to integration of methadone treatment into the health care system. In 1989, response to the HIV and AIDS epidemic, an attempt by the FDA and NIDA to provide methadone under less stringent regulatory conditions was not received favorably, even within the treatment community. More recent attempts to facilitate the delivery of methadone, and bring it into medical practice (see [19]) have made only minimal progress. A few long-term methadone maintenance patients who have demonstrated adherence to treatment rules and made significant social adjustments have been allowed to receive methadone in a general medical setting but mostly as an experiment. Attempts to deliver methadone in settings outside of the traditional clinic to addicts earlier in their course of recovery have not been put into practice, and only recently was the regulatory process required to dispense methadone for addiction replaced by a less rigorous process of accreditation. These changes to the delivery system have not yet resulted in any significant visible changes in the care of these patients. In this era of pharmacotherapy for the treatment of mental disorders, pharmacologic developments continue to be the primary response to the social and political concerns surrounding the treatment of opiate addiction.

### *2.1. From methadone to LAAM to naltrexone*

Methadone was synthesized by German scientists during WW II. It is a potent opiate analgesic with properties similar to morphine and has been used extensively for the treatment of pain. It is still frequently used for management of moderate to severe pain, especially for cancer. It is well-absorbed following oral administration and suppresses symptoms of opiate withdrawal. Its relatively long duration of action allows for once daily dosing, which was an

advantage in treatment of heroin addiction since heroin itself, to be effective, must be administered several times a day. For purposes of social rehabilitation however, once daily dosing is less than ideal as it requires patients to attend clinic daily, which impedes vocational rehabilitation, or be given take-home medications with the risk of street diversion and occasionally accidental overdose. This shortcoming did not lead to changes in the regulatory policies for methadone delivery, however, but instead was a major impetus for development of other pharmacological agents with longer durations of action to mitigate the need for take home doses.

This in fact was the primary motivation for the development l-alpha-acetylmethadol (LAAM), a congener of methadone, which can be administered three times weekly because of the presence of active metabolites which combine to confer a longer duration of action. Unfortunately, while a substantial body of research data was accumulated during the 1970s and early 1980s, LAAM's approval did not come until 1994. By that time, the opiate addiction pharmacotherapy scene had changed considerably and a combination of a very cumbersome regulatory process and resistance among methadone providers made clinical implementation of LAAM anything but a success ([20]). More recently, LAAM's cardiac effects led to its withdrawal from the European union and the imposition of a 'black box' warning in the US. Eventually, the manufacturer simply decided to cease manufacturing the medication. The reality of LAAM's removal from the market has much more to do with social, political and economic factors than pharmacological ones; its cardiac risks appear largely overstated.

While methadone's ability to substitute for heroin and suppress symptoms of withdrawal was a great pharmacological success, it is nonetheless an opiate and there was always a sense of unease in its use both in the medical community and society at large. The fact that its delivery was so stringently regulated and attempts to ease its control were always meager largely reflects this ambivalence. Instead, further pharmacological development was sought to alleviate the situation, resulting in the development of an antagonist that would block the effects of heroin and make it physiologically impossible for addicts to use narcotics. Naltrexone seemed to fit the bill perfectly.

Synthesized by N-allyl substitution of naloxone with cyclopropylmethyl radical of cyclazocine, naltrexone possesses both the pure antagonist properties of naloxone and the long duration of action of cyclazocine ([21]). It is orally effective with rapid onset of action after ingestion with long lasting clinical effects, and safe with relatively mild side effects. A single oral dose of 50 mg blocks the euphoric effects of 25 mg heroin for up to 24 h and at a 150 mg dose, it can provide therapeutic blockade for up to 72 h, thus be administered three times a week. It was, therefore, regarded as an ideal medication for the treatment of heroin addiction ([22]). Unfortunately, its great advantage, i.e. the complete blockade of narcotic effects, proved

to be its greatest drawback as there is very little patient acceptance. Because naltrexone precipitates acute withdrawal in patients physically dependent on opiates, initiation of naltrexone treatment is difficult since patients first have to be detoxified from opiates. This often fails and few patients succeed in being inducted onto the medication. Even those who are successful often simply discontinue the medication. Relapse is frequent and long-term success is rare except in a few highly motivated patients and those who are under duress. Consistent with the philosophical approach dictated by social attitudes, few attempts have been made to make naltrexone more palatable to patients but instead a great deal of effort has gone into developing a naltrexone preparation that will last longer and that once given would be difficult to discontinue. These efforts have included the development of various injectible and implantable formulations over the last two decades. Only recently has there been some success worth noting but its eventual impact on opiate pharmacotherapy remains to be seen ([23,24]; [25]). In concert with the development of an injectible and implantable form of naltrexone were various attempts at rapid and ultra-rapid detoxification to prepare patients for this form of treatment, although these treatments were sometimes touted on their own virtues as treatments in and of themselves ([26]). While these procedures have been highly commercialized, few have been subjected to vigorous scientific scrutiny ([27–29]).

The serendipitous observation that clonidine, an alpha agonist, can suppress symptoms of opiate withdrawal led to its adoption for opiate detoxification throughout much of the 1980s and 1990s. The effectiveness of clonidine is limited in part because of considerable side effects, notably sedation and hypotension. An analogue of clonidine, lofexidine, has been marketed in the UK and is undergoing further testing in the US, but its full development and its advantage over clonidine remain to be seen ([30]).

The evolving story of modern advances in opiate pharmacotherapy, beginning with the re-emergence of the disease concept, the introduction of methadone and the subsequent development of other related pharmacotherapies, and the various attempts to change the delivery system and treatment environment were all encouraging and can be counted as a measure of success. The most significant advance in opiate pharmacotherapy in the last 50 years is by far the introduction of buprenorphine ([31]); all else pales in comparison.

## 2.2. Buprenorphine

The Harrison Narcotic Act not only affected the treatment of opiate addiction, it also profoundly influenced the subsequent development of narcotic analgesics. In fact, it instigated the long search for a non-addicting or at least less addicting substitute for morphine. The quest to separate the analgesic properties of opiates from their addictive properties continue to this day and has much to do with

buprenorphine's discovery and development. Shortly after enactment of the Harrison Narcotic Act, the National Research Council, within the National Academy of Science (NAS NRC), established the Committee on Problems of Drug Dependence (CPDD), now the College on Problems of Drug Dependence, to systematically search for a non-addicting opiate analgesic; buprenorphine is a product of that search.

First synthesized in 1963, buprenorphine is a potent analgesic that has been available worldwide for more than two decades for treatment of moderate to severe pain of various origins ([32,33]), including peri-operative pain and pain associated with malignancy. In the US, it is available in an injectable formulation for use in post-surgical pain. It was initially selected for development as an opiate analgesic because animal studies had shown it to have a slow 'off rate' from the mu opioid receptor with limited physical dependence and less toxicity compared to other opiates ([32,34,35]). Early human studies revealed its partial agonist properties, especially its ceiling effect on respiratory depression, which confers a high clinical safety profile and produces a low degree of physical dependence ([36–38]). It was repeatedly shown to effectively block the effect of subsequent opioid challenges ([39–41]). Additionally, its tight binding to the opiate mu receptor and slow dissociation from the receptors produces a long duration of action ([42–44]) and upon discontinuation results in a relatively mild abstinence syndrome ([45]).

In the 1970s, Jasinski and colleagues [46] showed that buprenorphine could substitute for morphine and suppress opiate withdrawal and that it produces only a modest withdrawal syndrome of its own. We were attracted to buprenorphine and thought that it would be a suitable medication for treatment of opiate addiction because its clinical profile partly resembles methadone, an opiate agonist, and partly resembles naltrexone, an antagonist. He reasoned that buprenorphine would be acceptable to patients because of its agonist properties but that physiologically it would, after a period of administration, resemble naltrexone. Mendelson and Mello ([47,48]) demonstrated, in human laboratory studies, that addicts maintained on buprenorphine reduced their consumption of heroin. A series of controlled clinical trials compared buprenorphine to methadone as the standard of treatment, compared various dose-ranges of buprenorphine, and compared buprenorphine to placebo, providing data for its safety and efficacy and forming the basis for its approval by the FDA ([49]).

Most of the early clinical studies of buprenorphine for treatment of opiate dependence were conducted with a liquid preparation (see [50]), but the liquid preparation became discolored with storage and was inconvenient for general clinical administration. A tablet formulation was thus developed and studies were conducted to compare the relative bioavailability of the two formulations. Results, generally, showed that the tablet delivers a sufficient level of

active medication and that with chronic dosing the blood level of the tablet formulation approaches that of the liquid ([51,52]).

To further reduce buprenorphine's abuse liability, a formulation was subsequently developed combining buprenorphine and naloxone. This strategy had precedence since a formulation of buprenorphine/naloxone was already available in some parts of the world for analgesic use. To this end, the ratio of buprenorphine to naloxone needed to best treat opiate addiction has been extensively evaluated ([50,53–59]). Jones and colleagues ([60]) administered a buprenorphine/naloxone combination in different ratios to groups of experienced heroin users maintained on a steady dose of morphine, demonstrating that by increasing the proportion of naloxone, the combination becomes increasingly less reinforcing and less attractive to addicts. Subjects were asked to rate their liking of the combination preparation and how much they would pay for the effect. The subjects showed increasingly less liking for the combination product as the ratio of naloxone increased and at the 4:1 buprenorphine/naloxone ratio the product was rated as mostly unrewarding and undesirable. Thus, this 4:1 ratio was adopted for the combination product ([61]).

Currently, the combination tablet is the product primarily being marketed in the US. The buprenorphine mono-product, under the trade name Subutex, has been available for some time in other countries, notably in France since 1996 and in Australia since 2002. The bulk of clinical research supporting the approval of buprenorphine and the buprenorphine/naloxone combination has been conducted by US investigators although a number of other studies in Europe ([26,62–66]) and in Australia ([67–69]) add to the weight of evidence for its clinical efficacy and safety. Some of the more crucial studies have been summarized in the Cochrane Reviews ([70]).

A major focus of buprenorphine's clinical development centered on the setting in which it would be delivered (i.e. [71–74]) since it was anticipated that it would be made available to general physicians ([75,76]). To that end, several large-scale studies were conducted in community-based general physician offices. One of these, dubbed the best practice protocol, has just been published in the *New England Journal of Medicine* ([77]) and attests to the feasibility of implementing buprenorphine treatment in general medical settings. Another recent effort in clinical research with buprenorphine relates to its implementation in the community-based drug abuse treatment facilities that had little prior experience conducting research on the use of opiate medications. Some of the programs were philosophically opposed to the use of any medications to treat addicts. The National Institute of Drug Abuse Clinical Trial Network (CTN) recently compared short-term use of the combination product to clonidine for opiate detoxification in an inpatient and an outpatient treatment setting ([78,79]). Several-hundred heroin users seeking detoxification were enrolled in this protocol, each randomly assigned to either



buprenorphine/naloxone or clonidine over a two-week course of treatment. Using a composite outcome measure of being present on the last day of the treatment and yielding an opiate-free urine sample as an indication of good outcome, the results were overwhelmingly in favor of buprenorphine. Fifty-nine (59) of the 77 patients assigned to buprenorphine in the inpatient setting were successful compared to only eight of the 36 patients similarly treated with clonidine, and 46 of the 157 patients in the outpatient buprenorphine group were successful compared to only four of 74 patients on clonidine. This study showed that implementing opiate treatment in the community setting is readily feasible. An unexpected result however, was that a number of facilities that previously had not embraced pharmacological treatment have now adopted buprenorphine as an integral part of their treatment strategy.

While results of these studies are encouraging, implementation of buprenorphine treatment in the US has been slow. Recall that it literally took an act of congress to make buprenorphine available and many compromises had to be made to overcome the political barriers ([11,76,80]). In addition, cost, regulatory barriers and training requirements were cited as contributing factors, but philosophical resistance appears to have played an important role and this is even more difficult to comprehend. If ever there were an organization that should welcome buprenorphine, it would be one that has advocated agonist therapy for opiate addiction, yet this has not been the case. Personal philosophy and life experience often get in the way even among experts who commonly remark that, ‘pharmacotherapy is not recovery’. Such is the paradox. If any group of physicians should understand the relationship between medication, brain chemistry and addiction, it is the experts in addiction medicine. Addiction is after all often called chemical dependency and it is by definition chemistry gone awry. It seems almost incomprehensible that these same experts would insist that pharmacotherapy has no place in recovery.

In the end, for this newest advance in opiate pharmacotherapy to succeed, the changes must come from within Ling & Smith 2002 [80,81]. Much of the effort in developing effective medications has been directed towards changing the patients. Buprenorphine, if it is to succeed, must change the physician. The introduction of buprenorphine has been characterized as the ‘great social experiment’. That ‘experiment’ is not an experiment in medication development or in treatment of patients; it is an experiment on the medical community to determine if it can respond with a new attitude, philosophy and approach to patients. For most of the last century, physicians have attempted by various means to change their patients. With buprenorphine, physicians will have to change and as leaders of society that change should translate into a new societal attitude towards addicts and the treatment of addiction. This would be a real advance in opiate pharmacotherapy.

### 3. Related issues

The availability of buprenorphine and its timing has implications in areas of medicine beyond treatment of opiate addiction. Especially, germane are the treatment of pain and the global concerns about HIV and AIDS. There has been worldwide outcry concerning the under treatment of pain and in particular the under utilization of opiates for pain management. In response, the pharmaceutical industry has introduced a number of new opiate formulations, which has been a mixed blessing. On the one hand, this certainly has provided clinicians with a richer armamentarium in the management of pain but on the other hand there has been a concomitant rise in prescription opiate abuse ([82]). The introduction of buprenorphine, although primarily for the purpose of treating opiate addiction, will undoubtedly lead to its off-label use for the treatment of pain, and whether this will prove to be an asset or a drawback is an issue clinicians still have to face. The role of buprenorphine in addressing the problem of prescription opiate abuse remains to be explored. Furthermore, in coming years an increasing number of patients will be maintained on buprenorphine; management of pain in these patients remains a significant clinical challenge.

The relationship between opiate addiction and HIV/AIDS is increasingly being appreciated ([83]). Many developing countries where HIV/AIDS is a major killer are just beginning to put into place, with assistance from the United Nations and other international organizations, efforts to combat the problem. While methadone treatment has been shown effective in reducing the spread of HIV and AIDS, its adoption has been slowest in these same developing countries where public policies appear mostly punitive and unenlightened, mirroring most closely those of the US. Hopefully, buprenorphine will change this and engender a more enlightened social attitude and corresponding policies both here and abroad ([84,85]).

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