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The history of the development of buprenorphine as an addiction therapeutic

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This paper traces the early 21st century success of the agonist–antagonist buprenorphine and the combination drug buprenorphine with naloxone within the broader quest to develop addiction therapeutics that began in the 1920s as the search for a nonaddictive analgesic. Drawing on archival research, document analysis, and interviews with contemporary actors, this paper situates the social organization of laboratory-based and clinical research within the domestic and international confluence of several issues, including research ethics, drug regulation, public attitudes, tensions around definitions of drug addiction, and the evolving roles of the pharmaceutical industry. The fervor that drove the champions of buprenorphine must be understood in relation to (1) the material work of research and pharmaceutical manufacturing; (2) the symbolic role of buprenorphine as a solution to numerous problems with addiction treatment evident by the mid-1970s; the destigmatization and individualization of addicts as patients; and (3) the complex configurations of public and private partnerships.

Keywords: addiction therapeutics; buprenorphine; narcotic antagonists; partial agonist–antagonists

The early 20th century project to develop nonaddicting analgesics

Addiction therapeutics arose within the historical context of efforts to develop a nonaddicting analgesic that began in the United States in the early 1920s. Early 20th century efforts to respond to the “opium problem,” through regulation and control at the source of supply and to address public health concerns through innovation in the research laboratory set the stage for the gradual shift in researchers’ interests toward developing a treatment for addiction therapeutics. Diplomacy directed toward control of opium and its derivatives drove the earliest interactions between the United States and the League of Nations. Policy elites considered the opium problem to be an acute threat to national public health that could only be met through international collaboration on drug control policy (p. 52 in Ref. 1).1,2 Pharmaceutical industry influence was typically represented by national governments at the time. Lacking in-house research capacity, the U.S. industrial and academic pharmacology was so underdeveloped that Harvard University pharmacologist Reid Hunt urged the chair of the Division of Medical Sciences (DMS) of the National Academies of Science (NAS), National Research Council (NRC) to strengthen drug discovery, “the field of medical research in which the United States is most conspicuously backward.”3 This rationale later led the NRC to adopt a committee formed to coordinate efforts to identify “non-habit forming opiates and local anesthetics so that the use of opium and cocaine (the abuse of which almost balances the benefits) may be restricted or abolished.”3 Convened in 1921 by the New York City Bureau of Social Hygiene, the Committee on Drug Addiction (CDA) undertook the search for morphine substitutes as a way to attack the root of the “opium problem,” which it considered to be not “vicious” (nonmedical) consumption but medical use leading to addiction. The CDA published The Opium Problem (1928), a hefty compendium reviewing 4,000 studies, which found that while the “consensus of opinion of the authors...
reviewed is that the majority of cases of chronic opium intoxication lies in the therapeutic use of the drug, "there was rising heroin use for ‘purposes of dissipation’" (p. 13). Committee sponsorship was assumed by the Rockefeller Foundation from 1932 to 1939, after which the CDA became part of the NAS/NRC and was relatively self-sustaining through modest contributions from the pharmaceutical industry and National Institute of Health (NIH; in 1949 renamed National Institutes of Health). The Committee undertook chemical dissection of the morphine molecule, seeking to dissociate analgesia from addiction liability and emphasizing direct manipulation of the morphine molecule to develop nonaddictive substitutes for each known medical use of morphine.

The solution to the “opium problem” was first sought at the laboratory bench at a time when the United States was becoming a major player within the evolving international drug control framework. For such a narrowly tailored goal to be understood as meeting a broad social problem of unclear etiology, it had to be translated into a fundable research program. Reliable methods to test compounds in animals and human beings had to be developed and validated. In the CDA’s first decade, some 150 compounds were produced and evaluated; all but one—Metopon (5-methylhydromorphone)—demonstrated the elusiveness of the goal.

Although iatrogenic addiction had declined with changes in medical practice, physicians remained the chief vectors of opiate addiction in the early 20th century. The Committee’s goals dovetailed with an American Medical Association (AMA) reform agenda to “reduce indications for opiates to an irreducible minimum” (p. 95). CDA leadership supported scientific investigation of narcotics, including analyses of the chemical and biological literature on addiction alkaloids; formulation of rules and regulations for legitimate use of alkaloids having addiction properties, and education of physicians and the public about these rules; and “replacement of all present use of addiction alkaloids by substitutes having no addiction properties” (p. 11) (emphasis ours).

Morphine was the Committee’s target because it had numerous specific uses in clinical practice, many of which, according to the first committee report, could already be satisfied by other drugs. William C. White, CDA chair from 1929 to 1947, reported that “since no one drug can function for all of these uses, it is necessary to replace the legitimate uses of morphine with a number of substitutes . . . [If it is . . .] possible to substitute for all legitimate uses of morphine other chemical compounds without addiction properties, it should render morphine an unnecessary commodity in international commerce” (p. 11). White noted that “setting up a machinery for a specific purpose; that is, of an attempt at a solution of a definite problem of international importance” was new for the NRC Division of Medical Sciences. The Committee was charged with reducing legitimate use by decreasing physician’s prescriptions and proprietary remedies containing narcotics, replacing each use of habit-forming drugs with a substance that was not habit-forming but capable of producing the medicinal action required, and reducing to a minimum the legitimate production of alkaloids and thus lessening the necessity for controls. The Committee was also asked to conduct public education seminars on the indispensable uses of morphine, to seek to prepare by synthesis and analysis compounds without addiction fractions, and to study the effects of these compounds in animals and later in human therapy. White arranged with Morris Fishbein, editor of the Journal of the American Medical Association, to publish the Committee’s rules and regulations governing morphine prescription, which was released as The Indispensable Uses of Narcotics.

The Committee’s research program was a highly organized, centrally orchestrated effort—one of the first scientific collaborations that focused the U.S. government scientific resources on solving a social problem. Cooperation between CDA and the U.S. Public Health Service (PHS) was secured by strategic appointments. Clinical studies commenced in 1933 at the federal penitentiary in Fort Leavenworth, Kansas. However, in 1929 the U.S. Congress passed the Porter Bill, authorizing construction of “narcotic farms” to rehabilitate addicts. When the first U.S. Narcotic Farm opened in Lexington, Kentucky, in 1935, a tiny research laboratory was housed within the 1,500-bed institution. In May 1938, the PHS broadened the NIH role in the Committee by establishing a chemotherapy unit consisting of several chemists who had been associated with CDA, including Nathan B. Eddy, Erich Mosettig, Everett L. May, and Lyndon F. Small. The Committee also
Eddy played a leadership role in the Expert Committee from its founding until his death. CDAN members served on it and supplied data to it, shaping its drug definitions and criteria for control. The Expert Committee, for example, depended “in large measure upon receipt of information” from American research, funneled through CDAN (p. 11).
The Addiction Research Center (ARC), as the laboratory at Lexington was called after 1948 when it joined the newly formed National Institute of Mental Health (NIMH), studied methadone in human subjects, finding that it produced a milder, more prolonged version of the abstinence syndrome than other opiates, according to the Himmelsbach scale. Research Director Harris Isbell, who had replaced Himmelsbach, instituted methadone detoxification at Lexington after 1948 for clinical management of opiate withdrawal. Isbell later opposed using methadone for maintenance given the results of studies he and Abraham Wikler conducted on former morphine and/or heroin addicts in the late 1940s indicating that the subjects expressed increased satisfaction as dosage increased.21 They concluded that “narcotic drug addicts would abuse methadone and would become habituated to it if it were freely available and not controlled” (p. 892).21 They also noted that methadone “completely alleviated the morphine abstinence syndrome in man” and itself exhibited a mild abstinence syndrome. On the basis of their findings of “satisfactory subjective reaction” to methadone, they argued that methadone would present a potentially serious public health problem if manufacture and distribution were not controlled.22

Despite controls, methadone was used as an “office-based” addiction treatment by a handful of physicians who prescribed it in the 1950s; the New York State Department of Mental Health ran an informal methadone maintenance program in 1959.23 However, the rabidly antimaintenance Federal Bureau of Narcotics (FBN) harassed physicians who prescribed methadone or other opiates. Neither Anslinger nor CDAN researchers considered maintenance a viable solution to the problem of “unsafe analgesics,” as it was framed. By the 1950s, the Committee’s drug development hopes fastened upon another class of drugs—the narcotic antagonists—as an alternative to agonists like morphine and methadone. A spirit of experimentality permeated the organizations and research networks through which addiction researchers and clinicians then worked.

The mid-20th century project to develop narcotic antagonists as “safe analgesics”

In 1963, Isbell and Wikler retired, handing over the ARC to neuropharmacologist William R. Martin, who joined the group in 1957. Martin studied the underlying neural mechanisms of addiction, and had immersed himself in Himmelsbach’s early findings, becoming convinced that tolerance was an extremely complex neuronal phenomenon. He set out to understand the “neuronal events that are responsible for morphine’s action as well as for a development of physical dependence and the emergence of the phenomena of early and protracted abstinence” (p. 108).24 Martin, a physician and World War II Army veteran, had prepared a doctorate in neuropharmacology under Klaus R. Unna, who, while working for Merck, discovered that nalorphine, a narcotic antagonist, could “prevent or abolish the action of morphine.”25 Martin worked in a highly original and theoretical way with a close-knit circle of chemists innovating in the analgesic area, including Sydney Archer, Louis Harris, Andrew Keats, and Everett May, from Small’s group.26 Highly active in the Committee, this network expanded in the late 1960s to include U.K. chemist John Lewis, whose work would become crucial to bringing buprenorphine to the attention of the ARC group.

Through its historical role in relation to the CDAN (which became the Committee on Problems of Drug Dependence [CPDD] in 1965), ARC researchers enjoyed constant access to new analgesic compounds. During the 1950s and 1960s, the Committee turned to studying the narcotic antagonists, including nalorphine;27–32 naltrexone;33 LAAM (long-acting methadyl acetate), a long-acting derivative of methadone May synthesized under CPDD auspices;34 cyclazocine;35 phenazocine;36 and pentazocine.37 Although dating from Committee discussions in the 1940s, this route of experimentation intensified during the synthetic flood of the 1950s. At the January 1953 CDAN meeting, Isbell had urged Henry K. Beecher and Louis Lasagna to run clinical trials of a nalorphine–morphine combination in order to establish nalorphine’s analgesic efficacy for post-operative pain. While these drugs were then being primarily studied as analgesics,38 suggestions surfaced at Lexington that narcotic antagonists might help prevent relapse. Another pathway pursued from 1952 onward was May’s work building upon incomplete morphine molecules, which led to the production of phenylmorphans and benzomorphans (p. 676 in Ref. 40).39,40 By the mid-1960s, the Committee’s efforts to find a “chemopharmacological approach to the addiction
problem” were focused on the narcotic antagonists. More than 30 years into its quest, the Committee was not overly optimistic about the chemopharmacological approach. Aware that heroin addiction could not be regarded solely as iatrogenic, the Committee did not think that a new medicine could effectively treat nonmedical addiction; rather, it focused on preventing potent new addictive compounds from being marketed. CDAN’s relevant historical touchstone was the “heroin mistake” stemming from initial claims that heroin was a “nonaddictive” alternative to morphine for analgesia (p. 673). The “solution” to the heroin problem had been framed as an alternative analgesic that would displace the need for opium production. Without the need for morphine or codeine (work was underway to replace codeine as an antitussive), the global opium supply could be controlled. However, by the 1960s, the Committee understood that its “chemical-pharmacological-clinical program” was founded upon an erroneous hypothesis concerning the potential ease of dissociating the analgesic effects of morphine from the dependence-producing and respiratory-depressing effects (p. 674). The Committee turned toward narcotic antagonists upon the suggestion of Andrew Keats, hoping that this class of drugs would be clinically useful as analgesics. Recognizing that if even one of the new antagonists proved a sufficiently powerful analgesic without undue side effects, Eddy noted that it would still not “solve the addiction problem overnight” (p. 679). Social and economic factors, he indicated, were paramount: “We shall still have the opium-producing countries. . . . We shall still have the established machinery for illicit production and distribution of heroin. . . . [and] we shall still have the social and psychological forces that encourage potential addicts to dose themselves with drugs” (p. 679). Eddy heralded the narcotic antagonists as progress in managing, rather than resolving, addiction problems: “We thought there might be found among the opiate antagonists one with the combination of antagonistic and analgesic properties which would give adequate clinical analgesia without excessive and disturbing side effects” (p. 679). CDAN was not naive to nonmedical use but rather conceived of its role as acting within the national and international drug control apparatus to prevent new analgesics with potential to produce dependence from going onto the market.

By the mid-1960s, the goals of the Committee (hereafter referred to as CPDD), underwent a conceptual shift toward finding a pharmacotherapy for addiction treatment and relapse prevention as a result of Martin’s experimental work with the narcotic antagonists, which he felt were the best candidate drugs for analgesics that did not produce dependence and for addiction therapeutics. Martin first studied cyclazocine, a long-acting, orally effective narcotic antagonist developed at Sterling-Winthrop, as a “modality for preventing recidivism in ex-heroin addicts.” Martin set up a trial based on Wikler’s postulation that “conditioning”—the association of positive pharmacological effects and alleviation of withdrawal distress with specific environmental “cues” and social settings—played a role in perpetuating addiction. Wikler reasoned that it might be possible to “extinguish” associations by allowing addicts to inject an antagonist drug that would block the effect of the agonist drug. This hypothesis dovetailed with Martin’s observations that cyclazocine produced a different type of physical dependence than morphine. In suggesting that cyclazocine might be efficacious as a new method for treating opiate addiction, Martin built upon findings that nalorphine, a narcotic antagonist his mentor (Unna) had developed at Merck, competed with morphine at a receptor site but worked through a different mode of action. To make sense of this observation, Martin introduced several concepts for which he became known: multiple opiate receptors’ “competitive antagonism” at the receptor level, and “receptor dualism.” Another piece of the puzzle had to do with why the effects of abstinence should be so long lasting. Martin’s experiments conducted with Donald Jasinski, who joined the ARC in 1965 from a postdoctoral position with Unna, led them to postulate a “secondary” or “protracted” abstinence syndrome that differed from the “explosive, early abstinence syndrome” tracked by Himmelsbach (p. 2). Tracing protracted abstinence, Martin and Jasinski found that its characteristics varied among individuals but fell within the range of normal physiological variables and were difficult to discern unless researchers were in close proximity with subjects. Martin and Jewell W. Sloan observed negative attitudes in subjects in an 18-month study of protracted abstinence and discussed their possible role.
in relapse, with a rationale for using narcotic antagonists in treatment of ambulatory narcotic addicts: “the view has been presented that the chronic administration of narcotic antagonists would prevent the exacerbation of protracted abstinence and may provide a circumstance whereby conditioned abstinence and conditioned drug-seeking behavior could be extinguished.”

While it was optimistic that further developments in neuroscience would yield a specific pharmacotherapy for addiction treatment and relapse prevention, Martin’s studies contained the germ of a shift in the addiction research community toward addiction therapeutics.

Relapse prevention had long been a problem for clinicians treating drug addicts. The idea that a pharmacotherapy could support relapse prevention by keeping patients in treatment helped change the goal from a nonaddictive analgesic to addiction therapeutics. CPDD held that the “ability of an antagonist to suppress the satisfying response (euphoric effect) of an opiate (heroin)” could deter relapse; even more useful would be “prolongation of antagonistic action, either in an inherently longer-acting antagonist or a depot preparation” (p. 24).

The Committee regarded an “antagonist-suppressant” as superior to agonist maintenance. In 1970, the Committee embarked on an intensive search for a drug exhibiting prolonged antagonistic action. Naltrexone had been synthesized in 1963 at Endo Laboratories, a small pharmaceutical company with whom Martin consulted to develop the drug before DuPont purchased the company and dropped the project. Naltrexone was conceptualized as a “blockade” that fended off agonist access to receptor sites. While naltrexone would be approved as a pharmacologic adjunct to treatment for opioid addiction and alcohol in 1984, it never gained social acceptability among physicians or addicted patients despite appearing to be a pharmacologically perfect solution at the receptor level. Naltrexone was later touted as an anticraving medication that had the social effect of “block[ing] the normal reactions of addicts to heroin and permit[ting] them to live as normal citizens in the community” (p. 304). In 1966, Dole reported on the first 84 methadone maintenance patients to the Committee, which concluded that a “significant number of patients through methadone maintenance management have attained a reasonable degree of social rehabilitation. Their dependence has not been ameliorated, it has not been treated, it may have been augmented, but the patient and society have gained” (p. 114). The Committee’s lukewarm reception of the methadone maintenance pilot program and grudging acceptance of its social benefits was no surprise. The Committee had never favored agonist maintenance. Debates over morphine maintenance had occurred in the 1920s as part of the context in which the Committee was formed. In the 1950s, there was an active national debate over the practice of morphine and/or heroin maintenance conducted conjointly by the American Bar Association and the American Medical Association. At that time, the Committee had opposed maintenance, aligning with the FBN against it. In the 1960s, the FBN was combined with the Bureau of Drug Abuse Control, an agency within the Department of Health, Education and Welfare, to form the Bureau of Narcotics and Dangerous Drugs (BNDD) in 1968, which in 1973 became the Drug Enforcement Administration (DEA). Committed to safeguarding public health against “unsafe analgesics,” the Committee aligned with the drug control apparatus in viewing methadone maintenance with skepticism. Similarly, the WHO Expert Committee on Drug Dependence considered methadone maintenance a research approach but not an established treatment (p. 112). Dole and Nyswander characterized such attitudes as those of a stodgy addiction research establishment opposed to methadone maintenance on political grounds.
New entrants to the field exemplified the attitude of experimentality then pervading drug treatment. Many embraced methadone maintenance despite acknowledging its limitations. For instance, Jerome H. Jaffe, who had spent a year working on the clinical side of the U.S. Narcotic Farm in the early 1960s, had heard Martin’s 1964 paper to the Committee on cyclazocine and theorized that narcotic antagonists might work to prevent relapse, keep addicts in treatment, and reduce overdose events. \(^{52}\) In New York City, Jaffe and Leon Brill detoxed former heroin addicts unable to access methadone maintenance and put them on cyclazocine obtained from Sterling Winthrop. Although he ultimately switched patients to oral methadone due to ease of use compared to short-acting injectables, Jaffe considered the narcotic antagonists as having therapeutic potential for optimizing compliance and extending treatment duration. \(^{53}\) Jaffe spent six months with Dole and Nyswander learning the ropes of methadone maintenance before he moved to Chicago to start a multimodality drug treatment program, the Illinois Drug Abuse Program, which brought his work to the attention of the Nixon administration.

The Nixon administration turned to methadone maintenance as a method for crime control and as a way to respond to concerns that a high percentage of heroin-addicted Vietnam veterans were returning opiate-addicted. \(^{54,55}\) In 1971, Nixon created the Special Action Office for Drug Abuse Prevention (SAODAP) and appointed Jaffe director. Despite concerns about methadone’s limitations, including the frequency of dosing, refusal, and refractory cases, Jaffe played a crucial role in expanding methadone maintenance as a treatment modality in the United States.

The Committee also shifted toward support for agonist maintenance in the 1970s and assisted in creating the first practice guidelines governing methadone maintenance, “Narcotics and Medical Practice,” which were issued in 1971 by a joint committee composed of NAS/NRC committees, including CPDD, and the AMA Council on Mental Health. These guidelines stated that “methadone maintenance is not feasible in the office practice of private physicians” because they could not meet all of the therapeutic needs of such patients. Concerns about methadone diversion played a major part in the decision not to allow office-based methadone prescription, as physicians in private practice were considered incapable of “assur[ing] control against redistribution of the drug into illicit channels” (p. 114). \(^ {18}\) Limiting diversion dominated discussions of methadone within the domestic drug control apparatus in the early 1970s.

Despite the widespread support for methadone maintenance, there remained recognition of its limitations within the addiction research community. Research on alternative medications ranging from long-acting methadone to narcotic antagonists continued even as methadone maintenance expanded. Research on long-acting methadone (LAAM) had been sponsored by the NIMH Division of Narcotic Addiction and Drug Abuse (DNADA) in the late 1960s. \(^ {56}\) Understood to lack abuse liability, LAAM and the narcotic antagonists were thought less likely candidates for diversion. Methadone treatment centers, with the notable exception of Dole and Nyswander’s program, operated under relatively informal FDA-issued Investigational New Drug (IND) designations, until SAODAP and FDA jointly imposed formal regulations to create a “hybrid IND-NDA (New Drug Application) that acknowledged the safety and efficacy of methadone maintenance as a treatment but imposed a number of conditions on how it could be used,” in 1973 (p. S5), \(^ {57}\) resulting in a system of stand-alone clinics and restriction of methadone in private practice. In 1974, Congress became concerned with methadone diversion and amended the Controlled Substances Act (CSA), in 1970, to give DEA considerable powers despite the inception of the National Institute on Drug Abuse (NIDA) and sunset of SAODAP in 1973. Many clinicians, including Dole and Jaffe, came to view the methadone regulations as government interference with the practice of medicine. \(^ {52}\) The restrictive climate had led SAODAP to prioritize development of narcotic antagonists; The White House office sought to contract with CPDD to conduct Phase III studies on narcotic antagonists. \(^ {58}\) While both organizations agreed that it was desirable to move beyond methadone maintenance in the addiction therapeutics arena, the organizational complexities of arranging for CPDD to run a SAODAP-initiated Narcotic Antagonist Project delayed the process.

Relapse was SAODAP’s target. Primary sources indicate that the push to develop narcotic antagonists as addiction treatment drugs was driven by a search for a viable alternative to methadone maintenance. \(^ {58–59}\) Narcotic antagonists were suggested as a “therapeutic maintenance agent for
opiate-dependent individuals” on the assumption that the high recidivism rate among opiate addicts resulted from a “biochemical abnormality induced by the prolonged use of a narcotic” or a continuing “psychological dependence” that could be blocked by an antagonist long enough for the behavior to be “deconditioned” (p. 1). Long-acting antagonists were ruled out because of “considerable agonist activity,” but a few series of new compounds were being shown to have strong antagonist properties with little or no agonist activity (p. 2). Four such compounds that appeared “very promising” to SAODAP officials were almost through the animal and human testing process for safety and toxicity. Although these compounds were ready to enter large-scale, Phase III human trials, the National Academy made it clear to SAODAP that it would not allow CPDD to assume responsibility for drug development or clinical trials management despite the social and political climate surrounding methadone in the early to mid-1970s making narcotic antagonists look comparatively hassle-free. The SAODAP decision to develop narcotic antagonists was based on their potential clinical value for treating patients unwilling or unable to participate in methadone maintenance, including “young users and early users inappropriate as maintenance subjects.” Despite the CPDD’s sustained interest in the development of antagonists for treatment of narcotics addiction, NAS president Philip Handler declined to allow CPDD to assume a managerial role in conducting clinical trials. Instead he created a new Committee for the Evaluation of Narcotic Antagonists (CENA), which conducted a study of naltrexone under NAS auspices.

The National Academy of Sciences reorganized its committee structure in 1975, leading to the termination of CPDD as an NRC committee. While the Committee had played a unique and invaluable role during its long and productive existence, the emergence of drug abuse as a national issue of major importance had attracted many new organizations with greater resources that overshadowed CPDD’s once unique capabilities.

Other uncertainties also pervaded the addiction research arena. The Federal Bureau of Prisons decided in April 1976 to phase out all participation of federal prisoners in clinical trials and shut down the ARC’s prison recruitment channel. When Martin traveled to Washington, DC, to defend addiction research, his rationale for continued investment was the compelling need to develop alternatives to methadone (agonist) maintenance. Still at the ARC in Lexington, Jasinski turned his scientific attention to addiction therapeutics. Both researchers pointed to buprenorphine as a sign of progress: “Recognizing the possibility of partial agonists of the morphine type such as profadol, propiram and buprenorphine and evolving methods for identifying them have opened the possibility of a narcotic analgesic whose agonistic activity will be great enough to fulfill clinical expectation but not produce dangerous side effects or a clinically significant degree of physical dependence.” The fervor that developed among buprenorphine’s champions must be understood in relation to the symbolic role the drug played in justifying continued federal investment in addiction research.

Building on SAODAP’s narcotic antagonist project, NIDA published a series of research monographs on drug development in the mid-1970s. One monograph named naltrexone as the most promising of these “new” methods. The editors introduced NIDA’s “newly established drug development program,” first applying the term “orphan drug” to addiction treatment: “With increasing frequency, Federal agencies are being called upon to evaluate and develop new drugs and treatments for a wide variety of diseases and related conditions. The so-called ‘orphan’ drugs, or drugs of little or limited commercial value, are being shunned by the pharmaceutical industry, due primarily to the ever-increasing developmental costs and risks associated with new drugs. Thus, within the Public Health Service, a drug development effort has emerged to fill this void.” Orphan drug designation would become key to buprenorphine’s career as an addiction therapeutic.

Buprenorphine’s career as an addiction therapeutic

Buprenorphine was discovered in 1966, at the research labs of a home products company, Reckitt & Colman (hereafter Reckitts), in Hull, England. Working for the company was Oxford-trained chemist John Lewis, a doctoral student of the Nobel prizewinning organic chemist, Sir Robert Robinson, who elucidated the active structure of morphine in 1925. Kenneth Bentley, father of the “Bentley compounds,” was a postdoctoral researcher at Oxford
when Lewis did his graduate studies there. Bentley went on to McFarlan Smith in Edinburgh, then the main U.K. producers of opium alkaloids. In 1958, the company entered into joint venture with Reckitts (1958–1963) to develop over-the-counter analgesics. According to Lewis, Bentley laid the “chemical foundations” for the Reckitts opioid drug development project in the 1950s. He believed that “opioids with structures substantially more complex than morphine could selectively retain the desirable actions whilst shedding the undesirable side effects,” a vision convergent with that of Eddy and the Committee. In 1963, Reckitts took over the joint project, after McFarlan Smith was absorbed into another company. Reckitts developed two unsuccessful opiates (etorpine, a potent µ-agonist, and its antagonist), before putting buprenorphine into Phase 1 studies on “committed volunteers” including Lewis himself, in the late 1960s.

Reckitts supplied buprenorphine to the ARC researchers in Lexington throughout the 1970s, and ARC’s Jasinski consulted regularly with the company. In 1972, Lewis disclosed buprenorphine’s pharmacological profile at the annual CPDD meeting. While an immediate impact seems not to have occurred, Lexington researchers went on to study buprenorphine as a potential addiction treatment drug because of its combination of analgesic (agonist) and antagonist properties. According to Lewis, “The story of the development of buprenorphine as an addict treatment” [emphasis ours] began in 1975, when Jasinski countered growing opposition to using prisoners as clinical research subjects by arguing that many prisoners were addicts and the pharmacology of buprenorphine made it such an “attractive candidate” as a treatment for opiate dependence that its human abuse potential was in urgent need of study. Jasinski et al. announced the addiction therapeutics potential of buprenorphine in a landmark paper in 1978.

In 1979, Jasinski classified the narcotic antagonists into three groups: (1) compounds that produced agonistic effects that do not resemble morphine (nalorphine and cyclazocine), (2) compounds that do not produce agonistic effects (naloxone and naltrexone), and (3) antagonists that produce agonistic effects that resemble those of morphine because they are also partial agonists of morphine. By then, six category 1 narcotic antagonists had been introduced as analgesics with low abuse potential. According to Jasinski’s scheme, propiram and buprenorphine fit category 3. Interest shifted to these “partial agonists of the morphine type,” which did not constitute a homogenous class due to their intrinsically different capacities for producing euphoria, sedation, and psychotomimetic effects.

At annual CPDD meetings from 1975 on, Jasinski suggested that buprenorphine usefully combined the characteristics of methadone with those of a pure opiate antagonist and effectively blocked morphine (p. 5). Jasinski singled out buprenorphine as having an “especially unique pharmacology in man” because it produced “very little physical dependence” even with chronic administration (p. 290S). Citing his 1978 study, he speculated that buprenorphine “would not only have a therapeutic application as an analgesic of low abuse potential but also as a new type of drug treatment of narcotic addiction.” Jasinski heralded buprenorphine’s unique potential because it alone produced long-lasting “changes in feelings that are acceptable to addicts,” and was “less toxic than methadone,” declaring that the committee’s 50-year project to “potentially utilize narcotics therapeutically to both relieve pain and treat addiction without the production of physical dependence” had yielded buprenorphine, which “appears to have the advantage of both methadone and naltrexone but without the major disadvantage of each” (p. 85). For at least some parties, the search had funneled down to one candidate drug.

Given the enthusiasm for buprenorphine within the addiction research network, its meandering path to market as an addiction therapy is puzzling. Why did it take almost three decades after Martin and Jasinski’s recognition of buprenorphine’s therapeutic potential for it to be approved by the FDA for treatment of opioid dependence? Buprenorphine faced many hurdles, including scheduling issues; reluctance of pharmaceutical companies to take on addiction medicaments; fall-out from experimental, diversion, abuse of its analgesic form; and still restrictive addiction treatment systems. As with methadone maintenance, many within the addiction research enterprise had become convinced of buprenorphine’s uniqueness as an opioid addiction treatment. However, the social and political context was quite different, given the maturity of the drug regulatory apparatus, the changing
knowledge base in the field, and what had been learned from the experience of methadone maintenance delivery through a stand-alone clinic system detached from office-based medical practice.

In 1979, following the ban on use of federal prisoners as research subjects, NIDA had moved the ARC’s Clinical Research Program, now under the direction of Jasinski, to the medical campus of The Johns Hopkins University (JHU) in Baltimore, Maryland; the preclinical program followed in 1981. The JHU site was chosen partly because Baltimore provided a suitable source of research subjects: inner-city heroin addicts. Addiction researchers considered it unethical and unwise to carry out research involving addictive substances on people who were not or had not been addicted. Furthermore, residential laboratories were necessary. As Martin told an interviewer in 1980, he “would never conduct an experiment in which I chronically administered a potentially addicting drug to a patient who could leave the setting at will.”

The Baltimore buprenorphine studies, conducted by the JHU Behavioral Pharmacology Research Unit (BPRU) headed by George Bigelow, grew out of the ARC’s move to the Hopkins campus, which brought buprenorphine to Baltimore. Bigelow recalled that the ARC brought with them “connections to new drugs, the pharmaceutical industry, and the medications development field, in a way that we had not really had before. In particular, they brought access to buprenorphine, which was difficult to make and supplied only by Reckitts. Don Jasinski had been working with buprenorphine and had published the first paper suggesting it could be useful in addiction treatment.” The BPRU collaborated early on with ARC researchers, including on a study evaluating buprenorphine in comparison to methadone and another evaluating a range of doses of buprenorphine in an opioid challenge. Bigelow recalled that these “marked the primary beginnings of using that methodology and incorporating [ARC] methods in our studies.”

One pharmacologist, R. Ed Johnson, who had compounded buprenorphine for Martin and Jasinski’s studies while a pharmacist in Lexington, assisted Jasinski in moving the ARC’s Clinical Research Program from Lexington to Baltimore in 1979. While working at the ARC (renamed the NIDA Intramural Research Program in the 1990s), Johnson served as lead investigator on several development studies of buprenorphine and published results from the first pivotal clinical trial of buprenorphine in 1992. Following his retirement from the U.S. Public Health Service in 1991, he joined the faculty of the BPRU at Johns Hopkins where he continued to conduct clinical trials with buprenorphine funded by NIDA and dedicated his scientific career to bringing buprenorphine to market as an addiction treatment.

Congress charged NIDA with assuming responsibility for new addiction treatment methods in the early 1980s. CPDD continued meeting annually, although its drug development and evaluation programs shrunk. In February 1983, CPDD held a symposium on agonist-antagonists that included a review of buprenorphine presented by John Lewis. At this symposium, Martin attributed his recognition of the possibility of developing a “less toxic, less addicting drug by developing a partial agonist of the morphine type” to the studies he had conducted with Jasinski on buprenorphine in the dog, which laid the foundation for understanding that “these antagonists do things that morphine does not do . . . [they are] much safer drugs . . . their abuse potentiality is less . . . they have a unique pharmacology that probably provides us hints about where we can go further in the future” (p. 84). Jasinski spoke to buprenorphine’s advantages over naltrexone, noting that his subjects liked buprenorphine better, and “felt comfortable on it. The induction of a feeling state that they found salient following buprenorphine was certainly there. Most of our subjects told us that it was, in fact, the most reinforcing drug that they had ever used” (p. 95). Despite this caution, buprenorphine was offered as a “safe and effective mode of pharmacotherapy for heroin addiction.”

By 1985, injectable buprenorphine had been marketed for analgesic applications in 29 countries and the sublingual tablet in 16 countries. In the United Kingdom, Reckitts had launched injectable buprenorphine for severe pain in 1978, with the sublingual analgesic following in 1982. It licensed Norwich–Eaton to distribute buprenorphine hydrochloride (Buprenex) in the United States, where the analgesic was launched in 1985, after FDA approval. However, scheduling incited lengthy struggles. Scheduling was still (and remains) an artifact of almost a century of domestic drug policy culminating in the 1970 U.S. Controlled
Substances Act (CSA) and, internationally, the Single Convention of 1961 and Psychotropic Convention of 1971. Domestic and international conventions are based on proving pharmacological equivalence. The classical antagonists, such as naloxone, naltrexone, and nalorphine, catalyzed considerable arguments about whether they really fit the definition of dependence-producing drugs. Charles O’Keeffe, a former Clinton advisor and later President of the U.S. company Reckitts Benkiser Pharmaceuticals, has explained, “You had to jointly defend the class of drugs, to keep the agonist/antagonists where they were.”

The DEA followed the international convention scheduling, even if technically they could do otherwise. Internationally, buprenorphine proponents fought to put buprenorphine under the less restrictive Psychotropic Convention, arguing that pharmacological effects and dependence liability were distinctly different. Domestically, the DEA tried to reschedule buprenorphine three times.

But the shift from research to industrial drug development for addiction treatment took off at the intersection of two trajectories: formal interest on the part of NIDA and a change of orientation within Reckitts. In 1989, the U.S. Congress mandated that a Medications Development Program be established in NIDA. The following year, NIDA established the Medications Development Division (MDD) to develop close working relationships between academia, the pharmaceutical industry, and government agencies, including the FDA, so as to develop and evaluate addiction treatment medications to the point that they could go through the FDA approval process. An Institute of Medicine (IOM) report identified relapse prevention as the proper focal point for the MDD, but noted that the basic knowledge about the pathophysiology of protracted abstinence and conditioned withdrawal remained rudimentary (p. 48). One of the MDD’s first priorities was to get LAAM approved for an addiction treatment indication. This objective was accomplished in 1993 and LAAM was launched in the United States in 1994. In 1993, MDD also approached Reckitts about formalizing their already existing mutual interest in developing buprenorphine for addiction treatment. NIDA was interested in buprenorphine by itself and in combination with naloxone (to prevent diversion). Reckitts was NIDA’s obvious choice for a Cooperative Research and Development Agreement (CRADA), as another company would have had to conduct safety and toxicology studies from scratch for a new indication. Bioequivalence studies for the addiction treatment indication had yet to be done, and the ideal dosing was unknown. Frank Vocci, a pharmacologist who had joined NIDA in 1989 from the FDA, became Director of MDD in 1998. He would play a crucial role in the CRADA development, including in the face of disappointment with LAAM’s outcome.

The time was propitious for Reckitts, as well. Disappointed with its analgesia business, the company had contracted out buprenorphine commercialization to numerous companies worldwide and had abandoned ethical drug development in the early 1980s. John Lewis moved to Bristol University, where Reckitts funded some pharmacology research. The company’s reluctance to enter the addiction therapeutics arena reflected a more general attitude among pharmaceutical companies that analgesics might, as Bigelow put it, be “tainted” in the eyes of prescribers and pain patients if also used for addiction. Methadone, for instance, had found little use as a pain medication. As Chris Chapleo, now Reckitt & Benkisher Director of Buprenorphine Business, recalled, Reckitts was under pressure at that time because of “misuse, abuse, diversion of buprenorphine, the analgesic product” and its off-label use to treat addiction. An estimated half of the buprenorphine analgesic (Temgesic) supply in France was being used off-label to treat addicts. Diversion resulted in buprenorphine, an unscheduled molecule, being put into the Psychotropic Convention in the late 1980s, with negative fall-out for the buprenorphine market. Doctors hesitated to prescribe scheduled drugs; sales of the buprenorphine analgesic in France had dropped by 50% after scheduling; patients had trouble obtaining it.

The International Narcotics Control Board (INCB) was mounting pressure to move buprenorphine from the Psychotropic Convention to the more restrictive Single Convention. Reckitts was also concerned by two “Phase 1–like” studies conducted

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"Six European countries put LAAM on the market by 1997, but it was withdrawn beginning in 2001, following reports of severe cardiotoxicity associated with its use."
by a Belgian psychiatrist, Marc Reisinger using a pharmacy-prepared buprenorphine compound from the analgesic. Though these supported Jasin-ski’s finding and showed that higher buprenorphine dosages were necessary for addiction treatment than for pain management, Reisinger’s studies involved off-label buprenorphine, which Reckitts felt it could not condone.67

Despite Reckitts’s ambivalence, the company was finally persuaded by Chapleo and O’Keeffe to “remove the For Sale sign and develop buprenor- phine for the treatment of opioid dependence” in partnership with NIDA, who “would be co-funding to ease the burden to Reckitts.”68 69 Reckitts bought back its U.S. distribution rights but had to set up a U.S. company (Reckitts Colman Pharmaceuticals), as well as develop an infrastructure (secure warehouse services, import permits, etc.) before entering into the CRADA. The agreement was finally ratified in 1994. According to Reckitts’s negotiators, the company was swayed by arguments about “social responsibility” toward drug addicts85 and the ethics of withdrawing, buprenor- phine when patients were being treated with it for pain.67 The following year, in the wake of a contami-nated blood transfusion scandal and the AIDS epidemic among injecting drug users, France became the first country to approve buprenorphine (Subutex) for treatment of opiate dependence in general medical practice, proving the national vi-ability of implementing the drug89 and preventing Reckitts licensee Schering-Plough from losing its license because of off-label use of Temgesic. France framed Subutex partly as harm reduction, as would some Asian countries in the following decades.67

In the United States, buprenorphine development faced funding issues, scheduling, and potential reg-ulatory problems, as well as competition with the methadone community. Public contributions to de-velopment eventually included millions of dollars in contracts and grants. Reckitts obtained orphan drug status for Subutex and Suboxone (the two buprenor-phine medications for addiction treatment) in the CRADA,85 arguing the rarely used Cost Recovery principle; that is, that the company risked not re-cuperating what it invested (buprenorphine is more expensive to manufacture than methadone).91 The orphan drug designation freed the company from competition with lower-priced generics for seven years.6 Once Suboxone and Subutex were launched, postmarketing surveillance by an independent con-tractor was subsidized by Reckitts as a requirement of the approval for marketing.92, c

Most NIDA-funneled resources contributed to the numerous clinical pharmacology studies be-tween 1980 and 1985, which compared various routes of administration and dosages, withdrawal, and cross-tolerance. Later studies concerned induc-tion, abrupt withdrawal, and short-term detoxifi-cation. In the 1990s, studies were extended to in-clude dose omission schedules, pharmacokinetics, and buprenorphine for pregnant, opiate-addicted women. These laid the groundwork for arguing that buprenorphine was not merely a “substitute ther-apy,” in order to differentiate it from methadone.

Buprenorphine proponents, however, perceived methadone regulation as an obstacle to pharmaceu-tical innovation for addiction treatment, an opinion the IOM 1992 Report also held.84 As the molecule proved less toxic than methadone or LAAM when ingested by nontolerant individuals, buprenorphine treatment was thought to require less oversight. And to compete with methadone, buprenorphine was mainstreamed into medicine,87,85 which required amending the CSA requirement so physicians could treat patients with a Schedule V narcotic. France had normalized addiction treatment by allowing general practitioners to prescribe Subutex, as they would.

"Originally, Reckitts argued for orphan status on the prevalence principle that the drug would affect a rare pop-ulation. The FDA rejected Reckitt’s prevalence estimate, which was based on the number of treatment-seeking ad-dicts, and not on the estimated number of addicts (treated and untreated) in the U.S. According to O’Keeffe, Subutex and Suboxone were the first drugs ever designated orphan status on an economic basis.85 The economic principle argument enabled Reckitts to obtain exclusivity for seven years, versus the 10 or 15 years they would have had under “normal” orphan drug status, making it one of the only orphan drugs based on this principle.

The study, which included 18,596 interviews with ap-plicants to substance abuse treatment programs, 8,194 surveys of federally certified physicians, as well as pub-licly available indicators of use and misuse of buprenorphine and buprenorphine with naloxone shows a steady increase in diversion and abuse from 2005 to 2009, al-though at lower levels than methadone. Like studies in other countries, the authors suggested much diversion was for therapeutic reasons.
any other treatment, in office-based practice. \textsuperscript{69} Addicts in many countries appropriated Subutex as “a medicine for them.” \textsuperscript{67} But NIDA, being a public agency, could only provide the data used for scheduling and testify regarding proposed laws; it fell to Reckitts and the network of pro-buprenorphine researchers and consultants to lobby for these changes. Lewis, for example, spent much time in Geneva convincing WHO to keep buprenorphine out of the Single Convention and on a moderate schedule in the Psychotropic Convention, as the outcome of this decision would affect the DEA’s view.

In the United States, Reckitts took the legislative route, with O’Keeffe as architect of a policy with complex technical and political repercussions, involving delicate negotiations with the FDA, DEA, SAMHSA, NIDA, Clinton administration, professional groups, and politicians. The Drug Addiction Treatment Act (DATA) was finally passed in 2000. It allowed office-based physicians who complete an 8-hour certification course to obtain a federal waiver and treat opiate-dependent persons. Public Law 109–460 (2006) extended the patient cap from 30 to 100 for physicians with at least one year’s clinical experience with buprenorphine. Subutex (for opiate-dependent pregnant women and lactating women) and Suboxone received FDA approval in 2002, but the DEA, which had expressed serious reservations before DATA 2000 passed, rescheduled them from Category 5 to Category 3. \textsuperscript{86}

When DATA 2000 passed, the analgesic section at Reckitts (by then merged as Reckitt–Benkhsier) consisted of two people: O’Keeffe and Chapleo. In 2002, Johnson was brought in. Since that time, the U.S. company has grown more than a hundredfold primarily due to the promotion of buprenorphine. Reckitts explicitly sought to move addiction from criminalization and toward medicalization through its concept of the “treatment space.” Reckitts’ international markets had previously focused on household products and nonethical drugs, mostly in the Commonwealth). Whereas in 1997, Reckitts had signed a 15-year Global Agreement giving exclusive worldwide distribution rights for buprenorphine hydrochloride prescription products, including Subutex and analgesics, to Schering Plough,\textsuperscript{87} essentially keeping buprenorphine’s growth at a distance, in the early 21st century. Reckitts remodeled its “treatment space” vision as a global one. By 2010, it had bought back much of its sales and marketing rights for Suboxone, Subutex, and Temgesic\textsuperscript{93–94} and assumed marketing in more than 30 countries in Europe as well as the United States, Australia, New Zealand, and South Africa and negotiated with other countries to buy back distribution rights before they expired. Reckitts moved toward being “a wholly-owned international franchise for Suboxone and Subutex.”\textsuperscript{92} While treatment contexts are shaped by national and regional policy, as buprenorphine circulates globally, it carries Western definitions of “addiction,” especially as an appropriate treatment object for medicine, though not without encountering resistance in countries where addiction is heavily criminalized.

In the United States, Suboxone lost the exclusivity afforded by its orphan drug status in October 2009. A year later, Reckitt–Benckiser Pharmaceuticals introduced Suboxone formulated as a sublingual film, a patent-protected and “patient-preferred delivery system,”… “to address the potential loss of up to 80% of the revenues and profits of the Suboxone tablet business in the year following the launch of prospective generic competitors.”\textsuperscript{95} The company’s overwhelming financial success can be attributed to Suboxone, which accounted for 23% of U.S. revenues for Reckitt–Benckiser in 2010.\textsuperscript{95}

Historical tensions between maintenance and abstinence, medicalization and criminalization, and the complex interplay among patient choice, provider authority, and regulatory constraints structure the addiction therapeutics arena. Aimed as both a social and pharmacological “fix,” buprenorphine must work at both levels if it is to work at all—that is, if buprenorphine is to shed the stigma of methadone symbolically. Buprenorphine for opiate dependence emerged from the long quest for a pharmacotherapy that worked not simply to block opiate effects but to attenuate them in ways acceptable to addicted people. First explored as a potential pharmacotherapy at the U.S. Public Health Service Hospital in Lexington obtained the status of an FDA-approved opioid addiction treatment in the 1970s, and Subutex and Suboxone were launched in the United States almost three decades later. The difficulties of coordinating public and private interests, local and global effects, changes in domestic regulatory mechanisms, and perceptions of addiction and its treatment charted buprenorphine’s tortuous, 30-year path to FDA.
approval and market. Buprenorphine arose as a maintenance therapy at a time when addicts—like other citizens—were expected to take personal responsibility for health and healthcare, and where such decisions were seen as individual matters of choice and political entitlement. Reckitt’s new treatment space dovetailed with this larger movement of decriminalization, destigmatization, and normalization of addiction treatment, and buprenorphine finally proved to be the “holy grail”—an office-based pharmacotherapy for opioid addiction.

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Conflicts of interest

The authors declare no conflicts of interest.

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