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Charles O'Keeffe, Professor

September 26, 2016

Memorandum For: Dr. Eric Ketcham
San Juan Regional Medical Center
Farmington, NM

CC: Rep. Bob Goodlatte, Chairman
House Judiciary Committee
Rep. Tom Marino, Chairman
Subcommittee on Regulatory Reform,
Commercial and Antitrust Law

From: Charles O'Keeffe

Subject: Hearing Testimony "Treating the Opioid Epidemic:…"
September 22, 2016

Dear Dr. Ketcham,

I observed with interest your testimony before the subcommittee last week and concur with your view that "access to buprenorphine means more potentially deadly overdose deaths would be avoided."

I would, however, probably disagree with some of your characterization of the pricing of buprenorphine being unnecessarily high, and your conclusion that the cost of these products obstructs access to treatment thus prolonging the scourge of addiction and putting lives at risk. Access to treatment with buprenorphine has been addressed by the Congress regularly for the past 15 years; most recently with passage of (CARA) legislation last month to further expand access to buprenorphine treatment. The Congress has examined carefully, and recognized by important bi-partisan legislation that the primary barrier to addiction treatment is the lack of interest/willingness of many (might I add most) physicians in treating patients with the disease.

Your testimony correctly refers to the crisis of opioid addiction as cited by the Centers for Disease Control and Prevention, and the economic burden this disease places on the country.

However, in your discussion of buprenorphine there are a number of statements regarding its development which deserve correction and perhaps restatement, and by providing a copy of this memorandum to the Chairmen of the committee and subcommittee I'm asking them to incorporate that history into the record of the hearing. I'd also suggest that if you plan further presentations of your testimony you may wish to make appropriate adjustments.

By way of introduction, during the period of buprenorphine's development for the treatment of opiate dependence (from 1987 through my retirement in 2000) I served as president of the company that developed it in concert with the National Institutes of Health, (NIDA). I continue to consult with the company on legislative and international organization regulatory matters.

On page 2 of your testimony, your supposition/statement that buprenorphine was developed beginning in 1966 for the purpose of treating opioid dependence is incorrect. A careful reading of Nancy Campbell's published history, which you referenced, correctly states that buprenorphine was developed as a potentially safe and effective over-the-counter analgesic. At that time Reckitt & Colman marketed the most popular O-T-C analgesic in England and the research effort was to discover an even more effective analgesic for moderate to severe pain.

Your interpretation (page 3 of your testimony) regarding the first use of buprenorphine in France and characterization of its dramatic success inspiring the company to return to its pursuit of use for addiction treatment is not in accord with its history or the document you cite for reference.

A careful reading of the history cited in the reference would inform us that in 1993 the National Institute on Drug Abuse approached the company and requested them to work jointly under a Cooperative Research and Development Agreement (CRADA) to make buprenorphine available for the indication. It would also inform us of the reluctance of the company, or any pharmaceutical company, to develop any product for this indication.

The reality of its first use in France is that French researchers had become aware of successful outcomes of the initial research in the US conducted under the CRADA, and their overdose death rate become so critical that the French government asked the company to apply for its approval based on the ongoing CRADA studies in the US. Consequently, France approved the use of buprenorphine with fewer clinical trials prior to its approval by the FDA.

Your testimony cites specific prices for specific buprenorphine products and I have no direct knowledge of these, but it's my understanding that the innovator products have not increased significantly over the last several years, but I must wonder why the generic product prices have "almost doubled during the past six months." It would be helpful to know if the diversion you mention is driven by the single-entity generic products.

I have long held that the single-entity product should have a more restrictive labeling than the combination buprenorphine/naloxone formulation. During the development period the company unsuccessfully asked the Drug Enforcement Administration to differentially schedule the two dosage formulations as a way to discourage prescription of the single-entity one. They refused. Consequentially, despite the increased cost of manufacturing the combination product the company decided to market it at a lower price than the single-entity product in an effort to discouraging physicians from using the unprotected form. It would be interesting to learn which dosage form is most diverted.

I think it's important for you, and the Congress, to understand how this important treatment was ultimately made available to patients, despite the reluctance of the pharmaceutical industry to invest in this disease space. Unfortunately, that reluctance still remains except for those few companies who are simply copying the first products. Until the disease is adequately recognized, the medical profession trains its students to recognize treat it (instead of avoiding it), and adequate insurance coverage is made available for treatment, I'm afraid we'll continue to attempt to look for simplistic solutions to this complex problem.

I'd ask that the attached publications be included in the record of the Subcommittee's hearing.

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Review

From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States

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Abstract

The practice of prescribing opioid drugs for opioid dependent patients in the U.S. has been subjected to special government scrutiny for almost 100 years. From 1920 until 1964, doctors who used opioids to treat addicts risked federal and/or state criminal prosecution. Although that period ended when oral methadone maintenance was established as legitimate medical practice, public concern about methadone diversion and accidental overdose fatalities, combined with political pressure from both hostile bureaucracies and groups committed to drug-free treatments, led to the development of unprecedented and detailed Food and Drug Administration (FDA) regulations that specified the manner in which methadone (and later, levo-alpha-acetyl methadol, or levomethadyl acetate, (LAAM)) could be provided. In 1974, Congress gave the Drug Enforcement Administration (DEA) additional oversight of methadone treatment programs. Efforts to liberalize the FDA regulations over the past 30 years have been resisted by both the DEA and existing treatment providers. Additional flexibility for clinicians may evolve from the most recent effort to create an accreditation system to replace some of the FDA regulations. The development of buprenorphine, a partial opioid agonist, as an effective treatment for opioid addiction reopened the possibility for having a less burdensome oversight process, especially because of its reduced toxicity if ingested by non-tolerant individuals. New legislation, the Drug Addiction Treatment Act (DATA) of 2000, created an opportunity for clinicians with special training to be exempted from both federal methadone regulations and the requirement to obtain a special DEA license when using buprenorphine to treat addicts. Some details of how the DATA was developed, moved through Congress, and signed into law are described.

Keywords: Buprenorphine; Methadone maintenance; Office-based pharmacotherapy; Opioid agonists; Regulations; Treatment; History; Policy

1. Early history of opioid-addiction treatment

The federal regulation of medical prescribing of opioids in the U.S. began with the Harrison Act of 1914. While the Harrison Act did not actually prohibit physicians from prescribing opioids for addicted patients within a legitimate medical context, the Treasury officials who were empowered to implement the Act vigorously opposed the practice and were successful in deterring physicians from engaging in it. By 1920, the American Medical Association (AMA) also condemned prescribing opioids to addicts, thereby opening the door further to the prosecution and conviction of physicians who continued to do so. This difficult situation for people who were dependent on opioids and for the practitioners who wanted to help them did not begin to change until 1964. It was then that Vincent Dole and Marie Nyswander first described their work treating heroin addicts with orally administered methadone (Musto, 1987; Jonnes, 1996).

Some of the milestones of those 50 years between the Harrison Narcotic Act of 1914 and the studies of methadone maintenance in 1964 include the rise and fall of morphine clinics (the last of them closed in 1923); the successful federal prosecution of physicians who prescribed morphine to addicts; and, following a period of relative stability in the 1930s and 1940s, a post-World

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War II rise in heroin addiction that led to new federal legislation increasing the severity of penalties for the use and possession of illicit drugs. In 1961, a report issued by a joint committee of the American Bar Association and the AMA questioned those repressive drug policies and encouraged research on opioid maintenance (Musto, 1987).

Throughout most of this period, and until he retired in 1962, Harry J. Anslinger headed the Bureau of Narcotics. Anslinger believed strongly that addiction would disappear in the face of severe penalties for the possession, use, or sale of drugs, and that getting rid of drugs, drug users, and drug pushers would solve the drug problem. Under Anslinger's influence, demonizing the drugs, especially heroin, became a key element of federal drug policy, and addiction to opioid drugs was portrayed as an incurable disorder that condemned its victims to a life of degradation (Musto, 1987; Courtwright, 1992).

2. Evolution of methadone treatment

The current system of opioid treatment regulations, as well as American attitudes towards addicts, were influenced not only by this history, but also by other equally important elements and events. These included a heroin epidemic that accelerated in the early 1960s; the rise of the therapeutic community movement, which convincingly demonstrated that heroin addicts were not beyond redemption; the Narcotic Addict Rehabilitation Act (NARA) of 1966, which established a federal civil commitment program modeled partly on similar programs in California and New York; and the work of Dole, Nyswander, and their collaborators at the Rockefeller Institute. Their work, from the early 1960s and onward, showed that heroin addicts who were maintained on oral methadone could give up heroin and lead productive, law-abiding lives (Glasscote et al., 1972; Gerstein and Harwood, 1990).

The data reported by Dole, Nyswander, and coworkers, and soon confirmed by others, showed that treatment in methadone treatment programs sharply reduced heroin use and criminal activity, increased gainful work, and resulted in generally improved health. Equally important, patients found the treatment acceptable, and several treatment centers began operation. Most of the treatment centers using methadone operated under Investigational New Drug (IND) applications issued by the Food and Drug Administration (FDA), and thereby claimed exemption from the policies of the Bureau of Narcotics, which still viewed providing opioids to addicts as illegal. It is of historical interest that Dole and coworkers at Rockefeller did not seek or obtain an IND, since they took the position that methadone was an approved therapeutic agent and that off-label use did not require an IND. From 1967 to 1970, the FDA liberally issued INDs for methadone research. Beginning in 1968, INDs were also issued for the study of LAAM, (levo-alpha-acetyl methadol, or levomethadyl acetate). By 1969, several thousand patients were enrolled in methadone maintenance treatment research programs (Jaffe, 1975; Gerstein and Harwood, 1990; Jonnes, 1996; Kreek and Vocci, 2002).

Yet, methadone was not well received in the early 1970s. Most federal agencies were hostile towards it or were at least skeptical about it. The Departments of Justice and the Treasury, still influenced by Anslinger's vision, saw methadone treatment as wrongheaded. Advocates for psychosocial programs within the treatment community derided it as a 'magic bullet' that was likely to lessen concerns about unemployment, housing, and the psychological and sociological origins of addiction; vocal groups of recovering heroin addicts saw it as both an irrational treatment and a threat to the therapeutic community movement; some minority activists described it as a government effort to control the behavior of young black men.

Even the FDA did not find the data that were generated sufficient to approve methadone as a safe and effective treatment for heroin addiction. Further, there was no rationale for determining how many INDs to issue and no practical mechanism to prevent their misuse as a cover for profit oriented prescribing of methadone unaccompanied by rehabilitative services. No standards had been established for what constituted minimally acceptable treatment, and no rules governed the amount of opioids that could be prescribed, or taken home, or for whom the treatment was appropriate, giving the recipients of the methadone INDs large leeway in making those decisions. Newspapers published stories about physicians who prescribed methadone for patients who were not seriously dependent on opioids; about methadone being diverted from the clinics to the street; and about children being poisoned by drinking methadone that was brought home legitimately by household members who were in treatment. Methadone maintenance also drew criticism from advocates and providers of 'drug-free' treatment, who saw it as another form of addiction, from law enforcement groups, and from minority groups who denounced it as 'genocide' (Jaffe, 1975; Jonnes, 1996).

In June of 1970, the FDA proposed a new ruling on methadone IND applications. Largely a response to the numerous Congressional and community concerns about the issues of diversion of methadone, iatrogenic methadone addiction, and accidental overdoses, the new IND regulations imposed such strict requirements on entry into treatment, dosage, and duration of treatment that they discouraged methadone use. With this ruling, which became final in April, 1971, the FDA avoided making a decision on whether methadone treatment was

safe and effective, but allowed it to continue 'thinly disguised as research.' These stringent regulations were of no help to the many heroin addicts who were seeking treatment but could only be put on waiting lists. The status of methadone treatment as 'research' made government authorities at all levels reluctant to provide funds to support its expansion.

Nevertheless, in June of 1971, the Nixon administration's initiative on drug abuse included the decision to accept methadone maintenance as an effective treatment, to develop ways of minimizing the real and perceived problems with its use, and to expand access to treatment for those who wanted it. The White House Special Action Office for Drug Abuse Prevention (SAODAP) worked with the FDA to revise the overly stringent regulations in order to achieve those objectives. First proposed in April 1972, the new regulations established the basic framework that governed the use of methadone and similar opioid agonist drugs in the treatment of heroin addiction for the following 30 years. These regulations created 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. Those conditions represented a substantial and unprecedented departure from the usual practice of allowing licensed physicians to use their own professional judgment, guided by a drug's labeling, to determine how to prescribe a medication. Among other things, the 1972 regulations specified, according to various criteria including age and duration of drug dependence, who could be eligible for methadone treatment. They also specified the maximum initial dosages that could be used, the minimum amount of counseling that must be provided, and the factors to be considered when deciding on take home medication, such as how long a patient had been in treatment and whether drug tests showed any evidence of illicit drug use. The new regulations also created a closed system for methadone, restricting its availability to approved clinics and hospital pharmacies, with the aim of deterring those few individual physicians who, in violation of the 1971 regulations, continued prescribing methadone for substantial fees (Jaffe, 1975; Rettig and Yarmolinsky, 1995; Jaffe, 1997; Kreek and Vocci, 2002).

Each element in the 1972 regulations was intended to reduce or prevent problems that had been experienced under the largely informal pre-1971 IND system; or to correct the overly restrictive aspects of the 1971 regulations; or to assure concerned parties, including Congress, that methadone would be used in combination with, not as a substitute for, rehabilitation. In short, the 1972 regulations were designed to allow expansion of treatment while maintaining some control over quality of treatment. They described 'medication units' because they anticipated a time when clinics and individual practitioners would be linked to pharmacies and other sites that would be authorized to dispense drugs, such as methadone, for the treatment of addiction. The drafters of the regulations did not intend for medication dispensing to be forever limited to a few large clinics. Although they recognized that access to treatment by individual physicians might temporarily be limited, they believed that the regulations would be revised as knowledge expanded and as opioid maintenance treatment became less controversial (Jaffe, 1975, 1997). The regulations became fully effective in March, 1973. However, throughout 1972 and the beginning of 1973, some members of Congress and certain journalists continued to see methadone diversion as a serious problem. In June 1973, the Senate passed the Methadone Diversion Control Act of 1973, which became the Narcotic Addict Treatment Act of 1974 (NATA). This law, which was an amendment of the Controlled Substances Act (CSA), gave the newly created Drug Enforcement Agency (DEA) jurisdiction over the storage and security of drugs used in the treatment of addiction. It also required separate DEA registration annually of practitioners and treatment sites. The Secretary of Health, Education, and Welfare (now Health and Human Services [HHS]) retained the responsibility for setting standards for proper professional practice in the medical treatment of addiction.

Since 1970, clinicians have criticized the Federal regulations as a burdensome interference with the practice of medicine. Some claim that the paperwork burdens and constraints on take-home doses contribute to patients' dropping out of treatment (Dole, 1992). Although some of the criticism is valid, it often fails to distinguish between federal, state, and local regulatory burdens. State and local jurisdictions have also seen fit to enact legislation governing these programs, and some of those regulatory requirements are far more restrictive than federal ones. For example, some localities do not permit any take-home medication. Another criticism is that regulatory oversight is concerned exclusively with process, although actual treatment outcome can be measured. But regulations alone are not responsible for all of the problems methadone treatment providers encounter. Not to be overlooked is the impact of the more than 50% reduction (inflation-adjusted) in the level of financial support for methadone treatment programs in most parts of the country over the past 30 years (Gerstein and Harwood, 1990).

Alternatives to the current regulatory framework have been sought and proposed over the years. There is no federal legislation that requires the Secretary of HHS to issue *regulations* dealing with the medical treatment of 'narcotic addiction.' *Guidelines* could accomplish this task equally well. In 1984, Congress amended the NATA, and gave the DEA authority to withdraw registration from treatment programs or

individual practitioners for committing (in DEA's judgment) 'such acts as would render registration inconsistent with public interest.' Since one federal agency (DEA) already has the authority to revoke licensure, there may be no good reason to have any HHS *regulations*. However, if the use of opioid agonists in the treatment of opioid dependence were governed only by HHS guidelines or professional judgment, any oversight of the quality of treatment would be left to the discretion of the DEA and to the tort system (Molinari et al., 1994).

In summary, for most of the past 30 years the regulatory framework dealing with the use of opioids in the treatment of addiction in the U.S. has consisted of a dual oversight at the federal level (HHS and DEA), as well as various (and varying) regulatory requirements at the state and local levels. Although the FDA regulations were intended to be more flexible and responsive than legislation to changing conditions, prior to the major revision that was finalized in 2001 they had been revised only twice, in 1980 and 1989. Those changes were relatively minor, mostly having to do with urine testing, on-site services, and easing constraints on admissions. Despite complaints about over-regulation, when the FDA and the National Institute on Drug Abuse (NIDA) issued a proposal in 1983 to convert most regulations to 'guidelines', most of the treatment providers who responded to the proposal stated a preference for the existing regulatory system (Rettig and Yarmolinsky, 1995). In 1989, largely as a response to the spread of HIV among intravenous drug users, NIDA and the FDA published a rule regarding 'interim methadone maintenance'—the provision of methadone without rehabilitative services to addicts waiting to get into full service programs (Rettig and Yarmolinsky, 1995). The methadone treatment providers and some state authorities reacted unfavorably. Many treatment providers believed that interim maintenance would inevitably lead local, state, and federal governments to further reduce funding and to pay only for dispensing methadone (Rettig and Yarmolinsky, 1995).

3. Opioid-agonist treatment regulations—recent changes

The number of patients in methadone treatment programs has grown since the early 1970s, from about 20,000 to about 180,000 (Kreek and Vocci, 2002). Some states still do not permit methadone or other opioid agonist treatment regulated by the NATA. In 1993, when the FDA finally approved LAAM for the treatment of heroin addiction, multiple state and local legislative and regulatory barriers still prevented it from being used. Even where it was permitted its utility was compromised because the FDA regulations that prohibited take-home doses entirely. (New regulations that took effect in 2001 now permit take-home doses.)

In 1992, the Institute of Medicine (IOM) undertook a review of the Federal regulation of methadone and LAAM in the treatment of addiction. Their report, issued in 1995, concluded (among other things) that the current regulation by multiple agencies: (1) overemphasizes the dangers of methadone diversion; (2) burdens programs with unnecessary paperwork; (3) constrains clinical judgment; (4) reduces access to treatment; and (5) contributes to premature discontinuation of treatment. The IOM recommended that the current detailed regulations be replaced by practice guidelines and sharply reduced regulations (Rettig and Yarmolinsky, 1995).

In response to the IOM recommendations, the federal agencies that comprise the Interagency Narcotic Treatment Policy Review Board (FDA, NIDA, Substance Abuse and Mental Health Services Administration [SAMHSA], Department of Veterans Affairs [VA], DEA, and the Office of National Drug Control Policy [ONDCP]) undertook the work of substantially revising the HHS regulations. The DEA did not propose any changes in its authority to require special licensing and to oversee addiction treatment that uses opioid drugs. Originally, the new system was to have as its central feature a set of HHS regulations requiring programs or practitioners that use opioid agonists for addiction treatment to be accredited by an approved accrediting body, and establishing an upper limit on the amount of opioid medication that could be given to patients for use outside the clinic at any one time. Accrediting bodies would base their decisions on a set of treatment standards approved by the Secretary of HHS, and representing the best clinical thinking of experts in the field, subject to change as knowledge changes. It was recognized at the outset that value judgments and trade-offs are implicit in how standards of care are set. Setting high standards that require competent initial assessments, good medical care, and some minimal level of psychosocial support will limit access for some addicts where states, localities, or insurance carriers are unwilling to pay for those services. If the standards are not met, neither programs nor individual practitioners can be accredited, and the power to accredit becomes the power to destroy. Conversely, if standards are set quite low, the cost of delivering care will be reduced and access may increase; but then it becomes likely that some programs would be no more than opioid dispensaries staffed by the lowest cost personnel, and with considerable risk of hazardous prescribing practices and drug diversion. Unless federal and state priorities were to be reordered so as to provide much greater financial support for opioid treatment, setting standards, whether by guideline or regulation, will involve difficult value judgments.

Some changes have now been approved, but the effort to shift from federal regulations with their implied criminal penalties for violations to a system of peer review accreditation did not result in as much freedom for clinical judgment as those within HHS, who originally proposed the accreditation process, had hoped for. Pressures from already licensed methadone providers and the DEA left in place many of the regulatory constraints on clinical judgment, particularly with respect to the compliance burden placed on virtually all new patients regarding take-home medication and clinic attendance. While the new regulations eased considerably the maximum take-home dosages permitted for long term patients (in treatment for more than 2 years), new patients, regardless of level of stability or need for other treatment services, are still required to obtain nearly all their medication at the clinic for a period of several months. Furthermore, the burdens of meeting the accreditation requirements are likely to prevent individual physicians, no matter how well trained, from using opioid medications such as methadone or LAAM to treat opioid dependent patients in their offices, unless the physician is administratively linked to an existing opioid treatment program. In addition, the NATA still requires all physicians who might wish to treat opioid addicts with Schedule II opioid medications to obtain a separate registration for this purpose from the DEA, even if they intend to treat only a few patients.

Although these latest changes in the regulations, including the institution of accreditation, are far greater than those accomplished by the two previous revisions, their modesty and the time it took to bring them from initial proposal to reality gives testimony to the inertia in the system, the complexity of forces that influence it, and the power of the current stakeholders. The notion of a system of accreditation to replace the regulations was raised by Curtis Wright and Jerome Jaffe at a meeting of the Interagency Narcotic Treatment Policy Committee in 1995, shortly after the release of the IOM report on methadone regulation. It did not get final approval within HHS until some time in December of 2000. There were considerable reservations voiced at ONDCP. Following the Presidential elections of 2000 and the change in administration, a hold was placed on all regulatory change. The modifications of the methadone regulations did not go into effect until May 18, 2001 (N. Reuter, personal communication).

4. Buprenorphine: a new pharmacotherapy for opioid addiction

A major justification for the regulation, accreditation, and separate DEA registration was to minimize the diversion of opioid drugs from treatment programs. Among the most important concerns about diversion are the serious toxic consequences that ensue when non-tolerant individuals ingest dosages of methadone or LAAM typically used in treatment. As early as Jasinski et al. (1978) had noted the possible clinical utility of buprenorphine, a partial opioid agonist. By the early 1990s, it became clear that buprenorphine could be used effectively for the treatment of heroin addiction (Johnson et al., 1992; Ling et al., 1996) and that its partial agonist properties resulted in very substantially decreased toxicity even for non-tolerant individuals (Walsh et al., 1994, 1995). Under these circumstances, one major justification for maintaining the 'closed system' for medications used in opioid maintenance was largely eliminated. It was not so much that diversion of a partial agonist could be considered a trivial issue, but rather that with lethality from diversion of prescribed medication sharply reduced, a fresh look could be taken at the costs and benefits of making opioid treatment both more accessible and less stigmatizing by moving it from the clinics into the offices of individual physicians. It seemed possible that, under the right circumstances and once approved by the FDA for use in the treatment of opioid dependence, buprenorphine might be exempted from some of the burdens associated with the use of methadone and LAAM.

To achieve such an outcome, two major hurdles had to be overcome. First, buprenorphine would have to win FDA approval for the treatment of opioid addiction; second, some regulatory or legislative action was needed that would exempt it from the provisions of the CSA of 1970 and the NATA of 1974. It is important to point out here that from the perspective of Reckitt and Colman (now Reckitt Benckiser Pharmaceuticals), the company that originally developed buprenorphine as an analgesic and still controlled its use, the legislative effort to be described and the effort to develop and win FDA approval for its use in addiction treatment were seen as being inextricably intertwined. It was obvious from the experience with LAAM that winning FDA approval for a drug used in the treatment of addiction in no way assures its utilization if it also requires legislative changes in each of the 50 states. Also, from a corporate perspective it seemed unlikely that a drug confined to a limited number of clinics that were already comfortable using generic methadone would be used enough to justify the investment involved in taking buprenorphine through the regulatory process.

Reckitt and Colman knew it would be at least a 5-year project and that it would be committing millions of dollars to develop a product that had no patent protection remaining. The Board of Directors decided to approve the process nevertheless. It was apparent that, to recover any significant portion of corporate expenditures, two conditions would be needed. First, buprenorphine would need to reach the mainstream

practice of medicine—a goal that certainly seemed achievable in light of the IOM report on methadone regulation. Second, a period of market exclusivity would be needed to protect the product once FDA approved it. The Company faced three challenges. To address the matter of market exclusivity they needed to seek Orphan Drug designation. This was accomplished fairly quickly in 1994. The next challenge was to somehow amend the CSA of 1970 to allow physicians to treat patients with buprenorphine in the normal course of the practice of medicine. This change would result in an exemption from the NATA, which is itself a modification of the CSA. The third was to submit an NDA to the FDA and gain its approval. What follows here is the story of how the legislation that largely exempts buprenorphine from certain provisions of the CSA made its way through Congress to the Oval Office.

5. A need for new legislation

Reckitt and Colman was convinced by the history of efforts to modify the methadone regulations that amending treatment program regulations through administrative change would be a long and cumbersome process unlikely to reach the goal of moving treatment into the mainstream of medicine and expanding access for new patients. The company therefore chose to seek a change in the law. The original aim of the proposed legislative solution seemed simple and straightforward: to change the law to waive the current requirements for physicians prescribing opioids to treat opioid dependence. The proposed legislation would leave the methadone system intact but expand the possibilities for treatment. The original draft of this legislation, called the Drug Maintenance and Detoxification Act, was written by Charles O'Keeffe and Robert Angarola in October, 1995. That first draft stated simply that the requirements of the CSA did not apply when a physician treated no more than 20 patients with a Schedule V narcotic. As it turned out, this proposed legislation went through many changes and was not finally passed by Congress until 2000. It took more than 5 years to enact a very minor amendment to the existing legislation.

The high points of that journey make an interesting lesson about the process of change in our democracy. In 1995, representatives of Reckitt and Colman approached Capitol Hill offices to explain the issue as they saw it: there is a new product which, when approved, will have the potential to bring a significant number of new patients into treatment. But there will be no market for it and the medical community will not be able to use it because of current legal requirements. In several offices, staff members were very receptive.

Senator Carl Levin, who has had a long standing personal interest in expanding and improving addiction treatment, became a supporter. Senator Orrin Hatch and his staff on the Senate Judiciary Committee, which has jurisdiction over the Controlled Substance Act, was also interested. Senator Joseph Biden, who had previously introduced legislation to encourage the development of new addiction treatment medication, was most interested. Strong allies in the House of Representatives included Congressman Thomas Bliley, who was then Chairman of the Commerce Committee, which shares jurisdiction over the CSA with the Judiciary Committee. With their efforts, several key members of the Judiciary Committee and others on both sides of the aisle became persuaded that the proposed legislative changes would be good policy. Despite this promising start, it was not until the end of the 1998 congressional year that the Company could rally enough support to get something going. But 1998 was an election year and the end of the 106th Congress. It was clear that the bill could not be enacted using the full legislative route. Senate staff suggested an alternate approach: using what is called a 'must-do' vehicle: that is, attaching it to a bill not necessarily related to the subject matter, but one such as an appropriation bill that must be signed into law. Senator Hatch's staff, with agreement from the offices of Senators Levin, Biden and Moynihan, arranged to have the proposed change to the CSA tucked into a multiagency appropriations bill for Senate action. This required negotiating with HHS, Justice, and the White House over provisions of the bill. The parties reached agreement in late October 1998, about 3 years after the original draft was written. Although Chairman Bliley of the House Commerce Committee was willing to let this amendment pass as part of the appropriations bill, the senior Democrat member of that committee, Congressman John Dingell, was not. He objected to the process, not the policy. He said the Committee had never held hearings on the matter and had never formally considered the legislation, and this, he said, deprived the members of the Committee of an opportunity to examine the policy, understand it, and either agree or disagree with it. He also noted that appropriations bills are not the place to change health care policy. The provision was removed from the bill.

Shortly thereafter the bill's supporters in the Senate produced a new draft of the legislation. This time the Company and the involved congressional staffers tried to follow everyone's rules. They worked with virtually all of the interested parties, including the Clinton administration, FDA, SAMHSA, NIDA, DEA, and the departments of HHS and Justice. FDA was concerned that the system could get out of hand unless limits were placed on the number of doctors and patients who initially could participate in the system. DEA worried that they would not be able to get a handle on whether physicians were appropriately registered. SAMHSA was concerned about the impact on

their resources and about the potential impact on current methadone clinics. The College on Problems of Drug Dependence (CPDD), the American Methadone Treatment Association (AMTA), the American Academy of Addiction Psychiatry (AAAP), the American Society of Addiction Medicine (ASAM), the American Psychiatric Association (APA), the AMA, the American Osteopathic Association (AOA), and others in the field, also had concerns and suggestions.

The new bill was introduced at the end of January, 1999, by Senators Hatch, Levin, and Biden. It provided that physicians who were qualified to treat opioid-dependent patients would be allowed to prescribe certain FDA approved opioids without being subject to current regulations, so long as they certified to their qualifications with the Secretary of HHS 30 days in advance of treating such patients and treated no more than 20 at a time. The bill also provided that the new federal paradigm would not be pre-empted by the states for at least a period of 3 years, but gave the Secretary of HHS and the Attorney General ample authority to stop the entire program if there was significant abuse. It was passed by the full Senate in November. Still needed was a House bill and agreement between the House and Senate, but some people on the Democrat side of the House were still irritated by the ill-fated effort to put the matter into an appropriations bill the year before. Congressman Dingell had written to the Secretary of HHS, Donna Shalala, raising questions and concerns about the buprenorphine bill that needed to be addressed before there could be further movement. Fortunately, Secretary Shalala responded in support of the policy change. She argued for changing the regulatory framework of drug treatment, for destigmatizing treatment, and for the promise of new treatment products such as buprenorphine. This was a positive development, but it was not until the end of July of 1999 that a bill was finally introduced into the House of Representatives. A hearing was held on July 30th, and although one witness raised concerns about the impact of new treatment arrangements on the current methadone system, and another raised the issue of whether insurance would cover new treatments, the witnesses were otherwise quite positive. Significantly, Senators Hatch and Levin testified in the House of Representatives in support of the bill. Dr Westley Clark, of the Center for Substance Abuse Treatment (CSAT), testifying for SAMHSA, noted the importance of ensuring that states would follow any new federal oversight arrangement from the outset to make certain it caught hold. He cited the LAAM experience as an example of how not to get new interventions broadly adopted. Another 3 months passed before the Commerce Committee acted and the bill was ready for House consideration. During that time various changes were made to the bill, including, for example, greater specificity about what makes a provider 'qualified'. Although state preemption remained a concern for some members, the final language was believed to provide sufficient opportunity after an initial transition period for states to make different rules.

Meanwhile, a bill aimed at shutting down illicit methamphetamine laboratories had been introduced into the Senate by Senator John Ashcroft and was arousing interest and support. This interest was shared by many House members as well, and it now gained priority in both the House and Senate Judiciary Committees. Thus, before the Drug Addiction Treatment Act (DATA) of 2000, or the 'Buprenorphine bill', as it came to be known, could be released, some activities on methamphetamine, including hearings in members' home districts, had to be undertaken. Furthermore, the members wanted to ensure that the methamphetamine bill would sail through the legislative process. This required a considerable amount of negotiation about both bills among interested parties. The House finally considered the buprenorphine bill on July 18, 2000 under 'Suspension of the Rules'. Under this procedure, only 1 h of debate is allowed and no amendments are accepted. While it is more predictable than a process where multiple amendments can be offered, under this procedure a two-thirds vote, rather than a simple majority, is needed to pass a bill, and for this reason the committee was concerned that the bill not be controversial. The debate was held, the bill was supported, and it seemed poised to be passed by the House on a voice vote, when Chairman Bliley made a motion to require a roll call vote to take place later that day. Then another glitch appeared: the version of the bill printed in the Congressional record was different from the version that had been considered on the House floor. This administrative error meant the bill would have to lay over until the next day at least.

Although the Secretary of HHS had been supportive, the DEA had serious reservations, and the 1-day layover gave them another opportunity to voice their concerns. They immediately contacted the House Judiciary Committee and attempted to add a requirement for physicians to register separately with the DEA or to get DEA approval before prescribing. The effort failed. The bill passed the House the next day with a vote of 412 to 1. It was then placed on the Senate calendar, but before it could come to consideration, the Senate Judiciary Committee passed the methamphetamine bill and attached to it their version of the buprenorphine bill. The Senate now had its own bill, quite different from the House version, a methamphetamine/buprenorphine bill, which it passed and sent to the House on January 27, 2000. Although the buprenorphine amendment to the CSA had now been passed by both House and Senate, there was still no law on the books that actually changed policy.

Throughout this process, staffers in the offices of Senators Hatch, Levin and Biden were seeking other vehicles for both the methamphetamine and buprenorphine bills. Ultimately, both bills were included in another 'must pass'—a huge bankruptcy reform bill. The House and Senate were in conference on this bill. Bankruptcy reform was hardly benign and the conference was not without some rancor. Senator Levin was determined to pass the buprenorphine bill, with or without the methamphetamine bill. As the ranking member of the Senate Armed Services Committee, and with the concurrence of the chairman of that committee, Senator John Warner, he had the buprenorphine bill placed in the Department of Defense Authorization conference, attached to another 'must pass' bill to allow the military to continue to function.

In the spring of 2000, there were six versions of the buprenorphine bill making their way through the legislative process: two versions of a stand-alone buprenorphine bill; two versions of a buprenorphine/methamphetamine bill; a buprenorphine/bankruptcy bill; and a buprenorphine/guns bill. Then events took another amazing turn. On May 9, 2000, the House passed a bill, H.R. 4365, to 'amend the Public Health Service Act with respect to children's health'. Without fuss or fanfare, this combination of several children's health bills was scheduled for action. It was now Chairman Bliley's chance to seize an opportunity; so H.R. 2634, Bliley's buprenorphine bill, became part of what came to be known as the 'Children's Health Act'. The House passed their bill and sent it to the Senate. After some behind the scenes negotiations, the bill passed the Senate on September 22, 2000, with an amendment that was, not surprisingly, the Senate version of the buprenorphine bill with the methamphetamine provisions. That amended bill, of course, had to be sent back over to the House and reconsidered. The House passed the bill exactly as the Senate had passed it, as Public Law 106–310, on September 27, 2000. On October 17th, President Clinton signed it into law. It is of some academic interest that the bankruptcy bill and the defense authorization conference were still in play, so at the last minute the buprenorphine provisions had to be snatched out of those bills. The President vetoed the bankruptcy bill on December 19, 2000.

6. The drug addiction treatment act of 2000

The new law, the DATA of 2000, offers an opportunity to make significant changes in the way addiction treatment is delivered. The change could be of benefit to hundreds of thousands of patients addicted to opioids. Perhaps as result of this legislation, other companies will see more opportunity in the development of new pharmaceuticals to treat addiction. The last hurdle was the final approval of the buprenorphine NDA by the FDA.

Buprenorphine for the treatment of opioid dependence was approved on October 8, 2002. This approval marks a new milestone in the evolution of the American response to opioid addiction, but it does not mark our crossing into therapeutic utopia. There will be problems. With FDA's approval of buprenorphine we will have, concurrently, two distinct oversight systems that deal with the use of opioid drugs in the treatment of opioid addicts. One is the modified set of regulations that emerged from the hybrid IND–NDA that developed and evolved over 30 years to provide a framework for oversight of methadone treatment. That system, which applies to all Schedule II opioids, such as methadone and LAAM, now incorporates a system of professional accreditation to oversee some aspects of treatment quality. It would not be inaccurate to describe this system as a hybrid–hybrid. And it still includes, by federal regulation, numerous constraints on the free exercise of judgment by treating clinicians. The other oversight system is the set of conditions that will govern the use of Schedule III–V opioid drugs, such as buprenorphine, that are approved for the treatment of addiction by the FDA. In this system, the judgment of the clinicians, who must attain certain qualifications or special training in order to be exempt from certain requirement of the NATA, is constrained by the requirement to limit the number of patients treated at any one time and the restriction on group practices.

7. Future challenges

It is not clear at this time how these two concurrent systems will interact and what the impact will be on patient access to treatment or the array of services provided. It is anticipated that the changes in the older system (the hybrid–hybrid) and the availability of buprenorphine in the offices of qualified physicians will serve both to increase access to treatment and to ease the compliance burdens on patients, and that both of these conditions will result in substantial benefits to the public and patients treated. But the law of unintended consequences has not been repealed, and it will remain for future commentators to judge what has been brought by these policy changes.

Undoubtedly, there will be some diversion of buprenorphine, and there will be some overdoses. We hope that few, if any, are fatal. Some young people will try buprenorphine and find it reinforcing. Somewhere, someplace, these events will be reported on by the media. It is difficult to predict the spin that such news will be given. The published articles and the television programs will probably not mention that in France the widespread therapeutic use of buprenorphine for the

treatment of 70,000 heroin addicts seems to have reduced significantly the opioids overdose death rate (Ling and Smith, 2002). What the coverage might underscore is that, other than peer pressure, neither government nor the medical profession will have mechanisms to deal with the individual rogue physician who prescribes inappropriately or too generously. If such behavior persists there is, at the federal level, only the extreme measure of reconsidering the status of buprenorphine as a Schedule III drug, or of the provisions of the Drug Abuse Treatment Act of 2000. What happens, of course, will reflect the peculiar American ambivalence about the opioid addict as not quite a patient and not quite a criminal. Thus, Americans seem willing to tolerate occasional untoward events and misuse of drugs for treatment of hyperactivity or anxiety, but not those associated with treatment of opioid addiction. The most optimistic scenario is that the use of buprenorphine in office based settings will simply increase access and lead the United States to a more pragmatic attitude towards dealing with the consequences of heroin addiction—and that such pragmatism will be long lasting and will demonstrate what can be achieved by easier and less stigmatizing access to treatment. With continued support from NIDA and CSAT, the new era of clinical freedom will be just another step in the long national effort to achieve the right balance between investing in supply control and demand reduction.

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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

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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).[4] 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.[5]

Although iatrogenic addiction had declined with changes in medical practice,[6] 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).[7] 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).[8]

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).[9] 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 Divison 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.[10] 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.*[11]

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

had at its disposal a PHS clinical researcher, Clifton K. Himmelsbach, who had worked with Eddy to pioneer the "morphine substitution technique" developed to compare the addiction liability of novel compounds to morphine. The Himmelsbach technique was based on the principle that, "A substance which will support and maintain the 'addicted state' is essentially addictive in and of itself" (p. 26).[12] Research objectives included "new treatment and substitution techniques, intensive study of physicochemical, psychiatric, and psychological changes resulting from single therapeutic and repeated doses of morphine in the non-tolerant individual, during stabilized addiction, and in the post-addiction state" (p. 30).[12] Himmelsbach investigated the relationship of chemical structure to addictiveness,[13–15] creating a point-score system to track the "Morphine Abstinence Syndrome."[16] Based on close observation of 65 subjects passing through cycles of tolerance, addiction, and withdrawal or "abstinence," Himmelsbach generated hourly and daily point scores that yielded a method for calculating the intensity of abstinence and predicting its course. He had previously gained insight into techniques for quantitatively comparing degrees of "addictiveness" through study of desomorphine and metopon, a drug developed by Small and marketed for chronic pain until the early 1950s. Metopon was considered proof of concept for the idea upon which the Committee was configured—the dissociation of analgesic activity from the undesirable tendency to produce dependence and respiratory depression. Simultaneously, German chemists produced pethidine (also called meperidine and trade-named Demerol), which was modified during World War II to produce methadone, the synthetic analgesic recovered by the Allies during a U.S. Department of Commerce investigation of German wartime industries.[17] During the war, the Committee's operations were suspended, but methadone came to the Committee's attention just as it resumed operation after the war's end (p. 52).[18]

Renamed the Committee on Drug Addiction and Narcotics (CDAN), the Committee's first postwar meeting was held at the NRC in 1947. Attending were Isaac Starr, the newly appointed chair; Harry J. Anslinger, chief of the Federal Bureau of Narcotics (FBN); Raymond N. Bieter, Head of Pharmacology at University of Minnesota Medical School; Dale C. Cameron, later chief of the Drug Dependence Section of the World Health Organization (WHO); Maurice H. Seevers, whose University of Michigan laboratory the committee had designated for animal testing; Eddy and Small from NIH; and representatives of the Armed Services, FDA, AMA Therapeutic Trials Committee, and the American Drug Manufacturer's Association. Amidon (methadone) was one of the postwar committee's first considerations, as several pharmaceutical firms were interested in manufacturing methadone or derivatives. Nathan B. Eddy, who had worked with the committee since 1930, proposed that CDAN serve as a clearinghouse to which manufacturers of analgesic drugs submit information useful for committee review of addiction liability and extent of clinical usefulness.

By the late 1940s, the U.S. government was actively attempting to determine the national and international controls to which new synthetic drugs would be subjected. At the first postwar CDAN meeting, Anslinger gained the Committee's approval of a draft protocol to bring synthetic drugs under international control. Whereas the opium-producing countries of the developing world viewed the new synthetics as dangerous and difficult to control, the United States feared it could not stem the flow of opiates from producing countries.[1] CDAN provided recommendations concerning levels of control and indications for a drug's use at the international level. The UN mandated the WHO Expert Committee on Drug Dependence (formerly "on Habit-Forming Drugs" and later renamed "on Drugs Liable to Produce Addiction") to recommend levels of control to regulatory bodies. Along with the WHO section that it advised, the Expert Committee rapidly forged a principle of balancing medical utility against the social risks of abuse. The international treaties, the Single Convention of 1961, and Psychotropic Convention of 1971 reflected the view that the more medically useful a drug, the less strict the controls should be.[19] In pharmacology, Eddy *et al.* demonstrated that synthetic drugs with "morphine-like effects are as good and as bad, as a class, as the drugs of natural origin."[20] 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).[18]

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.[40]

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).[40] 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).[40] The Committee turned toward narcotic antagonists upon the suggestion of Andrew Keats, hoping that this class of drugs would be clinically useful as analgesics.[41]

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).[40] 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).[40] 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).[40] 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."[35] 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.[42] 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.[35] 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."[43–45] 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).[46] 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."[47] 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).[18] 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.[48] Naltrexone was later touted as an anticraving medication that had a "healing" effect on the endorphin system. CPDD also considered a novel combination in which oral opiates would be formulated with a small amount of naloxone to prevent diversion of morphine-like analgesics. In the mid-1970s, a search for the optimal components of such possible agonist–antagonist combinations commenced. By the early 1970s, however, the social and political context had changed in ways that facilitated the shift toward addiction therapeutics that was occurring among the U.S. addiction research network.

From safe analgesics to "chemotherapeutics"

In 1964, Vincent Dole and Marie Nyswander initiated a pilot research program on methadone maintenance at the Rockefeller Institute (later renamed the Rockefeller University).[49] They cast methadone as a *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). [50] 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).[18] 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).[18] Dole and Nyswander characterized such attitudes as those of a stodgy addiction research establishment opposed to methadone maintenance on political grounds.[51]

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"[59] 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 "decondition[ed]" (p. 1).[59] 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).[59] 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."[59] 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.[60]

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.[61]

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."[62] 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.[63–65] One monograph named naltrexone as the most promising of these "new" methods.[65] 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."[65] 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,[66] 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.[67] Reckitts developed two unsuccessful opiates (etorpine, a potent μ-agonist, and its antagonist),[67] before putting buprenorphine into Phase 1 studies on "committed volunteers" including Lewis himself,[66] 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.[67] 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.[66] Jasinski *et al.* announced the addiction therapeutics potential of buprenorphine in a landmark paper in 1978.[68]

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.[69] 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.[70]

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).[71] 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).[69] 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."[69] 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,"[70] 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).[70] 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 experiment, diversion, and abuse of its analgesic form[71]; 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.[72–73] 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."[74]

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."[75] The BPRU collaborated early on with ARC researchers, including on a study evaluating buprenorphine in comparison to methadone[76] and another evaluating a range of doses of buprenorphine in an opioid challenge.[77] Bigelow recalled that these "mark[ed] the primary beginnings of using that methodology and incorporating [ARC] methods in our studies."[75] 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.[78] 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[79–80] 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 shrank. 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).[81] 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).[81] Despite this caution, buprenorphine was offered as a "safe and effective mode of pharmacotherapy for heroin addiction."[81–82]

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 Benckiser Pharmaceuticals, has explained, "You had to jointly defend the class of drugs, to keep the agonist/antagonists where they were."[83] 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).[84] 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.[85–87] 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.[a]

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.[63] 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.[72] Methadone, for instance, had found little use as a pain medication. As Chris Chapleo, now Reckitt & Benkhiser 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.[67] 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.[67] 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

[a]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.[88ci]

by a Belgian psychiatrist, Marc Reisinger using a pharmacy-prepared buprenorphine compound from the analgesic. Though these supported Jasinski'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 buprenorphine for the treatment of opioid dependence" in partnership with NIDA, who "would be co-funding to ease the burden to Reckitts."[67] 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 addicts[85] and the ethics of withdrawing, buprenorphine when patients were being treated with it for pain.[67] The following year, in the wake of a contaminated 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 viability of implementing the drug[89] and preventing Reckitts licensee Schering–Plough from losing its license because of off-label use of Temgesic. France framed Subutex partly as harm reduction,[90] as would some Asian countries in the following decades.[67]

In the United States, buprenorphine development faced funding issues, scheduling, and potential regulatory problems, as well as competition with the methadone community. Public contributions to development eventually included millions of dollars in contracts and grants. Reckitts obtained orphan drug status for Subutex and Suboxone (the two buprenorphine medicaments for addiction treatment) in the CRADA,[85] arguing the rarely used Cost Recovery principle; that is, that the company risked not recuperating 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.[b] Once Suboxone and Subutex were launched, postmarketing surveillance by an independent contractor 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 between 1980 and 1985, which compared various routes of administration and dosages, withdrawal, and cross-tolerance. Later studies concerned induction, abrupt withdrawal, and short-term detoxification. In the 1990s, studies were extended to include dose omission schedules, pharmacokinetics, and buprenorphine for pregnant, opiate-addicted women. These laid the groundwork for arguing that buprenorphine was not merely a "substitute therapy," in order to differentiate it from methadone.

Buprenorphine proponents, however, perceived methadone regulation as an obstacle to pharmaceutical 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,[67,85] 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

[b]Originally, Reckitts argued for orphan status on the prevalence principle that the drug would affect a rare population. The FDA rejected Reckitt's prevalence estimate, which was based on the number of treatment-seeking addicts, 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.

[c]The study, which included 18,596 interviews with applicants to substance abuse treatment programs, 8,194 surveys of federally certified physicians, as well as publicly available indicators of use and misuse of buprenorphine and buprenorphine with naloxone shows a steady increase in diversion and abuse from 2005 to 2009, although 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.[89] Addicts in many countries appropriated Subutex as "a medicine for them." [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.[86]

When DATA 2000 passed, the analgesic section at Reckitts (by then merged as Reckitt–Benkhiser) 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,[67] 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[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."[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."[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.[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 a 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 Subxone 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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