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Herbert D. Kleber

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# Methadone Maintenance 4 Decades Later

## Thousands of Lives Saved But Still Controversial

### SUMMARY OF THE ORIGINAL ARTICLE

**A Medical Treatment for Diacetylmorphine (Heroin) Addiction: A Clinical Trial With Methadone Hydrochloride**

**Vincent P. Dole, MD, and Marie Nyswander, MD**

*JAMA. 1965;193(8):646-650.*

Twenty-two male patients, addicted to heroin 9.5 years (median), were stabilized using oral methadone hydrochloride and then observed for approximately 1 to 15 months (median, 3 months). The medication had 2 main effects: (1) relief of narcotic hunger (craving); and (2) induction of sufficient tolerance to block the average illegal dose of heroin.

A combination of the methadone treatment and a comprehensive program of rehabilitation was associated with marked improvement in patient problems such as jobs, returning to school, and family reconciliation. No adverse effect other than constipation was found.

The authors note that "careful medical supervision and many social services" were necessary and stressed that "both the medication and supporting program were essential." The small size of the group studied and short duration of the follow-up would best describe this as a promising and exciting but preliminary report.

See [www.jama.com](http://www.jama.com) for full text of the original *JAMA* article.

### Commentary by Herbert D. Kleber, MD

**T**HE EFFECTS OF THE ARTICLE BY DOLE AND NYSWANDER<sup>1</sup> are best understood by knowing what preceded it. The current scientific consensus is that opioid dependence is a chronic and severe medical disorder, and withdrawal alone is usually followed by rapid relapse.<sup>2</sup> A century ago, however, withdrawal was often considered adequate to treat narcotic addiction, with methods used often more dangerous than withdrawal. Individuals who relapsed were viewed as doing so out of choice rather than necessity.

The frequency of relapse, however, led to the establishment of narcotic clinics to legally provide heroin or morphine to individuals with addiction. By 1923, all these clinics had closed, deemed failures because they did not lead to abstinence. Federal agencies interpreted the 1914 Harrison Act as prohibiting maintenance of individuals with active addiction and threatened or prosecuted physicians doing so. Between 1919 and 1935, approximately 25 000 physicians were indicted under the Harrison Act and 10% were imprisoned. Despite 1921 and 1926 Supreme Court rulings that the act did not forbid such prescribing, most physicians avoided it, ending the role of the medical profession in treating patients with addiction for 4 decades.

Heroin became the street narcotic of choice. During World War II, with heroin scarce and purity as low as 1%, addiction hit a record low. By the late 1940s, the flow of smuggled heroin had resumed, but addicts were more likely younger, from a racial or ethnic minority group, and living in northern impoverished communities. Treatment was scarce, prison common, and relapse likely.<sup>3</sup>

### Methadone Maintenance

Forty years after the last maintenance clinics closed, the 1965 article by Dole and Nyswander landed with a bang.<sup>1</sup> Dole, an internist, believed narcotic addiction was a metabolic disease, not very different from diabetes; Nyswander, a psychiatrist, had frustrating years of treating individuals with narcotic addiction with psychotherapy only to see them relapse. Their study,<sup>1</sup> conducted in New York City first at the Rockefeller Institute and later moving to Manhattan General Hospital, included 22 participants with heroin addiction. One year later, Dole et al reported empirical data on the induced narcotic blockade.<sup>4</sup> Long-term follow-up studies later confirmed that therapeutic success on a larger scale was possible.

**Author Affiliations:** Columbia University College of Physicians and Surgeons, Division on Substance Abuse, The New York State Psychiatric Institute, New York.

**Corresponding Author:** Herbert D. Kleber, MD, Columbia University College of Physicians and Surgeons, Division on Substance Abuse, The New York State Psychiatric Institute, 1051 Riverside, PI Unit 66, New York, NY 10032 (hdk3@columbia.edu).

Methadone replaced morphine as the preferred agent for heroin withdrawal. As a maintenance agent for treating addiction, methadone prevents withdrawal for 24 to 36 hours, enabling a system in which addicted patients come for treatment once a day, in contrast to the 1920s clinics using short-acting opioids.

Following the 1965 article,<sup>1</sup> scientists systematically expanded the science behind methadone maintenance treatment (MMT). Large-scale programs using more cost-effective induction methods opened in New York City, and the US Food and Drug Administration approved a limited use of methadone in large research programs.<sup>5</sup>

In 1970, the federal government faced 2 major heroin-related problems: heroin use and associated crime was increasing, especially in urban areas; and soldiers in Vietnam were using heroin. Concerned about possible increased crime when these soldiers returned home and influenced by the early success of DuPont's Narcotics Treatment Administration in reducing crime by treating individuals with heroin addiction,<sup>6</sup> President Nixon announced the war on drugs on June 17, 1971, created the Special Action Office for Drug Abuse Prevention (SAODAP), and hired Jerome Jaffe to be its first director. This new federal structure was charged with coordinating and rapidly expanding drug treatment, including changing existing regulations.<sup>5</sup>

Even as SAODAP and New York City moved to expand MMT, strong reaction began against it, fueled partly by reports of methadone-related deaths and diversion, but primarily by its substituting one addiction for another. Psychosocial program advocates opposed MMT as likely to reduce concerns about poverty and social ills. The director of a therapeutic community remarked, "I think methadone is a great idea. We should give money to bank robbers, women to rapists, and methadone to addicts."<sup>7</sup>

In those first 2 years, more federally supported treatment capacity developed than in the previous 50 years. In 1974, two-thirds of the \$750 million drug budget was devoted to treatment, research, and prevention, compared with the recent 25 years during which two-thirds of the budget targeted supply reduction.<sup>5</sup>

### Positive Outcomes of MMT

Numerous studies have demonstrated the effectiveness of MMT for reducing illicit opioid use, morbidity and mortality, risk of human immunodeficiency virus (HIV) infection, illegal activities, and improving overall functioning. Patients in MMT had a 1-year mortality rate of 1% compared with 8% among patients who discontinued treatment.<sup>8</sup> In a 1993 prospective study conducted in Philadelphia, Pennsylvania, HIV seroconversion rates were 4 times higher among individuals who were actively using street heroin compared with patients receiving MMT.<sup>9</sup> Risk decreased in relation to length of time continuously receiving MMT; risk of hepatitis B and hepatitis C also was reduced but to a much lower extent.<sup>9</sup>

In a 1991 study, crime days per year among individuals addicted to narcotics decreased more than 70% while receiving MMT.<sup>10</sup> In a random assignment study, patients in the standard and enhanced treatment groups had marked reductions in illicit opiate use and improvements in overall functioning compared with the minimal counseling group.<sup>11</sup> However, the increase of for-profit MMT centers (often realizing very large profits), and decreased funding for nonprofit centers left many programs inadequately staffed. This remains a major unresolved public health problem.

Average methadone maintenance doses of 60 to 120 mg or higher have consistently better results than use of lower average doses, especially because heroin purity is now often greater than 40%. Methadone's plasma half-life, once stabilized, averages 24 to 36 hours with a range of 13 to 56 hours. However, as many as 10 days may be needed to reach a steady state, and new patients, either to MMT or given methadone for analgesia, are at risk for fatal overdose. Most deaths have been from methadone prescribed for pain rather than from methadone treatment programs.

Although MMT has been lifesaving for thousands of individuals, it is not a panacea. High levels of psychopathology remain. Abuse of cocaine and benzodiazepines and disruptive behavior are problems in many programs. Many patients do not change their behavior even when services are available. What to do under such circumstances remains contentious, given the likely severe postdischarge consequences vs the effect on other patients and the possibility that more intensive residential intervention might be helpful.

During the past 2 decades, evidence has accumulated regarding the neurobiology of opiate dependence. Opiate dependence is now seen as a brain-related disorder with genetic and environmental overlays characteristic of a medical illness. The endorphin system and opioid receptors have now been discovered. Dole was ahead of his time.<sup>1,4,12</sup>

### Safety

Studies on MMT in the 1970s by Kreek found no long-term damage to the heart, kidneys, liver, or lungs.<sup>13</sup> Long-acting maintenance medications normalized the neuroendocrine alterations induced by short-acting opioids<sup>12</sup> with minimal psychoactive impairment. MMT has been shown not to impair driving ability. In the past decade, it was found that methadone, especially at high doses, when beginning treatment, or when combined with certain drugs, may lead to QTc prolongation and possibly to torsade de pointes, a potentially fatal cardiac arrhythmia. A black box warning was added to the prescribing information for methadone in December 2006. However, the clinical significance of this abnormality is not yet clear regarding deaths.

### Federal Regulations

MMT is one of the most heavily regulated medical treatments in the United States.<sup>5</sup> With few exceptions, methadone may only be dispensed for opioid withdrawal or maintenance by certified opioid treatment programs. An increasing

number of take-home doses is permitted, depending on the patient's history of illicit drug use and employment, with a maximum 1-month supply after 2 years. Regulations and decreased public financing have made it more difficult to start or expand programs. An Institute of Medicine review<sup>14</sup> concluded, "... current policy puts too much emphasis on protecting society from methadone, and not enough on protecting society from the epidemic of addiction, violence, and infections that methadone can help reduce." However, regulation that is too lenient may lead to worsened problems and increased hostility; a balance is needed.

### Stigma

In the late 1980s, the backlash against MMT became stronger. Community complaints about loitering and bartering of drugs outside clinics exacerbated the hostile environment. Complaints often coincided with decreased ancillary supports.

In 1988, the White House Conference for a Drug-Free America, vehemently antimethadone, demonized methadone and the National Institute on Drug Abuse and called for a congressional investigation.<sup>7</sup> In 1990, the Office of National Drug Control Policy reversed this position, and its White Paper on treatment stated clearly that methadone maintenance was both legitimate and an important part of the spectrum of drug abuse treatment.<sup>7</sup> Ironically, even though 12-step programs have often been hostile to MMT,<sup>15</sup> Dole, a friend of the cofounder of Alcoholics Anonymous recounted, "He [Bill W.] suggested that in my future research, I should look for an analogue of methadone, a medication that would relieve the alcoholic's sometimes irresistible craving and enable him to progress in AA toward social and emotional recovery. . . ." <sup>15</sup>

In the United States, approximately 260 000 individuals are currently receiving MMT (M. Perrino, written communication, October 2008), although it is estimated that fewer than 10% of individuals who are addicted to heroin and prescription opioids are receiving MMT. Worldwide, about 1 million individuals are receiving MMT; in some countries such as Russia, government opposition to agonist maintenance prevents its use even when high HIV rates exist.

The long-acting sublingual partial agonist buprenorphine, a Schedule III opioid, has been available since 2002 for office-based prescribing by physicians with special training<sup>5</sup> and with current limits of 100 patients per physician. Approximately 140 000 patients are now receiving maintenance using buprenorphine (R.E. Johnson, written communication, October 2008) and results to date appear comparable to MMT albeit with somewhat different populations. It is not clear whether it will be any easier to remain abstinent after withdrawal from buprenorphine treatment than from MMT, especially if inadequate ancillary support is provided. While buprenorphine's formulation makes overdose or diversion to parenteral use less likely, like all  $\mu$  agonists, this drug has that possibility and limited diversion is already occurring.

### Methadone: Terminable or Interminable

The benefits of long-term methadone maintenance are borne out by data.<sup>2</sup> Two years of MMT appears to be the minimum duration before attempting withdrawal.<sup>5</sup> Even patients receiving maintenance for long periods with substantial lifestyle changes often relapse after leaving treatment, and death rates are much higher than for individuals who remain in treatment. For many patients, therefore, years or even lifetime maintenance may be needed, but there is often patient and family opposition. Office-based medical maintenance has been used on a limited basis for patients stable at least a few years with generally successful results, although some patients increased their use of illicit drugs. This approach avoids the clinic problem of mixing stable and unstable patients but the number of eligible stable patients appears limited. Ultimately, the problem of interminable maintenance vs relapse may require learning how to reverse the brain changes associated with addiction. Until then, long-term agonist treatment remains a reasonable alternative.

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