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EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION

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The vision

EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide

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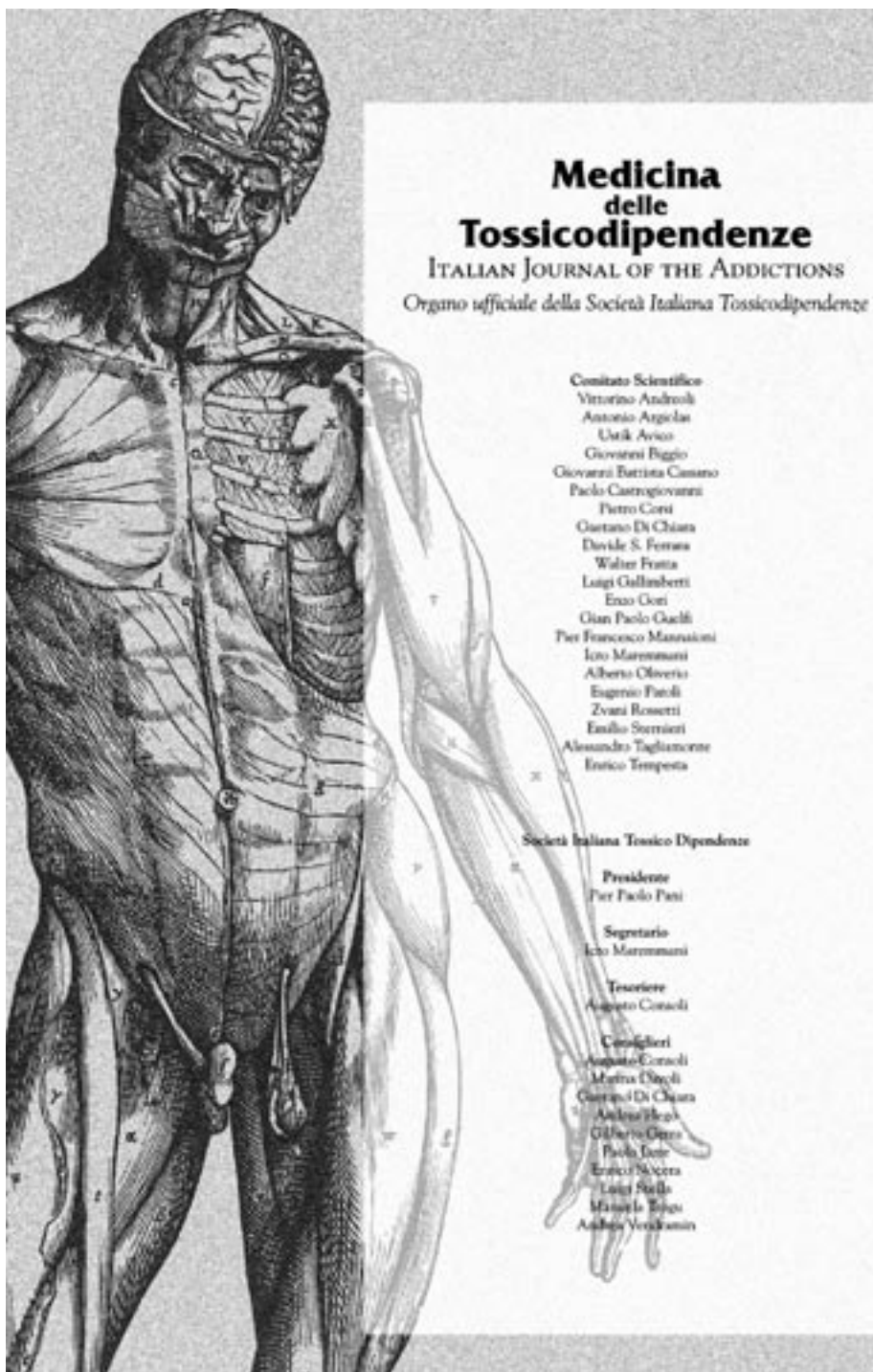


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Combating the Stigma: Discarding the Label “Substitution Treatment” in Favour of “Behaviour-Normalization Treatment”

Icro Maremmani^{1,2,3} and Matteo Pacini^{1,2}

The 7th EUROPAD Meeting took place, as scheduled, from October 6th to October 9th in Bratislava. The choice of Eastern Europe for this year's meeting was made for two main reasons. First, it was a way to acknowledge and underline the contribution provided by Eastern European researchers and clinicians in the consolidation, and then expansion, of the body of knowledge regarding addiction and related clinical problems. Second, this meeting symbolized the will and the hope that a scientific “soul” leads the practice and policies of Eastern European countries in the field of drug addiction. Therefore, Eastern governments should give increased decision-making power to scientific boards regarding drug-related legislation, in order to grant increased standards of safety and health to their populations. We might say that EUROPAD proposes itself as a watchtower to enforce the uniformity of approaches to addictive diseases in European countries.

During the Bratislava conference, the importance of reaching all categories of addicted patients was underlined in different workshops, each dealing with a special setting or diagnostic category. Moreover, different speakers emphasized that a major effect of addiction treatment is in increasing the therapeutic potential of other somatic treatments, such as those for HCV and HIV. Prevention campaigns and therapeutic appeals by governmental and non-governmental organizations should always be tailored to the patients' behavioural patterns in order to be easily accessible and thereby effective. Hence, since addicts are typically unreachable and lack compliance with any form of structured relationship, the tailoring of maintenance programs to these addictive behaviours is crucial to empower therapeutic campaigns. Methadone and buprenorphine programs are also roundabout and subtle means to create those “prevention prone addicts” which are so unlikely to be found in nature.

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Because the global focus of the Bratislava Conference was rather medical in nature, the interest taken by those working with the psychosocial and psychological aspects was eventually enhanced, rather than diminished. Therefore, a medically based perspective of addictive diseases is the best viewpoint for medical and non-medical practitioners. As Dr. Gerra from Italy pointed out, we have never been closer to a medical approach, and the scientific level of presentations is now similar to what one can witness in a congress dealing with any other medical discipline, as opposed to just two decades ago. Further research and clarification about methadone and buprenorphine safety was presented in order to help clinicians manage and prevent side effects with special regard to cardiologic risks, endocrine normalization and cognitive functioning.

As time goes by, therapeutic experience with buprenorphine is becoming long-term, and allows clinicians to improve their capability of selecting patients for long-term buprenorphine programs with the prospect of favourable results. False myths about abuse liability and difficulty of transition were thus clarified, and improper switching between successful programs was indicated as one of the major causes of negative results in some experiences with buprenorphine.

Polysubstance abuse was discussed both on epidemiological and pathophysiological grounds. Observations made by German researchers regarding the use of dihydrocodeine in the treatment of alcohol-abusing former heroin addicts widened the prospects for future research regarding the relationship between alcoholism and the opioid system. This suggests possibility of using opioid agonists in the treatment of alcohol addiction.

In the trail of studies concerning dual-diagnosed addicts, primary psychotropic properties of methadone were discussed by Dr. Deglon from Switzerland, and the potential of buprenorphine as a psychotropic drug was described by Dr. Maremmani from Italy. Such interventions were meant to encourage future research regarding the use of opioids in mental illness and to highlight the therapeutic nature of methadone and buprenorphine as disease-modifying drugs as opposed to disease-inducing drugs such as heroin.

Dr. Vincent Dole was commemorated by several speakers, and the philosophy and principles of his work were recalled and summarized by Dr. Herman Joseph. In the spirit of Dr. Dole's effort, it is our hope that the conception of the addict as an ill person with a metabolic brain disorder is always maintained as the main criterion for the measurement of treatment outcomes. Therefore any non-medical approach to the treatment of this metabolic brain disease should definitely be left behind.

With special regard to the situation in some countries of Eastern Europe, we hope that ignorance and prejudice do not pollute decision-making regarding heroin addiction treatment, as had happened in the USA since before the very beginning of the methadone era. Finally, it is our opinion that the worst obstacle against effective treatment of heroin addicts is that kind of stigmatizing attitude which may come from addiction practitioners themselves, and may be referred to as "iatrogenic stigma". Such stigma is commonly, but mistakenly, represented by the definition of methadone

or buprenorphine treatment as “substitution treatment” or “replacement treatment”. These are medical terms but they are bound to allow non-medical minds to develop the misbelief of methadone treatment as “harm reduction” or a “legal administration of toxic narcotics” disguised as therapy and to regard patients as “maintained addicts”. We remember that Dr. Dole never spoke about “substitution treatment” and that, in his experience, methadone was a behaviour-normalizing drug which would re-balance the endogenous opioid system persistently damaged by toxic narcotics such as heroin. This happens only when methadone is administered at adequate dosages and as a maintenance regimen.

In honour of Dr. Dole, we trust that authors of future articles for this magazine should avoid such expressions as “substitution treatment” or “replacement treatment” and which should otherwise be considered unacceptable on ethical grounds.

Received and Accepted October 22, 2006

In the Service of Patients: The Legacy of Dr. Dole

Herman Joseph^{1,2} and Joycelyn Sue Woods¹

Summary

The underlying theme in Dr. Vincent P. Dole's work is the effect of metabolism on behavior. This led to ground breaking investigations at The Rockefeller University in electrophoresis, lipids, obesity, addiction, and the development of methadone maintenance in 1964 with his late wife, Dr. Marie E. Nyswander. Dr. Mary Jeanne Kreek, a research resident in his laboratory in 1964, is now continuing addiction research as a professor at Rockefeller. Dole developed methadone detoxification in the New York City jail system and office based methadone medical maintenance with Nyswander. His major concern was to resolve the stigma that methadone patients encounter.

Key Words: Development of methadone maintenance -
Dr. Dole legacy

Introduction

With the death of Dr. Vincent P Dole in August of 2006 at the age of 93, the end of an era has come to pass in 20th century medicine-namely the initial unraveling of heroin addiction from what was thought to be compulsive immoral behavior to a legitimate medical disorder that could be treated with medication within clinics and private physicians' offices^(4,5,8,41). Although, known primarily for his work in developing methadone maintenance treatment for heroin addiction and the promulgation of the metabolic

theory of addiction, his ground breaking accomplishments in this area can only be fully appreciated in the context of a distinguished career as a research scientist dating back to the 1940s. His work can be subdivided into two periods, the pre-addiction and the addiction period which started in the 1960s. However, upon examination it is really one continuous interconnected arc of metabolic research. His underlying major concern was the effect of metabolism on human behavior. The range of his work is unique as is the range of his scientific skills. He made original contributions to the understanding of electrophoresis, lipid chemistry, the treatment of hypertension and the metabolic foundations of obesity among other topics ^(3,4,31). He showed that very obese people metabolize food differently than others, and that the craving for food was similar to the craving of a smoker for a cigarette and the craving of a narcotic addict for heroin although the metabolic pathways resulting in the various cravings differ ^(2,4,17,20).

His studies in obesity challenged popular belief that obese people lack will-power to control their food intake. He also noted the tendency for obese people to regain weight or relapse after dieting and that this relapse had a metabolic basis ^(2,4).

After finishing his studies in the metabolism of obesity, Dr. Dole embarked on the study of addiction and the development of methadone maintenance. His partner and wife in this historical research was Dr. Marie Nyswander, a psychiatrist who died in 1986. In addition to his scientific background, Dr. Nyswander brought to the development of methadone treatment a unique insight into the social and personal issues that heroin addicts and methadone patients face.

Prior to their collaboration, Dr. Nyswander had worked for almost two decades treating narcotic addicts in various venues including as a Lieutenant in the US Public Health Hospital in Lexington KY, the Musicians Clinic in NYC, in private psychiatric practice and with Dr. Beatrice Berle in a storefront in East Harlem that was part of the addiction program of the East Harlem Protestant Parish. She was a founder of Narcotic Anonymous (NA) based on the model of Alcoholics Anonymous (AA) ^(2,43,50).

Dr. Nyswander wrote several papers about her experiences treating addicts including the book, *The Drug Addict as a Patient* in 1956 which was the primary influence on Dole's understanding of addicts and addiction. For addicts to be considered patients was a revolutionary concept in the United States ⁽⁴³⁾. Addiction and heroin addicts were relegated to the criminal justice system or prison-like hospitals by a series of supreme court decisions, and national and local laws emanating from the Harrison Act of 1914 which, although only a tax and registration act, was interpreted by the Treasury Department to exclude physicians from treating addiction with maintenance medications ⁽²⁾. However, from her experiences treating addicts as a psychiatrist, Dr. Nyswander concluded that many addicts need to be maintained on a narcotic to function since talking therapies of psychiatry and NA were unable to alleviate the craving which for many was the focal point leading to relapse ⁽⁴³⁾.

It was the complementary knowledge and collaborative efforts of Dole and Nyswander that shaped both the research and the clinical development of methadone maintenance as a medical regimen: Dr. Dole was in charge of the laboratory research. Dr. Nyswander

recruited heroin addicts from the East Harlem for pilot at the Rockefeller University. From her years of experience she developed clinical protocols both at The Rockefeller University and at The Beth Israel Medical Center where the pilot moved into an expanded clinical research phase.

Although the pilot did not begin officially at The Rockefeller University until February of 1964, Dole and Nyswander were meeting during 1962/63 planning the research, the need for a maintenance medication and discussing the theories of addiction. Notwithstanding her psychiatric orientation, Nyswander accepted Dole's concept that, like extreme obesity, heroin addiction was a metabolic disease ⁽⁸⁾.

Dr. Mary Jeanne Kreek, a first year medical resident at New York Hospital–Cornell Medical Center in internal medicine and neuroendocrinology was recruited towards the end of 1963 to assist in the research pilot that began in February of 1964. Her duties included bone marrow biopsies and tests of narcotic tolerance. She worked with Dole and Nyswander on the seminal paper, *Narcotic Blockade* ⁽⁷⁾. However, Kreek had to leave the project temporarily to finish her residency at Cornell. Upon returning to the Dole Laboratory she embarked on a landmark series of studies concerning the medical safety and side effects of methadone, how methadone functions in a stabilized patient, the biological basis of addictive disease: opiate, cocaine, and nicotine addiction and alcoholism ^(14,16,19,37). She is now Professor and Head of the Laboratory of the Biology of Addictive Diseases at The Rockefeller University. A summary of the extent of her work and a list of her publications are available at the website of The Rockefeller University.

For the clinical phase at The Beth Israel Medical Center Dr. Nyswander recruited Dr. Joyce Lowinson in 1964, a second year psychiatric resident at New York Medical College who had shown an interest in the treatment of addicts on the detoxification ward at Metropolitan Hospital. Dr. Lowinson subsequently became a professor of psychiatry at the Albert Einstein College of Medicine (AECOM), developed the first methadone program associated with a medical school at AECOM and became the senior editor of *Substance Abuse: A comprehensive textbook*.

Dole also enlisted Dr. Norman Gordon, a psychologist to administer and analyze reaction time, coordination and related studies on methadone patients. Dr. Gordon's research demonstrated that stabilized patients were not impaired from methadone and could perform in all jobs for which they were trained or qualified ⁽²⁸⁾.

Other researchers, administrators, and physicians who were affiliated with Dr. Dole during the program's development include Dr. Enoch Gordiss who subsequently became the head of NIAAA, Dr. Ann Ho who worked on various laboratory studies with Dr. Dole and then with Dr. Kreek, Dr. Jerome Jaffe who became head of President Nixon's drug programs in the Special Action Office of Drug Abuse Prevention and from 1971 to 1973 developed a network of methadone programs in the United States, Dr. Robert Newman who made the initial major expansion of methadone treatment in N.Y., Dr. Ray Trussell who transferred the original pilot to Beth Israel Medical Center, Dr. Harold Trigg who was the first medical director at Beth Israel; Dr. Melissa Freeman of Beth

Israel Medical Center who treated the first female methadone patients; Dr. Elizabeth Khuri and Dr. Robert Millman who developed the first adolescent methadone program; and this author who worked with Dr. Dole on topics related to the criminal justice system, the adjustments of patients during and after treatment, and the establishment of office based prescribing of methadone.

Modern Theory of Addiction

Possibly Dole and Nyswander's greatest achievement was to shift the paradigm of addictive behavior from a moral stigmatizing psychological failing to a chronic metabolic disease⁽⁸⁾. The metabolic theory evolved from a seminal paper published in 1966, *Heroin addiction: A metabolic disease*. Dole and Nyswander suggested the adaptation of a metabolic theory of addiction. Factors were introduced such a neurological susceptibility, an altered biological response to narcotics that results in continued use, a protracted abstinence syndrome and metabolic narcotic craving which precipitate relapse. According to Dole at the time the specific narcotic hunger leading to relapse was symptomatic of a metabolic alteration within the central nervous system irrespective of the addict's psychological profile, social class or emotional state⁽⁸⁾.

In 1970 Dr. Dole published *The Biochemistry of Addiction*. In this article he predicted the existence of opiate receptors in the brain, their location, density and the technology needed to isolate them⁽⁹⁾. The complexity of the endogenous opioid receptor system was discovered, and is being currently mapped out and studied^(16,48). According to Dole, the metabolic alteration responsible for the specific narcotic craving described earlier in his work, appears now to be associated with as yet an undiscovered impairment or deficit in the function of the opioid receptor system⁽¹⁶⁾.

In his paper written for the Lasker Award for Clinical Medical Research in 1988, Dole discussed methadone maintenance and its implications for theories of addiction and stressed the following⁽¹⁶⁾:

- 1) The high rate of relapse of addicts after withdrawal is due to a persistent disorder or defect within the endogenous opiate narcotic ligand system caused by long use of powerful narcotics such as heroin.
- 2) Methadone administered orally in daily adequate doses with blood levels in a range of 150ng/ml and 600ng/ml can compensate for this defect with continuous and stable occupancy of the narcotic receptors.
- 3) Methadone normalizes the neurological and endocrinologic processes in patients with this disorder.
- 4) The major purpose of long term research is to identify the derangement or defect within the endogenous opiate narcotic ligand system and correct it.
- 5) Methadone treatment is corrective not curative since most patients but not all relapse after withdrawal.
- 6) The return of specific narcotic craving after withdrawal is symptomatic of the defect within the endogenous opiate narcotic ligand system.

In 1994 Dole summarized the metabolic theory of addiction that has evolved over the past 40 years.

“A modern theory of narcotic addiction is that the compulsive and quite specific craving for narcotic drugs is a symptom of a deficiency in function of the natural opiate-like substances in the brain. To be sure, sociological and psychological forces enter into the making of an addict, but these factors determine exposure—whether or not addictive drugs are available in the environment and whether a person chooses to experiment with them. In any person with repeated exposure to a narcotic drug, the brain adapts and becomes pharmacologically dependent on a continuing input. In some susceptible persons —fortunately a minority of the population—the adaptation becomes fixed and with repeated use a regular input of narcotic becomes a necessity. The experimenter has become an addict. From this perspective methadone maintenance is replacement treatment, compensating for impairment in function of natural opiate-like substances”⁽²¹⁾.

With this statement of the modern theory of addiction, social, psychological and biological components are incorporated, each with a defined and interrelated role. Eventually biological forces take over irrespective of the psychosocial elements that may be responsible for experimentation or initial use. The continued craving, relapse and tolerance associated with addiction have biological component, which are independent of will power and a person’s psychological profile. The basic characteristics of a continued addiction are therefore biologically influenced. The resolution of personal problems does not mean that the majority of addicted individuals can subsequently resolve drug craving or other biological components of an addiction. A minority of addicted individuals can resolve their cravings but studies have shown that addiction in a majority of the persons can continue indefinitely irrespective of a person’s emotional or intellectual characteristics ⁽³⁹⁾. Most important, methadone treatment is not a substitution of one addiction for another (methadone for heroin) but is compensation or replacement for the body’s impaired natural opioids ^(7,8,14,16,17,20,36).

The Role of Adjunct Services in Methadone Maintenance Treatment

In reviewing the early papers produced by Dole, Nyswander and colleagues the reverberating theme is that although methadone is essential to relieve craving no one medication is able to address the many social, personal, and medical issues that patients present to methadone programs, and social services are essential for rehabilitation ^(6,43). In 1988 when he received the Lasker Award for Clinical Medical Research, Dole reiterated the need for social services as follows:

“When somatic functioning has been normalized (by methadone), the ex-addict supported by counseling and social services can begin the long process of social rehabilitation”⁽¹⁶⁾.

The issues of homeless and unemployment were recognized from the beginning of the program. In the 1960s these social ills were more readily addressed than today. Furnished rooms for the homeless and jobs requiring minimal skills were available. Although at program entry most of the patients were unemployed in need of housing

and estranged from families within a few months after entering the program most were productively engaged in employment, enrolled in school, housed, reunited with families and where applicable, functioning as homemakers. This dramatic turnaround within a period of 6 months to one year was a testimony to the efficacy of adequate doses of methadone, the resources in the community and the reality oriented counseling offered in the clinics which may have included legal help to address old warrants and court cases ^(17,23,32).

To assist in rehabilitation, Dole and Nyswander created a position in the clinics known as research or patient assistants. Successfully stabilized methadone patients were hired as a link to resolve issues between mistrustful patients and the professional clinic staffs ⁽⁴⁴⁾. Although the position no longer exists, eligible patients were hired and eventually absorbed into the clinics as counselors and administrators. McLellan et al showed that outcomes of methadone patients in a Veteran's Medical Center methadone program improved with enhanced on site services to patients which included a psychiatrist responsible for medical and psychiatric issues, a vocational counselor, and a family therapist over patients who received standard counseling in the study. Patients who only received methadone did less well than patients who received standard counseling. About 69% of the subjects who received only methadone had to be transferred to standard counseling since their adjustments were poor in regard to continuing use of opioids and cocaine ⁽³⁸⁾. However, these onsite services are expensive and may not be available to all programs unless they are located within large medical institutions such as the Veterans Administration which offer a panoply of medical, psychiatric and social services to veterans.

However, beginning in the 1970s a confluence of social changes and medical epidemics converged on the patient and addicted population. Economic downturns and the changing nature of work from manufacturing jobs to employment in the emerging information age which demanded a degree of computer skills and literacy adversely affected the employability of patients except for those with the skills and educations applicable in the new job market. Affordable housing for lower middle class and the poor began to disappear, and social benefits were reduced.

These social changes produced a new era of destitution, homeless and hunger affecting many cities and rural areas in the United States ⁽⁴⁹⁾. By the 1980s and 1990s improvised dwellings constructed from cartons and discarded materials were seen on the streets. Lack of affordable housing and chronic unemployment produced a modern form of destitution across the country and impacted negatively on the methadone patient population into the 21st century ⁽⁴⁹⁾. HIV and hepatitis C emerged within the population starting in the 1970s and possibly earlier for hepatitis C ^(30,42).

The methadone clinics were usually the patient's only point of contact with medical and social services. As conditions deteriorated for marginal populations, the needs of patients became more complex, diversified and more difficult to obtain and deliver. Clinics located in facilities without services would have to develop linkages with community agencies in order to address the issues that patients presented. This may entail

obtaining funds through grant applications.

Within the past two decades, services were developed in methadone programs to meet women's issues including partner violence ⁽²⁴⁾. In her evaluations of the methadone program in the mid 1960s through the early 1970s, Dr. Gearing noted decreasing retention rates over the course of time and in the 1970s, patients were entering treatment with life threatening medical conditions including pneumonias. She recommended that to obtain needed medical services, methadone treatment should be affiliated with medical centers ⁽²³⁾. Dole and Joseph also noted decreasing retention rates in treatment in cohorts that entered methadone treatment in the early 1970s. There existed a group of transient, chronically unemployed, ill patients who were cycling in and out of treatment and getting arrested on petty charges. There are no adequate services available to help stabilize these patients other than the methadone programs which had limited facilities to address their problems ⁽¹³⁾. Problems related to social issues such as homelessness, chronic unemployment and polydrug abuse continue in methadone programs to the present day. While Dole advocated counseling, he was concerned about the philosophy of counseling with the primary goal of removing patients from methadone. Dole's premise was that the primary goal of counseling should be productive functioning in the community while the patient is enrolled in treatment. He believed that patients should be assisted in solving serious problems before attempting withdrawal, considering the serious risks that are involved such as high probabilities of relapse and death ⁽³⁹⁾. Also, Dole was against overly intrusive counseling that may threaten a patient's job or education because of the time that counseling was scheduled and the hours spent in counseling activities which may detract from employment and educational opportunities and family obligations.

Dole and the Criminal Justice System

In 1972 at the invitation of the New York City Department of Corrections Commissioner, Benjamin J. Malcolm, Dr. Dole, as a non-compensated volunteer, set up the first detoxification service in the New York City jails to withdraw arrested addicts from heroin using methadone. This was the first service of its kind in the United States. Dole was also responsible for enlisting the services of a major hospital, Montefiore Medical Center, to provide the ongoing detoxification services and primary medical care to prisoners in New York City Rikers Island Jail ^(10,11). Dole established the jail medical services as a non-compensated volunteer. In 1972 he received a "Citation by the City of New York for Extraordinary Voluntary Service for Establishing the Methadone Detoxification Program- Volunteer of the Year".

In 1987, the service was developed into KEEP (Key Extended Entry Program) by the New York State Office of Alcoholism and Substance Abuse Services and the Department of Corrections. Heroin addicts were not only withdrawn from heroin but if they chose, they could be maintained on methadone and referred for treatment in the community upon their release. Arrested methadone patients could also be maintained on methadone in the jails and, when released, referred back to their programs for continued treatment. KEEP became a model worldwide for methadone treatment

in jails and prisons.

Adolescent Program

In 1968 Dole and Nyswander began research into the needs of addicted adolescents between the ages of 14 and 18 who were unable to enter methadone treatment because of their age. This was the first such research undertaken on an adolescent group. Linkages were made between a local high school located near The Rockefeller University, Dr. Dole's laboratory at the university and the Department of Public Health and Pediatrics Divisions of the New York /Cornell Medical Center now known as the Weill Cornell Medical Center ⁽³⁵⁾.

In 1971 an ambulatory adolescent clinic to house the program was opened near the high school, the university, and the hospital. Applicants had to present a well documented history of heroin addiction of at least two years with at least one failure in treatment program. Parental consent was required and students had to be registered in the local high school. The students reported daily to the clinic and were eventually stabilized on average doses of 35 mg/dy with a maximum of 50/mg/dy. Emphasis was on rehabilitation although detoxification was available when the social situation warranted it. A panoply of supportive services were available: medical services either at the clinic or the hospital, counseling to continue education with tutoring if indicated, vocational referrals and job placements, legal services and recreational activities within NYC through an organization called Hospital Audiences. Over a three year period with 85 admissions there was an overall retention rate of 83%, 22 adolescents had been detoxified although two had to be restabilized because of relapses ⁽³⁵⁾. The physicians assigned to the program were Drs. Elizabeth Khuri, a pediatrician and Dr. Robert Millman, a psychiatrist. Both physicians had joint appointments at Cornell and in the Dole laboratory at The Rockefeller University.

Methadone Medical Maintenance

Methadone medical maintenance, the prescribing of methadone by a private physician in an office based practice was originally developed in 1983 at The Rockefeller University by Dole, Nyswander, Kreek and Joseph. The purpose of this program is to enable socially stable patients to be treated in the offices of private physicians or other venues of medical practice such as primary care centers instead of the traditional methadone clinics with rigid reporting regulations. The program gives patients the opportunity to further improve their social adjustments, job and educational opportunities. In this program patients report once month to their physicians who prescribe the methadone and receive a month's supply of methadone in a convenient tablet form in one or two vials rather than individual daily liquid formulations in vials which may spill and are difficult to store. Patients submit a urine sample at the time of their visit ^(41,46). It was Dole's idea to transfer socially rehabilitated patients into the practices of physicians who had never worked in a methadone clinic to determine whether the doctors could treat the disease of addiction within their practices as they would treat other conditions. At the time of its initial expansion from The Rockefeller University, the

program was transferred to the office-based practices of internists Drs. David Novick, a hepatologist and Edwin A. Salsitz, a pulmonologist. While Dr. Novick did work with Dr. Kreek at The Rockefeller University on research projects, and Dr. Salsitz worked on the detoxification wards at Beth Israel, neither physician ever worked in a traditional clinic. Dr Salsitz harbored negative opinions about methadone as a maintenance medication since his only experience was on the detoxification wards with dysfunctional methadone patients who were poly drug abusers, alcoholics, chronically unemployed and some, destitute and homeless. He was unprepared, psychologically, for the first office patients in medical maintenance who were employed, well dressed, and well behaved. He advised this author that he never met or treated successful methadone patients. When he started to treat stable patients his attitudes changed, and he made "a 180 degree turn." Salsitz realized that his previous negative perceptions about the ineffectiveness of methadone treatment were really about the effects of poverty, chronic unemployment and destitution on human behavior and not about the success or failure of methadone treatment as a medical regimen.

Different models of medical maintenance have been developed in NY State by this author while employed at the N.Y. State Office of Alcoholism and Substance Abuse Services prior to 2003. They are still in existence and are being monitored by the agency.

During the past two years in Albany, NY methadone maintenance treatment for socially stable patients was added to an existing primary care center which has a pharmacy on the premises. At present 25 socially stable methadone patients have been integrated into medical care at the center with a physician who prescribes methadone. The patients receive their monthly methadone at the center pharmacy without observed ingestion. They are seen by the methadone prescribing physician and other specialists in the center, and if needed, the social service counseling staff. Patients are employed and most are married with families. This primary care center has proven to be successful for the delivery of multi-services without taxing the limited financing and space of a traditional methadone clinic. The use of primary care centers to offer methadone treatment is as yet an untapped resource for the expansion of the program and integration of methadone patients into mainstream medical practice.

The physician/commercial pharmacy model was developed at Weill Cornell Hospital with the medical director of the clinic assuming responsibility for care of 14 patients who receive their methadone in a neighborhood pharmacy upon presenting a photo ID card. The patients also receive psychiatric care if indicated, in this program since the medical director is a psychiatrist and will prescribe needed medications for anxiety and depression. The patients in this program are employed and report once per month. However, if there are any problems of a psycho-social nature, then the patients may see the psychiatrist more often.

The pharmacy and the primary care center had to be brought into compliance with the regulations of Federal Drug Enforcement Administration, the Federal Center for Substance Abuse Treatment, and the NY State Office of Alcoholism and Substance

Abuse Treatment as Narcotic Treatment programs with the installation of alarm systems and special safes to store the methadone.

Although the network of seven methadone medical maintenance programs in New York State has been successful according to records maintained at OASAS, the program has not been duplicated on a large scale in the United States. This may be due to the regulations for setting up programs and the expenses involved. Nevertheless, the successful implementation of a few medical maintenance projects in the United States did serve as a model for the introduction of buprenorphine treatment in office-based practices.

The Need for Evaluation

Inherent in Dr. Dole's work was his insistence on objective evaluation of the methadone program. When the pilot project of six patients moved to Beth Israel Medical Center in late 1964 a major evaluation was planned with the Columbia School of Public Health under the direction of Professor Frances Rowe Gearing. Patient retention in treatment, reasons for discharges, duration of treatment, employment status and patient demographics were among the variables studied. In addition a committee was formed to oversee the evaluation, make recommendations concerning the direction of the evaluation and the expansion of the program. No other treatment for addiction was subject to such a continuous investigation for a period of six years. The major findings were that the majority of the patients improved made favorable adjustments with reductions in or elimination of heroin abuse and crime, and increases in productive behavior such as employment, school and child care. However, because of the changes in social conditions patients were entering into treatment in the 1970s with life threatening major medical illnesses, chronic unemployment, and homelessness. It was recommended that methadone treatment be developed in conjunction with medical centers⁽²³⁾. Also, in the 1970s the federal government introduced regulatory measures which Dole considered excessively intrusive into patient care. Paper work increased in the clinics and the perception of the program became one of control rather than treatment. Patients perceived a strong social stigma targeted to methadone and were ambivalent about entering and remaining in treatment^(39,40).

In addition Dole and this author completed a major follow-up study of patients who were discharged from the program in good standing, against medical advice or death. Post treatment outcomes were studied including death rates both in treatment and during the post treatment period⁽¹³⁾. Taking the lead from the Gearing, Dole-Joseph studies, other investigators began to evaluate their programs including follow-up data. A mega analysis by Magura and Rosenblum showed a consistency of trends in all follow up studies: high relapse rates after leaving treatment, post-treatment death rates were at least twice the in-treatment rates with the excess of deaths in the post treatment period associated with heroin use. They recommended that care should be taken in recommending termination from treatment because of the high risks such as relapse rates and deaths⁽³⁹⁾.

However, evaluation was not confined to the overall clinical management of the

program but also to medical safety of methadone as studied by Kreek. Pregnancy and neonatal development were extensively studied in numerous investigations and methadone was found to be safe for use in pregnancy ⁽²²⁾. Most important are studies that showed methadone can stop the transmission of HIV if patients receive adequate doses ⁽³⁴⁾.

Both this author and Dole indicated that claims about the success or failure of a program without evaluation was only propaganda irrespective of what a program is capable of achieving. Another factor about evaluation is the study not only of the successes but also of failures in treatment which will define the limits inherent in the program and/or the need for further services ⁽³²⁾.

Interim Methadone Maintenance

Interim Methadone Maintenance although controversial, is a needed service in cities and countries where limited funding is available, and a heroin epidemic exists with the presence of HIV, hepatitis C, high mortality rates and drug related criminality among the addicted population. The concept has the support of Dr. Dole who wrote an editorial favoring this approach when there is limited access to comprehensive treatment ⁽¹⁸⁾. Interim methadone maintenance provides patients with adequate doses of methadone to eliminate heroin use and counseling on an emergency basis. It is an alternative to traditional waiting lists where patients do not receive medication and continue to inject heroin. It is not an alternative for comprehensive treatment which must be developed. Evaluations of two interim clinic programs in New York City and Baltimore showed that: 1) heroin use and crime were reduced as compared to applicants on the traditional waiting lists, 2) an increase in the likelihood of patients in the interim program entering comprehensive treatment and 3) in New York City a higher rate of interim patients retained in treatment at 16 months than those on traditional waiting lists (72% vs. 56%) ^(47,51).

While an interim program is not a traditional clinical service, it is a service to the community by helping to reduce crime and to heroin addicts by reducing or possibly eliminating the transmission of HIV and hepatitis C until they enter a comprehensive program ⁽¹⁸⁾. Notwithstanding favorable research the interim methadone maintenance concept has been rejected by the treatment community, the US Public Health Working Group on Methadone and state authorities such as the NY State Office of Alcoholism and Substance Abuse Services since the interim clinic is not a full service program with many of the social services that patients may require. It is now up to communities to evaluate the need for such a program which does have the ability to reduce heroin use, crime and the transmission of HIV and hepatitis until the patient enters a full service program. The National Alliance of Methadone Advocates supported the development of interim methadone maintenance to assist addicts on waiting lists until they entered regular treatment.

Awards

Dole received numerous distinguished awards throughout his career. Among these are the following:

- The Stouffer Award (1972) for his original work in isolating free fatty acids from plasma, demonstrating their origin in body fat stores and their inter-relationships with insulin and carbohydrate metabolism.
- The Albert Lasker Award for Clinical Medical Research (1988) for hypothesizing the physiological basis of addiction and developing methadone maintenance treatment for heroin addiction.
- The Fourth annual New York City Mayor's Awards of Honor for Science and Technology (1988) for the development of methadone maintenance to treat heroin addiction.
- Prince Mahidol Award in Public Health (1996) for research into addiction and the development of methadone maintenance for heroin addiction

Stigma: the most destructive social force that methadone patients face.

The social stigma that methadone patients face appears to be pervasive throughout society although some progress is being made through education and advocacy. Patients are especially concerned about their treatment in the criminal justice system where they can be ordered to withdraw from methadone by probation and parole officers and judges irrespective of the adjustments they are making. It appears that physicians' judgments about the applicability of methadone treatment for a particular patient before the court is secondary to the judgments of non medically trained personnel in the court system. Also, methadone treatment for withdrawal or maintenance is not widespread in the jails and prisons. The New York City Rikers Island Jail addiction treatment programs have as yet not been widely accepted in the United States. There is now a campaign spearheaded by enlightened lawyers, judges and advocates to implement nationwide programs and changes in court practices. However, at the last AATOD meeting in 2005, Kathy Coughlin, the Assistant Commissioner of the New York City Department of Corrections reported that few if any referrals were made to methadone treatment in the Drug Courts of New York City.

Patients are also concerned about their treatment in hospitals if their enrollment in methadone maintenance is discovered by medical staff. They are concerned that they may not receive proper pain management or they may be withdrawn from their medication. Most of all they are concerned about the biased attitudes of physicians, nurses, and other health personnel.

The fear of social stigma pervades the patients' lives in the workforce if it is discovered that they are enrolled in methadone treatment. Patients may lose jobs or be placed under unusual surveillance. Furthermore if there should be a theft in an office, methadone patients feel that they would be the first to be suspected. Dr. Norman Gordon reported that in the workforce stable methadone patients are more stigmatized than alcoholics

who may have relapsed. He indicated that “methadone patients are very conscious of the fact that employers and potential employers frequently view their employment with a jaundiced eye”⁽²⁹⁾. If a stable methadone patient is in the “closet” and never revealed on an application that he is in the program and urine tests are implemented in the firm, the patient faces indecision, panic about the tests and fear of possibly losing his job. A prime activity for patients therefore is to act consciously in a manner to avoid detection or bring attention to themselves especially at work. Patients therefore develop behaviors to conceal their enrollment in methadone treatment ^(26,27,40).

Dr. Dole was always at the service of patients and advocacy groups such as the National Alliance of Methadone Advocates to help resolve issues of stigma and mis-directed policies that came to his attention. For him, his greatest legacy would be the elimination or reduction of the stigma that is directed to methadone patients, programs, and the medication itself. He communicated with patients through letters, email, phone contacts and personal interviews. Both Dole and Nyswander were concerned about the way methadone is perceived. In an article published on the tenth anniversary of methadone treatment they expressed their misgivings as follows:

“What was not anticipated at the onset was the nearly universal reaction against substituting one drug for another, even when the second drug enabled the addict to function normally. The analogous long term use of other medications such as insulin and digitalis in medical practice has not been considered relevant”⁽¹²⁾.

Kosten and George indicate in the following statements that Dole’s metabolic theory can lessen the stigma associated with addiction and methadone treatment if patients understand their condition.

“Brain abnormalities resulting from chronic use of heroin, oxycodone and other morphine-derived drugs are underlying causes of opioid dependence (the need to keep taking drugs to avoid withdrawal syndrome) and addiction (intense drug craving and compulsive use)”⁽³⁶⁾.

“...patients who are informed about the brain origins of addiction can benefit from understanding that their illness has a biological basis and does not mean they are ‘bad’ people” ⁽³⁶⁾.

Dr. Edwin A Salsitz who treats employed patients in his medical maintenance private office based practice at the Beth Israel Medical Center in New York City and this author found that stigma directed towards methadone treatment is the most destructive force that methadone patients face. They are concerned that revealing their status to family, employers and friends will lead to social alienation and possible job loss. Salsitz indicated that almost all of the patients and families have little or no conception of the nature of addiction and the role of methadone. Methadone is regarded as a heroin substitute, and therefore the patients are not considered cured since they do not have will power and are substituting one drug for another. The term opioid substitution therapy adds to the stigma. Salsitz advised that he must schedule sessions with patients and their families to explain that addiction is a metabolic disorder, and that methadone is a legitimate medication and not a heroin substitute. The conception of methadone maintenance as

a legitimate medical regimen is sometimes difficult to impart since the patients and their families harbor entrenched beliefs and misinformation received from the media, the general public and unfortunately from the medical profession itself ⁽⁴⁶⁾.

In a speech to the 1997 AATOD conference Dr. Avram Goldstein, professor emeritus of pharmacology at Stanford University, stated that it is wrong to consider methadone a heroin substitute. He reported that the continuous occupancy of methadone on the mu receptor is the stabilizing factor that allows patients to stop the abuse of heroin and normalize their behavior.

“It is therefore not correct to think of methadone as a “substitute” for heroin; its totally different pharmacokinetic properties make it, in effect, a completely different drug. It is true that both heroin (morphine) and methadone can occupy the mu opioid receptors. But the steady, stable occupancy by methadone contrasts sharply with the repeated excessive “highs” followed by excessive “lows” with heroin”⁽²⁵⁾.

In a December 9, 1998 New York Times article “Report backs methadone for addicts”, Dr. Alan Leshner, the then director of the National Institute on Drug Abuse, stated that “... probably the biggest disservice that has been done to getting effective treatment to heroin addicts is the inaccurate statement that methadone is a heroin substitute.”

A major source of stigma and rejection for methadone patients comes from abstinence oriented therapeutic communities and 12 step programs based on the Alcoholics Anonymous model. What is not widely known is that Dr. Dole was on the board of AA and was a friend of its founder Bill Wilson. Wilson had a great deal of respect for Dole’s development of methadone treatment for heroin addiction.

Wilson was not against the use of effective medications such as methadone to treat people with addiction. He realized that many alcoholics did not respond to AA, dropped out or did not enter the program only to disintegrate or die from the disease. He asked Dole to create a methadone for alcoholism. This encouraged Dole towards the end of his career to conduct alcoholism studies in his laboratory. However, he was unable to find an analogue of alcohol which could be used as a medication ⁽¹⁹⁾.

That the founder of AA, Bill Wilson, accepted methadone as a legitimate medication is in direct contrast to the philosophy of 12 step programs based on AA concepts such as therapeutic communities, Narcotics Anonymous, and local AA groups. Methadone patients have never been allowed to fully participate in 12 step programs or until recently to enter treatment in therapeutic communities since methadone is considered a mood altering drug akin to heroin. Methadone patients, therefore, formed their own MA groups (Methadone Awareness and Methadone Anonymous).

Patients are now beginning to organize and confront the media about biased presentations of methadone treatment. Recently a film maker who did not understand methadone produced a documentary, “Methadonia.” By interviewing dysfunctional patients, some enrolled in methadone programs and some not, who were attending an abstinence-based group therapy program. It was a misguided effort. Methadone treatment was portrayed in a negative light adding to the stigmatization of patients. The title itself is stigmatizing derived from the term ‘methadonians’ which stable patients reject

as a subhuman description of themselves. This perception of the term, methadonians, by patients conforms to the observation of Goffman, the sociologist, that stigmatized individuals are regarded as “not quite human,” and subjected to bias and discrimination which reduces their chances for life advancement^(27,28).

Patients from the National Alliance of Methadone Advocates (NAMA) and the Committee of Methadone Program Administrators (COMPA) of New York State met with the producer. The representatives from NAMA were the first methadone patients he met who were not living in the streets, who were employed and socially stable. He was educated about methadone and agreed to add a 10 minute segment to the documentary by interviewing two patients: a married female lawyer with two children and a businessman who now devotes himself full time to advocacy work. A highly respected physician from a major medical school was enlisted to participate in the segment to explain methadone maintenance. Nevertheless, the damage was already done since the film was aired on nationwide television before patients were aware of it, and the segment was included in the documentary.

In the summer of 2005, NAMA posted an informal survey on its website with the following question: In Europe methadone treatment is called “Substitution Therapy.” Do you think this term is positive, negative, not good for the US, or can’t decide? Of the 389 respondents, only 26% thought the term was positive, 54% thought the term was negative, 11% thought that it was not a good term for use in the United States, and 8% could not decide. One patient indicated that when she hears the term substitution therapy all of the shame of heroin addiction returns. Gordis observed that the term substitution implies for the public and policy makers that there is little difference between heroin as used in addiction and methadone treatment⁽²⁶⁾. Several patients were angered by the term since they felt it added to their stigmatization. The Center for Substance Abuse Treatment (CSAT) in the United States has now adopted the term Medical Assisted Treatment (MAT) to describe methadone and buprenorphine treatment.

Patients and applicants may incorporate the biases of society and enter methadone with great ambivalence including mythologies about methadone (e.g., it rots the teeth and bones) and self negation thereby potentially affecting their progress and the duration of treatment⁽³⁹⁾. Education is needed if patients are to understand addiction, methadone treatment and confront the many aspects of stigma in their families, the media and the community.

Recently, NAMA and the methadone program of the Albert Einstein College of Medicine received a four year grant from CSAT to develop educational materials and new patient advocates to address addiction, treatment, stigma, the semantics of vocabulary, legal and medical issues. This is the first grant awarded to a methadone patient organization which will allow a systematic development of materials for patients and professionals to improve treatment, promote advocacy and to destroy myths and stigma by creating a scientific base of accessible knowledge for patients and others to disseminate. It is almost a throw back to the 1960s when Dole and Nyswander created the patient assistants in the original methadone clinics to educate the professional staffs

about addiction, methadone treatment and the patients.

Summary and Conclusion

Throughout his lifetime in research, Dr. Dole's insights transformed whatever topic he investigated. In a sense he planted the seeds and set the direction for further research and clinical development. However, Dr. Dole was always at the service of patients and advocacy groups such as NAMA to help resolve issues of stigma and misdirected policies that came to his attention. For him, his greatest legacy would be the elimination of stigma that is directed to methadone patients, programs, and the medication itself. He communicated with patients through letters, email, phone contacts and personal interviews. Dr. Dole always regarded methadone as a legitimate medication to normalize aberrant metabolism and thus behavior in the chronic disease of opioid addiction. Neither he nor Dr. Nyswander used the term "substitution therapy" in speech or in writing to describe methadone maintenance treatment. When one examines addiction research and the development of treatment today with all of its advances and set backs, the ideas of Dr. Dole seem to pervade those leading the good fight.

References

1. Appel P.W., Joseph H., Richman B.L. (2001): Causes and rates of death among methadone maintenance patients before and after the onset of HIV/AIDS epidemic. *Mt Sinai Journal of Medicine* 67(5&6):444-453.
2. Brecher E.M. and the Editors of Consumer Reports Magazine (1972): *Licit and Illicit Drugs*. Little Brown and Company, Boston, Mass.
3. Dole V.P. (1945): A theory of moving boundary systems formed by strong electrolytes. *J Am Chem Soc* 67:119-1126.
4. Dole V.P. (1959): Body fat. *Sci Amer*. 201:71-76.
5. Dole V.P., Nyswander M.E. (1965): A medical treatment for diacetylmorphine (heroin) addiction. *JAMA* 193:646-650.
6. Dole V.P., Nyswander M.E. (1966): Rehabilitation of heroin addicts after blockade with methadone. *NY State J Med* 66:2011-2017.
7. Dole V.P., Nyswander M.E., Kreek M.J. (1966): Narcotic Blockade. *Arch Intern Med* 118: 304-309.
8. Dole V.P., Nyswander M.E. (1967): Heroin addiction-A metabolic Disease. *Arch Intern Med* 120: 19-24
9. Dole V.P. (1970): Biochemistry of Addiction. *Ann Rev Biochem* 39:821-840.
10. Dole V.P. (1972): Detoxification of sick addicts in prison. *JAMA* 220:366-369.
11. Dole V.P. (1974) Medicine and the criminal justice system. *Ann Intern Med* 81: 687-689.
12. Dole V.P., Nyswander M.E. (1976): Methadone maintenance treatment: A ten year perspective. *JAMA* 235:2117-2119.

13. Dole V.P., Joseph H. (1978): Long-term outcomes of patients treated with methadone maintenance. *Ann NY Acad Sci* 311: 181-189.
14. Dole V.P. (1980): Addictive behavior. *Sci Amer* 243: 138-154.
15. Dole V.P., Nyswander M.E., DesJarlais D., Joseph H. (1982): Performance-based ratings of methadone maintenance programs. *N Engl J Med* 306: 169-172.
16. Dole V.P. (1988): Implications of methadone maintenance for theories of addiction. The Albert Lasker Medical Awards. *JAMA* 220: 3025-3029.
17. Dole V.P. (1989): Interview with Dr. Dole. In Courtwright D., Joseph H., DesJarlais D. *Addicts Who Survived*, The University of Tennessee Press, Knoxville, Tennessee pp 331-343.
18. Dole V.P. (1991): Interim methadone clinics: An undervalued approach. *Am J Public Health* 81:1165-1191.
19. Dole V.P. (1991): Addiction as a public health problem. *Alcohol Clin Res* 15(5): 749-752.
20. Dole V.P. (1994): Journal interview 33. Conversation with Vincent Dole. *Addiction* 89: 23-29.
21. Dole V.P. (1994): Methadone maintenance: Optimizing dosage by estimating plasma level. *J Addict Dis* 12: 1-4.
22. Finnegan L.P., Kandall S.R. (2005): Maternal and neonatal effects of alcohol and drugs. In Lowinson J.H., Ruiz P., Millman R.B., Langrod J.C. *Substance Abuse: A comprehensive textbook*, Lippincot, Williams and Wilson pp 805-839.
23. Gearing F.R., Schweitzer M.D. (1974): An epidemiological evaluation of long term methadone maintenance treatment for heroin addiction. *Am J Epidemiol* 100(2): 101-112.
24. Gilbert L., El-Bassel N., Rajah V., Foleno A., Fontdevila J., Frye V., Richman B.L. (2000): The converging epidemics of mood-altering-drug use, HIV, HCV and partner violence: A conundrum for methadone maintenance treatment. *Mt Sinai Journal of Medicine* 67(5&6): 444-451.
25. Goldstein A. (1997): Neurobiology of heroin addiction and of methadone treatment. Presentation at AATOD Methadone Conference. Available on website: <http://www.aatod.org>
26. Gordis E. (1991): From science to social policy. An uncertain road. *J Stud Alcohol* 52(2): 101-109.
27. Goffman E. (1963): *Stigma: Notes on the management of a spoiled identity*. Englewood Cliffs: New Jersey: Prentice Hall.
28. Goffman E. (1973): *The presentation of self in everyday life*. Woodstock, New York: Overlook Press.
29. Gordon N.B. (1973): The functional status of the methadone maintained person. In L.R.S. Simmons & M.B. Gold *Discrimination and the Addict*, Sage Publications, Beverly Hills, London pp.101-123.
30. Hagan H., DesJarlais D.C. (2000): HIV and HCV among injecting drug users. *Mt Sinai Journal of Medicine* 67(5&6): 423-430.

31. Hirsch J. (2004): One thing leads to another. *J Clin Invest* 114:1040-1043.
32. Joseph H., Dole V.P. (1970): Methadone Patients on Probation and Parole. *Federal Probation* June: 42-70
33. Joseph H. (1988): Opiate addiction and the criminal justice system. In *NIDA Research Monograph #86: Compulsory Treatment of Drug Abuse* pp108-125.
34. Joseph H., Stancliff S., Langrod J.(2000): Methadone maintenance treatment: A review of historical and clinical issues. *Mt Sinai J of Medicine* 67(5&6):340-346.
35. Khuri E., Millman R. (1973): Administering methadone to adolescents. In. L.R.S. Simmons & M.B. Gold *Discrimination and the Addict*, Sage Publications, Beverly Hills, London pp. 235-248.
36. Kosten T.R., George T.P. (2002): The Neurobiology of Opioid Dependence: Implications for Treatment. *Science and Practice* 1(1): 13-21.
37. Kreek M.J. (1973): Medical safety and side effects of methadone in tolerant individuals. *JAMA* 223: 665-668.
38. McLellan A.T., Arndt I., Metzger D.S. (1993): The effects of psychosocial services in substance abuse treatment. *JAMA* 269(15): 1953-1959.
39. Magura S., Rosenblum A. (2000): Leaving methadone treatment: Lessons learned, lessons forgotten, lessons ignored. *Mt Sinai J of Medicine* 67(5&6): 62-64.
40. Murphy S., Irwin J. (1992): "Living with the dirty secret": Problems of disclosure for methadone maintained clients. *Journal of Psychoactive Drugs* 24 (3): 257-264.
41. Novick D.M., Pascarelli E. F., Joseph H., Salsitz E.A., Richman B.L., DesJarlais D.C., Anderson M., Dole V.P., Nyswander M.E. (1998): Methadone maintenance patients in general medical practice. *JAMA* 259:3299-3302.
42. Novick D.M.(2001): The impact of hepatitis C virus infection on methadone maintenance treatment. *Mt Sinai Journal of Medicine* 67(5&6):437-443.
43. Nyswander M.E. (1956): *The drug addict as a patient*. Grune and Stratton, New York.
44. Nyswander M.E. (1967): The methadone treatment of heroin addiction. *Hosp Prac* 2: 27-33.
45. Rosenblum A., Magura S., Joseph H. (1991): Ambivalence toward methadone treatment among intravenous drug users. *J Psychoactive Drugs* 23(1): 21-27.
46. Salsitz E.A., Joseph H., Frank B. et al.(2000): Methadone medical maintenance: Treating chronic opioid dependence in private medical practice. *Mt Sinai Journal of Medicine* 67(5&6): 388-397.
47. Schwartz R.P., Highfield D.A., Jaffe J.H. (2006): A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry* 63: 102-09.
48. Simon E.J. (2005): Opiates:Neurobiology. In Lowinson J.H., Ruiz P., Millman R.B., Langrod J.C. *Substance Abuse: A comprehensive textbook* Lippincot, Williams and Wilson pp 164-180.

49. U.S. Conference of Mayors (2005): Hunger and Homelessness Survey 2005. U.S. Conference of Mayors Washington D.C. URL: www.usmayors.org.
50. Winick C., Nyswander M.E. (1961): Psychotherapy of successful musicians who are drug addicts. *American J of Orthopsychiatry* 31(3): 622-636.
51. Yancovitz S.R., Des Jarlais D.C., Peyser N.P. et al.(1991): A randomized trail of an interim methadone maintenance clinic. *Am J of Public Health*: 81(9): 1185-1191.

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Injecting Buprenorphine Tablets: A Manageable Risk

Marc Reisinger

Summary

Buprenorphine for the treatment of heroin addicts was launched on the French market in February 1996. Ten years on, more than 85,000 patients are undergoing this treatment and most reports are positive. However, it has been observed that a certain proportion of patients are using buprenorphine inappropriately. Instead of taking buprenorphine sublingually, as prescribed, these users crush tablets to inject them. This practice of injection also involves individuals not undergoing this treatment. The same problem of buprenorphine diversion and injection has been observed in several other countries, like England, Scotland, Ireland, New Zealand, Australia, Finland and the Czech Republic. Given the reported substantial benefits of buprenorphine for individuals and for public health generally, it is important to analyse the problem of buprenorphine injection to get a better understanding of the origins of this problem, its incidence, consequences, causes and remedies.

Key Words: Buprenorphine misuse - Incidence -
Consequences - Causes - Remedies

Buprenorphine for the treatment of heroin addicts was launched on the French market in February 1996. Ten years on, more than 85,000 patients are undergoing this treatment and most reports are positive ⁽¹⁾. However, it has been observed that a certain proportion of patients are using buprenorphine inappropriately. Instead of taking buprenorphine sublingually, as prescribed, these users crush tablets to inject them ^(9, 14, 32). This practice of injection also involves individuals not undergoing this treatment.

The same problem of buprenorphine diversion and injection has been observed

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in several other countries, like England ⁽³⁷⁾, Scotland ⁽²⁷⁾, Ireland ⁽³¹⁾, New Zealand ⁽³⁶⁾, Australia ^(20, 28), Finland ⁽³⁸⁾ and the Czech Republic ⁽³⁰⁾.

Given the reported substantial benefits of buprenorphine for individuals and for public health generally, it is important to analyse the problem of buprenorphine injection to get a better understanding of the origins of this problem, its incidence, consequences, causes and remedies.

Background

Before evaluating the problem, it is important to relativize it to the context. Most individuals who inject buprenorphine tablets were already injecting drugs. Probably few, if any, were primary buprenorphine injectors (except in situations where buprenorphine was available only in injectable form). Thus buprenorphine injectors are generally individuals who already run a variety of risks associated with intravenous injections (overdoses, infections, and so on).

It is easy to argue that the injection of illegal drugs (heroin, cocaine, and several more) is more dangerous than the injection of buprenorphine, especially in terms of mortality, because pure buprenorphine seems to carry a very low overdose risk. This seems to be confirmed by the fact that the global mortality rate among heroin addicts has fallen spectacularly since the introduction of buprenorphine for the treatment of heroin addicts in France ⁽²⁴⁾, despite the risks associated with using buprenorphine illicitly (injecting crushed tablets, plus the risk of respiratory depression when combined with alcohol and benzodiazepines).

Another point to highlight when investigating the practice of injecting buprenorphine is the variability of the incidence of the intravenous use of drugs in terms of time and space. Obviously, the practice of injecting buprenorphine becomes more common when the practice of injecting illegal drugs (rather than sniffing or smoking them) is common.

At the time when buprenorphine was introduced in France, heroin was mainly consumed intravenously, unlike in the United Kingdom and the Netherlands, where heroin was mostly smoked rather than injected ⁽⁴⁰⁾. This was probably due to the combination of a longstanding epidemic of heroin consumption in France (dating back some 20 years) and the virtual absence of any substitution treatment. For example, up to 1993 in France, only fifty patients were benefiting from methadone treatment.

Buprenorphine was therefore introduced at a time when no therapeutic assistance other than detoxification was available to the tens of thousands of people addicted to heroin. Nevertheless, the latent demand for substitution treatment was high, as the rapid success of buprenorphine revealed in 1996. Other medications, such as codeine, morphine, dextropropoxyphene and flunitrazepam, were previously widely used by heroin addicts as a 'wild' form of substitution.

The transition from intravenous heroin to sublingual buprenorphine may have proven difficult for some drug users, especially if they were being prescribed insufficient doses

of buprenorphine (see below).

Another aspect of the historical context affects the problem of buprenorphine injections in France. Before the introduction of buprenorphine for the treatment of heroin addicts (0.4 mg, 2 mg and 8 mg tablets), buprenorphine was marketed as an analgesic in two forms: sublingual tablets (0.2 mg per tablet) and injection ampoules (0.3 mg per ampoule). These injection ampoules were introduced in France in September 1987, two and a half years before sublingual tablets (which only became available in February 1990).

Contrary to what many people suppose, the treatment of heroin addicts with buprenorphine in France did not begin in 1996, but more than ten years earlier – on a smaller scale – following the chronological landmarks summarized in table 1 and described below:

Table 1. Time line of the availability of buprenorphine for the treatment of heroin addicts in Belgium and France		
Year	Country	Form
1983	Belgium	Sublingual tablets (0.2 mg)
1987	France	Intravenous ampoules (0.3 mg)
1990	France	Sublingual tablets (0.2 mg)
1996	France	Sublingual tablets (0.4 mg, 2 mg, 8 mg)

One of the first countries where the practice of substitution treatment for heroin addicts with buprenorphine began was Belgium – France’s neighbouring country – in 1983^(33,35). Several years before the introduction of buprenorphine – as an analgesic – in France, hundreds of French drug users living in Paris or the north of France travelled regularly to Belgium for buprenorphine prescriptions (in the form of sublingual tablets). Some French drug users also went to Switzerland or Spain to obtain buprenorphine (Deglon and Daulouede, personal communication). This kind of ‘medical tourism’ was not observed towards other neighbouring countries (Luxembourg, Germany, Italy), where buprenorphine was not available for the treatment of opiate users.

As soon as buprenorphine became available in France in 1987, French general practitioners in all regions began to prescribe buprenorphine as an analgesic, or as a substitution medication based on the Belgian practice reported in publications⁽³⁴⁾ and by the experience of numerous patients.

Between 1987 and 1990, buprenorphine became available in France, from office-based practices, but only in the form of injection ampoules. Sublingual buprenorphine became available from French office-based practices more than two years after injectable buprenorphine. The practice of injecting buprenorphine therefore became established in

France – as a consequence of buprenorphine being available only in injectable form – almost ten years before the introduction of high-dose buprenorphine.

Incidence

The current incidence of buprenorphine injections is not well known, as it is “il-legal” behaviour and therefore remains hidden. In Australia, a study conducted at the needle exchange programmes in Melbourne (Victoria) indicates that 33% of clients had injected buprenorphine in the last 6 months, while in the rest of Australia this percentage was much lower, at 5% ⁽²⁰⁾. The result obtained in the state of Victoria must be put into perspective by the fact that at another needle exchange programme in the same state, it was observed that while 25% of the clients had tried to inject themselves with buprenorphine, only 3.5% did so every now and then ⁽²⁸⁾.

A three-city study made in France, in which 140 patients received buprenorphine prescriptions shows that 40% of them had ever injected their buprenorphine ⁽¹⁷⁾.

Another French study by Fontaa, on almost 400 patients undergoing buprenorphine substitution treatment, reveals that 14% of patients treated with buprenorphine had injected in the previous month ⁽¹⁴⁾. This observation is similar to the results of other French studies which indicate, for example, a rate of 15% of injectors among drug users who take buprenorphine ⁽³⁹⁾, or 16% in a group of 159 women who take buprenorphine ⁽²³⁾.

The study of Fontaa shows that the percentage of people who injected buprenorphine in the previous month is identical to that in a group of 200 patients undergoing methadone treatment (14%). The two groups differ, however, in the nature of the substances injected.

This study shows that 83% of patients undergoing buprenorphine treatment who practice injections inject buprenorphine only, while 93% of the patients undergoing methadone treatment who practice injections exclusively inject heroin, cocaine and other illegal psychoactive substances. We can therefore conclude that the majority of patients undergoing buprenorphine treatment inject buprenorphine instead of heroin and cocaine, and not in addition to these substances, which – in terms of curbing the associated risks – can be considered as relative progress.

Risks

The practice of injection exposes drug users to complications that are both local and systemic: (1) the absence of asepsis during injection, leading to skin infections and infection of the surrounding soft tissue, (2) the ‘spread’ of infections to osteo-articular infections, infectious endocarditis, cerebral infection, pulmonary infection through septic pulmonary embolism, disseminated candidiasis, and (3) the risk of infectious contamination with hepatitis B, hepatitis C, hepatitis D and HIV.

Etiology

Before analysing the reasons why people inject buprenorphine, it is important to clear up a frequent misconception. It has not been established that the intravenous injection of buprenorphine produces a ‘rush’ comparable with that produced by heroin or other opiates.

Studies on analgesia ⁽⁵⁾ have shown that the speed of onset of the action of buprenorphine is apparent within 5 to 15 minutes, whether given intravenously or intramuscularly ⁽⁴⁾. When it is taken sublingually, the onset of analgesia occurs between 15 and 45 minutes ^(6, 10, 18). This difference can be explained by the difference in absorption: the bioavailability of buprenorphine is greater when injected (intravenously or intramuscularly) than when taken sublingually.

Buprenorphine, therefore, takes effect more quickly when injected. However, following the studies on analgesia, even when injected, buprenorphine does not produce a ‘rush’ of the type produced by heroin, because of the delayed onset of its effects (5 to 15 minutes). This delay is due to the fact that the effects of buprenorphine depend on the speed of its attachment to the morphine receptors, which is slow, whatever the mode of absorption.

A study on experienced opioid users confirms that the onset of effects occurred 6 to 10 minutes after intravenous administration of 12 mg of buprenorphine ⁽⁴¹⁾. This delay produces an outcome rather different from the immediate effects of intravenous heroin, which have been described as a warm and intensely pleasant sensation occurring in a few seconds.

The subjective experience of a ‘rush’ after buprenorphine injection – which seems pharmacologically impossible – is reported anecdotally (Byrne, personal communication). It might be comparable with the rush following the injection of a placebo, which has itself been reported anecdotally by some patients.

Of course, when an individual experiences withdrawal symptoms, because he is not undergoing regular buprenorphine treatment or because the doses he does receive are insufficient, the delayed onset of the effects of buprenorphine (from a minimum of 5 minutes parenterally to a maximum of 45 minutes sublingually) becomes important in the choice between intravenous or sublingual self-administration. This probably constitutes an important factor in understanding why people inject buprenorphine.

Globally, the causes of injecting buprenorphine can be analyzed as the difficulty of breaking an injection habit, the need to reduce withdrawal symptoms, depression, impulsiveness and under-dosing with buprenorphine.

The injection habit

Injection is a conditioned behaviour, reinforced by meeting other people who inject themselves ⁽⁴²⁾. This behaviour subsides progressively during treatment. Fontaa observes that the frequency of injections (regardless of the product used) falls with the time spent undergoing substitution treatment ⁽¹⁴⁾.

This tendency to decrease buprenorphine injections also seems to occur among drug users on needle exchange programmes, who are not necessarily undergoing regular treatment. A study carried out at an Australian needle exchange programme shows that 25% of clients had tried injecting buprenorphine, but only 3.5% continued to do so at least occasionally ⁽²⁸⁾. A Finnish doctor reports that 90% of his own patients have injected buprenorphine at least once, and that 7% continue to do so ⁽³⁸⁾.

This extinction of the habit of buprenorphine injection should be attributed to the fact that – except in a state of opiate withdrawal – injecting buprenorphine is not very gratifying, because it does not produce a ‘rush’ (see above), and because it is a partial agonist whose opiate effect is limited. A study of buprenorphine intravenous administration to experienced opioid users provides evidence for a ceiling on the parameters that indicate the potential for abuse in that population ⁽⁴¹⁾.

Withdrawal symptoms

The immediate reduction of withdrawal symptoms is often the objective expressed by people who inject themselves with buprenorphine. The absorption rate of buprenorphine when taken intravenously is twice as high as when taken sublingually ^(26, 29). Injecting buprenorphine can therefore be a way to compensate for an insufficient therapeutic dosage or for the absence of a regular prescription. Later, we will discuss the fact that the risks of injecting buprenorphine seem lower among patients who regularly receive adequate doses of buprenorphine, which enables them to avoid the withdrawal syndrome.

Depression, anxiety

Depression constitutes a determining factor in the use of psychoactive substances in general and in the continuance of the practice of injections in particular ⁽¹⁴⁾. Controlling depression therefore constitutes a supplementary method for reducing the risk of injection. Some authors have observed that buprenorphine seems to be more effective than methadone among depressed patients ⁽¹⁶⁾. This coincides with previous observations concerning the antidepressant properties of buprenorphine ^(2, 11, 12). Depression, a factor that leads to the injection of buprenorphine, must therefore be treated, with or without the addition of antidepressants.

Impulsiveness

Impulsiveness – careless behaviour, acting without thinking, impatience to fulfil one’s desires and uncontrolled expression of emotions – is a factor that leads to injection, in combination with or independently of depression ⁽¹⁴⁾. Impulsiveness can be curbed by some antidepressants (selective serotonin reuptake inhibitors) ⁽⁸⁾ and by prioritizing care for patients in the greatest difficulty.

Cocaine ⁽⁷⁾, alcohol and other substances produce impulsiveness. Abstinence from

those substances and from alcohol could help curb impulsiveness. Some clinical experience reports show that, in patients with primary opiate dependence and secondary cocaine use, aggressive methadone titration combined with antidepressant therapy can be helpful to motivated patients ⁽²⁵⁾. With buprenorphine treatment, a retrospective study of almost one thousand patients, observed by 200 general practitioners, showed a steep decrease in the intake of cocaine and alcohol ⁽¹⁵⁾. Another longitudinal quantitative survey carried out with 1083 patients showed that patients treated with high-dose buprenorphine for six months consumed fewer psychoactive drugs (heroin, cocaine, benzodiazepines) and had fewer associated risks ⁽²²⁾.

Under-dosing with buprenorphine

As already mentioned, inadequate doses of buprenorphine probably play a key role in the continuation of injection practices. Thus, in Fontaa's study, 48% of people who inject buprenorphine were given a dose of less than 7 mg/day, while the percentage was just 39% among those who had stopped injections ⁽¹⁴⁾. Patients' propensity to turn to several prescribers ("doctor shopping") is also lower among GPs who reported inducing treatment with 8 mg of buprenorphine per day or more ⁽¹³⁾.

An adequate dosage (8 to 16 mg/day) helps prevent withdrawal symptoms between doses of buprenorphine and facilitates the extinction of conditioned injection behaviour. By contrast, injection behaviour is reinforced by the association between injections and the relief of withdrawal symptoms. So, when there are no withdrawal symptoms between buprenorphine doses, the 'reward' from injections disappears and this behaviour tends to decrease.

If the antidepressant properties of buprenorphine are confirmed, an adjusted dosage should also enable depression, which is related to the practice of injecting ⁽²¹⁾, to be combated more effectively.

In addition to increasing the dose level, we also need to check if patients know how to take buprenorphine in a way that will optimize its rate of absorption. Buprenorphine tablets must dissolve for 5 minutes under the tongue, without the swallowing of any saliva ⁽³⁾.

If increasing the dose level of buprenorphine is ineffective, consider prescribing methadone rather than buprenorphine. However, the risk of patients injecting does not disappear during methadone treatment, because some patients inject that medication, too. One Australian study has, for example, determined that 11% of patients inject methadone syrup ⁽¹⁹⁾.

Conclusions

1. The risk of injecting buprenorphine tablets is dependent on the particular region and period ^(20, 28). When buprenorphine was launched in France for the treatment of heroin addicts, various conditions were already in place which encouraged the

practice of injecting buprenorphine tablets. Thus the risk could be lower in other regions.

2. Injecting buprenorphine does not constitute an 'additional' risk, in the sense that: Most of the individuals concerned were, in any case, injectors from the outset. Buprenorphine injections may substitute for injections of substances that are potentially more dangerous (illicit heroin, cocaine, amphetamines, and so on). The risks attributable to injection(s) are the same as those for patients undergoing methadone treatment.
3. Injecting buprenorphine is a 'manageable' risk, because there are ways in which this risk can be reduced (adjustment of the dose level, treatment for depression and impulsiveness, reduction of alcohol and cocaine consumption). Moreover, there is a tendency among patients to reduce the frequency of injections during the course of treatment.
4. In addition, the risks of injecting buprenorphine could be reduced by improving the medication itself. Tablets combining buprenorphine with naloxone (a morphinic antagonist) – are already available in several countries.

As a general conclusion, given the reported substantial benefits of buprenorphine, it seems preferable to manage the risks of buprenorphine injection rather than restrict this treatment, because restriction would entail greater risks to the health of individuals, as well as to public health.

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References

1. AURIACOMBE M., FATSEAS M., DUBERNET J., DAULOUÈDE J. P., TIGNOL J. (2004): French field experience with buprenorphine. *Am J Addict.* 13 S17-S28.
2. BODKIN J. A., ZORNBERG G. L., LUKAS S. E., COLE J. O. (1995): Buprenorphine treatment of refractory depression. . *J Clin Psychopharmacol* 15:(1) 49-57.
3. BRUNELLE E., ROBINET S. (2004): Buprenorphine haut dosage. Evaluation d'une intervention éducative sur le temps de prise sublingual. *Alcoologie et Addictologie.* 26:(1) 121-136.
4. BUDD K. (1981): High dose buprenorphine for postoperative analgesia. *Anaesthesia.* 36:(9) 900-903.
5. BUDD K. (1983): Buprenorphine. *Clin Anaesthesiol.* I:(1) 139-179.
6. BULLINGHAM R. E., MCQUAY H. J., DWYER D., ALLEN M. C., MOORE R. A. (1981): Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. *Br J Clin Pharmacol.* 12:(2) 117-122.
7. CASCELLA N. G., NAGOSHI C. T., MUNTANER C., WALTER D., HAERTZEN C. A., KUMOR K. M. (1994): Impulsiveness and subjective effects of intravenous cocaine administration in the laboratory. *J Subst Abuse.* 6:(4) 355-366.

8. COCCARO E. F. (1989): Central serotonin and impulsive aggression. *Br J Psychiatry*. 155 52-62.
9. COURTY P. (2003): Buprénorphine haut dosage et pratique d'injection. *Ann Med Interne*. 154:(Hors serie 1) 1S35-31S45.
10. EDGE W. G., COOPER G. M., MORGAN M. (1979): Analgesic effects of sublingual buprenorphine. *Anaesthesia*. 34:(5) 463-467.
11. EMRICH H. M., GUNTHER R., DOSE M. (1983): Current perspectives in the pharmacopsychiatry of depression and mania. *Neuropharmacology*. 22:(3) 385-388.
12. EMRICH H. M., VOGT P., HERZ A. (1982): Possible antidepressive effects of opioids: action of buprenorphine. In: VEREBEY K. (Ed.) *Opioids in mental illness: theories, clinical observations and treatment possibilities Ann NY Acad Vol 398*. The New York Academy of Sciences, New York, N.Y. pp.
13. FERONI I., PERETTI-WATEL P., PARAPONARIS A., MASUT A., RONFLE E., MABRIEZ J. C., OBADIA Y. (2005): French general practitioners' attitudes and prescription patterns toward buprenorphine maintenance treatment: does doctor shopping reflect buprenorphine misuse? *J Addict Dis*. 24:(3) 7-22.
14. FONTAA V., BRONNER C. (2001): Persistance de la pratique d'injection chez des patients substitués par méthadone ou buprénorphine haut dosage. *Ann Med Interne*. 152:(7S) 2S59-52S69.
15. GAGNON A., ROBINET S., BRONNER C., PARQUET P. J. (2000): Substitution des opiaces: places et role des reseaux. Analyse d'une enquete aupres des medecins generalistes. *Rev Prat Medecins Generalistes*. 509 1627-1635.
16. GERRA G., BORELLA F., ZAIMOVIC A., MOI G., BUSSANDRI M., BUBICI C., BERTACCA S. (2004): Buprenorphine versus methadone for opioid dependence: predictor variables for treatment outcome. *Drug Alcohol Depend*. 75:(1) 37-45.
17. GUICHARD A., LERT F., CALDERON C., GAIGI H., MAGUET O., SOLETTI J., BRODEUR J. M., RICHARD L., BENIGERI M., ZUNZUNEGUI M. V. (2003): Illicit drug use and injection practices among drug users on methadone and buprenorphine maintenance treatment in France. *Addiction*. 98:(11) 1585-1597.
18. HAYES M. J., FRASER A. R., HAMPTON J. R. (1979): Randomised trial comparing buprenorphine and diamorphine for chest pain in suspected myocardial infarction. *Br Med J*. 2:(6185) 300-302.
19. HUMENIUK R., ALI R., MCGREGOR C., DARKE S. (2003): Prevalence and correlates of intravenous methadone syrup administration in Adelaide, Australia. *Addiction*. 98:(4) 413-418.
20. JENKINSON R. A., CLARK N. C., FRY C. L., DOBBIN M. (2005): Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? *Addiction*. 100:(2) 197-205.
21. LATKIN C. A., MANDELL W. (1993): Depression as an antecedent of frequency of intravenous drug use in an urban, nontreatment sample. *Int J Addict*. 28:(14) 1601-1612.

22. LAVIGNASSE P., LOWENSTEIN W., BATEL P. (2002): Economic and social effects of high-dose buprenorphine substitution therapy. Six-month results. *Ann Med Interne*. 153:(S3) 1S20-21S26.
23. LEJEUNE C., SIMMAT-DURAND L., GOURARIER L., AUBISSON S. (in press): Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenorphine substitution. *Drug Alcohol Depend*.
24. LEPERE B., GOURARIER L., SANCHEZ M. (2001): Diminution du nombre de surdoses mortelles a l'heroine en France depuis 1994. *Ann Med Interne*. 152:(S3) 5-12.
25. MAXWELL S., SHINDERMAN M. S. (1999): Optimizing Response to Methadone Maintenance Treatment: Use of Higher-Dose Methadone. *J Psychoactive Drugs*. 31:(2) 95-102.
26. MENDELSON J., UPTON R. A., EVERHART E. T., JACOB P., 3RD, JONES R. T. (1997): Bioavailability of sublingual buprenorphine. *J Clin Pharmacol*. 37:(1) 31-37.
27. MORRISON V. (1989): Psychoactive substance use and related behaviours of 135 regular illicit drug users in Scotland. *Drug Alcohol Depend*. 23:(2) 95-101.
28. MUHLEISEN P., SPENCE J., NIELSEN S. (2003): Crushing buprenorphine tablets. *Drug Alcohol Rev*. 22:(4) 471-472.
29. NATH R. P., UPTON R. A., EVERHART E. T., CHEUNG P., SHWONEK P., JONES R. T., MENDELSON J. E. (1999): Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J Clin Pharmacol*. 39:(6) 619-623.
30. NESPOR K., CSEMY L. (2005): Buprenorphine abuse has become a problem in Czech Republic. *Psychiatrie*. 9:(4) 333-334.
31. O'CONNOR J. J., MOLONEY E., TRAVERS R., CAMPBELL A. (1988): Buprenorphine abuse among opiate addicts. *Br J Addict*. 83:(9) 1085-1087.
32. OBADIA Y., PERRIN V., FERONI I., VLAHOV D., MOATTI J. P. (2001): Injecting misuse of buprenorphine among French drug users. *Addiction*. 96 267-272.
33. REISINGER M. (1985): Buprenorphine as new treatment for heroin dependence. *Drug Alcohol Depend*. 16:(3) 257-262.
34. REISINGER M. (1985): Essai de traitement des heroimanes par la buprenorphine. *Psychotropes*. 2:(1) 76-82.
35. REISINGER M. (1988): Treatment of heroin addicts with buprenorphine: evaluation over a three-year period. *NIDA Res Monogr*. 81 340.
36. ROBINSON G. M., DUKES P. D., ROBINSON B. J., COOKE R. R., MAHONEY G. N. (1993): The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug Alcohol Depend*. 33:(1) 81-86.
37. STRANG J. (1985): Abuse of buprenorphine. *Lancet*. 2:(8457) 725.
38. TACKE U. (2002): Abuse of buprenorphine by intravenous injection--the french connection. *Addiction*. 97:(10) 1355.
39. THIRION X., BARRAU K., MICALLEF J., HARAMBURU F., LOWENSTEIN W., SANMARCO J. L. (2000): Traitements de substitution de la dependance aux opiaces dans les centres de soins; le programme OPPIDUM des centres d'evaluation e d'information

- sur la pharmacodépendance. *Ann Med Interne*. 151:(SA) A10-A17.
40. TOUFIK A. (1999): Distribution of intravenous injection in France. *Tendance*. 5.
41. UMBRIGHT A., HUESTIS M. A., CONE E. J., PRESTON K. L. (2004): Effects of high-dose intravenous buprenorphine in experienced opioid abusers. *J Clin Psychopharmacol*. 24:(5) 479-487.
42. WIKLER A. (1980): A theory of opioid dependence. In: LETTIERI D. J., SAYERS M., PEARSON H. W. (Eds.): *Theories on drug abuse Selected contemporary perspectives Nida Research Monograph 30*. N.I.D.A., Rockville. pp. 174-178.

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QTc Prolongation in Methadone Maintenance: Fact and Fiction

John Schmittner ¹ and Mori J. Krantz ^{2,3}

Summary

Methadone is an effective treatment for opioid dependence- and, until recently, was viewed as a medication without cardiac properties. High-dose therapy has been linked to prolongation of the rate-corrected QT interval (QTc) and torsade de pointes (TdP), a form of ventricular tachycardia requiring QTc prolongation. To date, only one prospective study has demonstrated a modest increase in QTc with methadone. Arrhythmia risk is related to the magnitude of the QTc change from baseline. Clinicians should be aware of methadone's potential cardiovascular effects and weigh the benefit-to-risk ratio for each patient, based upon individual risk for arrhythmia.

Key Words: Methadone, QTc prolongation, Torsade de pointes

Introduction

Prolongation of the rate-corrected QT-interval (QTc) on the surface electrocardiogram (ECG) is associated with the development of a form of polymorphic ventricular tachycardia known as torsade de pointes (TdP). Although TdP is frequently self-terminating, it may lead to sudden cardiac death due to degeneration into ventricular fibrillation. TdP is rarely caused by a single pro-arrhythmic insult and usually results from a confluence of multiple factors leading to QTc prolongation. QTc prolongation

is therefore the mandatory substrate for defining TdP and is most commonly associated with drugs and electrolyte disorders, primarily hypokalemia and hypomagnesemia^{7,29,30}. Additional etiologies include congenital long-QT syndrome, subendocardial ischemia, and central nervous system disease such as intracerebral hemorrhage^{57,63}. Women have a slightly longer QTc interval than males; therefore a prolonged QTc interval is defined as > 450 ms for men and > 470 ms for women^{7,14}. Though there is disagreement over the exact risk QTc prolongation confers,^{7,14,43,52,57} it is generally accepted that measurements over 500 ms exceed a biologic threshold where there is a significant risk of developing TdP. Additionally, increases in the QTc interval > 40 ms over baseline also increase the risk of TdP^{7,14,25,43,52,53,57}. This paper reviews the current data linking the synthetic opioid, methadone, with QTc prolongation and provides a practical framework for improving cardiac safety in methadone maintenance therapy.

Methadone and QTc prolongation

Methadone and its long-acting derivative levacetylmethadol (LAAM)^{17,55} appear to prolong the QTc interval, and may predispose susceptible patients to ventricular arrhythmias specifically TdP^{16,20,32,33,34,35,37,38,47-49,58,66}. LAAM was withdrawn from both the European and US markets due to its risk of QTc prolongation and TdP^{37,55}. The likely mechanism of arrhythmia development is blockade of the human cardiac ether-a-go-go-related gene (HERG) delayed-rectifier potassium current^{28,57}. Blockade of this cardiac ion channel prolongs the terminal portion of the cardiac action potential (delayed repolarization), which manifests as QTc interval prolongation on the surface 12-lead ECG^{62,64}.

Among certain medications (e.g. sotalol), there is a clear relationship between dose and plasma levels and the magnitude of QTc interval prolongation^{29,57}. For methadone, the relationship is less clear. However, one study by Martell and colleagues showed that oral methadone results in QTc increases of 12.4 ms at 6 months, 10.7 ms at 12 months, and that QTc change from baseline to 12 months correlated with trough ($r=+0.37$, $p=0.008$) and peak ($r=+0.32$, $p=0.03$) serum methadone concentrations⁴⁸. A retrospective analysis of 17 methadone-treated patients who developed TdP also demonstrated a dose dependent relationship between methadone and the absolute QTc interval ($r=+0.51$, $p=0.03$)³³. The mean daily methadone dose in this series was 397 mg/day. These data suggest that escalating doses of methadone are likely to increase the risk of QTc interval prolongation.

Conflicting evidence

A large retrospective analysis by Maremmani and colleagues evaluated cardiac repolarization among heroin addicts receiving methadone maintenance therapy⁴⁶. Among 83 patients on long-term methadone maintenance, the authors noted that 69 of 83 individuals (83.1%) had a baseline QTc interval exceeding a population expected

value based upon age and gender. However, there was no statistically significant correlation between methadone dose and the absolute QTc interval ($r = +0.14$, $p = \text{NS}$).

With respect to a dose-dependent effect of methadone on cardiac repolarization, these data stand in contrast to the findings of Martell and colleagues⁴⁸. However, in both studies the QTc interval either increased with methadone induction or was greater than age and sex-matched controls in the majority of participants. Varying methodologies may explain some of the discrepancy with regard to dose-related effects. Martell and colleagues examined serum levels, which may be more reflective of drug effects on cardiac repolarization. This study also correlated the change in QTc interval from baseline with dose/serum levels whereas Maremmani correlated absolute QTc interval with dose. These differences notwithstanding, both studies suggest a clear “signal” with regard to active cardiac repolarization properties of oral methadone.

Medication interactions with methadone

Methadone is metabolized by the hepatic cytochrome P-450 3A4 enzyme and in contrast to LAAM does not possess active metabolites^{51, 56}. Therefore, medications that inhibit or induce CYP3A4 may alter plasma methadone levels dramatically,^{37, 44, 56, 66} increasing a patient’s propensity for arrhythmia^{29, 37, 52, 66}. Such medication interactions are especially important for HIV patients, as many HIV drug treatments have P-450 effects^{13, 20, 41, 56}.

There are also a multitude of FDA-approved medications and herbal preparations that cause QTc prolongation^{7, 37, 68}. Reassuringly, medications associated with QTc interval prolongation far outnumber those proven to cause TdP⁶⁸. Selected medications associated with QTc prolongation are shown in Table 1. As a general rule of thumb there are a number of medication categories with the prefix “anti”, which are commonly associated with QTc prolongation: Antiarrhythmics, antihistamines, anti-infective agents, and antipsychotics/antidepressants. It is notable, however, that the majority of patients receiving such QTc-prolonging drugs manifest no adverse cardiac sequelae^{7, 43, 57, 68}. This supports our contention that the development of TdP often requires a confluence of multiple pro-arrhythmic factors rather than a single drug in isolation. Selected medications that may induce or inhibit the metabolism of methadone are depicted in Table 2.

Cardiac evaluation of methadone patients

For most heroin addicts presenting in acute opioid withdrawal, screening electrocardiography is probably unwarranted and creates a barrier to accessing care. However, a screening ECG may be indicated if other pertinent risk factors for QTc prolongation or drug-drug interactions are present. ECG screening should be considered when methadone dosages exceed 150 mg. Screening should also be considered in patients with multiple risk factors for QTc prolongation; a family history of Long QT syndrome or

Table 1. QTc interval prolonging medications	
Antiarrhythmics	Sotalol Amiodarone Disopyramide Dofetilide Procainamide Quinidine
Antihistamines	Terfenadine Astemizole
Anti-infective agents Antibiotics	Azithromycin Clarithromycin Erythromycin Pentamidine Sparfloxacin Moxifloxacin
Anti-infective agents Antiparasitics	Chloroquine Quinine
Anti-infective agents Antifungals	Itraconazole Ketoconazole
Antipsychotic/depressants	Chlorpromazine Haloperidol Thioridazine Fluoxetine Nefazadone Olanzapine
Miscellaneous agents	Ephedra Cisapride Levacetylmethadol (LAAM) Organophosphates Cocaine

early sudden cardiac death; a history of electrolyte depletion; and upon initiation of a cytochrome P450 inhibitor (Table 3).

Echocardiography is not indicated, unless a patient presents with a history consistent with structural heart disease such as congestive heart failure, or myocardial infarction. A 24-hour ambulatory Holter monitor could provide useful information, but only if the symptoms are frequent enough to be captured with brief monitoring. In cases where true syncope due to TdP is suspected, immediate hospitalization with electrocardiographic monitoring is warranted. Plasma levels of methadone may be of academic interest, but probably will not alter treatment decisions. Genetic testing for congenital long-QT syndrome is expensive and not widely available. At present, it should be performed only if a congenital disorder is suggested by the family history

Table 2. Hepatic Cythochrome P450 methadone interactions

Decreases plasma methadone concentration via hepatic P450 induction	Carbamazapine Dexamethasone Ethanol Efavirenz Griseofulvin Nevirapine Phenobarbital Phenytoin Rifampin Rifabutin
Increases plasma methadone concentration via hepatic P450 inhibition	Cimetidine Ciprofloxacin Clarithromycin Diltiazem Erythromycin Ketoconazole Amitriptyline Fluvoxamine Fluoxetine Grapefruit juice Itraconazole Ketoconazole Nifedipine Omeprazole Protease inhibitors Verapamil
Adapted with permission from Krantz et al, Treating Opioid Dependence Growing Implications for Primary Care. Table 2. Arch Internal Medicine. 2004; 164: 277-288. Copyright © 2004 American Medical Association. All Rights Reserved.	

or as part of a research initiative.

Challenges in quantifying arrhythmia risk

Identifying clinically relevant QTc prolongation remains difficult given variability of ECG machine measurements, different formulas for the “corrected” QT interval (e.g, Bazett vs. Fridericia) and difficulty in defining the actual arrhythmia risk a prolonged QTc portends for a given individual^{7, 14, 27, 29, 31, 36, 39, 52, 53, 63, 65}. Due to inaccuracy of automated ECG programs in measuring the QTc interval, manual confirmation with calipers may be required, particularly if the ST-segments are grossly abnormal or U-waves are present. The QTc interval is most often calculated using Bazett’s formula: $QTc = QT \text{ interval (in msec) divided by the square root of the preceding RR interval (in sec)}$ ^{5,43}. It is preferable to measure the QTc interval in limb leads, however, precordial interpretation is acceptable if the termination of the T-wave is better discerned⁵². Mul-

Table 3. Clinical indications for electrocardiography in patients receiving methadone

Definitely Warranted - Prior history of LQT or torsade de pointes - Known history of ventricular arrhythmia or high-grade heart block (2nd or 3d degree AV-block) - Unexplained overt syncope - Unexplained tonic-clonic seizure activity
Probably Warranted - Family history of LQT syndrome or early sudden cardiac death - Unexplained presyncopal symptoms - Anorexia nervosa - Electrolyte depletion (potassium, calcium, magnesium) - HIV infected patients on multiple antiretroviral therapies - Structural heart disease: - Congestive heart failure - Left ventricular systolic dysfunction - Coronary artery disease - Active Cocaine abuse - Methadone dosages greater than 150 mg/d - Initiation of a cytochrome P450 inhibitor - Initiation of medications associated with QTc prolongation

tip factors including heart rate, supine versus upright position, time of day, and food intake are known to alter the QTc interval^{42, 43, 54}. If there is uncertainty regarding the presence of significant QTc prolongation it may be prudent to repeat the ECG and/or have the tracing interpreted by a cardiologist.

Therapeutic options in cases of QTc prolongation: balancing safety and efficacy

Methadone is an opioid agonist with a longer duration of action than morphine, making it effective for both opioid dependence and chronic pain management^{1, 9, 10, 56}. In opioid-dependent patients, the benefits of methadone (particularly when combined with psychosocial services) include reducing illicit drug use, crime, HIV/hepatitis risk, death, and improving employment and social adjustment^{3, 4, 8, 12, 19, 21, 50}. Randomized trials have shown that higher doses of methadone are associated with decreased opioid use and improved treatment retention^{40, 59, 60} and in retrospective analyses of outcome in clinical populations^{11, 24, 45, 67}. Even temporary dose increases can lead to decreases in illicit drug use and improvement in social functioning²³.

In patients with chronic pain, methadone presents a therapeutic alternative to

other narcotics, as it is well-absorbed orally, has a long half life, and provides analgesia similar to that of morphine (via affinity to μ receptors) without detrimental euphoria^{6, 15}. Methadone appears to possess other ancillary properties that enhance analgesic efficacy. In particular, it has been demonstrated to have antagonist activity at the N-methyl-D-aspartate (NMDA) receptor in animal studies^{22, 56}. This antagonist activity may decrease both pain and development of tolerance to the analgesic effects of methadone^{18, 26, 61}.

Despite the conflicting data, the preponderance of evidence suggests that methadone modestly prolongs the QTc interval in some patients. QTc increases may occur over a wide range of doses, but as seen with most QTc-prolonging drugs, is more likely to occur at higher doses. Thus, a paradox exists: higher doses of methadone may increase risk of arrhythmia, but may also be more effective for both opioid maintenance and alleviation of chronic pain. Because the metabolism of methadone can be altered by other drugs via multiple hepatic P450 pathways, complex medication interactions may occur (Table 2). Delineating the etiology of a medication-induced QTc change may therefore present a clinical challenge.

As noted above, routine ECG screening during methadone induction is probably not indicated unless risk factors for QTc prolongation/arrhythmia are present. Clinicians faced with QTc prolongation in the setting of methadone maintenance therapy have a number of therapeutic options: 1) methadone discontinuation, 2) methadone dose-decrease, 3) removal of other offending agents, 4) correction of underlying conditions not related to drugs (e.g., electrolyte depletion), and finally 5) substitution with another approved synthetic opioid such as buprenorphine. Buprenorphine is widely utilized in France and in an uncontrolled analysis described as a potentially safer option for substitution therapy compared with methadone².

Decreasing methadone dosages or drug discontinuation has been shown to result in normalization of QTc prolongation^{16, 32, 58}. This is a viable option, but may lead to other unfavorable results: For patients with opioid dependence, undertreatment may lead to relapse to intravenous heroin use and its associated morbidity. For patients with chronic pain, undertreatment may cause unacceptable pain and loss of functional capacity. Conversely, maintaining a patient on medications or dosages of medication that pose potential cardiovascular risk is unacceptable from a safety perspective. Finally, substitution of buprenorphine has been shown to be safe and effective in a case report of an opioid-dependent patient who experienced TdP secondary to methadone therapy³². Larger studies of buprenorphine with regard to QTc interval changes are currently underway. This is necessary since buprenorphine is a synthetic opioid that also inhibits the cardiac delayed rectifier potassium ion-channel in vitro, albeit to a lesser extent than methadone and LAAM²⁸.

Regardless of the approach taken, close clinical and ECG monitoring in follow-up is required to ensure adequate patient safety. Because methadone's cardiac properties are not predictable, QTc prolongation may occur even in individuals without predisposing risk factors. Therefore, patients should be monitored for symptomatic

manifestations of arrhythmia (syncope, presyncope, palpitations) during clinical follow-up. Electrocardiography is probably indicated for patients with structural heart disease and among patients receiving QTc prolonging drugs, and when methadone doses exceed 150 mg/day (Table 3). As noted previously, any QTc interval exceeding 500 ms confers a significant risk for the development of TdP as does an increase of 40 ms from baseline.

Conclusion

Heroin addiction remains a major clinical problem worldwide. Currently, opioid substitution therapy is the most common treatment approach. Regarding cardiac safety, treatment decisions must weigh patient benefits (e.g. alleviation of pain, abstinence from illicit opioids, and decreased risk of HIV/hepatitis) versus their risk profile for arrhythmia. This may include evaluating patients for underlying cardiac disease (e.g. left ventricular dysfunction), optimizing electrolytes, and altering medication portfolios. QTc-prolonging drugs may be given safely so long as there is appropriate oversight. With regard to methadone, we believe it can be dispensed with both safety and efficacy, so long as the potential for QTc prolongation is recognized and appropriate patients are screened and evaluated promptly. The addiction treatment field should embrace this opportunity to provide more rigorous clinical oversight; it enhances patient safety while providing more credibility to our field, which is often subject to external stigmatization. This will become increasingly important given the worldwide expansion of opioid substitution therapy.

References

1. ANDERSON I.B., KEARNEY T. (2000) Use of methadone. *West J Med* 172:43-46.
2. AURIACOMBE M., FRANQUES P., TIGNOL J. (2001) Deaths attributable to methadone vs buprenorphine in France. *JAMA* 285:45.
3. BALL J., LANGE W.R., MYERS C.P., FRIEDMAN S.R. (1988) Reducing the risk of AIDS through methadone maintenance treatment. *J Health Soc Behav* 29:214-226.
4. BARTHWELL A., SENAY E., MARKS R., WHITE R. (1989) Patients successfully maintained with methadone escaped human immunodeficiency virus infectuib. *Arch Gen Psychiatry* 46:957-958.
5. BAZETT H. (1920) An analysis of the time relations of electrocardiograms. *Heart* 7:353-370.
6. BEAVER W.T., WALLENSTEIN S.L., HOUDE R.W., ROGERS A. (1977) Comparisons of analgesic effects of oral and intramuscular oxymorphone and of intramuscular oxymorphone and morphine in patients with cancer. *J Clin Pharmacol* 17:186-198.
7. BEDNAR M., HARRIGAN E., ANZIANO R., CAMM A., RUSKIN J. (2001) The QT interval.

- Prog Cardiovasc Dis 43:1-45.
8. BELL J., MATTICK R., HAY A., CHAN J., HALL W. (1997) Methadone maintenance and drug-related crime. *J Subst Abuse* 9:15-25.
 9. BLAKE A.D., BOT G., FREEMAN J.C., REISINE T. (1997) Differential opioid agonist regulation of the mouse mu opioid receptor. *J Biol Chem* 272:782-790.
 10. BRUERA E., SWEENEY C. (2002) Methadone use in cancer patients with pain: a review. *J Palliat Med* 5:127-138.
 11. CAPLEHORN J.R.M., BELL J. (1991) Methadone dosage and retention of patients in maintenance treatment. *Med J Aust* 154:195-199.
 12. CAPLEHORN J.R.M., DALTON M., CLUFF M.C., PETRENAS A.M. (1994) Retention in methadone-maintenance and heroin-addicts risk of death. *Addiction* 89:203-209.
 13. COHEN O.J., FAUCI A.S. (2002) Current strategies in the treatment of HIV infection. *Dis Mon* 48:150-184.
 14. CPMP (1997) Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products. In: European Agency for the Evaluation of Medicinal Products CPMP: Committee for Proprietary Medicinal Products (CPMP). Human Medicines Evaluation Unit, London, England.
 15. DAVIS M.P., WALSH D. (2001) Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer* 9:73-83.
 16. DE BELS D., STAROURKINE M., DEVRIENDT J. (2003) Torsades de pointes due to methadone. *Ann Intern Med* 139:E156.
 17. DEAMER R.L., WILSON D.R., CLARK D.S., PRICHARD J.G. (2001) Torsades de pointes associated with high dose levomethadyl acetate (ORLAAM (R)). *J Addict Dis* 20:7-14.
 18. EBERT B., ANDERSEN S., KROGSGAARD-LARSEN P. (1995) Ketomidone, methadone, and pethidine are noncompetitive N-methyl-d-aspartate (NMDA) antagonists in the rat cortex and spinal cord. *Neurosc Lett* 187:165-168.
 19. GERSTEIN D.R., LEWIN L.S. (1990) Treating drug problems. *NEJM* 323:844-848.
 20. GIL M., SALA M., ANGUERA I., CHAPINAL O., CERVANTES M., GUMA J.R., SEGURA F. (2003) QT prolongation and torsades de pointes in patients infected with human immunodeficiency virus and treated with methadone. *Am J of Cardio* 92:995-997.
 21. GOLDSTEIN A., HERRERA J. (1995) Heroin addicts and methadone treatment in Albuquerque: A 22-year follow-up. *Drug Alcohol Depend* 40:139-150.
 22. GORMAN A.L., ELLIOTT K.J., INTURRISI C.E. (1997) The d- and l- isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosc Lett* 223:5-8.
 23. GOSSOP M., STRANG J., CONNELL P.H. (1982) The response of outpatient opiate addicts to the provision of a temporary increase in their prescribed drugs. *Br J*

- Psychiatry 141:338-343.
24. HARTEL D.M., SCHOENBAUM E.E., SELWYN P.A., KLINE J., DAVENNY K., KLEIN R.S., FRIEDLAND G.H. (1995) Heroin use during methadone-maintenance treatment - the importance of methadone dose and cocaine use. *Am J Public Health* 85:83-88.
 25. HAVERKAMP W., BREITHARDT G., CAMM A.J., JANSE M.J., ROSEN M.R., ANTZELEVITCH C., ESCANDE D., FRANZ M., MALIK M., MOSS A., SHAH R. (2000) The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: Clinical and regulatory implications: report on a policy conference of the European Society of Cardiology. *Cardiovasc Res* 47:219-233.
 26. HE L., WHISTLER J. (2005) An opiate cocktail that reduces morphine tolerance and dependence. *Curr Biol* 15:1028-1033.
 27. HOLLANDER J., LOZANO M., FAIRWEATHER P., GOLDSTEIN E. (1994) "Abnormal Electrocardiograms in patients with cocaine-associated chest pain are due to "normal" variants. *J Emerg Med* 12:199-205.
 28. KATCHMAN A.N., MCGROARY K.A., KILBORN M.J., KORNICK C.A., MANFREDI P.L., WOOSLEY R.L., EBERT S.N. (2002) Influence of opioid agonists on cardiac human ether-a-go-go related gene K⁺ currents. *J Pharmacol Exp Ther* 303:688-694.
 29. KHAN I.A. (2002) Clinical and therapeutic aspects of congenital and acquired long QT syndrome. *Am J Med* 112:58-66.
 30. KHAN I.A. (2002) Long QT syndrome: diagnosis and management. *Am Heart J* 143:7-14.
 31. KRAHN A., NGUYEN-HO P., KLEIN G., YEE R. (2001) QT dispersion: An electrocardiographic derivative of QT prolongation. *Am Heart J* 141:111-116.
 32. KRANTZ M.J., GARCIA J.A., MEHLER P.S. (2005) Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. *Pharmacotherapy* 25:611-614.
 33. KRANTZ M.J., KUTINSKY I.B., ROBERTSON A.D., MEHLER P.S. (2003) Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. *Pharmacotherapy* 23:802-805.
 34. KRANTZ M.J., LEWKOWIEZ L., HAYS H., WOODROFFE M.A., ROBERTSON A.D., MEHLER P.S. (2002) Torsade de pointes associated with very-high-dose methadone. *Ann Intern Med* 137:501-504.
 35. KRANTZ M.J., MARTELL B.A., ARNSTEN J.H., GOUREVITCH M.N. (2003) Medications that prolong the QT interval. *JAMA* 290:1025-1025.
 36. KRANTZ M.J., MEHLER P.S. (2004) Methadone and QT prolongation: a dose-dependent effect? *Am J Cardiol* 93:952-952.
 37. KRANTZ M.J., MEHLER P.S. (2004) Treating opioid dependence - growing implications for primary care. *Arch Intern Med* 164:277-288.
 38. KRANTZ M.J., ROWAN S.B., MEHLER P.S. (2005) Cocaine-related torsade de pointes in a methadone maintenance patient. *J Addict Dis* 24:53-60.
 39. Lehmann M., Morady F. (2003) QT interval: metric for cardiac prognosis? *Am J Med* 115:732-734.

40. LING W., WESSON D.R., CHARUVASTRA C., KLETT C.J. (1996) A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Archives Gen Psychiatry* 53:401-407.
41. LUCCHINI A., BARBARO G., BARBARINI G. (2004) Methadone and QT prolongation in HIV-infected patients. *Am J Cardiol* 94:147-148.
42. LUO S., MICHLER K., JOHNSTON P., MACFARLANE P. (2004) A comparison of commonly used QT correction formulae: The effect of heart rate on the QTc of normal ECGs. *J Electrocardiol* 37:81-90.
43. MALIK M., CAMM A. (2001) Evaluation of drug-induced QT interval prolongation. *Drug Saf* 24:323-351.
44. MANZI S., SHANNON M. (2005) Drug interactions-a review. *Clin Pediatr Emer Med* 6(2).
45. MAREMMANI I., NARDINI R., ZOLESI O., CASTROGIOVANNI P. (1994) Methadone dosages and therapeutic compliance during a methadone-maintenance program. *Drug Alcohol Depend* 34:163-166.
46. MAREMMANI I., PACINI M., CESARONI C., LOVRECIC M., PERUGI G., TAGLIAMONTE A. (2005) QTc interval prolongation in patients on long-term methadone maintenance therapy. *Eur Addict Res* 11:44-49.
47. MARTELL B., ARNSTEN J.H., KRANTZ M.J., GOUREVITCH M.N. (2004) The impact of methadone induction on cardiac repolarization and conduction in opioid users. *J Gen Intern Med* 19:220-221.
48. MARTELL B.A., ARNSTEN J.H., KRANTZ M.J., GOUREVITCH M.N. (2005) Impact of methadone treatment on cardiac repolarization and conduction in opioid users. *Am J Cardiol* 95:915-918.
49. MARTELL B.A., ARNSTEN J.H., RAY B., GOUREVITCH M.N. (2003) The impact of methadone induction on cardiac conduction in opiate users. *Ann Intern Med* 139:154-155.
50. McLELLAN A.T., ARNDT I.O., METZGER D.S., WOODY G.E., OBRIEN C.P. (1993) The effects of psychosocial services in substance-abuse treatment. *JAMA* 269:1953-1959.
51. MERCADANTE S., CASUCCIO A., FULFARO F., GROFF L., BOFFI R., VILLARI P., GEBBIA V., RIPAMONTI C. (2001) Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: A prospective study. *J Clin Oncol* 19:2898-2904.
52. MOLZON J. (2002) The Clinical Evaluation of Qt/QTc Interval Prolongation and Proarrhythmic Potential for non-Antiarrhythmic Drugs. <http://www.diahome.org/Content/Events/03025.pdf>
53. MORGANROTH J. (2004) A definitive or thorough phase 1 QT ECG trial as a requirement for drug safety assessment. *J Electrocardiol* 37:25-29.
54. NELWAN S., MEIJ S., VAN DAM T., KORS J. (2001) Correction of ecg variations caused by body position changes and electrode placement during ST-T monitoring. *J Electrocardiol* 34:213-216.

55. PRODUCTS. EAFTeOM (2001) EMEA public statement to suspend the marketing authorization for Orlaam (Levacetylmethadol) in the European Union. <http://www.emea.eu.int/pdfs/human/press/plus/877601en.pdf>
56. RIPAMONTI C., BIANCHI M. (2002) The use of methadone for cancer pain. *Hematol Oncol Clin North Am* 16:543-555.
57. RODEN D. (2004) Drug-induced prolongation of the QT interval. *NEJM* 350:1013-1022.
58. SALA M., ANGUERA I., CERVANTES M. (2003) Torsades de pointes due to methadone. *Ann Intern Med* 139:W64.
59. SCHOTTENFELD R.S., PAKES J.R., OLIVETO A., ZIEDONIS D., KOSTEN T.R. (1997) Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Archives Gen Psychiatry* 54:713-720.
60. STRAIN E.C., STITZER M.L., LIEBSON I.A., BIGELOW G.E. (1993) Methadone dose and treatment outcome. *Drug Alcohol Depend* 33:105-117.
61. TRUJILLO K. (2000) Are NMDA receptors involved in opiate-induced neural and behavioral plasticity? A review of preclinical studies. *Psychopharmacology* 151:121-141.
62. VINCENT G.M. (2000) Long QT syndrome. *Cardiology Clinic* 18:309-325.
63. VINCENT M. (2003) The long-QT syndrome-bedside to bench to bedside. *NEJM* 348:1837-1838.
64. VISKIN S (1999) Long QT syndromes and torsade de pointes. *Lancet* 354:1625-1633.
65. VISKIN S., ROSOVSKI U., SANDS AJ, CHEN E. (2005) Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one. *Heart Rhythm* 2:569-574.
66. WALKER P., KLEIN K., KASZA L. (2003) High dose methadone and ventricular arrhythmias: a report of three cases. *Pain* 103:321-324.
67. WARD J., BELL J., MATTICK R.P., HALL W. (1996) Methadone maintenance therapy for opioid dependence - A guide to appropriate use. *Cns Drugs* 6:440-449.
68. WWW.TORSADES.ORG (2005) In: www.torsades.org. The University of Arizona Center for Education and Research on Therapeutics, Tucson, Arizona 85724-5018.

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Methadone: Is It Enough?

Michael Gossop

Summary

This paper looks at the applications of methadone in day-to-day clinical practice. It reviews the evidence of effectiveness, including those areas in which the outcomes of methadone treatment are less satisfactory. Although the majority of patients respond well to methadone maintenance, about one in four tends not to respond well to treatment. An important question is how to achieve a better understanding of the reasons why patients respond or fail to respond to methadone treatment. The paper considers some ways in which methadone treatments could be strengthened.

Key Words: Methadone Maintenance - Treatment goals
- Outcomes - Non-responding patients

What is the purpose of methadone treatment?

One issue which is of considerable importance to our understanding of methadone treatment programmes concerns the choice of treatment goal. Methadone is used both as a medium- or long-term replacement treatment that is intended to meet a goal of harm reduction (elimination or reduction of illegal drug use, injecting, needle sharing, criminal behaviour, etc), and also as a treatment in which abstinence from drugs is the goal.

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Detoxification with methadone treatment

For dependent opiate users, an intermediate treatment goal, and a preliminary phase of treatments which are aimed at abstinence, involves withdrawal from drugs or “detoxification”. Within US federally funded treatment programmes, more than 40 percent of those who were treated for heroin dependence during the early 1980s received treatment in a detoxification programme ⁽⁹⁾. This compared with about a quarter who were admitted to methadone maintenance programmes and about a third who were admitted to drug-free treatment during the same period. A more recent estimate suggested that 50%, or about 116,000 admissions per year in the United States were for detoxification as a primary form of treatment ⁽²²⁾.

The reasons why detoxification is popular with some users and treatment providers are easy to understand. Detoxification attracts drug misusers who believe (generally incorrectly) that this is all they need to get off drugs and remain drug-free, as well as those who want only short-term relief from their habit. Detoxification can also be a first step in a longer treatment process. Some residential programmes require drug users to be drug-free before they enter treatment, and some methadone maintenance programmes require patients to have made at least one detoxification attempt before they are eligible to receive maintenance. For service providers, detoxification alone also offers the tempting prospect of a comparatively inexpensive treatment.

Attempts to treat opiate addiction by means of detoxification alone have repeatedly been shown to have high rates of relapse to addictive drug use, and most patients achieve little benefit from detoxification alone. Usually, detoxification needs to be supplemented with some sort of relapse prevention or rehabilitative programmes. Outcomes for detoxification patients are consistently worse than for those who receive methadone maintenance, therapeutic community, or outpatient drug-free treatment ⁽²⁶⁾. Outpatient detoxification offers no more therapeutic benefit than formal intake-only procedures (i.e. without treatment).

The specific goals of detoxification are limited. Detoxification is a clearly delineated phase of treatment designed to eliminate or to reduce the severity of withdrawal symptoms when the physically dependent user stops taking drugs. The criteria by which the effectiveness of detoxification should be judged are: symptom severity (is the treatment effective in the specific sense of reducing or eliminating the discomfort and distress of withdrawal?), duration of withdrawal (does the treatment reduce the overall duration of the withdrawal syndrome?), and completion rate (do a sufficient number of patients complete the programme and achieve a drug-free state at the end of the detoxification treatment?). Other relevant criteria could include: acceptability (is the user willing to seek and undergo the intervention?), and side-effects (the treatment should have no side-effects, or less severe effects than the untreated withdrawal symptoms).

One of the most widely used methods to manage withdrawal from opiates involves gradually reducing doses of methadone. Typically, methadone is substituted for heroin prior to withdrawal, and detoxification is implemented with gradually reducing doses of methadone over periods of 10-28 days ^(10,11,29).

One drawback of gradual methadone withdrawal is that it leads to a protracted residual withdrawal response, with withdrawal symptoms persisting well beyond the last methadone dose ^(11,13). Residual withdrawal symptoms may continue for as long as the original detoxification procedure. When given over a 21 day period, patients are not fully recovered until 40 days after the beginning of withdrawal ⁽¹¹⁾. The same residual withdrawal effect can be seen for 10-day reductions with symptoms persisting for about 20 days ⁽¹⁶⁾. The period around the end of the methadone reduction schedule is generally associated with the greatest levels of discomfort. This can cause clinical management problems since many patients expect the last methadone dose to coincide with the last day of withdrawal discomfort, and the continued presence and relatively high severity of the residual withdrawal symptoms may be unsettling. It is likely that the place of methadone as the first choice for detoxification medication may be challenged by newer, and possibly more effective medications such as lofexidine and buprenorphine.

Although detoxification offers various opportunities for benefit, the achievement of a drug-free state is not a risk-neutral event. Among patients who have been detoxified in inpatient or residential services, an initial lapse to opiate use often occurs very soon after leaving the programme. The first few weeks after discharge represent a critical period in terms of the individual's chances of staying off drugs. Within one week of leaving an inpatient treatment programme many patients will have used opiates on at least one occasion, and within six weeks of discharge, as many as three quarters could be expected to have used opiates ^(2,11). Although this initial lapse to opiate use does not necessarily herald a full-blown relapse to addiction, the reduction or loss of tolerance that occurs during and subsequent to detoxification puts the individual at risk of a drug overdose if opiate use is resumed. Drug overdose continues to be one of the most frequent causes of death among drug misusers, and increased rates of fatal overdose have been reported among recently detoxified opiate addicts ⁽²⁸⁾. Detoxification programmes need to be aware of the potential risks of overdose among patients who have been successfully withdrawn from opiates and who have lost their tolerance to the effects of opiates.

Despite the limited impact of detoxification programmes on the long-term addiction career of drug users, it seems likely that these will continue to be extensively used. Detoxification services have high utilization rates because they are desirable to addicts and acceptable to treatment funders. They have become an established part of treatment services. For this reason, it is necessary to consider how further supportive procedures or services can be used to improve programme completion rates and patient outcomes. Of importance here would be better integration of services, and especially closer ties between detoxification and aftercare services. Thus, while detoxification is often used as a stand-alone treatment or as a crisis management response, this service should be viewed as one component within the broader context of long-term treatment and intervention strategies.

Methadone reduction treatment (MRT)

Outpatient detoxification is often implemented over prolonged periods of time, as with methadone reduction treatment (MRT), for example, which has been widely used in the UK for many years. Typically, MRT involves prescribing methadone over relatively long periods of time, with the expectation that the dose will gradually be reduced, and that the patient will eventually be withdrawn from the drug and become abstinent from opiates.

MRT programmes are implemented in the UK and in many other countries. Such programmes share some similarities with the gradual methadone detoxification programmes⁽²⁵⁾, and with the 90-day, and 180-day detoxification programmes that have been implemented in the United States^(18,20,23). The 180-day methadone programmes were made available as an “intermediate” form of treatment between short-term 21-day detoxification and long-term maintenance. In the United States, methadone reduction is sometimes provided in what are referred to as “maintenance-to-abstinence” programmes.

Such programmes are widely used. It has been suggested that “it would be impossible to overstate the importance of this form of methadone prescribing in the UK”⁽²⁴⁾. Typically, MRT involves prescribing methadone over relatively long periods of time, with the expectation that the dose will gradually be reduced, and that the patient will eventually be withdrawn from the drug and become abstinent from opiates. Although the objectives of methadone reduction treatment are seldom stated, its practice generally involves providing the lowest dose at which the discomfort of withdrawal can be prevented.

In this type of treatment, the prescription of opiates is often seen as a “lure” to attract drug misusers into the treatment services so that “regular contact between the addict and the doctor ... gives the opportunity for a relationship to be built up which may eventually lead to the addict requesting to be taken off the drug”⁽³⁾. The role of the clinic is “not for the continuing handouts of drugs, but for treatment: the patient may not initially be motivated to accept withdrawal but motivation will gradually be built [and] dosage gradually reduced”⁽⁸⁾.

Methadone reduction is not simply a detoxification procedure. It is a less well-defined, and, in practice, a more complicated intervention. In principle, outpatient methadone reduction programmes provide a form of medium-term, abstinence-oriented substitution treatment, but the parameters of methadone reduction programmes are frequently not clearly stated, and such programmes are implemented in a variety of ways. Reduction programmes may vary in duration from a several weeks to many months, and possibly even years.

In contrast to methadone maintenance, relatively little research has been done with methadone reduction treatments. Studies of shorter-term outpatient reduction programmes have found generally poor outcomes with high drop-out rates, and few patients achieving even short-term abstinence at the end of the treatment regime^(6,13,30).

In a detailed study of methadone treatment, it was found that MRT was frequently

not delivered as intended ⁽¹⁴⁾. Whereas the majority of patients allocated to methadone maintenance received maintenance doses, only about a third of patients allocated to MRT received reducing doses. The more reducing doses that patients actually received, the worse their outcomes. Where MRT patients achieved improved outcomes, this may have occurred because of some generic treatment effect conferred by receiving a medically prescribed supply of methadone, or, alternatively, because many of them actually received some form of maintenance. Where MRT was delivered as intended, it was associated with poor outcomes.

Studies of methadone reduction treatments have raised serious questions about their effectiveness. Patients who receive MRT have poorer outcomes than those who receive stable dosing and faster dose reduction is associated with poorer outcomes than slower reduction ^(14,23,25). A major problem for MRT is that it represents an uneasy compromise between maintenance and detoxification: in many cases, it fails to achieve the benefits of either form of treatment.

Methadone maintenance treatment (MMT)

First – the good news

The pragmatic rationale for methadone maintenance is that it enables opiate addicts to be assessed and supported in tackling a range of behavioural, social and health problems, and that the evidence from many studies suggests that it can be effective in this respect ^(20,31).

Marked and statistically significant reductions in frequency of use of illicit opiates and benzodiazepines were found among methadone patients after admission to treatment in the National Treatment Outcome Research Study (NTORS)^a. Frequency of heroin use was more than halved after one year and remained at this level throughout the full follow-up period. Illicit methadone use was reduced after one year and remained low at 5 year follow-up (where it was at 20% of intake levels). Improvements were also found in the use of non-prescribed benzodiazepines. The greatest reduction in use occurred during the first year. At 5 year follow-up, benzodiazepine use had dropped to less than a quarter of levels of use at intake.

With regard to the risks associated with injecting drugs, the results are also encouraging. The percentage of methadone patients who were injecting drugs fell from 61% at intake to 37% after 5 years. The rate for sharing injecting equipment fell from 15% at intake to 5% at 5 years. Both for injecting and for sharing, the greatest reductions were found after 1 year.

The reductions in crime are among the more striking findings from NTORS. One year after starting treatment, there were substantial reductions in the numbers of crimes, and these reductions were maintained through to 5 years. Reductions were found both

^a The National Treatment Outcome Research Study (NTORS) was commissioned by a UK Government Task Force to investigate the outcomes over a 5 year period of people treated for drug dependence problems in national treatment agencies. Much of the data presented in this paper is taken from NTORS.

for acquisitive crimes and for drug selling crimes. The number of acquisitive crimes at 1 year fell to less than a third (28%) of intake levels, and this type of crime remained low throughout the follow-up period. At 5 years, levels of acquisitive crime were at 23% of intake levels, significantly lower than at intake. Drug selling crimes were also lower during the full follow-up period than at intake. For drug selling, at 1 year the number of offences fell to 13% of intake levels and at 5 year follow-up, drug selling was at 17% of intake levels.

The high levels of criminality that are associated with opiate addiction represent a formidable social and economic problem. The NTORS results point to the role that treatment interventions can play in helping to tackle crime among drug misusers. The reductions in crime among patients treated with methadone maintenance represent improvements which are of practical importance. They provide substantial and immediate benefits to society through the reduced economic costs of crime, and they provide equally important if less tangible benefits through the reduced levels of distress caused to victims.

Now – the not so good news

Alcohol is an important if often neglected component within the multiple substance use problems of drug misusers in treatment services. Heavy drinking and alcohol problems are often reported among patients in drug treatment services, and some drug misuse treatment programmes pay insufficient attention to the drinking problems of their patients. Heavy drinking can be a serious threat to the health of drug misusers because of the increased risk of overdose when alcohol and sedative drugs are used together ⁽¹⁵⁾. Heavy drinking can also increase the risk of health problems because of the high rates of chronic infection with hepatitis B and C among drug injectors. Indeed, heavy drinking among patients with liver disease leads to a greatly increased risk of mortality.

In contrast to the generally satisfactory outcomes that were achieved in terms of reduced illicit drug use at follow-up, the results with regard to alcohol use were poor. There was no reduction in the numbers of patients who were drinking heavily. At one year, about a quarter of the sample were drinking above recommended limits. Almost one in five of the drinkers was drinking more than 15 units (equivalent to about half a bottle of spirits) on a typical drinking day. Even among the patients who reduced or ceased to use illicit drugs, there was often no reduction in rates of heavy drinking. The findings suggest that the drinking behaviour of the methadone patients in our sample was largely independent of illicit drug use outcomes.

Where reductions in drinking were found within the NTORS cohort, this was often a reduction from extremely heavy drinking to heavy drinking rather than to non-problematic levels ⁽¹²⁾. The heavy drinking of many patients in the methadone treatment services is a problem area that has not received the attention it deserves, and the poor drinking outcomes of many patients represents an area of weakness which deserves to be given priority as an issue to be addressed by the existing methadone treatment services.

Methadone treatment may also not lead to improved crack cocaine outcomes.

Results from NTORS appear to show no change in rates of use for crack cocaine at 5 years. However, these overall figures disguise different patterns of crack use among those who were using crack and those who were not using crack during the period prior to intake. Among those who were using crack at intake, levels of use were more than halved at all follow-up points. In contrast, among those who were not using crack at intake, there was a gradual increase in the use of this drug. For this reason, the results regarding use of crack cocaine should be interpreted not as indicating a tendency to relapse to pre-admission patterns among those who were already using this drug at intake, but as being largely driven by the initiation of crack use among those who were not using crack at intake.

Non-responding patients

Although overall improvements in many problem areas have been found among patients receiving methadone treatment, most studies report overall or aggregated results. It is known that some patients demonstrate greater benefit than others. The US Institute of Medicine report ⁽⁹⁾ noted that a significant proportion of patients treated in methadone programmes will not respond well to treatment, and estimated this proportion at about one in four. An important research question, therefore, is how to achieve a more precise differentiation of the ways in which patients respond to methadone treatment.

The patterns of drug use among the NTORS patients, as among most problem drug takers typically involve a range of different substances. Whilst looking at improvement in drug use one drug at a time is a useful exercise, a deeper examination of outcomes must consider changes within the broader drug-use profile. The NTORS results, which are based upon changes in the frequency of use of illicit opiates, stimulants and benzodiazepines, show considerable variation in treatment outcome based upon a broader picture of problems prior to intake and the extent of change at follow-up.

More than half of the methadone patients (59%) showed reductions in illicit drug use after treatment. This result is consistent with, and adds to previous findings which have reported aggregated improvement scores ^(1,17). The patients who showed improvements in illicit drug problems after treatment also showed reductions both in their use of drugs by injection and in their sharing of injecting equipment. Such findings confirm that many patients achieve substantial and wide-ranging improvements in their illicit drug use behaviours.

However, there were also those patients (almost a quarter of the sample) who failed to show improvement at follow-up on virtually all outcome measures. In some respects, it is encouraging that only a minority of patients showed achieved such poor outcomes. On the other hand the failure of these patients to improve on a range of different outcome measures despite their access to, and often extensive input from the methadone treatment services, is a matter for concern. The finding that these patients were least likely to have remained in their index treatment at one year may be reflected in their poor outcomes.

There were improvements in areas other than those involving substance use behaviours. There was an overall improvement in the physical and psychological health

problems of the sample at follow-up. Again this improvement was not found for all patients. Physical and psychological health symptoms were reduced among patients in the Improved Response groups. The patients in the Poor Response group showed no improvement in psychological health symptoms.

Patient responses may be related to the variation in treatment procedures. An important clinical question, therefore, is how to achieve a more precise understanding of the ways in which patients respond to different procedures and interventions provided in methadone treatment.

Strengthening methadone treatment

No single, uniform treatment response can be expected to be appropriate to the needs of all drug dependent patients. This is not a viable objective. Different patients are likely to require different treatment packages. Patients with serious psychological or psychiatric problems will require different treatment input to those without such problems. The need for vocational and rehabilitative counselling will be different in a programme where most of the patients are already employed at admission to that in a programme where few patients are employed. Similarly, programmes in which the patient group includes a large proportion of mothers with young children or pregnant women should provide different treatment components to meet the special needs of these individuals.

After decades of clinical experience and research with methadone as a treatment for opiate dependence, the question of appropriate dosing remains controversial. Clinics vary greatly in the average dose of methadone prescribed, with some clinics prescribing low-doses and others using high doses.

Comprehensive reviews of the research literature have been conducted on the relationship between methadone dose and treatment outcome^(4, 31). These reviews concluded that treatment outcomes are improved when doses of 50 mg or more are used, when compared to lower doses. They also concluded that there was no evidence to suggest that routine dosing at levels in excess of 100 mg per day resulted in any benefit for the majority of patients, though relatively few studies of high dose treatment have been carried out. Ward et al.⁽³¹⁾ suggested that the evidence from both randomised controlled trials and from observational studies showed better outcomes for patients in programmes where the majority of patients are maintained in the range of 50-100 mg per day. However, it is possible that some patients may be successfully maintained on lower doses, especially if they are more highly motivated to change and more psychologically stable.

In a randomised double-blind trial of moderate- versus high-dose methadone⁽²⁷⁾, it was found that patients receiving doses of between 80-100 mg showed greater reductions in illicit heroin use than the moderate-dose group who received doses of between 40-50 mg. Both groups showed substantial and significant reductions in illicit drug use compared to pre-treatment levels. There were no differences in treatment retention between the high-dose and moderate-dose groups.

Where clinical problems arise in establishing an effective dose level for methadone,

this may be due to individual differences in the metabolism of methadone⁽³²⁾. Therapeutic drug monitoring of methadone concentrations in the blood provides a better measure of the amount of methadone available to the opiate receptors than the ingested dose. Dole⁽⁷⁾ suggested that the correct dose of methadone for the patient is the amount that sustains the plasma concentration above a critical minimum needed for continuous opioid receptor occupancy for the complete dosing interval.

In practice, the provision of methadone treatments is rarely restricted merely to the provision of methadone pharmacotherapy. Dole and Nyswander's original treatment regimen provided comprehensive medical and rehabilitative services, and the label "methadone treatment" may be misleading because it gives undue emphasis to the pharmacological aspects of treatment. Methadone treatment is generally a combination of both pharmacological and nonpharmacological therapies. Optimal outcomes are obtained when both are provided. For the majority of patients, improved clinical outcomes are seldom achieved simply by ingesting a daily dose of methadone.

These non pharmacologic aspects of methadone treatment can include individual counselling, group therapy, couples counselling, urine testing, contingency contracting, HIV testing and counselling, primary medical care services, and psychiatric assessments and treatment of comorbid disorders. The methadone clinic may be best viewed as a site for the comprehensive treatment of patients.

Nonetheless, there is some evidence that even the provision of a methadone-only intervention may help some patients. In an "interim methadone clinic" the provision of methadone alone, without counselling or other services, was found to produce significant reductions in opiate use when compared to the patients' pretreatment levels of drug use, and also when compared to patients on a waiting list comparison group⁽³³⁾.

In an investigation of the additional effects of counselling, medical care, and psychosocial services with methadone treatment, patients were randomly assigned to one of three treatment groups⁽²¹⁾. The three conditions were: minimum methadone services (MMS) - methadone alone (a minimum of 60 mg/day) with no other services; standard methadone services (SMS) - the same dose of methadone plus counselling; and enhanced methadone services (EMS) - the same dose of methadone plus counselling and medical/psychiatric and family therapy.

The provision of additional counselling, medical, and psychosocial services produced improvements in the efficacy of treatment compared to methadone alone. The enhanced treatment produced improvement in employment status, decreases in alcohol and other drug use and illegal activity, improved family relations, and improved psychiatric status. The enhanced group showed better outcomes than the standard treatment condition on 14 of the 21 outcome measures, with significantly better outcomes among the EMS patients in the areas of employment, alcohol use, and legal status.

Some patients who received the minimum methadone services showed improvements, but their response to treatment was generally unsatisfactory. More than two thirds of the patients in the MMS condition had to be "protectively transferred" from the trial because of problems associated with their continued use of opiates or cocaine,

or because of medical/ psychiatric emergencies.

This need for additional psychosocial treatment was emphatically stated by Dole, "Some people became overly converted. They felt, without reading our reports carefully, that all they had to do was give methadone and then there was no more problem with the addict. ...I urged that physicians should see that the problem was one of rehabilitating people with a very complicated mixture of social problems on top of a specific medical problem, and that they ought to tailor their programs to the kinds of problems they were dealing with..... The stupidity of thinking that just giving methadone will solve a complicated social problem seems to me beyond comprehension." (quoted in 5: p.338)

A concluding observation.

As a final point, it is worth stating that those involved with addiction treatment sometimes have an unfortunate tendency to be excessively partisan about their favourite treatment. The least attractive feature of this is that it is often manifested as a tendency to attack or denigrate other treatment options. This is no way to approach the serious business of providing and improving the delivery of treatment services to our patients.

Methadone maintenance has been extensively studied in different countries, with different treatment groups, and over a period of four decades. It is the most thoroughly evaluated form of treatment for drug dependence and has yielded positive results for most of those who seek it. Supporters of methadone maintenance bring discredit upon themselves and their treatment by mean-spirited attacks on other forms of treatment.

An important conclusion to be reached from a study of the treatment research literature is that no single type of treatment can be expected to be effective for everyone who has a drug addiction problem. Methadone treatment alone is not enough to meet the clinical needs of all patients. Drug users are a diverse and heterogeneous group, and these individual differences are relevant to the selection of an appropriate and effective treatment. Different individuals prefer and may benefit from different kinds of treatment. A range of promising alternatives are available, each of which may be optimal for drug misusers with different problems and needs.

References

1. Ball, J., Ross, A. (1991): *The Effectiveness of Methadone Maintenance Treatment*. Springer-Verlag, New York.
2. Chutuape, M., Silverman, K., Stitzer, M. (1999): Contingent reinforcement sustains post-detoxification abstinence from multiple drugs: a preliminary study with methadone patients. *Drug Alcohol Depend* 54: 69-81.
3. Connell, P.H. (1969): Drug dependence in Great Britain: a challenge to the

- practice of medicine. In: H. Steinberg Ed: *Scientific Basis of Drug Dependence*. Churchill-Livingstone, London. pp. 291-299.
4. Cooper, J.R., Altman, F., Brown, B. and Czechowicz, D. Eds. (1983): *Research on the Treatment of Narcotic Addiction: State of the Art*. National Institute on Drug Abuse, Rockville, MD.
 5. Courtwright D., Joseph H., Des Jarlais D. (1989): *Addicts Who Survived: An Oral History of Narcotics Use in America, 1923-1965*. University of Tennessee Press, Knoxville.
 6. Dawe, S., Griffiths, P., Gossop, M., Strang, J. (1991): Should opiate addicts be involved in controlling their own detoxification? A comparison of fixed versus negotiable schedules. *Brit J Addiction* 86: 977-982.
 7. Dole, V. (1989): Methadone treatment and the acquired immunodeficiency syndrome epidemic. *JAMA* 262: 1681-1682.
 8. Edwards, G. (1969): The British approach to the treatment of heroin addiction. *Lancet* I: 768-772.
 9. Gerstein, D., Harwood, H. Eds. (1990): *Treating Drug Problems. Vol.1*. Institute of Medicine, National Academy Press, Washington, DC.
 10. Gossop, M., Bradley, B., Phillips, G. (1987): An investigation of withdrawal symptoms shown by opiate addicts during and subsequent to a 21-day inpatient methadone detoxification procedure. *Addict Behav* 12: 1-6.
 11. Gossop, M., Bradley, B., Phillips, G., Green, L. (1989): Circumstances surrounding the initial lapse to opiate use following detoxification. *Brit J Psychiatry* 154: 354-359.
 12. Gossop, M., Browne, N., Stewart, D., Marsden, J. (2003): Alcohol use outcomes and heavy drinking at 4-5 years among a treatment sample of drug misusers. *J Subst Abuse Treat* 25: 135-143.
 13. Gossop, M., Johns, A., Green, L. (1986): Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. *BMJ* 293: 103-104.
 14. Gossop, M., Marsden, J., Stewart, D., Treacy, S. (2001): Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. *Drug Alcohol Depend* 62: 255-264.
 15. Gossop, M., Marsden, J., Stewart, D., Treacy, S. (2002): A prospective study of mortality among drug misusers during a four year period after seeking treatment. *Addiction* 97: 39-47.
 16. Gossop, M., Strang, J. (1991): A comparison of the withdrawal responses of heroin and methadone addicts during detoxification. *Brit J Psychiatry* 158: 697-699.
 17. Hubbard, R.L., Marsden, M.E., Rachal, J.V., Harwood, H.J., Cavanaugh, E.R., Ginzberg, H.M. Eds (1989): *Drug Abuse Treatment: A National Study of Effectiveness*. Chapel Hill, N.C., University of North Carolina Press.
 18. Iguchi, M.Y., Stitzer, M.L. (1991): Predictors of opiate drug abuse during a 90-

- day methadone detoxification. *Am J Drug Alcohol Abuse* 17:279-294.
19. Lipton,D.,Maranda,M.(1983)Detoxification from heroin dependency: an overview of method and effectiveness. In B.Stimmel Ed: *Evaluation of Drug Treatment Programs*. New York, Haworth. pp.31-55.
 20. Marsch, L.A. (1998): The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behaviour and criminality: a meta-analysis. *Addiction* 93: 515-532.
 21. McLellan, A.T., Arndt,I., Metzger,D., Woody,G., O'Brien,C. (1993): The effects of psychosocial services in substance abuse treatment. *JAMA* 269: 1953-1959.
 22. SAMHSA: Substance Abuse and Mental Health Services Administration. (1999): Treatment episode data set 1992-1997. US Department of Health and Human Services, Bethesda, MD.
 23. Sees,K., Delucchi,K., Masson,C., Rosen,A., Westley Clark,H., Robillard,H., Banys,P. Hall,S. (2000): Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence: a randomized controlled trial. *JAMA* 283: 1303-1310.
 24. Seivewright,N. (2000): *Community Treatment of Drug Misuse: More than Methadone*. Cambridge University Press, Cambridge.
 25. Senay, E.C., Dorus, W., Goldberg, F., Thornton, W. (1977). Withdrawal from methadone maintenance: rate of withdrawal and expectation. *Arch Gen Psychiatry* 34: 361-367.
 26. Simpson, D., Sells, S. (1990): *Opioid Addiction and Treatment*. Krieger, Malabar.
 27. Strain, E.C. (1999): Methadone dose during maintenance treatment. In E.Strain and M.Stitzer Eds: *Methadone Treatment for Opioid Dependence*. Johns Hopkins, Baltimore.
 28. Strang,J., McCambridge,J., Best,D., Beswick,T., Bearn,J., Rees,S., Gossop,M. (2003): Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow-up study. *BMJ* 326: 959-960.
 29. Strang,J., Gossop,M. (1990): Comparison of linear versus inverse exponential methadone reduction curves in the detoxification of opiate addicts. *Addict Behav* 15: 541-547.
 30. Unnithan,S., Gossop,M. and Strang,J. (1992): Factors associated with relapse among opiate addicts in an outpatient detoxification programme. *Brit J Psychiatry* 161: 654-657.
 31. Ward,J., Mattick,R., Hall,W. (1998): *Methadone Maintenance Treatment and Other Opioid Replacement Therapies*. Harwood, Australia.
 32. Wolff,K., Strang,J. (1999): Therapeutic drug monitoring for methadone: scanning the horizon. *Eur Addict Res* 5: 36-42.
 33. Yancovitz S., Des Jarlais D., Peyser N. (1991): A randomized trial of an interim methadone clinic. *Am J Pub Health* 81: 1185-1191.

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