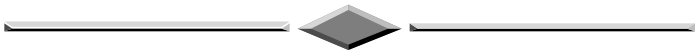
Effective Medical Treatment of Heroin Addiction

NIH Consensus Development Conference

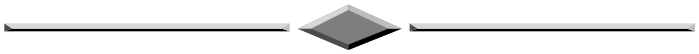
PROGRAM AND ABSTRACTS

Office of the Director
National Institutes of Health

NIH Consensus Development Conference on Effective Medical Treatment of Heroin Addiction



November 17-19, 1997
William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland



Sponsored by the National Institute on Drug Abuse and the NIH Office of Medical Applications of Research; cosponsored by the NIH Office of Research on Women's Health.

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Introduction

In the United States alone, approximately one-half million people are addicted to heroin. Estimates of heroin incidence (122,000 new users) in recent years suggest an increased incidence and an emerging pattern of drug use among the young. For many years, heroin addiction has been associated with increased criminal activity and human suffering. In the past 10 years, there has been a dramatic increase in the prevalence of human immunodeficiency virus (HIV), hepatitis C virus (HCV), and tuberculosis among intravenous heroin users. From 1991 to 1995 in major metropolitan areas, the annual number of heroin-related emergency room visits has increased from 36,000 to 76,000, and the annual number of heroin-related deaths has increased from 2,300 to 4,000. The associated morbidity and mortality further underscore the human, economic, and societal cost of heroin addiction.

Over the last 20 years, a significant body of evidence has accumulated on the neurobiology of heroin addiction and on the safety and efficacy of narcotic (methadone) maintenance treatment. Although there have been other medications (e.g., levo-alpha acetylmethadol [LAAM]) subsequently determined safe and effective in narcotic maintenance treatment, the focus of this consensus development conference will be on methadone, because methadone has been the medication used in most narcotic treatment research. Evaluation studies have consistently shown methadone treatment to be effective in reducing drug use and crime and in enhancing social productivity. More recent studies demonstrate that methadone treatment is an effective method for preventing the spread of HIV, HCV, and tuberculosis among intravenous drug users.

Most heroin users are not receiving treatment. Most recent data indicate that there are approximately 112,000 patients in narcotic maintenance treatment. Barriers exist to both access to narcotic maintenance treatment and effective treatment, despite the science on the neurobiology of heroin addiction and the evidence demonstrating the effectiveness of treatment in reducing drug use and crime and preventing the spread of HIV and HCV. An important reason for some of these barriers is that narcotic maintenance treatment remains controversial. The science has not yet overcome the stigma of addiction and public perception about narcotic maintenance treatment. Many members of the medical community and the public conceive of opiate addiction as a self-inflicted disease of the will, methadone treatment as mere narcotic substitution with relapses likely to follow treatment, drug-free treatment as the only valid rehabilitative method, and total abstinence from all drugs, including methadone, as the only valid treatment goal. Other obstacles include Federal and State government regulations limiting treatment providers and patient access and concerns about methadone diversion by patients and its consequences.

To address the most important and controversial issues surrounding narcotic maintenance treatment, the NIH has organized this 2 1/2-day conference to present the available data on opiate agonist treatment for heroin addiction. The conference will bring together national and

international experts in the fields of basic and clinical neuroscience, epidemiology, natural history, prevention and treatment of heroin addiction, and representatives from the public.

After 1 1/2 days of presentations and audience discussion, an independent, non-Federal consensus panel chaired by Dr. Lewis Judd, Mary Gilman Marston Professor, Chair of the Department of Psychiatry, University of California, San Diego School of Medicine, will weigh the scientific evidence and write a draft statement that will be presented to the audience on the third day. The consensus statement will address the following key questions:

- What is the scientific evidence to support a conceptualization of opiate addiction as a medical disorder including natural history, genetics and risk factors, and pathophysiology, and how is diagnosis established?

- What are the consequences of untreated opiate addiction to individuals, families, and society?

- What is the efficacy of current treatment modalities in the management of opiate addiction including detoxification alone, nonpharmacological/psychosocial treatment, treatment with opiate antagonists, and treatment with opiate agonists (short term and long term)?

- What is the (scientific evidence for the) most effective use of opiate agonists in the treatment of opiate addiction?

- What are the important barriers to effective use of opiate agonists in the treatment of opiate addiction in the United States, including perceptions and the adverse consequences of opiate agonist use and legal, regulatory, financial, and programmatic barriers?

- What are the future research areas and recommendations for improving opiate agonist treatment and improving access?

General Information

Conference sessions will be held in the Natcher Conference Center, National Institutes of Health, Bethesda, Maryland. Sessions will run from 8:30 a.m. to 6:15 p.m. on Monday, from 8:30 a.m. to 11:15 a.m. on Tuesday, and from 9:00 a.m. to 11:00 a.m. on Wednesday. A press conference will follow to allow the panel and chairperson to respond to questions from media representatives. The telephone number for the message center is (301) 496-9966. The fax number is (301) 480-5982.

Cafeteria

The cafeteria in the Natcher Conference Center is located one floor above the auditorium on the main floor of the building. It is open from 7:00 a.m. to 2:00 p.m., serving breakfast and lunch.

Continuing Education Credit

The NIH/FAES is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The NIH/FAES designates this continuing medical education activity for a maximum of 14 credit hours in Category I of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Sponsors

The sponsors of this conference are the NIH Office of Medical Applications of Research and the NIH National Institute on Drug Abuse. The conference is cosponsored by the NIH Office of Research on Women's Health. This is the 108th Consensus Development Conference held by the NIH since the establishment of the Consensus Development Program in 1977.

Agenda

Monday, November 17, 1997

8:30 a.m. Welcome
Alan I. Leshner, Ph.D., Director, National Institute on Drug Abuse

8:35 a.m. Charge to the Panel
John H. Ferguson, M.D., Director, Office of the Medical Applications of Research

8:45 a.m. Conference Issues
Lewis L. Judd, M.D., D.Sc., Conference and Panel Chairperson

I. Overview and Natural History

9:00 a.m. The History and Current Status of Opiate Agonist Treatment
Jerome H. Jaffe, M.D., Substance Abuse and Mental Health Services Administration

9:15 a.m. The Natural History of Opiate Addiction
M. Douglas Anglin, Ph.D., UCLA Drug Abuse Research Center

II. Molecular Neurobiology and Pathogenesis of Opiate Addiction

9:30 a.m. Genetic and Other Risk Factors in Opiate Addiction
Roy W. Pickens, Ph.D., National Institute on Drug Abuse

9:45 a.m. Neurobiological Substrates for Opiate Addiction
Eric J. Nestler, M.D., Ph.D., Yale University School of Medicine

10:00 a.m. Methadone Maintenance and Regional Cerebral Glucose Metabolism in Opiate Abusers: A Positron Emission Tomographic Study
Igor I. Galynker, M.D., Ph.D., Beth Israel Medical Center

10:15 a.m. Establishing a Diagnosis of Heroin Abuse and Addiction
George E. Woody, M.D., University of Pennsylvania

10:30 a.m. Discussion

Monday, November 17, 1997 (continued)

III. Consequences of Untreated Opiate Addiction

11:35 a.m. Narcotic Drugs and Crime: Addict Behavior While Addicted Versus Nonaddicted
David N. Nurco, D.S.W., University of Maryland School of Medicine

11:50 a.m. Lunch

12:50 p.m. Societal Costs of Heroin Addiction
Henrick J. Harwood, The Lewin Group

1:05 p.m. The Impact of Methadone Maintenance on HIV Seroconversion and Related Costs
Jeffrey Merrill, Ph.D., University of Pennsylvania

1:20 p.m. Transmission of Bloodborne Viruses Among Heroin Injectors
Donald C. Des Jarlais, Ph.D., Beth Israel Medical Center and National Development and Research Institutes

1:35 p.m. Prenatal Care and Antiretroviral Use Associated with Methadone Treatment of HIV-Infected Pregnant Women
Barbara J. Turner, M.D., Thomas Jefferson University

1:50 p.m. Deaths Among Heroin Users In and Out of Methadone Maintenance
David P. Desmond, M.S.W., University of Texas Health Science Center

2:05 p.m. Discussion

IV. Current Opiate Addiction Treatment Modalities

3:05 p.m. Detoxification With or Without Opiate Agonist Treatment
Herbert D. Kleber, M.D., Columbia University College of Physicians and Surgeons

3:20 p.m. Behavioral Therapies: A Treatment Element for Opiate Dependence
John Grabowski, Ph.D., University of Texas at Houston

3:35 p.m. Opiate Agonist Treatment, Molecular Pharmacology, and Physiology
Mary Jeanne Kreek, M.D., Rockefeller University

3:50 p.m. Discussion

Monday, November 17, 1997 (continued)

V. Predictors of Treatment Outcome

4:25 p.m. Factors Related to Retention and Posttreatment Outcomes in Methadone Treatment: Replicated Findings Across Two Eras of Treatment
Rose M. Etheridge, Ph.D., National Development and Research Institutes, Inc.

4:40 p.m. Patient Engagement and Duration of Treatment
D. Dwayne Simpson, Ph.D., Texas Christian University

4:55 p.m. Problem-Service Matching in Methadone Maintenance Treatment: Policy Suggestions From Two Prospective Studies
Thomas McLellan, Ph.D., DeltaMetrics in Association With Treatment Research Institute

5:10 p.m. Methadone Dose and Outcome
J. Thomas Payte, M.D., Drug Dependence Associates

5:25 p.m. Discussion

6:15 p.m. Adjournment Until Tuesday

Tuesday, November 18, 1997

8:30 a.m. Methadone Substitution Treatment in the United Kingdom: Outcome Among Patients Treated in Drug Clinics and General Practice Settings
Michael Gossop, Ph.D., Maudsley Hospital, London

VI. Barriers to the Effective Use and Availability of Opiate Agonist Treatment

8:45 a.m. Community, Staff, and Patient Perceptions and Attitudes
Joan E. Zweben, Ph.D., 14th Street Clinic and East Bay Community Recovery Project

9:00 a.m. Access to Narcotic Addiction Treatment and Medical Care
David C. Lewis, M.D., Brown University

9:15 a.m. Diversion of Methadone: Expanding Access While Reducing Abuse
Thomas Gitchel, U.S. Drug Enforcement Administration

9:30 a.m. Narcotic Agonist Treatment as a Benefit Under Managed Care
Dennis McCarty, Ph.D., Brandeis University

9:45 a.m. Legal, Regulatory, and Funding Barriers to Good Practice and Associated Consequences
Mark W. Parrino, M.P.A., American Methadone Treatment Association, Inc.

10:00 a.m. Discussion

11:15 a.m. Adjournment Until Wednesday

Wednesday, November 19, 1997

9:00 a.m.	Presentation of the Consensus Statement **Lewis L. Judd, M.D., D.Sc.**, Conference and Panel Chairperson
9:30 a.m.	Discussion
11:00 a.m.	Panel Meets in Executive Session
1:00 p.m.	Press Conference
2:00 p.m.	Adjournment

Panel Members

Panel Chair: Lewis L. Judd, M.D.
Mary Gilman Marston Professor
Chair, Department of Psychiatry
School of Medicine
University of California, San Diego
San Diego, California

Clifford Attkisson, Ph.D.
Dean of Graduate Studies
Associate Vice Chancellor for Student Academic Affairs
Professor of Medical Psychology
University of California, San Francisco
San Francisco, California

Wade Berrettini, M.D., Ph.D.
Professor of Psychiatry and Director
Center for Neurobiology and Behavior
Department of Psychiatry
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Nancy L. Buc, Esq.
Buc & Beardsley
Washington, DC

Benjamin S. Bunney, M.D.
Charles B.G. Murphy Professor and Chairman
Professor of Pharamcology
Department of Psychiatry
Yale University School of Medicine
New Haven, Connecticut

Roberto A. Dominguez, M.D.
Professor and Director of Adult Outpatient Clinic
Department of Psychiatry
University of Miami School of Medicine
Miami, Florida

Robert Friedel, M.D.
Herman E. Drummond Professor and Chairman
Department of Psychiatry
University of Alabama School of Medicine
Birmingham, Alabama

John S. Gustafson
Executive Director
National Association of State Alcohol and Drug Abuse Directors, Inc.
Washington, DC

Donald Hedeker, Ph.D.
Associate Professor of Biostatistics
Division of Epidemiology and Biostatistics
School of Public Health
University of Illinois, Chicago
Chicago, Illinois

Howard H. Hiatt, M.D.
Professor of Medicine
Harvard Medical School
Senior Physician
Division of General Medicine
Brigham and Women's Hospital
Boston, Massachusetts

Radman Mostaghim, M.D., Ph.D.
Greenbelt, Maryland

Robert Petersdorf, M.D.
Distinguished Professor of Medicine
University of Washington
Seattle, Washington

Speakers

M. Douglas Anglin, Ph.D.
Director
UCLA Drug Abuse Research Center
Los Angeles, California

Donald C. Des Jarlais, Ph.D.
Director of Research
Chemical Dependency Institute
Beth Israel Medical Center and National Development and Research Institutes
New York, New York

David P. Desmond, M.S.W.
Instructor, Department of Psychiatry
University of Texas Health Science Center
San Antonio, Texas

Rose M. Etheridge, Ph.D.
Senior Research Psychologist
National Development and Research Institutes, Inc. (NDRI, Inc.)
Raleigh, North Carolina

Igor I. Galynker, M.D., Ph.D.
Physician-in-Charge
Division of Psychiatric Functional Brain Imaging
Department of Psychiatry
Beth Israel Medical Center
New York, New York

G. Thomas Gitchel
Chief, Liaison and Policy Section
Office of Diversion Control
U.S. Drug Enforcement Administration
Washington, DC

Michael Gossop, Ph.D.
Head of Research
National Addiction Centre
Institute of Psychiatry
Maudsley Hospital
London, United Kingdom

John Grabowski, Ph.D.
Director, Substance Abuse Research Center
Professor, Department of Psychiatry
Health Science Center
University of Texas, Houston
Houston, Texas

Henrick J. Harwood
Senior Manager
The Lewin Group
Fairfax, Virginia

Jerome H. Jaffe, M.D.
Director, Office for Scientific Analysis and Evaluation
Center for Substance Abuse Treatment
Substance Abuse and Mental Health Services Administration
Rockville, Maryland

Herbert D. Kleber, M.D.
Professor of Psychiatry
Division of Substance Abuse
Department of Psychiatry
Columbia University College of Physicians and Surgeons
New York, New York

Mary Jeanne Kreek, M.D.
Professor and Head
Senior Physician
Laboratory of the Biology of Addictive Diseases
Rockefeller University
New York, New York

David C. Lewis, M.D.
Director
Center for Alcohol and Addiction Studies
Brown University
Providence, Rhode Island

Dennis McCarty, Ph.D.
Human Services Research Professor
Institute for Health Policy
Heller Graduate School
Brandeis University
Waltham, Massachusetts

A. Thomas McLellan, Ph.D.
Scientific Director
DeltaMetrics in Association With
Treatment Research Institute
Philadelphia, Pennsylvania

Jeffrey Merrill, Ph.D.
Director
Economic and Policy Research
Treatment Research Institute
University of Pennsylvania
Philadelphia, Pennsylvania

Eric J. Nestler, M.D., Ph.D.
Elizabeth Mears and House Jameson
Professor of Psychiatry and Pharmacology
Department of Psychiatry
Connecticut Mental Health Center
Yale University School of Medicine
New Haven, Connecticut

David N. Nurco, D.S.W.
Research Professor
Department of Psychiatry
University of Maryland School of Medicine
Baltimore, Maryland

Mark W. Parrino, M.P.A.
President
American Methadone Treatment
Association, Inc.
New York, New York

J. Thomas Payte, M.D.
Medical Director
Drug Dependence Associates
San Antonio, Texas

Roy W. Pickens, Ph.D.
Senior Scientist
Division of Intramural Research
Addiction Research Center
National Institute on Drug Abuse
National Institutes of Health
Baltimore, Maryland

D. Dwayne Simpson, Ph.D.
Director and S.B. Sells Professor
of Psychology
Institute of Behavioral Research
Texas Christian University
Fort Worth, Texas

Barbara J. Turner, M.D.
Professor of Medicine
Director of Research in Health Care
Thomas Jefferson University
The Center for Research in Medical
Education and Health Care
Philadelphia, Pennsylvania

George E. Woody, M.D.
Chief, Substance Abuse Treatment Unit
Veterans Affairs Medical Center
Clinical Professor
Department of Psychiatry
University of Pennsylvania
Philadelphia, Pennsylvania

Joan E. Zweben, Ph.D.
Executive Director
14th Street Clinic and
East Bay Community Recovery Project
Clinical Professor of Psychiatry
University of California, San Francisco
Berkeley, California

Planning Committee

Chairperson: James R. Cooper, M.D.
Associate Director for Medical Affairs
Division of Clinical and Services Research
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

Elsa A. Bray
Program Analyst
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Mona Brown
Press Officer
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

Kendall Bryant, Ph.D.
Coordinator
AIDS Behavioral Research
National Institute on Alcohol Abuse
and Alcoholism
National Institutes of Health
Rockville, Maryland

Jerry Cott, Ph.D.
Chief
Pharmacologic Treatment Research
Program
National Institute of Mental Health
National Institutes of Health
Rockville, Maryland

Donald C. Des Jarlais, Ph.D.
Director of Research
Chemical Dependency Institute
Beth Israel Medical Center and National
Development and Research Institutes
New York, New York

John H. Ferguson, M.D.
Director
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Bennett Fletcher, Ph.D.
Acting Chief
Services Research Branch
Division of Clinical and Services Research
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

Joseph Frascella, Ph.D.
Chief
Etiology and Clinical Neurobiology Branch
Division of Clinical and Services Research
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

G. Thomas Gitchel
Chief
Liaison and Policy Section
Office of Diversion Control
U.S. Drug Enforcement Agency
Washington, DC

William H. Hall
Director of Communications
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Jerome H. Jaffe, M.D.
Director
Office for Scientific Analysis
and Evaluation
Center for Substance Abuse Treatment
Substance Abuse and Mental Health
Services Administration
Rockville, Maryland

Lewis L. Judd, M.D., D.Sc.
Panel and Conference Chair
Mary Gilman Marston Professor
Chair, Department of Psychiatry
University of California, San Diego
School of Medicine
La Jolla, California

Herbert D. Kleber, M.D.
Professor of Psychiatry
Division of Substance Abuse
Department of Psychiatry
Columbia University College of
Physicians and Surgeons
New York, New York

Mitchell B. Max, M.D.
Chief, Clinical Trials Unit
Neurobiology and Anesthesiology Branch
National Institute of Dental Research
National Institutes of Health
Bethesda, Maryland

A. Thomas McLellan, Ph.D.
Scientific Director
DeltaMetrics in Association
With Treatment Research Institute
Philadelphia, Pennsylvania

Eric J. Nestler, M.D., Ph.D.
Elizabeth Mears and House Jameson
Professor of Psychiatry and Pharmacology
Department of Psychiatry
Connecticut Mental Health Center
Yale University School of Medicine
New Haven, Connecticut

Stuart Nightingale, M.D.
Associate Commissioner
for Health Affairs
U.S. Food and Drug Administration
Rockville, Maryland

Roy W. Pickens, Ph.D.
Senior Scientist
Division of Intramural Research
Addiction Research Center
National Institute on Drug Abuse
National Institutes of Health
Baltimore, Maryland

Nick Reuter, M.P.H.
Associate Director for Domestic
and International Drug Control
U.S. Food and Drug Administration
Rockville, Maryland

Charles R. Sherman, Ph.D.
Deputy Director
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Alan Trachtenberg, M.D., M.P.H.
Medical Officer
Office of Science Policy and
Communications
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

Frank Vocci, Ph.D.
Acting Director
Medications Development Division
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

Anne Willoughby, M.D., M.P.H.
Chief
Pediatric, Adolescent and
Maternal AIDS Branch
Center for Research for Mothers
and Children
National Institute of Child Health
and Human Development
National Institutes of Health
Rockville, Maryland

Stephen R. Zukin, M.D.
Director
Division of Clinical and
Services Research
National Institute on Drug Abuse
National Institutes of Health
Rockville, Maryland

Abstracts

The following are abstracts of presentations to the NIH Consensus Development Conference on Effective Medical Treatment for Heroin Addiction. They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors, who have summarized their materials and made them available in a timely fashion.

James R. Cooper, M.D.
Associate Director for Medical Affairs
Division of Clinical and Services Research
National Institute on Drug Abuse
National Institutes of Health
Rockville, MD

Elsa A. Bray
Program Analyst
Office of Medical Applications of Research
National Institutes of Health
Bethesda, MD

The History and Current Status of Opiate Agonist Treatment

Jerome H. Jaffe, M.D.

Soon after Congress passed the Harrison Act of 1914, providing opiates to opiate-dependent patients to maintain their addiction was defined as an activity that was outside the bounds of accepted medical practice and therefore tantamount to selling narcotics. Physicians who continued to prescribe opiates to addicts risked prosecution and imprisonment, and the few morphine clinics that had been established by local governments for that purpose were closed, the last in 1923. Except for occasionally providing detoxification services (usually using non-opioid drugs), most physicians ceased treating opiate addicts. The field was left to the police, self-help groups, and two Federal hospitals at Ft. Worth, Texas, and Lexington, Kentucky (Musto, 1987; Jaffe, 1975; Courtwright, 1992; Terry, Pellens, 1928).

In the early 1960s, a resurgence of heroin use and its related crime and overdose deaths led several prestigious professional organizations to call for new research efforts aimed at finding effective treatment alternatives for the largely punitive policy that was then in place (Musto, 1987; Jaffe, 1975; Courtwright, 1992). The "British System" of allowing physicians to prescribe opiates was frequently mentioned as one option worthy of consideration. Among the treatment approaches for heroin addiction initiated in the early 1960s were civil commitment, therapeutic communities, the use of opioid antagonists, such as cyclazocine, and studies of opioid agonists such as methadone (Musto, 1987; Jaffe, 1975; Courtwright, 1992; Glasscote, Sussex, Jaffe, et al., 1972).

Studies of high oral doses of methadone, begun in the early 1960s, were first published in 1965 (Dole, Nyswander, 1965). This work by Dole, Nyswander, and coworkers in New York City was initially defined as research and was very reluctantly tolerated as such by the post-Anslinger Bureau of Narcotics, later the Bureau of Narcotics and Dangerous Drugs (Courtwright, 1992). Since the work was conducted by individual physicians, and Food and Drug Administration (FDA) policies at the time did not require an Investigational New Drug (IND) application from individual physicians, no IND was submitted or sought (Rettig, Yarmolinsky, 1995). By 1968, the methadone program in New York had expanded to treat several hundred patients, and other research groups had initiated similar methadone programs in other States. Positive results in terms of decreased drug use, decreased crime, and relative safety were reported (Dole, Nyswander, 1965; Gerstein, Harwood, 1990). By 1969, there were several thousand patients in methadone maintenance treatment in the United States. All of these programs defined themselves as "research." Some operated under a blanket IND application submitted in late 1968 by Dr. Sidney Cohen, of the National Institute of Mental Health (NIMH), and approved by the FDA. Inclusion under this NIMH IND was extended only to NIMH grantees (Courtwright, 1992; Rettig, Yarmolinsky, 1995; Besteman, 1992).

The "research" status of methadone maintenance raised a number of problems: The FDA had no formal mechanism for determining whether any useful research data were being gathered,

no effective mechanism for preventing the use of INDs as a cover for prescribing methadone unaccompanied by rehabilitative services, and no rationale for determining how many such INDs should be issued. Despite the fact that increasing numbers of addicts were being treated with methadone, the data generated were judged by the FDA as an insufficient basis for approving methadone as safe and effective in the treatment of heroin addiction (Rettig, Yarmolinksy, 1995).

Widely reported in the media were stories about methadone diversion and methadone overdoses, patients selling take-home doses, the prescribing practices of a few venal physicians, patients who were not seriously dependent on opioids receiving prescriptions for methadone; and stories about children overdosing on methadone legitimately taken home by household members who were methadone patients. There was also criticism from other sources on other grounds. Some "drug-free" providers and advocates viewed methadone maintenance as merely another form of addiction; most law enforcement groups were particularly skeptical, if not overtly hostile to it; and some minority groups labeled it "genocide" (Jaffe, 1975; Courtwright, 1992).

In June of 1970, the FDA issued a proposed ruling on methadone IND applications that became final in April 1971. In addition to requiring annual reports on patient safety, the new IND regulations imposed such strict requirements on entry into treatment, duration of treatment, and dosage that they actually discouraged use, yet they were not designed to yield the kind of data needed for FDA approval of methadone as "safe and effective" for the treatment of heroin addiction. They were, rather, a response to the numerous congressional and community concerns about the issues of diversion, iatrogenic addiction to methadone, and accidental overdoses. With this ruling, FDA avoided deciding on whether methadone treatment was safe and effective, but allowed it to continue "thinly disguised as research" (Rettig, Yarmolinksy, 1995).

By this time, however, evidence for methadone's effectiveness had been well documented in randomized controlled studies and dose-response studies published in peer-reviewed scientific journals (Jaffe, 1975; Gerstein, Harwood, 1990). Still, the mass media continued to focus on the occasional methadone overdose, instances of diversion, and the behavior of a few rogue physicians who used the great demand for treatment as an opportunity to set up dispensing-for-fee operations. Although stringent, the 1971 FDA regulations did not provide entirely satisfactory ways to deal with the "script doctors" or with diversion of methadone from otherwise legitimate clinics. They were definitely of little help in meeting the problem of accommodating the increasing numbers of heroin addicts who were seeking treatment but were only put on waiting lists because the status of methadone treatment as "research" made government authorities at all levels reluctant to support its expansion.

The White House's decision, in the spring of 1971, to support expanded access to all forms of treatment for drug addiction was complicated, therefore, not only by skepticism about methadone within the Federal bureaucracy (Courtwright, 1992; Besteman, 1992; Ad Hoc Interagency Committee, 1970), but also by the fact that no effort had been made by any party to seek formal FDA approval for the use of methadone as a maintenance agent in the treatment of heroin addiction, even though thousands of patients had been benefiting from such treatment for at least 4 years.

One element of the Nixon administration's initiative on drug abuse, in June of 1971, included a decision to accept methadone as an effective treatment, to develop ways of minimizing the real and perceived problems with its use, and to expand access to methadone treatment for those who wanted it. To accomplish these ends, the Special Action Office for Drug Abuse Prevention, the first White House office dedicated to the problem of drug abuse, worked with the FDA to revise the overly stringent 1971 regulations. The goal was to produce a set of regulations that would allow for expansion of treatment but still minimize the problems that had arisen in the first few years (Jaffe, 1975; Courtwright, 1992; Rettig, Yarmolinsky, 1995; Besteman, 1992).

The new 1972 regulations, first proposed in April 1972 and issued in final form in December 1972, established the basic framework that still governs the use of methadone and similar opioid agonist drugs in the treatment of heroin addiction. The regulations were a hybrid FDA-IND that legitimized methadone maintenance treatment (i.e., acknowledged the safety and efficacy of methadone maintenance as treatment) but imposed a number of conditions on the use of the drug. In this sense, these conditions represented a departure from the usual practice, which allows licensed physicians to be guided by the drug labeling and professional judgment in determining how best to prescribe a medication once it is approved by the FDA (Rettig, Yarmolinsky, 1995).

The 1972 regulations specified, among other things, who was eligible for treatment (according to criteria of age, duration of dependence, etc.), the maximum initial dosages to be permitted, the minimum amount of counseling to be available, and the factors to be considered when deciding about the amount of methadone to be dispensed for take-home purposes. They also created a closed system for methadone, restricting its availability to approved clinics and hospital pharmacies. The purpose of this restriction was to deter those few individual physicians who, despite the 1971 regulations, had continued to prescribe methadone for substantial fees (with higher fees resulting in larger supplies of methadone).

In general, each element in the 1972 regulations (restrictions on clinical judgment, specifications about comprehensiveness of treatment, etc.) was intended to reduce or prevent problems that had been experienced under the conditions of the largely informal pre-1971 IND system; or to correct the overly restrictive aspects of the 1971 regulations; or to assure concerned parties, including Congress, that methadone would be used in combination with, not as a substitute for, rehabilitation.

For example, age limits on admission to treatment and the duration of addiction criteria were intended to restrain overly zealous practitioners from prescribing large doses of methadone to individuals who might do well with other treatments. (Subsequent followup data from Army enlistees who were dependent on heroin while in Vietnam showed that recovery rates from heroin addiction can be surprisingly high if drug exposure has been less than a year [Robins, 1993].) Regulations dealing with methadone dosage and the amount of medication provided for take-home were intended to prevent diversion (typically to other heroin addicts not enrolled in treatment) and to reduce the likelihood of nontolerant individuals (such as children) ingesting methadone and also the likelihood of such accidental ingestion being fatal. (It remains the case that the average single daily dose of methadone for a patient in treatment is likely to be lethal for a nontolerant individual.) The clinic staffing requirements of these regulations were intended to ensure the

provision of some minimal level of rehabilitation services.

In short, the 1972 regulations were designed to allow expansion of treatment while maintaining some control over quality of treatment. The author can also state, as one of the drafters of those original 1972 regulations, that the drafters described "medication units" because they looked forward to a time when clinics and individual practitioners would be linked to pharmacies and other sites that would be authorized to dispense drugs such as methadone for treatment of addiction. It was not the intention of the 1972 regulations to forever limit medication-dispensing to a few large clinics.

The 1972 FDA regulations became fully effective in March 1973 and probably could have controlled the problems associated with methadone maintenance treatment in its early years. However, throughout 1972 and early 1973, certain newspapers and some members of Congress continued to view diversion of methadone as a serious problem, and in June 1973, the Senate passed a bill entitled the Methadone Diversion Control Act of 1973. The House of Representatives, also concerned about "script doctors," passed legislation as well. The legislation adopted by the full Congress was titled the Narcotic Addict Treatment Act of 1974 (NATA). It gave the Drug Enforcement Agency (DEA) jurisdiction over the storage and security of narcotic drugs used in the treatment of narcotic addiction; required special registration annually of practitioners and treatment sites; and gave the DEA the right to inspect any site providing treatment. The NATA assigned to the Secretary of Health, Education, and Welfare the responsibility for setting the standards for the use of opioid drugs in the treatment of addiction (Rettig, Yarmolinksy, 1995; Molinari, Cooper, Czechowicz, 1994).

Since the first regulations were proposed in 1970, there have been strong criticisms of the regulatory oversight of the use of opiate agonists in treating heroin addiction (Courtwright, 1992; Dole, 1992; Dole, Nyswander, Des Jarlais, 1982). While the criticisms are often directed at the Federal regulations, it is important to recognize that many State and local jurisdictions have also seen fit to enact legislation governing the operation of opioid treatment programs. Some State regulatory requirements are far more restrictive than the Federal ones. For example, some localities do not permit take-home medication. Some critics attribute to these requirements, their paperwork burdens, and constraints on take-home dose the fact that the proportion of patients who remain in treatment for more than 1 year continues to decline. While some of these criticisms are no doubt valid, they often fail to distinguish between the burdens of regulations and the inflation-adjusted reductions in the level of support for methadone treatment programs over the past 25 years. This reduction in support has inevitably forced a shift of resources once devoted to patient services to meeting the requirements of local, State, and Federal oversight agencies. Still another reason for dissatisfaction with regulatory oversight is that it is concerned exclusively with process, and although actual treatment outcome can be measured, within the current regulatory framework, outcome is ignored (Dole, 1992; Dole, Nyswander, Des Jarlais, 1982).

Alternatives to the current regulatory framework have been sought and proposed over the years. At the Federal level, there is no legislation requiring the Secretary of HHS to issue regulations establishing "the appropriate methods of professional practice in the medical treatment of narcotic addiction." The setting of such standards could be accomplished equally

well through guidelines (Molinari, Cooper, Czechowicz, 1994). However, prior to the passage of the Narcotic Addiction Treatment Act of 1974, there was no mechanism to deal with practitioners who chose to ignore guidelines, and without regulations the problems of diversion, prescribing excessive doses, and prescribing without providing any services would have persisted.

Molinari et al. (Molinari, Cooper, Czechowicz, 1994) have pointed out that since the NATA amendments of 1984 gave DEA the authority—which it has since exercised—to withdraw registration from narcotic treatment programs or individual practitioners, not just on the basis of those criteria required for registration and licensure (which include felony convictions under laws related to controlled substance), but also for committing (in DEA's judgment) "such acts as would render registration inconsistent with public interest…," there may be no good reason to have any HHS regulations. However, if the use of opioid agonists in the treatment of opioid dependence were governed only by guidelines or professional judgment, as is the case with most other approved pharmaceuticals, protection of public welfare and the quality of treatment would be left solely to the DEA and the tort system.

In summary, the basic Federal framework regulating the use of opioid drugs in the treatment of addiction evolved in response to problems seen in the operation of the methadone treatment programs that had emerged between 1967 and 1971, to the prescribing practices of a few unethical physicians, and to the concerns of policymakers that social rehabilitation of patients would be neglected. The framework was constructed over the course of several years (1971-74) and consists of a dual oversight at the Federal level (HHS and DEA) (Rettig, Yarmolinsky, 1995; Molinari, Cooper, Czechowicz, 1994).

The FDA regulations were intended to be more flexible and responsive to changing conditions than legislation. However, the FDA regulations have been revised only twice, in 1980 and 1989 (Rettig, Yarmolinsky, 1995; Molinari, Cooper, Czechowicz, 1994). Casual observers might not have noticed any differences since the changes were relatively minor (mostly easing constraints on admissions, required frequency of urine testing, and required on-site services) and the basic HHS regulatory scheme remained intact. Curiously, despite complaints about over-regulation, when FDA and the National Institute on Drug Abuse (NIDA) issued a proposal in 1983 to convert most regulations to "guidelines," most of the respondents who were actually delivering treatment preferred the existing regulatory system (Rettig, Yarmolinsky, 1995). And when FDA and NIDA, in 1989, published a rule on the use of "interim methadone maintenance" (provision of methadone without rehabilitative services to people waiting to get into full-service programs), the reactions of treatment providers and some State authorities to the reduced services requirements of "interim maintenance" were unfavorable (Rettig, Yarmolinsky, 1995; Molinari, Cooper, Czechowicz, 1994). Many expressed fear that allowing rehabilitative services to become optional would inevitably lead local, State, and Federal governments to cut funding except for dispensing methadone. Responding to these concerns, the Public Health Service considered rescinding the proposal for "interim maintenance," but the concept was given a statutory basis in the Alcohol, Drug Abuse, and Mental Health Administration Reorganization Act of 1992 (Rettig, Yarmolinsky, 1995).

Over the past 25 years, the effectiveness of methadone treatment in reducing illicit opioid use, criminal activity of drug users, and health problems of the patients/clients in treatment has been repeatedly confirmed, not only in the United States, but also in Europe and Australia as well (Gerstein, Harwood, 1990). Being in methadone treatment also reduces the likelihood of HIV infection (Cooper, 1989). The number of patients in methadone treatment programs has grown from about 20,000 in the early 1970s to about 110,000 at present. The FDA estimates that there are about 750 programs in operation in 40 of the 50 States; some States do not permit treatment with methadone or other opioid agonists. When the opioid agonist L-alpha-acetyl-methadol (LAAM) was finally approved by the FDA for treatment of heroin addiction in 1993, 25 years after its effectiveness was first described (Jaffe, Schuster, Smith, et al., 1970), it could not be used in most States because of multiple State and local legislative and regulatory barriers. Even in those States where LAAM was approved, its utility was compromised because the FDA package insert prohibited take-home doses.

In 1992, NIDA and the Center for Substance Abuse Treatment asked the Institute of Medicine (IOM) to review Federal regulation of methadone and LAAM. The report issued by IOM concluded, among other things, that the current regulation by multiple agencies overemphasizes the dangers of diversion of methadone and unnecessarily burdens programs with paperwork, constrains clinical judgment, and in so doing both reduces access to treatment and contributes to premature discontinuation of treatment. The IOM recommended that detailed regulations be replaced by practice guidelines and sharply reduced regulations (Rettig, Yarmolinsky, 1995).

In response to these recommendations, Federal agencies (FDA, NIDA, Substance Abuse and Mental Health Services Administration, Veterans Administration, DEA, Office of National Drug Control Policy) plan to issue a proposal to radically reduce regulations. One of the remaining regulations will require programs that use opioid agonists in opioid addiction treatment to be accredited by an approved accrediting body. The accrediting body will base its decisions on a set of treatment standards that are approved by the Secretary of HHS and essentially represent the best clinical thinking of experts in the field but are subject to change as knowledge changes.

Whether this latest effort to reduce regulatory burdens and to refocus oversight more on outcomes and less on compliance with detailed regulations will be accepted by clinicians or will strike the right balance between unsupervised clinical discretion and public concern remains to be seen.

References

Ad Hoc Interagency Committee Report to the White House. Towards a national policy and program on narcotics and drug abuse: a staff report of the Ad Hoc Interagency Committee, Washington; 1970.

Besteman KJ. Federal leadership in building the national drug treatment system. In: Gerstein DR, Harwood, HJ, editors. Treating drug problems. Vol. 2. Institute of Medicine. Washington: National Academy Press; 1992.

Cooper JR. Methadone treatment and acquired immunodeficiency syndrome. JAMA 1989;252:1664-8.

Courtwright DT. A century of American narcotic policy. In: Gerstein DR, Harwood HJ, editors. Treating drug problems. Vol. 2. Institute of Medicine. Washington: National Academy Press; 1992.

Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. JAMA 1965;193:80-4.

Dole VP, Nyswander ME, Des Jarlais D. Performance-based rating of methadone maintenance programs. N Engl J Med 1982;306:169-71.

Dole VP. Hazards of process regulations: the example of methadone maintenance. JAMA 1992;267:2234-5.

Gerstein DR, Harwood HJ, editors. Treating drug problems. Vol. 1. Institute of Medicine. Washington: National Academy Press; 1990.

Glasscote R, Sussex JN, Jaffe JH, Ball J, Brill L. The treatment of drug abuse—programs, problems, prospects. Joint Information Service. Washington: American Psychiatric Association; 1972.

Jaffe JH, Schuster CR, Smith B, Blachly P. A comparison of acetylmethadol and methadone in the treatment of chronic heroin users: a pilot study. JAMA 1970;211:1834-6.

Jaffe JH. The maintenance option and the Special Action Office for Drug Abuse Prevention. Psychiatr Ann 1975;5:12-42.

Molinari SP, Cooper JR, Czechowicz DJ. Federal regulation of clinical practice in narcotic addiction treatment: purpose, status, and alternatives. J Law Med Ethics 1994;22(3)231-9.

Musto DF. The American disease. Origins of narcotic control. Expanded edition. New York: Oxford University Press; 1987.

Rettig RA, Yarmolinsky A, editors. Federal regulation of methadone treatment. Institute of Medicine. Washington: National Academy Press; 1995.

Robins LN. Vietnam veterans' rapid recovery from heroin addiction: a fluke or normal expectation. Addiction 1993;88:1041-54.

Terry CE, Pellens M. The opium problem. New York: Bureau of Social Hygiene, Inc; 1928.

The Natural History of Opiate Addiction

M. Douglas Anglin, Ph.D.

The longitudinal natural history, life cycle, or career approach to the study of narcotics addiction yields a dynamic description of sequential patterns of dependence and treatment. This perspective recognizes the context of a person's life and the events, transitions, and patterns that are meaningful to them (Hser, Anglin, Powers, 1993; Hser, Anglin, Grella, et al., 1997; Tims, Ludford, 1984; Vaillant, 1966). Numerous studies conducted during the past 30 years have demonstrated that, once initiated, drug use often escalates to more severe levels, with repeated cycles of cessation and resumption occurring over extended periods. This process has been referred to as a "drug use career," "dependence career," or "addiction career" (Frykholm, 1985; Hser, Anglin, Powers, 1993; Maddux, Desmond, 1981; McGlothlin, Anglin, Wilson, 1977; Simpson, Sells, 1982; Stephens, 1991) while cycles of treatment, abstinence, and relapse have been called the "treatment career" (Hser, Anglin, Grella, et al.; Senay, 1984). Careers may vary widely in length, patterns, and ultimate outcomes.

Previous research has identified the initiation, maintenance, relapse, and termination of drug use as important stages for opiate users (Simpson, Sells, 1990; Hser, Yamaguchi, Anglin, et al., 1995). The life cycles of opiate addicts appear to be relatively long, requiring a longitudinal research design to describe their full addiction career. The career perspective recognizes that drug treatment often extends beyond a single episode (Anglin, Hser, 1990; Nurco, Balter, Kinlock, 1994; Vaillant, 1988) because some drug users require multiple treatment episodes. Moreover, research on addiction and criminal patterns has shown that many drug users do not initially utilize treatment until they are well into a lifestyle committed to drug use and criminal activity (Stephens, 1991).

In 1961, the California Civil Addict Program (CAP) was established as a compulsory drug treatment program for narcotics-dependent criminal offenders who were committed under court order, and it consisted of an inpatient period followed by supervised community aftercare. The program was the only major publicly funded treatment available in the 1960s, although methadone became available in the 1970s.

Between 1962 and 1964, 581 male narcotic addicts admitted to the program were selected to participate in a longitudinal study of the natural history of narcotics addiction. The cohort was first interviewed in 1974-75 and again in 1985-86. The majority of the subjects were Hispanic (55.6 percent); 36.5 percent were white, and 7.9 percent were African American, and these proportions have remained fairly stable across all three followups. Their mean age when admitted to the CAP was 25.4 years, and more than 60 percent had started using narcotics before the age of 20. The initial DARC studies were evaluations of the California CAP and are described in several articles by McGlothlin, Anglin, Wilson (1975-76, 1977, 1978).

Results have shown that, once initiated, narcotic use progressed to dependence fairly rapidly. Although initiation into heroin use appeared as early as age 17, by age 22 daily use

became common. For those who were not incarcerated, the percentage engaged in daily narcotics use continued at a relatively high level to about age 30 and then decreased because of the availability of methadone maintenance. After age 32, daily use periods remained stable for the entire length of followup, to an average age of 47. Incarceration rates were highest between ages 20 and 30 and became relatively stable by age 36. Currently, we are conducting the third followup of this sample of aging addicts; it has been 33 years since their commitment to the CAP. Findings from all three followup studies will be discussed.

We have used a face-to-face natural history interview, adapted from Nurco, Bonito, Lerner, et al. (1975) and Valliant (1966), to collect data on patterns of drug use and related criminal and treatment activities year by year beginning with 1 year prior to the respondents' first use of narcotics. Because the subjects in the 33-year followup are now middle-aged (average age is 57, compared with average ages of 37 and 48 in 1975 and 1986, respectively) the instrument now also includes measures of depression and anxiety, social support, health and mental health status, HIV, and family relationships. Extensive tracking and locating procedures have been employed to ensure a high response rate. So far, almost 90 percent of the original sample can be accounted for and have been interviewed, died, refused to complete, or been unable to complete the interview because of poor health.

To date, 210 interviews have been conducted. Results to date are reported, and further analyses will have been completed by the November consensus meeting. Demographic data on 153 subjects are presented in table 1.

Almost one-half (47 percent) of the original sample of 581 have died. Death certificates were coded for underlying cause by a certified nosologist, using the ICD-9. Preliminary results are shown in figure 1.

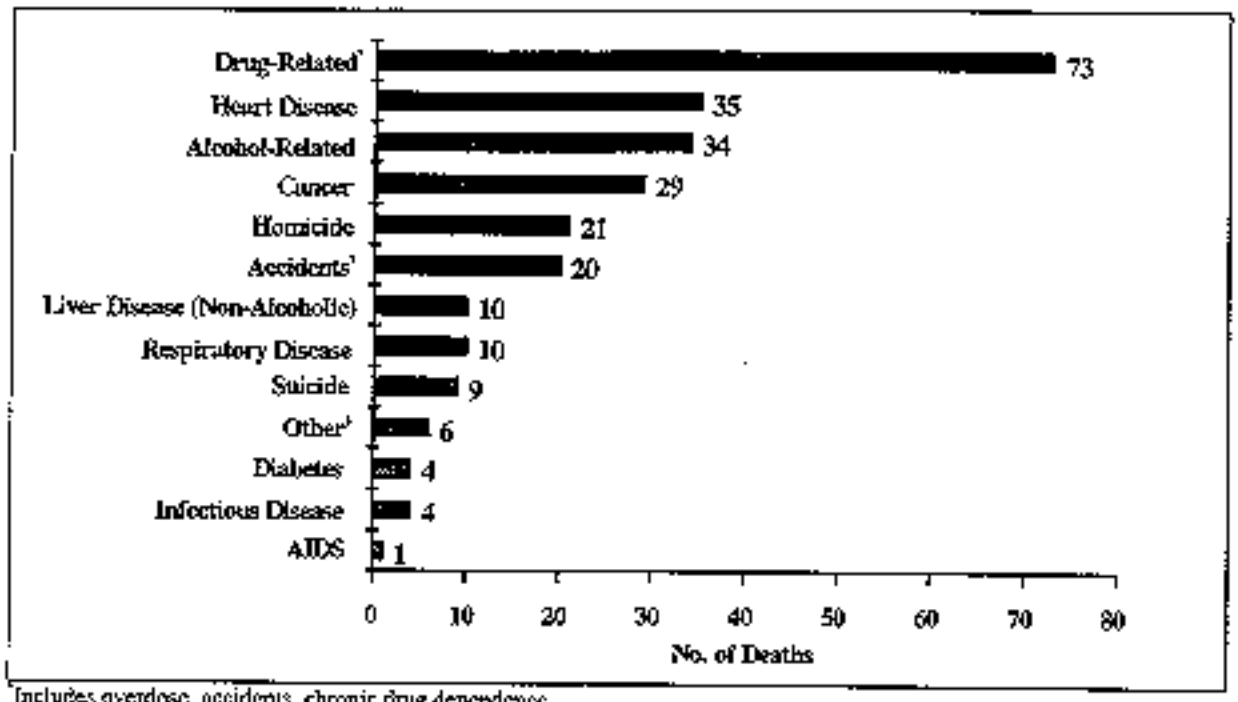
Of the 256 deaths that have been confirmed, the leading causes have been drug-related (n = 73) including accidental poisoning, drug-related accidents, and causes due to chronic drug dependence. Other leading causes of death were heart disease (n = 35); alcohol-related causes, including alcoholic liver disease (n = 34); malignant neoplasms (n = 29); homicide (n = 21); and other accidents including those involving motor vehicle, boating, and falls (n = 20). Only one death due to AIDS was reported.

The percentage of subjects reporting they injected heroin during the 12 months prior to their interview has decreased to 33 percent, down from 55 percent in 1975 and 58 percent in 1986. A large majority (90 percent) of those who injected heroin reported they had been in drug treatment during the previous 10 years. Cocaine was used by only 20 percent of the respondents at the 1997 point, compared with 16 percent in 1975 and 47 percent in 1986.

Table 1. Demographic characteristics of current sample ($n = 153$)

	n	
Age (Mean)*	202	57.1
Ethnicity*		**Percent**
White	72	35.7
Latino	115	56.8
African American	15	7.5
Educational level		
Less than high school	57	37.7
High school grad.	34	22.5
College/trade school	60	39.7
Marital status		
Never married	10	6.5
Married/living as married	72	47.1
Widowed/separated/divorced	71	46.4
Current employment status		
Unemployed	23	15.0
Employed	61	39.9
Retired	10	6.5
Disabled/unable to work	59	38.6
Occupational status		
Unskilled	48	31.4
Semi-skilled	71	46.4
Skilled	18	11.8
Sales/service	7	4.6
Other	8	5.9
Income support		
SSI	43	28.1
Social security	25	16.3
Welfare/food stamps	20	13.1
Pension/unemployment	8	5.3
Housing status		
Owns or rents house/apt./room	98	64.0
Lives with relatives or friends	33	21.6
Lives in hotel/boarding house or homeless	11	7.2
Hospitalized	3	2.0
Other	8	5.2

*n = 202 for these items.



[a]Includes overdose, accidents, chronic drug dependence.
[b]Includes motor vehicle, boating, falls.
[c]Includes kidney disease, epilepsy, ulcer, non-infectious disease.

Figure 1. Causes of death among original Civil Addict Program sample (N = 256).

The career approach to addiction that we have utilized provides a display of criminal activity, drug use, and drug treatment over the lifespan. Our research on opiate addicts now spans more than three decades. The policy implications suggested by these data include the need for provision of treatment (coerced or mandated) much earlier in the addiction career, possibly linked to the criminal justice system. Moreover, given the persistence of daily use of narcotics into their forties and fifties for many, treatment must be long term. Our perspective must also become long term, utilizing more longitudinal research designs, in order to assess the impact of successive treatment episodes over time. Finally, examination of the careers of narcotics users illustrates the need for different intervention strategies and policies to address the diverse needs of clients.

References

Anglin MD, Hser Y. Treatment of drug abuse. In: Tonry M, Wilson JQ, editors. Drugs and crime. Chicago: University of Chicago Press; 1990. p. 393-458.

Frykholm B. The drug career. J Drug Issues 1985;15:333-46.

Hser Y, Anglin MD, Powers K. A 24-year follow-up of California narcotics addicts. Arch Gen Psychiatry 1993;50:577-84.

Hser Y, Anglin MD, Grella C, Longshore D, Prendergast M. Drug treatment careers: a conceptual framework and existing research findings. Manuscript under review.

Hser Y, Yamaguchi K, Anglin MD, Chen J. Effects of interventions on relapse to narcotics addiction. Eval Rev 1995;19:123-40.

Maddux JF, Desmond DP. Careers of opioid users. New York: Praeger; 1981.

McGlothlin WH, Anglin MD, Wilson BD. Outcome of the California civil addict commitments: 1961-1972. Drug Alcohol Depend 1975-76;1:165-81.

McGlothlin WH, Anglin MD, Wilson BD. An evaluation of the California Civil Addict Program. NIDA Services Research Monograph Series. DHEW Publication No. (ADM 78-558). Washington: U.S. Government Printing Office; 1977.

McGlothlin WH, Anglin MD, Wilson BD. Narcotic addiction and crime. Criminology: An Interdisciplinary Journal 1978;16:293-315.

Nurco DN, Balter MB, Kinlock T. Vulnerability to narcotic addiction: preliminary findings. J Drug Issues 1994;24:293-314.

Nurco DN, Bonito AJ, Lerner M, Balter MB. Studying addicts over time: methodology and preliminary findings. Am J Drug Alcohol Abuse 1975;2:107-21.

Senay E. Clinical implications of drug abuse treatment outcome research. In: Tims FM, Ludford F, Ludford JP, editors. Drug abuse treatment evaluation. Rockville (MD): National Institute on Drug Abuse; 1984.

Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. Adv Alcohol Subst Abuse 1982;2:7-29.

Simpson DD, Sells SB, editors. Opioid addiction and treatment: a 12-year follow-up. Malabar (FL): Krieger; 1990.

Stephens RC. The street addict role: a theory of heroin addiction. Albany (NY): State University of New York Press; 1991.

Tims, FM, Ludford JP. Drug abuse treatment evaluation: strategies, progress, and prospects. NIDA Treatment Research Report (ADM 84-1349). Rockville (MD): National Institute on Drug Abuse; 1984.

Vaillant GE. A 12-year follow-up of New York narcotic addicts: some social and psychiatric characteristics. Arch Gen Psychiatry 1966;15(Pt 3):599-609.

Vaillant GE. What can long-term follow-up teach us about relapse and prevention of relapse in addiction? B J Addict 1988;83:1147-57.

Genetic and Other Risk Factors in Opiate Addiction

Roy W. Pickens, Ph.D.

Identifying genetic and familial risk factors in opiate dependence is made difficult by the low prevalence and illicit nature of the disorder. Because of the latter, individuals are often unaware of or reluctant to reveal illicit drug use by other family members; however, information about family members is an essential requirement of most genetic and family studies. Strict legal sanctions against illicit opiate use provide strong environmental influences that reduce drug exposure and make genetic and environmental influences more difficult to detect. In addition, secular trends in drug use pose methodological problems that make research strategies spanning generations (i.e., adoption studies) less appropriate for use. Nevertheless, over the past several years, a sufficient amount of data has been collected to indicate that opiate dependence often "runs in families" and that this familial tendency is caused by genetic as well as environmental influences.

More than 30 years ago, studies first suggested opiate dependence may have a familial tendency and be genetically influenced. At the U.S. Public Health Service narcotics hospital in Lexington, Kentucky, investigators found high rates of drug dependence in relatives of opiate-dependent patients (Ellinwood, Smith, Vaillant, 1966; Vaillant, 1966). Approximately 20 percent of parents and siblings of male patients and 23 percent of parents and siblings of female patients were found to be drug dependent. Because these percentages clearly exceeded the prevalence of drug dependence in the U.S. population, they suggested that familial influences can contribute to increased risk for opiate dependence.

Subsequent research has refined the extent of opiate familial influence. In one recent study (Maddux, Desmond, 1989), 8.4 percent of relatives of opiate-dependent individuals in treatment were found to be opiate dependent. The opiate dependence was reported to be higher in male relatives (fathers and brothers) than in female relatives (mothers and sisters). In another recent study (Rounsaville, Kosten, Weissman, et al., 1991), 16 percent of siblings of opiate-dependent individuals in treatment were illicit opiate users. Although comparable control groups were not included in either study, these prevalence rates clearly exceed the most recent estimates of population base rate of opiate dependence of less than 1 percent (Anthony, Warner, Kessler, 1994).

Although these data concern the specific familial transmission of opiate dependence, it is clear that opiate dependence in families is associated with other forms of drug abuse as well. For example, in the early family studies of opiate dependence, 46 percent of parents and siblings of male opiate-dependent individuals and 40 percent of parents and siblings of female opiate-dependent individuals were alcoholic (Ellinwood, Smith, Vaillant, 1966). In an extensive study of relatives of opiate-dependent probands, Rounsaville and colleagues (1991) reported substantially higher rates of both alcoholism and drug abuse than typically occur in the U.S. population. In opiate-dependent individuals without other psychiatric disorders, 38 percent of their first-degree relatives met research diagnostic criteria for alcoholism and 44 percent met research diagnostic

criteria for drug abuse. These rates compare with community base rates of 11 percent for alcoholism and 6 percent for drug abuse. Having an individual in a family with opiate dependence increased the risk of other first-degree relatives having alcoholism by 3.5 times and having drug abuse by 6.7 times. Similar results also have been reported by a number of other investigators (Kosten, Rounsaville, Kleber, 1985; Mirin, Weiss, Sollogub, et al., 1984). Other types of psychopathology occur at higher rates in siblings of opiate-dependent individuals (Luthar, Anton, Merikangas, et al., 1992). Among siblings of opiate-dependent individuals, 92 percent of those who ever tried a single class of drugs eventually came to abuse that drug, and the majority (65 percent) reported using three or more illicit substances (Merikangas, Rounsaville, Prusoff, 1992).

Family studies, however, show only that factors arising within the family contribute to opiate dependence. They do not tell whether the influence is the result of genetic or environmental factors. Genetic factors are the genes passed down from parents to offspring at conception, whereas environmental factors are all other influences, including drug availability, family discord, parental role modeling, and so forth. Two methods that allow genetic and environmental influences to be separated are adoption and twin studies. Adoption studies involve offspring who are separated from their biological parents shortly after birth and raised by adoptive (foster) parents. The purpose of the studies is to determine whether the individuals develop to resemble their biological parents (who supplied the genes) or their adoptive parents (who supplied the rearing environment). Twin studies involve comparing agreement for a disorder in monozygotic (MZ) and dizygotic (DZ) twins. Because MZ twins share all their genes and DZ twins share only half their genes, higher rates of agreement for the disorder in MZ than in DZ twins indicate a genetic influence. Both environmental influences related to shared and unique experiences also can be estimated from a comparison of MZ and DZ agreement.

To date, no adoption studies of opiate dependence have been conducted primarily because of the relative rarity of the disorder in individuals of the parental generation. However, adoption studies have found evidence of both genetic and environmental influences in the transmission of drug abuse in general. Adoptee drug abuse was found to be related to alcohol problems in biological relatives and divorce and psychiatric disturbance in the adoptive family (Cadoret, Troughton, O'Gorman, et al., 1986; Cadoret, Yates, Troughton, et al., 1995).

Although twin studies also have found evidence of genetic and environmental influences in drug abuse in general (Pickens, Svikis, McGue, et al., 1991; Gynther, Carey, Gottesman, et al., 1995), few twin studies of opiate dependence in specific have been conducted. Tsuang and colleagues (1996) examined concordance for DSM-III-R opiate abuse or dependence in a large sample of twins in the Vietnam Era Twin Registry (comprising male twin pairs who served in the U.S. military between 1965 and 1975). Pairwise concordance rates were 13.3 percent (4/30) in MZ and 2.9 percent (1/34) in DZ twins. The heritability of opiate abuse or dependence was estimated at 43 percent for additive genetic influences ($p<.05$) and 26 percent for nonadditive genetic influences (suggesting the possible influence of a single major gene effect). Johnson and Van den Bree (1997) examined twin concordance for DSM-III-R opiate abuse or dependence in a sample of male and female twins where the proband also met diagnostic criteria for alcohol abuse or dependence. Heritability of opiate abuse or dependence was estimated to be 57 percent for males and 60 percent for females. Only the heritability estimate for females was statistically

significant, however. Heritability for the more narrowly defined opiate dependence was estimated to be 48 percent for males and 62 percent for females (only female heritability was statistically significant).

Finally, a number of factors have been correlated with opiate dependence and thus may be genetically or environmentally determined. These include early age of onset of deviant behavior and social involvement with delinquent peers (Nurco, Balter, Kinlock, 1994), economic and social privations (Vaillant, 1992), and drug availability (Robins, 1973).

These results suggest that both genetic and environmental influences are involved in the etiology of opiate dependence, with genetic influences being the basis for at least some of the familial aggregation that is seen with the disorder. Although more research is needed, preliminary results from twin studies suggest genes may play an important role in the etiology of the disorder. The results also suggest a relationship between opiate dependence and other forms of drug dependence (including alcoholism) that also may reflect common genetic or environmental influences.

References

Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the national comorbidity survey. Exp Clin Psychopharm 1994;2:244-68.

Cadoret RJ, Troughton E, O'Gorman TW, Heywood E. An adoption study of genetic and environmental factors in drug abuse. Arch Gen Psychiatry 1986;43:1131-6.

Cadoret RJ, Yates WR, Troughton E, Woodworth G, Stewart MA. Adoption study demonstrating two genetic pathways to drug abuse. Arch Gen Psychiatry 1995;52:42-52.

Ellinwood EH, Smith WG, Vaillant GE. Narcotic addiction in males and females: a comparison. Int J Addict 1966;1:33.

Gynther LM, Carey G, Gottesman II, Vogler GP. A twin study of non-alcoholic substance abuse. Psychiatric Res 1995;56:213-20.

Johnson EO, Van den Bree M. Drug abuse: toward a refined phenotype. Paper presented at the Annual Meeting of the College on Problems of Drug Dependence, Nashville, TN; 1997.

Kosten TR, Rounsaville BJ, Kleber HD. Parental alcoholism in opioid addicts. J Nerv Ment Dis 1985;173:461-9.

Luthar SS, Anton SF, Merikangas KR, Rounsaville BJ. Vulnerability to substance abuse and psychopathology among siblings of opioid abusers. J Nerv Ment Dis 1992;180:153-61.

Maddux JF, Desmond DP. Family and environment in the choice of opioid dependence or alcoholism. Am J Drug Alcohol Abuse 1989;15:117-34.

Merikangas KR, Rounsaville BJ, Prusoff BA. Familial factors in vulnerability to substance abuse. In: Glantz M, Pickens R, editors. Vulnerability to drug abuse. Washington: American Psychological Association; 1992. p. 75-97.

Mirin SM, Weiss RD, Sollogub A, Michael J. Psychopathology in the families of drug abusers. In: Mirin SM, editor. Substance abuse and psychopathology. Washington: American Psychiatric Association; 1984. p. 80-106.

Nurco DN, Balter MB, Kinlock T. Vulnerability to narcotic addiction: preliminary findings. J Drug Issues 1994;24:293-314.

Pickens RW, Svikis DS, McGue M, Lykken DT, Heston LL, Clayton PJ. Heterogeneity in the inheritance of alcoholism. A study of male and female twins. Arch Gen Psychiatry 1991;48:19-28.

Robins LN. A follow-up of Vietnam drug users. Special Action Office Monograph, Series A, No. 1. Washington: Executive Office of the President; 1973.

Rounsaville BJ, Kosten TR, Weissman MM, Prusoff B, Pauls D, Anton SF, et al. Psychiatric disorders in relatives of probands with opiate addiction. Arch Gen Psychiatry 1991;48:33-42.

Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, et al. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. Am J Med Genet 1996;67:473-7.

Vaillant GE. A 12-year follow-up of New York narcotic addicts. III. Some social and psychiatric characteristics. Arch Gen Psychiatry 1966;15:599-609.

Vaillant GE. Is there a natural history of addiction? In: O'Brien CP, Jaffe JH, editors. Addictive states. New York: Raven Press; 1992. p. 41-57.

Neurobiological Substrates for Opiate Addiction

Eric J. Nestler, M.D., Ph.D.

Opiates produce addiction by eliciting changes in specific neurons of the central nervous system after long-term exposure. Considerable progress has been made in recent years in identifying the specific molecular and cellular adaptations involved and in relating them to specific behavioral features of addiction.

One of the most complete understandings of opiate action involves neurons of the locus coeruleus, noradrenergic neurons in the brain stem that mediate aspects of physical opiate dependence. This dependence occurs at a cellular level and is mediated at least in part via upregulation of the cAMP second messenger and protein phosphorylation pathway in these neurons. Opiates induce this upregulation in part at the level of gene expression via regulation of the transcription factor, CREB. Upregulation of the cAMP pathway is one mechanism driving activation of locus coeruleus neurons during opiate withdrawal, which is responsible for many of the signs and symptoms of the withdrawal syndrome. Another factor driving activation of the locus coeruleus during opiate withdrawal is increased glutamatergic transmission from medullary nuclei.

Similar types of mechanisms contribute to opiate action in other regions of the brain implicated in the reinforcing effects of opiates as well as in motivational aspects of opiate addiction. Such regions include the mesolimbic dopamine system, which consists of dopaminergic neurons in the ventral tegmental area and their projections to the nucleus accumbens. Thus, upregulation of the cAMP pathway occurs in the nucleus accumbens and has been related to alterations in opiate reinforcement mechanisms. Different types of adaptations have been identified in the ventral tegmental area, where chronic opiate exposure leads to altered levels of glutamate receptor function and to morphological changes in the neurons. These adaptations also have been related to the reinforcing effects of opiates.

This evolving neurobiological understanding of opiate action will provide fundamentally new insight into the mechanisms by which opiates lead to addiction and guide efforts for the development of truly effective treatments for opiate addiction.

References

Koob GF. 1996. Drug addiction: the yin and yang of hedonic homeostasis. Neuron 1996;16:893-6.

Nestler EJ. Under seige: the brain on opiates. Neuron 1996;16:897-900.

Sklair-Tavron L, Shi W-X, Lane SB, Harris HW, Bunney BS, Nestler EJ. Chronic morphine induces visible changes in the morphology of mesolimbic dopamine neurons. Proc Natl Acad Sci USA 1996;93:11202-7.

Wise RA. Neurobiology of addiction. Curr Op Neurobiol 1996;6:243-51.

Methadone Maintenance and Regional Cerebral Glucose Metabolism in Opiate Abusers: A Positron Emission Tomographic Study

Igor I. Galynker, M.D., Ph.D., Edythe D. London, Ph.D., Sniezyna Ganz, Ph.D., Richard N. Rosenthal, M.D.

Methadone maintenance is the primary treatment modality offered to opiate-dependent patients in the United States. Although marked by considerable controversy, it reduces illicit opiate use, the societal costs of the drug abuse problem, and antisocial behavior associated with use of illicit drugs (Ward, Mattick, Hall, 1992). Opiate receptors, particularly the F subtype, serve as the immediate targets that mediate the behavioral and physiological effects of heroin and methadone, but a complete elucidation of the neurobiological substrates of opiate dependence and the effects of methadone maintenance is lacking. One theory posits that heroin self-administration is an attempt to compensate by self-medication for an endogenous opioid deficiency syndrome (Goldstein, 1991). In support of the hypothesis that opiate-dependent individuals suffer from an opioid deficiency syndrome, patients maintained on methadone often show improved behavior and begin to function in a manner indistinguishable from that of individuals without dependence on an illicit drug of abuse, as indicated by their performance on neuropsychological tests or by ratings of their behavior by observers blinded to their diagnoses (Dole, 1988).

Positron emission tomography (PET) is a nuclear medicine imaging modality that allows assessment and comparison of regional brain function in human subjects. Quantitative maps of glucose metabolism, an index of function in the brain, are obtained using PET and the [F-18] fluorodeoxyglucose (FDG) method (Reivich, Kuhl, Wolf, et al., 1979). Measures of regional cerebral metabolic rate(s) for glucose (rCMRglc) provide assessment of regional brain function because glucose is the primary source of energy for the adult brain (Sokoloff, 1977).

A variety of PET studies have been performed using the FDG method in individuals with addictive disorders, such as alcoholism (Volkow, Wang, Hitzemann, et al., 1994), cocaine dependence (Volkow, Fowler, Wolf, et al., 1991; Volkow, Wang, Hitzemann, et al., 1992), and polydrug abuse (Stapleton, Morgan, Phillips, et al., 1995). Of particular interest are studies that demonstrated long-term differences in cocaine abusers, as compared with control subjects who did not abuse cocaine. Although global glucose metabolism appeared to be unaffected by cocaine abuse, cocaine abusers who had no history of intravenous drug abuse showed persistent (3 to 4 months after detoxification) deficits in rCMRglc in the frontal lobe (Volkow, Wang, Hitzemann, et al., 1992). These data are consistent with findings on cerebral perfusion, obtained with PET (Volkow, Mullani, Gould, et al., 1988) or with single photon emission computed tomography (SPECT) (Holman, Carvalho, Mendelson, et al., 1991). In contrast, studies of rCMRglc in polydrug abusers with histories of intravenous drug abuse (cocaine as well as heroin) revealed abnormally low metabolism in visual association cortex, as compared with levels in matched control subjects (Stapleton, Morgan, Phillips, et al., 1995). As this difference was not observed in the aforementioned studies of cocaine abusers, it may be related to history of opiate abuse

and/or dependence.

The FDG PET method was also used to evaluate the acute effects of morphine (London, Broussolle, Links, et al., 1990) and buprenorphine (Walsh, Gilson, Jasinski, et al., 1992) on CMRglc in human polydrug abusers. Both drugs significantly reduced glucose utilization in the whole brain, and the effects on rCMRglc did not distinguish morphine, a pure opioid agonist, from buprenorphine, a mixed agonist/antagonist (Walsh, Gilson, Jasinski, et al., 1994). Effects of morphine and buprenorphine on rCMRglc followed the distribution of opioid receptors in human brain only to some extent.

Although the neuroanatomical substrates of the opiate withdrawal syndrome have been studied extensively in rats (Kimes, London, 1989; Wooten, DiStefano, Collins, et al., 1982), only a preliminary study of cerebral perfusion during opiate withdrawal in human subjects has been published (Krystal, Woods, Kosten, et al., 1995). In addition, study of precipitated withdrawal from heroin in only one human subject by investigators in the Intramural Research Program of NIDA has indicated that acute withdrawal is associated with stimulation of rCMRglc in subcortical areas and in the visual cortex (London, Kimes, Stapleton, et al., unpublished observation). Recent research did not provide evidence for dopamine involvement in opiate withdrawal (Wang, Volkow, Fowler, et al., 1997). A rational approach to the development of new treatments for opiate dependence would be aided by a systematic study of the central components of the opiate withdrawal syndrome. Furthermore, it would be of interest to determine whether individuals with histories of opiate dependence have evidence of persistent cerebral dysfunction that would be ameliorated by chronic treatment.

Data will be presented on rCMRglc, an index of local brain function, in subjects who have histories of opiate dependence, under two conditions: (1) in an opiate-free state and (2) stabilized on methadone maintenance. In parallel, rCMRglc was tested in non-opiate-abusing control subjects, matched for socioeconomic status, gender, and age. The data to be presented will help to answer the following questions: (1) Is history of opiate dependence associated with persistent abnormalities in regional brain function, as assessed by measurement of rCMRglc after a 3-month period of abstinence? (2) Are such potential abnormalities in rCMRglc resolved in patients maintained on methadone for 6 months? Answers to these questions would have bearing on the theory that long-term deficiency of endogenous opioids leads to persistent cerebral dysfunction that can be ameliorated by methadone maintenance.

References

Dole VP. Implications of methadone maintenance for theories of narcotic addiction. JAMA 1988 Nov 25;260(20):3025-9.

Goldstein A. Heroin addiction: neurobiology, pharmacology, and policy. J Psychoactive Drugs 1991 Apr;23(2):123-33.

Holman BL, Carvalho PA, Mendelson J, Teoh SK, Nardin R, Hallgring E, et al. Brain perfusion is abnormal in cocaine-dependent polydrug users: a study using technitium-99m-HMPAQ and ASPECT. J Nucl Med 1991;32(6):1206-10.

Kimes AS, London, ED. Glucose utilization in the rat brain during chronic morphine treatment and naloxone-precipitated morphine withdrawal. J Pharmacol Exp Ther 1989 Feb;248(2):538-45.

Krystal, JH, Woods SW, Kosten TR, Rosen MI, Seibyl JP. Opiate dependence and withdrawal: preliminary assessment using single photon emission computerized tomography (SPECT). Am J Drug Alcohol Abuse 1995 Feb;21(1):47-63.

London ED, Broussolle EP, Links JM, Wong DF, Cascella NG, Dannals RF, et al. Morphine-induced metabolic changes in human brain. Studies with positron emission tomography and [fluorine 18] fluorodeoxyglucose. Arch Gen Psychiatry 1990 Jan;47(1):73-81.

Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, et al. The [18F] fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ Res 1979 Jan;44(1):127-37.

Sokoloff L. Relation between physiological function and energy metabolism in the central nervous system. J Neurochem 1977 Ju1;29(1):13-26.

Stapleton JM, Morgan MJ, Phillips RL, Wong DF, Yung BCK, Shaya EK, et al. Cerebral glucose utilization in polysubstance abuse. Neuropsychopharmacology 1995 Aug;13(1):21-31.

Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K. Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. Br J Psychiatry 1988 May;152:641-8.

Volkow ND, Fowler JS, Wolf AP, Hitzemann R, Dewey S, Bendriem B, et al. Changes in brain glucose metabolism in cocaine dependence and withdrawal. Am J Psychiatry 1991 May;148(5):621-6.

Volkow ND, Hitzemann R, Wang GJ, Fowler JS, Wolf AP, Dewey SL, et al. Long-term frontal brain metabolic changes in cocaine abusers. Synapse 1992 Jul;11(3):184-90.

Volkow ND, Wang GJ, Hitzemann R, Fowler JS, Overall JE, Burr G, et al. Recovery of brain glucose metabolism in detoxified alcoholics. Am J Psychiatry 1994;151:178-83.

Walsh SL, Gilson SF, Jasinski DR, Stapleton JM, Phillips RL, Dannals RF, et al. Buprenorphine reduces cerebral glucose metabolism in polydrug abusers. Neuropsychopharmacology 1994 May;10(3):157-70.

Wang, GJ, Volkow ND, Fowler JS, Logan J, Abumrad NN, Hitzemann RJ, et al. Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. Neuropsychopharmacology 1997;16:174-82.

Ward J, Mattick R, Hall W. Key issues in methadone maintenance treatment. National drug and alcohol research center. Kensington: New South Wales University Press; 1992.

Wooten GF, DiStefano P, Collins RC. Regional cerebral glucose utilization during morphine withdrawal in the rat. Proc Natl Acad Sci USA 1982 May;79(10):3360-4.

Establishing a Diagnosis of Heroin Abuse and Addiction

George E. Woody, M.D.

Background

Heroin abuse and addiction are defined in DSM-IV as two separate disorders. Addiction, technically called "dependence," is "a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems. There is a pattern of repeated self-administration that usually results in tolerance, withdrawal, and compulsive drug-taking" (DSM-IV, 1994). The defining features are behavioral, and there is no biological test for addiction as there is for pneumonia, diabetes, asthma, or other medical conditions. Since many persons with addiction demonstrate tolerance and/or withdrawal, it is subclassified into dependence with or without physiological features. In the case of heroin abuse and addiction, almost all persons who meet criteria for dependence demonstrate physiological features.

The current emphasis on behavioral features, particularly compulsive self-administration despite substance-related problems, reflects a shift in the way addiction is defined. This shift began to occur in the mid-1970s and has been reflected by changes in the official diagnostic criteria for substance dependence that are published by the World Health Organization and the American Psychiatric Association. Before the mid-1970s, tolerance and withdrawal were the defining features of addiction, but this concept was modified on the basis of findings from at least four directions: (1) behavioral pharmacology studies in which animals were shown to self-administer drugs compulsively in the absence of tolerance and withdrawal, (2) work describing behavioral characteristics that are associated with the alcohol dependence syndrome (Edwards, Gross, 1996), (3) the clinical observation that many persons developed tolerance and withdrawal as consequences of long-term use of steroids, opioids, and other drug classes but never demonstrated the compulsive self-administration that is typical of addiction, and (4) the cocaine epidemic, in which compulsive use often was not associated with tolerance or withdrawal.

Unlike dependence, abuse is a pattern of less regular and compulsive use but one that is serious enough to result in recurring social or legal problems. Examples of these problems are repeated difficulty fulfilling major role obligations, recurrent use of the substance in situations where it is physically hazardous, recurrent substance-related legal problems, or repeated use despite social or interpersonal problems (DSM-IV, 1994). Because abuse and addiction are conceptually separate entities and have different implications for treatment, it is important to distinguish them in addiction treatment programs, particularly if one is considering using methadone or LAAM.

Establishing a Diagnosis of Addiction

Addiction to heroin or other opioids is diagnosed by medical history and a physical examination, essentially the same methods used to diagnose other medical disorders. Typically, there is a long history of heroin self-administration, with the drug usually injected into the arms or legs. More recently, with the advent of purer heroin, programs are seeing addicts who use the intranasal route ("snorting") or smoking ("chasing the dragon"). Although some addicts manage to use heroin for years with no apparent adverse medical or social consequences, most have problems in one or more areas. They may become involved in drug-related crimes such as shoplifting or burglary or suffer from drug overdoses, skin infections, hepatitis, HIV infection, or nasal and pulmonary irritation. Family, psychiatric, and employment problems related to the addiction are also common.

A physical examination typically finds one or more of the following: fresh puncture marks, "tracks" resulting from sclerosis of peripheral veins secondary to repeated injections, active or healed skin abscesses, cellulitis, and sometimes peripheral edema from venous stasis. In the case of persons who are snorting or smoking heroin, inflamed nasal mucosae or bronchial irritation is often present. Patients usually demonstrate subjective discomfort and restlessness (feeling "sick") and other signs or symptoms of opioid withdrawal such as rhinorrhea, lacrimation, nausea, and occasionally vomiting. Urine testing can support the diagnosis of addiction by confirming the presence of opioid drugs; however, a positive urine test does not prove addiction and a negative test does not rule it out.

A medical history and one or more of these signs and symptoms of addiction make it easy to diagnose. Problems can arise, however, in patients who give a history consistent with addiction but have no physical signs of use or withdrawal. These diagnostic problems can occur in persons who are snorting or smoking heroin; persons who have no track or puncture marks because they are using opioids orally; or patients who have "shot up" just before arriving for an intake appointment and show no signs or symptoms of withdrawal. The diagnosis can be established or ruled out in these cases by repeated observations of the patient over a period of hours or days, often accompanied by observed urine testing to establish the presence of opioid use and withdrawal, or by administering a narcan challenge test to precipitate withdrawal.

Criteria for Admission to Methadone or LAAM Treatment

Admission to either of these therapies generally requires that the person meet DSM-IV criteria for current opioid dependence with evidence of tolerance or withdrawal, that physiologic dependence must have begun 12 or more months before entering the program, and that physiologic dependence must have been present, continuously or intermittently, for 6 or more months during the past year.

Exceptions to the rule of current physiologic dependence for most of the past year are allowed for persons with a clear history of addiction who have lived in a penal or chronic care institution for 1 month or longer, who met criteria for methadone or LAAM before being institutionalized, who are to be discharged within 14 days or who have been discharged for not more than 6 months, and for whom substitution therapy is currently medically justified; for pregnant addicts who are currently addicted or have been addicted in the past and who are

medically judged to need substitution therapy; and for persons who have been treated for 6 months or more in a comprehensive maintenance program, who voluntarily detoxified from methadone within the last 2 years, and for whom substitution therapy is judged medically appropriate.

Persons younger than 18 must have had two or more attempts at drug-free treatment or detoxification, and 1 or more weeks must have elapsed after each attempt for a person to qualify for methadone treatment. A young person cannot be treated with LAAM and must have the written consent of a parent, legal guardian, or other responsible adult designated by the State authority. These criteria are provided in detail in the Code of Federal Regulations (Part 291).

Evidence That Supports Opioid Addiction as a Medical Disorder

Several lines of evidence point to opioid addiction as a medical disorder with behavioral components, rather than a problem of motivation or willpower. One is the consistency of the signs and symptoms associated with addiction, even among persons with varying socioeconomic backgrounds (Cottler, Schuckit, Helzer, et al., 1995). Another is the compulsive self-administration that continues in spite of medical and social problems and the strong tendency to relapse even after extended periods of abstinence. A third is the strength of the patient's desire for opioids despite all the problems that have occurred or might occur in association with opioid use. Many examples of this phenomenon are well-known to clinicians, such as addicts relapsing to heroin use shortly after being incarcerated for drug-related crimes or addicts being treated with intravenous (IV) antibiotics for bacterial endocarditis who are found injecting into their IV lines. This consistent pattern of specific signs and symptoms that persist over time is similar to that seen in other medical or psychiatric disorders such as asthma, diabetes, arthritis, bipolar illness, schizophrenia, and many others.

Current Deficiencies in Our Knowledge That May Require Further Research

There are many areas for research on understanding and treating heroin addiction. Some relate to this presentation: (1) Is the patient harmed by instituting substitution therapy once the diagnosis of current opioid dependence is established rather than requiring that the patient must have been addicted for most of the past year? (2) What is the long-term result of maintenance therapy on a person's chances of achieving full sustained remission? Stated differently, does substitution therapy increase, decrease, or have no effect on a person's chances for eventually becoming drug-free? (3) Is there evidence that LAAM is harmful to persons 18 or younger? (4) What factors are responsible for the widespread and persistent ambivalence about agonist substitution therapy despite the overwhelming evidence of its efficacy?

References

Cottler LB, Schuckit MA, Helzer JE, Crowley T, Woody G, Nathan P, Hughes J. The DSM-IV field trial for substance use disorders: major results. Drug Alcohol Depend 1995;38:59-69.

Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. Br Med 1996;1:1058-61.

Food and Drug Administration, DHHS. Drugs used for treatment of narcotic addicts. Code of Federal Regulations 1993:125-46.

Frances A, Pincus HA, First MB, editors. Substance related disorders. In: Diagnostic and statistical manual of mental disorders. Fourth edition. (DSM-IV). Washington: American Psychiatric Association Press; 1994. p. 175-272.

Narcotic Drugs and Crime: Addict Behavior While Addicted Versus Nonaddicted

David N. Nurco, D.S.W.

Although literature reviews have documented that hundreds of studies of the relationship between addiction and crime were performed from the 1920s to the late 1970s, it has been only in the past 20 years that the drug-crime connection has been effectively examined (Inciardi, 1981; Johnson et al., 1985). Recent research conducted by independent investigators concerning the relationship between crime and narcotic (primarily heroin) addiction has revealed a remarkable degree of consistency of findings across studies (Nurco, Ball, Shaffer, et al., 1985). Although the relationship between drug abuse and crime is complex, it has been unequivocally established that narcotic addiction in the United States is associated with exceptionally high crime rates. With few exceptions, narcotic addicts engage in a great amount of criminal activity, frequently on a daily basis, and as a consequence commit hundreds and, at times, thousands of offenses per individual during their addiction careers (Ball, Shaffer, Nurco, 1983).

Examination of a direct, functional relationship between narcotic drug use and crime has been made possible through the application of a unique longitudinal study design in which crime data are collected on narcotic-abusing individuals over sequential periods varying with respect to frequency of narcotic drug use. Inasmuch as the life course of an addiction career is characterized by numerous periods of addiction and nonaddiction, it is feasible to compare the amounts of crime committed by individuals during addiction periods with the amounts committed by individuals during nonaddiction periods when they are in the community or, in addict parlance, when they are "on the street."

In one of the earliest studies employing this longitudinal approach, we found that for a rigorously defined community-wide sample of Baltimore narcotic addicts, higher levels of criminality and illegal income among the addicts were consistently associated with periods of addiction (Nurco, Cisin, Balter, 1981; Ball, Rosen, Flueck, et al., 1981). When crime rates were compared in this manner, it was found that after the onset of addiction, the number of crime-days per year-at-risk[1] averaged 248 during periods of active addiction and only 41 during periods of nonaddiction. There was, then, a sixfold increase in criminality during addiction as contrasted with nonaddiction periods (Ball, Rosen, Flueck, et al., 1981). Subsequent evidence collected by us and others, providing additional support for a causal component in the relationship between narcotic drug use and crime, revealed that crime levels significantly increase from preaddiction to addiction, remaining high over subsequent addiction periods and comparatively low across intervening nonaddiction periods (Nurco, Shaffer, Ball, et al., 1984; Anglin, Speckart, 1986; Hanlon, Nurco, Kinlock, et al., 1990).

The conclusion that crime is functionally related to narcotic addiction status is

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1 Prorated on the basis of 1 year, a "crime day" is conceptually defined as a 24-hour period during which one or more crimes are committed by an individual while in the community.

additionally supported by the uniform finding of other study approaches that frequency of narcotic use is generally associated with higher crime rates. Johnson and associates (1985) found that the heaviest heroin users were more likely to be classified as serious offenders. Examining a broader range of drug abusers, Hubbard and coworkers (1984) reported that "expensive" drug use was at least a partial explanation for income-generating crime. These investigators found that more-than-once-a-day heroin use predicted comparatively high levels of illegal income. Further examination of the drug-use-frequency/income-from-crime relationship suggested that whereas low-use levels are supportable without resort to illegal activity, frequent daily use rarely is. Also, Chaiken and Chaiken (1982), classifying prison and jail inmates as addicted heroin users, nonaddicted heroin users, nonheroin drug users, nonaddicted heroin users, nonheroin drug users, and nondrug users, found that addicted heroin users had markedly higher levels of criminal activity than did nonheroin drug users.

It is apparent that the magnitude of the crime problem associated with narcotic addiction is attributable not only to the frequency with which addicts commit "victimless" crimes and lesser offenses but also to the fact that many of their offenses are serious and destructive (Chaiken, Chaiken, 1982). It is clear that narcotic abusers commit a wide range of offenses of varying degrees of seriousness. Findings from subsequently conducted studies have indicated that, as a group, addicts commit far more violent crimes than previously assumed. For example, on the basis of his extensive research on drug abusers in Miami, Inciardi and colleagues (1997) have demonstrated that drug-related crime is at times exceedingly violent. Although violent crimes constitute a relatively small proportion of all crimes committed by narcotic addicts (much smaller, for example, than the proportion of theft crimes), the actual number of violent crimes is still large because addicts commit so many crimes (Inciardi, 1986; Nurco, Hanlon, Balter, et al., 1991; Shaffer, Nurco, Kinlock, 1984). Within the drugs-crime field, a matter of great concern in the United States is the nature and scope of the relationship between drugs and violent crime (Goldstein, 1989). It has been suggested that heavy narcotic drug use has contributed to record numbers of homicides in large cities in the United States, including the Nation's capital, either directly or through the generation of distribution-related violence (Tardiff, Gross, Messner, 1986; National Institute of Justice, 1990).

Narcotic addiction among addicts in a free society is characterized by periods of remission and relapse (Ball, Shaffer, Nurco, et al., 1983; Maddux, Desmond, 1981; Leukefeld, Tims, 1988; Anglin, Hser, 1990). Most of the addicts we have followed over the years have been arrested a number of times and have spent considerable time in prison; however, these arrests and periods of incarceration have had little subsequent impact on their addiction and drug-related criminal careers. Many factors, including drug abuse treatment, account for periods of remission from narcotic addiction. There are demonstrable effects of treatment on narcotic drug use and associated criminal activity. Significant during-treatment reductions in narcotic drug use and crime have been documented for individuals in methadone maintenance (Senay, 1985; Ball, Ross, 1991), therapeutic communities (DeLeon, 1985; DeLeon, 1990; Inciardi, Martin, Butzin, et al., 1997), and outpatient drug-free programs (McGlothlin, Anglin, Wilson, 1978; Anglin, McGlothlin, 1984). Since crime rates are much higher during heavy narcotic drug use, it appears that drug abuse treatment aimed at reducing narcotic drug consumption represents a reasonable crime reduction strategy for most addicts. Regardless of treatment modality, however, outcomes of treatment of less than 3 months are generally poor (Simpson, Sells, 1981). Also, individuals

who have extensive criminal histories (Nurco, Ball, Shaffer, et al., 1985; Anglin, Hser, 1990; DeLeon, 1990) and/or a history of little or no stable employment (Rounsaville, Tierney, Crits-Christoph, et al., 1982; Hubbard, Marsden, Rachal, et al., 1989; Kleber, 1989) are likely to have less favorable outcomes.

References

Anglin MD, Hser Y. Treatment of drug abuse. In: Tonry M, Wilson JQ, editors. Drugs and crime. [Crime and justice: A review of research, Vol.13] Chicago: University of Chicago Press; 1990. p. 393-460.

Anglin MD, McGlothlin WH. Outcome of narcotic addict treatment in California. In: Tims, FM, Ludford, JP, editors. Drug abuse treatment evaluation: strategies, progress, and prospects. Washington, DC: US Government Printing Office; 1984. p.106-28.

Anglin MD, Speckart G. Narcotics use, property crime and dealing: structural dynamics across the addiction career. J Quantitative Criminology 1986;2:335-75.

Ball JC, Rosen L, Flueck JA, Nurco DN. The criminality of heroin addicts: when addicted and when off opiates. In: Inciardi JA, editor. The drugs-crime connection [Sage annual reviews of drug and alcohol abuse, Vol.5]. Beverly Hills (CA): Sage Publications, Inc.; 1981. p. 39-65.

Ball JC, Ross A. The effectiveness of methadone maintenance treatment: patients, programs, services, and outcomes. New York: Springer-Verlag; 1991.

Ball JC, Shaffer JW, Nurco DN. The day-to-day criminality of heroin addicts in Baltimore: a study in the continuity of offense rates. Drug Alcohol Depend 1983;12:119-42.

Chaiken JM, Chaiken MR. Varieties of criminal behavior. Santa Monica (CA): Rand; 1982.

DeLeon G. Handbook of drug control. Inciardi JA, editor. Westport (CT): Greenwood Press; 1990. p. 115-38.

DeLeon G. The therapeutic community: status and evolution. Int Addict 1985;20:823-44.

Goldstein PJ. Drugs and violent crime. In: Weiner NA, Wolfgang ME, editors. Pathways to criminal violence. Newbury Park (CA): Sage Publications, Inc; 1989.

Hanlon TE, Nurco DN, Kinlock TW, Duszynski KR. Trends in criminal activity and drug use over an addiction career. Am J Drug Alcohol Abuse 1990;16:223-38.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. Drug abuse treatment: a national study of effectiveness. Chapel Hill: University of North Carolina Press; 1989.

Hubbard RL, Rachal JV, Craddock SG, Cavanaugh ER. Treatment outcome prospective study (TOPS): client characteristics and behaviors before, during, and after treatment. In: Tims FM, Ludford JP, editors. Drug abuse treatment evaluation: strategies, progress, and prospects [NIDA Research Monograph #51]. Rockville (MD): National Institute on Drug Abuse; 1984. p. 42-68.

Inciardi JA. The war on drugs: heroin, cocaine, and public policy. Palo Alto (CA): Mayfield; 1986.

Inciardi JA, editor. The drugs-crime connection [Sage annual reviews of drug and alcohol abuse, Vol.5]. Beverly Hills (CA): Sage Publications, Inc.; 1981.

Inciardi JA, Martin SS, Butzin CA, Hooper RM, Harrison LD. An effective model of prison-based treatment for drug-involved offenders. J Drug Issues 1997;27(2):261-78.

Johnson BD, Goldstein P, Preble E, Schmeidler J, Lipton DS, Spunt B, Miller T. Taking care of business: the economics of crime by heroin abusers. Lexington (MA): Lexington Books; 1985.

Kleber HD. Treatment of drug dependence: what works. Int Rev Psychiatry 1989;1:81-100.

Leukefeld CG, Tims FM, editors. Compulsory treatment of drug abuse: research and clinical practice [NIDA research monograph 86]. Rockville (MD): National Institute on Drug Abuse; 1988.

Maddux JF, Desmond DP. Careers of opioid users [Praeger studies on issues and research in substance abuse]. New York: Praeger; 1981.

McGlothlin WH, Anglin MD, Wilson BD. Narcotic addiction and crime. Criminology 1978;16:293-316.

National Institute of Justice. Research program plan: fiscal year 1990. Washington: U.S. Department of Justice; 1990.

Nurco DN, Ball JC, Shaffer JW, Hanlon TE. The criminality of narcotic addicts. J Nerv Ment Dis 1985;173:94-102.

Nurco DN, Cisin IH, Balter MB. Addicts career II: the first ten years. Addict 1981;8:1327-56.

Nurco DN, Hanlon TE, Balter MB, Kinlock TW, Slaght E. A classification of narcotic addicts based on type, amount, and severity of crime. J Drug Issues 1991;21:429-48.

Nurco DN, Shaffer JW, Ball JC, Kinlock TW. Trends in the commission of crime among narcotic addicts over successive periods of addiction and nonaddiction. Am J Drug Alcohol Abuse 1984;10:481-89.

Rounsaville BJ, Tierney T, Crits-Christoph M, Weisman MM, Kleber HD. Predictors of outcome in treatment of opiate addicts: evidence for the multidimensional nature of addicts' problems. Compr Psychiatry 1982;23:462-7.

Senay E. Methadone maintenance treatment. J Addict 1985;20:803-21.

Shaffer JW, Nurco DN, Kinlock TW. A new classification of narcotic addicts based on type and extent of criminal activity. Compr Psychiatry 1984;25:315-28.

Simpson DD, Sells SB. Evaluation of drug abuse treatment effectiveness: summary of the DARP followup research [NIDA treatment research report]. Rockville (MD): National Institute on Drug Abuse; 1981.

Tardiff K, Gross EM, Messner SF. A study of homicide in Manhattan, 1981. Am J Public Health 1986;76:139-43.

Societal Costs of Heroin Addiction

Henrick J. Harwood

Studies of the societal costs of heroin addiction can tell us why society should care about heroin addiction; however, they cannot tell us what should be done to address the problem. Such cost studies are descriptive and even taxonomic in nature. Societal cost studies define and quantify the impacts and costs. There are actually many different ways to examine the aggregate costs. The most basic approach to understanding societal costs is an examination of the sector of the economy in which the costs occur, combined with some understanding of why and how the costs arise.

Health Sector Costs

The following estimates reflect use of health sector resources to prevent, diagnose, treat, rehabilitate, and domicile persons who experience heroin addiction. In the United States, about $1 trillion, or 14 percent of the gross domestic product, is spent in the health sector (Levit, Lazenby, Braden, 1996).

Health treatment for drug abuse in 1992 cost $8 billion, of which $3 billion was spent for specialized drug treatment services and about $5 billion was spent for treatment of related diseases (Harwood, Fountain, Livermore, in review). Somewhat less than one-third of drug treatment funding is used for heroin addiction. The majority of heroin addiction treatment is delivered in methadone programs (methadone treatment costs about $500 million per year) (Office of Applied Studies, 1997; NASADAD, 1996; Brandeis University, 1993a, 1993b), even though most health comorbidities are heroin-related (e.g., HIV and hepatitis costs are primarily related to needle use for heroin administration).

National expenditures on substance abuse prevention in 1992 were about $1.8 billion (Harwood, Fountain, Livermore, in review); however, it is difficult to allocate these costs between drugs and alcohol, much less among different types of drugs.

Criminal Justice Sector

Law enforcement authorities spent more than $90 billion in 1992 (Bureau of Justice Statistics, 1995) to enforce laws (police protection), adjudicate those arrested (prosecution, public defense, and courts), and deliver correctional sanctions (prison, jail, and pre-trial and post-adjudication community supervision). About $17 billion of these costs is attributable to drug abuse (Harwood, Fountain, Livermore, in review). This includes both drug-defined criminal activities (growing, manufacturing, processing, importing, transporting, distributing, sales, possession, and related activities such as money laundering) and drug-related criminal activities. The latter include crime that is caused or motivated by heroin addiction, such as participation in income-generating illegal activity in order to obtain money to buy drugs, or criminal acts performed under the influence of drugs.

Unlike the situation in the 1970s (Cruze, Harwood, Kristiansen, et al., 1981), heroin is implicated in only a fraction of drug-involved criminal justice costs. Data on arrestee drug use show that opiate use is detected in only about 10 percent of arrestees testing positive for any illicit drug use (Bureau of Justice Statistics, 1995), while two-thirds to three-quarters have used cocaine (including any individuals who have used both or multiple substances).

Employment and Household Productivity

These costs represent the potential value heroin addicts might have contributed to the legitimate economy (and to productive activities in the household) had they experienced a typical, in terms of employment experience, life course instead of one affected by drugs. The majority of the general population are employed (Bureau of the Census, 1993) and/or contribute to upkeep of their own households, including child-raising, cleaning, cooking, etc. For employed men and women aged 40, average annual earnings are about $40,000 and $25,000 and the values attributed to household services are $5,000 to $8,000 and $10,000 to $15,000, respectively (D. Rice, personal communication, 1997).

Although studies of drug addicts show that about half of those entering treatment have some participation in the legitimate labor force, heroin addicts tend to have the lowest participation rates of any type of addict (National Opinion Research Center, 1996; Gerstein, Johnson, Harwood, et al., 1994; Office of Applied Studies, 1997). On average, employed addicts work infrequently or at low-wage jobs because of drug intoxication or associated health problems (including time spent in hospitals and treatment residences). Other addicts turn away from the legitimate economy to get income from the drug trade or from income-generated predatory (burglary, robbery) or consensual (gambling, sex for hire, or receiving stolen property) crime. Finally, others may not work while they are incarcerated for drug-specific or drug-related infractions.

Some heroin/opiate addicts (2 to 3 percent, or about 1,000, per year) die from overdose or illnesses such as HIV infection and hepatitis (about 10,000 and 3,600 per year, respectively) (tabulation from the NCHS Public Use ICD-9 Data Tape, and CDC AIDS Public Use Information Data Set; Harwood, Fountain, Livermore, in review). A death of this type constitutes a one-time loss of discounted lifetime expected productivity.

Victim Losses

The belief that heroin addicts will inflict damage on others (including family members) as well as themselves is what motivates much of our public policy toward heroin. Victim losses are similar to and can be related to the categories above: crime victims are often injured (or even killed), incurring health costs and lost time from jobs and household responsibilities. Other losses include stolen and damaged property (Bureau of Justice Statistics, 1994). Heroin addicts have been found to be relatively overrepresented in property and consensual crimes relative to violent crimes (Bureau of Justice Statistics, 1993).

Intangible and/or Currently Unmeasured Costs

It is quite difficult to place a value on many of the losses related to addiction and its consequences. These intangible or unmeasured costs include the pain and suffering experienced by crime victims and their families and friends, as well as the impacts on the families and friends of the opiate addicts. For significant others and children, these effects include direct victimization, as well as longer term problems and pathologies experienced such as poor educational attainment, requirements for mental health and substance abuse services, and lack of success in gaining a stable position in society and the legitimate economy. These intangible or unmeasured costs may motivate policy and policymakers as much as measured costs.

Who Bears the Costs

Actual expenditures on health and criminal justice services compose less than a third of costs; the balance is primarily in lost potential employment and household productivity of addicts (Harwood, Fountain, Livermore, in review). Governments pay for most of the health services (methadone, HIV infection, and hepatitis treatment) and criminal justice services. The lost potential productivity primarily worsens the well-being of the abuser and his/her household, although a portion of this is shifted to government through welfare payments and losses to the government of tax revenues, and addicts may shift other parts of such losses to victims via crime.

References

Brandeis University. Drug services research survey: phase I. Report to the National Institute on Drug Abuse. Waltham (MA): The University; 1993a.

Brandeis University. Drug services research survey: final report, phase II. Report to the National Institute on Drug Abuse. Waltham (MA): The University; 1993b.

Bureau of the Census. Statistical abstract of the United States: 1993. Washington: Dept. of Commerce (US); 1993.

Bureau of Justice Statistics. Criminal victimization in the United States, 1992. Washington: Dept. of Justice (US); 1994.

Bureau of Justice Statistics. Correctional populations in the United States, 1991. Washington: Dept. of Justice (US); 1993.

Bureau of Justice Statistics. Sourcebook of criminal justice statistics—1994. Washington: Dept. of Justice (US); 1995.

Cruze A, Harwood H, Kristiansen P, Collins J, Jones D. Selected measures of economic costs to society of alcohol and drug abuse and mental illness—1977. Final report to Alcohol, Drug Abuse, and Mental Health Administration. Research Triangle Park (NC): Research Triangle Institute; 1981.

Gerstein D, Johnson R, Harwood H, Fountain D, Souter N. Evaluating recovery services: The California drug and alcohol treatment assessment (CALDATA): general report. Submitted to the State of California, Department of Alcohol and Drug Programs, by the National Opinion Research Center at the University of Chicago. Chicago: The University; 1994.

Harwood H, Fountain D, Livermore G, et al. The economic costs of alcohol and drug abuse in the United States, 1992. Report to the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism. Fairfax (VA): The Lewin Group. In review.

Levit K, Lazenby H, Braden B. National health expenditures 1995. Health Care Financing Review 1996:18(1);175-214.

National Association of State Alcohol and Drug Abuse Directors (NASADAD). State resources and services related to alcohol and other drug problems. A Report to the Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Rockville (MD): NASADAD; 1996.

National Opinion Research Center. The national treatment improvement evaluation study, preliminary report. Report to the Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, Rockville (MD): The Center; 1996.

Office of Applied Studies. National admissions to substance abuse treatment services: the treatment episode data set (TEDS) 1992-1995. Advance Report Number 12, Treatment Episode Data Set. Rockville (MD): Substance Abuse and Mental Health Services Administration; 1997 Feb.

Impact of Methadone Maintenance on HIV Seroconversion and Related Costs

Jeffrey Merrill, Ph.D.

Study Objective

The purpose of this paper is to look beyond the usual focus (i.e., abstinence) of clinical studies and examine how methadone treatment affects the broader health effects of intravenous (IV) heroin abuse. Specifically, this study will assess the impact of methadone maintenance on the incidence of HIV infection in this high-risk population. In addition, reductions in HIV prevalence will be converted into potential savings in overall U.S. health care expenditures.

Background

In 1996, Dr. Gerry Stimson of the University of London reported that the prevalence of HIV infection in the United Kingdom related to IV drug use was far lower than had been anticipated (Stimson, 1996). While earlier projections indicated that, by the mid-1990s, prevalence rates in the United Kingdom would reach 50 percent, only 2.5 to 3.0 percent of IV drug users became HIV-positive. One reason Dr. Stimson cites for this successful effort to reduce seroconversion in such a high-risk population is the expansion of methadone treatment programs.

The Stimson article points to an avenue of research that would address how we can judge the effectiveness of a substance abuse treatment modality: examining the impact that treatment has on the sequelae of drug addiction. It is difficult to judge the success of any treatment modality solely on the basis of whether it results in abstention. This is particularly true for methadone programs where a high percentage of patients may continue to use heroin, albeit at greatly reduced rates. Thus, studies can be more meaningful if, in addition to measuring urine results, they examine other, societally important outcomes. In the study discussed here, that outcome is the rate of HIV seroconversions.

A corollary issue is the treatment's impact on broader health care costs. In an era of managed care, cost-containment has become a principal focus. The question is no longer simply whether treatment reduces future costs for substance abuse relapse, but whether it can lessen overall health care costs. For this study, those costs are measured in terms of reducing the high health care costs of treating HIV infection and AIDS.

Study Methodology

The focus of the study is on subjects both in and out of methadone treatment in Philadelphia. The subjects were organized in two waves, one starting in 1989 (261 subjects) and the other in 1992 (396). Of these, 19 percent of the 1989 cohort received no treatment nor did 12 percent of the 1992. The rest were in treatment for varying lengths of time.

Baseline data were gathered by using a battery of instruments including the Addiction Severity Index (ASI) and the Risk Assessment Battery (RAB). In addition, through 1996, periodic HIV tests were conducted on all the subjects.

The average age of the subjects at the time the study began was 38 for the 1989 cohort and almost 40 for the 1992 cohort. The following table provides some basic information on the two groups.

Table 1. Selected population characteristics

	1989 Cohort	1992 Cohort	Total
N	261	396	657
	Percentage		
Gender			
Men	75	75	75
Women	25	25	25
Race			
White	28	35	32
Black	67	57	61
Hispanic	5	8	7
Employment[1]			
Full time	26	24	24
Unemployed	52	58	55
On welfare[2]	70	81	76
Psychiatric status[3]	24	20	21
Medical status[3]	22	24	23
HIV+ at baseline	13	16	15

[1]Typical employment status over last 3 years (at baseline).
[2]Percentage receiving some form of public assistance in last 30 days (at baseline).
[3]Percentage indicating serious problems over last 30 days (at baseline).

The focus of this study was to track seroconversion rates over time. Whereas 7 years of blood test data were available for the 1989 cohort, the 1992 cohort had only 4 years of these test data. In addition, for the purposes of the study, the subjects were placed into three groups representing their treatment status. These groups included:

- Group 1: individuals who had received no treatment (N = 74).
- Group 2: individuals who were in treatment for up to 2 years (N = 291).
- Group 3: individuals who were in treatment for more than 2 years (N = 189).

Results

Table 2 shows the percentage of individuals in each group who converted to HIV-positive over the 4 years. (Year 1 for the 1989 cohort was 1990, and 1993 for the 1992 cohort.)

Table 2. Percentage converted to HIV-positive

Year	Group 1	Group 2	Group 3
1	9.5	4.8	1.1
2	10.8	6.2	1.6
3	11.1	7.7	2.3
4	13.5	8.2	3.2

This table demonstrates that, for each year of followup, there is a correlation between the length of time in treatment and lower rates of seroconversion ($p<.05$). After 4 years, those who had received no treatment were 4.2 times more likely to have converted than those with 2 or more years of treatment. Obviously, other factors are at play here that will affect seroconversion, including clean needle programs (started in 1992-93) and increased publicity about IV drug use. Nevertheless, while these results do not prove causality, they do show a strong statistical relationship between treatment and reduced seroconversion.

It can be argued that, rather than a treatment effect, we are observing selection bias. The lower 4-year prevalence of HIV-positive in Group 3 may be attributed to the much higher incidence for the other two groups during the first year (9.5 percent and 4.8 percent versus 1.1 percent for Group 3). However, further exploration of the data indicates that this first year incidence is also a function of the length of time in treatment during that initial year. Of those who had no or only a few weeks of treatment during the first year, 9.5 percent converted; of those who received between 13 and 48 weeks, the prevalence was 4.5 percent; and of those with

more than 48 weeks, 2.1 percent converted. (The weeks in treatment during the first year are highly correlated [0.8] with the treatment intervals used to designate the three groups.)

Cost Reductions

Based upon the decreased incidence of seropositivity, we can make some estimates on reductions in health costs. Currently, the incidence of HIV-positive for IV drug users is 3 to 4 percent. This is based upon CDC surveillance data indicating about 25,000 new conversions per year among this population and between 500,000 and 750,000 IV heroin users. Assuming that everyone were put into a treatment program similar to the one under study, the overall incidence rate would decrease to about 1.5 percent. This is based upon a weighted average of the 4-year incidence rates for both Groups 2 and 3. (The incidence rate for Group 2 was 2.0 percent and for Group 3, 0.7 percent.)

Even using this conservative estimate, the number of new cases nationwide would decrease from the current 25,000 per year to 7,500 to 11,250. This represents a decrease of 55,000 to 70,000 individuals who become HIV-positive over the 4-year period. If one assumes that the cost of treating an individual who is seropositive averages about $10,000 per year (NIDA estimate), then the total 4-year cumulative savings would range from about $1.325 to $1.75 billion.

Given the fact that expanding methadone treatment to the entire IV drug-using population would cost an estimated $3 billion (still a rough estimate), these savings do not yield a positive net cost benefit. Nevertheless, it should be noted that this represents only one of the multiple health problems associated with IV drug use. Work by Merrill et al. (1994) found that, based upon the epidemiologic literature, there are a number of associated disease entities for which heroin use is a major etiologic factor, including hepatitis, cellulitis, TB, and adverse birth outcomes. All of these would potentially be affected by treatment as well. In addition, savings in nonmedical costs, most specifically criminal justice and welfare, would have to be factored into the cost-benefit equation.

But, in addition, these costs assume no effort to target methadone efforts at those who are at highest risk and who might benefit most from this treatment. For example, with the population studied, there were significant differences in both risk and impact based on race. For example, blacks and Hispanics were nearly twice as likely to be HIV-positive at baseline than whites (17.1 percent versus 8.8 percent, $p<.05$). At the same time, blacks were more likely to benefit from treatment: blacks who completed treatment were more than five times less likely to seroconvert than were blacks who received no treatment (16.1 percent versus 3.2 percent, $p<.05$). Further, although women were at no higher risk than men, they were significantly more likely to complete at least 2 years of treatment than were the men (52 percent versus 34 percent, $p<.001$). While a woman in treatment 2 or more years was no less likely to convert than a man, the fact that a higher percentage of women were in treatment longer meant that the overall

conversion rate for those in treatment was lower for females (5.4 percent versus 6.6 percent). Thus, by targeting methadone maintenance programs, benefits can be maximized while less is spent on treatment.

The results of this study are by no means conclusive. Yet they illustrate two important concepts in the current cost-conscious health system. Looking solely at the specific treatment outcomes associated with abstinence and reduced relapse rates may not be sufficient. The effects of substance abuse treatment on broader health concerns may yield as important and even more dramatic results. In addition, future interventions may be judged and compared as much by their ability to reduce costs as by their clinical outcomes.

References

Merrill, et al. Cost of substance abuse to the health care system. New York: Center on Addiction and Substance Abuse; 1994.

Stimson, GV. Has the United Kingdom averted an epidemic of HIV-1 infection among drug injectors? Addiction 1996;91(8):1085-8.

Transmission of Bloodborne Viruses Among Heroin Injectors

Donald C. Des Jarlais, Ph.D.

When a person injects drugs intravenously, he or she will insert the needle under the skin and search for a vein. When the injector thinks that a vein has been located, he or she will then pull back on the plunger of the syringe to see whether blood enters the barrel of the syringe. Blood entering the barrel shows that a vein has been located successfully. Pushing the plunger completely into the barrel of the syringe does not, however, completely expel all the blood/drug mixture in the needle and syringe; a modest amount of the mixture will be retained in the needle and syringe. If a second person then injects with the same needle and syringe without intensive cleaning of the needle and syringe, some blood of the first person will be injected into the vein of the second person. These microtransfusions from multiperson use (sharing) of needles and syringes are a relatively efficient method of transmitting bloodborne infectious agents. Although it has not yet been possible to quantify the probability of transmission, it is likely that multiperson use of other injection equipment, including the "cookers," "filters," and rinse water, may also transmit bloodborne pathogens among injecting drug users (IDUs).

Scope of the Problem

By 1996, the injection of illicit psychoactive drugs had been reported in 120 different countries . This is an increase over the 80 countries known to have illicit drug injection in 1989. Heroin is by far the most commonly injected drug throughout the world. Although the reasons for the spread of illicit drug injection have not been studied in detail, this spread is likely to be a result of improved global transportation and communication networks and economies of scale in the production of illicit drugs. Intravenous injection offers important economic advantages as a route of drug administration: it produces a very strong immediate drug effect, and almost all the drug is used.

Although it may be possible to improve the effectiveness of efforts to prevent the injection of illicit psychoactive drugs, the trend over the past several decades has clearly been an increasing spread of this practice. Public health officials will need to develop policies based on the great likelihood that illicit drug injection will continue in areas where it is currently established and continue to spread into new areas.

Human immunodeficiency virus (HIV), the virus that causes AIDS; hepatitis B virus (HBV); and hepatitis C virus (HCV) are the most important of the bloodborne infectious agents that are transmitted through multiperson use of drug injection equipment. HIV has been reported among IDUs in 81 different countries . Although the data on HBV and HCV transmission among IDUs are less complete than the data for HIV, these viruses are more readily transmitted than is

HIV, and a best estimate would be that HBV and HCV infections are present among IDUs in all countries with injecting drug use.

Injecting drug use does not by itself transmit HIV or other bloodborne viruses. Interventions that reduce injecting drug use would, however, have the potential for reducing multiperson use of injection equipment and thus reducing transmission of bloodborne infectious diseases. In particular, large-scale implementation of effective treatment for heroin addiction has the potential for reducing HIV transmission in many countries throughout the world.

Although HIV infection is a problem among drug injectors in a growing number of countries in the world, it is of particular importance in the United States. In the most recent estimates of new HIV infections in the United States, approximately one-half of all new infections occur among injecting drug users, and another one-fifth of the new infections occur among heterosexual partners of drug injectors. **Transmission of HIV among drug injectors is now the engine driving the continuing AIDS epidemic in this country. If we do not control the transmission of HIV among injecting drug users, we will not be able to control the AIDS epidemic as a whole**.

Rapid Transmission of HIV Among IDUs

There are many well-documented instances of rapid transmission of HIV among persons who inject illicit drugs, particularly among persons who inject heroin. Table 1 presents data on a sample of these rapid transmission epidemics of HIV among IDUs.

HIV Risk Reduction Among IDUs

IDUs will change their behavior in response to the threat of AIDS. Behavior change has been reported in association with education-only programs, HIV counseling and testing, street outreach, syringe exchange, increased pharmacy sales of injection equipment, and drug abuse treatment . The recent Consensus Development Conference on Behavioral Programs to Prevent HIV Infection concluded that there is strong evidence for the effectiveness of street outreach, syringe exchange, and methadone maintenance as methods for reducing HIV transmission among IDUs. Table 2 presents selected studies of HIV incidence among IDUs participating in methadone maintenance.

These studies illustrate what is currently known about the protective effect of methadone maintenance against HIV transmission. In the Swedish study, none of the IDUs who joined and were retrained in methadone maintenance became infected with HIV. In sharp contrast, one-half of the comparison group became infected with HIV. The comparison group comprised IDUs who had applied for treatment in the methadone program but did not receive treatment because the program had reached its licensed capacity. This study is the closest to a random assignment clinical trial of all studies to date.

Table 1. Instances of rapid transmission of HIV among injecting drug users

Bangkok, Thailand: HIV seroprevalence among IDUs increased from 2 percent to more than 40 percent in a single year.

Edinburgh, Scotland: HIV seroprevalence reached more than 40 percent in the year following introduction of the virus into the local population of IDUs.

Ho Chi Minh City, Vietnam: Seroprevalence increased from less than 10 percent to more than 40 percent in a period of 2 years.

Manipur, India: Seroprevalence reached 50 percent within the year following introduction of HIV into the local population of IDUs.

New York City, USA: Seroprevalence increased from less than 10 percent to 27 percent in a single year and then rose to more than 50 percent within the next 4 years.

Note: "Seroprevalence" refers to the percentage of drug injectors in a local population who are infected with HIV. These data are excerpted from a paper by Des Jarlais and colleagues (Des Jarlais, Friedman, Hagan, et al., in press). Note that these rapid transmission epidemics have occurred in both industrialized and developing countries. Analyses of these epidemics suggest three common conditions: (1) The IDUs at risk were not aware of the local threat of HIV/AIDS. (2) There were shortages of sterile injection equipment caused by laws and police practices that limited access to sterile injection equipment and the ability of IDUs to carry equipment with them. (3) Mechanisms such as "shooting galleries" and "dealer's works" facilitated rapid, efficient mixing among persons engaging in unsafe injections.

Table 2. HIV incidence among methadone maintenance patients

Location	Rate per 100 person-years at risk	Reference
Sweden	0.00	Blix, Gronbladh, 1988
Los Angeles	0.07	Kerndt, Weber, Ford, 1995
New York	0.88	Orr, Friedmann, Glebatis, et al., 1996
Philadelphia	2.30	Metzger, Woody, McLellan, et al., 1993
Amsterdam	4.00	van Ameijden, van den Hoek, Coutinho, 1991

In the Philadelphia study, 3.5 percent of methadone patients became infected with HIV over the 18-month study period (a rate of 2.3 new infections per 100 person-years at risk). Among the comparison group of IDUs who were not in drug abuse treatment during the study period, 22 percent became infected with HIV (a rate of 14.7 per 100 person-years at risk).

The Los Angeles study shows a very low HIV incidence rate, in part due to the low HIV seroprevalence rate among IDUs in that city (less than 10 percent seroprevalence). The New York City study shows that it is possible to achieve a low HIV incidence rate even with a high seroprevalence among the local population of IDUs (approximately 40 percent during the time of the study).

In the Amsterdam study, a relatively high HIV seroprevalence rate was observed among methadone maintenance patients, and this rate was the same as that observed among IDUs who were not participating in methadone treatment. The Amsterdam program used low methadone dosages during the time of the study, and the dosages prescribed were increased as a result of the study.

Causal Mechanisms

There are many ways in which participation in methadone treatment might reduce HIV transmission among IDUs. The most likely method is simply by reducing injection of heroin and thus reducing the opportunities for sharing injection equipment. Many methadone programs also provide education about safer sex and distribute condoms to their patients. Some programs in Europe and Australia also provide sterile injection equipment for persons who continue to inject, and some programs in the United States provide information on where sterile injection equipment might be obtained legally. This may be of particular importance to persons who are dependent on both heroin and cocaine. Methadone programs can also provide access to treatment for HIV infection, which may reduce infectiousness. There are not yet sufficient data to quantify the effects of these other modes of reducing HIV transmission among methadone patients.

Areas for Future Research

Although present data would strongly support a conclusion that methadone maintenance can substantially reduce risk behavior and HIV transmission among IDUs, a number of areas need to be addressed in future research. Participation in drug abuse treatment other than methadone maintenance has also been associated with reduced injection of heroin (Gerstein, Harwood, 1990; Hubbard, Marsden, Rachal, et al., 1989), but there have not been sufficient studies of HIV incidence among participants in other types of drug abuse treatment to test this hypothesis. Some drug abuse treatment programs, such as the Amsterdam program discussed above, may not be sufficient to reduce HIV incidence to a reasonable level. The reasons such programs are not sufficient need to be identified and then modified. How to reduce unsafe sexual behavior among persons in drug abuse treatment also requires additional study. In general, it has been much easier

to reduce injection risk behavior than to reduce sexual risk behavior among IDUs . Reducing HIV transmission among methadone patients who continue to inject drugs, particularly those who are dependent on cocaine, also requires additional research. Participation in drug abuse treatment should also provide a protective effect against infection with hepatitis B and hepatitis C, although studies to test this have not yet been conducted. Getting IDUs into treatment early enough in their injection careers—before they are infected with these viruses—may be a challenge.

The present data, however, indicate that in any future research, it would be highly unethical to deny access to methadone maintenance treatment to persons who inject heroin.

References

Blix O, Gronbladh L. AIDS and IV heroin addicts: the preventive effect of methadone maintenance in Sweden. Fourth International Conference on AIDS; Stockholm, Sweden; 1988.

Prenatal Care and Antiretroviral Use Associated With Methadone Treatment of HIV-Infected Pregnant Women

Barbara J. Turner, M.D., Craig Newschaffer, Ph.D., Thomas Fanning, Ph.D., and Walter Hauck, Ph.D.

With the advent of effective therapies that can modify the course of HIV disease and prevent perinatal transmission from mother to child, access to high-quality prenatal care for HIV-infected women is of paramount importance. Previous research by the authors' group on more than 2,000 HIV-infected women who delivered in the late 1980s revealed that methadone-treated women were more likely than other drug-using women to have an adequate number of prenatal visits. HIV-infected pregnant women not only need adequate prenatal care but also should have access to providers with HIV expertise and antiretroviral therapy during pregnancy. In this study, we examined diverse features of prenatal care for 1,205 HIV-infected women delivering in January 1993 through September 1994 while on New York State Medicaid. We also evaluated antiretroviral therapy use for 433 of these women who delivered after February 1994, the month when the results of the national clinical trial of zidovudine to prevent vertical transmission were first announced in public. We hypothesized that improved prenatal care of methadone-treated women would persist into the 1990s and translate into greater access to other services such as care from a provider with HIV expertise and antiretroviral therapy.

Our study data came from Medicaid claims and enrollment files linked to vital statistics birth records. To identify HIV-infected women, a validated case-finding method was applied to diagnostic data on claims. We identified illicit drug users from diagnostic and service codes on claims supplemented by vital statistics data; this approach has also been evaluated. Methadone and medically supervised drug treatment were defined from service bills. Five outcomes were analyzed:

1. Adequacy of prenatal care determined by the adequacy of prenatal care utilization measure applied to prenatal care claims from the following specialties—generalist, family practitioner, obstetrics/gynecology, and HIV-specific services;

2. Receipt of services from the Special Supplemental Food Program for Women, Infants and Children (WIC) Program documented on claims and reports on vital statistics;

3. Continuity of care determined by the largest proportion of prenatal visits delivered by a single clinic or physician;

4. Receipt of HIV-focused care from a provider paid at an enhanced Medicaid rate to provide a specific set of HIV services and to meet specified quality of care standards;

5. Antiretroviral therapy use from pharmacy claims during pregnancy.

Logistic regression models were used to estimate odds ratios for each outcome comparing methadone-treated women with drug-using women untreated during pregnancy after adjusting for diverse maternal characteristics.

Of 1,205 women, 7.6 percent were in methadone treatment during pregnancy, and 22.5 percent used illicit drugs during pregnancy without any evidence of ambulatory drug treatment. Sixty percent of the methadone-treated women received adequate prenatal care, and 53 percent received antiretroviral therapy during pregnancy compared with 50 and 32 percent, respectively, of drug users without treatment during pregnancy. In separate models for each of the five service use outcomes, we found an increased adjusted odds ratio (exceeding 1.2) for methadone-treated women compared with untreated drug users (the reference group), indicating a greater likelihood of beneficial health care services among methadone-treated women. The adjusted odds of adequate prenatal care, WIC during pregnancy, and higher continuity of prenatal care for methadone-treated women were 1.29, 1.23, and 1.21, respectively. Larger increases in the adjusted odds were observed for receipt of HIV-focused care during pregnancy (1.57; 95 percent confidence interval (CI) = 0.95, 2.60) and for antiretroviral therapy during pregnancy (2.75; CI = 1.00, 7.58). It should be noted that the CI for all these adjusted odds ratios are fairly wide and include unity. The sample of women enrolled in methadone treatment is relatively small, contributing to the lack of significant effects observed.

We also compared the outcomes of women who received medically supervised drug treatment during pregnancy (3.9 percent of the cohort) and women whose only evidence of drug use was outside pregnancy (7.6 percent of the cohort) with those of drug users untreated during pregnancy. These two groups' outcomes had higher odds of using most services compared with untreated drug users during pregnancy but showed a less consistently favorable pattern than the methadone-treated women.

We acknowledge that the higher probability of using important prenatal services for methadone-treated women may be the result of unmeasured maternal characteristics such as a greater belief in the benefits of health care rather than methadone treatment. However, it is also quite likely that these favorable outcomes are caused by factors associated with methadone treatment, such as regular monitoring of drug-using pregnant women and avoidance of the chaotic lifestyle characteristic of illicit drug users.

Taken together, these data suggest that methadone-treated HIV-infected women are receiving better care during pregnancy than drug-using women who were not in treatment. Better

care during pregnancy for HIV-infected women with substance abuse problems can translate into substantial neonatal health benefits and societal cost savings. Published analyses indicate an ultimate health care cost savings of $0.5 to $2 million per 100 HIV-infected women treated with prenatal antiretroviral therapy that is attributable to the prevention of HIV infection in the offspring. These data suggest that methadone is likely to be cost-effective in HIV-infected pregnant women.

Selected Bibliography

Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl J Med 1994;331:1173-80.

Silverman NS, Rohner DM, Markson LE, Turner BJ. Attitudes toward health care and human immunodeficiency virus infection among inner-city, pregnant women. Am J Perinatol 1997;14:341-6.

Turner BJ, Markson LE, Hauck WW, Cocroft J, Fanning T. Prenatal care of HIV-infected women: analysis of a large New York State cohort. J Acquir Immune Defic Syndr Hum Retrovirol 1995;4:371-8.

Turner BJ, Hauck WW, Fanning TR, Markson LE. Cigarette smoking and maternal-child HIV transmission. J Acquir Immune Defic Syndr Hum Retrovirol 1997;14:327-37.

Turner BJ, McKee-Nelsen L, Fanning TR, Hauck WW. Prevention of vertical HIV transmission with zidovudine: projected impact of HIV testing and prenatal care. AIDS Care. In press.

Turner BJ, Newschaffer C, Fanning TR, Zhang DZ, Hauck WW. Antiretroviral use by Medicaid-enrolled, HIV-infected pregnant women. National Conference on Women and HIV, Pasadena, CA. May 1997.

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Deaths Among Heroin Users In and Out of Methadone Maintenance

David P. Desmond, M.S.W., and James F. Maddux, M.D.

Methadone is a potent opioid agonist, and, when taken in doses exceeding a person's tolerance, it has a depressant effect on nervous system function, with special, prolonged effect on respiratory function (Verebely, Volavka, Mule, et al., 1975; Olsen, Wilson, Robertson, 1981). Thus, two of the pharmacologic properties of the drug that make it ideal for maintenance—slow onset of action when taken orally and a long half-life—also contribute to the likelihood of fatal outcome when misused.

Methadone is consistently found among the top 20 drugs mentioned in annual surveys of deaths reported by medical examiners in the Drug Abuse Warning Network (DAWN) (Substance Abuse and Mental Health Services Administration, 1996). Methadone toxicity ranks high among the list of problems cited by opponents of methadone treatment (Newcombe, 1996; Marks, 1994), and periodic outbreaks of methadone-related deaths (Zimney, Luke, 1981; Drummer, Opeskin, Syrjanen, et al., 1992; Barrett, Luk, Parrish, et al., 1996) appear to lend credence to these critics. In contrast, standard substance abuse textbooks (Lowinson, Ruiz, Millman, et al., 1992; Galanter, Kleber, 1994) often emphasize the safety of methadone in the treatment of opioid dependence.

Death directly attributable to methadone toxicity is, in fact, relatively rare among patients on maintenance. When such deaths do occur, they tend to happen during induction to maintenance, when assessment of patients' tolerance to opioids and concurrent use of other substances is especially problematic (Drummer, Opeskin, Syrjanen, et al., 1992). The majority of deaths involving methadone occur among persons who are not enrolled in a treatment program (Baden, 1970; Greene, Luke, DuPont, 1974; Manning, Bidanset, Cohen, et al., 1976; Barrett, Luk, Parrish, et al., 1996).

The early data on mortality during methadone maintenance were equivocal. Sells, Chatham, and Retka (1972) compared death rates and causes of death among 9,276 opiate addicts in various treatment modalities studied in the 1970-71 DARP (Division of Application Review and Policy, NIH) cohort. Patients in methadone maintenance had higher death rates (18 per 1,000) than did persons in therapeutic communities (6 per 1,000) or in outpatient drug-free treatment (10 per 1,000). Gearing (1972) presented data from a large New York City study that demonstrated markedly reduced death rates among methadone maintenance patients compared with patients discharged from treatment and patients admitted to detoxification only. In Gearing's study, death rates of patients on methadone approached those of the general New York

City population for similar age groups.

We reviewed published studies of mortality among opioid users in order to summarize current knowledge about the impact of methadone maintenance on drug users' death rates and to identify areas in need of additional research. The studies were divided into four groups: (1) studies of death rates before the introduction of methadone maintenance, (2) studies after the introduction of methadone, (3) studies of deaths during methadone maintenance, and (4) studies comparing death rates in and out of methadone maintenance within the same study. Studies in Group 4 provide the best data for evaluation of the effect of methadone maintenance on mortality because they minimize the effects of variations in methodology and in social environments that hamper between-study comparisons. These studies are summarized in Table 1.

Table 1. Studies comparing death rates of opioid users on and off methadone maintenance*

Author/Year	Location	Comparison Groups	No.	Person-Years	Deaths	Rate†	Relative Risk
Gearing, Schweitzer (1974)	USA	Patients on methadone. Discharged patients.	3,000 850	14,474 1,170	110 33	7.6 28.2	0.27
Cushman (1977)	USA	Patients on methadone. Discharged patients.	547 158	1,623 291	25 14	15.4 47.1	0.32
Des Jarlais (1984)	USA	Patients on methadone. Discharged patients.	1,545 n/r‡	6,118 2,351	93 83	15.2 35.3	0.43
Grönbladh, Öhlund, Gunne (1990)	Sweden	Patients on methadone. Discharged patients (n = 87) and untreated controls (n = 115).	166 202	1,143 1,406	16 80	14.0 56.9	0.25
Poser, Koc, Ehrenreich (1995)	Germany	Patients on methadone. Injecting heroin users.	151 188	149 167	3 14	20.1 83.8	0.24
Caplehorn, Dalton, Haldar, et al. (1996)	Australia	Patients on methadone. Discharged patients.	296 n/r‡	1,792 2,004	9 33	5.0 16.5	0.30
Maddux & Desmond (unpublished)	USA	Patients on methadone. Discharged patients.	610 321	435 110	4 3	9.2 27.3	0.34

* Adapted from Caplehorn, et al. (1996), with additional data.
† Rate per 1,000 person-years.
‡ n/r = not reported.

Death rates on methadone maintenance ranged from 5.0 to 20.1 per 1,000 person-years; the median was 14.0. Death rates among subjects not on methadone maintenance ranged from 16.5 to 83.8 per 1,000 person-years; the median was 35.3. The relative risk (RR) of dying on methadone maintenance ranged from 0.24 to 0.43. Capelhorn and associates (1996) performed a meta-analysis using data from five of the seven studies in Table 1. The combined results indicated that methadone maintenance reduced addicts' risk to one-fourth; RR = 0.25 (95% CI, 0.19 to 0.33).

Reduction in mortality was best explained by reductions in number of deaths due to opioid drug overdoses, especially heroin overdoses (Capelhorn, Dalton, Haldar, et al., 1996; Des Jarlais, 1984; Maddux, Desmond, unpublished data; Texas Department of Health, unpublished data).

Two additional studies (Weber, Ledergerber, Opravil, et al., 1990; Fugelstad, Rajs, Bottiger, et al., 1995) offer strong support for these conclusions. Both found marked reductions in death, on the order of one-third to one-fourth, among methadone-maintained persons. Neither reported all the data needed to compute death rates comparable to those in Table 1. Nevertheless, the direction of the findings was clear: deaths among opioid users on methadone maintenance are only a fraction of those observed in persons discharged from or never admitted to methadone maintenance.

Discussion

Improved health and reduced mortality are important goals of substance abuse treatment, but relatively little attention is paid to these benefits in outcome studies (Poser, 1995). Although death rates among opioid users continue to be elevated even during periods of treatment, there is credible evidence that methadone maintenance significantly reduces addicts' risk of death. The improved survival during maintenance is attributable in large part to protection from heroin overdose. This benefit, as with other benefits of methadone maintenance, is closely associated with retention in treatment; the effects do not persist beyond termination of therapy.

References

Baden MM. Methadone related deaths in New York City. Int J Addict 1970 Sep;5(3):489-98.

Barrett DH, Luk AJ, Parrish RG, Jones TS. An investigation of medical examiner cases in which methadone was detected, Harris County, Texas, 1987-1992. J Forensic Sci 1996 May;41(3):442-8.

Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. Subst Use Misuse 1996 Jan;31(2):177-96.

Cushman P. Ten years of methadone maintenance treatment: some clinical observations. Am J Drug Alcohol Abuse 1977;4(4):543-53.

Des Jarlais DC. Research design, drug use, and deaths: cross study comparisions. In: Serban G, editor. The social and medical aspects of drug abuse. Jamaica (NY): Spectrum Publications; 1984. p. 229-35.

Drummer OH, Opeskin K, Syrjanen M, Cordner SM. Methadone toxicity causing death in ten subjects starting on a methadone maintenance program. Am J Forensic Med Pathol 1992 Dec;13(4):346-50.

Fugelstad A, Rajs J, Bottiger M, De Verdier MG. Mortality among HIV-infected intravenous drug addicts in Stockholm in relation to methadone treatment. Addiction 1995 May;90(5):711-6.

Galanter M, Kleber HD, editors. The American Psychiatric Press textbook of substance abuse treatment. Washington: American Psychiatric Press; 1994.

Gearing FR. Deaths before, during, and after methadone maintenance treatment in New York City. Proceedings of the Fourth National Conference on Methadone Treatment. New York: National Association for Prevention of Addiction to Narcotics; 1972. p. 493-4.

Gearing FR, Schweitzer MD. An epidemiologic evaluation of long-term methadone maintenance treatment for heroin addiction. Am J Epidemiol 1974 Aug;100(2):102-12.

Greene MH, Luke JL, DuPont RL. Opiate overdose deaths in the District of Columbia. II. Methadone-related fatalities. J Forensic Sci 1974 Jul;19(3):575-84.

Grönbladh L, Öhlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. Acta Psychiatr Scand 1990 Sep;82(3):223-7.

Lowinson JH, Ruiz P, Millman RB, Langrod JG, editors. Substance abuse: a comprehensive textbook. Baltimore: Williams & Wilkins; 1992.

Manning T, Bidanset JH, Cohen S, Lukash L. Evaluation of Abuscreen® for methadone. J Forensic Sci 1976 Jan;21(1):112-20.

Marks J. Deaths from methadone and heroin [letter]. Lancet 1994 April 16;343(8903):976.

Newcombe R. Live and let die: is methadone more likely to kill you than heroin? Druglink 1996 Jan-Feb.

Olsen GD, Wilson JE, Robertson GE. Respiratory and ventilatory effects of methadone in healthy women. Clin Pharmacol Ther 1981 Mar;29(3):373-80.

Poser W, Koc J, Ehrenreich H. Methadone maintenance treatment. Methadone treatment can reduce mortality [letter]. BMJ 1995 Feb 18;310(6977):463.

Sells SB, Chatham LL, Retka RL. A study of differential death rates and causes of death among 9276 opiate addicts during 1970-1971. Contemporary Drug Problems 1972;1:665-706.

Substance Abuse and Mental Health Services Administration (SAMHSA). Annual medical examiner data 1994. Series I, Number 14-B. DHHS Publication (SMA) 96-3078. Bethesda (MD): SAMHSA; 1996.

Verebely K, Volavka J, Mule S, Resnick R. Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. Clin Pharmacol Ther 1975 Aug;18(2):180-90.

Weber R, Ledergerber B, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. BMJ 1990 Dec 15;301(6765):1362-5.

Zimney EL, Luke JL. Narcotic-related deaths in the District of Columbia, 1971-1979. J Forensic Sci 1981 Jul;26(3):462-9.

Detoxification With or Without Opiate Agonist Treatment

Herbert Kleber, M.D.

Although detoxification is often the route into treatment, many who begin detoxification do not complete it, and many completers do not go on to more definitive treatment. Some enter detoxification only to lower their level of dependence and make their habit cheaper; others fully believe that detoxification is all that is necessary and that they will then be able to remain drug-free. When they return for a second or third detoxification, they are often more realistic and more willing to consider longer term treatment.

What Is Detoxification?

Detoxification refers to the process whereby an individual who is physically dependent on a drug is taken off that drug either abruptly or gradually. Drugs used to aid in detoxification include (1) the drug on which the individual is dependent, (2) other drugs that produce cross-tolerance, (3) medications to provide symptomatic relief, and (4) drugs that affect the mechanisms by which withdrawal is expressed.

When Is Detoxification Successful?

Because relatively few narcotic-addicted patients discontinue their drug habit after detoxification alone, detoxification is usually viewed as pretreatment or, at best, the first stage of treatment. It is thus unrealistic to expect to achieve the more ambitious goals for long-term treatment. Success is a function of safety and minimal discomfort as well as how many patients are retained and how many go on to longer term treatment.

Choice of Setting

Detoxification can take place in an inpatient, partial hospitalization, or outpatient setting (Kleber, 1996). Outpatient detoxification is the least expensive and enables the patient to remain at work or otherwise to carry on his or her life. It forces patients to cope with the settings where they will be after they have become drug-free. The disadvantages include being surrounded by temptations when least able to handle them, greater difficulty assessing and dealing with other medical conditions, and the possible need for detoxification to proceed more slowly so as not to subject the patient to undue stress in the unprotected environment. Inpatient detoxification has the advantages of taking place in a protective setting where access to drugs or craving-inducing stimuli are absent, allowing closer observation for possible medical problems or complications and more rapid withdrawal. It has both higher completion rates (Gossop, Johns, Green, et al., 1986) (70 to 84 percent compared with as low as 13 to 17 percent) and higher costs compared with outpatient detoxification. The disadvantages are primarily the cost but also the disruption

of the patient's life and the need to be away from work and home. Day programs are considerably less expensive than inpatient programs, have some of their advantages, but are relatively uncommon. The clinician is usually forced to choose between inpatient and outpatient, with the decision often being made by factors such as insurance coverage and availability of programs in the community. There is little evidence that the higher initial rate with an inpatient setting is associated with better sustained abstinence.

Factors Influencing Symptom Severity

The nature and severity of withdrawal symptoms when use of opioid-type drugs is halted relate to a variety of factors, including the specific drug and total daily amount used, duration and regularity of use, and psychological factors.

Techniques of Withdrawal

Methadone substitution and withdrawal. Currently the most common, but not necessarily the best, method of opioid withdrawal is methadone substitution and withdrawal. The advantages of methadone over other narcotics are the following: it is orally effective, long acting, and an easy and safe method of opiate detoxification as long as certain precautions are followed regarding initial dosing. Food and Drug Administration (FDA) guidelines for narcotic detoxification describe two types of detoxification: short term and long term. Short-term detoxification is for a period of not more than 30 days (usually for heroin addicts); long-term detoxification is for a period of not more than 180 days (usually for patients coming off methadone maintenance). Disadvantages of methadone withdrawal include the need for a special license to prescribe it, arguments with patients as to whether enough narcotic is being prescribed, and the reappearance of mild withdrawal symptoms (rebound) lasting more than 1 month after the last dose of methadone (Gossop, Griffiths, Bradley, et al., 1989). This last disadvantage is frequently associated with relapse; thus, the ease of use is counterbalanced by a higher relapse rate (Rounsaville, Kosten, Kleber, 1985).

Even with gradual withdrawal, all withdrawal symptoms may not be totally suppressed, and certain mild symptoms may persist after the last methadone dose. There is no consensus on use of other drugs during these periods. Muscle aches can be helped by nonsteroidal anti-inflammatory drugs (NSAIDs) or benzodiazepines such as oxazepam; α-adrenergic agonists such as clonidine are sometimes used during post-methadone withdrawal to decrease lingering signs and symptoms; and insomnia can be handled by cautious short-term use of benzodiazepines, diphenhydramine, or chloral hydrate. Nonpharmaceutical supports can also play an important and useful role; these can include a warm, kind, and reassuring staff attitude; warm baths; and exercise (when the patient feels up to it).

Clonidine hydrochloride. The α-2 agonist drug clonidine, marketed as an antihypertensive, has been used to facilitate opioid withdrawal (Gold, Redmond, Kleber, 1978) in both inpatient and outpatient settings. In dosages of 0.6 to 2 mg/day, it reduces many of the autonomic components of the opioid withdrawal syndrome, although craving, insomnia,

irritability, and muscle aches are not well suppressed. Clonidine exerts its ameliorative actions by binding to α-2 autoreceptors in the brain, suppressing the activity of the locus coeruleus and spinal cord. Clonidine has been used for outpatient detoxification from both heroin and methadone maintenance. Detoxification from 20 mg/day or less of methadone is about as successful after abrupt substitution of clonidine as after reduction of methadone by 1 mg/day (Kleber, Riordan, Rounsaville, et al., 1985). With heroin-addicted patients, approximately one-half are successfully withdrawn by use of clonidine on an outpatient basis. Other α-2 adrenergic agonists such as lofexidine (Gold, Penash, Sweeney, et al., 1982) and guanfacine (Schubert, Fleischhacker, Meise, et al., 1984) also appear to ameliorate aspects of the opioid withdrawal syndrome. Lofexidine appears to decrease withdrawal with less hypotensive side effects and is currently used for this in England (Wylie, Stewart, 1995). The use of clonidine for controlling withdrawal has not yet been given FDA approval, but clonidine has been used so widely, both in the United States and abroad, that it has become accepted as an alternative to gradual methadone reduction. Clonidine is better than methadone for detoxification because it has less diversion potential, postwithdrawal rebound is less likely to occur, and no special license is needed. Disadvantages include less symptom suppression and more need to monitor blood pressure. Clonidine's mild analgesic effects may help in withdrawing "medical addicts." Pain usually returns within 24 to 48 hours after the last clonidine dose.

Rapid clonidine/naltrexone withdrawal. Although clonidine can be an effective alternative to methadone for opiate withdrawal, it does not substantially shorten the withdrawal time or have an adequately high success rate. To solve these two problems, researchers combined clonidine and naltrexone. Naltrexone produces an immediate and severe withdrawal syndrome as it displaces the opioid from the endogenous receptor. However, when clonidine is used both before and after the naltrexone, symptoms are substantially relieved. For those symptoms not adequately controlled, other medications such as oxazepam and NSAIDs for muscle spasms and antiemetics (e.g., ondansetron) for vomiting are used. The method was first described at Yale in the early 1980s (Riordan, Kleber, 1980; Charney, Heninger, Kleber, 1986) and improved over the next decade (Kleber, Topazian, Gaspari, et al., 1987; Vining, Kosten, Kleber, 1988; O'Connor, Waugh, Schottenfield, et al., 1992). The patient is premedicated with clonidine and oxazepam; an hour later, 12.5 mg of naltrexone is given. The clonidine and oxazepam are then given every 4 to 6 hours over the next 3 days as needed. On day 2, a dose of 25 mg of naltrexone is given, and on day 3, the full maintenance dose of 50 mg of naltrexone is given. Ninety-five percent of the patients in one study (O'Connor, Waugh, Schottenfield, et al., 1992) were able to successfully complete detoxification in an outpatient primary care setting and move on to the next phase of treatment. One month later, however, there was no difference in percentage of treatment retention between the clonidine alone and the clonidine with naltrexone.

Advantages of this method are the marked shortening of time to 48-72 hours and higher completion rate. The limitations of this method are the need for intensive monitoring of patients by experienced staff for 8 hours on day 1 and 4 hours on day 2 as well as more discomfort, especially during the first few hours. Because the dose of clonidine needed actually decreases after the first day even though the dose of naltrexone is increasing, naltrexone may be rapidly

normalizing the number and sensitivity of opioid receptors and reversing the opioid-induced central noradrenergic hypersensitivity (Vining, Kosten, Kleber, 1988). An even more rapid version has been developed for inpatient use. Through the use of higher doses of naltrexone and clonidine on day 1, the average withdrawal time was reduced from approximately 2 days to a little more than 1 day (Brewer, Rezae, Bailey, 1988).

Ultrarapid anesthesia-aided (or sedation) detoxification. A much more rapid method reduces withdrawal time to 5-6 hours by having the patient under intravenous sedation with midazolan (Loimer, Lenz, Schmid, et al., 1991) or under general anesthesia (e.g., propoful) with clonidine premedication, increasing doses of naltrexone via a nasogastric tube, and antiemetic and antidiarrheal agents. Although use of intubation and the other agents decreases side effects, the risk of general anesthesia remains. Controlled outcome studies are yet to be done, but there are claims of high success rates in open studies in other countries. Some programs offer postdetoxification counseling and maintenance on naltrexone, whereas others provide just the detoxification. Possible advantages of the technique include rapid withdrawal with probably a high completion rate and ability to reach addicts who fear any withdrawal discomfort. Disadvantages include the risks of anesthesia (or aspiration under deep sedation if not intubated), probably less elimination of postwithdrawal discomfort than claimed, and high cost (Stephenson, 1977). If research shows that long-term patients are more likely to have remained opiate-free and that risks are not substantial, such a finding could shift the risk/benefit ratio toward the benefit side.

Rapid buprenorphine, naltrexone, and clonidine detoxification. Recent studies have involved rapid detoxification using buprenorphine, naltrexone, and clonidine. In one study, 23 patients maintained on buprenorphine for 1 month at a dosage of 3 to 6 mg/day were abruptly given 1 mg of naltrexone 24 hours after the last buprenorphine dose, followed by 6, 12.5, 25, and 50 mg of naltrexone on successive days. Minimal withdrawal occurred, and 20 of the 23 patients took the initial 6-mg naltrexone dose (Kosten, Morgan, Kleber, 1991). In a more recent version, patients were switched from heroin to sublingual buprenorphine 3 mg/day for 3 days. On day 4, the clonidine/naltrexone procedure was implemented, starting with 25 mg of naltrexone. On day 5, a dose of 50 mg of naltrexone was given. Eighty percent of patients successfully completed the withdrawal (O'Connor, Waugh, Weiss, et al., 1993). Because withdrawal from buprenorphine is milder than that from heroin or methadone, a rapid detoxification method involving first a transition to buprenorphine and then some variant of the clonidine/naltrexone approach may be least painful and have the highest chance of success.

Acupuncture. On the basis of studies to date, traditional and electroacupuncture therapies appear more promising in reducing symptoms of opiate withdrawal than does cranioelectric stimulation or neuroelectric therapy. Individuals with small habits appear to do better than those with larger ones in withdrawal, but insufficient data exist to make other generalizations. There are also insufficient data to draw any conclusions about the usefulness of these therapies postwithdrawal in decreasing relapse. Acupuncture could find a useful place as a relatively inexpensive adjunct to existing treatment methods, both pharmacologic and psychologic, especially for patients who prefer not to use medications for withdrawal or to treat

the rebound symptoms postmethadone (Brewington, Smith, Lipton, 1994).

Research Issues

The ideal detoxification method would be relatively short, safe, cheap, and painless; it could be done in an outpatient setting and leave the patient with a desire to seek longer term help. Although none of the techniques reviewed meet all these criteria, researchers are closing in on methods for dealing with the pharmacologic aspects of detoxification. In addition, it is necessary to focus on finding the best psychological approaches and combining them to ensure that the patient completes detoxification and moves on to the next stage. After all, the critical issue is not detoxification, but the prevention of relapse.

Questions on existing techniques include which α-2 agonist is the best to use in terms of effectiveness and fewer side effects; whether any of the existing techniques decrease craving and the protracted withdrawal syndrome; whether any of the existing techniques are superior for abstinence or treatment retention 3 to 6 months postdetoxification; and, finally, whether there are subsets of patients that do better with one or another technique.

References

Brewer C, Rezae H, Bailey C. Opioid withdrawal and naltrexone induction in 48-72 hours with minimal drop-out, using a modification of the naltrexone-clonidine technique. Br J Psychiatry 1988;153:340-3.

Brewington V, Smith M, Lipton D. Acupuncture as a detoxification treatment: an analysis of controlled research. J. Subst Abuse Treat 1994;11:289-307.

Charney DS, Heninger GR, Kleber HD. The combined use of clonidine and naltrexone as a rapid, safe, and effective treatment of abrupt withdrawal from methadone. Am J Psychiatry 1986;143:831-7.

Gold MS, Penash AC, Sweeney DR, et al. Lofexidine blocks acute opiate withdrawal. Natl Inst Drug Abuse Res Monogr Ser 1982;41:261-3.

Gold MS, Redmond DE, Kleber HD. Clonidine blocks acute opiate withdrawal symptoms. Lancet 1978;2:599.

Gossop M, Griffiths P, Bradley B, Strang J. Opiate withdrawal symptoms in response to 10-day and 21-day methadone withdrawal programmes. Br J Psychiatry 1989;154:360-3.

Gossop M, Johns A, Green L. Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. BMJ 1986;293:103-4.

Kleber HD. Outpatient detoxification from opiates. Primary Psychiatry 1996;1:42-52.

Kleber HD, Riordan CE, Rounsaville B, et al. Clonidine in outpatient detoxification from methadone maintenance. Arch Gen Psychiatry 1985;2:391-4.

Kleber HD, Topazian M, Gaspari J, et al. Clonidine and naltrexone in the outpatient treatment of heroin withdrawal. Am J Drug Alcohol Abuse 1987;13:1-17.

Kosten TR, Morgan C, Kleber HD. Treatment of heroin addicts using buprenorphine. Am J Drug Alcohol Abuse 1991;7(1):119-28.

Loimer N, Lenz K, Schmid R, et al. Technique for greatly shortening the transition from methadone to naltrexone maintenance of patients addicted to opiates. Am J Psychiatry 1991;148:933-5.

O'Connor PG, Waugh ME, Schottenfield RS, et al. Ambulatory opiate detoxification and primary care: a role for the primary care physician. J Gen Intern Med 1992;7:532-4.

O'Connor P, Waugh ME, Weiss EC, et al. A comparison of clonidine, clonidine naltrexone, and buprenorphine in primary care based ambulatory opioid detoxification [abstract]. Clin Res 1993;41:545A

Riordan CE, Kleber HD. Rapid opiate detoxification with clonidine and naloxone. Lancet 1980;1:1070.

Rounsaville BJ, Kosten TR, Kleber HD. Success and failure at outpatient opioid detoxification: evaluating the process of clonidine and methadone-assisted withdrawal. J Nerv Ment Dis 1985;173:103-10.

Schubert H, Fleischhacker WW, Meise U, et al. Preliminary results of guanfacine treatment of acute opiate withdrawal. Am J Psychiatry 1984;141:1271-3.

Stephenson J. Experts debate merits of 1-day opiate detoxification under anesthesia. JAMA February 5, 1977;277(5).

Vining E, Kosten TR, Kleber HD. Clinical utility of rapid clonidine-naltrexone detoxification for opioid abuse. Br J Addict 1988;83:567-75.

Wylie AS, Stewart AM. Lofexidine based regimen for opiate addicts [Letter]. Br J Gen Pract 1995;45:217-8.

Behavioral Therapies: A Treatment Element for Opiate Dependence

John Grabowski, Ph.D.

Extensive clinical research has demonstrated the effectiveness of some behavioral therapies as adjuncts in treatment of opiate dependence. No behavioral intervention alone has been demonstrated to be more effective than methadone alone or methadone combined with adjunctive behavioral therapy. Precise delineation of setting conditions and behavioral therapies is critical to application. It is important to (1) identify when collateral behavioral therapies are necessary, (2) determine which behavioral therapies will be effective in a particular clinical setting, (3) define the degree to which they should be applied, and (4) determine which therapies are of little value, or even detract from successful treatment with medication.

Setting Conditions of Treatment

Setting conditions include medication administration, clinical environment (inpatient, residential, or outpatient; location; physical characteristics; relation to other services), treatment cost (fee vs. free), conditions of behavioral therapy (group or individual, visit frequency, duration), the characteristics or qualifications of service providers, and the characteristics of the patient population. For example, Grabowski and colleagues (Rhoades, Creson, Elk, et al., in press; Yarmolinsky, Pechura, 1996) have demonstrated that the requirements for frequent clinic attendance specified by Federal methadone maintenance guidelines can reduce patient retention, whereas reduced attendance requirements enhance retention and reduce treatment cost. The setting conditions are also defined by a series of requirements within the environment ranging from the general clinic rules through the specific application of therapeutic interventions.

Typically, the methadone treatment setting is not integrated with other health care services. Rather, it is provided in separate drug dependence treatment clinics often located at some distance from other health care facilities. These clinics focus therapeutic efforts on a cadre of patients with common problems. There are at least two resulting disadvantages: (1) there is no dilution of common social and behavioral problems that might occur in traditional drug abuse treatment settings; (2) there is little opportunity for integration of services, although as with other patient populations, other behavioral, social, drug, and medical problems commonly emerge. The result is that methadone maintenance clinics become unusual "institutionalized" settings in which behavioral treatment is provided outside the usual health care delivery system (Institute of Medicine, 1995; Cooper, 1991). General clinic rules are prominently posted for patients in these settings, who are often stereotyped as antisocial, or even dangerous. These settings emphasize stigmatization, may deter some patients from entering treatment, and limit access to behavioral therapies that might be useful. These setting features may increase the likelihood of stereotypic "drug user" behaviors such as loitering, drug dealing, and patient drop-out. Despite this sometimes adverse therapeutic climate, the pharmacological effects of

methadone in the opioid-dependent patient enhance patient retention, thereby providing the opportunity for behavioral treatments to be applied.

Clinics emphasizing health care, while minimizing a "criminal justice" atmosphere, may be more likely to engender appropriate treatment-oriented behavior (Elk, Grabowski, Rhoades, et al., 1993; Grabowski, Rhoades, Elk, et al., 1993). Use of standardized clinical procedures such as appointment scheduling, confidentiality, and individualization can further modulate patient behavior.

Therapy Forms

The treatment philosophy, training of the providers, and stated treatment goals vary widely across clinics. They range from well-documented procedures, such as supportive expressive psychotherapy, to cognitive behavioral therapy, contingency management approaches, and strictly defined cue reactivity to a spectrum of interventions for which there are no supporting data on clinical effectiveness. The latter are poorly defined and may be countertherapeutic.

Even in the application of well-studied, professionally-delivered behavioral treatments, there is often an underlayer of perspectives derived from social beliefs or folklore on the causes of, and cures for, drug dependence. These compete with established, well-documented therapies for patient and staff time. The need for change and integration of demonstrably effective behavioral treatment with medication has been discussed in an excellent series of research monographs from the National Institute on Drug Abuse (Krasnegor, 1979; Grabowski, Stitzer, Henningfield, 1984; Tims, 1984; Ashery, 1985; Onken, Blaine, 1990; Pickens, Leukefeld, Schuster, 1991; Onken, Blaine, Boren, 1995) over the last 25 years. Despite an impressive research history, application of rigorous data-based interventions for opiate dependence has been hindered (Miller, 1993).

Several behavioral therapies have been demonstrated effective in standard opiate treatment clinic settings. Woody and colleagues (Woody, Luborsky, McLellan, et al., 1983) reported benefit of supportive expressive therapy and behavior therapy in the treatment of methadone-maintained patients. McLellan and colleagues (O'Brien, Woody, McLellan, 1995) have described elements of treatment that contribute to positive outcomes. Recently, Nunes and colleagues (Nunes, Coyne, Young, et al., 1997) provided a positive, albeit descriptive, report of use of group psychotherapy in refractory methadone patients, with discussion of the broad range of social problems encountered by some drug users. Substantial refinement is needed to identify patient populations for which this approach is appropriate. Many patients do not require intense interventions, and treatment retention may be diminished with high-functioning patients or those preferring individual therapy.

Carroll and colleagues (Carroll, 1993) have provided impressive demonstrations of the

utility of behavioral/psychotherapy techniques in the treatment of collateral problems in various forms of drug dependence. Stitzer, Bigelow, and colleagues have conducted an extensive series of carefully controlled trials in which contingency management procedures were applied to specific features of behavior (Stitzer, Kirby, 1991; Stitzer, Bigelow, Liebson, et al., 1984) without additional psychotherapies. Behavioral strategies manipulating the number of patient take-home doses and thus clinic-visit frequency and patient-based dose adjustment are but two variables demonstrated to influence treatment compliance and reduce use of illicit drugs. This research emphasizes the role of methadone not only as a medication with pharmacological effects that reduce opioid use, but also as a valuable tool in sustaining patient access to, compliance with, and success of behavioral therapies. Data from Childress, O'Brien, and colleagues suggest that a focus on attenuating drug-related cues that elicit drug seeking and taking can be important (Childress, Hole, Ehrman, et al., 1993). In the context of setting conditions, results from Senay (Senay, Barthwell, Marks, 1993) imply that well-stabilized methadone maintenance patients benefit most from minimum contact and no adjunctive behavioral therapy. Recent data from clinical trials also suggest that even new methadone patients benefit from systematic but less, rather than more, intrusive behavioral interventions (Rhoades, Cresson, Elk, et al., 1996).

Conclusions

In combination, the extensive research database indicates that behavioral treatments can be effective when systematically administered in a therapeutic setting clearly contrived to emphasize therapeutics. Protocol-driven interventions focused on avoiding drug use and strengthening positive behaviors and structured to more closely resemble mainstream health care may enhance effective pharmacotherapy, particularly when service is unimpeded by social stigma. At the same time, in the absence of psychiatric disorders or behavioral deficits, therapy beyond careful medication management may have little benefit.

References

Ashery R, editor. Progress in the development of cost-effective treatment for drug abusers. National Institute on Drug Abuse Research Monograph Series #58. Washington: DHHS; 1985.

Carroll KM. Psychotherapeutic treatment of cocaine abuse: models for its evaluation alone and in combination with pharmacotherapy. In Tims F, Leukefeld C, editors. Cocaine treatment: research and clinical perspectives. National Institute on Drug Abuse Research Monograph Series #135. Washington: DHHS; 1993. p. 116-32.

Childress AR, Hole AV, Ehrman RN, Robins SJ, McLellan AT, O'Brien CP. Cue reactivity and cue reactivity interventions in drug dependence. In: Onken L, Blaine J, Boren J, editors. Behavioral treatments for drug abuse and dependence. National Institute on Drug Abuse Research Monograph Series #137. Washington: DHHS; 1993. p. 73-97.

Cooper JR. Establishing a methadone quality assurance system: rationale and objectives.

In: Improving drug abuse treatment. National Institute on Drug Abuse Research Monograph Series #106. Washington: DHHS; 1991. p. 358-64.

Elk R, Grabowski J, Rhoades HM, McLellan AT. A substance abuse research-treatment clinic. Substance Abuse Treatment 1993;10(5):459-71.

Grabowski J, Stitzer M, Henningfield J, editors. Behavioral intervention techniques in drug abuse treatment. National Institute on Drug Abuse Research Monograph Series #46. Washington: DHHS; 1984.

Grabowski J, Rhoades H, Elk R, Schmitz J, Creson D. Clinic-wide and individualized behavioral interventions in drug dependence treatment. In: Onken L, Blaine J, Boren J, editors. Behavioral treatments for drug abuse and dependence. National Institute on Drug Abuse Research Monograph Series #137. Washington: DHHS; 1993.

Institute of Medicine. Federal regulation of methadone treatment. Rettig R, Yarmolinsky A, editors. Washington: National Academy Press; 1995.

Krasnegor N, editor. Behavioral analysis and treatment of substance abuse. National Institute on Drug Abuse Research Monograph Series #25. Washington: DHEW; 1979.

Miller W. Behavioral treatments for drug problems: where do we go from here? In: Onken L, Blaine J, Boren J, editors. Behavioral treatments for drug abuse and dependence. National Institute on Drug Abuse Research Monograph Series #137. Washington: DHHS; 1993.

Nunes E, Coyne TH, Young S, Hoffman M, Woytek R, Bertino L, et al. Group psychotherapy for treatment of refractory methadone maintenance patients: a clinical experience. Journal of Maintenance in the Addictions 1997;1(1):103-13.

O'Brien CP, Woody G, McLellan AT. Enhancing the effectiveness of methadone using psychotherapeutic interventions. In: Onken L, Blaine J, Boren J, editors. Integrating behavioral therapies with medications in treatment of drug dependence. National Institute on Drug Abuse Research Monograph Series #150. Washington: DHHS; 1995. p. 5-18.

Onken L, Blaine J, editors. Psychotherapy and counseling in the treatment of drug abuse. National Institute on Drug Abuse Research Monograph Series #104. Washington: DHHS; 1990.

Onken L, Blaine J, Boren J, editors. Behavioral treatments for drug abuse and dependence. National Institute on Drug Abuse Research Monograph Series #137. Washington: DHHS; 1993.

Onken L, Blaine J, Boren J, editors. Integrating behavioral therapies with medications in treatment of drug dependence. National Institute on Drug Abuse Research Monograph

Series #150. Washington: DHHS; 1995.

Pickens R, Leukefeld C, Schuster C, editors. Improving drug abuse treatment. National Institute on Drug Abuse Research Monograph Series. Washington: DHHS; 1991.

Rhoades H, Creson D, Elk R, Schmitz J, Grabowski J. Retention, HIV risk, and illicit drug use during treatment: methadone dose and visit frequency. Am J Public Health. In press 1997.

Senay EC, Barthwell AG, Marks R, Boros P, Gillman D, White G. Medical maintenance: a pilot study. J Addict Dis 1993;12(4):59-76.

Stitzer M, Bigelow GE, Liebson IA, McCaul ME. Contingency management of supplemental drug use during methadone maintenance treatment. In: Grabowski, Stitzer, Henningfield, editors. Behavioral intervention techniques in drug abuse treatment. National Institute on Drug Abuse Research Monograph Series #46. Washington: DHHS; 1984. p. 84-103.

Stitzer M, Kirby K. Reducing illicit drug use among methadone patients. In: Pickens R, Leukefeld G, Schuster CR, editors. Improving drug abuse treatment. National Institute on Drug Abuse Research Monograph Series #106. Washington: DHHS; 1991. p. 178-203.

Tims F, editor. Drug abuse treatment evaluation: strategies, progress, and prospects. National Institute on Drug Abuse Research Monograph Series. Washington: DHHS; 1984.

Woody G, Luborsky L, McLellan AT, O'Brien CP, Beck AT, Blaine J, et al. Psychotherapy for opiate addicts: does it help? Arch Gen Psychiatry 1983;40:639-45.

Yarmolinsky A, Pechura CM. Methadone revisited. Issues Sci Tech Spring 1996;38-42.

Opiate Agonist Treatment, Molecular Pharmacology, and Physiology

Mary Jeanne Kreek, M.D.

The National Household Survey, Monitoring the Future Survey, and Drug Abuse Warning Network, as well as other surveys sponsored by the National Institute on Drug Abuse of the National Institutes of Health, Substance Abuse and Mental Health Services Administration, and other governmental resources have estimated that more than 2.7 million persons in the United States have used heroin at some time and that between 600,000 and 1 million meet the U.S. Federal Government criteria for entry into long-term opioid agonist maintenance treatment for heroin addiction (methadone or l-alpha-acetylmethadol [LAAM]). These official criteria are defined as 1 year or more of daily multiple-dose self-administration of illicitly obtained opiate, usually heroin, with the development of tolerance, physical dependence, and drug-seeking behavior, with harm to self, family, and/or society (Rettig, Yarmolinsky, 1995).

Rationale for Use of Chronic Long-Acting Opioid Agonist Pharmacotherapy

Numerous studies during this century up to the present have shown that few heroin addicts meeting the above-defined criteria of 1 year of multiple daily self-administrations of short-acting opiates, usually heroin, with the development of tolerance, physical dependence, and drug-seeking behavior, coupled with drug hunger and drug craving and harm to self and/or society, are manageable with short-term pharmacotherapy, such as that used in detoxification treatment, followed by purely abstinence-based treatment, or by treatment with an opioid antagonist such as naltrexone; nor are such heroin addicts effectively treated by so-called abstinence-based or drug-free treatment alone. Studies have shown that more than 70 percent of long-term heroin addicts will relapse to illicit opiate use within 1 to 2 years (Pescor, 1943; Dole, Nyswander, Kreek, 1966; Rettig, Yarmolinsky, 1995; Kreek, 1991; Kreek, 1996a, 1996b).

The initial research work to develop a pharmacotherapy for the long-term treatment of heroin addiction (performed under the leadership of Professor Vincent P. Dole at the Rockefeller Institute for Medical Research [now The Rockefeller University] with the late Dr. Marie Nyswander [a psychiatrist with years of work related to the management of heroin addiction both in New York City and at the U.S. Public Health Service Resource at Lexington, Kentucky], and the author [Mary Jeanne Kreek, M.D., an early career clinical investigator]) evaluated both the stages of opiate addiction and the impact of heroin addiction on the physiology, medical status, and behavior of the individual (Dole, Nyswander, Kreek, 1966; Dole, Nyswander, 1965; Kreek, Dodes, Kane, et al., 1972; Kreek, Garfield, Gutjahr, et al., 1976; Cooper, Altman, Brown, et al., 1983; Kreek, 1973a, 1973b, 1973c, 1978, 1996a, 1996b). In late 1963, the research team developed studies that were initiated in early 1964 at the Rockefeller University Hospital (Dole, Nyswander, Kreek, 1966; Kreek 1996a). It had been documented by many groups for more than a century that chronic, illicit self-administration of short-acting opiates, such as heroin, may lead

to addiction. It had been shown that tolerance to the effects of short-acting opiates develops and increasing amounts of heroin (or morphine) are needed to achieve the desired euphoria or "high" (or alternatively, in some individuals, a sense of well-being), and, with continued self-administration of the short-acting opiate, increasing amounts are needed simply to prevent the onset of signs and symptoms of opiate withdrawal or the abstinence syndrome. (The abstinence syndrome is a physiological syndrome that has been repeatedly documented in both animal models of opiate addiction and in humans, although its mechanisms have yet to be fully elucidated in molecular, biochemical, and neurobiologic terms.) The short-acting properties of illicit opiates, which are the primary drugs of abuse, usually heroin, lead to self-administration of the drug three to six times each day, both to prevent the onset of opiate withdrawal and also to respond to the inherent or drug-induced drug hunger or craving. Thus, it has been shown in repeated studies that both negative and positive reinforcing factors play a role in the continued self-administration of short-acting opiates. The potential effect of frequent use of unsterile needles, often with direct sharing of these needles, on the spread of infectious diseases such as hepatitis B and C and also the virus that causes AIDS, HIV-1, is obvious. The average heroin addict self-administers illicit opiates 1,000 to 2,000 times each year. Scrutiny of available research data, as well as anecdotal reports, available in 1963 and 1964, including the numerous studies from the U.S. Public Health Service hospital at Lexington, Kentucky, as well as experiences in the New York City area, had shown that, for most addicts, detoxification treatment (of any type) is never effective (Dole, Nyswander, Kreek, 1966). The usual and rapid relapse to illicit opiate use leads to the "revolving door" description of such an approach to management (Stimmel, 1975).

The author's team hypothesized that opiate addiction is indeed a "metabolic" or neurobiologic disease; that drugs of abuse alter normal physiology and functioning as well as behavior; and that appropriate treatment requires an opioid agonist, both to prevent signs and symptoms of opiate withdrawal or abstinence and to reduce drug hunger or drug craving (Dole, Nyswander, Kreek, 1966; Kreek, Dodes, Kane, et al., 1972; Kreek, 1973a, 1973c, 1991, 1992, 1996a, 1996b). It was also appreciated at the beginning of the 1964 studies that the opioid agonist used would need to be in medication that did not have any reinforcing properties and thus would *not* be a "substitution" therapy. (This would simply be replacing a licit for an illicit, short-acting narcotic, as had been done in the unsuccessful experience of the legalization of heroin and heroin treatment in Great Britain at that time.) Instead the therapy would need to use an appropriate, medically based pharmacotherapy with a long-acting opioid agonist. Thus, from the beginning of our research, a long-acting opioid agonist was hypothesized to be the type of medication needed.

Initial overall goals in developing a chronic, pharmacotherapeutic-based treatment for heroin addiction were as follows:

- To prevent all signs and symptoms of opiate abstinence or withdrawal.
- To reduce or prevent drug hunger or drug craving.

- To ideally allow normalization of all physiological abnormalities caused by chronic use of short-acting illicit opiates, primarily heroin (Kreek, 1992).

Type of Medications Studied and Used—Long-Acting Opioid Agonists

In early 1964 the author and colleagues conceptualized that the ideal medication would be orally effective; have a very slow onset of action to prevent any reinforcing effects, which characterize drugs of abuse including heroin; and have no classical opiate effects (which could, in theory, serve as a cue resembling that of an illicit opiate). Rather, the medication would have a very slow onset of action, coupled with a long duration of action and a very slow offset of action. Such a medication thus would provide a steady state of action, with no resultant opiate or euphoric effects and no withdrawal effects. The medication identified and selected for the first studies in early 1964 was dl-methadone, a racemic mixture, synthetic opioid agonist, which as normally synthesized contains equal amounts of the active l-methadone and inactive d-methadone enantiomer. By 1964 this medication had been used on a limited basis for the management of pain. It appeared to have a short duration of action in single dose studies, yet when multiple doses were administered, they caused signs and symptoms suggesting protracted opiate effects. Thus, it was not extensively used or further studied. Methadone also had been used in a limited number of centers including Lexington and the Bellevue Hospital (where both Drs. Nyswander and Kreek had worked as staff psychiatrist and medical student, respectively) in the short-term detoxification management of addiction. In the early 1960s when methadone was used in detoxification, it was administered several times each day; however, both Dr. Nyswander and Dr. Kreek had observed that one or two doses a day were apparently effective in preventing opiate withdrawal symptoms. Thus, it was predicted that methadone might have a longer duration of action than heroin, or its major metabolite, morphine, although the analytical technology for making that pharmacokinetic determination was not available and would not be available until the early 1970s.

The 1964 research studies showed that methadone could be effectively administered orally; had a very slow onset of action; and had a sustained duration of action for a 24-hour dosing interval (Dole, Nyswander, Kreek, 1966; Kreek, Dodes, Kane, et al., 1972; Kreek 1991, 1992). Thus, in these very early studies it was found that methadone, delivered orally once a day, allowed a former heroin addict to feel essentially “normal” throughout the 24-hour dosing interval, with no signs or symptoms of opiate narcotic withdrawal and with no opiate or narcotic-like effects even at times of peak action.

Early Studies of the Effects of Methadone as Used in Maintenance Treatment of Addiction

In those initial studies, the research team learned that if methadone treatment was started at an initial dose of 20 to 40 mg per day (depending in large part on clinical assessment of the patient) and was increased at a rate of approximately 10 mg per week up until a full treatment dose (then determined to be 80 to 120 mg per day, a dose range which, in fact, still is appropriate for most patients in treatment in the late 1990s), then former heroin addicts entering treatment

would experience no signs or symptoms of opiate withdrawal beyond the first 2 to 3 days of dose escalation and at no time would have any opiate or narcotic-like effect, even at time of peak action (Dole, Nyswander, Kreek, 1966; Kreek, 1991, 1992, 1996a, 1996b). We also found that drug craving and drug hunger were markedly reduced and that patients' thoughts turned to finishing an education, getting a job, and returning to a more stable lifestyle (Dole, Nyswander, Kreek, 1966).

A series of inpatient studies was then conducted to determine whether such methadone pharmacotherapy would be safe if heroin addicts in methadone treatment were to superimpose a short-acting narcotic such as heroin or morphine in an attempt to reach euphoria or get a "high." A study of narcotic "blockade" or cross-tolerance was performed using a double-blinded, random-order, Latin-square-design protocol, conducted over 4 weeks each. In patients stabilized on 80 to 120 mg per day of methadone, the author and coworkers determined the effects of superimposition of an intravenous dose of short-acting narcotics, including heroin, hydromorphone, and morphine, as well as methadone itself and saline (Dole, Nyswander, Kreek, 1966). When the studies were completed and the codes broken, it was found that heroin addicts maintained on methadone could not perceive the short-acting narcotics when doses administered exceeded the usual illicit amounts purchased and self-administered on the street. The only symptom observed was a "pins-and-needles" sensation identified by subjects after morphine administration; when no euphoria or other narcotic signs followed, each subject would ask "where is the high?" Thus, in these studies it was found that in addition to preventing signs and symptoms of opiate withdrawal and reducing drug craving, methadone also blocked, through the mechanism of cross-tolerance, the effects of any superimposed short-acting narcotic (Dole, Nyswander, Kreek, 1966). In these early studies it was found that there were both a beneficial neurobiological or metabolic effect of methadone and the expected pharmacological effect and that, in addition, an effect derived from classical conditioning phenomena could be achieved; that is, if heroin addicts now in methadone treatment would self-administer an illicit dose of heroin (and more than 50 percent of former heroin addicts do try illicit heroin at least once after initiation of methadone maintenance treatment), they would achieve no desired effect from the heroin, and the phenomenon of deconditioning or extinction would ensue. All three of these mechanisms—the direct pharmacological effects, the long-term neurobiological or metabolic effects allowing normalization of altered neurobiology and physiological status caused by chronic use of short-acting opiates such as heroin (or in some persons, possibly existing before opiate exposure on a genetics or environmental-induced basis), as well as the classical deconditioning or extinction phenomenon—undoubtedly play a role in the effectiveness of long-term methadone maintenance treatment.

Pharmacology-Pharmacokinetics

By the early 1970s, several groups developed analytical techniques primarily utilizing gas chromatography, initially for the quantitation of opioid agonists including methadone (Inturrisi, Verebely, 1972; Kreek, 1973b). It was found that the half-life of racemic dl-methadone, as used in the maintenance treatment of opiate addictions, was 24 hours in humans. (Other studies showed that this is in contrast to animal models where methadone has a half-life of 60 minutes in

mice and 90 minutes in rats, explaining some of the discrepancies noted in the preclinical science literature [Dole, Kreek, 1973; Inturrisi, Verebely, 1972; Kreek, 1973b, 1979]). In further studies, stable isotope technology was used to study the pharmacokinetics of methadone in humans. Again, it was found that the half-life of racemic methadone is 24 hours; but, when the individual enantiomers were studied, it was found that the active enantiomer l(R) has a half-life of 36 to 48 hours, whereas the half-life of the inactive d(S)methadone is about 16 hours (Hachey, Kreek, Mattson, 1977; Kreek, Hachey, Kline, 1979; Nakamura, Hachey, Kreek et al., 1982).

A second opioid agonist that has been successfully developed for the pharmacotherapy of opiate addiction, LAAM, has been shown to have an even more prolonged pharmacokinetic half-life than methadone (Kreek, 1996a, 1996b). Whereas methadone is metabolized by the P450-dependent microsomal-related enzymes systems by successive N-demethylation, the major metabolites are not pharmacologically active. In contrast, LAAM, which also is metabolized primarily by N-demethylation, yields two active metabolites: norLAAM and dinorLAAM, which are active and contribute to the long-acting properties of LAAM in humans. Similar to methadone, the doses of LAAM recommended for treatment are 60 to 120 mg per day. LAAM needs to be administered only every other day; it may be delivered over a 3-day dosing interval, and if such an interval is elected, the dosing for the 48-hour interval, the dose needs to be increased by 25 percent to 40 percent. The usual doses of LAAM recommended are 1.2 to1.3 times that of methadone. LAAM may be effective for 48, 72, or up to 96 hours (Kreek, 1996a, 1996b).

Since the cloning of the human mu opioid receptor, it is known that methadone is one of the most highly selective mu receptor agonists—even more selective than heroin or morphine—which may contribute to its efficacy in treatment (Mestek, Hurley, Bye, et al., 1995).

Specific Primary Goals and Specific Secondary Goals of Long-Acting Opioid Agonist Pharmacotherapy

As detailed in a review by the author, the primary goal of opioid agonist pharmacotherapy using methadone (or LAAM) is “significant reduction or cessation of illicit narcotic (opiate; heroin) use (specific pharmacologic effect of methadone or LAAM)” with “a related goal of voluntary retention in treatment for one year, two years or more” (Kreek, 1991).

The secondary goals of long-acting opioid pharmacotherapy for heroin addiction include:

- Significant reduction or cessation of cocaine, alcohol, and polydrug abuse (a nonspecific treatment program effect, primarily).

- Significant reduction of exposure to and infection with diseases transmitted by unsterile injection equipment use in parenteral drug abuse such as hepatitis B, C, delta, and HIV-1 infection.

- Significant reduction in criminality and antisocial behaviors and therefore reduction in arrest and imprisonment.

- Significant improvement in socialization and productivity, including employment, reception of education and homemaking.

All these goals have been achieved by methadone maintenance treatment and the results have been documented in innumerable clinical research studies. Similarly, although studied to a lesser extent and over fewer years, chronic maintenance treatment with LAAM has been shown to achieve each of these goals. It has been shown that the success or effectiveness of methadone maintenance treatment is primarily dependent upon three factors. First, adequate doses of methadone must be used. Federal regulations specify 60 to 120 mg per day, but now, especially with the increasing purity of heroin, probably the original 80 to 120 mg per day recommended and even higher doses are needed by many patients (Dole, Nyswander, Kreek, 1966; Cooper, Altman, Brown, et al., 1983; Dole, 1989; Kreek, 1991; Ball, Ross, 1991; Rettig, Yarmolinsky, 1995). Second, adequate on-site counseling and access to psychosocial services and medical and psychiatric care are important components of effective treatment (Kreek, 1991; Ball, Ross, 1991; McLellan, Arndt, Metzger, et al., 1993). Finally, staff must be well educated, nonjudgmental, and nonpejorative in its attitude and able to guide the patient through the complexities of a multifaceted disorder while delivering pharmacotherapy with highest medical skill.

> "Thus, clinical experts in the area of treatment of chemical dependency, especially those involved in the treatment of opiate addiction, along with scientists and epidemiologists working in this area, are arriving at a consensus that the most effective treatment for heroin addiction is long-term methadone maintenance treatment for an indefinite period which may be essential for the majority, but certainly not all such patients. Also, there is considerable research evidence that increasing the total length of time in treatment, including from the later time points ranging from one year to more than five years, results in progressive improvement in all of the primary and secondary goals of treatment of narcotic addiction" (Kreek, 1991; Dole, Nyswander, 1967; Cooper, Altman, Brown, 1983; Blix, 1988; Ball, Ross, 1991).

> "However, it is also the consensus that until and unless similarly effective (and similarly specific) pharmacologic treatment approaches become available for other types of chemical dependency—such as alcoholism and cocaine abuse (both prevalent in), street addicts at this time, and thus (in), all new entrants into methadone maintenance treatment—drug-free behavior, 12-step-oriented, and/or psychosocial approaches for the management of these additional problems must be combined with effective chemotherapy of methadone maintenance for narcotic addiction in patients with these dual and multiple chemical dependency problems" (Kreek, 1991).

Further assessments by other scientists, as well as by the Institute of Medicine, have concurred with and supported these earlier evaluations and conclusions (Kreek, 1992; Rettig, Yarmolinsky, 1995; McLellan, Arndt, Metzger, et al., 1993; Kreek, 1996a, 1996b, 1996c).

Achievement of Goals

As referred to above, multiple studies have shown that the primary goal, as well as each of the secondary goals, can be achieved by appropriate methadone maintenance treatment. Documentation has been provided by both rigorous assessments of clinical experiences and prospective and retrospective studies. The first positive event following entry of a street heroin addict into methadone maintenance treatment is a rapid and sharp reduction in criminal behavior, with a reduction of arrests and imprisonment. Ball and colleagues (1991) showed a 60-percent reduction in the first 4 months of treatments and a 90-percent reduction in the first year of treatment. With respect to the primary goal, studies from the author's laboratory conducted in the 1960s, 1970s, 1980s, and most recently from 1996 to 1997 have shown that more than 60 percent of unselected heroin addicts seeking and entering methadone maintenance treatment may be voluntarily retained in treatment for 1 year or more. These studies also have shown that in clinics where adequate doses of methadone are used (60 to 120 mg per day or more, with a current median dose of 90 mg per day) and adequate counseling is offered, as well as access to psychosocial services on site and access to medical and psychiatric care, all of which augment retention in treatment, the other goals are also achieved. The primary goal of illicit use of heroin is achieved, along with retention in treatment. At the end of 9 months of treatment, less than20 percent of heroin addicts continue to use any illicit opiates. Also, less than 30 percent continue to use cocaine, despite the fact that more than 90 percent had a codependency with cocaine at the time of entry.

Disruption of Physiology by Short-Acting Opiate (Heroin) Use

Numerous studies have shown that specific aspects of human physiology are profoundly disrupted by self-administration of heroin during cycles of addiction because of the impact of the short-acting opiate following opiate withdrawal three to six times each day, with an "on-off" effect at specific opioid receptor sites (Kreek, Dodes, Kane, et al., 1972; Kreek, Wardlaw, Friedman, et al., 1981; Kreek, Wardlaw, Hartman, et al., 1983; Kreek, Raghunath, Plevy, et al.,1984; Kreek 1973a, 1973c, 1978, 1992, 1996a, 1996b, 1996c; Kreek, Hartman, 1982; Cooper, Altman, Brown, et al., 1983; Novick, Ochshorn, Ghali, et al., 1989). Similarly, numerous studies conducted in human, as well as in animal models, have shown that chronic exposure to short-acting opiates disrupts specific indices of molecular neurobiology, as well as neurochemistry, integrated physiology, and behavior. In humans some of the most important disruptions include alterations of two systems that are critical for survival: the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis and the reproductive function controlling hypothalamic-pituitary-gonadal (HPG) axis. During cycles of heroin addiction, it has been shown that there is suppression of release of the stress-responsive hormones ACTH and beta-endorphin from the anterior pituitary with resultant lower plasma levels or flattened circadian rhythm of cortisol released from the adrenal cortex. Also, studies have shown that

during cycles of heroin addiction, there is an atypical reduced hypothalamic pituitary reserve as determined by challenge tests with metyrapone (Kreek, Dodes, Kane, et al., 1972; Kreek, Raghunath, Plevy, et al., 1984; Kreek, 1973a, 1973c, 1978). Several studies have shown that pulsatile release of luteinizing hormone (LH) is reduced during cycles of heroin addiction (Kreek, 1978). This reduction leads to the frequently observed anovulatory cycles, hypomenorrhea, or amenorrhea in female heroin addicts. It also leads to reduced testosterone levels and altered libido and sexual performance in males. In addition, diverse studies have shown that immune function is profoundly disrupted in cycles of heroin addiction (Kreek, Dodes, Kane, et al., 1972; Kreek 1973a, 1973c, 1978; Novick, Ochshorn, Ghali, et al., 1989). These abnormalities may be due in part to direct opiate effects; it has been shown that opiate drugs may act upon opioid receptors on specific components of the immune system. A variety of indirect effects may also play a role, including disruption of the HPA axis and the HPG axis. Enhanced prolactin release with increased plasma levels of prolactin occurs after every use of a short-acting opioid; prolactin also acts in immunomodulation (Kreek, 1973a, 1973c, 1978). Diverse diseases, injection of foreign substances, and poor nutritional status may contribute to the immune disfunction seen in heroin addicts (Kreek, Dodes, Kane, et al., 1972; Kreek, 1973a, 1973c, 1978; Novick, Ochshorn, Ghali, et al., 1989). There is increasing evidence that opiate withdrawal can more profoundly disrupt immune function in opiate effects. Specifically, natural killer cell activity has been shown to be profoundly altered in heroin addicts (Novick, Ochshorn, Ghali, et al., 1989). Gastrointestinal function is also abnormal during cycles of heroin addiction, with slowed gastrointestinal motility causing constipation during regular short-acting opiate use and diarrhea due to hypermotility during each episode of opiate withdrawal, which may occur several times a day (Kreek, Dodes, Kane, et al., 1972; Kreek, 1973a, 1973c, 1978).

Normalization of Physiology During Methadone Maintenance Treatment

Several studies, including prospective studies of heroin addicts entering and during long-term methadone maintenance treatment, and one-point-in-time studies, have shown that normalization of physiology that has been disrupted from cycles of heroin addiction can occur during chronic stable dose methadone maintenance treatment (Kreek, Dodes, Kane, et al., 1972; Kreek, 1973a, 1973c, 1978, 1992, 1996a, 1996b, 1996c; Novick, Ochshorn, Ghali, et al., 1989; Kling, Borg, Zametkin, et al., 1997). Specifically, it has been shown that normalization of the stress-responsive HPA axis occurs, with normalization both of basal plasma levels of ACTH, beta-endorphin and cortisol, normal circadian rhythm of these levels, and normal responsivity to a chemically induced stressor, that is, the metyrapone challenge test. Similarly, it has been shown that normalization of the HPG axis occurs during chronic methadone maintenance treatment, with return of normal pulsatile release of LH and normal ovulation in women, along with restoration of normal menses, ability to conceive, and resultant normal pregnancies and delivery of normal babies (Kreek, 1979; Cooper, Altman, Brown, et al., 1983; Pond, Kreek, Tong, et al., 1985). It also has been shown that immune function normalizes during long-term treatment. Control studies have shown that after 11 years or more of steady normal- to high-dose methadone maintenance treatment, all immune function indices are normalized, including reduction in the elevated levels of immunoglobulin, return to normal levels of absolute

numbers of T cells and B cells and return to normal levels of natural killer cell activity (Novick, Ochshorn, Ghali, et al., 1989). Gastrointestinal function also has been shown to return to normal after 3 years or more of stabilized methadone maintenance treatment (Kreek, Dodes, Kane, et al., 1972; Kreek, 1973a, 1973c, 1978, 1991, 1996a; Cooper, Altman, Brown, et al., 1983).

Medical Safety of Methadone Maintenance Treatment

Numerous studies have studied the medical effects of chronic methadone treatment, including evaluation of the medical status of heroin addicts entering treatment and prospective evaluation of the medical status of persons during chronic methadone maintenance treatment (Kreek, Dodes, Kane, et al., 1972; Kreek, 1973a, 1973c; Cooper, Altman, Brown, et al., 1983; Novick, Richman, Friedman, et al., 1993). These studies have been carried out in conjunction with and, on a larger scale, separate from studies of specific aspects of physiology. In these prospective and retrospective studies, it has been shown that no deleterious effects of any type result from long-term methadone maintenance treatment. Normalization of functions disrupted by heroin use occur with time as detailed above. The one side effect of methadone maintenance treatment that has been observed to persist during 3 or more years of treatment is increased sweating or perspiration; this has not been shown, however, to cause any problems to the individuals, even when they work at manual labor and in hot environments (Kreek, 1973a, 1973c, 1978; Cooper, Altman, Brown, et al., 1983).

Recently, a study was conducted to determine the medical status of persons in methadone maintenance treatment for 10 or more years, all subjects who were prospectively followed during the first 3 years or more of treatment (Kreek, 1973a, 1973c; Novick, Richman, Friedman, et al., 1993). In these studies it was shown again that long-term methadone treatment causes no deleterious effects of any type. Long-term methadone-maintained patients have significantly fewer disorders related to injection of foreign substances or to crime and violence, and significantly less ongoing drug and alcohol abuse was found with them than with untreated long-term heroin addicts (Novick, Richman, Friedman, et al., 1993).

Numbers of Treatment Programs and Persons Currently in Methadone and LAAM Pharmacotherapy

Currently there are approximately 760 methadone maintenance treatment programs in the United States. The numbers of programs have been curtailed, especially over the past two decades, by increasing fiscal constraints coupled with decreasing numbers of staff, including physicians, nurses, and social workers trained in problems related to the addictive diseases and in the pharmacotherapy of addictive diseases. It is estimated that between 120,000 and 140,000 persons are currently in methadone maintenance treatment in the United States. Approximately a similar number are in treatment in other parts of the world, primarily in Europe and Australia and some locations within Asia. A much smaller number of former heroin addicts are currently in LAAM maintenance treatment programs, primarily in the United States.

Special Programs of Medical Maintenance Treatment

Over a decade ago a pilot research project conducted under a Food and Drug Administration IND was initiated in New York City under the leadership of Dr. David Novick and colleagues (Novick, Joseph, Salsitz, et al., 1994). In this research program, long-term methadone maintained patients in successful treatment for 5 years or more with no ongoing illicit opiate use, no ongoing drug abuse of any type, and no ongoing alcohol abuse; all these patients had undergone satisfactory rehabilitation and were entered into a special medical maintenance program (Novick, Joseph, Salsitz, et al., 1994). In this program, patients were seen by physicians, either internists or psychiatrists, once every 2, 3, or 4 weeks. At each visit, a complete interim history and physical were taken and urine was screened for drugs of abuse. Patients were seen in a conventional general medical clinic setting. Medication (methadone pharmacotherapy) for up to a 4-week interval was provided by the hospital pharmacy. Patients at any time could elect to return to a full-service methadone maintenance treatment program. This program was shown to be highly successful, with more than 90 percent of persons continuing in medical maintenance and with most patients experiencing no special problems requiring a return to a conventional methadone maintenance program (Novick, Joseph, Salsitz, et al., 1994).

Positive Impact Against HIV-1 Infection by Appropriate Methadone Maintenance Treatment

Through a study conducted in the author's laboratory by unbanking, classifying by treatment states, ongoing drug abuse, and demography, and removing all identifiers from bloods banked prospectively from 1969 onward from volunteer subjects coming to our hospital and clinic for either basic neurobiological research or treatment research, we were able to identify that the AIDS epidemic, that is, infection with HIV-1, entered the New York City drug-abusing population in 1978 (Des Jarlais, Marmor, Cohen, et al., 1984; Novick, Khan, Kreek, 1986; Novick, Kreek, Des Jarlais, et al., 1986). In that study, we found that the numbers of untreated heroin addicts who became infected with HIV-1 escalated dramatically between 1978 and 1982; by 1983 more than 50 percent of the untreated drug-abusing population was infected with HIV-1. We also found that of those persons who had entered into an effective methadone maintenance program before 1978 and who had continued in methadone maintenance treatment, only 9 percent were HIV-positive when studied in 1983 and 1984, a time when 50 percent of the untreated heroin addicts were HIV-positive. These 9 percent were all persons who continued to use cocaine by parenteral route. Similar findings have been made by Blix in Sweden and numerous other groups in the United States and worldwide (Blix, 1988). It has been repeatedly shown that appropriate methadone maintenance treatment provides an extremely impressive and positive impact against HIV infection by reducing drug hunger and craving, significantly reducing any illicit opiate use, significantly reducing all other illicit drug use, and, therefore, removing the chance of infection.

Over the past decade with increasing AIDS risk reduction behavior intervention and education efforts in the New York City area, there has been a progressive decline in the

prevalence of hepatitis B infection, which through 1985 was present in more than 90 percent of untreated heroin addicts entering treatment and now is present in fewer than 40 percent seeking treatment. There also has been a decline in new cases of hepatitis C infection. Thus, AIDS risk reduction education and access to sterile needles and injection equipment have reduced exposure to infectious diseases. Methadone maintenance treatment earlier, and even more robustly, reduces infection with a variety of infectious disease agents including hepatitis B and C and HIV-1 and also allows normalization of immune function, which protects against progression of those diseases already present.

Summary

In summary, methadone maintenance treatment has been shown to be highly effective in the field as well as to have intrinsic efficacy in the pharmacotherapy and overall management of heroin addiction. Methadone has been shown to be a highly selective mu opioid receptor agonist that has a long-acting pharmacokinetics profile in humans: a half-life with a racemic mixture of more than 24 hours in sharp contrast with the 3-minute half-life of heroin and the 4- to 6-hour half-life of its major morphine metabolite. The methadone congener LAAM, with its active metabolites, has an even longer half-life of more than 48 hours. Both these medications may be effectively used in the pharmacotherapy of opiate addiction, and they are maximally effective when coupled with counseling and access to medical and psychiatric care. The medical safety of methadone has been repeatedly documented in prospective studies extending over 10 years as well as rigorous single-time-point assessments. Short-term studies have shown that LAAM is similarly safe. Normalization of physiology occurs during chronic methadone maintenance treatment. Drug hunger or craving is significantly reduced with a significant concomitant reduction or elimination of other illicit opiate use. Long-acting opioid agonist pharmacotherapy, primarily methadone and also LAAM, has been shown to be far more effective than any other approach to the management of opiate addition—more effective for unselected long-term heroin addicts than any drug-free or abstinence-based treatments, more effective than treatments with opiate antagonists such as naltrexone, and far more effective than any detoxification approach, either preceded or followed by any other kind of behavioral modification attempts or antagonist pharmacotherapy.

References

Ball JC, Ross A. The effectiveness of methadone maintenance treatment: patients, programs, services and outcome. New York: Springer-Verlag; 1991.

Blix O. AIDS and IV heroin addicts: the preventive effect of methadone maintenance in Sweden. Proceedings of the 4th International Conference on AIDS; 1988; Stockholm, Sweden.

Cooper JR, Altman F, Brown BS, Czechowicz D, editors. Research in the treatment of narcotic addiction: state of the art. National Institute on Drug Abuse Monograph; 1983. DHHS Pub. No. (ADM) 83-1281.

Culpepper-Morgan JA, Kreek MJ. HPA axis hypersensitivity to naloxone in opioid dependence: a case of naloxone induced withdrawal. Metabolism 1997;46:130-4.

Des Jarlais DC, Marmor M, Cohen H, Yancovitz S, Garber J, Friedman S, et al. Antibodies to a retrovirus etiologically associated with acquired immunodeficiency syndrome (AIDS) in populations with increased incidences of the syndrome. MMWR 1984;33:377-9.

Dole VP. Implications of methadone maintenance for theories of narcotic addiction. The Albert Lasker Medical Award. JAMA 1989;260:1880.

Dole VP, Kreek MJ. Methadone plasma level: sustained by a reservoir of drug in tissue. Proc Natl Acad Sci U S A 1973;70:l0.

Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. Arch Intern Med 1966;118:304-9.

Dole VP, Nyswander ME. A medical treatment for diacetylmorphine (heroin) addiction. JAMA 1965;193:646-50.

Hachey DL, Kreek MJ, Mattson DH. Quantitative analysis of methadone in biological fluids using deuterium-labeled methadone and GLC chemical ionization mass spectrometry. J Pharm Sci 1977;66:l579-82.

Inturrisi CE, Verebely K. The levels of methadone in the plasma in methadone maintenance. Clin Pharmacol Ther 1972;13:633-7.

Kennedy JA, Hartman N, Sbriglio R, Khuri E, Kreek MJ. Metyrapone-induced withdrawal symptoms. Brit J Addict 1990;85:1133-40.

Kling M, Borg L, Zametkin A, Schluger J, Carson R, Matochik J, et al. Opioid receptor binding in methadone maintained former heroin addicts by PET imaging using ^{18}[F]cyclofoxy. In: Harris LS, editor. Problems of drug dependence, 1996. Proceedings of the 58th Annual Scientific Meeting of the College on Problems of Drug Dependence. National Institute of Drug Abuse Research Monograph Series 174. Washington: U.S. Government Printing Office; 1997. DHHS Pub. No. (ADM) 97-4236. p. 120.

Kreek MJ. Opiate and cocaine addictions: challenge for pharmacotherapies. Pharm Biochem Behav. In press 1997.

Kreek MJ. Opioid receptors: some perspectives from early studies of their role in normal physiology, stress responsivity and in specific addictive diseases. J Neurochemical Res 1996a;21(11):1469-88.

Kreek MJ. Opiates, opioids and addiction. Mol Psych 1996b;1:232-54.

Kreek MJ. Long-term pharmacotherapy for opiate (primarily heroin) addiction: opiate agonists. In: Schuster CR, Kuhar MJ, editors. Pharmacological aspects of drug dependence: toward an integrated neurobehavioral approach. Berlin: Springer-Verlag; 1996c. p. 487-541.

Kreek MJ. Rationale for maintenance pharmacotherapy of opiate dependence. In: O'Brien CP, Jaffe JH, editors. Addictive states. New York: Raven Press; 1992. p. 205-30.

Kreek MJ. Using methadone effectively: achieving goals by application of laboratory, clinical, and evaluation research and by development of innovative programs. In: Pickens R, Leukefeld C, Schuster CR, editors. Improving drug abuse treatment. National Institute of Drug Abuse Research Monograph Series 106. Washington: US Government Printing Office; 1991. p. 245-66.

Kreek MJ. Multiple drug abuse patterns and medical consequences. In: Meltzer HY, editor. Psychopharmacology: the third generation of progress. New York: Raven Press; 1987. p. 1597-604.

Kreek MJ. Methadone disposition during the perinatal period in humans. Pharmacol Biochem Behav 1979;11(Suppl):1-7.

Kreek MJ. Medical complications in methadone patients. Ann NY Acad Sci 1978;311:110-34.

Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA 1973a;223:665-8.

Kreek MJ. Plasma and urine levels of methadone. NY State J Med 1973b;73:2773-7.

Kreek MJ. Physiological implications of methadone treatment. Proceedings of the Fifth National Conference of Methadone Treatment. NAPAN II-NIMH 1973c. p. 85-91.

Kreek MJ, Des Jarlais DC, Trepo CL, Novick DM, Abdul-Quader A, Raghunath J. Contrasting prevalence of delta hepatitis markers in parenteral drug abusers with and without AIDS. J Infect Dis 1990;162:538-41.

Kreek MJ, Dodes L, Kane S, Knobler J, Martin R. Long-term methadone maintenance therapy: effects on liver function. Ann Intern Med 1972;77:598-602.

Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin induced methadone withdrawal. New Engl J Med 1976;294:1104-6.

Kreek MJ, Hachey DL, Klein PD. Stereoselective disposition of methadone in man. Life Sci 1979;24:925-32.

Kreek MJ, Hartman N. Chronic use of opioids and antipsychotic drugs: side effects, effects on endogenous opioids and toxicity. Ann NY Acad Sci 1982;398:l5l-72.

Kreek MJ, Raghunath J, Plevy S, Hamer D, Schneider B, Hartman N. ACTH, cortisol and beta-endorphin response to metyrapone testing during chronic methadone maintenance treatment in humans. Neuropeptides 1984;5:277-8.

Kreek MJ, Wardlaw SL, Friedman J, Schneider B, Frantz AG. Effects of chronic exogenous opioid administration on levels of one endogenous opioid (beta-endorphin). In: Simon E, Takagi H, editors. Advances in endogenous and exogenous opioids. Tokyo: Kodansha Ltd. Publishers; 1981. p. 364-6.

Kreek MJ, Wardlaw SL, Hartman N, Raghunath J, Friedman J, Schneider B, et al. Circadian rhythms and levels of beta-endorphin, ACTH, and cortisol during chronic methadone maintenance treatment in humans. Life Sci 1983;(Suppl I)33:409-11.

Mestek A, Hurley JH, Bye LS, Campbell A, Chen Y, Tian M, et al. The human mu opioid receptor: modulation of functional desensitization by both calcium/calmodulin-dependent protein kinase and protein kinase. J Neurosci 1995;15:2396-406.

McLellan AT, Arndt IO, Metzger DS, Woody GE, OBrien CP. The effects of psychosocial services in substance abuse treatment. JAMA 1993;269(15):1953-9.

Nakamura K, Hachey DL, Kreek MJ, Irving CS, Klein PD. Quantitation of methadone enantiomers in humans using stable isotope labeled $^{2}H_{3}$, $^{2}H_{5}$, $^{2}H_{8}$ methadone. J Pharm Sci 1982;7l:39-43.

Novick DM, Joseph H, Salsitz EA, Kalin MF, Keef JB, Miller EL, et al. Outcomes of treatment of socially rehabilitated methadone maintenance patients in physicians' offices (medical maintenance): follow-up at 3_ to 9_ years. J Gen Intern Med 1994;9:127-30.

Novick DM, Khan I, Kreek MJ. Acquired immunodeficiency syndrome and infection with hepatitis viruses in individuals abusing drugs by injection. United Nations Bulletin on Narcotics 1986;38:15-25.

Novick D, Kreek MJ, Des Jarlais D, Spira TJ, Khuri ET, Raghunath J, et al. Antibody to LAV, the putative agent of AIDS, in parenteral drug abusers and methadone-maintained patients: abstract of clinical research findings: therapeutic, historical, and ethical aspects. In: Harris LS, editor. Problems of drug dependence, 1985. Proceedings of the 47th Annual Scientific Meeting of the Committee on Problems of Drug Dependence. National Institute on Drug Abuse Research Monograph Series 67. Washington: U.S. Government Printing Office; 1986. HHS Pub. No. (ADM) 86-1448. p. 318-20.

Novick DM, Ochshorn M, Ghali V, Croxson TS, Mercer WD, Chiorazzi N, et al. Natural killer cell activity and lymphocyte subsets in parenteral heroin abusers and long-term methadone maintenance patients. J Pharm Exper Ther 1989;250:606-10.

Novick D, Reagan K, Croxson TS, Gelb A, Stenger R, Kreek MJ. Hepatitis C virus serology in parenteral drug users with chronic liver disease. Addiction 1997;92:167-71.

Novick DM, Richman BL, Friedman JM, Friedman JE, Fried C, Wilson JP, et al. The medical status of methadone maintained patients in treatment for 11-18 years. Drug Alcohol Depend 1993;33:235-45.

Pescor MJ. Follow-up study of treated narcotic drug addicts. Public Health Rep 1943;(Suppl)170:1.

Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharm Exper Ther 1985;233:l-6.

Rettig RA, Yarmolinsky A, editors. Federal regulation of methadone treatment. Washington: National Academy Press; 1995.

State Methadone Maintenance Treatment Guidelines. Office for Treatment Improvement, Rockville (MD): Division for State Assistance; 1992.

Stimmel B, editor. Heroin dependency: medical, economic and social aspects. New York: Stratton Intercontinental Medical Book Corp.; 1975.

Tong TG, Pond SM, Kreek MJ, Jaffery NF, Benowitz NL. Phenytoin-induced methadone withdrawal. Ann Intern Med 1981;94:349-5l.

Zhou Y, Spangler R, LaForge KS, Maggos CE, Kreek MJ. Modulation of CRF-R1 mRNA in rat anterior pituitary by dexamethasone: correlation with POMC mRNA. Peptides 1996;17:435-41.

Zhou Y, Spangler R, Maggos CE, LaForge KS, Ho A, Kreek MJ. Steady-state methadone in rats does not change mRNA levels of cortisotropin-releasing factor, its pituitary receptor or poopiomelanocortin. Eur J Pharm 1996;315:31-5.

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Factors Related to Retention and Posttreatment Outcomes in Methadone Treatment: Replicated Findings Across Two Eras of Treatment

Rose M. Etheridge, Ph.D.

Introduction

For this consensus conference, research findings are presented as three tiers of evidence by which the outcomes and effectiveness of methadone treatment can be judged. The first tier comprises those findings that are strongest and most persuasive and have been consistently replicated across studies, treatment programs, and client samples. Outside the boundaries of these more robust findings are those less well-validated findings, where results are conflicting or have been inconsistently replicated. These second-tier findings represent well-defined areas for additional investigation to identify factors accounting for the absence of replication. Finally, the third tier comprises those more preliminary or exploratory findings that suggest promising new areas for investigation.

The research data of primary focus for this paper are from the two most recent large-scale national multisite studies of drug abuse treatment that included outpatient methadone clients: the National Institute on Drug Abuse (NIDA)-sponsored Treatment Outcome Prospective Study (TOPS), conducted on 11,750 clients entering treatment in 41 programs across 3 modalities of treatment in 10 U.S. cities from 1979 to 1981, and the Drug Abuse Treatment Outcome Study (DATOS), conducted on 10,000 clients entering treatment in 96 programs across 4 modalities of treatment in 11 U.S. cities from 1991 to 1993 (Hubbard, Marsden, Rachal, et al., 1995; Flynn, Craddock, Hubbard, et al., 1997). Collectively, these studies represent research across 2 decades of treatment and encompass extensive data on 50 methadone programs (21 TOPS and 20 DATOS programs) and face-to-face interviews with more than 5,000 methadone clients conducted at intake (4,184 TOPS and 1,540 DATOS clients) and a smaller subset of interviews with clients at 3 months during treatment and at 12 months (and beyond) after treatment entry. The use of a common research design and measures in TOPS and DATOS and the inclusion of eight overlapping programs in six U.S. communities across the two studies provide the opportunity for comparison of client outcomes across treatment eras. Considering the changes in clients and the treatment system that occurred during the 1980s (e.g., proliferation of cocaine use combined with heroin and other drugs, spread of HIV/AIDS and other infectious diseases, shift in treatment-funding authority to the States, and decreases in funding for community-based services), findings replicated over the two treatment eras represented by TOPS and DATOS can be considered strong evidence for the robust effects of treatment (Hubbard, Craddock, Flynn, et al., 1997).

System-Level Changes, Program and Patient Characteristics

Major changes occurred in the 1980s in the financing of treatment, drug use patterns, and the health status of clients entering methadone treatment (Etheridge, Hubbard, Anderson, et al., 1997). Compared with TOPS clients a decade earlier (1979-81), DATOS clients (1991-93) were older, better educated, had higher female representation, and were more likely to be married. Few TOPS or DATOS methadone clients were referred to treatment through the criminal justice system (2.6 percent and 2.2 percent, respectively) (Craddock, Rounds-Bryant, Flynn, et al., 1997; Fletcher, Hubbard, 1994). The percentage of methadone clients with private health insurance decreased from TOPS to DATOS (from 16.9 percent to 11.3 percent), and the percentage of clients with public coverage nearly doubled (31.3 percent to 60.1 percent) (Hubbard, Craddock, Etheridge, et al., 1997). Compared with TOPS clients at treatment entry, DATOS methadone clients had 4 times the odds of weekly heroin use, more than 1_ times the odds of weekly cocaine use, and about _ the odds of heavy alcohol use and suicidal thoughts and/or attempts.

Compared with TOPS clients, DATOS methadone clients also had odds of .57 of being fully employed and odds of .80 of involvement in predatory criminal activity in the year prior to treatment entry (all significant, $p<.01$) (Craddock, Rounds-Bryant, Flynn, et al., 1997). At entry, approximately 18 percent of DATOS methadone clients reported health limitations and more than 30 percent listed the emergency room as their primary health care provider (Fletcher, Hubbard, 1994). Although risky sex practices were high in the DATOS intake population (more than one-third of DATOS methadone clients had multiple sex partners in the year prior to treatment and 70 percent reported that they did not always use a condom during sex), injection as the usual route of heroin use declined from 93.2 percent to 73.4 percent from TOPS to DATOS (Hubbard, Craddock, Flynn, et al., 1997).

Methadone Dose

An adequate maintenance dose of methadone appears to be critical for preventing physical withdrawal symptoms and drug craving. Recent research suggests that for most clients, maintenance doses range from 60 to 120 mg daily (Institute of Medicine, 1995). Average DATOS maintenance doses fell within this recommended range, unlike some TOPS programs where methadone doses were generally low. As many as 40 percent of TOPS clients were maintained on subtherapeutic doses, below 30 mg (Hubbard, Marsden, Rachal, et al., 1995).

Counseling and Services

Accompanying the changes in the treatment system during the 1980s has been a decline in services to clients in drug abuse treatment, a phenomenon that became evident in the four treatment modalities studied in DATOS but was more pronounced in the DATOS methadone programs (Etheridge, Craddock, Dunteman, et al., 1995). Aside from methadone dose and medical services, DATOS methadone clients, on average, reported receiving little drug abuse counseling or services during treatment, although there was much variation in the levels of

counseling and services across programs. During the first 3 months of treatment in DATOS methadone programs, client self-reported counseling contact averaged less than 1 hour per week, ranging from an average of 0 to 3 hours counseling contact per client per week. Although some clients reported that service needs were discussed during drug abuse counseling, it is doubtful that the relatively low counseling contact evident in many DATOS methadone programs allowed clients' service needs to be addressed in depth (Etheridge, Craddock, Dunteman, et al., 1995).

Outcomes of Methadone Treatment in TOPS and DATOS

The basic analytic strategy employed in DATOS was to test the models employed in TOPS to determine whether basic findings could be replicated with a contemporary sample of clients who entered treatment from 1991 to 1993. Findings from TOPS showed that stays of 1 year or more in treatment were necessary to achieve statistically significant posttreatment reductions in heroin use (Hubbard, Craddock, Flynn, et al., 1997).

Although clients in TOPS and DATOS showed reductions in posttreatment drug use, as well as improvements in other areas of functioning compared with pretreatment levels, the 1-year time-in-treatment effect for heroin use demonstrated in TOPS for methadone clients was not replicated in DATOS (Hubbard, Marsden, Rachal, et al., 1995; Hubbard, Craddock, Flynn, et al., 1997). In DATOS, staying in treatment for 12 months and remaining in treatment at the 12-month followup point reduced the odds of heroin use by three-fourths compared with remaining in treatment less than 3 months (table 1), very similar to the odds ratio of .23 calculated in TOPS ($p<.01$). In neither TOPS nor DATOS were statistically significant posttreatment reductions in cocaine use found. Improvements accruing from shorter lengths of stay in treatment were demonstrated in DATOS only for marijuana use (greater than 6 months in treatment, odds ratio of .44, $p<.05$), with no such beneficial effects for alcohol use, unlike the findings from TOPS. In DATOS, multivariate analyses revealed no significant time-in-treatment effects on any area of psychosocial functioning, in contrast with TOPS, where significant reductions in predatory illegal activities were found for clients in long-term maintenance.

Services

In addition to the importance of length of stay and retention in treatment, findings from several studies have provided evidence supporting the critical role that services play in improving client functioning when services are targeted to specific domains of client need (Institute of Medicine, 1995; McLellan, Woody, Luborsky, et al., 1988; McLellan, Arndt, Metzger, et al., 1993; McLellan, Alterman, Metzger, et al., 1994; Appel, 1988). Because service levels were so low in DATOS and the numbers of clients in methadone who received any services were low, consideration of service effects was confined to findings from TOPS.

Although log-linear regression analyses in TOPS indicated that neither the number nor the intensity of services was strongly related to regular heroin use at followup, exploratory analyses suggested that services can compensate for shortened lengths of stay in treatment and extend the positive impacts of treatment for those clients who remain in treatment for less than 1 year

Table 1. Impact of client background characteristics, drug use patterns, referral source, treatment exposure, and time in treatment on regular heroin use in the year after treatment

Variable ($N = 727$)	Odds Ratios for Weekly or Daily Heroin Use	Significance Level
Male	1.69	p<.01
Married		
Never married		
Age, >40		
Age, 31-40		
Black	2.34	p<.0001
Hispanic-other	1.72	p<.05
Prior treatment, 1-2		
Prior treatment, 3+		
Family referral		
Criminal justice referral		
Heroin drug use pattern		
Heroin-cocaine use	3.46	p<.05
Days in treatment, 92-180 days		
Days in treatment, 181+ days		
Still in treatment at followup	.24	p<.0001

Note: Only statistically significant odds ratios are reported. Comparison groups for the significant odds ratios are males and females; blacks and Hispanic-other; whites; heroin-cocaine use; all other drug use patterns; still in treatment; staying in treatment less than 3 months.

(Hubbard, Marsden, Rachal, et al., 1995; Hubbard, Marsden, Cavanaugh, et al., 1987). An analysis of services provided to TOPS methadone clients during the first 3 months of treatment found a statistically significant positive effect of medical services on heroin use, alcohol use, and criminal activity. Beneficial impacts of vocational services on criminal activity involvement were also found. Clients who received three or more services they rated as helpful also showed statistically significant improvements in heroin use and criminal activity (Appel, 1988). Because

these findings are, at this stage, exploratory and preliminary, they require further confirmatory analyses to support more definitive conclusions regarding the impact of services on outcomes in TOPS.

Exploratory Treatment Structure and Process Analyses

Because the low levels of counseling and services in DATOS methadone programs precluded an analysis of service effects of sufficient power to draw valid conclusions, additional exploratory DATOS analyses focused on other treatment structure and process variables for which previous smaller scale studies have shown relationships with outcomes of methadone treatment: methadone dose (measured at the client level as "dose too small" and at the program level as lower methadone dose programs), good relationship with counselor, and spouse support for treatment. Building on the logistic regression models developed in TOPS and DATOS for time-in-treatment effects, the extended analyses with the above-mentioned treatment process variables showed independent effects of the two dose variables (Hubbard, Marsden, Rachal, et al., 1995; Hubbard, Craddock, Flynn, et al., 1997). The odds of heroin use were 1¾ times greater in the lower dose programs than in higher dose programs, and the odds of marijuana use more than doubled for those clients complaining of too small medication doses ($p<.05$). Interestingly, the seemingly paradoxical finding of lowered odds of suicidal ideation found in lower dose programs was shown through additional analyses to be an artifact of an elevated enrollment of blacks in low-dose programs who were found in DATOS to have levels of suicidal ideation considerably lower than those of other DATOS clients (Fletcher, Hubbard, 1994). This finding emphasizes the importance of replication in the weighting of research evidence, particularly where new areas of investigation are undertaken.

In addition, clients reporting strong spouse support for treatment involvement had less than half the odds of engaging in risky sex practices ($p<.05$). The impact of a good counselor relationship was significant only for employment, where clients who reported having a good relationship with their counselor had triple the odds of working full time ($p<.01$).

Conclusions

Findings from two national, multisite studies of drug abuse treatment over two eras of treatment support the conclusion that methadone is effective in reducing heroin use. However, unlike TOPS, recent findings from DATOS indicate that long-term maintenance is necessary for positive impacts on heroin use to accrue. These conflicting findings require further investigation, as well as additional research on factors related to retention in methadone treatment (Simpson, Joe, Broome, et al., 1997; Simpson, Joe, Brown, 1997). Neither TOPS nor DATOS found statistically significant reductions in cocaine use as an outcome of methadone treatment, and evidence of positive impacts on the use of other substances is mixed. Although improvement in some areas of psychosocial functioning was found in both TOPS and DATOS, these improvements were not statistically significant in DATOS, in contrast with TOPS, where significant reductions in illegal involvement were found.

Some research suggests that methadone dose level, counseling, and services may be related to improved posttreatment outcomes; however, these findings require additional confirmatory investigation to support stronger conclusions. Finally, exploratory analyses of treatment process variables in DATOS have revealed positive impacts of spouse support and the client-counselor relationship on some areas of psychosocial functioning. However, these preliminary findings do not support definitive conclusions; they only suggest new areas for further exploration.

Although findings from a large body of drug abuse treatment studies over the past three decades have produced evidence supporting the effectiveness of methadone treatment in reducing heroin use, its effectiveness as a treatment agent continues to be questioned. Some of this continuing controversy and the apparent ambivalence toward methadone can be traced to methadone's origins in the 1960s (Dole, Nyswander, 1965). At that time, the rapid public acceptance of methadone and expansion of methadone treatment programs appears to have occurred because of the public's expectation that, first and foremost, methadone would be effective in achieving social rehabilitation goals, such as reduced crime and unemployment and improved functioning in other socially desirable domains (Newman, 1987). Because the 1980s ushered in an array of public health problems, such as the spread of cocaine use, HIV/AIDS, and increases in violent crime, public expectations for methadone treatment and the criteria by which they have come to judge its success have expanded, despite the fact that methadone, as a treatment for opiate dependence, is a medical agent designed to address the physiological problem of addiction. Evaluated by the wider standard of improved psychosocial functioning, in addition to reductions in opiate use, the cumulative research evidence is less conclusive and definitive. Indeed, the criteria by which methadone's effectiveness is judged require reexamination and realistic expectations.

References

Appel P. Outcomes after drug treatment: the role of services received early in treatment in the TOPS study. Treatment Issue Report No. 65;1988:1-18. Unpublished manuscript.

Craddock SG, Rounds-Bryant JL, Flynn PM, Hubbard RL. Characteristics and pretreatment behaviors of clients entering drug abuse treatment: 1969 to 1993. Am J Drug Alcohol Abuse 1997;23(1):43-59.

Dole VP, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. JAMA 1965;193:80-4.

Etheridge RM, Craddock SG, Dunteman GH, Hubbard RL. Treatment services in two national studies of community-based drug abuse treatment programs. J Subst Abuse Treat 1995;7:9-26.

Etheridge RM, Hubbard RL, Anderson J, Craddock SG, Flynn PM. Treatment structure and program services in DATOS. Psychology of Addictive Behaviors 1997;11(4).

Fletcher B, Hubbard RL. The drug abuse treatment outcome family of studies. Presentation to the National Institute on Drug Abuse; Rockville, MD; 1994.

Flynn PM, Craddock SG, Hubbard RL, Anderson J, Etheridge RM. Methodological overview and research design for DATOS. Psychology of Addictive Behaviors 1997;11(4).

Hubbard RL, Marsden ME, Cavanaugh ER, Rachal JV, Ginzburg HM. Drug use after drug abuse treatment. Report submitted to the National Institute on Drug Abuse; Research Triangle Park (NC): Research Triangle Institute; 1987.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. Drug abuse treatment: a national study of effectiveness. Chapel Hill: The University of North Carolina Press; 1995.

Hubbard RL, Craddock SG, Etheridge RM, Flynn PM, Anderson, J. Drug abuse treatment need, access, selection and utilization: correlates for the insured versus the uninsured in the 1980s and 1990s. Poster presented at the American Health Services Research Conference; Chicago, IL; 1997.

Hubbard RL, Craddock SG, Flynn PM, Etheridge RM. Effect of HIV risk behavior on treatment need, access, and selection. Poster presented at the American Health Services Research Conference; Chicago, IL; 1997.

Hubbard RL, Craddock SG, Flynn PM, Anderson J, Etheridge RM. Overview of one-year followup outcomes in DATOS. Psychology of Addictive Behaviors 1997;11(4).

Institute of Medicine. Federal regulation of methadone treatment. Washington: National Academy Press; 1995.

McLellan AT, Alterman AI, Metzger DS, Grissom G, Woody GE, Luborsky L, et al. Similarity of outcome predictors across opiate, cocaine and alcohol treatments: role of treatment services. J Consult Clin Psychol 1994;62:1141-58.

McLellan AT, Arndt IO, Metzger D, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. JAMA 1993;269(15):1953-9.

McLellan AT, Woody GE, Luborsky L, O'Brien CP. Is the counselor an 'active ingredient' in substance abuse treatment? J Nerv Ment Dis 1988;176:423-30.

Newman RG. Methadone treatment: defining and evaluating success. N Engl J Med 1987;317(7):447-50.

Simpson DD, Joe GW, Broome KM, Hiller ML, Knight K., Rowan-Szal GA. Program diversity and length of stay in treatment in DATOS. Psychology of Addictive Behaviors 1997;11(4).

Simpson DD, Joe GW, Brown BS. Length of stay in treatment and follow-up outcomes in DATOS. Psychology of Addictive Behaviors 1997;11(4).

Patient Engagement and Duration of Treatment

D. Dwayne Simpson, Ph.D.

Duration of drug abuse treatment has been one of the most consistent predictors of followup outcomes (Gerstein, Harwood, 1990). Findings from the first national treatment evaluation study in the United States, however, indicated that therapeutic effects for the average patient emerge only after a period of about 90 days for drug-free residential or outpatient programs and about 300 days for methadone maintenance (MM). Longitudinal followup studies of opioid addicts from this treatment population over the next 12 years (Simpson, Sells, 1982, 1990) showed that 61 percent had quit opioid use in the 4 years after discharge, three-fourths of whom credited treatment as the major reason. By year 12, one-fourth still used opioids daily, and the overall death rate was about seven times higher than that for the general population (age-adjusted), with heavy alcohol use being the major risk factor.

The general relationship between treatment retention and outcomes has been replicated in the second and third national evaluations funded by the National Institute on Drug Abuse (Hubbard, Marsden, Rachal, et al., 1989, and National Evaluations of Drug Abuse Treatment Outcomes). Although length of stay often represents a focal indicator of treatment effectiveness, it should be regarded essentially as a convenient index of several therapeutic and environmental factors. Even in the first national study, these treatment retention effects were attributed to "interactions among individual needs, motivation factors, family or social influences, and treatment (and counselor) assignments" (Simpson, 1981), and the need for further examination of these factors was emphasized. Attention was given to program differences in treatment philosophy and services, and there have been continued improvements over time in assessing patient functioning and the treatment process in relation to outcomes. It is becoming increasingly clearer that several attributes of programs, including accessibility, policy and practices, organizational and clinical expertise, and level of services, have an impact on patient retention and outcomes (Ball, Ross, 1991; Joe, Simpson, Sells, 1994) Especially important in methadone maintenance programs is methadone dose.

The "holy grail" of drug abuse treatment has been matching patients to treatment. Although frequently overstated, there is evidence that matching is feasible within certain limits of patient needs, assessment techniques, and availability of services. At issue is a widely shared interest in improving the overall effectiveness and efficiency of treatment, preferably in a shorter time. Studies of treatment process and therapeutic components of the engagement sequence are fundamental to reaching these goals.

To disaggregate the ingredients underlying treatment retention effects, better assessment and process models are required. When treatment is conceptualized in discrete phases—spanning induction, treatment, and after-care activities (Simpson, 1997)—evaluation objectives and measurement strategies come into sharper focus. Outreach to out-of-treatment drug users as well

as continuing care following discharge from treatment for HIV/AIDS risk reduction are part of this general model (Brown, Beschner, 1993). The primary emphasis of the current presentation is on the treatment engagement process. As illustrated in the right half of figure 1, the more favorable outcomes commonly associated with longer retention are a general reflection of patients who reach more advanced recovery stages during treatment. In the center section, portions of the "black box of treatment" have been filled in through recent research conducted on the dynamics of therapeutic interactions. Several patient attributes and interventions found to facilitate the engagement and recovery process are listed around the box.

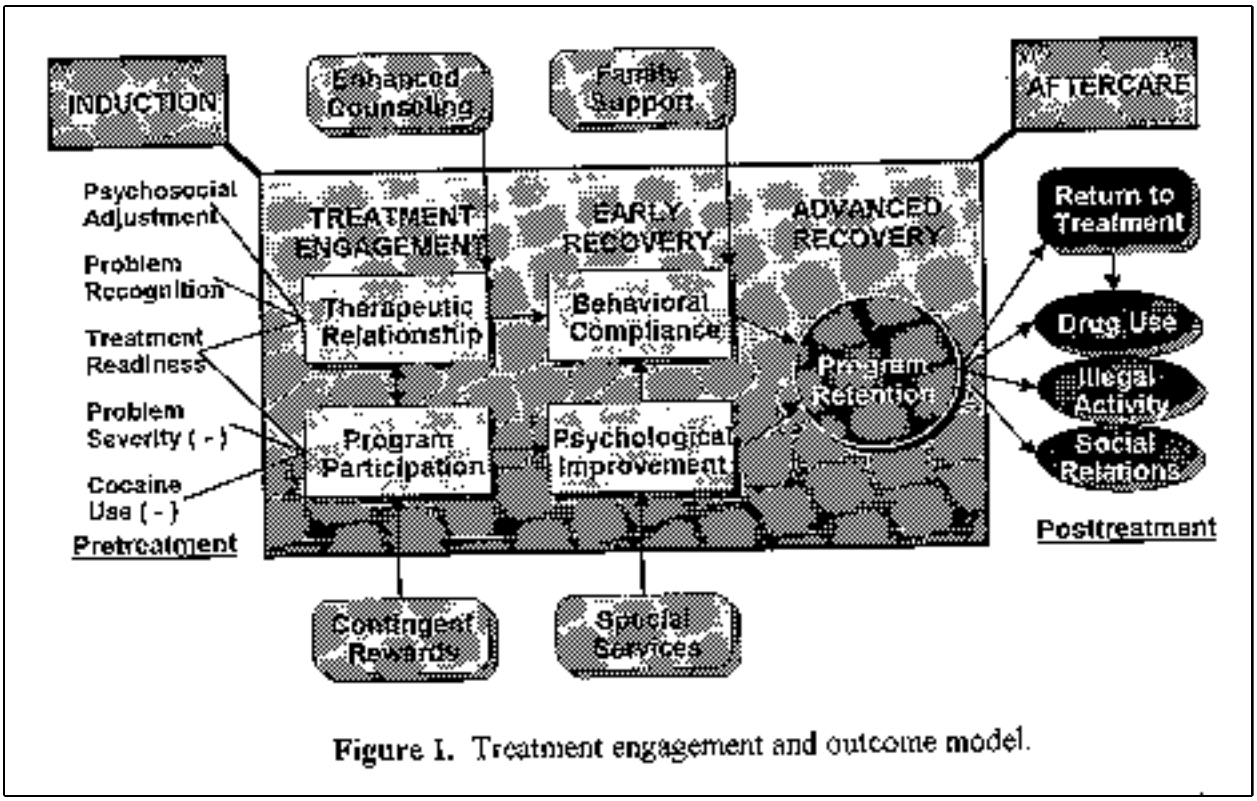

Figure 1. Treatment engagement and outcome model.

Patient sociodemographic and other pretreatment characteristics typically have not been prominent predictors of outcomes (Anglin, Hser, 1990), but improved assessments of patient functioning and analytic techniques in recent years are modifying this view. Psychiatric symptoms, social dysfunction, criminal history status, addiction severity and history, gender-related AIDS risks, heavy alcohol use, and cocaine use at the time of treatment intake influence engagement and retention indicators (Stark, 1992). Of particular importance are the patient's cognitive readiness for change and motivation for treatment (Miller, 1985; Prochaska, DiClemente, Norcross, 1992).

Treatment intensity is related to the effectiveness of MM programs (McLellan, Arndt, Woody, et al., 1993), and program participation as measured by session attendance is related to better therapeutic relationships, behavioral changes, and psychosocial functioning. Multivariate

analytic models have helped establish directional relationships between patient motivation, treatment process variables, retention, and followup outcomes more clearly, as summarized in figure 1 (Simpson, Joe, Rowan-Szal, et al., in press).

Several interventions have been applied successfully to impact these treatment engagement and early recovery indicators for MM patients (Simpson, Joe, Dansereau, et al., 1997). For example, social recognition using small gifts or treatment privileges can help increase session attendance and the rate of "clean" urines, thereby strengthening positive behaviors early in treatment. Counseling based on visual representation techniques (called node-link mapping) represent cognitive strategies shown to improve patient engagement, progress during treatment, and followup outcomes (Dansereau, Joe, Simpson, 1993). Another strategy is the use of motivational interviewing and role induction (Stark, 1992). Preparation of counselor-friendly manuals on special topics—such as HIV/AIDS education, women's sexual health and assertiveness training, and transition to aftercare—also has been shown to have a direct impact on knowledge and psychosocial functioning. Likewise, positive changes in the family and other social support networks accompany early recovery.

More systematic attention should be given to dynamic indicators of the therapeutic process, including program participation, therapeutic relationships, psychological improvements, and behavioral compliance. These are measurable domains that promote better treatment retention and outcomes. Patient cognitive and behavioral responses to services therefore should be gauged by using these as criteria for reaching progressive stages of engagement and recovery. Efficient assessment systems that include routine monitoring of patients in clinical settings are needed, and these will facilitate matching services with patient needs and overall management of care.

References

Anglin MD, Hser YI. Legal coercion and drug abuse treatment. In: Inciardi J, editor. Handbook on drug control in the United States. Westport, CT: Greenwood Press; 1990.

Ball JC, Ross A. The effectiveness of methadone maintenance treatment: patients, programs, services, and outcome. New York: Springer-Verlag; 1991.

Brown BS, Beschner GM, the National AIDS Research Consortium. Handbook on risk of AIDS: injection drug users and sexual partners. Westport, CT: Greenwood Press; 1993.

Dansereau DF, Joe GW, Simpson DD. Node-link mapping: a visual representation strategy for enhancing drug abuse counseling. J Counseling Psychol 1993;40(4):385-95.

Gerstein DR, Harwood HJ, editors. Treating drug problems: Vol. 1. A study of the evolution, effectiveness, and financing of public and private drug treatment systems (Committee for the Substance Abuse Coverage Study Division of Health Care Services, Institute of Medicine). Washington: National Academy Press; 1990.

Hubbard RL, Marsden ME, Rachal JV, Harwood HJ, Cavanaugh ER, Ginzburg HM. Drug abuse treatment: a national study of effectiveness. Chapel Hill: University of North Carolina Press; 1989.

Joe GW, Simpson DD, Sells SB. Treatment process and relapse to opioid use during methadone maintenance. Am J Drug Alcohol Abuse 1994;20(2):173-97.

McLellan AT, Arndt IO, Woody GE, Metzger D. Psychosocial services in substance abuse treatment: a dose-ranging study of psychosocial services. JAMA 1993;269(15):1953-59.

Miller WR. Motivation for treatment: a review with special emphasis on alcoholism. Psychol Bull 1985;98(1):84-107.

National evaluations of drug abuse treatment outcomes. Psych Addict Behav [Special Issue]. In press.

Prochaska JO, DiClemente CC, Norcross JC. In search of how people change: applications to addictive behaviors. Am Psychologist 1992;47(9):1102-14.

Simpson DD. Treatment for drug abuse: followup outcomes and length of time spent. Arch Gen Psychiatry 1981;38(8):875-80.

Simpson DD, Sells SB. Effectiveness of treatment for drug abuse: an overview of the DARP research program. Adv Alcohol Subst Abuse 1982;2(1):7-29.

Simpson DD, Sells SB. Opioid addiction and treatment: a 12-year followup. Malabar, FL: Krieger; 1990.

Simpson DD. Effectiveness of drug-abuse treatment: a review of research from field settings. In: Egertson JA, Fox DM, Leshner AI, editors. Treating drug abusers effectively. Cambridge, MA: Blackwell Publishers of North America; 1997. p. 42-73.

Simpson DD, Joe GW, Dansereau DF, Chatham LR. Strategies for improving methadone treatment process and outcomes. J Drug Issues 1997;27(2):239-60.

Simpson DD, Joe GW, Rowan-Szal GA, Greener J. Drug abuse treatment process components that improve retention. J Subst Abuse Treat. In press.

Stark MJ. Dropping out of substance abuse treatment: a clinically oriented review. Clin Psychol Rev 1992;12:93-116.

Problem-Service Matching in Methadone Maintenance Treatment: Policy Suggestions From Two Prospective Studies

A. Thomas McLellan, Ph.D.

Problem

Is it possible and practical to increase treatment effectiveness by matching different types of patients to particular kinds of programs or treatments? What are the system barriers to matching?

Data and Methods

Data from a prospective study of patient-treatment matching involving two treatment settings and four treatment programs treating 460 patients. In stage I, patients were evaluated by a central intake unit using a standard clinical interview and referred in the normal manner to one of the four programs. All patients were followed weekly by independent researchers monitoring the nature and number of the services received. Ninety-four percent of patients were recontacted 6 months later and reevaluated. These data were used to develop a model of patient-program and treatment service matching for the second stage of the study.

In stage II, the stage I decision tree was used to randomly assign 387 new patients to matched service profiles. Matched patients were compared with controls treated at the same programs in the standard manner but not given the matched services. Outcome measures were drug and alcohol use, employment, crime, and use of medical and social services.

Results and Conclusions

It was impossible to actually match patients to the programs because of insurance constraints, managed care, geography, and patient resistance. However, matching treatment services to patient problems at the program level was quite successful. Matched patients received the same total services as control patients but were less likely to drop out early. Six-month outcome comparisons showed that matched patients had better outcomes (by 15-25 percent) than control patients treated in the same programs by the same staff under standard conditions.

Implications for Audience

Patient-setting and patient-program matching is impractical to implement. Problem-service matching at the program level was easy to implement, well accepted by clinical and administrative staff, and cost an additional 3 percent (of program budgets) to institute.

References

Ball JC, Ross A. The effectiveness of methadone maintenance treatment. New York: Springer Verlag; 1991.

Hubbard RL, Marsden ME. Relapse to use of heroin, cocaine and other drugs in the first year after treatment. In: Relapse and recovery in drug abuse. NIDA Research Monograph 72. Rockville (MD): U.S. Government Printing Office; 1986.

Khantzian EJ, Treece K. DSM-III psychiatric diagnosis of narcotic addicts. Arch Gen Psychiatry 1985;42:1067-71.

McLellan AT, Luborsky L, Woody GE, O'Brien CP, Druley KA. Is treatment for substance abuse effective? JAMA 1982;247:1423-8.

McLellan AT, Luborsky L, O'Brien CP. Alcohol and drug abuse in three different populations: is there improvement and is it predictable? Am J Drug Alcohol Abuse 1986;12(2):101-20.

McLellan AT, Woody GE, Luborsky L, O'Brien CP. Is the counselor an "active ingredient" in substance abuse treatment? J Nerv Ment Dis 1988;176(7):423-30.

McLellan AT, Arndt IO, Alterman AI, Woody GE, Metzger D. Psychosocial services in substance abuse treatment: a dose-ranging study of psychosocial services. JAMA 1993.

Metzger DS, Platt JJ. Solving vocational problems. Proceedings of the Dutch American Conference on the Effectiveness of Drug Abuse Treatment. In press.

Platt JJ, Metzger DS. The role of employment in the rehabilitation of heroin addicts. In: Progress in the development of cost effective treatments. NIDA, Research Monograph 58; 1985. p. 111-25.

Rounsaville BJ, Weissman MM, Wilber CH. The heterogeneity of psychiatric diagnosis in treated opiate addicts. Arch Gen Psychiatry 1982;39:161-6.

Sells SB, Demaree RG, Hornick CW. Comparative effectiveness of drug abuse treatment modalities. NIDA Services Research Administrative Report. Washington, DC: U.S. Government Printing Office; 1979.

Stanton MD. The client as family member. In: Brown BS, editor. Addicts and aftercare. New York: Sage Pub; 1979.

Stanton MD, Todd T, et al. The family therapy of drug abuse and addiction. New York: Guilford Press; 1982.

Woody GE, Luborsky L, McLellan AT, et al. Psychotherapy for opiate addicts: does it help? Arch Gen Psychiatry 1983;40:639-45.

Woody GE, McLellan AT, Luborsky L, et al. Severity of psychiatric symptoms as a predictor of benefits from psychotherapy: the Veterans Administration-Penn Study. Am J Psychiatry 1984;141(10):1172-7.

Woody GE, McLellan AT, Luborsky L, O'Brien CP. Psychotherapy for opiate dependence: a 12-month follow-up. Am J Psychiatry 1987;145:109-14.

Yancovitz SR, Des Jarlais DC, Peyser NP, Drew E, Friedmann P, Trigg HL, et al. Am J Public Health 1991;81(9):1185-91.

Methadone Dose and Outcome

J. Thomas Payte, M.D.

Historically, methadone dose has been more a regulatory and philosophical issue than a matter of optimum and adequate dosing based on clinical considerations. In the early days of methadone maintenance treatment (MMT), the basic principle of pharmacotherapy was to establish a high degree of opioid cross-tolerance, and programs typically relied on doses in the 80 to 120 mg range. Beginning in the late 1960s and early 1970s, a shift in attitudes occurred coinciding with a rapid expansion of treatment, seen as a growing preoccupation with lowering the maintenance dosage and limiting the duration of MMT (Henderson, Harkey, 1990).

In 1972, Inturrisi and Verebely described a time course of methadone in the plasma of five patients on doses of 100 or 120 mg: a mean peak of 0.86 µg per mL 4 hours after dose and a trough level of 0.46 µg per mL at 24 hours. Note that the peak is less than doubled, with a peak to trough ratio of 1.86. The authors made reference to variations in individual plasma methadone levels. They suggested that "…the most complete evaluation of the effectiveness of MMT may require a determination of plasma methadone in all subjects regardless of the dose taken."

Kreek (1973) measured plasma methadone levels in a group of patients taking 100 mg daily at 24, 2, and 6 hours after dosing. The mean trough level was 0.58 µg per mL and the peak was 0.90 µg per mL. The peak to trough ratio was 1.55. Again, reference is made to individual variations in levels. Kreek suggested that plasma (and urine) levels could be useful in (1) patients experiencing symptoms of opioid withdrawal or excess and (2) patients with significant medical conditions or who are concomitantly taking medications that might influence metabolism and clearance of methadone.

Holmstrand, Änggård, and Gunne (1978), in a study of 21 patients, encountered sixfold interpatient variations in methadone levels. Patients were ranked by dose and rehabilitative outcome. Patients doing well had the highest plasma levels, and patients with poorer records of rehabilitation tended to have lower plasma levels. Improved rehabilitation is seen at steady-state plasma concentrations above 200 ng/mL.

In 1983, Tennant and colleagues examined 24-hour methadone levels in two groups of MMT patients, all taking 80 mg daily. Two groups of patients were identified: the good performers with negative urines, etc. and the poor performers with concurrent multiple drug and alcohol use. The mean 24-hour methadone level was 410.4 ng/mL for the good performers and 101.8 ng/mL for the poor performers. Clinicians should avoid confusing bad patients with poor treatment.

In 1983, *Research on the Treatment of Narcotic Addiction: State of the Art* was published (Cooper, Altman, Brown, et al.). The issue of methadone dose and duration of treatment was

extensively reviewed by Hargreaves (1983) and followed by a critique by Goldstein and Judson. The discussion summary by Cooper and colleagues (p. 92) distilled the state of the art in 1983 by supporting the need for empirically individualized dosing, with the most effective doses being in the range of 50 to 100 mg and with doses in excess of 100 mg being required under certain circumstances.

The search for an optimal dose failed, and practices to ensure individualized adequate and flexible dosing were slow to evolve over the next 10 years. The assumptions that methadone blood levels were of little utility were based on a general lack of correlation with symptoms and dose. That fourfold and sixfold variations in blood levels could be observed at identical doses did little to point to the possible utility. What was becoming apparent was that improved treatment outcomes did correlate with sustained blood levels of 150-200 ng/mL to $\geq$600 ng/mL (Holmstrand, Änggård, Gunne, 1978; Dole, 1988; Loimer, Schmid, 1992).

The primary measures of treatment outcome in relation to methadone dose were reduction in use of opioids and retention in treatment.

Examples of the many references demonstrating impact of dose on opioid drug use and retention in treatment include the following:

- Considerable evidence that methadone doses of 50 to 100 mg improve program retention and reduce the use of illicit opiates (Hargreaves, 1983);
- John Ball's 1988 data published by Dole (1989) showing a dramatic reduction in 490 patients using heroin in the previous month for those receiving more than 60 mg of methadone;
- Caplehorn and Bell's (1991) demonstration that patients maintained on methadone doses of less than 60 mg were approximately five times as likely to leave treatment as those receiving more than 80 mg daily;
- Loimer and Schmid (1992) showing optimum plasma levels at greater than 150 ng/mL, with best results in patients receiving more than 90 mg daily;
- Strain and colleagues (1993) comparing 0, 20, and 50 mg of methadone daily and demonstrating significant reductions in illicit opiate use and improved retention at the higher dose; and
- Hartel and associates (1995) finding recent heroin use to be highest in patients receiving less than 70 mg per day.

The remaining issue concerning utility of methadone blood levels is resolved by observing the rate of change over a period of time (Kreek, 1983; Kreek, personal communication, 1992). Most useful results require both peak and trough levels as described earlier. Although levels of 150 to 200 ng/mL and higher have been shown most effective in maintaining stability, it may be

that optimum results, including a cross-tolerance "blockade," are obtained at levels more than 400 ng/mL (Loimer, Schmid, Grünberger, et al., 1991; Goldstein, personal communication, 1994; Kreek, 1994; Verebely, personal communication, 1993).

The justification for dose flexibility is further illustrated by demonstration of interindividual differences in metabolism (Woosley in Grudzinskas et al., 1995) and rare cases of drug interactions requiring up to 100 mg methadone every 6 hours (Payte in Grudzinskas et al., 1995). DePetrillo (1995), doing a study of population kinetics in a methadone program with no ceiling dose, found that approximately 25 percent of patients required more than 100 mg daily for stability.

In summary, it is clear that realization of optimum pharmacologic goals of MMT requires individualized empirically determined methadone dosing that will ensure stable opioid receptor occupation (Dole, 1988). The ideal methadone dose range is likely between 60 and 120 mg, with some patients doing well at less than 60 and others requiring doses in excess of 120 mg (Payte, Khuri, 1993).

References

Caplehorn JR, Bell J. Methadone dosage and retention of patients in maintenance treatment. Med J Aust 1991;154(3):195-9.

Cooper JR, Altman F, Brown BS, Czechowicz D, editors. Research on the treatment of narcotic addiction: state of the art. Rockville (MD): National Institute on Drug Abuse; 1983. p. 95-118.

DePetrillo PB. Population kinetics of methadone in a high dose patient population. 1995. (Available from: URL: http>//www.well.com/user/pdeep/popkin/popkin.html)

Dole VP. Methadone treatment and the acquired immunodeficiency syndrome [editorial comment]. JAMA 1989;262(12):1681-2.

Dole VP. Implications of methadone maintenance for theories of narcotic addiction. JAMA 1988;260(20):3025-9.

Grudzinskas CV, Woosley RL, Payte JT, Collins J, Moody DE, Tyndale RF, et al. The documented role of pharmacogenetics in the identification and administration of new medications for treatment drug abuse. Problems of drug dependence 1995. Proceedings of the 57th Annual Scientific Meeting. NIDA research monograph; 1995. p. 60-3.

Hargreaves WA. Methadone dosage and duration for maintenance treatment. In: Cooper JR, Altman F, Brown BS, Czechowicz D, editors. Research on the treatment of narcotic addiction: state of the art. Rockville (MD): National Institute on Drug Abuse. 1983. p. 19-79.

Hartel DM, Schoenbaum EE, Selwyn PA, Kline J, Davenny K, Klein RS, et al. Heroin use during methadone maintenance treatment: the importance of methadone dose and cocaine use. Am J Public Health 1995;85(1): 83-8.

Henderson GL, Harkey MR. The use of therapeutic drug monitoring to improve the effectiveness of methadone treatment programs. Report submitted to Department of Alcohol and Drug Programs, State of California; January 1990.

Holmstrand J, Änggård E, Gunne LM. Methadone maintenance: plasma levels and therapeutic outcome. Clin Pharmacol Ther 1978;23:175-80.

Inturrisi CE, Verebely K. The levels of methadone in the plasma in methadone maintenance. Clin Pharmacol Ther 1972;13(5):633-7.

Kreek MJ. Plasma and urine levels of methadone. NY State J Med 1973;73:2773-7.

Kreek MJ. Factors modifying the pharmacological effectiveness of methadone and summary. In: Cooper JR, Altman F, Brown BS, Czechowicz D, editors. Research on the treatment of narcotic addiction: state of the art. Rockville (MD): National Institute on Drug Abuse; 1983. p. 95-118.

Kreek MJ. Biological correlates of methadone maintenance pharmacotherapy. Ann Med Interne (Paris) 1994;145 Suppl 3:9-14.

Loimer L, Schmid R. The use of plasma levels to optimize methadone maintenance treatment. Drug Alcohol Depend 1992;30:241-6.

Loimer N, Schmid R, Grünberger J, Jagsch R, Linzmayer L, Presslich O. Psychophysiological reactions in methadone maintenance patients do not correlate with methadone plasma levels. Psychopharmacology 1991;103:538-40.

Payte JT, Khuri ET. Principles of methadone dose determination. In: Center for Substance Abuse Treatment (1992) State Methadone Treatment Guidelines. Treatment Improvement Protocol (TIP) Series 1. DHHS Publication No. (SMA) 93-1991. Rockville (MD); 1993.

Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Methadone dose and treatment outcome. Drug Alcohol Depend 1993;33(2):105-17.

Tennant FS, Rawson RA, Cohen A, Tarver A, Clabout C. Methadone plasma levels and persistent drug abuse in high dose maintenance patients. Subst Alcohol Actions Misuse 1983;4:369-74.

Methadone Substitution Treatment in the United Kingdom: Outcome Among Patients Treated in Drug Clinics and General Practice Settings

Michael Gossop, Ph.D., John Marsden, Duncan Stewart, Petra Lehmann, Carolyn Edwards, Alison Wilson, and Graham Segar

The National Treatment Outcome Research Study (NTORS) is the largest study of treatment outcome for drug misusers ever conducted in the United Kingdom and plays an important role in the development and guidance of United Kingdom national drug treatment policy responses. NTORS is a prospective, multisite study of treatment outcome among clients admitted to four modalities. Two modalities were provided in residential settings: specialist inpatient units and residential rehabilitation units. Two modalities were provided in community settings: methadone maintenance and methadone reduction programs. Methadone substitution treatments were provided in both specialist drug treatment clinics and general practitioners' office-based settings.

This paper examines the client characteristics and 6-month outcomes among clients who received either clinic-based or general practitioners' office-based methadone treatments. The followup results show significant improvements among both groups in terms of drug-related problems, health, and social functioning. There were no substantial differences between the clinic-based and the office-based groups in intake characteristics or in improvements at 6-month followup. The implications of these results are discussed in terms of service delivery differences between the two treatment settings. The extension of NTORS to permit the continuing followup of clients over a 5-year period will enable its findings to provide further assistance to the direction of services within the United Kingdom.

Community, Staff, and Patient Perceptions and Attitudes

Joan E. Zweben, Ph.D.

Little systematic data exist on perceptions and attitudes that profoundly affect the daily life of patients and staff in methadone treatment programs. Both patients and treatment providers are keenly aware of their second-class status in a stigmatized endeavor; this status is all the more remarkable given the impressive data supporting the safety and efficacy of methadone treatment. We will review the rather sparse empirical data as well as descriptive work to better understand the context in which this treatment takes place.

The Stigma and Its Impact

Multiple layers of stigma affect this patient population and those who treat them (Murphy, Irwin, 1992; Hunt, Lipton, Goldsmith, et al., 1985-86; Sutker, Allain, Smith, et al., 1978; Sutker, Allain, Moan, 1974; Zweben, Payte, 1990; Zweben, Sorensen, 1988). Heroin addicts tend to be viewed as lowest on the totem pole in street status hierarchy, and the methadone client is seen as even more of a "loser" (Hunt, Lipton, Goldsmith, et al., 1985-86). Clinical records and research on heroin addicts reported inappropriately high frequencies of antisocial personality disorder (Gerstley, Alterman, McLellan, et al., 1990), a diagnosis that carries a poor prognosis and evokes negative attitudes on the part of staff, thus contributing to the stigma. Prior to the advent of the DSM-IV (American Psychiatric Association, 1994), it was common to find substance abuse confounding diagnosis, both in clinical situations and in research studies, because the criteria did not adequately distinguish between an independent psychiatric disorder and the consequences of alcohol and drug use.

The initial public policy decision to use methadone to transition patients to a "drug-free life style" left a legacy in which patients themselves often feel like failures if they cannot discontinue their medication. The patients internalize the stigma. The conviction that successfully treated patients taper off methadone persists among some patients and staff, despite the voluminous evidence of a brain chemistry imbalance that will require indefinite maintenance for most of those who qualify for this treatment.

Ironically, the AIDS epidemic has played a key role in reducing the isolation of methadone treatment providers and improving attitudes toward this modality. Research documenting the role of methadone maintenance treatment (MMT) in limiting the spread of AIDS has brought favorable attention; it has provided opportunities to present the strong research base supporting the safety and efficacy of MMT. In recent years, clarification of issues of dosing and duration of treatment has made it possible for maintenance pharmacotherapy to elicit a more favorable reception among educated professionals.

Patient/Staff Attitudes and Perceptions

Patient perceptions of this modality were studied by Sutker and her colleagues in the

1970s (Sutker, Allain, Smith, et al., 1978; Sutker, Allain, Moan, 1974). Clients representing the therapeutic community, methadone maintenance, and multimodality approaches rated methadone clients negatively, particularly in comparison with therapeutic community residents. Addicts, both in and out of treatment, agreed that methadone was "just another addiction." It is important to note that it was common to find subtherapeutic doses contributing to the perception that the patients are not motivated, or that the treatment does not work. Adequate dosing practices were not widely known to clinicians and other program staff until 1993, when the Center for Substance Abuse Treatment distributed the State Methadone Treatment Guidelines, which summarized recent research on these issues (Parrino, 1993).

Clinicians note the existence of a hidden middle- and upper-middle class population of heroin users, who find the methadone treatment system completely unacceptable and who develop a variety of effective and ineffective coping mechanisms. A study of opiate dependency among subscribers of a private insurance plan concluded that there is a large population of insured opiate users who are less likely to have contact with government agencies and whose social characteristics are not well described in the literature (Eisenhandler, Drucker, 1993).

Current U.S. data are limited with respect to staff and programs, but one recent examination indicates that program staff attitudes may be quite negative. Capelhorn and his colleagues (1997) compared the attitudes and beliefs of staff working in New York methadone maintenance programs and found significant differences as a function of staff post-graduate education. More educated and experienced staff generally rejected policies oriented toward discontinuing methadone, while less qualified staff tended to support them. Although this influence has not been studied empirically, practitioners attest that some negative staff attitudes are introduced or perpetuated by the increasing number of 12 step-oriented, recovering counselors, who harbor negative attitudes toward a variety of medications despite efforts from within the recovering community to discourage this bias.

Workplace Drug Testing

Many methadone patients fear exposure through workplace drug testing, which likely reduces the acceptability of this treatment for heroin users, who find themselves unable to abstain from drug use despite the consequences of being detected.

Community Resistance

A number of studies document the consequences of "natural" experiments, whereby communities in California limited or discontinued some or all of their methadone programs. Anglin and his colleagues (Anglin, Speckart, Booth, et al., 1989; McGlothlin, Anglin, 1979) studied Bakersfield and San Diego clients following the reduction or elimination of public funding in the 1970s; they found major adverse consequences—higher crime and dealing rates, more contact with the criminal justice system, and higher rates of illicit drug use. Rosenbaum and her colleagues (Rosenbaum, Washburn, Knight, et al., 1996; Murphy, Rosenbaum, 1988; Rosenbaum, Murphy, Beck, 1987) studied the impact of funding restrictions in the San Francisco Bay area and documented higher HIV risk behaviors, increased drug use and crime, and decreased employment.

In Alameda County, one of Rosenbaum's study sites, severe limitation of Medicaid funding for methadone led to the Sobky v. Smoley (1994) lawsuit, which centered on discriminatory denial of access to care. A permanent injunction issued in August 1994 prohibits denial of methadone maintenance services because of budget reasons if an eligible Medi-Cal patient seeks services from a Medi-Cal certified provider. Between July 1991 (prior to the injunction) and June 1997, MMT capacity in California expanded from 20,688 to 26,328 slots, and the number of programs grew from 115 to 146 (California Department of Alcohol and Drug Programs, 1997). Many indigent heroin users still have no access to treatment (because they are not Medi-Cal eligible), but these events are a testament to the importance of removing financial barriers.

Areas for Future Research

Deficiences in research are so extensive that it is possible to identify only a few:

1. What are current attitudes among patients, staff, other professionals, and the public?
2. What are the most effective ways to change negative attitudes?
3. What are the characteristics of the middle-class heroin-using population? What is the course of their addiction? How many would be appropriate for maintenance pharmacotherapy? How many would accept it if the treatment delivery system were more rational?
4. How widespread are discriminatory practices, such as workplace mandates to discontinue MMT, denial of access to residential treatment, prohibitions imposed by judges and others in the criminal justice system, etc.?
5. What are effective ways to reduce discriminatory practices?
6. What are other major sources of community resistance, and how can they be addressed?

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders 1994. Washington: The Association; 1994

Anglin MD, Speckart GR, Booth MW, Ryan TM. Consequences and costs of shutting off methadone. Addict Behav 1989;14:307-26.

California Department of Alcohol and Drug Programs. Narcotic treatment program expansion, July 1991-June 1997. The Department; 1997 June.

Capelhorn JRM, Hartel DM, Irwig L. Measuring and comparing the attitudes and beliefs of staff working in New York methadone maintenance clinics. Subst Use Misuse 1997;32(4)1:399-413.

Eisenhandler J, Drucker E. Opiate dependency among the subscribers of a New York area private insurance plan. JAMA 1993;269(22):2890-1.

Gerstley LJ, Alterman AI, McLellan AT, Woody GE. Antisocial personality disorder in patients with substance abuse disorders: a problematic diagnosis? Am J Psychiatry 1990;147(2):173-8.

Hunt DE, Lipton DS, Goldsmith DS, Strug DL, Spunt B. “It takes your heart”: the image of methadone maintenance in the addict world and its effect on recruitment into treatment. Int J Addict 1985-86;20(11-12):1751-71.

McGlothlin WH, Anglin MD. Effects of closing the Bakersfield methadone clinic. Problems of drug dependence. Proceedings of the 41st annual scientific meeting, The Committee on Problems of Drug Dependence, Inc. NIDA Research Monograph 27; 1979. p. 135-41.

Murphy S, Irwin J. “Living with the dirty secret”: problems of disclosure for methadone maintenance clients. J Psychoactive Drugs 1992;24(3):257-64.

Murphy S, Rosenbaum M. Money for methadone. II: unintended consequences of limited-duration methadone maintenance. J Psychoactive Drugs 1988;20(4):397-402.

Parrino M. State Methadone Treatment Guidelines 1993. Rockville (MD): Dept. of Health and Human Services (US); 1993.

Rosenbaum M, Washburn A, Knight K, Kelley M, Irwin J. Treatment as harm reduction, defunding as harm maximization: the case of methadone maintenance. J Psychoactive Drugs 1996;28(3):241-9.

Rosenbaum M, Murphy S, Beck J. Money for methadone: preliminary findings from a study of Alameda County’s new maintenance policy. J Psychoactive Drugs 1987;19(1):13-9.

Sobky v. Smoley, 855 F. Supp. 1123 (E.D. Cal. 1994).

Sutker PB, Allain AN, Smith CJ, Cohen GH. Addict descriptions of therapeutic community, multimodality, and methadone maintenance treatment clients and staff. J Consult Clin Psychol 1978;3:508-17.

Sutker PH, Allain AN, Moan CE. Addict attitudes toward methadone maintenance: a preliminary report. Int J Addict 1974;9(2):337-43.

Zweben JE, Payte JT. Methadone maintenance in the treatment of opioid dependence: a current perspective. West J Med 1990;152(5):588-99.

Zweben JE, Sorensen JL. Misunderstandings about methadone. J Psychoactive Drugs 1988;20(3):275-81.

Access to Narcotic Addiction Treatment and Medical Care

David C. Lewis, M.D.

The most unusual feature of methadone, and by extension LAAM (Eissenberg, Bigelow, Strain, et al., 1997), maintenance treatment is the discrepancy between the significant body of evidence concerning its safety and effectiveness and its equally significant underutilization (Gerstein, Harwood, 1990; Institute of Medicine, 1995). Of nearly 1 million heroin addicts nationwide, 125,000 are in methadone treatment (Institute of Medicine, 1995). In New York City, for example, there are an estimated 200,000 intravenous heroin addicts who potentially could benefit from methadone treatment, but current capacity for treatment is only about 35,000. Eight States have no opioid agonist treatment available at all. Overall, roughly 85 percent of heroin addicts have no legal access to methadone (New York Academy of Medicine, 1997). A combination of overregulation, stigma, inadequate medical education, and high costs have combined to limit access to and expansion of this modality of care. The most comprehensive review of this situation was undertaken by the Institute of Medicine (1995).

The regulatory hurdle is both a well-documented problem (Parrino, 1992) and the one most amenable to repair. With respect to treating heroin addiction, methadone regulations represent an "unprecedented restriction on the physician's right to prescribe an approved drug" (Dole, 1996). Originating with restrictions on maintenance therapy (largely with opium and morphine), in the decade following the passage of the Harrison Act in 1914 (Musto, 1973; Courtwright, 1982), renewed legislation and regulations aimed at methadone treatment in the 1970s (Molinari, Cooper, Czechowicz, 1994) were not intended to stifle maintenance therapy at the time. They were meant to establish uniform program requirements as well as to prevent the diversion of methadone onto the street market. The 1974 Narcotic Addiction Treatment Act set clinical practice parameters by statute and regulation to limit the prescription of methadone to opiate addicts. Also, State-specific legislation enacted during this period often added significantly more restrictive rules on top of the Federal legislation (Institute of Medicine, 1995), although some States are now reforming these statutes (Connecticut State Senate).

The 1974 Act instituted special physician registration and record-keeping (now via the DEA), which, while intended to put constraints on excessive physician prescribing, instead virtually precluded the development of methadone dispensation outside mostly large, urban-based clinics (Cooper, 1995a). The consequence of relying on "programs" and of limiting office-based prescribing is that the program delivery system can be expensive, stigmatizing, inaccessible, and, because of congestion and loitering, bothersome to the public (Cooper, 1995a). Medical care often suffers because it has been difficult to link these large methadone clinic programs to primary health care and specialized hospital-based services (Cooper, 1995a; Senay, Lewis, 1997). Yet, health services, particularly those dealing with communicable diseases like AIDS, hepatitis C, and tuberculosis, are essential for these patients.

After reviewing information on the usage of diverted methadone (Rosenbaum, Murphy, Beck, 1987; Spunt, Hunt, Lipton, et al., 1986), the Institute of Medicine report concluded:

"Methadone has rarely been the preferred drug of abuse by users of illegal drugs. Its action is too slow, and the level of euphoria it provides, particularly when taken orally, is too mild for most drug users to select it over other opiates. Rather, it has mainly served as a way to avoid or end withdrawal symptoms, as a form of self-treatment for heroin addiction, or as a substitute for heroin or other opiates when they are in short supply." (Institute of Medicine, 1995, p. 115)

Many countries with significant regulatory controls on the dispensation of methadone, and significant problems with the stigmatization of addiction, have still moved ahead and expanded their opiate agonist programs in the face of the AIDS epidemic, although not without occasional difficulties (Jepson, 1996, 1997). Much of the expansion was through prescription by general practitioners. Thousands of heroin addicts have been treated in office-based practices in the United Kingdom, Belgium, Netherlands, Germany, Switzerland, Australia, and Canada (Rehm, Fischer, 1997; Farrell, Neeleman, Gossop, et al., 1996; Gossop, Grant, 1990; Farrell, Neeleman, Gossop, et al., 1995; Byrne, Wodak, 1996; Brussel, 1995; Caplehorn, Batey, 1992; Klingemann, 1996; Newman, 1995; Brewer, 1995; Fleming, 1995; Lewis, Gear, Laubli Loud, et al., 1997). During the same period, U.S. program expansion has been stagnant. Given the medical needs of patients on methadone, bringing routine medical care closer to the delivery of addiction care is obviously a desirable medical and public health goal.

The example of the Province of Ontario in Canada is illustrative and recent. Like the United States, Canada instituted significant restrictions (in 1971) that included a special licensure for physicians to prescribe methadone. This licensure required 15 full days of training at accredited, methadone-maintenance treatment facilities. After the guidelines were officially introduced in 1972, the number of methadone clients in all of Canada fell by two-thirds during the following decade, from 1,509 in 1972 to 566 in 1982. The number of physicians prescribing methadone also fell, from 135 in 1972 to 56 in 1982, and continued to fall until the 1990s. A recent reversal of this restrictive approach has shown similarly striking results in the direction of greater methadone availability. Methadone control was decentralized from the Federal level to the provinces. In Ontario, the local health authority joined with the Ontario College of Physicians and Surgeons to create new practice standards. The College took on the function of recruiting local physicians into the provision of methadone maintenance treatment, providing referral information and overseeing the quality of methadone maintenance treatment service through physician audits. They also developed practice guidelines that were used for training physicians (College of Physicians and Surgeons of Ontario, 1996). As a result, between 1993 and April 30, 1997, the number of methadone maintenance treatment clients in Ontario increased from 525 to 2,047; the majority are under the care of local physicians (GPs). In the same period, the number of physicians authorized for methadone maintenance treatment rose from 36 to 68 (Rehm, Fischer, 1997; Fischer, 1997).

In the United States, a select but small group of "stabilized" methadone maintenance patients have been treated successfully in New York City general medical practice settings over several years. A first report of patient outcomes of this medical maintenance approach showed 82.5 percent were in good standing, 5 percent dropped out, and 12.5 percent responded unfavorably and were returned to the clinics (Novick, Joseph, 1991).

In a subsequent report of 100 patients maintained on methadone in general practice settings in New York City, 72 percent remained in good standing, while 15 percent were unfavorably discharged (though only three patients for misuse of medication). The conclusion of investigators was that "carefully selected methadone maintenance patients in medical maintenance have a high retention rate and a low incidence of substance abuse and lost medication" (Novick, Joseph, Salsitz, et al., 1994). In another report, office-based treatment by an addiction specialist psychiatrist was highly beneficial when compared with the usual clinical population experience. The report concluded that "the results of this pilot study indicate that stability can be maintained for at least a one-year period for three out of four methadone maintenance patients with a six month history of good performance in treatment. This can be achieved: (a) with lower levels of contact than are currently mandated by FDA regulations, (b) with a reduction in cost, (c) without risking serious untreated relapse" (Senay, Barthwell, Marks, et al., 1993). A follow-up report confirmed the earlier findings (Senay, Barthwell, Marks, et al., 1994). A trial of medical maintenance is under way in Baltimore, but results are not yet reported.

The advantages of office-based treatment include more patient privacy, dignity, and ready access to medical care. Problems encountered were not different from those experienced with addicts generally, namely, the occasional use of other nonprescribed medications (the most problematic were cocaine and alcohol). Diversion was not perceived to be a problem. While fewer than 300 patients have been so treated, it is estimated that at least 5 percent to 7 percent of current methadone clinic patients would fit likely "stability" criteria (about 7,500 patients) (New York Academy of Medicine, 1997; American Methadone Treatment Association, 1997). This would also open up a corresponding number of clinical treatment spots.

Stigma (Gerstein, Harwood, 1990; Institute of Medicine, 1995; Bell, Chan, Kuk, 1995; D'Aunno, 1992; Lewis, 1994), inadequate medical education (Sirica, 1995), and cost (Gerstein, Harwood, 1990; Rosenbaum, Washburn, Knight, et al., 1996) all contribute to the under-utilization of opioid maintenance therapy in the United States. But, as we have learned from positive experiences abroad and with the medical maintenance trials here, regulatory barriers that block physician care of addicts in the name of public safety may, in fact, do the opposite by constraining the growth of effective addiction treatment.

References

American Methadone Treatment Association. Expanding access to care. News Report 7. The Association; 1997.

Bell J, Chan J, Kuk A. Investigating the influence of treatment philosophy on outcome of methadone maintenance. Addiction 1995;90:823-31.

Brewer C. Recent developments in maintenance prescribing and monitoring in the United Kingdom. Bull N Y Acad Med 1995;72:359-70.

Brussel GV. Methadone treatment by general practitioners in Amsterdam. Bull N Y Acad Med 1995;72:348-58.

Byrne A, Wodak A. Census of patients receiving methadone treatment in a general practice. Addiction Research 1996;3:341-9.

Caplehorn JRM, Batey RG. Methadone maintenance in Australia. Drug Issues 1992;22:661-79.

College of Physicians and Surgeons of Ontario, Addiction Research Foundation, Ontario College of Pharmacists. Methadone maintenance guidelines. Ontario, Canada: The College of Physicians and Surgeons of Ontario; 1996.

Connecticut State Senate Bill #1259.

Cooper JR. Including narcotic addiction treatment in an office-based practice. JAMA 1995a;273:1619-20.

Cooper JR. Methadone: prescribing maintenance, pursuing abstinence. Int J Addict 1995b;30:1303-9.

Courtwright D. Dark paradise: opiate addiction in America before 1940. Cambridge (MA): Harvard University Press; 1982.

D'Aunno T. Variations in methadone treatment practices: results from a national study. JAMA 1992;267:253-8.

Dole VP. On federal regulation of methadone treatment. Conn Med 1996;60:428-9.

Eissenberg T, Bigelow G, Strain E, Walsh S, Brooner R, Stitzer M, et al. Dose-related efficacy of levomethadyl acetate for treatment of opioid dependence. JAMA 1997;277:1945-51.

Farrell M, Neeleman J, Gossop M, Griffiths P, Buning E, Finch E, et al. Methadone provision in the European Union. Int J Drug Policy 1995;6:168-72.

Farrell M, Neeleman J, Gossop M, Griffiths P, Buning E, Finch E, et al. A review of the legislation, regulation and delivery of methadone in 12 member states in the European Union. Brussels: The European Commission; 1996.

Fischer B. Recent developments of MMT policy and practice in Canada. Unpublished manuscript; 1997.

Fleming PM. Prescribing policy in the UK: a swing away from harm reduction? Int J Drug Policy 1995;6:173-7.

Gerstein DR, Harwood HJ, editors. Treating drug problems. Washington: National Academy Press; 1990.

Gossop M, Grant M. The content and structure of methadone treatment programmes: a study in six countries. New York: World Health Organization; 1990.

Institute of Medicine. Federal regulation of methadone treatment. Washington: National Academy of Medicine; 1995.

Jepsen J. Danish methadone policy under change? Newsletter Euro-Methwork 3-4; 1996 Nov.

Jepsen J. Primary care prescribing for opiate users, a flawed policy? Newsletter Euro-Methwork 11-12; 1997 Mar.

Klingemann HK. Drug treatment in Switzerland: harm reduction, decentralization and community response. Addiction 1996;91:723-36.

Lewis D, Gear C, Laubli Loud M, Langenick-Cartwright D, English edition editors. The medical prescription of narcotics, Rihs-Middel M, editor. Toronto: Hogrefe & Huber Publishers; 1997.

Lewis DC. Political pharmacology: thinking about drugs. Daedalus 1994;121(3):164-94.

Molinari SP, Cooper JR, Czechowicz DJ. Federal regulation of clinical practice in narcotic addiction treatment: purpose, status, and alternatives. J Law Med Ethics 1994;22:231-9.

Musto DF. The American disease: the origins of narcotic control. New Haven: Yale University Press; 1973.

New York Academy of Medicine. Addiction treatment: promoting a medical approach to substance use. New York: The Academy; 1997.

Newman RG. Another wall that crumbled--methadone maintenance treatment in Germany. Am J Drug Alcohol Abuse 1995;21:27-35.

Novick DM, Joseph H. Medical maintenance: the treatment of chronic opiate dependence in general medical practice. J Subst Abuse Treat 1991;8:233-9.

Novick DM., Joseph H, Salsitz EA, Kalin MF, Keefe JB, Miller EL, et al. Outcomes of treatment of socially rehabilitated methadone maintenance patients in physicians' offices (medical maintenance): follow-up at three and a half to nine and a fourth years. J Gen Intern Med 1994;9:127-30.

Parrino MW. State methadone maintenance treatment guidelines. Rockville (MD): Dept. of Health and Human Services (US); 1992.

Rehm J, Fischer B. Preface from the Canadian editors. In: Uchtenhagen A, editor. Swiss methadone report. Zurich, Switzerland: Swiss Narcotic Substances Commission; 1997. p. ii-iii.

Rosenbaum M, Murphy S, Beck J. Money for methadone: preliminary findings from a study of Alameda County's new maintenance policy. J Psychoactive Drugs 1987;19:13–9.

Rosenbaum M, Washburn A, Knight K, Kelley M, Irwin J. Treatment as harm reduction, defunding as harm maximization: the case of methadone maintenance. J Psychoactive Drugs 1996;28:241-9.

Senay EC, Barthwell AG, Marks R, Bokos P, Gillman D, White R. Medical maintenance: a pilot study. J Addictive Diseases 1993;12:59-76.

Senay EC, Barthwell A, Marks R, Bokos PJ. Medical maintenance: an interim report. J Addictive Diseases 1994;13:65-9.

Senay E, Lewis DC. The history and current status of drug substitution therapy for narcotic addiction in the United States. In: Lewis D, Gear C, Laubli Loud M., Langenick-Cartwright D, editors, English edition; Rihs-Middle M., chief editor. The medical prescription of narcotics. Seattle: Hogrefe & Huber Publishers; 1997.

Sirica C, editor. Training about alcohol and substance abuse for all primary care physicians. New York: Josiah Macy, Jr., Foundation; 1995.

Spunt B, Hunt D, Lipton DS, Goldsmith DS. Methadone diversion: a new look. J Drug Issues 1986;18:569-83.

Diversion of Methadone: Expanding Access While Reducing Abuse

G. Thomas Gitchel

Since the inception of treatment for addiction, furnishing a narcotic drug to narcotic addicts as part of the treatment has been and remains a controversial issue among health care providers, public officials, and policymakers. The vast majority of methadone produced annually in the United States is distributed to narcotic treatment programs (NTPs). The annual production has increased from 1,690 kg in 1986 to approximately 4,500 kg in 1996. This is an increase of 166 percent, which equals enough methadone to provide 100 mg per day to approximately 123,000 patients for 1 year. In 1972, there were 65,000 patients in 450 facilities in the United States. In recent years, this number has risen to approximately 115,000 patients in 1,016 facilities. During the late 1960s and early 1970s, methadone maintenance increasingly became the subject of policy debate, in part because it was recognized not as medical treatment but as research and because there was an absence of medical and legal standards governing its use in addiction treatment programs. There was, in effect, no clear means to differentiate legitimate treatment efforts using the drug as part of a program of treatment services from bogus clinics or unethical physicians distributing methadone to addicts under the guise of treatment. As a result, Congress passed the Narcotic Addict Treatment Act of l974 (NATA), which required that specific standards of practice and control be established, along with specific Federal licensing, for narcotic addict treatment programs that dispensed a narcotic drug to an addict as part of the treatment plan.

Congress held hearings on the diversion of methadone in 1978, 1989, and 1990. A 1978 report of the House Select Committee on Narcotics Abuse and Control concluded, "From a public health perspective, methadone diversion and illicit use represent a significant threat. This committee documented numerous cases of primary methadone addiction, of drug death due to illicit methadone, and of emergency episodes involving methadone. Illicit methadone must be minimized; for this reason, the committee has concluded that take-home dosage units represent a major threat. The benefits of methadone treatment are great, but the social and public health costs of its widespread use are also great" (House Select Committee on Narcotic Abuse and Control, 1978). The parallels between the types of diversion during 1978 and today, some 20 years later, are strikingly similar.

The diversion of methadone from programs and patients continues to be a health and law enforcement concern. The illegal sale and illicit demand for methadone have been present over the past 23 years. National estimates from the Drug Abuse Warning Network (DAWN) of emergency room mentions show that methadone is routinely among the top 20 controlled substances. Also, the Drug Use Forecasting (DUF) system shows that among the 23 sites that reported in 1996, 1.6 percent of adults arrested tested positive for methadone. In New York, the figure was approximately 12.2 percent. Yet, this drug is almost exclusively available only through treatment programs.

Based on DAWN emergency room data for the first 6 months of l996, methadone ranked 15th of all controlled substances mentioned. By way of reference, LSD ranked 14th and PCP 16th. In New York City, methadone ranked fourth among emergency room mentions of the top 20 controlled substances, exceeded only by cocaine, heroin, and marijuana. In 1988 and again in 1995, the Drug Enforcement Administration (DEA) conducted a limited undercover buy program in New York City to examine the availability of methadone in the illicit traffic. Methadone was found to be readily available in the neighborhoods reviewed. Undercover operatives ran out of money before sellers ran out of methadone. In June 1997, an armed robbery at a methadone clinic in Florida resulted in the theft of $12,000 in cash and approximately 12,000 mg of methadone.

Several studies conducted by various groups regularly note that the diversion of methadone from NTPs does occur; however, they disagree as to the extent of the diversion. In 1995, the Institute of Medicine (IOM) recommended a broad revision of methadone treatment regulation. According to the IOM study, "Data presented . . . indicate that while methadone has some potential for abuse when diverted from normal channels, the extent of the abuse associated with diverted methadone is small relative to heroin and cocaine (Institute of Medicine, 1995)." In the November/December 1996 edition of *Pulse Check*, published by the Office of National Drug Control Policy, it was reported that "the illicit market for methadone, a narcotic used to treat heroin addiction, is growing. This suggests that more heroin users are becoming addicted and searching for ways to control or reduce their use."

Methadone may be diverted by internal diversion within a given program, sale of take-home dosages, and the inappropriate dispensing of methadone by loosely administered programs. As a result of the DEA's inspection program for NTPs, there appears to be minimal diversion of methadone through illegal sales by clinic employees. However, investigations and surveys regularly document the selling of take-home dosages of methadone by patients. In addition, methadone is diverted into the illicit market as a result of lax practices in loosely operated treatment programs. Despite urinalyses that show that their clients either are not ingesting their methadone or are regularly abusing illicit drugs, these programs continue to dispense take-home methadone.

The sale or diversion of take-home doses of methadone represents the primary source of methadone in the illicit market. As mentioned, DEA investigations reveal the ease with which take-home doses can be purchased on the street. The majority of NTPs, both private and public, do not seek Federal law enforcement intervention when they encounter a diversion problem. However, the Department of Veterans Affairs (VA), Office of Inspector General (IG), in its effort to address the problem of diversion, sought the intervention of another law enforcement agency. In 1996, the IG contacted the DEA about suspected diversion of methadone near an NTP located at the St. Louis, Missouri, VA. A joint DEA and VA investigation was initiated and resulted in 13 arrests for take-home sales.

In correspondence dated July 13, 1990, James S. Benson, then Acting Commissioner of the Food and Drug Administration (FDA); Charles R. Schuster, Ph.D., Director, National Institute on Drug Abuse, and Terrence Burke, Acting Administrator of DEA, jointly issued a statement addressing the methadone take-home diversion problem. Program sponsors, medical directors, NTPs, and State methadone authorities were cautioned to review and reemphasize

take-home regulations to ensure compliance and otherwise decrease diversion of take-home medication.

Research conducted by Barry Spunt in 1981-82 disclosed that 10 percent of his sample population of treatment clients routinely sold their take-home doses. Many of these clients, he found, diverted their methadone to supplement income, purchase a drug of choice, or share with a family member or friend. Their primary customers were heroin addicts not in treatment. Sales also were made to those persons whose primary drug of abuse is methadone.

As publicly funded programs cut back, for-profit programs are expanding. In an effort to maximize profit, some of these proprietary programs minimize comprehensive services and are lax in their adherence to treatment standards. This type of program can become a source of diverted methadone. DEA investigations have identified NTPs that ignore urinalysis results that are negative for methadone or positive for illicit drugs and continue to authorize take-home doses. This practice creates an atmosphere that undercuts treatment because the patient's steady supply of methadone provides a constant source of illicit income with which to purchase other drugs. The dispensing of take-home methadone becomes the only constant in such programs. Current take-home standards are subjective and thus have allowed this lax practice to develop, ultimately permitting patient sales of take-home medication.

The 1995 IOM report concluded that "in general, raising the standard of treatment entails authorizing greater clinical discretion in medical treatment and reducing the scope of government regulation (Institute of Medicine, 1995). Many have interpreted the IOM report as a signal to move narcotic addict treatment into private physicians' offices and, correspondingly, expand current methadone take-home standards. This is evidenced by an increase in applications for "medication units." Medication units, as currently defined by FDA regulations, recognize the possibility that licensed private practitioners and community pharmacists may dispense narcotic drugs and collect urine samples as an extension of an NTP offering comprehensive services. Although the law currently allows medication units, such operations have not previously existed. However, the Controlled Substance Act does require a separate registration as an NTP for the dispensing of a narcotic for narcotic addiction treatment. This type of delivery system should be based on accurate identification of patients who have demonstrated stability and will continue to function without any diversion or drug abuse.

The need to increase treatment opportunities is obvious to anyone in law enforcement. However, expansion of treatment cannot and need not be at the expense and risk of expanding the abuse of the treatment drug itself. The IOM committee also concluded "that a need exists to maintain certain enforceable requirements in order to prevent substandard or unethical practices that have socially undesirable consequences (Institute of Medicine, 1995). The dual goals of expanding treatment and reducing diversion are achievable. Dispensing a narcotic drug to a narcotic-dependent person for treatment without diversion and abuse is possible. A case in point is levo-alpha-acetylmethadol (LAAM), which is now being dispensed nationwide but has not been subject to diversion or abuse. The experience with LAAM in no way parallels the experience with methadone and demonstrates that the goal of treatment expansion without abuse or diversion can be achieved. This type of treatment also can be achieved with methadone if programs are held to a high standard that safeguards the privilege of take-home medication.

Maintenance or improvement of several simple principles would ensure controls for stopping the diversion by patients and lax programs without hindering treatment expansion: continued separate registration as an NTP, required comprehensive treatment services for an extended period on program entry, required bona fide doctor/patient relationships (i.e., the patient must be evaluated by the doctor on a required basis), a central registry for patients to prevent their enrollment in multiple treatment programs, continued limitations on the quantity of take-home doses and required action to reduce or eliminate take-home doses for patients with urinalyses positive for other drugs of abuse or negative for methadone, and a demonstrated need in a geographic area before approval is given for a new treatment program.

The controversy surrounding methadone maintenance treatment, prevalent during its infancy, lingers. The illicit market for methadone persists and is supplied primarily by the sale of take-home dosages and loosely administered programs. Those who take shortcuts either for profit or in the rush to expand treatment by minimizing standards, regardless of the consequences, hamper those who are truly serious about helping addicts. To relax controls in clearly identified areas that contribute to diversion would not enhance treatment but instead would further erode public confidence in methadone treatment and expand the abuse of methadone.

References

House Select Committee on Narcotic Abuse and Control. Methadone diversion. Washington: US Government Printing Office; 1978. p. 29.

Institute of Medicine. Division of Biobehavioral Sciences and Mental Disorders. Committee on Federal Regulation of Methadone Treatment. Federal regulation of methadone treatment; Washington: National Academy Press; 1995. pp. 4, 5, 114.

Office of National Drug Control Policy. Pulse check: national trends in drug abuse. The NarcOfficer-Conference Issue; 1996 Nov-Dec. p. 18.

Spunt B, Hunt DE, Lipton DS, Goldsmith DS. Methadone diversion: a new look. J Drug Issues 1986;16(4):569-83.

Narcotic Agonist Treatment as a Benefit Under Managed Care

Dennis McCarty, Ph.D., Rhona Millar, and Richard Frank

Introduction

Escalation in expenditures for the treatment of alcohol and drug dependence and mental illness has led public and commercial health plans to use managed care strategies to facilitate access to appropriate levels of care and to control costs (Institute of Medicine, 1997). Even without managed care, however, benefits for substance abuse treatment services typically have annual and lifetime limits on inpatient and outpatient services (Larson, Horgan, Marsden, et al., 1993; Rogowski, 1992; Scott, Greenberg, Pizarro, 1992) and are usually limited to acute care services. Long-term residential care and methadone maintenance services are rarely available in commercial health plans. Many States, moreover, have not provided coverage for methadone maintenance in their Medicaid plans. As a result, financing for narcotic agonist treatment has been primarily based on funds from the Federal Substance Abuse Treatment and Prevention Block Grant and from State appropriations to the State substance abuse authority.

The introduction of managed care, however, provides opportunities for restructuring the organization and financing of substance abuse treatment services and, potentially, for expanding benefits to specifically include prolonged use of narcotic agonist therapies. It is critical, therefore, to examine the evolution of managed care for substance abuse treatment and to assess benefits for methadone and LAAM medication and related counseling services.

Managed Care for Substance Abuse Treatment Services

Managed behavioral health care introduces financial risk sharing, provider selection, and utilization management to control costs, inhibit or enhance access and utilization, and maintain or improve the quality and effectiveness of substance abuse treatment services (Goplerud, 1995; Institute of Medicine, 1997; Mechanic, Schlesinger, McAlpine, 1995). There is little consensus on the positive and negative influences associated with managed behavioral health care, especially for publicly funded services. Although some suggest that a well-developed managed care program can enhance access to mental health and substance abuse treatment and maintain the quality of care (Boyle, Callahan, 1995; Callahan, Shepard, Beinecke, et al., 1995; England, Vaccaro, 1991; Frank, McGuire, Notman, et al., 1996), others distrust prepaid capitated financing because the financial incentives encourage minimal service to maximize profit (Kassirer, 1995; Schlesinger, Dorwart, Epstein, 1996; Woolhandler, Himmelstein, 1995; Woolhandler, Himmelstein, 1996).

Policymakers, however, are not waiting for the debate to be resolved. States are enrolling Medicaid recipients into managed care plans and are exploring the use of managed care principles to restructure the delivery and reimbursement of services for individuals who are uninsured or have exhausted limited insurance benefits. Many States are making fundamental changes in the

structure and delivery of substance abuse treatment services, including the use of methadone and LAAM, as they design and implement managed care systems.

Opiate Agonist Treatment and Managed Care

Managed behavioral health organizations and health maintenance organizations (HMOs) have had little experience managing narcotic agonist therapies. Inclusion of benefits for methadone medication and counseling in State managed care initiatives, therefore, requires creative design and careful program implementation. A review of substance abuse managed care initiatives suggests that the design of a methadone benefit varies substantially among States, and many States explicitly exclude methadone treatment from the managed care benefits. To add perspective and context to the analysis of State managed care plans, the use of opiate agonist therapy was also examined in selected commercial health plans.

State managed care plans. States use three general strategies to address opiate agonist medication and counseling services within their managed care initiatives: full coverage, limited coverage, and exclusion from the managed care plan. Table 1 summarizes coverage for opiate agonist therapy under State Medicaid managed care plans.

Some States grant methadone services parity with other behavioral health benefits. Massachusetts Medicaid, for example, lists methadone maintenance as one of the benefits available under the Mental Health and Substance Abuse Program. Both medication and counseling services are authorized, and neither the medication nor the counseling is limited. During the first year of the Massachusetts Medicaid managed care program, admissions to methadone services increased approximately 5 percent (Callahan, Shepard, Beinecke, et al., 1995).

States may limit either the days of medication or the number of counseling sessions available under their managed care plan. Delaware and Tennessee have a ceiling of 20 counseling visits per year for all outpatient substance abuse treatments and extend the constraint to individuals enrolled in methadone services. The design of the plan does not recognize that methadone patients may be more impaired than typical outpatient clients and may require more intensive services. Rhode Island, on the other hand, limits the financial risk that HMOs assume for methadone; HMOs serving Medicaid recipients are responsible for 30 weeks per year of narcotic agonist therapy. At the end of 30 weeks, if the health plan determines that continued methadone care is required, the State substance abuse authority reimburses Medicaid for the additional costs; fees paid to the treatment program, however, are reduced by 20 percent. Other

Table 1. Summary of methadone coverage under state managed care plans

State	No limits with prior authorization	Limits on counseling or medication	Not in managed care (MC) plan
Arizona	capitated through regional authorities		
Delaware		20 visits	
Iowa		medication excluded; counseling included	medication excluded from MC plan
Massachusetts	statewide managed behavioral health care carve out		
Minnesota	cannot be self-referred		
Missouri		20 visits	medication covered under pharmacy plan
Mississippi			no Medicaid coverage
Nebraska			no Medicaid coverage
New York			not in MC plan
Ohio			not in MC plan
Oregon	included in substance abuse carve in without limits but must conform to ASAM type criteria		
Rhode Island		30 weeks of service per year	additional care reimbursed by State authority
Tennessee		20 visits	
Utah			Not in MC plan
Wisconsin			Not in MC plan; methadone patients may exempt from HMOs

Note: Based on personal interviews and Exhibit 1 in the Policy Resource Center and the George Washington University, Center for Health Policy Research, *SAMHSA Managed Care Tracking Study: Second Report, Summer 1996.*

States split the responsibility for payment of the medication and counseling benefits. The Iowa Medicaid managed care plan excludes methadone medication (methadone is purchased by using non-Medicaid funds) but covers unlimited outpatient counseling services for methadone clients. Missouri uses its Medicaid pharmacy plan to pay for methadone medication and applies a 20-visit limit to counseling services.

Many States exclude methadone medication and counseling services from managed care initiatives. Mississippi and Nebraska, for example, do not include methadone services in the Medicaid managed care plan because Medicaid does not cover methadone. Wisconsin, on the other hand, asserts that methadone patients have special needs that are not easily met within typical managed health care plans and permits methadone patients to disenroll from HMOs.

Commercial health plans. Commercial health plans often separate (or carve out) the management and delivery of mental health and substance abuse services from the management of acute care and primary care services. A review of benefit design, analyses of claims and encounter data, and interviews with managed behavioral health care organizations suggest that carve outs within HMOs and employer-based carve outs may offer specialized substance abuse services, including methadone treatment. These programs, however, tend to impose limits on the duration of treatment and are unlikely to support methadone maintenance.

Discussion

Exclusion of methadone maintenance services from many State and commercial managed care plans suggests that opiate agonist treatments are still perceived as separate service systems for a few difficult-to-service individuals rather than as medically necessary services for some individuals dependent on opiates. The variety of benefit arrangements and the structure of the benefit limits also suggest policymaker and health plan ambivalence toward addressing opiate addiction using methadone maintenance. Attitudinal biases and awkward benefit designs, therefore, may be barriers to accessing the service and to delivering the most effective service. Moreover, without stronger linkages to behavioral health and primary care services, individuals in narcotic agonist treatment may not benefit from the potential service improvements and innovations associated with effective managed care strategies.

At the same time, methadone maintenance programs may need to rethink their services and be responsive to managed care organizations that seek cost-effective services. Treatment providers must accept the value of utilization review and management and be able to justify the length and intensity of care. Managed care systems will also expect counseling and medication to effectively address patient needs in the treatment for alcohol, cocaine, and other psychoactive medication dependencies.

The effects of managed care on the organization, delivery, effectiveness, and financing of opiate agonist services must be investigated to contribute empirical data to the sometimes emotional debates on the value of managed care and the value and role of opiate agonist therapies. Further, services research on the delivery and effectiveness of narcotic agonist therapy within managed care environments is required to promote greater utilization of these services within managed health care plans.

References

Boyle PJ, Callahan D. Managed care in mental health: the ethical issues. Health Aff 1995;14(3):7-22.

Callahan JJ, Shepard DS, Beinecke RH, Larson MJ, Cavanaugh D. Mental health/substance abuse treatment in managed care: the Massachusetts Medicaid experience. Health Aff 1995;14(3):173-84.

England MJ, Vaccaro VA. New systems to manage mental health care. Health Aff 1991;10(4):129-37.

Frank RG, McGuire TG, Notman EH, Woodward RM. Developments in Medicaid managed behavioral health care. Mental Health U.S. Rockville (MD): Center for Mental Health Services; 1996.

Goplerud, E. Managed care for mental health and substance abuse services. Rockville (MD): Substance Abuse and Mental Health Services Administration; 1995.

Institute of Medicine. Managing managed care: quality improvement in behavioral health. Washington: National Academy Press; 1997.

Kassirer JP. Managed care and the morality of the marketplace. N Engl J Med 1995; 333:50-2.

Larson MJ, Horgan C, Marsden ME, Tompkins C, Wallack S, Hendricks A. Health insurance coverage for substance abuse services. Waltham (MA): Brandeis University, Institute for Health Policy; 1993.

Mechanic D, Schlesinger M, McAlpine DD. Management of mental health and substance abuse services: state of the art and early results. Milbank Q 1995;73:19-55.

Rogowski, JA. Insurance coverage for drug abuse. Health Aff 1992;11(3):137-48.

Schlesinger M, Dorwart RA, Epstein SS. Managed care constraints on psychiatrists' hospital practices: bargaining power and professional autonomy. Am J Psychiatry 1996;153:256-60.

Scott JE, Greenberg D, Pizarro J. A survey of state insurance mandates covering alcohol and other drug treatment. J Ment Health Adm 1992;19(1):96-118.

Woolhandler S, Himmelstein DU. Extreme risk—the new corporate proposition for physicians. N Engl J Med 1995;333:1706-8.

Woolhandler S, Himmelstein DU. Annotation: patients on the auction block. Am J Public Health 1996;86:1699-1700.

Legal, Regulatory, and Funding Barriers to Good Practice and Associated Consequences

Mark W. Parrino, M.P.A.

Introduction

The social stigma associated with heroin addiction has transferred to methadone treatment, its patients, staff, and any entity that is involved with its practice. This stigma is both conscious and unconscious. The legal, regulatory, and funding barriers to providing access to methadone treatment must be analyzed within the context of such a pervasive stigma. There have been numerous newspaper articles opposing methadone treatment, reminding the public that it is more frequently associated with failure than success. Society's perception of methadone treatment is best viewed through several negative news stories that have appeared over the course of the past 15 years.

Methadone Treatment in the News

The *Sun Sentinel News* in Florida published a damaging series about methadone treatment during June 1983 (Exhibit No. 1). The series was packaged and sent to members of Congress and State legislators throughout the United States.

The *Oklahoma City Times* ran a story on June 7, 1995 (Exhibit No. 2) explaining that the proposed methadone treatment program had been shunned by the community. One of the most compelling quotes from a president of a neighborhood association underscored the community's antipathy: "I am going to fight against it for as long as I live."

The *Courier-Journal* of Louisville, Kentucky, ran a story on September 30, 1995 (Exhibit No. 3) reporting the fear of siting methadone treatment programs. The article focused on the fact that narcotics officials were concerned that an increase in treatment availability would lead to an increase in diverted methadone: "They certainly could have a lot of people coming in just to buy methadone . . . Addicts are notorious hustlers. They're very skillful and very manipulative."

The *New York Post* ran a story during 1995 (Exhibit No.4) with the following lead: "A four year old Queens girl died yesterday after her drug abusing father gave her a massive dose of methadone to keep her quiet." The article did not deliver any diatribe against methadone treatment; however, the characterization was damaging.

The *Staten Island Advance* published several articles during January 1995 (Exhibit No. 5) concerning the community's opposition to a proposed methadone treatment program. One of the community residents stated: "They ruined our neighborhood." Other neighbors commented: "The bottom line is they don't get cured and Staten Island is constantly getting dumped on." The community prevailed, and the program did not open.

Professional journals also have published negative methadone stories and editorials, including one that appeared in the *Professional Counselor Magazine* during 1990 (Exhibit No. 6). The editor wrote: "Methadone maintenance is not treatment in the context of treating an addiction with the outcome goal of assisting an addict to achieve abstinence and sobriety. A person undergoing methadone maintenance is not in recovery."

These stories have been cited as a means of understanding the legal, regulatory, and funding barriers to treatment. Why would the public have favorable views toward methadone maintenance in the face of such consistent and clear condemnation, especially in the absence of equally compelling, positive news stories?

Legal Barriers to Methadone Treatment

Publicly elected officials represent the interests of the electorate. If such an electorate, viewed through the prism of community action groups and town counsels, oppose the siting of methadone treatment programs, their representatives are expected to support such opposition. A number of State legislatures have fulfilled this expectation with prohibitions, dosage ceilings, duration of treatment limits, and zoning ordinances. Such legislation represents a rejection of medicine and scientific research in favor of political expediency and ideology. It is as pervasive as the stigma associated with heroin addiction. Seven examples of such legislation are cited for this conference.

New Hampshire. The New Hampshire legislature passed House Bill 1107 on May 3, 1994, "prohibiting the operation of methadone maintenance programs" (Exhibit No. 7). Section 186:2 of the bill states: "No person shall operate a methadone program in this State." The language of this bill was subsequently amended through additional legislation (House Bill 1576(Exhibit No. 8), which was enacted into law on June 10, 1996.

Arkansas. The Arkansas general assembly considered House Bill 1123 (Exhibit No. 9) during January 1993 as "an act to prohibit the distribution of methadone by any agency of the state." The legislation was worded in an extremely specific manner. Section 1 indicated "No agency of this state shall hereafter distribute or administer the drug commonly referred to as methadone. Any state agency employee who violates this act shall be terminated from employment by the state and shall not thereafter be eligible for employment by the state."

Washington State. A senator in the State legislature sponsored Senate Bill 0909 (Exhibit No. 11) during January 1995 to eliminate the existing methadone treatment programs in the State. "The State of Washington declares that there is no fundamental right to opioid substitution treatment. The State of Washington further declares that because methadone and other like opiate substitutes are addictive and are listed as schedule II controlled substances, the State of Washington has the legal obligation, authority and right to regulate and control the use of methadone and other opiate substitutes. The State of Washington does not recognize the use of methadone and other opiate substitutes in the treatment of persons addicted to or habituated to opioids." This legislation was subsequently withdrawn after public hearings, with the State Alcohol and Drug Authority joining with the methadone providers to oppose its enactment.

Georgia. A representative in the Georgia house of representatives proposed House Bill 839 (Exhibit No. 12) during the 1993 legislative session. The intent of the legislation was to restrict methadone dosages. "The maximum daily dosage of methadone, which may be administered or dispensed for any person from or by a methadone treatment center shall be 80 milligrams. Any person who administers or dispenses methadone in violation of the Code section shall be guilty of a misdemeanor. Any center in which such a violation occurs may be prohibited from further participation in the methadone treatment program."

New York State. A New York State assemblyman proposed Bill 8937 (Exhibit No. 13) during February 1996. The intent of the legislation was to limit the duration of methadone treatment. "In order to retain certification or prior to certification, the methadone treatment program shall not exceed a period of eighteen months of treatment per patient; the Director shall set the requirements for the administration and regulation of the methadone maintenance program; failure to comply with such regulations shall result in the loss of state funding."

New Jersey. Two New Jersey assemblymen sponsored Bill 2840 during March 1997 (Exhibit No. 14). The intent of the legislation was to add another layer of municipal approval for the siting of methadone treatment programs. "The outpatient [methadone] program shall be required, as a condition of each relicensure, but at least annually, to furnish documentation to the Commissioner of Health and Senior Services that the governing body of the municipality in which the facility is located has formally approved the location of the facility."

Massachusetts. The Massachusetts legislature is considering Senate Bill 462 (Exhibit No. 15) restricting zoning for methadone treatment programs. "Notwithstanding the provisions of general or special law to the contrary and in addition to the regulations promulgated by the Department of Public Health, no methadone treatment facility shall be allowed to operate until approval has been received by the legislative body of the city or town in which it seeks to be sited on a permanent or temporary basis." The legislation represents a continued effort concerning the longstanding matter of siting methadone treatment programs in Boston.

Regulatory Impediments

Methadone treatment is the most regulated form of medicine in the United States. The Institute of Medicine published report findings during December 1994 indicating the need to evaluate existing Federal oversight of methadone treatment. At present, the Food and Drug Administration and the Center for Substance Abuse Treatment within the Department of Health and Human Services are reviewing a transition of regulatory oversight to accreditation standards, which will be applied to methadone treatment programs throughout the United States. It is too soon to report on the outcome.

Maine. The State of Maine approved "a long term narcotic dependency treatment project," which was executed during July 1995 (Exhibit No. 17). This represented a major breakthrough in one of the States that had prevented the development of methadone treatment programs. A public hearing was convened by the Office of Substance Abuse in Augusta on February 9, 1995. Testimony was presented during the course of this hearing drawing on the findings of a Federal agency report. A January 1995 Drug Enforcement Administration report, "Rural Drug Enforcement in Maine: A Strategic Analysis of Drug Trafficking Trends," indicated

that “recent estimates place the heroin abusing population in the Portland area at approximately 500 persons.” The report also indicated that heroin use was increasing in outlying regions of Maine and that Dominican heroin traffickers were “obviously sophisticated and responsible for large scale distribution of heroin using five separate (marketing) logos.”

Washington State. As indicated in the previous section, the State legislature enacted new oversight requirements for methadone treatment, effective July 1995 (Exhibit No. 18). The Department of Alcohol and Drug Services in Washington was legislatively required to “establish criteria for evaluating the compliance of opioid substitute treatment programs with the goals and standards established under this chapter. As a condition of certification, opioid substitution programs shall submit an annual report to the department and county legislative authority, including data as specified by the department necessary for outcome analysis.”

Funding Impediments

The most critical funding impediment occurs when the State funding authority decides not to use Federal funds for intravenous drug treatment services or eliminates funding because of fiscal limitations within the State or municipality.

The most recent example occurred in the District of Columbia, which reduced the number of publicly funded methadone maintenance treatment slots from the prior level of 2,400 to the current level of 900 slots. The existing methadone treatment programs throughout the District, both public and private, exceeded their treatment capacity in an effort to absorb some of the displaced patients. The majority of the displaced patients were not able to access care as the result of the restricted capacity.

Managed Care

The implementation of managed care programs in different States also has undermined the integrity of methadone treatment services, depending on the intent of the State funding authority and the willingness of the managed care program to impose arbitrary limits on treatment duration. At times, managed care organizations require frequent patient recertification in spite of the knowledge that heroin addiction is a chronic relapsing disease.

Medicaid/Medi-Cal

A court case in the U.S. District Court for the Eastern District of California reversed a county administrative ruling, limiting medical reimbursement for methadone treatment (Exhibit No. 19). The court ruled against the county, ordering the State “to expeditiously take all practicable steps to assure that, in all counties where Drug Med-Cal methadone maintenance services are available, they are available without regard to Medi-Cal beneficiaries' county of residence.” The State Department of Health Services was ordered to implement a plan, ensuring that “Medi-Cal Methadone Maintenance services are available to Non-Medi-Cal patients.” The court decision represented a landmark ruling, creating enormous turbulence in the process of implementing the court-ordered requirements.

Related Fiscal and Policy Issues

A new group of funding impediments limit the effectiveness of methadone treatment as patient characteristics change. An increasing number of methadone-maintained patients are struggling with HIV infection and other debilitating diseases. Some of these patients are not able to travel to the methadone programs on a frequent basis, requiring home delivery services.

Skilled nursing facilities are not able to treat methadone-maintained patients unless the patient is detoxified or the methadone is provided by the program site. In some cases, Federal and State regulatory bodies preclude the administration of methadone in the skilled nursing facility by the treatment program.

Methadone treatment is not recognized as a medical treatment in the prisons of this country. The only prison that administers methadone to inmates is Rikers Island in New York City, which operates in conjunction with the Montefiore Medical Center.

Methadone treatment has been restricted to specially licensed treatment programs under Federal law for the past 25 years. The State of Connecticut recently passed legislation allowing methadone treatment programs to refer stable patients to "off-site" general medical practice settings (Exhibit No. 20) as part of a pilot research program.

It is hoped that the recommendations of this Consensus Development Conference will be able to take all the information that has been presented and craft policy recommendations that will assist in expanding access to care for thousands of people currently needing treatment in the community and prison systems. In the authors' judgment, no major change in treatment access will occur without a long-term national educational campaign and an increase in funding at national and State levels.