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ABSTRACT

Concerned with clarifying some of the more complex issues in drug abuse, the National Clearinghouse for Drug Abuse Information has prepared this special report on methadone. Background information is provided through a summary of its history, legal status, and the opinions of authorities in the field. Significant research on the subject is presented together with major findings on various aspects of the problem. The pharmacology, chemistry, clinical and physiological effects, treatment, and patterns of use of the drug are dealt with. Bibliographic references are also listed. (BL)

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The National Clearinghouse for Drug Abuse Information Report Series 11 through 18 are concerned with clarifying some of the more complex issues in drug abuse by gathering the significant research on each subject and summarizing the major findings on various aspects of the problem. They deal with the pharmacology, chemistry, clinical effects, treatment and the patterns of use of each drug and provide a background in the area by outlining the history, legal status and the opinions of authorities in the field. These fact sheets were prepared in part by the Student Association for the Study of Hallucinogens (STASH), Beloit, Wisconsin, under Contract No. HSM-42-71-26.

# METHADONE

## Introduction

For over one-hundred years medical science has endeavored to develop an effective technique for the treatment of addiction to narcotic drugs, such as heroin (diacetylmorphine). Attention was directed toward a search for non-narcotic agents which would abolish or decrease the addict's drug hunger. Along similar lines, non-pharmacological treatment methods have evolved including therapeutic communities (e.g., Synanon, Daytop, etc.). Until recently attempts at rehabilitation of narcotics addicts have been largely unrewarding and discouraging. What has prompted a partial reversal of treatment outcomes has been an accompanying shift in the goals of many treatment programs. Emphasis is being placed on social and vocational rehabilitation rather than on abstinence (i.e., complete cessation of drug

use). This change in emphasis has achieved widespread acceptance for maintenance therapy with narcotic drugs, principally methadone.

## History, Pharmacology and Chemistry

Methadone, a potent narcotic analgesic drug with pharmacological properties similar to those of morphine, was uncovered by an intelligence team of the U.S. Department of Commerce investigating the German pharmaceutical industry at the close of World War II. Methadone (dl-4,4-diphenyl-6-dimethylamino-3-heptanone) was assigned as the generic term for the drug by the American Medical Association in 1947. Methadone has been referred to by a variety of other names including: dolophine, adanone, amidone, physeptone, miadone, butalgin, diadone and polamidone. Classified as a narcotic drug, methadone exhibits a depressant effect upon the central nervous system and may produce a range of side effects of which nausea, vomiting, sweating, constipation, sedation and pupillary constriction are the most common. Tolerance develops to many of these drug effects and physical dependence occurs following prolonged use. One of methadone's most useful properties is that of cross-tolerance with other narcotic drugs. That is, withdrawal symptoms in subjects physically dependent on a narcotic drug can be suppressed by oral administration of methadone.

Utilizing this property of cross-tolerance, Dr. Vincent P. Dole and Dr. Marie E. Nyswander of New York City (1965) established a program of rehabilitation of narcotics addicts by employing the administration of methadone to alleviate narcotic hunger and prevent the appearance of withdrawal symptoms. The advantages of methadone to other forms of "maintenance therapy" were manifold: (1) the drug can be taken orally; (2) it has an extended duration of

action (24-36 hours); (3) no serious side effects are seen at maintenance doses; (4) at sufficient dose levels it will "block" the effects of heroin; and, (5) administered therapeutically, it does not produce euphoric effects of its own, whereas intravenous self-administration may produce a euphoric experience.

## Therapeutic Uses

Numerous methadone maintenance programs have been instituted in recent years, many of which are modelled on the Dole-Nyswander treatment program. The Dole-Nyswander program accepts addicts for treatment if they meet the following criteria: voluntary; aged 20 - 40; a history of at least four years of "mainline" heroin use with repeated relapses following detoxification; no current non-narcotic drug dependence (i.e., alcohol, barbiturates, amphetamines); and, not psychotic. Following admittance to the program, patients are hospitalized for a period of six weeks, during which time they receive thorough medical and psychological examinations and are gradually stabilized on a "blockading" dose of methadone. Small divided doses of 10 to 20 mg. per day of oral methadone are slowly increased as tolerance permits to a stabilization level of 80 to 120 mg. per day. At the termination of this six-week period, individuals receive this single dose daily on an outpatient basis and are required to give urine specimens for determination of whether there is any continued illicit drug use. A range of medical, psychiatric, social and vocational services are available to the patient during this phase of treatment. The patient now faces a very crucial period of adjustment--a life once devoted to drug seeking and "hustling" must be transformed into a self-supporting, socially acceptable one. Methadone establishes

the potential for such a change in life-style, but it is the patient's determination and capabilities that determine the success of rehabilitation.

Drs. Dole and Nyswander concluded their initial report which outlined the clinical procedures of the program and studied its results in 22 male patients: "We believe that methadone contributed in an essential way to the favorable results, although it is quite clear that giving of medicine has been only part of the program. This drug appears to relieve narcotic hunger, and thus frees the patient for other interests, as well as protects him against readdiction to diacetylmorphine by establishing a pharmacological block.

Reports of treatment success continued to be impressive. In 1966, Dole and Nyswander reported that heroin use and related crime had discontinued in the 107 patients being treated with blocking doses of methadone. Of these patients, a majority were engaged in socially useful activities. Indications of psychopathic behavior or intractable non-narcotic (e.g., alcohol or barbiturates) drug abuse resulted in discharge of 11% of the original 120 patients from the program. Seventy-nine patients had been in the program for three months or longer and, of these, 71% were steadily employed and/or attending school.

An evaluation of all patients admitted for treatment under methadone maintenance from January, 1964 to June, 1968 was reported by Dole, Nyswander and Warner. Criminal activity (according to arrest records) had been reduced by at least 90% in this patient population of 863. The majority of the patients were employed (including school and homemaking) and supporting families. Thirteen per cent (109) were discharged from the program (10 voluntary, 9 for non-heroin drug abuse, 27 for medical disability, 54 for disruptive behavior

and death accounted for 9). Regarding continued usage of heroin or other narcotic drugs, the authors reported: "Since blockade with methadone makes heroin relatively ineffective, a patient cannot use heroin for the usual euphoria, nor will he experience abstinence symptoms after an experiment with the drug. He can, however, remain drug-oriented in his thinking, and be tempted to return to heroin. Many patients have made sporadic attempts to use heroin again, especially during the first six months of treatment. . . . The majority of patients have stopped heroin use completely after starting methadone treatment. This fact has been verified by repeated analyses of urine. For example, in a group of 174 patients, in which the analyses were done three times weekly for the first year of treatment, 55% did not show a single positive for self-administered narcotics. On the other hand, a minority of these patients, about 15%, continued to user heroin intermittently (e.g., on weekends) even though the euphoric effect was blocked." Of those patients remaining in the program, no incidence of re-addiction to heroin was observed.

Other researchers have instituted methadone treatment programs either to replicate the Dole-Nyswander results in another location with a different staff or have attempted to modify the procedures and admissions criteria. These modifications were, in general, motivated by criticisms and recommendations of the methadone maintenance program as it was originally formulated and implemented. Some of the more significant modifications have included alteration of dose levels, omission of the six-week hospitalization (i.e., complete outpatient treatment), variations of ancillary services, withdrawal from methadone, and incorporation of methadone maintenance therapy into a multi-modality treatment orientation. Research is currently being conducted

into the use of drugs related to methadone (methadols) which have a longer duration of action (48-72 hours), thereby diminishing the number of visits per week a patient would have to make to the dispensing clinic. Evaluation of these modifications and an examination of methadone's effectiveness with patients who fail to meet the criteria established by the Dole-Nyswander program are in progress.

Suppression of the euphoric and other disabling effects of the narcotics has been achieved through the establishment of a daily, oral administration of methadone. Dole, Nyswander and Kreek in a double-blind setting administered intravenous injections of heroin, Dilaudid, morphine, methadone or saline to seven patients in different stages of induction to methadone (oral) tolerance. The euphoric effects of the narcotic drugs tested (including intravenous methadone) were markedly attenuated by the cross-tolerance properties of the oral methadone which the patients were receiving daily. Another facet of this study included the substitution, unknown to the patient, of the pharmacologically inactive isomer, d-methadone, for the normal daily dose of the active l-isomer. The patients were unable to detect the substitution and when mild symptoms appeared some 36 hours later they failed to identify the symptoms with withdrawal. This experiment indicates that no significant drug sensations are evident when receiving daily maintenance doses of methadone. However, non-tolerant individuals would experience drug effects similar to those elicited by other narcotic drugs upon administration of methadone. These might include feelings of body warmth, numbness of the extremities, drowsiness, sweating, nausea, slowed breathing and pulse, reduced activity and, in some, euphoria.

## Physiological Effects

Constipation appears to be the chief medical problem associated with methadone maintenance. No serious signs of drug toxicity or impairment of neuromuscular or cognitive functioning have been reported during the controlled administration of methadone. Methadone has not been found to adversely affect menstrual function or pregnancy. "Withdrawal symptoms" in infants born to patients participating in methadone maintenance programs have been reported to be of minor consequence and have not required intensive therapy.

## Legal Aspects

Methadone maintenance programs are subject to controls jointly exercised by the Bureau of Narcotics and Dangerous Drugs (BNDD) and the Food and Drug Administration (FDA). Methadone treatment for narcotic dependence is considered to be under experimental evaluation for safety and efficacy. Therefore, an Investigational New Drug (IND) permit must be obtained by a physician seeking to establish a methadone program, the operation of which must adhere to the regulations of the Federal Food, Drug, and Cosmetic Act relating to the investigational use of drugs and to special regulations concerning methadone itself.

Diversion of methadone into illicit channels to date has been limited. Careful supervision and dispensing techniques disabling the drug for intravenous use have appeared to be effective. However, with ever-expanding programs and the desire to allow responsible patients "take-home doses," the problem of illicit methadone use has increased. Under the Comprehensive Drug Abuse Prevention and Control Act of 1970, illegal possession of methadone could result in a sentence to a term of imprisonment of not more than one

year, a fine of not more than $5,000, or both. Conviction of illicit manufacture or sale could result in a sentence to a term of imprisonment of not more than 15 years, a fine of not more than $25,000, or both. Subsequent convictions would result in increased penalties.

## Authoritative Opinions

The use of methadone in the treatment of narcotics addicts has prompted considerable interest, discussion and controversy. The controversy centers primarily around scientific and moral questions. However, the efficacy of methadone treatment programs as compared to other treatment techniques will only be accurately assessed by strictly controlled research studies. The moral questions surrounding narcotics addiction and methadone maintenance cannot be resolved by scientific means, but rather by intelligent consideration of the psychological and sociological problems involved.

> The results of this program (Dole-Nyswander) continue to be most encouraging in this group of heroin addicts, who were admitted to the program on the basis of precise criteria. For those patients selected and treated as described, this program can be considered a success. It does appear that those who remain in the program have, on the whole, become productive members of society, in contrast to their previous experience and have, to a large extent, become self-supporting and demonstrate less and less antisocial behavior. It should be emphasized that these are volunteers, who are older than the average street addict and may be more highly motivated. Consequently, generalization of the results of this program in this population to the general addict population probably are not justified. There remain a number of related research questions which need further investigation.
>
> --HENRY BRILL

> It is abundantly clear . . . that one does not cure a craving for heroin-induced euphoria by substituting a methadone-induced euphoria that is euphemistically labeled "stabilization dosage," and by then asserting that this latter state is "normal" and should be perpetuated indefinitely. I fail to appreciate how legalized addiction is any improvement over illicit addiction. Morally, in fact, it is much less defensible, because it indicates that society is actively abetting the

well-proven personality deterioration and social demoralization that have invariably accompanied narcotic addiction over the past 350 years.

--DAVID P. AUSUBEL

Opposition to methadone maintenance has been considerable but may be waning because the results of the programs continue to be so impressive. The argument that this is merely substituting one addiction for another seems inconsequential when one considers the alternatives, disease, death, degradation, and prison, which await most addicts in our society. The fact that methadone is dependency-producing is irrelevant if we determine that long-term treatment is essential.

--JOHN C. KRAMER

It is clear, I think, that for a particularly selected group of persistent heroin abusers methadone maintenance has brought about significant social and economic gain at relatively low cost, compared to the losses to the individual and to society in these patients' previous experience. It must be emphasized, however, that until the recommended control studies have been instituted and evaluated, conclusions cannot be drawn in respect to general applicability, nor plans formulated for broad extension of the program as an established treatment modality. Until such controls are carried out and their evaluation is at hand, the program is one of research only.

--NATHAN B. EDDY

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