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Rx:3x/WEEK LAAM

ALTERNATIVE TO METHADONE

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • PUBLIC HEALTH SERVICE • ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

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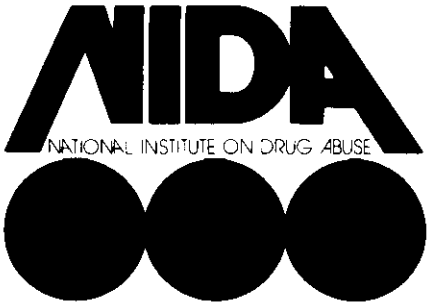
ALTERNATIVE TO METHADONE

EDITORS

JACK D. BLAINE, M.D.

PIERRE F. RENAULT, M.D.

NIDA Research Monograph 8



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FOREWORD

This monograph is a biomedical review and assessment of LAAM (Levo-alpha acetylmethadol), a new treatment drug for heroin addiction now undergoing large scale clinical trials, following several years' intensive research and development under the auspices of the National Institute on Drug Abuse (NIDA) and its predecessor, the Special Action Office for Drug Abuse Prevention (SAODAP).

LAAM was developed as an alternative to methadone. Over 800 methadone-related deaths per year are being reported by the Drug Abuse Warning Network (DAWN) from 24 major cities across the country. Moreover, heroin use has been increasing nationally since mid-1973 and 15 percent of heroin-related deaths (from 1,440 in 1973 to over 2,000 in 1975) reported by DAWN also involve methadone.

Many of these deaths are directly attributable to illicit methadone diversion from drug treatment programs to street sale. Because methadone patients must take their dose daily while simultaneously trying to stabilize their work, school, training, family and personal lives, they have been allowed take-home doses to reduce the number of clinic visits they must make. But this practice has made methadone widely available, accounting for much illicit diversion and subsequent painful record of methadone overdose deaths. In contrast, LAAM dosage is three times a week, it does not yield a quick high and appears to provide a level, sustained effect. Animal toxicity studies and clinical research experience indicate that LAAM is a safe and effective opiate maintenance drug, under appropriate medical supervision.

A wide spectrum of treatments is needed for various degrees of addiction and kinds of dependent persons. But LAAM seems promising for patients who may need opiate stabilization to ease the difficult switch from a drug-hustling street life to a less self-destructive one. LAAM provides one more choice in tailoring treatment to each individual's needs.

Robert L. DuPont, M.D.
Director
National Institute on Drug Abuse

CONTENTS

INTRODUCTION

Jack Blaine, M.D. and Pierre Renault, MD.

MEDICAL DETOXIFICATION

For many years heroin addicted individuals were "treated" by abrupt or gradual discontinuation of heroin, leading to abstinence. Resulting withdrawal symptoms were either untreated or treated palliatively with non-opiate medications including sleeping pills, tranquilizers, analgesics, antidiarrheals, and/or antispasmodics. The failure of heroin withdrawal alone as a treatment with the goal of long-term continued abstinence has been voluminously documented.

At best, medically controlled detoxification has only inmediate and temporary value as a first step in a comprehensive rehabilitation program. Thus, regulated detoxification reduces human suffering and frees the individual from his compulsive search for and use of the drug, permitting a shift in attention to other more constructive pursuits. Long periods of confinement in a hospital, therapeutic commmity, or prison, even with traditional psychotherapeutic intervention have not significantly altered subsequent relapse to heroin abuse for the vast majority of addicts.

Further, efforts at treatment by large scale maintenance of heroin addicts on legally dispensed heroin appears to be an inadequate treatment approach due to the practical problems arising from the need to administer the drug intravenously several times daily.

METHADONE DETOXIFICATION

During World War II, German chemists at the I.G. Farbenindustrie developed a synthetic narcotic analgesic, 6-dimethylamino-4-4-diphen-y1-3-heptanone (methadone, dolorphine) as a substitute for morphine. After the war, American investigators (Isbell et al. 1948) found that methadone's pharmacological pmfile was similar to that of morphine and demonstrated that methadone could substitute for morphine in morphine-dependent subjects to relieve the abstinence symptoms after discontinuation of morphine. Furthermore, methadone could prevent the appearance of withdrawal signs and symptoms when substituted for morphine in equipotent doses. So methadone seemed a likely candidate to substitute for heroin when detoxifying heroin addicts.

Methadone has several advantages over morphine for detoxification of heroin dependent persons. Methadone is almost as effective orally as parenterally, thus avoiding problems of intravenous dosage. Also, methadone is metabolized to inactive substances more slowly than morphine. These two factors extend the duration of action of methadone to 24 hours which permits once-a-day &sage and smooths the time-effect curve. Thus, an oral daily dose of

methadone can be substituted for several times daily intravenous doses of morphine or heroin. The dose of methadone can then be lowered gradually until it is completely withdrawn, producing only a mild abstinence syndrome.

METHADONE MAINTENANCE

In 1965, Dole and Nyswander (1965) extended the clinical use of methadone to a medical maintenance or stablization treatment, used with a comprehensive program of rehabilitation. In a clinical research setting, they demonstrated that heroin addicts could be "stabilized" for many months on a single daily oral dose of methadone (50-150 mg) achieved by gradually increasing the dose over a period of four weeks as tolerance developed to the dose which relieved the abstinence syndrome. At the stabilization-maintenance dose, the medication appears to relieve narcotic "hunger" or craving, induce sufficient tolerance to prevent an abstinence syndrome and block the euphoric effect of intravenous heroin. The maintenance dose is not intoxicating itself. Thus methadone stabilization produces a normal steady functional state rather than the wave-like fluctuating feeling states of euphoric intoxication ("high"), normality ("straight"), and abstinence ("sick") commonly experienced in the street heroin addict life style. This stabilization on methadone appears to free the patient from heroin-oriented hustling, allowing participation in the treatment and rehabilitation program and development of less destructive interests and activities.

In the ensuing several years, many other clinical researchers, some with support from the Division of Narcotic Addiction and Drug Abuse, National Institute for Mental Health (DNADA, NIMH) NIDA's precursor, intensively evaluated the use of methadone as a maintenance drug for the treatment and rehabilitation of heroin addicts. (Jaffe 1972; Goldstein 1971, 1972; Blachly 1972; Zaks and Feldman 1972). By 1970 a rapid proliferation of methadone maintenance programs had occurred across the country, and almost 9,000 heroin addicts were in treatment (Dole, 3rd Methadone Maintenance Conference, November 1970). Data from these patients indicated safety and efficacy of this form of treatment under good medical supervision.

The concept of methadone maintenance, with several variations from the original prototype of Dole and Nyswander, achieved widespread acceptance. Programs and number of patients in treatment continued to expand. On December 15, 1972 the Food and Drug Administration, after an extensive review of the methadone treatment experience, approved the New Drug Application for methadone maintenance treatment of heroin or morphine-like drug dependent persons and published rules and regulations in the Federal Register controlling its use.

METHADONE DISADVANTAGE

While methadone maintenance had been shown repeatedly to be the most effective treatment of opiate addiction available, several investigators realized in the late sixties (Jaffe et al. 1970; Blachly 1971) that significant problems related to the pharmacology of methadone existed. Methadone did not suppress the narcotic craving for a full 24 hours in many addicts. Very large doses of methadone were necessary to provide sustained relief of abstinence of symptoms for 24 hours for these patients. These doses often produced unwanted sedation causing the patient to "nod" for the first several hours after consumption.

Furthermore, the patient was required to attend a methadone dispensing clinic daily to consume his medication under staff supervision. This inconvenient and burdensome time and travel demand was often draining physically and emotionally. When the patient was assuming responsibility and trying to engage in work, rehabilitation or education programs, or responsible homemaking, this requirement was considered by some to be antitherapeutic. A compromise solution was reached.

> After demonstrating satisfactory adherence to the program regulations for at least 3 months, and showing substantial progress in rehabilitation by participating actively in the programs' activities and/or participating in educational, vocational and homemaking activities, those patients whose employment, education, or homemaking responsibilities would be hindered by daily attendance may be permitted to reduce to three times weekly the times when they must ingest the drug under observation.
>
> (Federal Register, Vol. 37, No. 242 page 26790, Dec. 15, 1972).

Take-home doses were dispensed for the other four days.

Unfortunately, the practice of permitting take home supplies of methadone for unsupervised self-administration away from the clinic contributed to new problems (Jaffe et al. 1970; Fink 1973). Accidental ingestion of methadone by non-tolerant persons, especially children, led to an alarming increase in methadone toxic reactions and overdose

fatalities. Also, a market developed for illicit sale and redistribution of methadone to heroin addict peers suffering from withdrawal or to non-addict drug users seeking a new euphorient. More recently, the phenomenon of primary methadone abuse without prior heroin addiction surfaced. That is the treatment agent was becoming a new source of addiction. Finally, the patient might skip or delay a dose of methadone in order to "shoot up" with heroin after the blockade has diminished. Thus, the take-home privileges inadvertently negated much of the usefulness of random urine monitoring for illicit heroin use. Furthermore, an adversary system or game was created in which the patient might attempt to deceive the staff in order to gain or retain take-home privileges (Goldstein and Judson 1974).

Thus, a longer lasting medication would have many practical therapeutic advantages over methadone and partially resolve some of these problems encountered in clinical treatment programs. Fortunately, chemical and pharmacological data were already available on optical and structural isomers of methadone as well as several derivatives (Pohland et al. 1949; Chen 1948; Eddy et al. 1950,1952; Speeter et al. 1949; Sung and Way 1954). This data suggested potential clinical usefulness for L-alpha-acetyl-methadol (LAAM, l-methadyl-acetate) because of its high oral effectiveness, long duration of action, and low toxicity.

NEW DRUG DEVELOPMENT

The development of a new drug product is a long and complex process. The 1962 Kefauver Harris Amendments to the Federal Food, Drug, and Comestic Act established investigative procedures to supply substantial scientific evidence that a drug is safe and effective. Before a new drug can be marketed to the general public, thorough testing must occur both in animals and humans under carefully controlled circumstances.

Before a new drug may be tested clinically on humans, the sponsor, usually a pharmaceutical company, must provide FDA with information as specified as a "Notice of Claimed Investigational Exemption for a New Drug" known as an IND. Among the requirements are:

(1) Complete composition of the drug, its source and manufacturing data.
(2) Results of all preclinical investigations demonstrating that there will not be unreasonable hazard in initiating studies in humans. The minimmum data required are the pharmacological profile, acute toxicity and short term (two weeks to three months) toxicity studies in several animal species.
(3) A detailed protocol of the planned investigation.

Following preclinical animal studies indicating the drugs presumptive safety for humans, the clinical investigation, consisting of three phases, accumulates substantial scientific evidence of safety and effectiveness in man. This is needed to approve or disapprove the drug for marketing. The Phase I clinical investigation involves a small number of healthy patients to establish baseline data. Pharmacological studies are used to determine drug action, toxicity, metabolism, absorption, elimination, preferred route of administration and safe dosage range. Phase II clinical trials are conducted on a limited number of diseased patients to determine safety and effectiveness of the drug. If Phase II studies indicate that the drug may be useful and safe in treating a disease and the long-term animal testing performed concomitantly indicates no unwarranted toxicity, Phase III studies may commence. The Phase III investigation involves extensive, careful controlled and monitored clinical trials assessing the drug's safety, effectiveness and most desirable dosage in treating a specific disease in a large number of patients. Phase III study approximates general clinical use.

Once Phase III is completed and claims of safety and effectiveness of the drug arc supported, a New Drug Application (NDA) is submitted to FDA requesting approval to market the drug. The NDA contains all the information available about the drug which has accumulated from studies in animals and several hundred to several thousands patients. The FDA reviews the NDA to determine whether the benefits of the drug when used properly outweigh the risks. Once an NDA is approved, the drug can be marketed to the general public. However, the manufacturer is still required to report regularly to FDA on any adverse reactions or toxicity which occurs. At any stage in this entire process the FDA may prohibit further testing or marketing based on unacceptable toxicity or ineffectiveness.

LEVO-ALPHA ACETYL METHADOL (LAAM)

The early clinical work on LAAM focused on morphine-like analgesic properties (Keats and Beecher 1952; David et al. 1956; David and Semler 1952). However, at the Addiction Research Center, NIDA, Fraser, Isbell and coworkers (1952, 1954) demonstrated LAAM's ability to relieve and prevent opiate withdrawal symptoms in addicts for long periods of time, up to 72 hours. They also noted that abrupt withdrawal from LAAM resulted in a mild but prolonged abstinence syndrome.

Merck & Company in the early and mid-sixties investigated LAAM's usefulness as an analgesic. However, the delayed onset of action and prolonged time course limited its clinical usefulness for analgesia. Thus, Merck did not proceed with LAAM beyond the early Investigational New Drug stage.

Jaffe and co-workers first utilized alpha-acetyl-methadol in a clinical narcotic treatment program (Jaffe et al. 1969, 1970). They substituted D, L-alpha-acetylmethadl (DLAAM) three times weekly for methadone daily in a small group of methadone maintenance patients in 1968. TIhe results of that initial pilot study corroborated the findings of Fraser and Isbell that D-LAAM could suppress opiate withdrawal symptoms for up to 72 hours and might be a useful agent for the treatment of heroin addicts.

Eased on the positive results of this pilot study, Dr. Sidney Cohen, Director, Division of Narcotic Addiction and Drug Abuse, NIMH, contracted with Merck & Company for production of four kilograms of LAAM in 1969. DNADA encouraged further clinical investigation by DNADA funded clinical research centers in the early seventies. Research by this group substantiated the comparable usefulness and safety of LAAM as a maintenance treatment of heroin addiction (Jaffe et al. 1971, 1972; Blachly et al. 1972; Zaks et al. 1972; Senay et al. 1974).

LAAM ADVANTAGES

These researchers found that LAAM offers the patient, clinician and treatment program several advantages over methadone. Due to LAAM's long duration of action, the frequency of visits to clinic can be reduced from daily to three times weekly even for patients just entering treatment (Levine et al. 1973). Addicts find participation in treatment more acceptable and return more regularly, especially those trying to engage in work, education or rehabilitation activities outside of the clinic, because travel time and effort is greatly reduced.

Some investigators found that LAAM offers the patient a smoother, sustained drug effect. The patients appeared more alert and more emotionally level. Oral consumption even during the period of escalating doses did not produce excessive sedation or subjective euphoria, i.e. the patients do not report being "loaded" or "nodding" (Blachly 1971). This effect is consistent with phanmacokinetic data on LAAM and its active metabolites (Goldstein 1975; Billings et al. 1974; Henderson 1974, 1975)

Jaffe et al. (1970), Goldstein and Judson (1974). and Senay and diMenza (1972) emphasized that LAAM is less likely to be a reinforcer of daily drug taking behavior than methadone. The three times weekly dosage schedule frees the patient from the daily necessity of engaging in drug seeking and drug taking behavior. This represents an important therapeutic step forward because the destructive, habitual pattern of behavior associated with the heroin addict daily life style is broken. The individual feels less psychologically and physically dependent when not involved with daily drug taking. This strengthens the addict's identification with the drug free population and breaks association with the drug taking culture.

These factors are consistent with the treatment program goal of de-emphasizing of the mystique of drugs and drug taking while empha sizing human relationship and alternate pursuits as sources of gratification. In the context of treatment, LAAM allows a reduction of emphasis on chemicals, since the life style no longer pivots around the consuming preoccupations associated with taking drugs several times a day or even once a day at the treatment clinic. So there can be less talking, seeking, taking and relating around chemicals. More energy is available for achievement of psychological, social, educational and vocational goals rather than biological stabilization (Senay and diMenza 1972; Jaffe et al. 1970).

Also, LAAM offers a practical answer to the problems related to take-home methadone. Illicit redistribution can be lessened because three times weekly LAAM reduces the amount of take-home medication a clinic must provide patients for out of clinic administration. If necessary, a no-take-home policy can be established by a clinic or program where redistribution and accidental overdose is especially prevalent (Jaffe et al. 1970; Fink 1973).

Further, several pharmacological properties make LAAM less prone than methadone to abuse. LAAM itself is one-tenth as active as its metabolites (Smits 1974; Nickander et al. 1974). Because metabolism requires time, several hours pass between taking LAAM and the onset of psychoactivity (Billings et al. 1974). Therefore, LAAM is less likely to be a reinforcer of drug taking because substances with a rapid, immediate onset of euphoric effects are much more desired by drug users. LAAM has another unique characteristic which makes it less desired. Unlike other narcotics? LAAM is more rapidly effective orally than intravenously, the preferred route of heroin addicts (Blachly 1971; Fraser 1952).

LAAM may offer treatment programs advantages over methadone by improving the logistics of

drug distribution. Three times weekly dosage allows for more controlled drug delivery to increasingly large numbers of patients. By reducing the required number of clinic visits, efficiency of treatment may be increased due to savings of staff dispensing and pharmacy services (Senay et al. 1972; Blachly 1971). Thus, conversion from methadone to LAAM can potentially either reduce the cost of treatment or increase the number of available treatment slots.

SAODAP UNDERTAKES COORDINATION OF LAAM DEVELOPMENT

In June 1971, the Special Action Office for Drug Abuse Prevention (SAODAP) was established by Executive Order "to focus the comprehensive resources of the Federal Government.... and to develop a comprehensive, coordinated, long-term federal strategy to combat drug abuse." The Drug Abuse Office and Treatment Act of 1972 (Public Law 92-255, Sec. 224, 86 stat. 72, March 21, 1972) mandated the expansion of research on "long-lasting, non-addictive, blocking and antagonist drugs or other pharmacological substances for the treatment of heroin addiciton." Based on the potential advantages of LAAM over methadone, Dr. Jerome Jaffe, SAODAP's first director, initiated in the summer of 1971 a comprehensive review of the status of LAAM and other long-lasting blocking drugs utilizing experts from the various government agencies and the private sector.

The conclusion of the review was that LAAM was the most promising compound available at the time, but that the pharmacological development of LAAM was not proceeding rapidly enough. Several problems were found to be delaying LAAM development. There was little general interest in or knowledge about LAAM in the treatment, research or pharmaceutical fields. No one in Federal Agencies or industry was promoting the drug. LAAM investigation was limited to a few research centers. Large quantities of LAAM necessary for use in treatment were not available from any source, and only a few kilograms remained from the LAAM produced for DNADA several years previously.

Furthermore, unlike methadone, which was marketed as an analgesic prior to its use in narcotic addiction treatment, LAAM was not patented or marketed for any indication. LAAM was not patentable because it had been in the public domain for many years. Thus, the pharmaceutical companies were not interested in spending research and development funds for a drug without exclusivity and with a limited market. Also, the pharmaceutical industry drew attention to the special precautions and regulatory controls pertaining to development of controlled, Schedule I, narcotic substances. Facilities were not available in the industry for preclinical narcotic testing nor was there an existing structure to perform the carefully monitored clinical studies required.

Thus, SAODAP recognized that LAAM was not proceeding because the pharmaceutical industry did not want to develop and promote it. Therefore SAODAP set a high priority on creating and coordinating a governmental mechanism for developing this type of drug using LAAM as the prototype. Therapeutic drug development had previously been the function of the pharmaceutical industry and not a practic of government. In fact, the recognized function of the Federal Government was to regulate the pharmaceutical industry. This led to the interesting and potentially anomolous situation of the government attempting to develop and also regulate the same compound, the former at SAODAP and DNADA and the latter at FDA.

Although LAAM was to be developed as rapidly as possible, it was imperative to avoid the many problems encountered by methadone due to inadequate and incomplete study. Federal Agencies had the assigned responsiblity to be certain that LAAM was a safe and effective drug before marketing. Therefore, SAODAP organized and promoted interagency cooperation in LAAM development, with DNADA and FDA playing the leading roles. SAODAP effectively utilized the expertise in academic and phamaceutical communities for advice and monitoring the process. A LAAM Medical Advisory Panel served this latter purpose.

The amount of LAAM available severely limited the progress of both animal and clinical investigation. A larger supply of LAAM was obtained through the cooperation of the Penick Pharmaceutical Company in 1972 and arrangements were made for an additional supply when needed. The recognition that further animal studies were needed to establish intermediate and long-term nontoxicity of LAAM prompted an agreement between DNADA and Department of Army's research facilities at Edgewcod Arsenal to perform the necessary studies in December 1971. In the Spring of 1972 an interagency Pharmacology Task Force was formed of representatives from SAODAP, the Veterans Administration, Department of the Army, Food and Drug Administration, FM, National Academy of Sciences. and the Division of Narcotic Addiction and Drug Abuse, National Institute of Mental Health DNADA,(NIMH). This group reviewed previous and ongoing work on LAAM and planned and coordinated the subsequent development toward the New Drug Application stage.

Through this coordinated effort, the necessary animal toxicological and teratological studies could be phased with the subsequent clinical

studies of humans. The animal toxicology studies done previously by Merck and Company were utilized for the clinical Phase I Investigational New Drug studies begun in June 1972 by DNADA. DNADA initiated extensive chronic animal studies including a one year study in dogs and rats to provide required toxicological data to support safe, prolonged administration in man.

The existence of these animal and early clinical studies stimulated clinical interest in LAAM. Planning began early in 1972 for larger scale cooperative clinical studies to test LAAM safety and efficacy which could follow by 6 to 8 months the chronic animal studies required to support long term administration to humans. Dr. Samuel Kaim, Director of the Alcohol and Drug Dependence Service of the Veterans Administration expressed V.A.'s interest to SAODAP. The VA had vast experience with large scale clinical cooperative studies of other psychotropic drugs. The administrative mechanism including the data gathering and analysis section and pharmacy was already functional at V.A. Hospital, Perry Point, Maryland, under the direction of James Klett, Ph.D. Also, the VA had recently established a network of Drug Dependence Treatment Centers for returning addicted soldiers.

The planning and initiation of further clinical studies proceeded cautiously. To protect the well-being of potential subjects, the Advisory Committee and Pharmacology Task Force wanted some data from the long-term animal studies available before long-term clinical studies were initiated. By the Spring of 1973 sufficient animal toxicity data was available from the Edgewood Arsenal study to support the cautious initiation of Phase II clinical studies. These studies were to proceed in successive stages contingent upon continued evidence of lack of toxicity in animals indicating probable safety in man.

In April 1973, pilot studies were initiated in three VA Hospitals to evaluate the safety and efficacy of LAAM maintenance (80 mg three times weekly) compared to high (100 mg daily) and low (50 mg daily) dose methadone maintenance. The study was conducted double-blind and utilized a common protocol for random selection of subjects, induction of street heroin addicts onto the study drugs, maintenance dosage, and for evaluating safety and efficacy. In the summer of 1973 based on the up&ted animal data, the existing data from the pilot studies and other available clinical data, the decision was made to continue tentatively the study for a total of 40 weeks and to proceed with the addition of nine more Veterans Administration Hospitals in the Cooperative Study. The clinical study was carried out over a 2 year period, terminating in the Spring of 1975. Four hundred thirty (430) male heroin addicts were studied. Of these, 142 received LAAM and the remainder were equally divided between high and low dose methadone.

Because of technical inadequacies in the Edgewood Arsenal Study, DNADA initiated additional acute and chronic rat and dog studies of LAAM in 1973. At approximately this time, SAODAP began planning and organizing another larger cooperative clinical study of LAAM to provide more patient data. The study was designed to complement the VA study.

Interested patients were selected from those already in methadone maintenance programs. In the major part of the new clinical study, patients were randomly assigned to the LAAM study group or the methadone control group. The study was open rather than double-blind. Take-home methadone was permitted according to clinic policy, while all LAAM patients attended the clinic three times a week. Cross-over dose from methadone to LAAM was fixed, but subsequent dose levels were flexible at the discretion of the clinic physician. In addition, sub-study was performed to examine further the use of LAAM on Friday only in place of weekend methadone.

The SAODAP cooperative study was initiated in February 1974 when the safety data from the second animal toxicity study and the clinical data from the VA Cooperative Study was adequate to support an additional 40 week human safety and efficacy study. Sixteen (16) outpatient drug treatment clinics throughout the country were chosen for participation in order to provide widespread experience with LAAM in local treatment programs in a controlled, carefully monitored and coordinated manner. Seven hundred sixty seven (767) male patients, of whom 383 received LAAM, participated in this study. Of these, 136 patients, of whom 65 received LAAM, participated in the LAAM Friday only substudy.

COORDINATION OF LAAM DEVELOPMENT TRANSFERRED TO NIDA

When SAODAP began to phase out in the Fall of 1974, the coordination and direction of the LAAM project, including the Pharmacology Task Force and Cooperative Studies were officially transferred to the recently established Division of Research, National Institute on Drug Abuse, (NIDA), successor to DNADA,(NIMH). Shortly thereafter, based on the available results of the animal and clinical studies, the Food and Drug Administration permitted the use of LAAM for up to 80 weeks to provide longer comparative toxicity data. Also, the inclusion of women with no child-bearing potential was permitted. Accordingly, NIDA extended the SAODAP clinical

studies until the Spring of 1976 to perform additional studies of LAAM.

Thus, by the Fall of 1974 all of the basic work necessary to initiate Phase III large scale clinical study of LAAM had been completed or was in the process of completion. LAAM appeared to be a safe and efficacious drug for use in the treatment and rehabilitation of chronic opioid dependent persons. The staffs of the Clinical-Behavorial Branch, Division of Research, NIDA and the Drug Abuse Section, Division of Neuroharmacology, FDA, began to plan the Phase III clinical study of LAAM through the Pharmacology Task Force. A Phase III clinical study is a full scale clinical trial of the drug under the conditions of the use in the general population. Thus, those groups of heroin addicts excluded from participation in a Phase II study can be included in Phase III. These Phase III studies can include subjects with medical and/or psychiatric illnesses, subjects concurrently taking other medication and women of childbearing potential.

In the Spring of 1975, NIDA advertised a RFP to perform the Phase III study under a cost sharing contract. In return for the cost-sharing NIDA provides patent-like protection for the contractor to protect his investment in LAAM and to assure the marketing of the drurg in the public's interest. NIDA agreed to give the contractor the right to exclusive possession and use of all data generated in the performance of this contract which would be necessary to prepare and file a New Drug Application on LAAM for eight years pending satisfactory performance of the contract.

Despite the investment and commitment already made by Federal Agencies the pharmaceutical industry did not respond. However, other competitive bids were received. In July 1975, a medical consulting firm, Whysner Associates, was contracted by NIDA to conduct Phase III Clinical Evaluation of LAAM for the treatment of chronic opioid dependence and to make appropriate arrangements for the eventual filing of the New Drug Application and marketing of LAAM.

The contract is currently ongoing and arrangements are made to formulate and distribute LAAM The Phase III Investigational New Drug Application has been submitted and clinics are being enlisted to carry out the clinical study. An estimated 6000 patients, including those already maintained on methadone and heroin addicts entering treatment, will be asked to participate in a 40 week study of safety and efficacy of LAAM. The open study will be performed in approximately 50 cooperating methadone maintenance programs nationwide. A common protocol for medical monitoring and evaluation of clinical efficacy will be utilized to produce uniform data. The study will require approxmiately two years to complete after which the New Drug Application for LAAM can be submitted to FDA to permit its marketing to interested chronic opioid dependence treatment programs.

Pending successful completion of this Phase III large scale clinical trial, the project has accomplished the formidable task of developing at an accelerated pace a drug which offers considerable potential benefit to heroin addicts and treatment programs. The task of developing a drug the private sector was unwilling or unable to undertake has been carried out, and in accordance with stringently applied Federal Regulations designed both to ensure the kind of scientific baseline data establishing LAAM safety and efficacy and to provide a mechanism that can be a model for future drug development in the narcotic dependence treatment field. Conjointly the task has entailed creating the means for cooperation between the many agencies and individuals involved in a far-flung and large scale project. This also, is a legacy for future drug development.

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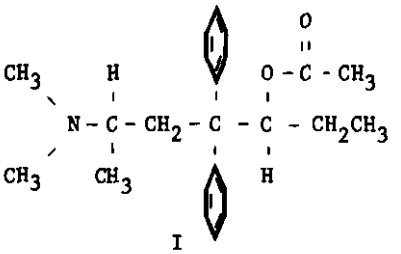
THE CHEMISTRY OF LAAM

Sydney Archer, Ph. D.

CHEMICAL S'TRUCTURAL. FORMULA AND DESCRIPTION

Levo-alpha-acetylmethadol (LAAM) is levo-alpha-6-dimethylamino-4, 4-diphenyl-3-heptyl acetate and is used as its hydrochloride salt. The chemical structure of LAAM is as follows:



I

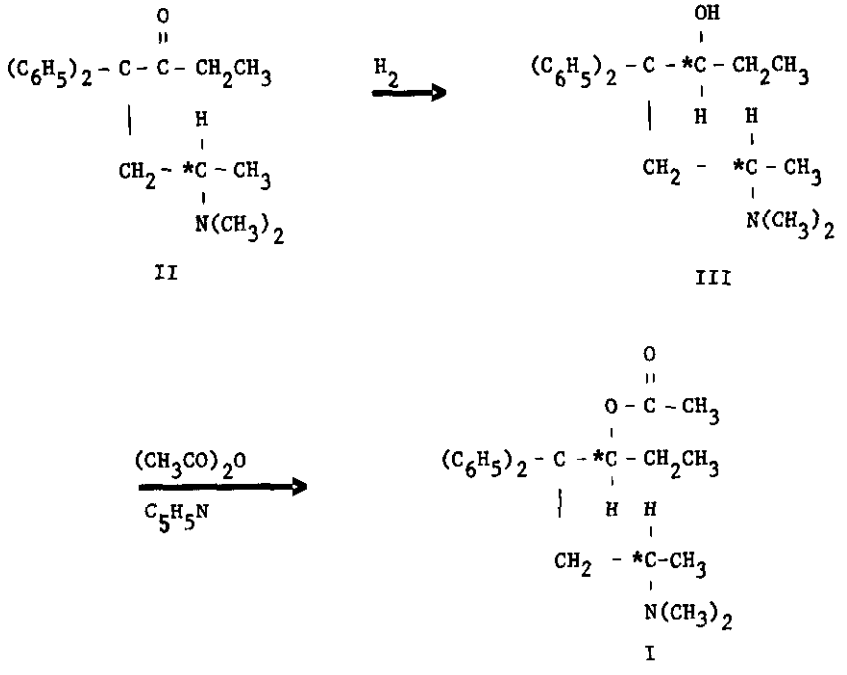
It is a white crystalline compound with a melting point of 215-218°C. It is levorotary and has a specific rotation of -59.0 to -61.3°. $[\alpha]_D^{25}$ D (c=1 in water). Infrared absorption conforms to structure in $CHCl_3$ solution and KBr Pellet.

RELATIONSHIP TO OTHER RELATED DRUGS

The compound was first reported by Pohland, Marshall and Carney (1949)[1] as a water-soluble substance with a melting point of 201-202°C and an observed rotation of $[\alpha]_D^{25}$ D = -59° (c=0.2 in water).

It was prepared by catalytic reduction of d-methadone (II) to afford 1-alpha-methadol (III) which on acetylation with acetic anhydride in pyridine furnished LAAM (I).

[1] *References cited my be found at the conclusion of the monograph in the LAAM Preclinical Bibliography.*



Pohland, Marshall and Carney (1949) also performed the same sequence of reactions on l-methadone. This yielded d-alpha-acetylmethadol whose hydrochloride was also water-soluble and melted at 200-303°C. The optical rotation was $[\alpha]^{25}$ D = +57° (*c*=0.2 in water).

It will be noted that the dextrorotary form of methadone gave levorotatory acetylmethadol, whereas the analgetically more active l-methadone gave the dextrorotatory isomer.

It will also be noted that whereas methadone (II) has only one chiral center (starred carbon) the acetylmethadols have two chiral centers (starred carbons). Two diastereomeric pairs of isomers are possible. However, catalytic hydrogenation gave only the alpha-series as reported by Pohland et al. May and Mosettig (1948) showed that catalytic hydrogenation of dl-methadone furnished the alpha-series exclusively and Speeter, Byrd, Cheney and Binkley (1949) found that lithium aluminun hydride reduction of dl-methadone furnished α-(dl-methadol exclusively also.

On the other hand Eddy, May, Mosettig (1952) found that sodium propanol reduction of either racemic or optically active methadone gave the beta-methadols, as the major but not exclusive products. These results are summarized in Chart I.

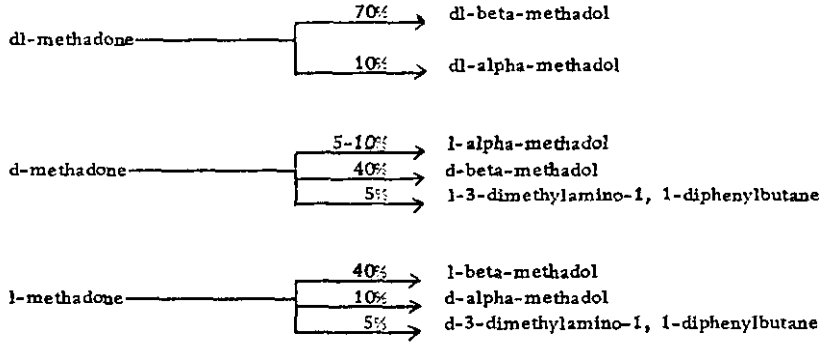


Chart I

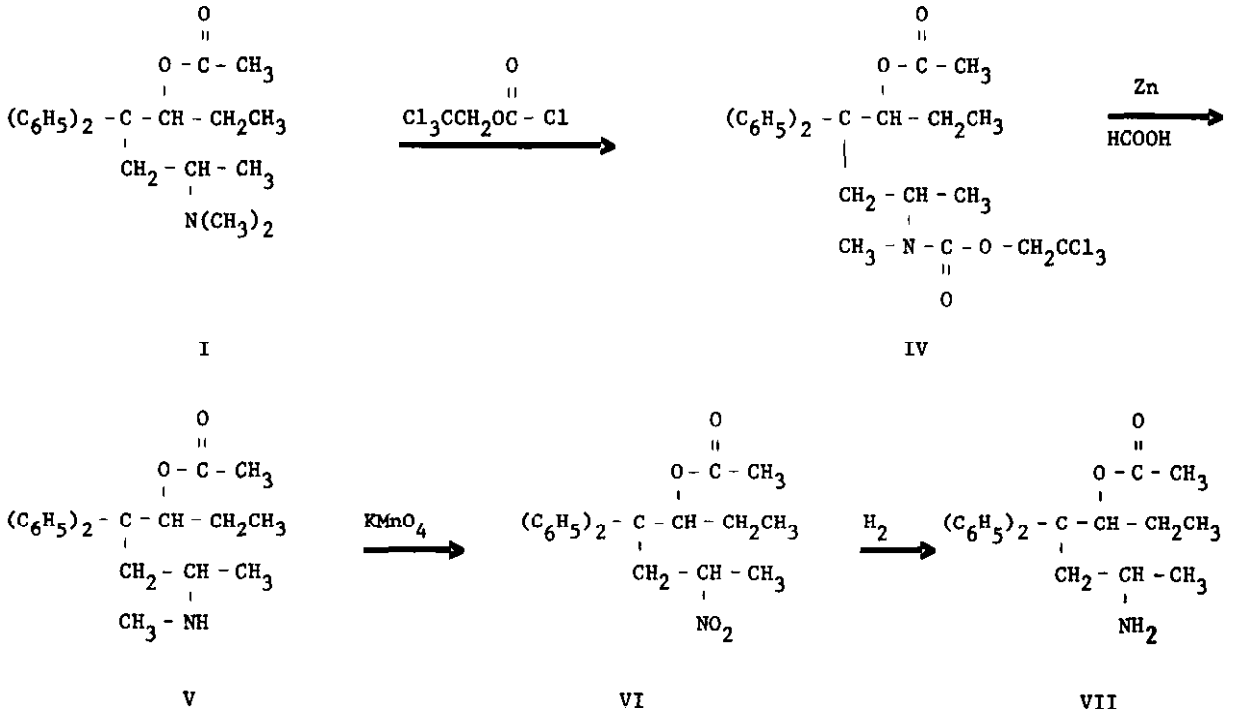


Chart II

These authors converted the isomers to the corresponding acetates. Thus, all four possible isometric acetates were synthesized.

In the course of studying the metabolism of LAAM, two new matabolites were discovered. These are 1-alpha-6-methylamino-4, 4-diphenyl-3-heptyl acetate (V), (Nor-LAAM), and 1-alpha-6-amino-4, 4-diphenyl-3-heptyl acetate (VII), (DiNor-LAAM). Their synthesis was reported by Booher and Pohland (1975) and is outlined in Chart II.

LAAM (I) was treated with trichlororthyl chloroformate to give the amide (IV), which was reduced with zinc in formic acid to give Nor-LAAM (V) in 44 percent overall yield from I. Oxidation with potassium permanganate gave the nitro ester VI in 24 percent yield. Reduction using Raney nickel gave DiNor-LAAM (VII) in 72 percent yield.

Chatterjie and Inturissi (1975) were able to prepare Nor-LAAM from LAAM in one step using a mercuric acetate demethylation procedure. The yield was 50 percent and is shorter than the method of Booher and Pohland (1975).

DESCRIPTION OF DOSAGE FORM AND QUANTITATIVE COMPOSITION

The dosage form of 1-alpha-acetylmethadol is a colorless, clear liquid with the odor of parabens. One ml of concentrate contains:

1-alpha-acetylmethadol	10 mg
methyl paraben	0-18 percent
propyl paraben	0.02 percent

in distilled water.

ASSAY OF LAAM FOR STABILITY

The following procedures were developed by the United States Public Health Service HSHMA Supply Service Center, Perry Point, Maryland (January, 1974), for the assay of samples of LAAM packaged in 16-ounce amber, polyethylene bottles and stored at 25°C and 45°C. The titrimetric procedure which follows is a modification of the USP XVIII procedure for Methadone Hydrochloride Injection:

Transfer a volume of concentrate equivalent to about 50 mg. of LAAM to a separatory funnel and wash with 25 Ml. of either. Transfer the aqueous layer quantitatively to the Watkins Continuous Extraction Apparatus set up for use with ether. Make alkaline with NaOH T.S. and charge the apparatus with ether. Reflux for 6 hours. Remove the receiving flask, add 20.0 ml. of 0.02 N sulfuric acid, and evaporate the ether. Cool, add methyl red T.S., and titrate the excess acid with 0.02 N sodium hydroxide. Each ml. of 0.02 n sulfuric acid is equivalent to 7.799 mg. of $C_{23}H_{31}NO_2$ HCl.

Recovery with this method was as follows:

Sample	Labeled Amount	Recovered
1	0.2 %	0.192%
2	0.2	0.194
3	1.616	1.575
4	0.2	0.194
5	0.2	0.194
6	1.616	1.568
7	1.616	1.598
8	1.616%	1.575%

Because of the need for a "stability indicating" assay method a gas chromatographic method was developed and is as follows:

Standand Solutions: Prepare two (2) standard solutions of LAAM-HCl in water such that standard solution #1 contains 11.0 mg. of LAAM-HCL per ml. and standard solution #2 contains 9.0 mg. LAAH-HCl per ml.

Internal Standard: Prepare a solution of Diphenhy dramine Hydrochloride in water at a concentration of 10.0 mg. per ml.

Sample: Dilute a portion of sample with water to a theoretical concentration of about 10.0 mg. / 10 ml.

GC Operating Conditions

Instrument: Beckman GC55 with flame ionization detector
Column: 6' x 2 mm ID glass - 1.9% UC-W98 on Chrom W-HP 100/120 mesh
Column Temperature: 220°C.
Detector Temperature: 270°C.
Inlet Temperature: 240°C.
Carrier Gas: N_2 Flow rate-30 cc/min.
Hydrogen: 45 cc/min.
Air: 255 cc/min.
Range 100: Attenuation: 4

Procedure: Treat the sample and each of the standard solutions as follows:

Transfer 10.0 ml. to a 100.0 ml. volumetric flask. Add 5.0 ml. of internal standard, dilute to volume with water, and mix. Inject 1 microliter of each solution into the apparatus. Run at least 3 injections of each standard and the sample. From the chromatograms obtained calculate the ratio of the peak area of LAAM-CHCl to the peak area of Diphenhydramine HCl. Plot the peak area ratios of the two standard solutions versus the weight ratios. Read the weight ratio of the sample and calculate the wt. of LAAM-HCl in the sample.

Recoveries with this method were as follows:

Sample	Labeled Amount	Recovered
1	1 %	0.985%
2	0.75	0.785
3	1	1.0
4	1	0.99
5	1.619%	1.675%

PRECLINICAL STUDIES

PHARMACOLOGY OF LAAM

Sydney Archer, Ph.D.

The synthesis of levo-alpha-acetylmethadol (LAAM) and early preclinical investigations into toxic and analgesic properties were carried out in 1948. The delayed onset and long duration of action of this compound was suggestive of the activity of metabolites, and further studies showed that two metabolites, noracetylmethadol (N-LAAM) and dinoracetylmethadol (DN-LAAM), were responsible for the unique time-response characteristics of 1-alpha-acetylmethadol. Currently, research is being carried out into the pharmacokinetics of 1-alpha-acetylmethadol, as well as long-term toxicity studies and studies of the effects of the drugs upon reproduction.

This chapter is devoted to an account of LAAM preclinical animal studies and provides a summary of all pharmacological studies of LAAM. The following chapter offers an account of the preclinical toxicology of LAAM.

PHARMACOLOGICAL SUMMARY OF FINDINGS

The following summary of LAAM preclinical studies presents a comprehensive overview of the pharmacological research which had been conducted with LAAM in animals, through summer of 1975.

Five areas of LAAM animal pharmacology research findings are discussed below:

Analgesic Activity of LAAM and Related compounds

K. K. Chen (1948)[1] first reported on the analgesic activity of 1-alpha-acetylmethadol (LAAM) and d-alpha-acetylmethadol (DAAM) LAAM was prepared from d-methadone which is less active as an analgesic than l-methadone. The latter is the precursor of DAAM. Chen found that in rats l-methadone is seven times as potent as d-methadone but in higher animals the difference in potency is even greater. The l-isomer is 25 times as active in dogs and 50 times as active in man. Thus, it may be expected that the analgesic activity of DAAM will be greater than LAAM. This proved to be the case. It was found that in rats using the Haffner technique for determining analgesic activity (F. Haffner, *Deutsch, Med. Wochenschrift* 55: 731, 1929) DAAM was 5.4 times as active as LAAM by the subcutaneous (s. c.) route of injection and

References cited my be found at the conclusion of the Monograph in the LAAM Preclinical Biography.

twice as active as dl-methadone. It was noted that LAAM had a delayed onset but a long duration of activity as compared with the d-isomer.

Smith and Lehman (1953) found that the analgesic effects of methadone and LAAM in rats were additive when both were injected subcutaneously using the D'Armour-Smith test.

Using the pinch test with rats, McCarthy (1974) found that at 30 minutes after subcutaneous administration, LAAM was about 0.67 (0.53-0.86) times as potent as morphine sulfate but at peak activity, which occurred three and one-half hours after drug administration, it was six times as potent as morphine. The onset of analgesic action was considerably later than that of morphine or methadone.

Leimbach and Eddy (1954) determined the analgesic activity in mice (s.c.) of all four of the stereoisomers as well as the LD_{50} values. Their analgesic results are summarized in Table I and Table II.

TABLE I: ANALGESIC ACTIVITY OF LAAM AND ITS STEREOISOMERS

Subcutaneous Administration

Compound	ED_{50} (S.E.) mg/kg	Onset (Minutes)	Peak (Minutes)	Duration (Minutes)
l-a-acetylmethadol (LAAM)	1.8 (1.7 - 2.0)	23	83	190
d-a-acetylmethadol (DAAM)	0.29 (0.26 - 0.32)	9	32	127
l-b-acetylmethadol	0.36 (0.33 - 0.40)	10	35	173
d-b-acetylmethadol	4.6 (4.0 - 5.2)	27	108	319
dl-methadone	1.6 (1.5 - 1.7)	10	23	70

TABLE II: ANALGESIC ACTIVITY OF LAAM AND ITS STEREOISOMERS

Oral Administration

Compound	ED_{50} (S.E.) mg/kg	Onset (Minutes)	Peak (Minutes)	Duration (Minutes)
l-a-acetylmethadol (LAAM)	1.1 (1.0 - 1.3)	15	58	190
d-a-acetylmethadol (DAAM)	1.6 (1.4 - 1.8)	10	34	174
l-b-acetylmethadol	2.0 (1.8 - 2.3)	10	34	173
d-b-acetylmethadol	4.3 (3.9 - 4.7)	47	136	260
dl-methadone	9.2 (7.3 - 11.6)	9	26	118

In agreement with K. K. Chen, these authors found that d-a-acetylmethadol (DAAM) is about six times as active as an analgesic than 1-a-acetylmethadol (LAAM). They also noted a delay in onset and a longer duration for LAAM as compared with DAAM. However, these differences tended to disappear when the durgs were administered orally (Table II). When the oral route was used, the ED_{50} doses, the onset, and duration were almost identical. When compared with dl-methadone, LAAM was more active orally (ED_{50} =1.1 vs 9.2) and had a greater duration of action.

The LD_{50} data for these compounds is summarized in Table III.

TABLE III: ACUTE TOXICITY IN MICE OF LAAM AND ITS STEREOISOMERS

Compound	Subcutaneous Administration LD_{50} (S. E.) mg/kg	Oral Administration LD_{50} (S. E.) mg/kg
l-a-acetylmethadol (LAAM)	110 (95 - 128)	173 (165 - 181)
d-a-acetylmethadol (DAAM)	72 (68 - 77)	130 (125 - 137)
l-b-acetylmethadol	42 (40 - 44)	87 (81 - 93)
d-b-acetylmethadol	56 (53 - 60)	81 (77 - 87)
dl-methadone	44 (43 - 45)	95 (93 - 98)

LAAM turned out to be the least toxic stereoisomer whether given orally or subcutaneously and was less toxic than dl-methadone also. It must be emphasized that these acute toxicities were determined in nondependent mice and caution must be observed in extrapolation of these results.

Veatch, Alder, and Way (1964) studied the nalorphine reversibility of the analgesic effects of DAAM and LAAM as compared with l-methadone and d-methadone. The ED values were obtained by intraventricular injection. Because of the long duration of action of LAAM and the relative short duration of action of nalorphine, the latter (50/mg/kg) was administered 40 minutes after the dose of LAAM and doses of the antagonist were given every hour thereafter for a total of six hours. The results are summarized in Table IV.

TABLE IV: NALORPHINE-REVERSIBILITY OF THE ANALGESIC EFFECTS OF LAAM, DAAM, AND METHADONE

Drug	ED_{50} (mg/kg Intraventricular Administration) No Pretreatment With Nalorphine	After Pretreatment With Nalorphine
l-a-acetylmethadol (LAAM)	1.0	0.78
d-a-acetylmethadol (DAAM)	0.032	0.98
l-methadone	0.029	2.10
d-methadone	1.40	1.80

It is surprising that no nalorphine reversibility was noted after administration of LAAM or d-methadone. The results are self-consistent in the sense that d-methadone is the precursor of LAAM and l-methadone is the precursor of DAAM.

Nevertheless, it would be expected that nalorphine would reverse these morphine-like effects of all the compounds. In contrast, Killam (1974) found that in monkeys the respiratory depressant effects of LAAM were nalorphine and naloxone reversible.

Analgesic Activity of LAAM Metabolites

When it became known that LAAM was metabolically converted to 1-alpha-noracetylmethadol (N-LAAM) and 1-alpha-dinoracetylmethadol (DN-LAAM), Nickander, Booher, and Miles (1973) compared the analgesic activity of these three compounds on the guinea pig ileum preparation. The results are summarized in Table V.

TABLE V: ANALGESIC ACTIVITY OF LAAM AND ITS METABOLITES ON THE GUINEA-PIG ILEUM

Drug	IC_{50} ng/ml*	95 Percent Confidence Limits
LAAM	333	(165 - 671)
N-LAAM	20	(9 - 43)
DN-LAAM	28	(12 - 68)

*IC_{50} Concentration producing a 50 percent inhibition of the twitch response

TABLE VI: ANALGESIC ACTIVITY OF LAAM AND ITS METABOLITES IN THE ACETIC ACID-INDUCED WRITHING TEST IN MICE

Drug	ED_{50} (95% CL) (mg/kg $_{SC}$)
LAAM	2.1 (1.3 - 3.6)
N-LAAM	0.34 (0.23 - 0.31)
DN-LAAM	2.0 (1.3 - 3.0)

Smits (1974 studied these drugs for analgesic activity in the acetic acid-induced writhing test in mice. The results are summarized in Table VI.

It was noted that LAAM had a slower onset of action than its metabolites.

Billings, Booher, Smits, Pohland, and McMahon (1973) found that ED_{50} of l-alpha-dinoracetylmethadol (DN-LAAM) in the acetic acid-induced mouse writhing test for analgesia was 1.5 mg/kg S.C. and 5.6 mg/kg peroral (p.o.)

It is clear that in both the in vitro and in vivo tests for analgesic activity that 1-alpha-noracetylmethadol (N-LAAM) is more active than LAAM. The slow onset of the latter coupled with the high activity of the metabolite, N-LAAM, is highly suggestive that LAAM is metabolically transformed to an active drug which is probably N-LAAM. The studies of Way using SKF-525A strongly support this proposition.

Addiction Potential of LAAM and Its Cogeners

Deneau and Seevers (1960, 1955) determined the physical dependence capacity (PDC) of some compounds related to LAAM although LAAM itself was not run. The usual single dose suppression technique, using morphine-dependent monkeys was employed. The results are summarized in Table VII.

TABLE VII: PHYSICAL DEPENDENCE CAPACITY (PDC) OF CONGENERS OF LAAM

Drug	Dose	Number of Monkeys	Remarks
a-dl-Acetoxy 6-methylamino-4,4-diphenylheptane-HCl (dl-a-noracetylmethadol)	0.5	5	Equivalent dose = 0.75 mg/kg
	1.0	5	Duration = 6 hours
	20	5	PDC: High
a-d-3-Acetoxy-6-methyl amino-4,4-diphenylheptane-HCl (d-a-noracetylmethadol)	1.0	5	Equivalent dose = 3.5 mg/kg
	2.0	5	Duration = 6.5 hours
	4.0	5	PDC: High
d-b-acetylmethadol	1.5	5	Equivalent dose = 3.0 mg/kg
	3.0	5	Duration = 7.5 hours
	6.0	5	PDC: High
dl-b-Acetoxy-6-methylamino-4,4-diphenylheptane-HCl (b-dl-noracetylmethadol)	0.5	5	Equivalent dose = 1.5 mg/kg
	1.0	5	Duration = 6 hours
	2.0	5	PDC: High
dl-b-acetylmethadol-HCl	0.5	5	Equivalent dose - 1.0 mg/kg
	1.0	5	Duration = 5 hours
	2.0	5	PDC: High

Although no studies were reported on LAAM itself, the racemic mixture of its primary metabolite (dl-alpha-noracetylmethadol) was run as was the d-isomer of alpha-noracetylmethadol. The former had an equivalent dose of 0.75 mg/kg and the latter required a dose of 3.5 mg/kg to suppress signs of morphine abstinence. Thus, it may be concluded that the l-isomer is more active than the d-isomer in suppressing abstinence in morphine-dependent monkeys. Since the 1-isomer is a metabolite of LAAM it may be concluded that LAAM will have a high PDC.

During the development of tolerance to morphine in rabbits, the hyperglycemia produced by regularly spaced injections of the drug gradually diminished and even turned to a hypoglycemia as tolerance developed. Phatak and David (1953) noted that LAAM produced a hyperglycemia on initial injection in rabbits which gradually diminished as tolerance developed. Abrupt withdrawal of the drug produced a hypoglycemic effect.

Moreton, Roehrs, and Khazan (1974) studied the pattern of self-administration of morphine, methadone, and LAAM in rats. Adult female albino rats weighing 250-300 g were made physically dependent on morphine and intravenous (i.v.) cannulated to permit self-administration of morphine (10 mg/kg/injection). EEG and EMG activity was recorded continuously.

Morphine was available 24 hours per day. Methadone (2 mg/kg/injection) was substituted for morphine and LAAM (1 mg/kg/injection) was then substituted for methadone.

In the naive rat, administration of morphine at 10 mg/kg intraperitoneal (i.p.) was followed by a biphasic pattern of behavioral stupor and subsequent stimulation. The depressed phase lasted 60-90 minutes and the EEG tracings showed the occurrence of high-voltage slow bursts. During the phase of stimulation, lasting 60-90 minutes, the EEG revealed desynchronized awake tracings. Only a few short episodes of behavioral stupor with EEG slow bursts intervened in this period. This phase was characterized by increased locomotor activity, stereotyped behavior, and episodes of startle reactions.

In the dependent rat, the duration of the biphasic response after self-injection of morphine was reduced by about 50 percent. The behavioral stuporous phase, concomitant with EEG slow bursts, appeared within a few minutes and lasted for only 15 to 30 minutes. The behavioral stimulation and EEG activation lasted for only 30-60 minutes. Sleep and REM sleep predominated before the next injection. Upon methadone substitution, the sleep-awake distribution within the interinjection intervals was qualitatively similar. In the case of LAAM self-administration, EEG slow bursts usually occurred several minutes after injection and were followed by brief episodes of sleep and REM sleep. These few sleep and REM sleep episodes were terminated by the appearance of wakefulness with EEG slow bursts and then behavioral arousal which lasted for two to three hours. The arousal state, as in the case of morphine and methadone, was followed by alternating episodes of sleep, REM sleep, and wakefulness prior to the next injection.

Under these experimental conditions of free access to the drug, morphine (10 mg/kg/injection) was self-administered as a single or multiple injection at intervals of 2.5±0.1 hours. When methadone (2 mg/kg/injection) was substituted for the morphine, the injection intervals were 1.4±0.1 hours. With LAAM, the interinjection interval was 8.8±0.8 hours.

LAAM possessed a relatively slow onset and long duration of action in dependent rats having free access to the drug. When low doses of naloxone were administered intravenously, there was an immediate precipitation of abstinence signs.

Killam (1974) studied the effects of LAAM on the morphine uptake of morphine-dependent monkeys. At 2.0 mg/kg intramuscular (i.m.) three morphine-dependent monkeys exhibited a slight decrease (2-16 percent) in morphine uptake, but a fourth showed a significant increase (40-50 percent). The next day all monkeys showed a significant increase which dropped on the second day and returned to baseline on the third day. At 4.0 mg/kg there was a 30.6 percent decrease in morphine uptake followed by an increase of 50-87 percent on the second day. On the third day, the intake returned to baseline values. At 6.0 mg/kg, both monkeys were depressed and ataxic. This lasted for 8-16 hours during which time there was no uptake of morphine. There was a rebound effect on the second day and morphine uptake varied for the following three days.

Other Pharmacological Effects

Henderson (1974a) found that a dose-dependent acute necrosis of the kidney of rats occurred following administration of LAAM (2 mg/kg (0 percent), 5 mg/kg (65 percent), 10 mg/kg (73 percent)). This effect was also noted after administration of 50 mg/kg of morphine sulfate (83 percent). Complete reversal

occurred after 32 hours. The fact that naloxone prevented this phenomenon indicated that it was the result of the pharmacological action of the analgesics rather than an intrinsic effect of LAAM.

Maickel (1974) found that at 0-10 minutes postadministration, LAAM caused a decrease in spontaneous activity of mice. At doses of 50 to 100 mg/kg s.c., the activity of the mice was about 50 percent of that of the control group and at 200 mg/kg the spontaneous activity decreased to only 60 percent of control. In comparison, methadone at 15 mg/kg S.C. increased spontaneous activity to about 200 percent of control. There was a marked decrease (<50 percent of control) at 45 mg/kg s.c.

Killam (1974) studied the effects of LAAM in the monkey. Using doses of 1 to 8 mg/kg i.m. and 2-6 mg/kg p.o., it was noted that the drug produced an initial decrease in hostility and increase in salivation followed by a markedly depressed state with low muscle tone. Respiratory arrest occurred which was reversible by nalorphine or naloxone. The EEG changes paralleled the behavioral changes. There was a delayed onset of action which occurred about 10-12 hours after oral administration and lasted 38 hours. Drug effects were noticed 40-50 minutes after intramuscular injection and lasted about 24 hours.

The interaction of LAAM with other drugs was also examined in the monkey (Killam, 1974). These were secobarbital, diazepam, ethanol, amphetamine, and diphenylhydantoin. The effects of amphetamine and secobarbital were slightly enhanced; those of ethanol and diazepam were slightly obtunded, and there were no effects on diphenylhydantoin.

Inwang et al., (1975) showed that LAAM was qualitatively similar but differed quantitatively from methadone in its effect on the rabbit cortex. New Zealand rabbits which had chronically implanted electrodes in the optic and posterior sensory motor cortex were treated by intracortical administration with 0.5 mg/kg and 1.25 mg/kg of LAAM. At the lower dose, an initial, facilitatory effect occurred four minutes postinjection and lasted 52 minutes. The onset of peak amplitude of the slow negative wave (SNW) was delayed, followed by a depression of the amplitude of the SNW with no recovery in delay of the SNW. At the higher dose, complete abolition of the SNW occurred without recovery.

Mice were electroshocked with 140 mV of D.C. by contacting their eyes with electrical terminals 10 or 20 minutes after intraperitoneal (i.p.) administration of LAAM (0.1-2.0 mg/kg); they had prolonged post-ictal recovery. At 0.21-0.5 mg/kg, the prolongation was followed by a decrease in post-ictal recovery.

Gary Henderson has studied the behavioral effects of LAAM in beagle dogs. One mg/kg dose was administered intravenously and two mg/kg doses were administered both intravenously and orally.

One Mg/Kg Intravenously--Immediately after dosing, dogs started to pant, become quiet, and lay down. By 30 minutes, three of four dogs defecated. The females were coordinated but moved slowly. The males were slightly ataxic. By one to one and one-half hours after drug administration, all dogs were quiet and unwilling to move. One male had vomited. At two to two and one-half hours postinjection, all dogs were laterally recumbent but alert. At the fourth hours, they were alert and fairly well-coordinated. At the eighth hours, they had recovered.

The body temperature fell from 98 degrees F to 94 degrees F, leveling at two hours and returning to normal after six hours. Heart rates decreased from about 65 to 55 and started to return to normal after six hours. Respiration rose initially due to panting, but became normal after two hours. The males seemed to be more affected with respect to changes in temperature, respiration and heart rate, whereas the females showed greater degrees of ataxia, vocalization, and shivering. Owing to the small number of animals involved, no firm conclusions about sex differences can be drawn.

Two Mg/Kg Intravenously--Stimulation or excitement appeared immediately after drug administration. There was salivation, increased motor activity (circling), urination, and defecation. Respiration increased but temperature and pulse decreased. This was followed by prolonged hind limb ataxia, decreased motor activity, and a sleep-like state. Respiration was only mildly depressed but body temperature dropped from 101.5 degrees F to 95 degrees F and returned to normal in 24 hours. The pulse was low and irregular during the first 24 hours.

Two Mg/Kg Orally--The beagles which received 2 mg/kg i.v. also received 2 mg/kg perorally (p.o.) after a suitable recovery period. After 30-45 minutes, the dogs licked their lips, panted, and salivated. One male vomited. The males were

depressed and were in a state of lateral recumbency, eyes partly closed and pupils constricted. At one to one and one-half hours, one female was also depressed. One male could only be aroused by shaking and did not respond to audio or visual stimuli. At two hours, the other female was depressed and showed hindquarter weakness. By the third to fourth hours, the males dragged their hindquarters and were ataxic. The ataxia in the males lasted for two hours and about four hours in the female.

In both the i.v. and p.o. studies, the males seemed to be more affected than the females. The only major difference between the two routes of administration is that, as expected, the onset of action by i.v. injection was more rapid.

Behavioral effects of LAAM in monkeys were also studied by Henderson (1975). Four naive and one morephine-depent monkey received 2 mg/kg (i.v.) H^3 -LAAM. Drug effects were noted within five minutes post-injection and lasted about one hour. Eyelids drooped or closed completely, pupils were dilated, and the frequency of eye blinking was decreased. *Some* catalepsy, muscle twitching, and shivering were observed.

There were little change in respiratory rate. The heart rate decreased slightly in the first three hours. The body temperature fell from 100 degrees F to 96 degrees F. The pupils and body temperature returned to normal within four hours.

In one morphine-dependent monkey, 2 mg/kg i.v. of LAAM had little effect. Papillary size did not change but there was a slight decrease in heart rate from 150 b.p.m. to 120 b.p.m. Heart rate was normal in two and one-half hours.

One naive male monkey was given 5 mg/kg p.o. of H^3 -LAAM. After three and one-half hours he was sedated and cataleptic. After six hours there was marked sedation, shallow breathing, and a rapid heart rate. He expired one hour after drug administration. The levels of radioactivity were high in the lung and liver but very high in the bile which indicated that biliary excretion was the major pathway of disposal of the drug.

H^3 -LAAN (2 mg/kg p.o.) was given to four naive monkeys and one morphine-dependent monkey. In the naive monkey, there was a decrease in heart rate and a slight decrease in respiratory rate beginning about one hour after drug ingestion which lasted about four hours. The pupils began to dilate in 30 minutes, reached a maximum in one hour, and lasted about 12 hours. By the end of the first hour, the animals were sedated and showed signs of muscle twitching and shivering. They were alert to external stimuli. Rectal temperature fell from 100 degrees F to 96 degrees F and stayed below normal for eight hours. Two monkeys were anorexic.

Absorption, Distribution, Excretion, and Metabolism

The first metabolic study on LAAM was carried out by Sung and Way in 1954. The compound was determined in tissues by a modification of Brodie's methyl orange technique. The sensitivity of this procedure is very poor when compared to modern methods.

After subcutaneous injection in rats, about 70 percent of the dose (20 mg/kg) was absorbed from the injection site after one hour. About 7 percent was recoverable after 13 hours. The rate of disappearance was much slower after oral administration; about 80 percent of the dose was recovered from the stomach after one hour and 50 percent of the dose was recovered after 24 hours. There was some experimental evidence adduced to suggest that the drug was being secreted into the stomach, because appreciable amounts of LAAM were found in the stomach after intravenous and subcutaneous administration.

The tissue levels of LAAM in Long-Evans rats were compared after administration of 20 mg/kg of the drug. Except for the gastrointestinal tract, levels in all other organs were higher after subcutaneous than oral administration. The highest concentrations were found in the lung. The kidney, spleen, liver, and fat contained appreciable levels, whereas very low levels were present in the heart, blood, and brain. As noted above, high concentrations were found in the stomach after oral and even subcutaneous and intravenous administration. A large proportion of the drug was accounted for in the carcass (chiefly muscle and bone). Tissue levels of the drug persisted for at least 24 hours.

Despite the rapid uptake and high tissue levels noticed after parenteral administration, the morphine-like effects did not become manifest until four-six hours after the injection. The effects lasted as long as 24 hours. Following oral administration, the tissue levels were lower, but the onset of action occurred about one hour later. In view of these results, the authors concluded that LAAM was being converted to an active

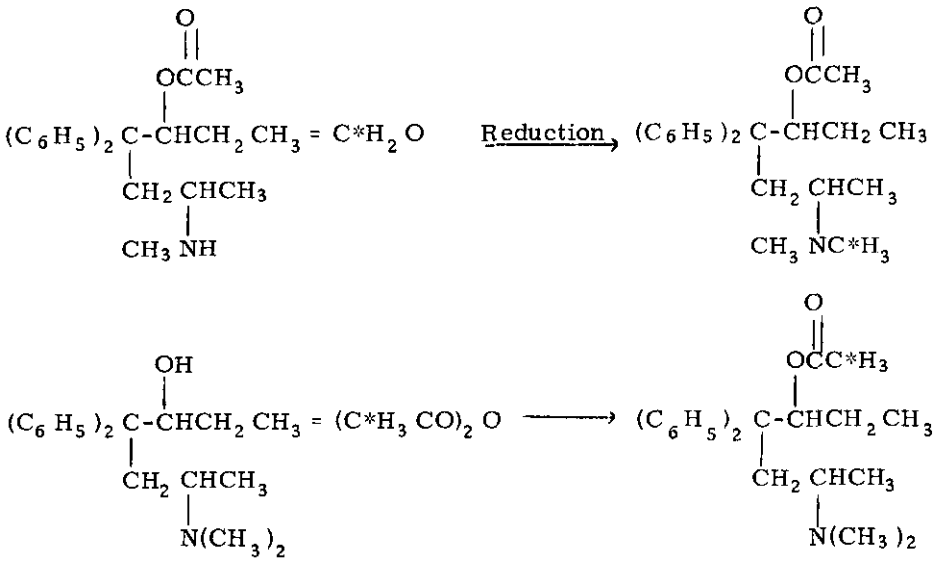
metabolite, a process which occurs more rapidly after oral than parenteral administration.

Very little (less than 3 percent) of the original dose was found in the feces and urine of rats after subcutaneous administration. Bile taken continuously from cannulated bile ducts yielded very small amounts of LAAM. The low recovery of LAAM supported the view that the drug was being metabolized.

Sung and Way found that in mice 40-50 percent of the drug was still present after 12 hours. Appreciable amounts were detected after 24 hours, but by 48-72 hours, LAAM was barely detectable. In rats, the decline in tissue levels was more rapid, but the pharmacological effects were more sustained.

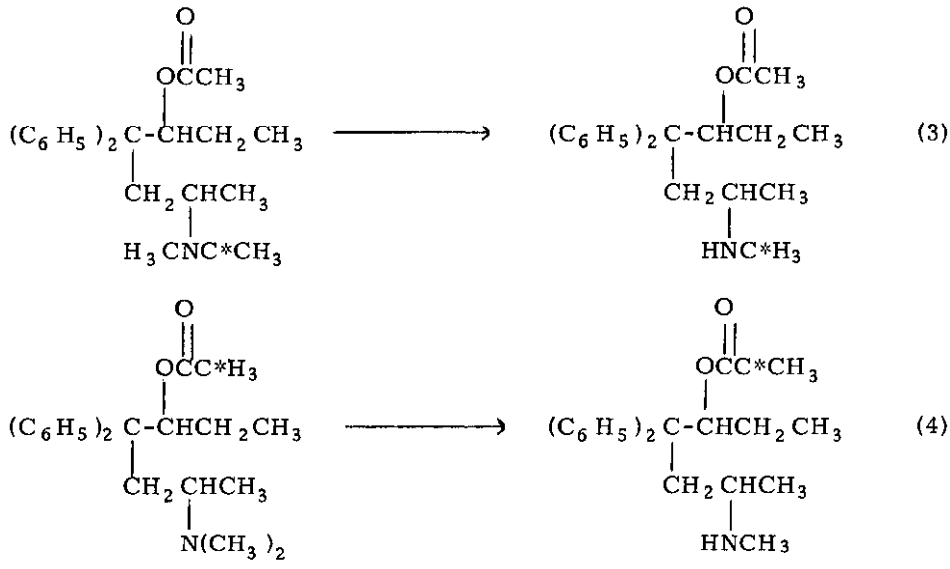
Veatch, Adler, and Way (1964) studied the effect of prior administration of the metabolic inhibitor SKF-525A. If microsomal biotransformation is converting LAAM to an active metabolite, then SKF-525A ought to interfere with the analgesic effectiveness of the drug. In preliminary experiments, they determined that in the Eddy-Leimbach hot-plate test for analgesia, the ED_{50} of LAAM is 3.25 mg/kg with an onset of 135 minutes, a peak effect at 210 minutes, and a duration of greater than six hours. The ED_{90} dose was 21 mg/kg. At this dose the onset time was reduced to 15 minutes and the peak was 110 minutes, after injection of the drug into the right thigh. 50 mg/kg of SKF-525A was given 20 minutes before the ED_{90} dose of LAAM and the mean analgesic response was recorded as the percentage of the control dose. After the first hour, the SKF-525A treated animals responded at 92 percent of the controls, after two hours at 72 percent, after three hours at 67 percent, after four hours at 59 percent, and after the fifth and sixth hours at about 28 percent of controls. Thus, it was clear that SKF-525A did decrease the analgesic response of LAAM.

McMahon, Culp, and Marshall (1965) succeeded in identifying the major metabolites of dl-alpha-acetylmethadol "sing radio-labeled drug. They labeled the N-methyl group and the O-acetyl group, using the synthetic methods shown in the following equations.



Note: The starred carbon atoms in equation (1) and (2) are C^{14}-labeled.

The C^{14}-labeled dl-alpha noracetylmethadols were prepared according to equation (3) and (4).



For in vivo studies, 150 g male albino rats (Harlan Industries) were used. Since this strain was sensitive to the drug, the dose of dl-alpha-acetylmethadol used was 2.5 mg/kg. The identity of the metabolites was secured by the isotope dilution technique. When C^{14} -labeled N-methyl was used, the rate and extent of expired $C^{14}O_2$ was measured. Urine samples were assayed directly in a scintillation counter and feces were treated by the Schoniger method before assay.

The in vitro metabolism of dl-alpha-acetylmethadol studied using rat liver homogenates. It was found that the drug was demethylated by microsomal N-demethylase to give dl-alpha-noracetylmethadol. The latter was also a substrate for this enzyme and furnished dl-alpha-dinoracetylmethadol but at a considerably slower rate.

The N-demethylation was studied in vivo by using N-$C^{14}H_3$ dl-alpha-acetylmethadol and following the respiration of $C^{14}O_2$. On intravenous injection, $C^{14}O_2$ formed rapidly. In five hours, 50 percent of the dose corresponding to complete removal of one N-methyl group was recovered in the respired air. Excretion continued until nearly 80 percent of the administered dose was recovered as $C^{14}O_2$ showing that a second N-methyl group was coming off. The half-life for the removal of one N-methyl group was about two hours.

Orally, the initial rate of N-demethylation was slower, but after 16 hours, it was almost as great as that following intravenous injection.

C^{14} -acetyl labeled dl-alpha-acetylmethadol was administered to rats. By following loss of the acetyl label (due to ester hydrolysis) it was found that this occurred to the extent of 30 percent following intravenous (i.v.) injection. About 15 percent of dl-alpha-noracetylmethadol hydrolyzed in the first 18 hours.

The tissue levels of radioactivity were measured following administration of N-methyl C^{14} -labeled dl-alpha-acetylmethadol and dl-alpha-noracetylmethadol. Following intravenous injection, peak levels of radioactivity were found in lung, muscle, and brain one to five minutes after injection. Peak levels in the liver and kidney occurred later. Plasma levels were low, tended to drop, and then reached a new maximum at about eight hours. Orally, much lower tissue levels were found except for the liver. Peak levels were observed to occur 0.5 to 1.0 hours postadministration of the drug.

At 0.5 hour postinjection, dl-alpha-acetylmethadol predominates over the nor-analog by a ratio of 2:1 in lung and liver and 6:1 in the brain. After two hours, the ratios decreased and at four hours, dl-alpha-noracetylmethadol predominated in the liver and the radio was about 1:1 in the lung. In the brain, the isomer ratio shifted from 6:1 to 2:1 in this period of time. No quantitative studies were carried out because of the low level radioactivity.

With NC^{14} methyl dl-alpha-noracetylmethadol, unmetabolized drug was found in the lung, liver, and brain at eight hours following intravenous injection. The drug persisted in the lung and liver for 24 hours. Radioactivity was detected for 14 days after administration, but this long-lasting effect could be due to the fact that some of the $C^{14}O_2$ from the N-C^{14} methyl. group was being incorporated into the body pool.

The radioactivity in the urine and feces following administration of C^{14} labeled dl-alpha-noracetylmethadol is shown in Table VIII.

TABLE VIII: DISTRIBUTION OF RADIOACTIVITY IN URINE AND FECES AFTER ADMINISTRATION OF C_{14}-LABELED dl-alpha-NORACETYLMETHADOL

Label	Time (Days)	Percent of Radioactivity	
		Urine	Feces
CH_3	0 - 1	4.18	4.52
	0 - 2	5.27	9.11
	0 - 3	5.87	9.71
	0 - 4	6.21	10.46
CH_3CO	0 - 1	7.02	24.20
	0 - 2	8.11	45.20
	0 - 3	8.36	50.00
	0 - 4	8.42	51.10

The metabolites from the N-methyl labeled drug can be either unchanged dl-alpha-noracetylmethadol or dl-alpha-normethadol. The metabolites from the acetyl-labeled drug can be unchanged drug, dl-alpha-denoracetylmethadol or a derivative of the latter. Inspection of the column on urinary excretion shows that the percentages for N-methyl and adetyl-labeled drug are almost the same. Thus, unchanged drug is the primary excretion product accompanied by some bisnoracetylmethadol. However, the differences in the fecal excretion patterns are very large. The major product in the feces is dl-alpha-dinoracetylmethadol or some conjugate thereof.

Biliary excretion studies show that the major metabolic pathway involves retention of the C^{14} -acetyl group and loss of the C^{14} -N-methyl group. About 60 percent of the administered drug is excreted via the bile in 24 hours.

Thus, the conclusion of Sung and Way that biliary excretion is a minor pathway for the disposition of LAAM requires modification. It will be recalled that these authors looked for unchanged LAAM whereas the material secreted in the bile are metabolites of the drug.

Billings, Booher, Smits, Pohland, and McMahon (1973) developed a gas-chromatographic method for the determination of alpha-noracetylmethadol and alpha-dinoracetylmethadol. They formed the trichloracetyl derivatives of these metabolites. These were separated on a two-foot siliconized glass column containing 3 percent OV 1 on 100-200 mesh Gas Chrom Q at 205 degrees. A ^{63} Ni Ec-detector was used. Under these conditions, alpha-noracetylmethadol had a retention time of 3.4 minutes and alpha-dinoracetylmethadol had a retention time of 2.4 minutes. The identity of the metabolites was confirmed by mass spectrographic analysis.

These authors determined the tissue levels of dl-alpha-noracetylmethadol after i.p. administration. The results are summarized in Table IX.

TABLE IX: TISSUE LEVELS OF dl-alpha-NORACETYLMETHADOL AFTER I.P. INJECTION OF dl-alpha METHADOL

Time Post-Injection	Tissue (mg/kg of Tissue Average of Two Rats)			
	Plasma	Brain	Liver	Lung
0.5	0.18	0.10	3.8	5.5
2.0	0.27	0.17	2.4	4.4
4.0	0.21	0.19	4.5	10.6

From these data, it is clear that the tissue build-up of dl-alpha-noracetylmethadol is a relatively slow process and confirms the suspicions voiced by Sung and Way (1954) about twenty years earlier.

Gary Henderson (1975b) is studying the metabolism and pharmacokinetics of LAAM in rats, dogs, and monkeys. These studies are not yet complete. The current Status of this work is reviewed below.

Rats (Excretion Patterns)--Four male Sprague-Dawley rats weighing between 204 and 273 g were given 2 mg/kg of H^3 -LAAM orally. The rats were constipated for about 12 hours. About 8 percent of the radioactivity was recovered from the urine in 96 hours and about 85 percent was found in the feces. Most of the urinary radioactivity was excreted in the first 48 hours and little (about 16 percent) was excreted in free form. The metabolites were separated on thin-layer chromatography (TLC) and quantitated. A summary of the findings is given in Table X.

Preliminary experiments showed that the recovery of l-alpha-acetylmethadol (LAAM was 91 percent, l-alpha-noracetylmethadol (N-LAAM) was 91 percent, alpha-methadol (MOL) was about 88 percent, nor-alpha-methadol (N-MOL) was 90 percent, and l-alpha-dinoracetylmethadol (DN-LAAM) was 96 percent. The pH had to be kept at 9.5 because at pH 13 O→N acetyl migration occurred rapidly.

It is clear that N-LAAM and DN-LAAM were the major metabolites excreted in unbound form and that most of the urinary metabolites were excreted as conjugates.

TABLE X: RECOVERY OF LAAM AND ITS METABOLITES IN UNBOUND FORM FROM RAT URINE

Drug	Cumulative Percent Recovery		
	0 - 12 Hours	12 - 24 Hours	24 - 48 Hours
LAAM	0.12	0.18	0.18
N-LAAM	0.14	0.35	0.35
DN-LAAM	0.40	0.71	0.71
MOL	0.07	0.10	0.10
N-MOL	--	--	--
N-Acetyl DN-MOL	--	--	--
Total Percent Free			1.34
Total Percent Bound			6.78
Total Percent In Urine			8.12

Higher doses of LAAM were also studied. Two male and four female Sprague-Dawley rats weighting between 212 and 371 g were given 5 mg/kg of H^3 -LAAM by gavage. Food was supplied ad lib and urine and feces were collected every 24 hours up through 96 hours. At this dose, the males exhibited hematuria. At the end of 96 hours, the males had excreted 6.66 percent of the administered radioactivity in the urine and 87.32 percent in the feces. The females excreted 13.55 percent in the urine and 59.86 percent in the feces.

Rats (Tissue Distribution)--Four of the male rats which received 2 mg/kc H^3 -LAAM p.o. were sacrificed after 96 hours and selected tissues were assayed for radioactivity. No attempt was made to identify the compounds in the tissues. The results are summerized in Table XI.

TABLE XI: TISSUE DISTRIBUTION OF LAAM AND/OR METABOLITES

Organ	Percent Dose
Brain (Cortex)	0.007 ± 0.003
Heart	0.010 ± 0.007
Liver	1.310 ± 0.390
Spleen	0.006 ± 0.002
Stomach	0.040 ± 0.020
Kidney	0.020 ± 0.010
Lungs	0.020 ± 0.010

In contrast to Sung and Way's results (1954), very little material was found in the stomach. This discrepancy can be explained by the difference in time interval between the initial medication and the subsequent sacrificing. In Henderson's case, the sacrificing took place much later than the original dosing. Despite the fact that tissues were examined 96 hours post-dosing, it is interesting to note that the only organ which contained more than trace amounts of LAAM and/or its metabolites was the liver.

Kinetics of H^3 -LAAM Elimination In Rat Bile--In the initial experiments, the interval between cannulation and dosing was so long that several rats were too sick to be used. The remaining animals were used to determine the nature of the biliary excretion patterns. Free metabolites were determined and then the remaining bile was treated with β -glucuronidase (Sigma) to deconjugate the water-soluble fraction. Hydrolysis was incomplete even after 36 hours incubation at pH 5.0 at 37 degrees. Thirty percent of the radioactivity was excreted in the bile as unbound drug and metabolites. Of the remaining 70 percent, about 81 percent underwent deconjugation. After six hours the bile contained detectable levels of free LAAM, N-LAAM, DN-LAAM, MOL, and N-acetyl-N-Mol. The major metabolites were DN-LAAM and N-acetyl-N-MOL. Following enzymic hydrolysis, N-acetyl-N-MOL and DN-LAAM proved to be the major metabolites. In addition, LAAM, N-LAAM, MOL, and N-MOL were detected. It is difficult to see what sort of conjugate LAAM itself can form.

The experiment was repeated with a modification which consisted of medication inmediately after the animals recovered from the surgery. The rats were given 5 mg/kg of H^3 -LAAM p.o. Bile was collected every 30-60 minutes up to 96 hours. This experiment is incomplete; however, initial results have been reported and are summarized below.

Biliary excretion appears to follow zero-order kinetics until 72-96 hours when it then apparently follows first-order kinetics. In two male rats, 80-85 percent of the administered radioactivity was recovered from the bile after 96 hours. The radioactivity appears in the bile five minutes after dosing and less than 10 percent of the dose appears in the feces of bile-cannulated rats. Thus, greater than 90 percent of LAAM is absorbed by the oral route. After 96 hours, about 96 percent of the administered radioactivity is eliminated in the male rats and about 74 percent in the females. The nature and abundance of LAAM and its metabolites was the same as

in the previous experiment. In rat urine DN-LAAM was the major metabolite followed by N-LAAM, LAAM, and MOL.

Dogs (Blood Levels)--Blood levels peaked in 30 seconds following a dose of 2 mg/kg i.v. and about the same time after 1 mg/kg i.v. The levels drowned in 15 minutes and were negligible after 96 hours. After 2 mg/kg p.o., blood levels peaked one hour postadministration.

Dogs (Excretion)--In dogs given 1 mg/kg i.v., 79 percent of the radioactivity was accounted for in the urine and feces after 96 hours. After 2 mg/kg i.v., 89 percent was accounted for in this time period. Urinary excretion peaked in the first 24 hours, whereas in the feces, peak excretion occurred at 24-48 hours. After 2 mg/kg p.o., 81 percent of the dose was excreted in 96 hours by the males and somewhat less by the females.

The urinary recovery of LAAM and its metabolites after 2 mg/kg p.o. is shown in Table XII.

TABLE XII: URINARY EXCRETION OF LAAM AND ITS METABOLITES IN MALE DOGS AFTER ORAL ADMINISTRATION OF 2 mg/kg P. O.

	Cumulative Percent of Dose Excreted In:			
Compound	0 - 24 Hours	24 - 48 Hours	48 - 72 Hours	72 - 96 Hours
LAAM	0.11	0.12	0.13	0.14
N-LAAM	0.09	0.09	0.11	0.14
DN-LAAM	0.09	0.10	0.11	0.11
MOL	0.15	0.20	0.22	0.23
N-MOL	0.03	0.04	0.04	0.05
N-Acetyl-N-MOL	0.10	0.12	0.13	0.13
Total Percent Free				0.72
Total Percent Conjugated				16.77
Total Percent In Urine				17.54

Monkeys (Blood Levels)--After some preliminary dosing, four naive and one morphine-dependent monkey were given 2 mg/kg (i.v.) of H^3 -LAAM. These same animals were used for the oral studies. The highest level of radioactivity was noted one minute after injection. This corresponded to a blood level of LAAM equal to 0.47 ug/ml. There was a rapid decrease in 15 minutes followed by a new peak one hour after injection which corresponded to a drug blood level of 0.35 ug/ml. This was followed by a steady decline in radioactivity which was negligible after 72 hours.

H^3 -LAAM (2 mg/kg p.o.) was given to four naive monkeys and one morphine-dependent monkey. The blood levels of radioactivity appeared in 30 minutes, peaked four to eight hours after drug administration, and were still detectable after 96 hours.

Monkeys (Excretion)--The urines of three female monkeys which were given 2 mg/kg of H^3 -LAAM i.v. were examined. A total of 21.55 percent of the radioactivitv was excreted over a 96-hour period. O f this, 19.11 percent was in the conjugated form, and 2.44 percent was free. The distribution of the radioactivity is summarized in Table XIII. The morphine-dependent monkeys excreted 13.7 percent of the radioactivity in 96 hours.

TABLE XIII: URINARY EXCRETION OF LAAM AND ITS METABOLITES IN FEMALE MONKEYS AFTER ADMINISTRATION OF 2 mg/kg I. V.

	Cumulative Percent of Dose Excreted In:			
Drug	0 - 24 Hours	24 - 48 Hours	48 - 72 Hours	72 - 96 Hours
LAAM	0.86	0.96	1.01	1.03
N-LAAM	0.10	0.19	0.23	0.23
DN-LAAM	0.08	0.21	0.25	0.28
MOL	0.32	0.48	0.52	0.54
N-MOL	0.05	0.14	0.18	0.19
N-Acetyl-N-MOL	0.09	0.15	0.16	0.17
Total				2.44%

Approximately 20 percent or less of the admininistered dose is excreted in the urine of rat, dog, and monkey. Of this amount, most is excreted as conjugates rather than free drug or metabolites. In the male monkey, about 65 percent of the drug is excreted in the feces and about 55 percent for the female.

A better recovery of the drug was noted when 2 mg/kg p.o. was given in an apple rather than by stomach tube. About 92 percent of the radioactivity could be accounted for in 96 hours. Most of this was in the feces. The distribution of H^3 -LAAM and its metabolites in monkey urine is summarized in Table XIV.

TABLE XIV: URINARY EXCRETION OF LAAM AND ITS METABOLITES IN MALE MONKEYS AFTER ADMINISTRATION OF 2 mg/kg P. O.

	Cumulative Percent of Dose Excreted In:			
Drug	0 - 24 Hours	24 - 48 Hours	48 - 72 Hours	72 - 96 Hours
LAAM	0.13	0.15	0.16	0.17
N-LAAM	0.10	0.11	0.12	0.13
DN-LAAM	0.10	0.13	0.14	0.15
MOL	0.09	0.10	0.11	0.12
N-MOL	0.07	0.09	0.10	0.11
N-Acetyl-N-MOL	0.04	0.05	0.06	0.06
Total Free				0.74%
Total Conjugated				12.55
Total				13.29%

As usual, the amount of free LAAM and its metabolites in the urine was very low. The bulk of the metabolites were excreted as conjugates.

Sullivan, Due, and McMahon (1973) reported some preliminary results on the metabolism of a l-alpha-methadol. They used the 2-C^{14} labeled derivative having a specific activity of 14.1 μCi/mg. Bile-cannulated Wistar rats were given 40 mg/kg s.c. and the urine and bile were collected for 24 hours. Unconjugated drug and metabolites were extracted with butyl chloride at pH 9.5. The pH of the body fluids was adjusted to 3.5 and the materials were incubated with gluselase to deconjugate metabolites and these were then taken up in butyl chloride.

After 24 hours, 10 percent of the administered radioactivity was found in the urine and 36 percent was found in the bile. The following were identified in the urine:

- Unaltered 1-alpha-methadol
- 1-alpha-nonethadol (N-MOL)
- 1-alpha-bisnormethadol (DN-MOL)
- l-alpha-6-acetamido-4,4-diphenyl-3-heptanol

The bile had only one major component which appeared to be a conjugate of 1-alpha-6-acetamido-4, 4-diphenyl-3-heptanol. These results suggest that the major biliary excretion product of LAAM itself may be a conjugate of 1-alpha-6-acetamido-4, 4-diphenyl-3-heptyl acetate. However, Henderson (1975b) found that DN-LAAM readily undergoes OtN acetyl migration so that the actual metabolite my be DN-LAAM rather than the N-acetyl derivative.

Kochhar (1975) isolated and identified metabolites of LAAM after incubation of the drug with a microsomal supernatant fraction obtained from liver homogenates of Sprague-Dawley rats and also from the urine of rats which were given the drug intraperitoneally. He identified methadol (MOL), nonnethadol (N-MOL) 2-ethyl, 1, 5-dimethyl-3, 3-diphenylpyrroline, noracetylmethadol (N-LAAM), and dinoracetylmethadol (DN-LAAM). The pyrroline may be an artifact derived from DN-LAAM.

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TOXICOLOGY OF LAAM

Ms. Ann Wolven and Sydney Archer, Ph.D.

INTRODUCTION

Before a new drug can be tested in humans, pre-clinical toxicity studies must be carried out to demonstrate that there will not be an unreasonable hazard to subjects to whom the drug will be administered. Acute and chronic toxicity studies can also demonstrate whether the observed toxic effects are such as to preclude administration of the drug to man and also to alert the clinician to those effects which would require particular attention. For these reasons the doses which are used in toxicity studies are selected so that some toxic effects will be produced.

Toxicity studies are so designed that information will be obtained about the relationship of toxic to effective doses. It must be kept in mind that such studies are not directly translatable to presumed effects in humans. The doses used in animals are much higher than the expected clinical dose. The life spans of man and the test animals are not comparable so that an 18 month chronic study in rats means that the drug is administered for at least half the life span of that species. There is usually a rapid increase in rodent mortality after 12 months so that deaths that occur in the second year of medication may be due to aging, the effects of the drug, or both.

The Food and Drug Administration (FDA) guidelines suggest that at least one rodent and one non-rodent species undergo toxicity tests. In this case, rats and beagle dogs were utilized. Fats are often used in toxicity studies for their test convenience and in addition because of their metabolic closeness to humans. Rabbits and rats are used in reproduction studies because of their reproductive capacity and because of their sensitivity to teratogenic agents.

For these chronic toxicity studies, animals of a given species were divided into four groups: a control group, and low, medium and high dosage groups. Hematological and clinical chemistry evaluations on the four groups were done periodically: e.g.,13 weeks, 26 weeks, 52 weeks, 79 weeks. At the end of each period, some portion of each group was sacrificed for gross and microscopic pathologic examination to determine possible effects of the drug. Postmortem examinations were also performed on animals which died during the experiment.

An additional complication occurs when the test drug is one in which drug tolerance occurs. In such a case tolerance is induced in the medium and high dosage groups by gradually increasing the dosage to the predetermined medim and high dosage level, in order to reach truly toxic levels while avoiding lethal depressant reactions that would occur if such doses were given to naive animals.

The initial chronic toxicity study on LAAM was carried out for one year in rats and dogs at Edgewood Arsenal. Because LAAM was administered for 5 days per week, further studies were carried out by Industrial Biotest wherein the drug was given daily to the test animals for a longer period of time.

ACUTE ORAL TOXICITY OF LAAM IN RATS (Industrial Biotest)

The acute oral toxicity of LAAM was determined in naive albino Charles River male and female rats. The LD_{50} of LAAM in the males was 28.6 mg/kg and in the females it was 35.0 mg/kg. The acute toxicity was determined in tolerant rats also. Rats were made tolerant by starting with a 2.0 mg/kg dose which was increased at two-week intervals until they were receiving 12.0 mg/kg/day. This dose level was maintained for a 13 week period of medication and then the LD_{50} values were determined. The LD_{50} in males was 93.0 mg/kg and in females it was 220.0 mg/kg. Thus prior exposure to the drug had a considerable effect on the acute toxicity of LAAM.

CHRONIC TOXICITY STUDIES

One Year Chronic Oral Toxicity in Rats (Edgewood Arsenal)

In this study Sprague-Dawley albino rats were used. The drug was administered by gavage at dose levels of 5.0, 10.0 and 15.0 mg/kg five days a week for 52 weeks. No induction schedule was employed. After the first 10 weeks all the rats that died during that time period were replaced by fresh rats in order to have a sufficient number of animals for terminal sacrifice and pathological examination. The mortality data is summarized in Table 1. Several rats that died after the first dose of LAAM were found to have intracellular calcification in the heart, liver and kidney. This phenomenon was not observed in any of the animals which died later or in any of the rats in the replacement groups. This effect was not observed in a later Industrial Biotest study. A special study was carried out in an additional group of rats to assess the significance of the intracellular calcification of the heart, liver and kidney observed in the rats dying after the first dose of LAAM in the original study. To this end 75 rats were given 15.0 mg/kg of the drug for 5 days and at the end of that time were sacrificed and examined. None of the animals in this group showed signs of calcification in the previously affected organs. As a result it was concluded that this phenomenon which was noted once was not drug related.

TABLE 1

Mortality of Rats Medicated With LAAM 5 days/week

Original Group	Dose Levels			
	Control	5.0 mg/kg	10.0 mg/kg	15.0 mg/kg
# deaths/treated	4/80	3/40	17/40	52/80
Week of last death	36	4	39	47
Replacement Group				
# deaths at 2 days/treated		0/12	0/24	14/74
# deaths at 38 weeks/treated		0/3	4/12	6/33
TOTAL		0/12	4/24	21/74

All of the test animals on the chronic toxicity study were observed for behavioral reactions and general physical appearance after each daily dosing and prior to the next dosing. Body weights, food and water consumptian and several clinical parameters, including hematology and blood chemistry were measured at specific intervals. A special study was carried out to determine the effect of hepatic N-demethylase on LAAM in vitro. In the latter study it was noted that like meperidine and 1,1-dimethylhydrazine, the two positive controls used in the experiment, hepatic microsomes did demethylate LAAM as evidenced by the production of formaldehyde in the incubation media.

Food and water consumption in all three groups on LAAM was decreased when compared to the control rats but only the decreased food consumption was felt to be dose related. Bloody eyes, and analgesia, as evidenced by a decreased response to pinching of the tail, were observed during the first two weeks of dosing. After that time sensitivity to tail pinching appeared to increase. Piloerection, exophthalmos and the Straub tail phenomenon were present during the entire period of medication. Hematological and blood chemistry values were all within normal limits for both the test and control groups, with the exception of plasma lactic dehydrogenase (LDH) which was higher in the 10.0 mg/kg and 15.0 mg/kg groups than in the controls at both the 6 month period of sacrifice and at the end of the year. After 12 months the LDH values were: 1072 (controls), 1688 (10.0 mg/kg) and 1833 (15.0 mg/kg).

Gross examination of tissues at necropsy and organ weights showed that with one exception there were no significant differences between the treated and control groups. Only the liver/body weight ratios in the female rats at all doses were higher than the controls after completion of medication. Histopathalogical examination of the tissues failed to reveal any incidence of dose related lesions. The most frequent finding was inflammation or congestion of the respiratory tract.

During the first two weeks of exposure to LAAM there was little if any gain in weight by the medicated rats. During the course of the study the rate of gain in weight in the treated groups was greatly retarded and appeared to be dose related. After the first two weeks the dosed rats began to show a weekly cyclic patter" of a large increase in body weight on the first two or three days of the week followed by a loss in weight during the remainder of the week. It is believed that this pattern was related to the fact that after the first weeks of medication the rats became tolerant to and dependent on the drug, because when medication was omitted over the weekend the animals showed withdrawal signs. The most prominent such sign in dependent rats upon abrupt withdrawal of an opiate-like drug is a rapid loss in body weight. Usually this body weight loss can be reversed by renewed administration of the drug.

One Year Chronic Oral Toxicity-
in Dogs (Edgewood Arsenal)

Beagle dogs were medicated by capsule 5 days a week for 52 weeks at dose levels of 2.0, 6.0 and 11.0 mg/kg. Dosing was started at 2.0 mg/kg in all test groups and was then gradually raised in the medium and high level groups until by the end of the sixth week the desired dose levels were achieved. Fourteen dogs served as controls. There were 12 dogs at the low and medium levels and 14 at the high dose.

All of the test animals were examined daily for clinical signs of systemic toxicity. Body weights, food consumption and clinical parameters including hematology and blood chemistry were measured at specific intervals during the course of the medication. Complete physical examinations were performed monthly including electrocardiograms and ophthalmologic exams.

Body weight, food and water consumption decreased for all three test groups. Behavioral reactions were observed at all dose levels and consisted of depression, hind limb weakness, emesis, salivation and prostration. The frequency and intensity of some of these signs decreased as the study progressed. Three dogs died at the high dose level, none at lower levels. Hematology and blood chemistry values in the test groups were comparable to those of the controls. Physical examination revealed the presence of tachycardia, slower reflexes and decreased respiration rates but these did not appear to be dose related. The medicated dogs had rough coats, appeared to be thin and presented a generally unkempt appearance as if they did not do any grooming. Electrocardiogram (EKG) recordings taken immediately after dosing showed an increase in duration of the S-T segment usually accompanied by bradycardia. Seventy-two hours after dosing the EKG tracings were normal. Reversibility can be determined since the dogs were not medicated on the weekend. Other than a large absolute liver weight in the high dose dogs when compared to controls, no other significant differences in organ weights were apparant. Histopathological examination of tissues disclosed no drug related abnormalities. This was true also for the three dogs which died spontaneously during the course of the medications.

79-Week Chronic Oral Toxicity in Rats (Industrial Biotest)

Charles River albino rats were used in this study. The final doses used were 2.0, 6.0 and 12.0 mg/kg administered daily by gavage throughtout the 79 week period of medication. The dose schedule is shown in Table 2.

The middle group (T-11) did not reach the 6.0 mg/kg daily dose until the 9th week and the high dose (12.0 mg/kg) was not reached until the 21st week.

All of the test animals were examined daily for behavioral reactions and general physical appearance including tumor palpation. Body weights, food consumption and clinical paramaters were determined at specific intervals.

tion period all values were in the normal range. Blood chemistry values were essentially normal for the test animals except for some scattered slightly elevated serum alkaline phosphatase (SAP) readings in medicated males. The females were comparable to untreated controls. The serum glutamic-pyruvic transaminase (SGPT) values were essentially normal but the serum glutamic-oxaloacetic transaminase (SCOT) values were slightly elevated in the high dose male and female rats. The albmin/globulin ratios of both male and female animals in the 6.0 and 12.0 mg/kg groups showed a moderate decrease at 52 and 78 weeks. All test females showed a moderate decrease at 52 and 78 weeks. All test females showed a moderate increase in total protein at week 52 but this parameter normalized by the 78th week. The remaining blood chemistry studies were normal.

TABLE 2

Schedule for Administration of LAAM

Group	No. of Animals		Dose Level mg/kg/day Week:					
	Male	Female	1-4	5-8	9-12	13-16	17-20	21-79
Control	110	110	0	0	0	0	0	0
T-I	110	110	2	2	2	2	2	2
T-II	110	110	2	4	6	6	6	6
T-III	110	110	2	4	6	8	10	12

The Body weight gain of all test animals was reduced significantly with the males showing a greater initial reduction, but at the end of the 79th week body weight gain depressions for both sexes were about the same. During the period of recovery the surviving animals at the 6.0 and 12.0 mg/kg dose levels exhibited body weight gains comparable to the controls. The test females consumed less food during the first 27 weeks of the medication period but thereafter their food consumption was the same as the controls.

Observations for phammcological and behavioral reactions during the 79-week treatment period showed that the rats displayed hyperirritability and hyperactivity gradually shifting to hypoactivity. The males in all test groups showed greater hyperirritability than the females. Alopecia and excretion of loosely formed stools were noted in the medicated groups. Hematological parameters for the test and control animals were comparable except for slight varlatlons in total leukocyte and erythrocyte counts in all groups of test animals. At the end of the medica-

The rat mortalities which occurred in this study are shown in Table 3 Also included are the animals which were deliberately sacrificed at 13, 26 and 52 weeks. There was an excessive mortality rate in the control animals between weeks 23 and 26. Mortality in all test groups at the end of week 52 was moderate, but increased markedly from week 52 to week 79. Mortality was high in the control group throughout the test period. In both control and treated groups mortality was higher in the male rats. The vast majority (if not all) of the deaths was attributed to naturally occurring disease characterized by bronchoneumonia associated with metastatic infections and polyserositis. None of the deaths was attributed to the medication but mortality did appear to be related to the length of exposure to LAAM.

There was a significant reduction of absolute organ weights of the livers of the 6.0 mg/kg male rats and of the kidneys of the 6.0 mg/kg and 12.0 mg/kg tiles but the organ to body

TABLE 3

Rat Mortality in the 79-Week Study

Dose Level mg/kg	Sex	Treatment Time Period (wks) Accumulated Deaths 0-52	53-79	Recovery 80-87	Total Mortality Number Tested
Control	M	37	54	4	58/110
	F	18	34	5	39/110
2.0	M	24	69	2	71/110
	F	10	31	3	34/110
6.0	M	16	73	3	76/110
	F	14	35	0	35/110
12.0	M	35	78	0	78/110
	F	27	54	2	56/110

and organ to brain weight ratios were normal and in most instances comparable to the controls. Histopathological changes in the tissue, except for the liver, were judged to be caused by spontaneous disease and were not unusual for the strain and age of the rats.

Treatment related changes were observed in the livers of most of the test animals at all dose levels of LAAM. These changes were characterized by hypertrophy of hepatocytes due primarily to an increase in cytoplasmic mass. The relative extent of the changes could be correlated with the dose of the drug and duration of treatment. These changes were considered to be an adaptive response of the hepatocytes to the metabolism of LAAM. A separate study demonstrated that there was an increase of microsomal enzyme activity in rats receiving LAAM. (A similar observation was made in the Edgewood Arsenal study). During the recovery period surviving rats were sacrificed the first and second months after cessation of medication. Marked but not complete regression of the hepatocyte hypertrophy was noted.

The remaining organ changes observed at each sacrifice interval were judged to be related to naturally occurring diseases or associated with the age of the animals at autopsy. These changes were present in the control as well as medicated groups, The types of tumors present in all groups were not unusual for a random population of the strain of rats used and there were no significant differences in numbers between test and control groups.

52-Week Chronic Oral Toxicity in Dogs (Industrial Biotest)

LAAM was administered orally, via gelatin capsule at final dose levels of 2.0, 4.0 and 8.0 mg/kg seven days a week for one year A fourth group served as controls. The medication schedule is shown in Table 4.

An initial dose of 4.0 mg/kg produced severe reactions, particularly sedation. Gradually increasing the dose from 0.5 mg/kg to 4.0 ng/kg over a twelve week period resulted in the production of only slight reactions to the drug, i.e. tolerance developed. Increased tolerance to the drug developed at all dose levels. Only one high (8.0 mg/kg) and one low (2.0 mg/kg) dose level male died at 26 and 49 weeks respectively. Neither death was considered to be drug related.

All of the test animals were examined daily for clinical signs of systemic toxicity, particularly after dosing, Body weight, food consuption and clinical parameters were measured at specific intervals during the medication period. Opthalmological examinations and EKG recordings were made.

Food consumption during the first six months was similar for both treated and control groups. In the latter half of the study there was a noticeable increase in food intake in the treated groups which was not reflected in a corresponding increase in body weight. When the dogs became tolerant to LAAM their weights were comparable to that of the controls.

TABLE 4

Medication Schedule For LAAM in Dogs

Group	Dose (mg/kg/day)	Weeks at dose level
T-I	0.5	1-4
	1.0	5-20
	2.0	21-52
T-II	0.5	1-4
	1.0	5-8
	2.0	9-12
	4.0	13-52
T-III	0.5	1-4
	1.0	5-8
	2.0	9-12
	4.0	13-16
	6.0	17-20
	8.0	21-52

Behavioral reactions were observed in the animals at the 4.0 and 8.0 mg/kg doses. These consisted of salivation, hyperactivity, vomiting and sedation. Increased tolerance to the drug occurred at all dose levels. The hematological parameters remained normal throughout the study. The only change in blood chemistry was a slight elevation of the serum alkaline phosphatase (SAP) levels at the 4.0 mg/kg and 8.0 mg/kg dose levels. These returned to normal during the 4 week recovery period.

Electrocardiogram tracings during the early stages of the study showed some T-wave and S-T changes, some tachycardia at the 4.0 mg/kg dose level. At 8.0 mg/kg QRS complex irregularities were observed and significant S-T and T wave changes as well as significant rate and rhythm disturbances were noted. These changes were present on later tracings but no further deterioration occurred. The tracings made during the 4-week recovery period were considered to be within normal limits. Histopathological examination of cardiac tissue at necropsy showed no significant abnormalities. Gross and histopathological examination of other organs and organ weights disclosed no significant differences between treated and control groups.

REPRODUCTIVE STUDIES WITH LAAM (Industrial Biotest)

Teratogenic Studies

1. Non-tolerant Rabbits

LAAM was administered orally via gelatin capsules to non-tolerant, pregnant, New Zealand rabbits at doses of 0.2, 0.6 and 2.0 mg/kg from day 6 through day 18 of gestation. A slight weight loss occurred during the treatment period but it was comparable to the untreated and thalidomide-treated control groups. No deaths or unusual reactions occurred. All dams were sacrificed on day 29 of the gestation period. Fetal examination revealed no external, internal or skeletal teratogenic abnormalities among the fetuses of the LAAM-treated rabbits and untreated controls. The thalidomide controls yielded the expected anomalies. The numbers of resorption sites and live young per 100 implantation sites was similar for LAAM and unmedicated controls. Body weights of fetuses from treated and untreated dams were comparable also.

2. Tolerant Rabbits

Rabbits were made tolerant to LAAM by administering the drug over a twelve week period

starting with 2.0 mg/kg/day and incrementally increasing the dose until the desired levels were reached. Then doses of 6.0, 8.0 and 10.0 mg/kg/day of LAAM were given to three groups of tolerant animals from day 6 to day 18 of gestation. A decrease in body weight was noted at the two higher dose levels and some non-dose related deaths occurred. It is concluded that pre-natal exposure to LAAM did not alter fetal skeletal development as compared to unmedicated controls. The number of implantation sites, resorption sites and live young were not adversely affected by LAAM.

3. Tolerant Rats

Rats were made tolerant to LAAM by gradually escalating the doses from 2 mg/kg/day to 12.0 mg/kg/day over a period of 90 days. The dose levels of LAAM were 2.0, 6.0 and 12.0 mg/kg/day administered to day 20 of gestation. The drug had no effect on the numbers of corpora lutea, implantation sites, resorption sites and viable fetuses. There was no effect on external and internal development but there was an increased incidence of angulated ribs among fetuses obtained from dams exposed to 6.0 and 12.0 mg/kg/day. No other skeletal abnormalities were found.

Perinatal and Lactation Performance in Albino Rats

0.06, 0.20 and 0.60 mp/kg to non-tolerant pregnant rats from day 15 of gestation throughout the period of lactation. A total of 28 or 29 doses were used. All dams were allowed to deliver their litters and carry them through weaning. In the cross-over portion of the study litters from the 0.6 mg/kg/day test group were exchanged with a control group with both dams carrying their litters through weaning.

In the first phase of this study no deaths occurred and no unusual behavior was observed. Only the dams at the 0.60 mg/kd/day dose showed a reduction in body weight from day 15 of gestation through day 4 of lactation. This dose group retained fewer pups than the controls but the difference did not appear to be statistically significant. The high dose group did show a statistically significant reduction in survival of the pups and reduction in body weight as lactation progressed. During the cross-over study both groups of dams exhibited a reduction in the number of pups surviving to weaning. The groups of pups exposed to LAAM in utero and reared by control dams revealed slightly meduced body weights through day 21. Pups untreated in utero but reared by treated dams also showed slightly reduced body weights.

Reproduction and Progeny Cross-over Studies in Tolerant Rats

Using the same dosing schedule described in Section A-3 above it was noted that body weight reductions and hyperirritability occurred in a dose related manner in both sexes. Mating experiments showed that there was no difference in reproductive performance among treated animals as compared to controls.

Female rats exposed to LAAM showed an increased number of stillbirths. Following delivery litters from drug treated rats were exchanged for litters from control rats and the progeny remained with the foster mothers tnrougnout the lactation period. Concurrent groups of progeny delivered by treated and control rats were retained by their natural mothers. Survival of each group of progeny exposed to LAAM was reduced during lactation. Progeny fostered by LAAN-treated rats did not exhibit as great a reduction in survival as those pups; exposed to the drug in utero and then fostered by non-treated rats or those delivered and retained by LAAM-treated mothers.

The body weights of progeny exposed to LAAM in utero and then fostered by unmedicated mothers were similar to drug-free controls. Those not exposed in utero but fostered by treated mothers showed reductions in body weight. Progeny delivered and retained by drug-treated rats showed body weight reductions only on day 1 and 4 of lactation. By day 12 of lactation only 1 litter was viable and at weaning these 4 pups displayed weights equal to that of the untreated controls.

DISCUSSION:

Methadone and LAAM were developed in the 1940's as analgesics. Although acute toxicological studies had been performed, relatively little animal toxicological data is available on subacute or chronic toxicity in the tolerant animal. Therefore, these current studies were performed because the drugs are now being utilized or proposed for long term, high dose maintenance in man. Because LAAM is being developed as an alternative to methadone, it is appropriate to compare the toxicological effects of both drugs in the same species.

Only one previous study reported toxicological data for LAAM. (A.S. Keats and N.K. Beacher, Analgesic activity-and toxic effects of acetylmethadol isomers in man, Journal of Pharmacology and Experimental Therapeutics, 105:210-215. 1952). The authors report that Merck and Company studies found that racemic-levo- and dextro-forms of acetylmethadol have a subcutaneous LD_{50} in mice of about 40 mg/kg. The levo- form exhibited delayed onset of toxicity.

In comparison, the subcutaneous LD_{50} of racemic methadone (the form used clinically) in mice is 33-48 mg/kg. (National Research Council Handbook of Toxicology, 1956, pp. 186-187). Although previous data is not available for LAAM in other animals or by other routes of administration, several studies have been performed for methadone. In the mouse, the following LD_{50}'s have been noted: oral 93.8 mg/kg, i.v., 17.3-9 mg/kg. In the rat, the following LD_{50}'s are reported: oral 90-95 mg/kg, subcutaneous, 45-48 mg/kg, and intravenous 9.2-14.6 mg /kg In the monkey subcutaneous LD_{50} of 10-20 mg/kg was reported No studies previously reported evaluated the LD_{50} or chronic toxicity for methadone or LAAM in animals dosed chronically. In the studies supported by NIDA, Industrial Biotest carried out similar studies using similar protocols in the same laboratory simultaneously with methadone and LAAM. These studies utilized the oral route of administration which is used clinically in man.

The LD_{50} of methadone in non-tolerant male rats was 94.0 mg/kg and 102-0 mg/kg in females. The corresponding values for LAAM were 28.6 mg/kg for males and 35.0 mg/kg for females. In tolerant male rats the methadone LD_{50} was 102 mg/kg in males and 114 mg/kg for females. The LAAM values in tolerant rats were 93.0 mg/kg for males and 220.0 mg/kg for females.

In the case of methadone there was no sex difference in toxicity in either naive or tolerant rats nor were there significant differences between naive and tolerant rats. In the case of LAAM there was a slight difference between sexes in the non-tolerant animals but a much larger difference in the tolerant ones.

Of even greater interest is the fact that tolerant animals of both sexes were less sensitive to the acute toxic effects of LAAM given orally than naive rats, whereas no such difference occurred with methadone. An explanation for this finding requires further study.

Although LAAM and methadone are structurally similar there are major differences in their metabolism and pharmacokinetic behavior. The major metabolites of LAAM are two N-demethylated derivatives, nor-LAAM and bisnor-LAAM which persist in the animal for long periods of time and are almost certainly responsible for the long duration of the pharmacological effects of LAAM. In contrast the metabolic products of methadone do not persist and probably contribute little to its pharmacological action.

In the Edgewood Arsenal rat and dog chronic toxicity studies, the animals were medicated for five rather than seven days a week and the duration of each study was 52 weeks. Because the dosage regimen may have influenced the toxicity findings, and in view of the non-reproducible organ calcifications which appeared after the initial dosing in rats, it was considered advisable to perform other chronic toxicity studies, using a seven day dosage regimen.

A Toxicity panel consisting of outside consultants was constituted to act as advisors to NIDA, review data and generally oversee the progress of the new chronic toxicity studies of LAAM and methadone, run simultaneously in the same laboratory (Industrial Bio-Test).

An 80-week chronic toxicity study in rats was carried out using gradually increasing doses of methadone to reach the final doses of 5, 10 and 15 mg/kg/day of methadone, 7 days a week. The protocol and design of the study resembled the LAAM experiment. The mortality ata for methadone is summarized in Table 5.

The above mortality also includes animals which were deliberately sacrificed and thus is comparable with Table 3. The dosages in both protocols are approximately the same, there was a greater mortality in males in both studies and a great number of animals died after the first year of treatment. In both studies a large number of animals died and the cause of death for LAAM, methadone and control animals was attributed to naturally occurring respiratory infections and are not drug related.

On the basis of mortality figures alone, in tolerant rats LAAM does not appear to be more toxic than methadone. In both studies the drugs were administered daily whereas it is anticipated that in man LAAM will be given three times a week with an average weekly intake of 180 to 240 mg. The average weekly intake of methadone is about 350 mg.

Hepatic changes were noted in both the LAAM and methadone studies. Separate experiments showed that administration of either drug induced an increase in N-demethylase activity. Such a phenomenon is commonly encountered on chronic administration of many drugs such as phenobarbital and diazepam which are subject to hepatic metabolism. In the case of methadone hepatic changes reverted to normal within one month of cessation of treatment. Recovery was not complete two months after LAAM treatment was stopped, but definite signs of normalization were apparent. The difference in metabolic behavior of the two drugs may account for this difference.

TABLE 5

Frequency and Distribution of Deaths in Rats Treated With Methadone

Group and Dose Level	Sex	Accumulated Deaths in Treatment Period 52 weeks	80 weeks	Recovery	Total Mortality Total Treated
Control	M	33	62	6	68/110
	F	12	29	5	34/110
5 mg/kg/day	M	39	65	4	69/110
	F	15	37	1	38/110
10 mg/kg/day	M	37	68	2	70/110
	F	15	30	5	35/110
15 mg/kg/day	M	58	77	1	78/110
	F	48	JO	0	70/110

Changes in the electrocardiogrm tracings of dogs on the middle and high dose levels of LAAM were noted in the Edgewood Arsenal and Industrial Bio-Test Studies. Owing to the medication schedule in the former study the reversibility of these changes could be observed. This could not be seen in the latter study, but four weeks after medication the EKG tracings in the Industrial Bio-Test experiment were essentially normal. Histopathological examination of cardiac tissue revealed no drug related abnormalities. However. in view of these findings careful attention was paid to the possibility of cardiotoxic effects of LAAM in the Phase I and Phase II clinical trials. No evidence of cardiotoxicity in man has been found to date.

Teratogenic studies were carried out in naive and tolerant rabbits and in tolerant rats. The highest dose used in naive rabbits was 2.0 mg/kg/day but it was possible to go to 10 mg/kg/day in tolerant rabbits. In both experiments no embryotoxic or teratogenic effects were observed. In tolerant rats the only abnormality noted was an increased incidence of angulated ribs at the middle and high dose levels.

Reproduction, perinatal and lactation performance studies with progeny cross-over were carried out in LAAM nontolerant and tolerant rats. The effects seen in the nontolerant animals were similar to but of lesser magnitude than those observed in the tolerant rats.

In the studies with tolerant rats the drug treated group evidenced an increased number of stillbirths, a decrease in progeny during lactation, and lower body weight of the progeny, although the weights were within the normal range. The cross-over studies indicated that in utero exposure to LAAM was the main cause for the decreased progeny survival. These findings would appear to be consistent with the effects of large, repeated doses of a narcotic drug, resulting in fetal LAAM exposure and neonatal dependence via placental transer. The decrease in progeny survival could be related to narcotic withdrawal during the neonatal period. The increase in number of stillbirths was also found in sinilar studies with methadone. The decrease in progeny survival and lowered birth weight is consistent with clinical observations for infants born to heroin and methadone dependent women.

On the basis of the toxicological studies carried out thus far it can be concluded that when the human dose regimens are taken into account the toxicity of LAAM and methadone are comparable in tolerant animals. The hepatic changes that were found are in all probability an adaptive response of the hepatocytes to the metabolism of both drugs.

The major difference between the two drugs is the greater sensitivity of non-tolerant animals to the toxicological and pharmacological effects of LAAM by the oral route. The difference should be kept in mind when LAAM is to be administered to humans.

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CLINICAL STUDIES

PHASE I

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Clinical studies on LAAM were conducted as early as 1952. Most investigations with the drug in the 1950's tested the use of LAAM as an analgesic. However, in the late 1960's and early 1970's, an interest developed in this drug as an alternative to methadone in the treatment of heroin addiction. These studies preceded the Phase II clinical trials on LAAM initiated by SAODAP in 1973. Here they are grouped as Phase I studies. Table XVII, provides a list of LAAM Preclinical, Phase I, and Phase II clinical investigators.

PHASE I S'IUDIES--CROSS S'IUDY SUMMARY OF FINDINGS

This section provides a comprehensive summary of clinical studies on LAAM exclusive of the current VA/SAODAP Phase II clinical trials. The summary has been organized into the following sections:

Pharmacokinetics
Clinical Pharmacology
Controlled Clinical Studies
Other Clinical Studies
Summary of Toxicity-Safety Findings and Observations

The sumnary of toxicity-safety findings and observations covers all clinical studies prior to Phase II (1952-1974).

Pharmcokinetics

The delayed onset and long duration of action of 1-alpha-acetylmethadol has been attributed to its biotransformation to two active metabolites, noracetylmethadol (N-LAAM) and dinoracetylmethadol (DN-LAAM) (Billings et al. 1974a). Other products of metabolism are methadol (MOL) and normethadol (NMOL) which are the result of deacetylation.

LAAM has two methyl groups attached to nitrogen, $-N<^{CH_3}_{CH_3}$. These are N-demethylated by N-demethylating enzymes in vivo to 1-alpha-noracetylmethadol by the removal of one methyl group and its replacement by hydrogen. This, in turn, may be converted to a di-nor form by the enzymatic removal of the second methyl group and its replacement by hydrogen (Billings 1974a). The demethylating enzymes are located in the liver and, hence, account for the more rapid onset of action of LAAM when orally administered , and also explain the delayed onset of effect when LAAM is administered intravenously, intramuscularly, and subcutaneously (Fraser 1952).

Techniques for identifying and quantitating plasma and urine levels of acetylmethadol and its metabolites in human biofluids have been developed by Kaiko and Inturrisi (1973). Plasma and urine samples were obtained from patients receiving maintenance dose of LAAM (level unspecified) for treatment of heroin addiction. Peak plasma levels of acetylmethadol were found to occur at four hours postadministration and had nearly disappeared at 24 hours. N-LAAM plasma levels peaked in four-eight hours and declined slowly over the next 40 hours. DN-LAAM levels remained constant during the dosing interval. The time cource of pupillary effect was found to be related to the plasma levels of the active metabolites. (Kaiko and Inturrisi 1975, in press). Henderson (1974, 1975) has found the time course of peak plasma levels of LAAM and its metabolites (N-LAAM and DN-LAAM) following acute administration of 60 mg LAAM to be similar to those for racemic

Table XVII(1) PHASE I STUDIES

Principal Investigator	Research Institute	Project Number
NIDA		
Frank Adler	Public Health Institute New York State	DA-00120
Mary J. Creek	Rockefeller University New York, New York	DA 1138
Jack Findley	University of Maryland, School of Medicine Baltimore, Maryland	DA-00123
Max Fink	New York Medical College New York, New York	HSM-42-72-207
Louis J. Glunz	Regis Chemical Co. Morton Grove, Illinois	HSM-42-72-124
Avram Goldstein	Addiction Research Foundation Palo Alto, California	R01-DA-00923
C. Gorodetzky	Addiction Research Center Lexington, Kentucky	R01-DA-00044
Louis Harris	Medical College of Virginia Richmond, Virginia	DA 000578
Gary Henderson	University of California, Medical School Davis, California	R01-DA-00284, R01-MH-22088
Charles Inturissi	Cornell University, Medical College New York, New York	DA 00297, DA 02458
Samuel Irwin	University of Oregon, Medical School Portland, Oregon	HSM-42-72-209
Gerald Kennedy and M. L. Keplinger	Industrial Bio-Test Labs, Inc. Northbrook, Illinois	HSM-42-72-171
Naim Khazan	Narcotic Addiction Control Comm. New York State	DA 01050
Keith Killam	University of California, School of Medicine Davis, California	HSM-42-73-263
Walter Levine	Albert Einstein Medical College Bronx, New York	R01-DA-00456
Roger P. Maickel	Indiana University Indianapolis, Indiana	HSM-42-73-226
Duncan A. McCarthy	Parke-Davis & Co. Ann Arbor, Michigan	HSM-42-72-167
Charles Savage	Maryland Psychiatric Research Center Baltimore, Maryland	R01-DA-00415 R01-MH-22973
Charles Schuster	University of Chicago Chicago, Illinois	DA-00047
Janet L. Stickney	Michigan State University East Lansing, Michigan	R01-DA-00962
J. Volavka	New York Medical College New York, New York	DA-00073
M. Wall	Research Triangle Institute Research Triangle Park, N. Carolina	HSM-42-73-184
SAODAP		
Raymond Houde	Sloan-Kettering Institute New York, New York	DA 4PG016
Robert F. Kaiko	Cornell University Medical College New York, New York	DA 3AA571
U.S. Army		
H. K. Beecher and A. S. Keats	Harvard Medical School of the Massachusetts General Hospital Boston, Massachusetts	DA-49-MD-007-76

Principal Investigator	Research Institute	Project Number
SAODAP (To be assumed by NIDA)		
Torrey C. Brown	Man Alive Research, Inc. Baltimore, Maryland	DA 01382-01
William A. Hargreaves	Langley Porter Institute, University of California San Francisco, California	DA 01388
Willard L. Harrison	Virginia Commonwealth University Medical College Richmond, Virginia	DA 01397
Alfred Howe	Suffolk County Narcotic Addiction Control Commission Hauppage, New York	DA 01394
C. James Klett	VA Hospital Perryville, Maryland	DA 01383
Walter Ling	VA Hospital Sepulveda, California	DA 01391
Sardashiv Parwatikar	Division of Mental Health Jefferson City, Missouri	DA 01386
Vernon D. Patch	Harvard Medical School Boston, Massachusetts	DA 01390
Beny J. Primm	Addiction Research and Treatment Corporation Brooklyn, New York	DA 01396
Richard B. Resnick	New York Medical College New York, New York	DA 01395
Arnold Schecter	Research Foundation of SUNY Stonybrook, New York	DA 3AC711
Jacob Schut	W. Philadelphia Community Mental Health Consortium Philadelphia, Pennsylvania	DA 01385
Edward Senay	University of Chicago Chicago, Illinois	DA 01389
Timothy Sharma	Texas Research Institute of Mental Science Houston, Texas	DA 01384
Zebulon Tainter	E. J. Meyer Memorial Hospital Buffalo, New York	DA 01393
Vincente Tuason	St. Paul-Ramsey Hospital Medical Center St. Paul, Minnesota	DA 01392
SAODAP (continued)		
Thomas Ungerleider	University of California School of Medicine Los Angeles, California	DA 01387
Arthur Zaks	International Association for Psychiatric Research Great Neck, New York	DA 01398
VA		
Voraldat Charuvastra	VA Hospital Los Angeles, California	
Julian A. David	VA Hospital Brooklyn, New York	
Edward T. Frank, Jr.	VA Hospital New Orleans, Louisiana	
Clarita Herrera	VA Hospital New York, New York	
Ruth Huggins	VA Hospital Allen Park, Michigan	
Isham Kimball	VA Hospital Dallas, Texas	
A.E. Kyle-Vega	VA Hospital Martinez, California	
Suhas Lahiri	VA Hospital St. Louis, Missouri	
Joseph McFadden	VA Hospital Atlanta, Georgia	
Charles P. O'Brien	VA Hospital Philadelphia, Pennsylvania	
John Prusmark	VA Hospital Palo Alto, California	
Richard Wang	VA Hospital Wood, Wisconsin	

Table XVII(2) PHASE II STUDIES

acetylmethadol: LAAM, 6 hours; N-LAAM, 2-6 hours; DN-LAAM 2-48 hours. After 90 days, a dose level of 85 mg of LAAM three times weekly was attained. LAAM plasma levels were only slightly higher than initially while N-LAAM and DN-LAAM levels were 5-10 times higher. Billings et al. (1974) found that DN-LAAM levels were substantially higher after repeated doses of LAAM, while LAAM and N-LAAM levels tended to remain the same.

Goldstein (1975 unpublished) found that plasma levels of LAAM were very low at 72 hours postadministration in patients maintained on LAAM; the plasma levels of N-LAAM and DN-LAAM, on the other hand, increased from 24 to 48 hours and were almost as high at 72 hours as at 48 hours. This is consistent with the proposition that it is the active metabolites which are responsible for the long duration of action of LAAM: the dosage was "holding" at 72 hours when LAAM plasma levels were practically nonexistent and N-LAAM and DN-LAAM plasma levels were still high.

The active metabolites of LAAM play a central role in the profile of action of this compound. An appreciation of their role is helpful in understanding the slow onset, long duration of action, and cumulative effects which have been observed.

In addition, individual variations in the rates of formation and elimination of these compounds have been noted (Billings et al. 1974 a; Kaiko and Inturrisi 1975, in press). Goldstein (1975 unpublished) has also found a great deal of variation among individuals in LAAM plasma levels (from 15 to 170 ng/ml at 24 hours postadministration). DN-LAAM levels also varied considerably among patients from undetectable (<30 ng/ml) to 278 ng/ml at 72 hours postadministration.

These individual variations with respect to the metabolism of LAAM may help to explain the differences in response which have been observed among LAAM patients in therapy. The extent of individual variability in the metabolism of this compound appears to be an important factor which should be taken into consideration in the formulation of dosage levels and intervals. Several pharmacokinetic studies are currently investigating these clinical issues.

Clinical Pharmacology

LAAM investigational studies on clinical pharmacology have been summarized below under four areas: (1) analgesic activity, (2) relief of abstinence syndrome (withdrawal), (3) opiate effects, and (4) cross tolerance.

(1) Analgesic Activity--Early interest in the acetylmethadols centered around their appropriateness for use as analgesics. Clinical trials were undertaken to evaluate the potential of these compounds as substitutes for morphine.

David et al. (1952) found that 20-30 mg of racemic alpha-acetylmethadol, administered orally and subcutaneously, relieved chronic pain for four to five hours and bad a cumulative effectiveness which enabled patients to skip doses in some instances.

Keats and Beecher (1952) in clinical trials with the levo isomer (LAAM) administered subcutaneously found it to be less effective as an analgesic than morphine. LAAM administered subcutaneously in a dose of 20 mg/70 kg produced analgesia within 90 minutes, but the analgesia was less than that produced by 10 mg of morphine. By extrapolation they estimated that 50 mg of LAAM would be needed to equal 10 mg of morphine in efffectiveness. They did not find the duration of action of LAAM to be longer than that of morphine. Cumulative toxic effects were noted after administration of LAAM, and coma occurred in four patients at dose levels below the estimated equivalent effective dose. They concluded that the margin of safety of this drug was too small to encourage its use as an analgesic.

There were subsequent interest in the analgesic potential of noracetylmethadol. Gruber and Baptisti (1962) found that oral doses of noracymethadol were three and one-fourth times as potent as morphine and also had fewer undesirable side effects.

Houde et al. (1962) found that noracetylmethadol subcutaneously administered was equivalent to morphine in 8 and 16 mg doses and had a similar duration of action.

The analgesic potential of the acetylmethadols has not been of interest currently and the results of the early studies, while of historical interest do not have particular relevance to the consideration of LAAM as a substitute for methadone in the treatment of heroin addiction. Adverse experiences and side effects noted in the course of these clinical investigations will be of interest in a consideration of the evidence pertinent to the safety of the drug to follow later in this summary.

(2) Relief Of Abstinence Syndrome (Withdrawal)--The early clinical investigations of Fraser and Isbell (1952) with alpha-acetylmethadol included the racemic form of the compound, as well as both optical isomers.

While only dl- and 1-alpha-acetylmethadol have been of clinical interest as substitutes for methadone in the treatment of heroin addiction, some findings on the dextro isomer are discussed herein to provide a perspective of the background of the development of interest in LAAM.

Fraser and Isbell (1952) investigated the potential of dl-, l-, and d-acetylmethadol to relieve withdrawal symptoms after abstinence from morphine. They found that 15-50 mg doses of dl-acetylmethadol administered subcutaneously between the 28th and 34th hours of abstinence from morphine brought relief from the abstinence syndrome within two hours and that relief of symptoms was complete after a second dose. d-acetylmethadol, on the other hand, was less effective than methadone in relieving abstinence syndrome. Fifteen-twenty mg doses of d-acetylmethadol administered subcutaneously at the 28th and 32nd hours of abstinence brought little relief; with 30-40 mg doses, relief was marked. Oral administration of the d-isomer resulted in a less rapid onset of action and less pronounced effects. Doses of d-alpha-acetylmethadol sufficient to suppress all signs of abstinence resulted in the development of toxic symptoms.

1-alpha-acetylmetbadol, on the other hand, was more effective than the parent compound, d-methadone, in relieving abstinence. One mg of LAAM was equivalent to 6-8 mg of methadone. Thirty mg of LAAM administered subcutaneously bad inconsistent results with respect to relief of abstinence; however, 30-60 mg administered orally completely abolished all signs of abstinence.

Fraser and Isbell (1952) also found that withdrawal from LAAM resulted in a mild but definite abstinence syndrome, similar in course and intensity to that following withdrawal from methadone. There appeared to be no significant difference in abstinence syndrome following either abrupt or gradual withdrawal from LAAM.

Suppression of abstinence syndrome with LAAM was of long duration. Sixty mg of LAAM administered orally was shown to be sufficient to prevent abstinence syndrome for 72 hours. Mild but definite abstinence symptoms did not appear until 84 hours postadministration. Significant withdrawal symptomes were not manifested until the interval was extended to 96 hours.

Levine et al. (1973) found that 20-50 mg doses of LAAM resulted in discomfort 48-72 hours posttreatment, 70 mg doses produced mild abstinence syndrome 60-72 hours posttreatment. and 80 mg doses prevented abstinence syndrome completely for 72 hours.

Subsequent clinical research has confirmed the ability of LAAM to prevent the development of withdrawal syndrome for long periods.

(3) Opiate Effects--Several investigators have established data on the onset, peak, and duration of opiate effects following administration of the acetylmethadols.

Fraser and Isbell (1952) used subjects who were formerly addicted to morphine and withdrawn ("post-addicts") to evaluate the effects of single doses of racemic acetylmethado1 and both isomers.

dl-alpha-acetylmethadadol produced morphine-like effects which included increased psychomotor activity, somnolence, garrulousness, pupillay constriction, itching, scratching, nausea, and insomnia. Fifteen-forty mg of dl-acetylmethadol administered subcutaneously produced morphine-like effects in 30 minutes which persisted for 24 hours.

The d-isomer produced morphine-like effects which were subjectively pleasing to the patients in 15 minutes following subcutaneous administration of single 5-20 mg doses. The duration of action was 24 hours. Twenty mg doses of d-alpha-acetylmethadol administered orally bad no effects on any patients tested.

Single ten-thirty mg subcutaneous doses of 1-alpha-acetylmetbadol bad a delay in onset of action of four-six hours. Effects were slow to appear (14 hours in some cases) and were always evident at 24 hours, usually evident at 48 hours, and occasionally evident at 72 hours postadministration. Thirty mg of 1-alpha-acetylmethl administered intravenously bad effects which were the same as those following subcutaneous administration. Thirty-forty mg of 1-alpha-acetylmethadol administered orally had a more rapid onset of action than that following subcutaneous or intravenous administration, effects being evident in one and one-half hours and persisting in all cases for 24 hours and in some cases for 72 hours.

The time course of miotic effects (decrease in pupillary diameter) was shown to parallel that of other drug effects. Following oral administration of the levo isomer, pupillary miosis began in 2 hours and was maximal in 4 hours with a return to baseline measures at 24 hours. Following subcutaneous and intravenous administration of the levo isomer, pupillary constriction appeared more slowly, was more intense, and lasted longer (48 hours),

Fraser et al. (1954) confined earlier find-

ings of more rapid onset of action following oral rather than subcutaneous administration of LAAM. Miotic effects were observed to last 72 hours and the time course of these effects were related to patient subjective reports of "euphoria." Oral administration of LAAM produced an earlier, more intense euphoria which diminished more rapidly than that following subcutaneous administration. Miosis correlated with the delay of abstinence until three days postadministration, but did not correlate well with analgesic actions of the drug.

In an unpublished study using nonaddicted subjects, Irwin, Blachly, Marks and Carter administered .2 mg/kg of LAAM and methadone orally and observed that the profile of action following acute administration was the same for both drugs. Peak effects, measured by the Irwin Comprehensive Humans Assessment Procedures, occurred in four hours and the duration of action of LAAM was not significantly longer than that of methadone. The period of observation was 10 hours. The only significant difference in effects were reductions in wakefulness and attentiveness following administration of LAAM.

In another unpublished study, Irwin, Kinohi, Cooler and Bottomly (1973) administered .8 mg/kg and .16 mg/kg oral doses of LAAM and .1 mg/kg and .2 mg/kg oral doses of methadone to nonaddicted subjects. Peak effects occurred three hours posttreatment with both drugs. The duration of action of LAAM was over 24 hours; that of methadone was 12 hours. The higher dose of LAAM produced effects similar to but less intense than those produced by the lower dose of methadone. LAAM and methadone produced bi-phasic effects which were: early activation, elevation of mood, and liking for the drug followed by later depressant effect and dislike of the drug. The effects of LAAM were primarily activating while those of methadone were generally depressant.

Levine et al. (1973) administered 100 mg doses of LAAM to heroin-addicted subjects and evaluated the effects on pupillary diameter. Twenty mg of LAAM produced maximum miosis in 24 hours. Greater doses of LAAM produced no further constriction; 30-50 mg doses sustained maximum constriction for 48 hours, and 80-90 mg doses sustained maximun constriction for 72 hours.

(4) Cross Tolerance--The ability of LAAM to provide blockade to the effects of heroin and the dose levels necessary for complete blockade have been studied by several investigators. Irwin, Blachly, Marks, and Carter (unpublished) studied the development of cross tolerance to 30 mg morphine sulfate in LAAM-maintenance subjects. It was found that most subjects experienced a slight rush after administration of morphine and could distinguish morphine from placebo. Responses were unrelated to levels of LAAM doses. One subject receiving 20 mg of LAAM showed a marked response to morphine injections, while subjects receiving 30, 85, and 140 mg doses all showed slight euphoric responses. Occasionally, a slight "high" was reported, usually either during the earlier (3-8 hours) or later (52-54 hours) intervals postadministration. LAAM was usually, but not always, effective in suppressing the effects of morphine.

Levine et al. (1973) undertook a study to determine the dosage of LAAM which is required to provide blockade to 25 mg heroin using heroin-addicted subjects who were detoxified and drug free at least seven days before the experiment. Patients were started on 10 mg of LAAM three times a week and dosages were increased by 10 mg per week up to 100 mg. Heroin challenges were performed at 72 hours after administration of varying doses of LAAM. At dose levels of 30 mg LAAM, four of six subjects reported some effects of heroin and two felt none. At dose levels of 50 mg, no effect of heroin was perceived and at dose levels of 70 and 100 mg LAAM blockade was complete.

Zaks et al. (1972) found that three of four subjects receiving 30-40 mg doses of LAAM responded to challenge with 50 mg heroin 24 hours after administration of LAAM with mile, transient euphoria, while blockade was complete in the fourth subject. All subjects receiving 80 mg of LAAM demonstrated complete blockade to 50 mg of heroin at 24 hours: one subject was challenged at 48 hours postadministration and demonstrated complete blockade to heroin.

Controlled Clinical Studies

Clinical trials prior to Phase I have provided some evidence as to the safety and effectiveness of LAAM as a substitute for methadone in the treatment of heroin addiction. A review of the studies undertaken and their results pertinent to the effectiveness of LAAM as a substitute for methadone will be presented here. Discussion of data from these studies pertinent to the safety of LAAM will be presented in the section titled Summary of Toxicity-Safety Findings and Observations. A summary of all controlled clinical studies prior to Phase II is presented in table XVIII, which follows this page

The term "controlled clinical studies" as used here refers to all studies in which a control group, i.e., a group of patients who are taking methadone, is used to provide a basis for comparison of outcomes with the LAAM-treated group. The study design may be open, where the patients are aware of the medication they are receiving; blind, where the patients are unaware of the medication they are receiving and are given placebo in place of active medication on nondrug days; or double-blind, where the identity of the medications which patients receive is not known to patients or the staff who administer the medication and evaluate the results.

The following section will discuss other clinical studies which likewise may be open or blind, but in which no control group is used.

The first clinical trial (Jaffe et al. 1970) was a double blind study of the effectiveness of dl-alpha-acetylmethadadol as a substitute for methadone in the treatment of 21 patients. Doses were administered in the ratio of 1.2 mg of dl-alpha-acetylmethadol to 1 mg of methadone. At 24 and 48 hours postadministration, there was no change from baseline measures on the Addiction Research Center Inventory (ARCI) and a withdrawal symptom checklist. At 72 hours, there was a slight rise in the opiate withdrawal subscale of the ARCI; however, there were no complaints on the checklist or in interviews with experimenters. Ninety-six hours postadministration there was a sharp rise in withdrawal symptoms and complaints. No differences were found between groups with respect to relief of withdrawal symptoms, illicit drug use or other indicators of social adjustment. One-third of the LAAM patients and 11 Percent of methadone patients dropped out of the study.

In a subsequent double-blind experiment comparing dl-alpha-acetylmethadol and methadone, 34 patients were studied for 15 weeks (Jaffe et al. 1972). The withdrawal symptoms of patients taking a mean dose of 36-80 mg of dl-alpha-acetylmethadol/active dose three times weekly did not differ from those of patients taking a mean of 30-90 mg of methadone daily. There were no significant differences between the two groups for the following outcome measures: dropout rate, employment, arrests, percentage of urines negative for illicit drugs, clinic attendance and requests for dose level changes. Twenty-six percent of the dl-alpha-acetylmethadol patients and 13 percent of methadone patients dropped out. The difference was not significant.

A double-blind, controlled study was carried out with 10 patients to determine if LAAM could be effectively substituted for methadone on weekends (Jaffe and Senay 1971). The duration of the study was three weekends and no differences were found between the experimental and control groups with respect to morphine-positive urines, clinic attendance, interviewer observations, self-reports of symptoms, or requests for change in medication. It was found that LAAM in doses equivalent to the patient's usual dose of methadone were sufficient to prevent abstinence symptoms for 48 hours. Abstinence syndrome was prevented for 72 hours by doses of a mean of 1.3 mg of LAAM for every 1 mg of daily methadone. Mean dose levels were 60 mg of LAAM and 68 mg of methadone. LAAM was found to be similar in potency to the racemic compound, not higher as anticipated.

Senay, Jaffe, diMenza and Renault (1974) in a 48-week, double-blind study started 157 patients on mean doses of 57.8 mg of LAAM three times weekly, with placebo on alternate days, 40.6 mg of methadone daily (Full Service Group), or 41.3 mg of methadone daily (Dispensary Group). Few significant differences were found between the LAAM Full Service group, the Methadone Full Service group, and a third treatment group (Dispensary) receiving methadone only and no counseling or other services. There were no significant differences in total number of weeks accumulated by patients in their original treatment groups. At the end of 48 weeks, 49 percent of the Dispensary group, 50 percent of the LAAM Full Service group, and 29 percent of the Methadone Full Service group had dropped out. There were no significant differences between treatment groups with respect to use of illicit drugs and employment and arrest rates. Requests for dose-level changes were significantly less in the Dispensary group.

Zaks, Fink and Freedman (1972) compared 40 LAAM (30-80mg/three times a week) and methadone (100 mg/day) patients in an open study of six months duration and found the groups to be equivalent with respect to patient acceptance, withdrawal symptoms, response to heroin challenges, and number of positive urines tested for morphine. Patients taking 40-50 mg doses of LAAM evidenced withdrawal symptoms 40-48 hours posttreatment and 80 mg of LAAM completely prevented abstinence syndrome for 72 hours. Twenty percent of methadone patients and 11 percent of LAAM patients dropped out.

In a controlled study with both double-blind and open comparisons, Lehmann (unpublished) studied 42 16-21 year olds on LAAM every 72 hours. Some camplaints of mild discomfort

after 60 hours were made by patients in the open group (who knew they were taking LAAM); however, complaints were not severe enough to warrant change in dosages or inter-emotional reactions, performance in jobs, school, athletics, and therapy. Withdrawal was accomplished from both drugs at the end of 16 weeks with equal ease.

Savage, Karp and Curran (unpublished) carried out a six-month double-blind crossover comparison between 99 patients on LAAM (1.3 times their usual methadone dose) and methadone. Treatment groups did not differ in frequency of positive urines, clinic attendance, and social and emotional adjustment. Those patients who were induced on LAAM initially dropped out at a significantly higher rate than those who started on methadone and transferred to LAAM (x^2 5.49, p=0.2). The dropout rate was also higher for LAAM patients in the second half of the study, after the crossover, but the difference was not significant. Fifty-three percent of all patients taking LAAM dropped out and 35 percent of all patients taking methadone dropped out.

Irwin, Blachly, Marks, Carlson, Loewen and Reade (1973) in an eight-month open study of 109 LAAM patients (mean dose 55 mg/day, group one; mean dose 57 mg/day, group two), methadone patients (mean dose 50 mg/day), and nonaddict controls found that dropouts from the study were disproportionately males and tended to occur in the first two months of the study. There was a higher percentage of dropouts in the LAAM group (42 percent) than in the methadone group (23 percent) or among the nonaddict controls (20 percent). There were no differences between treatment groups in social adjustment indicators.

In an open study comparing 65 patients on LAAM and methadone, Senay, Renault, diMenza, Collier, Daniels and Dorus (1974, unpublished) found that patients can be maintained on a mean dosage of 44.4 mg of LAAM three times weekly in comparison with patients maintained on 36.5 mg of methadone daily. Mean initial dose levels were 44.7 mg of LAAM and 33.5 mg of methadone. No significant differences in illicit drug use and employment and arrest records were noted at 14 weeks. LAAM patients tended to drop out earlier than methadone patients. The difference was significant at five weeks but was no longer significant by 14 weeks. The dropout rate was 32 percent for LAAM patients and 22 percent for methadone patients.

Goldstein and Judson (1974) compared 44 patients receiving 50 mg of methadone daily to 14 patients receiving 75 mg of LAAM three times weekly on a double-blind basis and 16 patients taking 75 mg of LAAM three times weekly on an open basis. No significant differences were noted in dropout rates, attendance records, and jailings. Urine tests for opiate use indicated the LAAM groups were superior to the methadone group in having less illicit use of narcotics. Methadone group members were superior in reduction of amphetamine and barbiturate use. Goldstein also investigated the question of whether complaints of medication not holding over the weekend were psychological or pharmacological in nature. He increased the Friday dose of LAAM from 75 mg to 100 mg on three successive weekends on a limited basis with the expectation that complaints would decrease if their origin was pharmacological rather than psychological. The effects of this dosage increase were inconsistent, indicating that complaints of withdrawal may well arise out of patients' concern that their medication will not hold than, rather than being pharmacological in origin.

The overall results of all controlled clinical studies prior to Phase II reveal few differences between LAAM and methadone patients on outcome measures such as use of illicit drugs, illegal activity and arrests, employment, clinic attendance and dose-level changes. A large number of studies have confirmed the initial findings of Fraser and Isbell that LAAM is capable of suppressing the development of abstinence syndrome for 72 hours. The dose levels necessary to achieve this have been shown to vary greatly, and the patient's attitudes and concerns about the ability of the medication to hold him for this period of time are important. The main differences between treatment groups appear to be in the percentage of patients who drop out of the studies. With one exception (Zaks et al. 1972), all studies reported a greater percentage of LAAM patients dropping out than methadone patients, although the differences between groups were often not significant.

Dropouts among LAAM patients tended to occur early in the studies. Goldstein and Judson (1974) noted a greater number of dropouts among LAAM patients than among methadone patients during the stabilization phase. Savage et al. (unpublished) noted a significantly greater number of dropouts among LAAM patients in the first half of their crossover study. Dropouts were also greater among LAAM patients after medications were switched, but not significantly so.

Senay et al. (1974 unpublished) noted that the significant difference in percentage of

TABLE XVIII: COMPARISON OF DIFFERENCES IN OUTCOMES FOR LAAM AND METHADONE PATIENTS
(CONTROLLED CLINICAL STUDIES)

Investigators	Number of Subjects	Duration	Study Design	Dosage Schedule	Dropout Rate	Presence of Illicit Drugs In Urine	Reports of Illegal Activity, Arrests	Employment	Clinic Attendance	Dose Level Changes
Goldstein & Judson (1974)	74	3 months	Open and blind	LAAM: 75mg/3T/wk; Methadone: 50mg/day	LAAM 23%; Methadone 16%; N. S.	LAAM: Less opiate use Methadone: Less use of barbiturates and amphetamines	N. S.	--	N. S.	--
Irwin, Blachly, Marks, Carlson, Loewen, and Reade (1973)	109	8 months	Open	LAAM I: Mean 55mg/day, range 30-90mg/day LAAM II: Mean 57mg/48 hrs, range 20-80mg/48 hrs; Methadone: Mean 50mg/day, range 25-115mg/day	LAAM 42%; Methadone 23%; Non-addict controls 29%	N. S.	N. S.	N. S.	--	N. S.
Jaffe, Schuster, Smith, and Blachly (1970) *dl-alpha-acetylmethadol	21	7 weeks	Double blind	DLAAM: 50mg/3T/wk, range 24-66mg/3T/wk Methadone: 37mg/day, range 20-55mg/day	LAAM 33 1/3%; Methadone 11%	N. S.	N. S.	--	--	--
Jaffe and Senay (1971)	10	3 weekends	Double blind	LAAM: Mean 60mg/3T/wk, range 48-72mg/3T/wk; Methadone: Mean 68mg/day, range 30-100mg/day		N. S.	--	--	N. S.	N. S.
Jaffe, Senay, Schuster, Renault, Smith, and diMenza (1972) *dl-alpha-acetylmethadol	34	15 weeks	Double blind	DLAAM: Range 36-80mg/3T/wk; Methadone: Range 30-80mg/day	LAAM 26%; Methadone 13%; N. S.	N. S.	N. S.	Significant improvement in both groups	N. S.	N. S.
Lehmann, Walter X. (unpublished)	42	16 weeks	Double blind and open	LAAM: 10mg/72 hrs; Methadone: Dosage not stated	--	N. S.	--	--	N. S.	--
Savage, Karp, and Curran (unpublished)	99	6 months	Double blind, crossover	LAAM: 1.3 times patient's usual dose of methadone/3T/wk; Methadone: Dosage not stated	LAAM 53%; Methadone 35%	N. S.	--	--	N. S.	--
Senay, Jaffe, diMenza, and Renault (1974)	157	48 weeks	Double blind	LAAM: Mean 57.8mg/3T/wk; Methadone (full service): Mean 40.6mg/day; Methadone (dispensary): Mean 41.3mg/day	LAAM full service 50%; Methadone full service 29%, dispensary 49%	N. S.	N. S.	N. S.	N. S.	Significantly less for dispensary group
Senay, Renault, diMenza, Collier, Daniels, and Dorus (1974)	65	14 weeks	Open	LAAM: Mean 44.7mg/3T/wk; Methadone: Mean 33.5mg/day	LAAM 32%; Methadone 22%; N. S.	N. S.	N. S.	N. S.	N. S.	N. S.
Zaks, Fink, and Freedman (1972)	40	6 months	Open	LAAM I: 30-50mg/3T/wk; LAAM II: 80mg/3T/wk; Methadone: 100mg/day	LAAM 11%; Methadone 20%	N. S.	--	N. S.	--	--

KEY: N. S. = Not statistically significant
-- = Data not reported

Prepared by MACRO Systems, Inc.

dropouts among LAAM and methadone patients at the 5th week of their study had disappeared by the end of the 14th week when the rate of dropouts for methadone patients increased to a level similar to that of LAAM patients.

Jaffe et al. (1970) noted that the four patients taking dl-alpha-acetylmethadol who dropped out of his study did so on the first day. Jaffe et al. (1972) found that the average stay of patients on dl-alpha-acetylmethadol was 5.8 weeks compared to 10 weeks for methadone patients.

In summary, investigators have found that on most outcome measures, LAAM compares favorably with methadone as a substitute drug in the treatment of heroin addiction. The dropout rate among LAAM patients has been shown to be generally higher than that for methadone patients, although differences are often not significant. Dropouts among LAAM patients often occur during the early, stabilization phase and may be related to physiological problems in inducing patients onto a new drug or to psychological concerns about the taking of an "experimental" drug. If, as is suspected, the metabolite N-LAAM is the active agent, there is a lag in buildup of pharmacologically active blood levels. During the period when patients are off methadone and just starting on LAAM, the blood levels of the desired agent may be too low and initial discomfort may occur.

Other Clinical Studies

Other clinical investigations have been carried out with LAAM where a methadone or other control group was not employed and have produced findings pertinent to the effectiveness of LAAM in the treatment of heroin addiction.

Blachly (1971) reported starting 74 patients on LAAM in an open study. The initial conversion factor of one-sixth the patient's usual dose of methadone proved to be inadequate, and all patients suffered withdrawa1. Twenty-two out of twenty-three patients started at those dose levels returned to methadone within a week. Twenty-four of 51 other patients continued on dose levels equal to their methadone dose. Doses of LAAM equivalent to the patient's usual methadone dose were sufficient to prevent abstinence in 18 patients for 48 hours and in 6 for 24 hours.

Wilson, in an unpublished open study, observed three treatment groups for 85 days:

Five patients transferred to 60-65 mg of LAAM on Monday and Wednesday and 80-85 mg of LAAM on Friday after having been maintained on methadone for three months

Five patients induced directly on LAAM (60-65 mg Monday and Wednesday and 80-85 mg on Friday) who had never taken methadone

Six patients who received methadone Monday through Thursday, and 80-85 mg of LAAM on Friday

The dropout rate was identical in both groups taking only LAMM (40 percent). The group who had never taken methadone stabilized on LAAM with less distress and fewer complaints than the group who had been transferred from methadone maintenance. The group of patients taking methadone during the week and LAAM on the weekends all experienced withdrawal on the third day after the Friday dose. Two-thirds of them dropped out of the study after five weekend doses; this part of the study was discontinued after two months.

Summary Of Toxicity-Safety Findings And Observations

When all the research which has been done with LAAM prior to Phase II is taken into consideration, it appears that there have been few unusual reports of toxicity; such adverse experiences as did occur resembled those of methadone, and particularly occurred after excessive dosage. The cumulative nature of the drug effects and the variability among individuals in the rate at which LAAM is metabolized necessitate close attention to dosage levels and intervals. Following is a summary of clinical experience which has accumulated as a result of investigations prior to Phase II and which has relevance to the safety of the drug. This summary is organized in the following categories: results of laboratory tests, adverse experiences, and side effects

Results Of Laboratory Tests

Laboratory tests have revealed few differences between LAAM and methadone patients and most results have been within normal limits, or unchanged from pretreatment values where pretreatment values were not normal. Following is a description of those results which are unusual in any respect.

Blachly et al. (1972) canpared 21 LAAM Patients to a matched sample of 19 methadone patients on laboratory findings (results of SMA 12 and SMA 6 screen and automated reagin tests) and electroencephalograms. The only

statistically significant finding (p.025) for LAAM patients was hyperglycemia (mean blood glucose 117 percent for LAAM patients 103 percent for methadone patients where 110 is defined as the upper limit of normal). Sixty-three percent of the methadone patients and 38.5 percent of the LAAM patients had EEG abnormalities but the difference was not significant (p 0.1-0.2, chi square=2.44).

Irwin, Blachly, Marks and Carter (unpublished) in another discussion of the same study also noted a higher incidence of abnormalities in SGOT, albumin, and alkaline phosphatese determinations in both the LAAM and the methadone groups, suggesting a slight impairment in liver function. 'Ihirty-five and 29 percent of methadone and LAAM subjects, respectively, also had abnormally high white blood counts. LAAM subjects' performance on cognitive tasks involving memory, learning, speed, and accuracy was significantly better than was methadone subject's performance.

Jaffe, Senay, Schuster, Renault, Smith and diMenza (1972) in a study of dl-alpha-acetylmethadol noted that only 7 of 66 patients bad normal results on liver-function tests upon entry and that profiles remained unchanged at the end of the study. With respect to hematology, most subjects were normal initially and at the end of the study. In one subject, the hematocrit dropped from 48 percent to 39 percent but hemoglobin level, RBC, and WBC remained normal. White blood cell counts decreased in two patients and increased in one; no symptoms were associated with any of these changes. Thirteen subjects had positive results for VDRL and PTA tests initially, which were unchanged at the end of the study, except for one subject whose values reverted to negative.

Wilson (unpublished) noted elevated SGOT determinations and slightly decreased hemoglobin, hematocrit, and white blood count in five of six LAAM patients.

Zaks et al. (1972) reported elevated transaminase levels which were sporadic and not dose-related for both the LAAM and the methadone groups. Results of all other laboratory tests (fasting, blood glucose, blood urea nitrogen, uric acid, blood cell count, and urinalysis) were normal.

Irwin, Blachly, Marks, Carlson, Leowen and Reade (1973) found the incidence of EBG abnormalities among methadone patients was 43 percent upon entry into the study and had increased to 53 percent at eight months. Incidence of EEG abnormalities increased less markedly for 48-hour LAAM patients (31 percent upon entry to 40 percent at eight months). There was a statistically significant increase in incidence of EEG abnormalities for 24-hour LAAM patients (34 percent upon entry to 100 percent at eight months) . There was no significant alteration of cognitive performance for LAAM or methadone patients and EEG abnormalities did not seem to be reflected in performance on cognitive tests.

Blood chemistry analysis revealed that both LAAM and methadone produced elevations in SGOT determinations and that methadone produced a greater incidence of lowered abnormal T-3 value. Incidence of abnormalities was sustained for methadone patients and decreased for LAAM patients over the eight-month study period. Urine analysis revealed no abnormalities.

Savage et al. (1974, unpublished) found no differences in LAAM patients pre- and post-treatment in EEG, blood chemistry analysis, or hematology. Methadone patients evidenced significant changes on three of seven hematology measures; the mean values of neutrophiles decreased and the mean values of lymphocytes and basophiles increased. All values were still within normal range, however.

Adverse Experiences

There have been several reports of adverse experiences in the course of investigations with LAAM prior to Phase II.

Keats and Beecher (1950) noted four incidents of coma among 81 patients receiving subcutaneous doses of LAAM for relief of chronic pain. The patients bad received 16 40 mg LAAM twice in 24-34 hours with one to three 6-10 mg doses of morphine in the same interval. Coma occurred 12-24 hours after the last dose of LAAM and lasted an average of 20 hours.

Blachly (1971) noted four cases of toxicity to LAAM at dose levels above 100 mg among 74 patients taking LAAM. Two patients had seizures while on 180 mg and 120 mg LAAM every 24 hours. A female patient on 110 mg LAAM every 24 hours lost consciosness, suffered cardiac arrest, and showed EEG abnormalities, and a patient on 220 mg LAAM per day complained of feeling as though he were going to have a fit and was returned to methadone. A fifth patient bad a manic attack when his dosage was reduced to 35 mg/48 hours from 55 mg/48 hours during voluntary withdrawal. He was returned to methadone (55 mg/day), treated with lithium and thorazine, and subsequently completed withdrawal

while on LAAM.

Side Effects

The response of patients on LAAM has been shown to vary considerably among individuals. Some patients evidence no side effects or complaints, while others experience distress from either withdrawal or side effects.

Billings et al. (1974) observed different responses in three LAAM subjects studied. The subject with the highest plasma levels NAM and NNAM reported only mild sweating and constipation. The two other subjects, whose plasma levels of the metabolites were similar to each other, reported more severe side effects. One reported anxiety, sweating, and gooseflesh in the early weeks of the study which disappeared later; the other reported considerable dysphoria, irritability, muscle weakness, tremors, and paranoia.

Zaks et al. (1972) received no complaints of side effects from methadone patients except constipation (4 out of 10 patients). Of the nine LAAM patients, three complained of irritability, one of anxiety, and two of involuntary, jerky movements of the extremities before falling asleep.

Jaffe, Senay, Schuster, Renault, Smith and diMenza (1972) noted few complaints of side effects in the 66 subjects in their study, and no toxic reactions. Two patients complained of impotence and two complained of jerking and twitching of arms and legs when at rest.

Withdrawal, irritability, restlessness, gastrointestinal upset, and anxiety were complained of by methadone patients who were taking LAAM on weekends (Wilson, unpublished). All five patients in the treatment groups who were transferred to LAAM from methadone all complained of amphetamine-like effects, irritability, anorexia, constipation, and diminished libido in the early weeks of the study. Other complaints were appetite and weight loss. The five patients in the treatment group who were induced directly on to LAAM stabilized with fewer side effects than the group which was transferred from methadone.

David and Semler (1956) found that side effects were minimal among patients receiving small doses of LAAN orally and subcutaneously for relief of chronic pain. Twenty-five of seventy-six patients were nauseated or vomited at some time while receiving LAAM. Ten of thirty-one patients treated for longer than 31 days complained of moderately severe constipation. Six patients in the total sample complained of dizziness, thirteen reported feeling lethargic, and two experienced severe depression attributable to intolerance to LAAM.

Fraser and Isbell (1952) found that repeated doses of dl-alpha-acetylmethadol and LAAM resulted in cumulative toxic effects in four patients: depression, approaching coma, nausea, respiratory depression, and mental confusion.

Reports of loss of sexual desire, constipation, drowsiness, and loss of energy were received from patients in both LAAM and methadone groups. The mean number of complaints was the same for each group, 2.6 (Irwin, Blachly, Marks, Carlson, Loewen and Reade, 1973).

Gruber and Baptisti (1962) found that nausea, dizziness, and drowsiness increased in proportion to the dose level of nor-acetylmethadol; constipation, headache, nervousness, and abdominal discomfort were reported as side effects but were not dose-related. Itching was volunteered as a complaint often enough to be added to the list.

Houde et al. (1962) observed that nausea and drowsiness occurred in some patients at higher doses of noracetylmethadol (8 and 16 mg) administered subcutaneously, and burning at the site of injection occurred after 25 percent of the 16 mg doses.

Jaffe et al. (1970) reported that four of twelve patients taking dl-alpha-acetylmethadol dropped out on the first day because of complaints of anxiety and nervousness. The d-isomer has been suspected of producing anxiety and nervousness (Fraser and Isbell 1952) and may be responsible for the side effects noted in this instance.

In an open study with LAAM, Levine (1973) noted that three of seven patients reported loss of appetite and abdominal discomfort at doses greater than 50 mg; all patients reported constipation.

Senay et al. (1974) found no instances of confusion, psychotic symptoms, or unpleasant subjective states among 157 patients studied. Anxiety was observed in all treatment groups. There were two deaths during the course of the study: a methadone patient committed suicide and a LAAM patient died of lung cancer .

Senay et al. (1974, in press) reported that 5 of 34 patients taking LAAM experienced side effects; four suffered from anxiety and nightmares early in treatment and one patient

exhibited bizarre behavior of which he had no recollection. One LAAM patient died as a result of heroin overdose 48 hours after his second dose of LAAM.

* * * * * * * *

This chapter has summerized the clinical trials with LAAM which have been conducted prior to Phase II. A sampling of selected abstracts follows.

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The following synopses were prepared to a standard format by Macro System, Inc., from a review of LAAM research, published and unpublished, up to July, 1975.

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INDEX

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1

1-ACETYLMETHADOL (LAM) TREATMENT OF OPIATE DEPENDENCE: PLASMA AND URINE LEVELS OF TWO PHARMACOLOGICALLY ACTIVE METABOLITES. 1974

RUTH E. BILLINGS, ROBERT E. MCMAHON, DAVID A. BLAKE

INTRODUCTION

Two active metabolites of LAAM, 1-noracetylmethadol (NAM) and 1-denoracetylmethadol (NNAM) have been identified and are thought to explain the characteristic pharmacological effects of LAAM. (Sung and Way, 1954; Billings et al., 1973). The determination of NAMl and NNAM levels in blood and urine of patients receiving LAAM for treatment of opiate addiction was undertaken in order to support the proposition that the activity of LAAM is due to its conversion to NAM and NNAM.

EXPERIMENTAL DESIGN

Subjects

Three white male ex-heroin addicts, ages 25, 28, and 37, previously stabilized on 80 mg/day methadone for two to six years, were taking 100 mg LAAM three times a week as volunteers in an experiment comparing LAAM to methadone and were asked to provide samples of blood and urine.

Methodology

One hundred mg of LAAM was taken orally on Mondays, Wednesdays, and Fridays. Blood samples (5-10 ml.) were taken at intervals in the succeeding 48 hours; total urine voided was collected for two days. Electron capture gas chromatography was used to determine the content of NAM and NNAM.

RESULTS

Plasma Levels

Plasma levels of both metabolites were established soon after dosing. During the first day, the levels of NAM were higher than those of NNAM. As time went on, NAM levels declined steadily while NNAM levels remained at peak levels (50-75 ng/ml) up to the time of the second dose. NHAM levels were higher after a repeat dose of LAAM than after the initial dose (100-300 ng/ml). NAM levels varied in all three subjects.

Urine Levels

Less unmetabolized LAM was excreted than NAM or NNAM. Excretion levels of all three were much greater (six to eight times greater) after repeat dose than after the initial dose. This is felt to be due to LAAM, NAM, and NNAM becoming tissue bound easily and not being excreted until subsequent doses have saturated the abilitv of the tissues to bind amines, at which point the rate of excretion will increase.

Adverse Reactions

The three subjects varied in the side effects they experienced.

One subject reported only mild excessive sweating and constipation during the first week. He had higher plasma and urine levels of NAM and NNAM than the other two subjects.

The second subject had difficulty with amphetamine-like stimulation, anxiety, sweating, and goose flesh for six weeks.

The third subject evidenced dysphoria, irritability, muscle weakness, tremors, and paranoia which decreased during the first four weeks. He asked to be switched back to methadone at the seventh week because of discomfort. Significant plasma levels of NAM and NHAM were still present seven days after his last dose of LAM.

2

1-ALPHA-ACETYLMETHADOL IN THE TREATMENT OF OPIATE ADDICTION: PROGRESS REPORT, 1971

P.H. BLACHLY

INTRODUCTION

Jaffe et al. (1970), demonstrated that dl alpha-acetylmethadol could be substituted for methadone and that it suppressed abstinence symptoms for 72-96 hours confirming the earlier findings of Fraser and Isbell (1952). In an unreported pilot study by this investigator using higher doses (mean 106 mg), dl-alpha-acetylmethadol produced oversedation and gradually increasing toxicity. Further studies have been limited to the levo isomer which has two features of interest:

It is more effective orally than parentera11y.

It is not psychologically addictive.

EXPERIMENTAL DESIGN

Subjects

Seventy-four patients were started on LAAM. They were told it was an experimental drug, that they might return to methadone if they wished, and there would be a transitional period during which dosages would be adjusted.

Methodology

Induction--Conversion from methadone was initially one-sixth the usual dose of methadone but was revised to doses of LAAM equal to the regular methadone dose.

Dose Levels--The mean dose was 89.1 mg (range 25-140 mg).

Frequency Of Administration--Six patients received their dose of LAAM every 24 hours; 18 received theirs every 48 hours.

RESULTS

Dropout Rate

Of the 23 patients started on doses of LAAM equal to one-sixth their methadone dose, all but one returned to methadone within a week because of withdrawal symptoms.

Of the 51 patients induced on LAAM in dose levels equal to their methadone dose, 24 continued on LAAM.

The mean number of days on LAAM of those who prefer it is 132 (range 18-300).

Reasons For Preference Of LAAM

The following reasons were given for preferring LAAM by the number of persons indicated:

Methadone did not hold them (19)
LAAM is cheaper (4)
They nodded too much on methadone (3)
LAAM is more convenient (2)
They are more emotionally level (3)
Sex life is improved (1)

Reasons For Discontinuing LAAM

The following reasons were given for returning to methadone by the number of persons indicated:

Somnolence and agitation (2)
Amphetamine-like effects (2)
"Didn't feel anything" (1)
Decreased sex life (1)
Nausea and vomiting (1)
"Effects lasted only 30 hours" (1)
Constipation (1)
Stomach cramps (1)
Irritability (1)
Sluggish, overly sedated (2)
Diffuse aches and pains (1)
Heartburn (1)
Insonmia (2)
Sweating (1)
Nine others could give no good reasons for wanting to return to methadone

Toxicity

There were four cases of toxicity to LAAM, all occurring in patients for whom high dose methadone would not prevent abstinence craving for a full 24 hours; all were receiving daily doses of LAAM in excess of 100 mg. In all cases toxicity developed between the 8th and 14th day.

Female patient switched to 180 mg LAAM daily developed panic and "seizures" on the 14th day which disappeared when dose was lowered to 110 mg every 48 hours; she also was a Ritalin addict. EEG was normal.

Female patient switched to 110 mg of LAAM every 24 hours experienced episodes of depersonalization and loss of contact with environment on the 9th day. She lost consciousness, suffered cardiac arrest, and showed EEG abnormalities; she had been a Doriden abuser with withdrawal seizures in the past.

Male patient started on 200 mg LAAM every 24 hours from 235 mg methadone. Dose was not holding him and was raised to 220 mg. On the 8th day he complained of feeling as though he were going to have a fit and was returned to methadone.

Male patient increased from 85 to 120 mg LAAM had an undocumented "seizure" but did not lose consciousness. Symptoms disappeared when dose was lowered below 100 mg.

A fifth patient had a manic attack during withdrawal from LAAM (at 35 mg from previous stabilization dose of 55 mg). He was placed on regular dose of methadone, treated with lithium and thorazine. In a few days when the manic attack disappeared he returned to LAAM, and accomplished withdrawal without further difficulty while on lithium.

3

1-ALPHA-ACETYLMETHADOL (LAM): COMPARISON OF LABORATORY FINDINGS, ELECTROENCEPHALOGRAMS, AND CORNELL MEDICAL INDEX OF PATIENTS STABILIZED ON LAM WITH THOSE ON METHADONE. 1972

P.H. BLACHLY, N.A. DAVID, SAMUEL IRWIN

INTRODUCTION

LAAM, an effective alternative to methadone (Jaffe et al., 1970; Jaffe and Senay, 1971), has several advantages over methadone:

- Suppression of abstinence syndrome two times longer than methadone (Fraser and Isbell, 1952)
- "Smoother" action
- Less "nodding"
- Oral effectiveness
- Less subjective euphoria

Several disadvantages are:

- Amphetamine-like effect and dysphoria in some patients
- Occasional complaints of feeling less "mellow"
- Occasional complaints of abdominal cramps

This paper reports on clinical laboratory studies in patients maintained on LAAM compared to those on methadone.

EXPERIMENTAL DESIGN

Subjects

Twenty--one patients were matched to 19 methadone patients on age, sex, race and years of opiate use.

Methadone--Mean age 31.4, seven females, two blacks, mean 10 years opiate use, mean 17 months on methadone program, mea" dose 95 mg (range 35-190 mg)

LAAM--Mean age 32.2, seven females, one black, one oriental, mean 10 years opiate use, mean 15 months in methadone program, mean 7 months on LAAM, mean dose 75 mg (range 60-100)

Methodology

LAAM dosages were adjusted to patient's preference.

Seven patients consumed their doses at 24-hour intervals because it would not "hold" them 48 hours.

Fourteen consumed theirs at 48-hour intervals.

Blood and urine samples were collected in the fasting state and before administration of regular dose of LAAM and methadone. Blood analysis was by SMA 12 and SMA 6 screen and automated reagin tests.

Eight channel EEG's were obtained at one or six hours after drug administration by a "blind" experimenter.

RESULTS

The results are as follows:

Urine And Blood Values

The only statistically significant finding ($p < .025$) for LAAM patients is hyperglycemia. Mean blood glucose was 117 percent for LAAM patients, 103 percent for methadone patients where 110 percent is given as the upper limit of normal.

EEG

Fifty-three percent of all patients had EEG abnormalities: 63 percent of those on methadone and 38.5 percent of those on LAAM. The difference was not statistically significant.

Cornell Medical Index

Those patients with normal EEG's differed significantly ($p < .001$) from those with abnormal EEG's on their total Cornell Medical Index score. The mean score for those with normal EEG's was 35.0, for abnormal EEG's, 69.3.

4

ACTIONS AND ADDICTION LIABILITIES OF ALPHA-ACETYLMETHADOLS IN MAN 1952

H.F. FRASER AND HARRIS ISBELL

INTRODUCTION

The pharmacology and analgesic effects of the acetylmethadols have been studied in animals (Chen, 1948; Specter, Byrd, Cheney and Binkley, 1949; Eddy, Touchberry and Lieberman, 1950; Eddy, May and Mosettig, 1952); this paper reports on some of the actions and addiction liabilities of dl-, d-, and 1-alpha-acetylmethadol in man. The findings with respect to l-alpha-acetylmethadol will be of primary interest in this summary.

EXPERIMENTAL DESIGN

Subjects

Subjects were adult white male volunteers.

Subjects in the single-dose studies were "post-addicts," previously addicted to morphine but withdrawn and no longer tolerant.

Subjects in the abstinence-alleviation studies were addicted to morphine at the time of the study.

Methodology

Single-Dose Studies (Post-Addict)--l-alpha-acetylmethadol was administered:

Subcutaneously (10-30 mgm) to 14 post-addicts

Intravenously (30 mgm) to 5 post-addicts

Orally (30-40 mgm) to 7 post-addicts

Pupillary diameters were measured before and at intervals after oral, subcutaneous, and intravenous administration of 30 mgm 1-alpha-acetylmethadol.

Subcutaneous (15 mgm) doses were administered twice daily for several days to six patients.

Relief Of Abstinence From Morphine--1-alpha-acetylmethadol was administered to currently addicted subjects:

Subcutaneously (30 mgm) at the 28th and 36th hour of abstinence to two subjects

Orally (30-60 mgm) at the 28th hour of abstinence to three subjects

Substitution Of 1-Alpha-Acetylmethadol For Morphine--Seventeen addicts received oral or subcutaneous doses of l-alpha-acetylmethadol; the administration of morphine

was then discontinued. Ten subjects who received the drug orally remained on it for fourteen days; the five who received it subcutaneously and two who received it orally returned to morphine after two days on the drug.

The 10 orally dosed subjects were withdrawn abruptly from the drug. Four additional subjects were withdrawn gradually over five to seven days.

Prolonged Suppression Of Abstinence By 1-Alpha-Acetylmethadol--Five addicted subjects received 40 mgm orally on a daily basis for 10 days after which the dosage was increased to 60 mgm and the interval was lengthened to 48 hours for a week, 72 hours-for two weeks, and 96 hours for two weeks.

RESULTS

Single Dose Studies

Single doses of 1-alpha-acetylmethadol produced the following results:

Symptoms of euphoria did not develop until 4-6 hours after subcutaneous administration and persisted 48 and sometimes 72 hours.

Intravenous administration of the drug produced results similar to subcutaneous administration.

Following oral administration, morphine-like effects were observed within one and one-half hours and persisted 24 and sometimes 72 hours.

Pupillary constriction following oral administration was observed in two hours, peaked in four hours, and disappeared in 24 hours. The onset of pupillary constriction was slower and less intense following subcutaneous or intravenous administration but persisted for 48 hours.

Repeated doses of 1-alpha-acetylmethadol resulted in the development of cumulative toxic effects which were depression, approaching coma; respiratory depression; severe nausea and vomiting; mental confusion.

Relief Of Abstinence From Morphine

Subcutaneous administration 1-alpha-acetylmethadol had inconsistent effects with respect to abstinence relief.

Oral administration of the drug abolished all signs of abstinence.

Substitution Of 1-Alpha-Acetylmethadol For Morphine

1-alpha-acetylmethadol was substituted for morphine effectively at a ratio of 1 mgm to each 6-8 mgm of the subject's usual dose of morphine.

Abrupt withdrawal from 1-alpha-acetylmethadol produced an abstinence syndrome which was mild and similar to that from methadone. Gradual withdrawal from the drug produce an abstinence syndrome that did not differ in course and intensity from that observed after abrupt withdrawal.

Prolonged Suppression Of Abstinence By 1-Alpha-Acetylmethadol

Sixty mgm oral doses of 1-alpha-acetylmethadol successfully prevented development of significant withdrawal symptoms for 72 hours in subjects stabilized on 240 mgm morphine daily.

5

USE OF MIOTIC EFFECT IN EVALUATING ANALGESIC DRUGS IN MAN 1954

H.F. FRASER, T.L. NASH, G.D. VANHORN, H. ISBELL

INTRODUCTION

The purpose of this report is to show the extent to which miotic effects of opiate-like drugs correlate with analgesic effects, side effects, and addiction liability as an aid to clinical evaluation of these drugs. Only the results with respect to l-alpha-acetylmethadol will be summarized here.

EXPERIMENTAL DESIGN

Subjects

Former opiate addicts were used as subjects; they were hospitalized and observed under "basal" conditions. Eight to ten men were used in each experiment.

Methodology

Predrug measures and observations provided baseline data; each individual served as his own control. An individual was studied on placebo and four to ten analgesics (one per week) and observed at intervals up to 72 hours.

The following observations were made:

Pulse and respiratory rates
Blood pressures
Temperature
Pupillary size
Respiratory minute volume
Behavioral changes ("euphoria")
Adverse side reactions

RESULTS

Route Of Administration

1-alpha-acetylmethadol induced effects more rapidly when given orally than subcutaneously. This difference was statistically significant.

Duration Of Action

Miotic effects of 1-alpha-acetylmethadol lasted as long as 72 hours.

Correlation Of Miosis With Fuphoria

The time-course of morphine-like "euphoria" relates to miotic measurements. l-alpha-acetylmethadol administered orally produced an earlier and more intense euphoria which diminished more rapidly than that produced by subcutaneous administration.

Correlation Of Miosis With Relief Of Abstinence Syndrome

1-alpha-acetylmethadol produced a long-lasting papillary constriction which correlates with the delay of abstinence symptoms until three days after withdrawal.

Correlation Of Miosis With Toxic Effects

The curves of miotic effect indicate that toxic effects would persist for long periods and too short an interval between doses would result in cumulative toxicity.

Correlation Of Miosis With Relief From Pain

Pupillay miosis does not correlate well with analgesic properties. 1-alpha-acetylmethadol is a potent pupillary constrictor hut a poor analgesic.

6

LAAM AND LAAM METABOLITES: PLASMA LEVELS IN PATIENTS. SUMMARY PROGRESS REPORT. 1975

AVRAM GOLDSTEIN

EXPERIMENTAL DESIGN

Plasma levels were determined on 14 patients being maintained on LAAM. In a few of these patients, it was possible to obtain blood at 24, 48, and 72 hours after a LAAM dose. In most patients, a blood sample could only be obtained at one or two occasions.

Determinations were carried out by GLC, using a modification of the customary method for determining methadone levels in plasma. The LAAM and its two N-demethylated metabolites--norxetylmethadol (NAM) and dinoracetylmethado1 (NNAM)--were identified by retention time on the column, as verified by standards obtained from Eli Lilly Co. Quantitation is most accurate for LAAM, less so for NAM and NNAM, because of their broader peak shapes. Peak areas rather than heights were used for this reason.

RESULTS

Plasma Levels

As with methadone plasma levels, the LAAM plasma levels at any given LAAM dosage are extremely variable from patient to patient; at 24 hours, for example, the levels ranged from 15 to 170 ng/ml. The same is true of the metabolites, which are considered to be the active compounds pharmacologically. At 72 hours, NNAM levels varied from undetectable (<30 ng/ml) to 278 ng/ml).

Time Course Of Plasma Levels And Drug Effects

LAAM itself was virtually absent from plasma 72 hours after a dose, but the dose seemed to "hold" quite well over that period. This is consistent with the view that the metabolites are primarily responsible for the LAAM effect, and also with the plasma levels of the metabolites, which were approximately as high as 72 hours as at 48 hours, and higher than at 24 hours.

7

CAN THE COMMUNITY BE PROTECTED AGAINST THE HAZARDS OF TAKE-HOME METHADONE? 1974

AVRAM GOLDSTEIN AND BARBARA JUDSON

INTRODUCTION

It is desirable to have methadone patients consume all medication under observation to eliminate:

Accidental poisonings

Diversion of methadone as a drug of abuse

Adversary nature of routine urine checks

However, seven day a week clinic attendance is a demand which may interfere with employment. LAAM is a long-acting substitute for methadone which has shown clinical promise (Jaffe et al., 1972; Zaks et al., 1972; Senay et al., 1973). This report covers the first three months of a clinical trial of LAAM.

EXPERIMENTAL DESIGN

Subjects

Patients were randomly assigned to one of five groups of 20 patients each. Females were subsequently excluded, hence, groups had fewer than 20 patients.

Methodology

Control Groups--Three groups (M-l, M-2, M-3) were stabilized on 50 mg of methadone daily and maintained at that level.

Experimental Groups--LAAM subjects were started on 30 mg LAAM and increased by 10 mg increments to 75 mg LAAM three times a week.

One group (L) was "open" and had knowledge that they were on LAAM; they came to clinic only Mondays, Wednesdays, and Fridays.

The other group (L-P) was "blind", came to clinic six days a week but received quinine placebo on Tuesdays, Thursdays, Saturdays, and Sundays. Take-home privileges were given on Sundays and other placebo days. (Comments by patients about taste differences have raised doubts in the minds of the investigator about the validity of the "blind" nature of the experiment.)

An additional experiment was carried out to determine whether Monday morning sickness was psychological or phannacological. The Friday LAAM dose was increased from 75 mg to 100 mg on three alternate Fridays for both LAAM groups on a "blind" basis.

Criteria For Effectiveness--The groups were compared on the following criteria of effectiveness:

Weekly urinalysis for opiates, barbiturates and amphetamines

Dropout rates (after a two-week stabilization phase)

Attendance records

Suspensions for absences

Jailing

Monday morning questionnaire concerning withdrawal symptoms (“feeling sick”) experienced on Sunday morning, Sunday evening, and Monday morning

RESULTS

The results for all five groups at three months are reproduced in the following table.

Dropout Rates

During the stabilization phase, dropouts were as follows:

M-1, (0)
M-2, (0)
M-3, (2)
L , (3)
L-P, (1)

Survivorship was slightly lower in the LAAM groups but not significantly so.

Attendance Records, Suspensions, And Jailings

Differences among groups in these dimensions were variable with neither LAAN nor methadone groups favored.

Urine Testing

Three-quarters of all patients discontinued heroin use by week 13, and at week 13, no consistent difference is evident between LAAM and methadone groups (see table, preceding this page). A running average of incidence of clean urines for opiates for the entire quarter was computed which showed both LAAM groups to be superior to the methadone groups.

"Feeling Sick"

Methadone groups had large differences initially in percentage of patients with complaints; the differences tended to decrease toward the end of the quarter.

The "open" LAAM group (L) showed an increase in percentage of patients with complaints from Sunday morning through Sunday evening to Monday morning. The "blind" LAAM group (L-P), however, did not show an increase in percent feeling sick between Sunday morning and Monday morning.

Increasing the Friday dose has inconsistent effects in reducing the percent of complaints in the LAAM groups. Complaints may be more psychological than pharmacological in origin.

Adverse Experiences

During induction to LAAM when tolerance was not established, delayed sedative actions of LAAM were noted (four to six hours). A problem of additive toxicity could develop if a patient were to take another drug in this interval on the assumption that the LAAM dose was not effective.

8

PHARMACODYNAMICS OF LAAM IN MAN: PLASMA LEVELS OF LAAM AND ITS METABOLITES FOLLOWING ACUTE AND CHRONIC ADMINISTRATION IN MAN (FOURTH AND SIXTH QUARTER PROGRESS REPORTS). 1974-75

GARY L. HENDERSON

INTRODUCTION

The purpose of this study was to investigate the pharmacokinetics of LAAM in man.

EXPERIMENTAL DESIGN

Subjects

Five male patients maintained on methadone for at least 90 days comprised Group 1. Addicts with no previous experience with methadone comprised Group 2.

Methodology

Day 1, Group 1

Patients were hospitalized. A symptom checklist was completed, blood and urine were collected, and temperature, pulse, respiration, blood pressure, and pupil size were recorded prior to administration of daily dose of methadone. Group 2 patients were started directly on 20 mg LAAM. Blood and urine were collected at six intervals after administration of methadone or LAAM. The following laboratory tests were done: CBC, urinalysis, SGOT, alkaline phosphatase, bilirubin, BUN, blood sugar, LDH, HAA, VDRL, and chest X-ray.

Day 2

A blood sample was taken 24 hours after hospitalization just prior to administration of 60 mg LAAM (1.2 times the usual methadone dose). Urine and blood were collected and the symptom checklist completed at six intervals on Day 2 and every 12 hours afterward until discharge from the hospital.

Day 3

Patients were discharged after final blood and urine sampling and the second dose of LAAM Weekly blood and urine samples were collected on an outpatient basis. Groups 1 and 2 received LAAM every three days for 90 days at which point they were rehospitalized, and laboratory and physical examinations were repeated.

Urinalysis

Urine was analyzed for pH, protein, glucose, ketones, bilirubin, and blood. Drug concentrations were calculated, and recovery studies for drug and metabolites were conducted at the beginning and end of the experiment.

Plasma

Plasma was analyzed by standard GLC procedures

RESULTS

Urine (Group 1)

Urine excretion patterns for LAAM and N-LAAM (noracetylmethadol) did not vary much among patients. Less than 2 percent of the drug dose was excreted as LAAM and N-LAAM at the end of the 72 hours.

Plasma

Group 1--Peak plasma levels of LAAM and its metabolites following acute administration were:

LAAM, 135 ng/ml at 6 hours

N-LAAM, 50 ng/ml at 2-6 hours

DN-LAAM (dinoracetylmethadol), 20 ng/ml at 2-48 or more hours

Plasma levels of LAAM decreased rapidly after 12 hours; N-LAAM and DN-LAAM levels remained fairly constant over a 48-hour period.

Plasma kinetics of methadone appeared to be altered by subsequent administration of LAAM; a slight increase in methadone plasma levels occurred 4-12 hours after LAAM administration.

Three patients completed 90 days on LAAM. After 90 days on LAAM, the LAAM plasma levels were only slightly higher than after the acute dose, but N-LAAM and DN-LAAM levels were 5-10 times higher than after the acute dose. The levels of DN-LAAM were highest followed by N-LAAM and LAAM. LAAM and N-LAAM decreased with time, while DN-LAAM levels remained at a constant high level for 72 hours.

N-MOL (normethadol) could not be detected in plasma after the first or the last dose of LAAM.

Group-2--After the initial dose of 20 mg LAAM, plasma levels of the drug were too low to quantitate. After 90 days (dose, 85 mg), the peak LAAM plasma levels were reached two and four hours after the last dose of LAAM, but the concentration was the same as that of Group 1.

9

THE BEHAVIORAL, COGNITIVE, AND PHYSIOLOGIC EFFECTS OF LONG-TERM METHADONE AND METHADYL TREATMENT 1973

SAMUEL IRWIN, PAUL H. BLACHLY, JOHN MARKS, ELAINE CARLSON, JAMES LOEWEN, NANCY READE

INTRODUCTION

1-alpha-acetylmethadol (LAAM) has been shown to be an effective, longer-acting substitute for methadone in maintenance therapy (Chen, 1948; Fraser and Isbell, 1952; Jaffe et al., 1970; Jaffe and Senay, 1971). The purpose of this study was to establish the basic data on the pharmacology, potential toxicity, and comparative safety of methadone and LAAM. The study will last 16 months; this report is based on 8 months' data.

EXPERIMENTAL DESIGN

Subjects

Subjects were 54 male and 31 female heroin addicts and 15 male and 9 female nonaddicted controls of similar socioeconomic status.

Methodology

Dosages--Three treatment groups were established.

Daily methadone (mean stabilization dose, 50 mg; range 25-115 mg)

Daily LAAM (mean stabilization dose 55 mg; range 30-90 mg)

Forty-eight hour LAAM (mean stabilization dose 57 mg; range 20-80 mg)

Assessments--Subjects were assessed just prior to receiving medication and at four hours afterward (time of peak drug action) 11-14 days after entry with the program (0 time) and at l-, 2-, 4-, 8-, and 16-month intervals by EEG, blood and urine analysis, Irwin Comprehensive Human Assessment Procedure, Subjective State Questionnaire, Adverse Symptom Checklist, Special Performance tests, social adjustment questionnaire, and oral interview. Urine was monitored weekly for the presence of illicit drugs.

RESULTS

Dropouts

Dropouts occurred most in the first two months of treatment and were disproportionately males, fairly equally divided between the races and much higher with LAAM (42 percent) than methadone (23 percent) or controls 29 percent).

The 16 LAAM patients who dropped out were distributed as follows:

Non-LAAM related hospitalization, (3)
Imprisonment, (4)
Switch to methadone, (6)
Withdrawal by request, (1)
Disappeared from study, (2)

The 11 methadone patients who dropped out were distributed as follows:

Nonmethadone related hospitalization, (1)
Imprisonment, (2)
Withddrawal by request, (2)
Suicide, (1)
Disappeared from study, (2)

The dropout rate was higher among those receiving 24-hour LAAM than among those receiving 48-hour LAAM.

Dose Level Changes

Mean daily methadone doses were 50 mg (range 25-115 mg) after stabilization and had increased to 90 mg (range 50-170 mg) at eight months.

Mean daily LAAM doses were 55 mg (range 30-90 mg) after stabilization and increased to 63 mg (range 35-90) at eight months.

Mean 48-hour LAAM doses were 57 mg (range 20-80 mg) after stabilization and decreased to 56 mg (10-100 mg) at eight months.

Blood Chemistry Abnormalities

Subjects had a high incidence of abnormalities consisting of lowered T-3 and elevated SGOT determinations upon entry into the study. The incidence of abnomality was sustained over time for methadone patients but decreased to almost normal values for LAAM patients by the eighth month.

EEG Abnormalities

There was an increased incidence of EEG abnormalities over time for all treatment groups, characterized primarily by diffuse or focal slowing.

The incidence of abnormalities for 48-hour LAAM patients was not statistically significant and changed from 31 percent at 0 time to 29 percent at four months to 40 percent at eight months.

The increase in abnormalities for methadone patients was significant ($p<0.01$) and changed from 43 percent at 0 time to 41 percent at four months to 53 percent at eight months.

The incidence of EEG abnormalities for 24-hour LAAM patients was statistically significant ($p<0.01$) and illustrated the cumulative effects of chronic administration. The incidence of abnormalities was 34 percent at 0 time, 75 percent at four months, and 100 percent at eight months.

Cognitive Performance Testing

Data analysis thus far has revealed little or no depressant effects or neurologic impairment. There was slightly less overall impairment of cognitive performance and functioning with LAAM than with methadone. Overall data, however, show very little alteration of cognitive performance with either drug and levels of cognitive performance do not seem to be affected by the increased incidence of EEG abnormalities.

Subjective State

LAAM patients indicated they felt a slightly greater intensity of drug effects than did methadone patients, and tolerance to drug effects did not develop during the study. Both drug treatment groups demonstrated improved affect relative to controls; the Change was greater for methadone than for LAAM patients hut not significantly so.

Social Adjustment

No major changes were seen in areas of social adjustment and only minor differences were evident between the two groups.

Conformity to law and work adjustment were increased for both treatment groups; and sexual performance, and illegal activities and earnings diminished. A slight but significant decrease in marihuana use was reported by LAAM patients.

Illicit Drug Use

There were no significant differences in the incidence of use of illicit narcotic and non-narcotic drugs between treatment groups.

Side Effects

Most frequent complaints for both drugs were loss of sexual desire, constipation, drowsiness, loss of energy, headache, increased or decreased appetite, and nausea. There were no significant differences betweem treatment groups in either the nature of complaints or mean number of complaints.

10

PRELIMINARY OBSERVATIONS WITH ACUTE AND CHRONIC METHADONE AND 1-ALPHA-ACETYLMETHADOL ADMINISTRATION IN HUMANS

SAMUEL IRWIN, PAUL BLACHLY, JOHN MARKS
C.CONRAD CARTER

INTRODUCTION

This paper reports the results of studies to determine:

Peak time effects for LAAM and methadone over 10 hours

Development of cross-tolerance to morphine in LAAM-treated subjects

Possible adverse effects of LAAM and methadone on:

EEG
Blood chemistry
Hematology
Thyroid function
Urinary function
Cognitive performance

EXPERIMENTAL DESIGN

Time-Course Of Action

Five nonaddicted male subjects received .2 mg/kg oral doses of LAAM and methadone in a cross-over study with one week between tests. The Irwin Comprehensive Human Assessment procedure was used to quantify the time-course of action and effects of the drugs on the psychosocial, physiologic, and cognitive state of the subjects.

Cross-Tolerance Of LAAM-Treated Subjects To Intravenous Morphine

Nine subjects maintained on LAAM were tested for cross-tolerance to 30 mg morphine sulfate, administered intravenously 3-54 hours after their LAAM dose. They were assessed for cross-tolerance with the procedure of Dole et al. (1966).

Clinical Laboratory Studies

Twenty methadone maintenance subjects (mean dose 93.5 mg, range 35-190 mg) were matched by age, sex, race, and years of opiate use with 21 LAAM maintenance subjects (mean dose 79.6 mg, range 12-140 mg). LAAM subjects were on methadone therapy an average of 13.9 months followed by an average of 8 months on LAAM. Methadone subjects were on methadone an average of 17.9 months.

They were assessed for electroencephalographic findings, blood chemistry, thyroid and urinary function, and cognitive performance.

RESULTS

Time Course Of Action

Peak effects with LAAM and methadone occurred four hours post-treatment and durations of action were similar with subjects reporting

an earlier peak and greater intensity and duration of effects with LAAM than with methadone. The only significant differences were greater reduction of wakefulness and attentiveness, and a higher incidence of nausea and vomiting with LAAM than with methadone.

The duration of action of LAAM was not significantly longer for LAAM than methadone.

Cross-Tolerance Of LAAM-Treated Subjects To Intravenous Morphine

Subjects experienced a slight rush and could distinguish morphine from placebo. A slight "high" was reported, usually soon (3-8 hours) or long (52-54 hours) after treatment with LAAM. Responses were not completely dose related and LAAM was not invariably effective in suppressing the effects of morphine.

Clinical Laboratory Studies

Electroencephalograph Findings--Sixty-five percent of methadone and 33 percent of LAAM subjects had abnormal EEG findings ($p < .10$, two-tailed test), consisting of diffuse slowing (usually in temporal and occipital regions), low level of paroxysmal activity and bursts.

All methadone subjects with high Cornell Medical Index scores on admission had significant EEG abnormalities (8/8); none of the LAAM subjects with high C.M. I. scores did (0/5).

The increase in slow wave activity which usually follows hyperventilation was suppressed in both groups with only 19-29 percent showing the expected response.

The "driving" of the EEG which generally occurs with photic stimulation was likewise suppressed in LAAM and methadone subjects occurring in only 35 percent and 5 percent.

Hyperglycemic Response--Both drugs produced a significant hyperglycemic response; the difference between mean blood glucose levels for methadone (103 mg percent) and LAAM (117 mg percent) was significant ($p.<0.05$). There was also a significant difference ($p.<0.05$) between the number of subjects with abnormally high blood glucose levels with LAAM (14) and with methadone (5).

Liver Function Abnormalities--The SGOT, albumin, and alkaline phosphatase determinations in both groups showed a higher incidence of abnormalities, suggesting slight impairment in liver function.

Hematology--Abnormally high white blood counts occurred in 35 percent of methadone and 29 percent of LAAM subjects.

Thyroid Function And Urine Analysis--No significant abnormalities were found in these areas.

Effects On Cognitive Performance

LAAM maintenance subjects' performance on cognitive tasks was significantly better than methadone maintenance subjects' on tests involving memory, learning, speed, and accuracy, and did not differ significantly from the past performance of a control group of college students.

11

ACUTE TIME-DOSE-RESPONSE EFFECTS OF CYCLAZOCINE, METHADONE, AND METHADYL IN MAN. 1973

SAMUEL IRWIN, ROBERTA G. KINOHI,

PAUL M. COOLER, DOUGLAS R. BOTTOMLY

INTRODUCTION

This study proposed to investigate the acute time-dose-response effects of cyclazocine, methadone, and 1-alpha-acetylmethadol with respect to psychosocial, cognitive, and physiologic functions. The profiles and durations of action were of particular interest, as were the nature of the differences between the three drugs. The investigations and findings with respect to cyclazocine will not he reported in this summary.

EXPERIMENTAL DESIGN

Subjects

Twenty-eight male, nonaddicted volunteers 21-35 years of age were paid to participate in the experiment and were screened for mental and physical health.

Methodology

Subjects received two doses of drug orally at least one week apart on a randomized, coded, double-blind basis. Fourteen subjects received placebo. Seven subjects were used per dose level of drug. Dosages were .l and .2 mg/kg methadone hydrochloride and 0.8 and .16 mg/kg l-alpha-acetylmethadol.

Trained observers assessed the subjects on a scale of 0.8 at -60, 20, 80, 160, 220, and 280 minutes before and after treatment using the Irwin Comprehensive human Assessment Procedures. A subjective state questionnaire (SSQ) and adverse symptom checklist (ASC) were completed by the subject at 12 and 24 hours posttreatment. A variety of special performance tests were also used. Placebo effects were subtracted from the scores in reporting data.

RESULTS

Peak, Duration, And Intensity

Peak time effects for all drugs tested occurred about three hours posttreatment.

The duration of effects with the high dose of 1-alpha-acetylmethadol was over 24 hours; for methadone it was 12 hours or less.

With respect to the intensity of drug effects, the higher dose of 1-alpha-acetylmethadol produces effects similar to hut somewhat less in intensity than the lower dose of methadone.

The two modes of assessment, observer rating and subject's self-reporting, correlate highly with each other.

Profiles Of Action

All drugs produced biphasic effects, most often an early activation, elevation of mood, and liking for the drug followed by a later depressant effect and dislike for the drug.

The effects of 1-alpha-acetylmethadol were primarily activating and included:

Slightly increased capacity for functioning

Increased arousal, drives, energy, speed and durations of movement and expressiveness

Slightly improved mood and emotions

Methadone, on the other hand was generally depressant and its effects were:

Impairing arousal, focusing, and psychomator activity

Distorted perceptions

Worsened moods and emotions

On several measures, however, 1-alpha-acetylmethadol produced effects similar to the effects of methadone in reducing:

Impulse control
Memory
Respiratory rate
Pupil size
Facial skin color

and in promoting:

Ataxia
Unusual body sensations
Distorted senses
Light headaches
Itching

As these effects are characteristic of the effects of narcotics in general, it would seem that methadone and 1-alpha-acetylmethadol are similar in potency but differ in their qualitative effects.

12

COMPARISON OF ACETYLMETHADOL AND METHADONE IN THE TREATMENT OF LONG-TERM HEROIN USERS: A PILOT STUDY. 1970

JEROME H. JAFFE, CHARLES R. SCHUSTER,
BETH B. SMITH, PAUL H. BUCHLY

INTRODUCTION

dl-alpha-acetylmethadol has been shown to prevent withdrawal symptoms for more than 72 hours (Fraser and Isbell, 1952). Its effectiveness as a substitute for methadone in maintenance treatment of narcotic addicts was the subject of this study.

EXPERIMENTAL DESIGN

Subjects

Twentyy-one participants in a methadone maintenance clinic stabilized on 20-90 mg of methadone per day served as subjects. Twelve were randomly assigned to the experimental group and nine to the control group.

Methodology

Study design

The study was a double-blind, controlled study lasting seven weeks.

Patients reported to the clinic three days per week.

Dosages--experimental group

Dosages were computed initially at 1.2 times the usual methadone dose and increased slightly in two cases.

Subjects received dl-alpha-acetylmethadol on Mondays, Wednesdays, and Fridays, and placebo (dextromethorphan hydrobromide added to the usual vehicle) on alternate days.

The average dose of dl-alpha-acetylmethadol was 50 mg three times weekly (range 24-66 mg).

Dosages--control groups

The control group received their usual daily dose of methadone hydrochloride.

The average dose was 37 mg/day (range 20-55 mg).

Criteria for effectiveness

Urines were checked for illicit opiate use at each clinic visit (three times/week).

The opiate withdrawal subscale of the Addiction Research Center Inventory (ARCI) and a symptom checklist measuring intensity of withdrawal were filled out three times weekly.

Open-ended interviews were held with the staff three times weekly.

Baseline measures were obtained for two weeks before the new drug was introduced.

Intensity of withdrawal from methadone and dl-alpha-acetylmethadol was studied by administering placebo in place of active medication in six control and six experimental patients. This was done on Monday of the seventh week, 48 hours after the last dose of methadone, and 96 hours after the last dose of dl-alpha-acetylmethadol. All patients were provided with a dose of methadone to take in case of emergency.

RESULTS

Dropout Rate

Four patients in the experimental group dropped out on the first day complaining of abdominal pain.

There were eight patients in each group at the end of the study.

Withdrawal Symptom Reports

There were no significant differences between the experimental and control groups on the opiate withdrawal subscale of the ARCI and the withdrawal symptoms checklist during the two week baseline period.

Control group

No change was evidenced from baseline with a 24-hour interval between doses.

of the six patients who experienced a 48-hour interval with placebo, two took their emergency doses of methadone at 36 hours and the remaining four experienced intense withdrawal distress at 48 hours.

Experimental group

No change was evidenced from baseline at 24- and 48-hour intervals between doses.

At 72 hours there was a slight rise in the opiate withdrawal subscale of the ARCI, but no change in the symptom checklist or during the interview.

At 96 hours there was a marked rise in intensity of withdrawal Symptoms as measured by the test and interviews.

Measures Of General Functioning

Urine analysis showed no difference between the two groups in illicit drug use.

The two groups also did not differ with respect to numbers employed, arrest rate, or admissions of illegal activity.

Adverse Experiences

Side effects of anxiety and nervousness were perceived as sufficiently troublesome to 4 out of 12 subjects in the experimental group to cause them to drop out of the study.

13

METHADONE AND 1-METHADYL ACETATE: USE IN MANAGEMENT OF NARCOTIC ADDICTS, 1971

JEROME H. JAFFE AND EDWARD C. SENAY

INTRODUCTION

Racemic methadyl acetate (dl-alpha-acetylnethadol) has been shown to be effective in suppressing narcotic withdrawal syndrome for periods up to three days (Jaffe, 1970). There are substantial differences between the d- and l-isomers in effectiveness in suppressing the withdrawal syndrome (Fraser and Isbell, 1952). In view of the limited clinical experience with either isomer, the purposes of this study were:

To gain further clinical experience with 1-alpha-acetylmethadol

To determine if 1-alpha-acetylmethadol could be used interchangeably with methadone

EXPERIMENTAL DESIGN

A controlled clinical study was carried out to determine if 1-alpha-acetylmethadol could be effectively substituted for methadone on weekends.

Subjects

The subjects were volunteers participating in a methadone maintenance program, stabilized on a 30-100 mg. dose of methadone per day for three weeks prior to the experiment.

Experimental Group--The experimental group consisted of five male patients taking a mean daily dose of 50 mg. (range, 40-60 mg/day) of methadone.

Control Group--The control group consisted of five male patients taking a mean daily dose of 68 mg (range, 30-100 mg/day) of methadone.

Methodology

Study Desire

The groups were studied for three weekends.

Patients were randomly assigned to drug or control groups; clinical observers were blind to who was in which group.

The experimental group received 1.2 mg of 1-alpha-acetylmethadol for every 1 mg of methadone in his daily dose (a three-day dose); they were given two 30 mg doses of dextromethorphan hydrobromide to take home as placebos.

The control group received their usual dose of methadone at the clinic and two doses of methadone to take at home.

Criteria For Effectiveness

Urine was collected and tested for the presence of narcotics.

Clinical interviews were held on Fridays and Mondays.

Symptom checklists were filled out by the subjects on Fridays and Mondays prior to receiving their medication.

Clinic attendance was noted.

Requests for increase in medication was noted.

RESULTS

The frequency of urine specimens positive for morphine was the same in both groups (one in each group).

"Blind" experimenters found nothing in the behavior or reports of subjects to indicate which medication they had received.

Patients in both groups complained of sweating; all had reported problems with sweating prior to the study.

No side effects were reported by either group.

The rates of clinic attendance did not differ.

Subjects in both groups complained of their medication not holding; the conversion factor was increased in the experimental group to 1.2 - 1.5 mg (mean 1.3 mg) 1-alpha. acetylmethadol to 1 mg methadone hydrochloride.

14

METHADYL ACETATE VS METHADONE: A DOUBLE-BLIND STUDY IN HEROIN USERS.1972

JEROME H. JAFFE, EDWARD C. SENAY,
CHARLES R. SCHUSTER, PIERRE F. RENAULT,
BETH SMITH, SALVATORE DIMENZA

INTRODUCTION

A pilot study using dl-alpha-acetylmethadol (DLAAM) interchangeably with methadone in a maintenance program (Jaffe et al., 1970), confirmed earlier findings of the ability of this drug to prevent development of abstinence syndrome for 72 hours (Fraser and Isbell, 1952). The purpose of this study was to gain further experience with the drug in more extensive trials.

EXPERIMENTAL DESIGN

Subjects

Subjects were 66 male heroin addicts, age 20 through 50, screened by physical and laboratory examination.

Methodology

The study was carried out under double-blind conditions and lasted 15 weeks.

Subjects were randomly assigned to one of four groups in the study design.

- Experimental group receiving DLAAM three times a week and dextromethorphan placebo on alternate days (19 subjects)
- Control group receiving methadone daily (15 subjects)
- Waiting list detoxified with methadone receiving no further medication (16 subjects)
- Treatment group of the patient's choice exclusive of the experimental and control groups in the study (16 subjects)

Adjustments were made in dosage of medication by patients' requests to the weekly visiting physician. The program physician was blind to medications and levels.

All medication was initially taken at the clinic under observation; take-home doses of methadone and placebo were later allowed.

Criteria For Effectiveness

The following measures were used to determine the relative effectiveness of the drugs:

- Frequency of illicit drug use as determined by urinalysis
- Twice weekly completion of the morphine and opiate withdrawal subscales of the Addition Research Center Inventory (ARCI) and a withdrawal symptom checklist

Weekly self-report of illicit drug use, criminal activity, and legitimate employ ment

Clinic participation defined as keeping clinic appointments and group therapy; a dropout was defined as a person who did not attend for two consecutive weeks and was discontinued in the study

Adverse Experiences Looked For

The following tests were taken initially and at the end of the study as indicators of the safety of the drug:

CBC
Urinalysis
Liver-function tests
BUN
Serrum uric acid determinations

RESULTS

Data for those subjects in the group assigned to clinics of their choice will not be reported; 12 of 16 of these patients did not report to clinics assigned to them.

Statistical analysis of data was based upon patients who completed at least eight weeks of treatment: 15 subjects in the experimental and 15 in the control group.

Dropout Rate

Five (26.3 percent) subjects left the DLAAM group; two (13.3 percent) left the methadone control group. This difference was not statistically significant.

The average length of stay for the dropouts was 5.8 weeks in the experimental group and 10 weeks in the control group.

Employment

Both groups evidenced increases in employment. The experimental group had 12 (80 percent) employed at the end of the study and 4 (26.7 percent) employed at the begin ning; 10 (66.7 percent) of the methadone control group were employed at the end, 4 (26.7 percent) at the beginning. These changes were statistically significant.

Arrests

Decreases were observed in arrest rates for both groups compared to arrest rates in the two years prior, however, the sample size was too small for a determination of statistical significance either between groups or as a result of treatment.

Illicit Drug Use

Seventy-one and one-tenth percent of the treatment weeks were characterized by "clean" urines for the control group and 49 percent for the experimental group. The difference was not statistically significant.

Clinic And Group Therapy Attendance

Clinic attendance was high for both groups and quite similar (93.3 percent, experimental; 91.8 percent, control). Group therapy attendance was lower for both groups (60.5 percent, experimental; 61 percent, control) and the difference between them was not significant.

Clinical Observations

There were no differences in the subjective reports of patients; the "blind" physician could not distinguish between DLAAM and methadone groups.

Dose Level Changes

Dosages were 30-80 mg methadone hydrochloride/day and 36-80 mg DLAAM/active dose. All patients requested increases in the initial two weeks; an equal number from each group requested increases thereafter. Most patients required a higher dose of DLAAM for the 72-hour (Friday to Monday) interval than the 48-hour intervals.

Withdrawal Scales

There was no significant difference between the two groups on any withdrawal scale.

Medical Data And Adverse Experiences

Liver Function--Only seven of the 66 patients had normal results on liver-function tests upon initial examination; profiles remained unchanged at the end of the study

Hematology--Most subjects were normal initially and at the end of the study.

Four reverted to normal
tie remained the same
Two did not return for reevaluation

In one subject, the hematocrit dropped from 48 percent to 39 percent but hemoglobin level, RBC, and WBC remained normal.

White Blood Cell Counts--All were stable except in three subjects.

In one subject, the initial count was 12,800/cu mm and the count at reevaluation was 3,400/cu mm; he had been treated with trifluoperazine hydrochloride prior to reevaluation.

Changes from 8,500 to 4,000/cu mm and 7,100 to 41,000 cu mm were observed in two other patients. No symptoms were associated with any of these changes.

VDRL And Fluorescent Treponemal Antibody Tests (FTA)--Thirteen subjects had positive results for VDRL and FTA tests initially; these values were unchanged at reevaluation except in one subject whose results reverted to negative.

Side Effects--There were few complaints of side effects and no toxic reactions. Complaints of decreased libido came out in conversations; two patients complained of impotence. Jerking and twitching of arms and legs when at rest was complained of by two subjects.

15

SIMULTANEOUS DETERMINATION OF ACETYLMETHADOL AND ITS ACTIVE BIOTRANSFORMATION PRODUCTS IN HUMAN BIOFLUIDS. 1975

ROBERT F. KAIKI, NITHIANANDA CHATTERJIE, CHARLES E. INTURRISI

INTRODUCTION

The long duration of acetylmethadol (AM) suggests the biotransformation of AM to active metabolites.

AM, noracetylmethadol (NAM), methadol (MOL) normethadol (NMOL) have been identified in the urine of AM maintenance subjects (Kaiko and Inturrisi, 1973). Dinoracetylmethadol (NNAM) was identified by Billings (1973) in the biofluids of rats given AM and has been found in plasma and urine of AM maintenance subjects (Kaiko and Inturrisi, *Fed. Proc.,* 1974).

This report describes a specific and sensitive method for quantifying AM, NAM, and NNAM in human plasma and urine. The details of the extraction, identification, and quantitation procedures are beyond the scope of this summary; results will be reported.

RESULTS

Plasma

Most plasma samples contained AM, NAM, and NNAM in concentrations above 0.020 ug/ml. Concentrations of MOL and NMOL above this were not observed in any samples obtained.

Urine

A mean of 20 percent of the administered dose was recovered as AM and biotransfomrmation products in total urine collected 48 hours after dosing; approximately 2 percent was recovered as AM, 8 percent as NAM, 5 percent as MOL, and 13 percent as NNAM. The pattern of excretion is the same regardless of dosage.

Summary

Other routes of elimination (the gastrointestinal tract) and other biotransformation products are likely. Biotransformation is a prerequisite for the elimination of AM and N-demethylation is quantitatively more important than deacetylation in the human.

16

DISPOSITION OF ACETYLMETHADOL IN RELATION TO PHARMACOLOGICAL ACTIVITY. 1975

ROBERT F. KAIKI AND CHARLES INTURRISI

INTRODUCTION

Acetylmethadol has been shown to have a 72-hour duration of action (Fraser and Isbell, 1952) which has been attributed to the biotransformation of acetylmethadol to active metabolites (McMahon et al., 1965; Sung and Way, 1954; Veatch et al., 1964). Acetylmethadol, noractylmethadol and dinor-acetylmethadol have been identified in human Plasma (Kaiko et al., in press; Kaiko and Inturrisi, 1973; Billings and McMahon, 1974).

This report describes the disposition of acetylmethadol in maintenance subjects with particular emphasis on the relationship between the time course of acetylmethadol and its biotransformation products in plasma and the timeaction of pupillary miosis.

EXPERIMENTAL DESIGN

Subjects

Subjects were 12 adult males; eight were maintained on a mean dose of 50 mg (range 40-60) acetylmethadol three times weekly for 4-25 weeks. Four others were inpatients, dosages and history not stated.

Methodology

Plasma--Venous blood samples were collected just prior to dosing (i.e., 72 hours after last dose) and at 4, 8, 24 and 48 hours from all patients.

Urine--The eight maintenance subjects provided urine specimens at 0, 24 and 48 hours after administration of acetyl-methadol; urine was collected at 0, 4, 8, 24 and 48 hours from the hospitalized patients.

Extraction And Estimation--A multistep solvent extraction procedure (Kaiko et al, in press) was employed; noractylmethadol and dinoracetylmethadol were converted to corresponding amides and measured as equivalents. Qantitation was achieved by the addition of an internal standard, SKF 525-A, prior to extraction.

Measurement Of Pupil Size--Miotic effect was calculated by subtracting the size of the pupil (determined photograph-ically) at each blood sampling time from the baseline (0-hour) size.

Apparent Half-Life, Renal Clearance And Urinary pH--Regression analysis program was used to calculate the apparent half-life for elimination of the compounds from plasma. Renal clearance values were

calculated using the average rate of urinary excretion of each compound for the four to eight hour collection period and the corresponding plasma concentration at the midpoint of the collection period (6 hours). Urinary ph was measured with a Metrohm E-512 pH meter.

RESULTS

Time Course, Mean Plasma Levels and Mean Pupillary Constriction in the Eight Maintenance Subjects

Acetylmethadol

None present at 0 hour
Peak level 0.060 µg/ml at 4 hours
Rapid decline to 0.013 µg/ml at 24 hours
Undetectable at 48 hours

Noracetylmethadol

0.042 ug/ml at 0 hour
Peak level 0.114 µg/ml at 4 and 8 hours
Slow decline to 0.068 µg/ml at 48 hours

Dinoracetylmethadol

0.052 µg/ml at 0 hour
Peak levels ranged from 0.057-0.123 µg/ml at 4 hours
Levels did not decline during sampling

Pupillary Constriction

Pupillary constriction was greatest at 8 hours, 1.8 mm.

Return to predose value was slower than rate of disappearance of acetylmethadol but faster than rate of disappearance of noracetylmethadol.

Time-action of miotic effect corresponds most closely with noracetylmethadol in plasma.

The effect of dinoracetylmethadol could not be ascertained since plasma levels did not decline.

Apparent Half-Life for elimination of compounds from Plasma

Acetylmethadol had an apparent half-life of 7 hours (range 2-12 hours).

Noracetylmethadol had an apparent half-life of 48 hours (range 13-78 hours).

Dinoracetylmethadol levels did not decline, therefore, no calculation of half-life value was possible.

Renal Clearance and Urinary pH--The subject with the lowest urinary pH exhibited the highest renal clearance of all three compounds; the subject with the highest urinary pH exhibited the lowest renal clearance values.

Correlation Between Plasma Levels and Drug Effect--Miotic effect is more closely associated with noracetylmethadol plasma levels ($p < 0.10$) than with the acetylmethadol dose ($p < 0.10$). Spearman's correlation coefficient was used to determine the relationship between noracetylmethadol plasma levels and parameters which might influence its magnitude. High plasma levels of any one of the compounds tend to be associated with high levels of the others.

Noracetylmethadol plasma level is a more reliable correlate of the effect of acetylmethadol than is the acetylmethadol dose.

Noracetylmethadol plasma level is more a function of other factors relating to its disposition than the acetylmethadol dose.

17

THE USE OF 1-ALPHA-ACETYL-METHADOL (LAAM) AS COMPARED TO METHADONE IN THE MAINTENANCE AND DETOXIFICATION OF YOUNG HEROIN ADDICTS, 1973

WALTER X. LEHMANN

INTRODUCTION

The purposes of the study were to:

- Compare LAAM with methadone for effectiveness in a short-term, low-dose maintenance program
- Determine whether LAAM has potential as a medication of choice for heroin addicts
- Compare LAAM with methadone with respect to ease of withdrawal and note any clinical problems which might arise

EXPERIMENTAL DESIGN

Subjects

Forty-two male and female heroin addicts between the ages of 16 and 21, enrolled in the heroin detoxification program at Vitam Center, Norwalk, Connecticut, served as subjects.

Methodology

Study Design--The study had two forms:

A double-blind comparison of LAAM and methadone

- Fourteen patients received 10 mg doses of LAAM every 72 hours and placebo on intervening days
- Twenty-one patients received methadone daily in doses sufficient to maintain a comfortable state

An open study in which the drug and dosage were know to the patients

- Seven patients received LAAM every third day
- No placebo was given on intervening days

The duration of the study was 16 weeks after which patients were detoxified; they were followed up as long as they remained in the program. Withdrawal was accomplished on an inpatient basis by lengthening the interval between doses for a week then stopping the drug completely.

Criteria For Effectiveness--Patients were observed daily with respect to the following:

- Physical and emotional reaction
- Performance of job functions in the center
- Performance in group and individual therapy
- Atheletic involvement

High school and special education involvement
Community and home involvement
Toxic reaction

Urines were collected and analyzed three times a week during the first two weeks; they were collected three times a week but only analyzed weekly thereafter.

RESULTS

Physical And Emotional Reactions

There were no differences in the physical condition of the three groups. No side effects such as nausea, vomiting, constipation, weakness, or fatigue were reported.

Half the patients in the open study complained of mild discomfort 60 hours after medication which disappeared during the third week.

Emotional reactions were similar for all patients with some tension, depression, and hostility noted initially which dissipated by the third week.

Performance Of Job Functions

There was no difference between groups; performance improved in all groups during the third week.

Performance In Groups And Individual Therapy

There was no difference between grows in either type of therapy; performance &proved during the fourth week.

Athletic Involvement

Athletic involvement was the same for all patients; there was no interference with coordination or ability to perform.

High School And Special Education Involvement

These activities did not start until the 8th and 12th weeks, respectively; there appeared to be no differences in performance.

Community And Home Improvement

This applied only to those living in; no differences were noted between groups and there was improvement after the fourth week.

Toxic Reactions

No toxic reactions were noted; it was not necessary to terminate treatment in any cases

Urinalysis

There were no urines positive for nonprescribed drugs in either group.

Withdrawal

Withdrawal from LAAM and methadone was accomplished with equal ease; no clinical problems were manifested during withdrawal

18

LEVOMETHADYL ACETATE: PROLONGED DURATION OF OPIOID EFFECTS, INCLUDING CROSS TOLERANCE TO HEROIN, IN MAN. 1973

ROBERT LEVINE, ARTHUR ZAKS, MAX FINK,
ALFRED M. FREEDMAN

INTRODUCTION

Levomethadyl acetate (LAAM)has been determined to have an onset of action which is delayed by four to six hours post-administration and has been demonstrated to have the ability to prevent the development of abstinence syndrome in methadone tolerant patients for 72 hours (Jaffe and Senay, 1971; Zaks et al., 1972), the purpose of this study was to determine the dosage of LAAM which is required to provide blockade to 25 mg of heroin, to prevent opiate withdrawal symptoms, and to provide maximal opiate effect for a minimum of 72 hours.

EXPERIMENTAL DESIGN

Subjects

Seven male volunteers ranging in age from 21-50 years with at least two years of narcotic abuse and two previous treatment failures were used as subjects. They were detoxified and drug free at least seven days before the experiment.

Methodology

Oral doses of LAAM were administered three times a week beginning with 10 mg and increasing 10 mg/week until doses of 100 mg were reached.

Pupillary diameter was measured prior to the experiment and at 24, 48, and 72 hours after the third dose each week. The mean predrug diameter was 6.7 nun. A symptom checklist was completed at these times also.

Heroin challenge of 25 mg was performed at 72 hours following various doses of LAAM.

RESULTS

Adverse Experiences

Three of the seven patients withdrew after five weeks. Dose levels of 50 mg had been obtained by that time.

All patients reported constipation throughout their participation in the study.

Three of the seven patients reported loss of appetite and abdominal discomforts which later disappeared at dose levels greater than 40 mg.

Abstinence Syndrome

At doses of 20-50 mg, six Out of seven patients reported discomfort, yawning, lacrimation, and uneasiness, occurring 48-72 hours post-treatment.

At doses under 70 mg, three out of four remaining patients reported yawning and uneasiness 60-72 hours post-treatment. Symptoms were milder and of shorter duration than at lower doses.

At doses greater than 80 mg, there were no reports of discomfort.

Heroin Challenges

One patient refused to receive heroin. At dose levels of 30 mg LAAM, four patients reported feeling some effects of heroin, two felt none. The mean change in pupillary diameter was 0.8 mm.

At dose levels of 50 mg LAAM, no effect of heroin was perceived. The mean pupillary diameter was 0.1 mm greater following the heroin challenges.

At dose levels of 70 and 100 mg LAAM, blockade was complete.

Sustained Opiate Effects

Twentymg of LAAM produced maximum miosis for 24 hours.

Doses greater than 20 mg produced no further decrease in pupillary diameter; maximum constriction was sustained for 48 hours at dose levels of 30-50 mg LAAM and 80-90 mg LAAM sustained a pupillary diameter of 5.0-5.2 mm for 72 hours.

19

A METHADONE/1-ALPHA-ACETYLMETHADOL (LAAM) MAINTENANCE STUDY.

CHARLES SAVAGE, ELAINE KARP, STEPHEN CURRABN

INTRODUCTION

LAAM has had clinical success as a substitute for methadone (Levine et al., 1973; Jaffe and Senay, 1971; Jaffe et al., 1972). The purpose of this study was to validate past clinical research, to determine the relative safety and effectiveness of LAAM and methadone, and to identify factors associated with treatment success and failure.

EXPERIMENTAL DESIGN

Subjects

Subjects were 99 male heroin addicts; they were, on the average, 28 years old with 11th grade education! seven years narcotic addiction, four to five arrests, and two treatment failures. Half were employed when they entered the study.

Prior to treatment the following data were collected:

Background characteristics

Medical and psychiatric history

Physical examination and chest X-ray

Laboratory examination: EEG, urinalysis, blood chemistry (BUN, glucose, bilirubin, total protein, albumin, alkaline phosphatase, and SGOT), hematology (white blood count, hematocrit and differential)

Cornell Medical Index

Psychological tests: Minnesota Multiphasic Personality Inventory (MMPA), Personal Orientation Inventory (POI), Benton Visual Retention Test, Psychological Evaluation Profile (PEP), Wechsler Adult Intelligence Scale (WAIS)

Methodology

Treatment Groups--Assignment to treatment groups was random and there were no significant differences between groups in background characteristics, EEG results, blood chemistry and hematology measures, and personality measures. Patients and staff were blind to the medications.

Group 1, 52 patients, received methadone daily for three months and then were switched to LAAM three times a week with dextromethorphan placebo on other days.

Group 2, 47 patients started on LAAM and were switched to methadone at three months.

Dosages--All Medication was mixed with Tang and dextromethorphan. Dosage was

flexible. LAAM patients received doses equal to 1.3 times their usual dose of methadone

Assessments--At the end of three and six months, the EEG, physical examination, blood chemistry and hematology tests, and MMPI were repeated.

Urine was checked one to three times a week for quinine, morphine, amphetamines, and barbiturates.

Clinic attendance and changes in social and occupational status were monitored throughout the study.

RESULTS

Dropout Rates

Sixty percent of the methadone group (Group 1) completed three months; 31 percent of the LAAM group (Group 2) completed. This difference was significant (X^2 5.49, p=0.2).

In the crossover phase of the study, 66 percent of the LAAM patients (Group 1) completed the three subsequent months on methadone; 81 percent of the methadone patients (Group 2) completed the three subsequent months on LAAM. This difference was not statistically significant.

With both phases combined, 65 percent of the patients completed treatment with methadone and 47 percent with LAAM.

Analysis Of Reasons For termination

Side effects were given as the most frequent reason for withdrawal regardless of which drug the patients were on by 31 percent of LAAN patients and 23 percent of methadone patients. The difference was not significant.

The specific symptoms reported were the same for both medications: experiencing withdrawal or feeling over medicated.

Urinalysis

The mean percentages of urines positive for illicit drugs were 5 and 8 percent for the methadone and LAAM groups, respectively. The difference was not significant.

Clinic Attendance

The mean absentee rates were 2 percent and 4 percent for the methadone and LAAM groups, respectively. The difference was not significant.

Dose levels

There was no difference in the dose levels of those who completed LAAM treatment and those who dropped out.

Lower dosage methadone patients dropped out more frequently than higher dosage patients.

Physiological Assessments

There were no differences between dropouts and completers in EEG, hematology and blood chemistry results except for bilirubin which was, nonetheless, within normal limits for both groups.

Personality

Dropouts differed from completers in several personality characteristics being:

More suspicious and distrustful (MMPI, Pa Scale)

More impulsive (POI Spontaneity Scale)

Less self-accepting (POI, Self-Acceptance Scale)

More grandiose (PEP, Great Cause Scale)

More easily fatigued, more frequently feeling ill, and more incapacitated due to illness (Cornell Fatigue and Frequency of Illness Scale)

Safety

No deaths or serious illness occurred in patients on either drug.

Methadone patients

EEG measures did not differ pre- and post-treatment

Three hematology measures showed significant changes, however, all were within normal range

Mean value of neutrophiles decreased

Mean values of lumphocytes and basophiles increased

LAAM patients--there were no differences in EEG, blood chemistry or hematology measures pre- and post-treatment.

20

A 48-WEEK STUDY OF METHADONE, METHADYL ACETATE, AND MINIMAL SERVICES. 1974

EDWARD C. SENAY, JEROME H. JAFFE,
SALVATORE DIMENZA, PIERRE F. RENAULT

INTRODUCTION

dl- and 1-alpha-acetylmethadol have been shown to be capable of suppressing narcotic withdrawal symptoms for long periods of time (Fraser and Isbell, 1952). These findings have been confirmed in pilot comparisons with methadone (Jaffe et al., 1970; Jaffe and Senay, 1971; Jaffe et al., 1972). This study reports investigations into the clinical acceptability and safety of the levo isomer, 1-alpha-acetylmethadol, (LAAM), and an evaluation of the role of auxiliary services in the treatment of heroin addiction.

EXPERIMENTAL DESIGN

Subjects

The subjects were male narcotic addicts between the ages of 20 and 50, randomly assigned to one of three groups:

Thirty to methadone with full services
Thirty-one to LAAN with full services
Ninety-six to methadone with no other services

There were no significant differences in the background characteristics of the groups with respect to race, education, employment, arrests, family stability, and drug use influences. The Dispensary group was significantly younger than the Methadone Full Service group but not the LAAM group; the Methadone Full Service group had used heroin longer than the LAAM group or the Dispensary group. The correlation of age with years of heroin addiction was .81; the difference in age is thought to account for the difference in mean number years of addiction.

Methodology

Study Design--The study was a double-blind, controlled study. The LAAM group received active medication three times a week and a 30 mg dextromethorphan placebo on alternate days; attendance at group therapy sessions was requested weekly, and other counseling, vocational, legal and recreational services were provided. The Methadone Full Service group received methadone daily and services as above. The Dispensary group received methadone daily for four weeks and then three times

weekly with take home doses on alternate days. No counseling or services were offered. Dosage modifications were made during the study. The mean initial administered doses were 57.8 for the LAAM group, 40.6 mg methadone for the Methadone Full Service group, and 41.3 mg for the Dispensary group.

Criteria For Effectiveness--The groups were compared with respect to the following variables:

- Dropout rate
- Changes in medication dosages
- Use of illicit drugs (as evidenced in biweekly urine checks)
- Employment rate
- Self-reports of illegal activity and arrests

RESULTS

Failure Of Research Design With Respect To Dispensary

Inpractice, counseling services, and support could not be withheld from the Dispensary patients by the clinic staff, so the comparison made by the study was between full and minimal services rather than between full and no services as intended.

Methadone with full services appeared to be superior to LAAM with full services and to methadone with minimal services.

Dropout Rate

Forty-nine percent of the Dispensary group, 50 percent of the LAAM group, and 29 percent of the Methadone Full Service group had dropped out by week 48. There were no significant differences among treatment groups in total number of weeks of participation in originally assigned group (Dispensary, 30.5 weeks; LAAM, 29.7 weeks; Methadone Full Service, 35.3 weeks). Methadone with or without services had more holding power than LAAM.

Illicit Drug Use

There was an increase in numbers of urines negative for morphine in the Dispensary, LAAM, and Methadone Full Service groups whether based on percentages of remaining sample (72.7 percent, 90.9 percent, and 60.0 percent, respectively), or percentages of the total sample (33.3 percent, 33.3 percent, and 38.7 percent, respectively). Differences between the groups were not significant.

Dosage Changes

Dispensary patients requested significantly fewer changes ($p<0.01$) than did patients in the full services groups (Dispensary: 3 changes/100 ma" weeks of treatment; LAAM: 7 changes/100 man weeks of treatment, Methadone Full Service: 8 changes/100 weeks of treatment). The mean LAAM dose at 48 weeks (93.9 mg) was significantly higher than the mean dose of the Dispensary group ($p<0.01$; 51.7 mg), or the Methadone Full Service group ($p<0.05$; 70.9 mg), but total weekly dosage was less than that of patients on methadone.

Employment Rates

There were no differences in employment rates among the three treatment groups.

Arrests And Illegal Activity

Self-reported illegal activity decreased in proportion to length of time in treatment for all groups. There was no significant difference among groups in self-reports of arrests (Dispensary: 2.1 arrests/100 man weeks in treatment; LAAM, 2.3 arrests/100 man weeks; Methadone Full Service, 3.0 arrests/100 man weeks.

Clinical Observations

There were no observations of confusion, psychotic symptoms, or unpleasant subjective states in any subjects. Anxiety was observed but was not associated with any treatment group in particular. Two deaths occurred, one from suicide and one from lung cancer.

21

THREE TIMES A WEEK LAAM EQUALS SEVEN TIMES A WEEK METHADONE: A PRELIMINARY REPORT OF A CONTROL STUDY. 1974

EDWARD C. SENAY, PIERRE F. RENAULT,
SALVATORE DIMENZA, WESLEY E. COLLIER,
STEPHEN J. DANIELS, WALTER DORUS

INTRODUCTION

LAAM has been shown to be an effective substitute for methadone in the treatment of heroin addiction (Jaffe and Senay, 1971; Jaffe et al., 1970, 1972; Senay et al., 1973). Medication is only one part of therapy, however; and the decreased frequency with which LAAM patients need to visit the clinic may weaken the influence of the rest of the program, i.e., therapy, vocational rehabilitation, and legal services. This paper reports an extension of previous studies to determine whether new LAAM patients attend clinic less frequently than new methadone patients and if treatment outcome is influenced by attendance.

EXPERIMENTAL DESIGN

Subjects

Subjects were randomly assigned to one of two groups.

Experimental (LAAM) Group--Thirty-four male patients were included in this group with the following characteristics:

Average age, 31.1 years

Average education, 11.2 years

Average years narcotic use, 11.7

32.3 percent married

20.6 percent employed

73.3 percent arrested at least once in two years prior to entrance in study

100 percent black

At least 14 weeks in treatment

Control (Methadone) Group--Thirty-one male patients were included in this group with the following characteristics:

Average age, 29.0 years

Average education, 11.5 years

Average years narcotic use, 9.7

30 percent married

25.8 percent employed

70 percent arrested at least once in two years prior to entrance in study

90 percent black, 6.4 percent white, 3.2 percent Spanish origin

At least 14 weeks in treatment

Methodology

Two clinics were established; one dispense LAAM and offered group therapy and individual counseling three times weekly, remaining open with support staff and recreational facilities Monday through Friday. The other dispensed methadone and was open six days a week with Sunday medication taken home.

The two groups were compared on the following criteria:

- Dropout rate
- Clinic attendance
- Urine negative for illegal drugs
- Dosage changes
- Employment
- Arrest
- Side effects

Dose levels were 10 mg higher on Friday for LAAM patients and dosage in both groups could be adjusted weekly. No other medications were prescribed.

RESULTS

Retention Rate And Clinic Attendance

LAAM patients dropped out earlier in treatment; the difference was significant at five weeks. By the end of the fourteenth week, however, there was no significant difference between the two groups. The LAAM clinic retained 23 of 34 subjects. The methadone clinic retained 23 of 31 subjects.

LAAM patients attended the clinic on 57.6 percent of the days it was open and 94.2 percent of the days on which medication was dispensed.

Methadone patients attended the clinic on 90.3 percent of the days it was open, medication being dispensed every day.

Urine Negative For Morphine

The two groups were similar in extent of use of unauthorized drugs. LAAM patients had urines negative for morphine a" average of 10 out of 14 weeks; methadone patients, 9.8 out of 14 weeks. The early tendency for the methadone group to have more urines negative for morphine was reversed after the eighth week when the LAAM group began to use drugs less.

Dosage Changes

The initial average LAAM dose was 44.7 mg; doses were 10 mg higher on Fridays than on Mondays and Wednesdays. At 14 weeks, the average LAAM dose was 44.4 mg.

The average initial daily methadone dose was 33.5 mg and was 36.5 mg at 14 weeks.

Dose levels were very stable throughout the duration of the study.

Employment And Arrests

Employment and arrest measures were identical in both groups:

Two subjects in each group were arrested.

Five of the six patients who had jobs initially still had them at 14 weeks.

One of the 17 unemployed in each group found a job.

Side Effects

No side effects attributable to methadone were reported.

No medical complications developed in either group.

One LAAM patient died due to heroin overdose 48 hours after his second dose of LAAM.

Five patients experienced side effects in the LAAM group.

Four patients had anxiety and nightmares, three in the first month of treatment and the fourth in the second month.

Dose levels were 30 mg (2) and 50 mg (2).

Dose levels were lowered 10 mg in two subjects, one on 30 mg and one on 50 mg. Symptoms did not persist nor did they return when dose levels were increased again.

Dose levels were maintained for the other two patients and symptoms did not persist more than one week.

One patient on 50 mg LAAM exhibited bizarre behavior of which he had no recollection. Medication was reduced to 40 mg and symptoms persisted. He was transferred to a methadone clinic. He subsequently reported having been hospitalized in a mental institution seven years before the study.

22

LEVOMETHADYL IN MAINTENANCE TREATMENT OF OPIATE DEPENDENCE, 1972

ARTHUR ZAKS, MAX. FINK, ALFRED M. FREEDMAN

INTRODUCTION

The 72-hour duration of action of methadyl acetate has been established in single dose and controlled clinical studies (Fraser and Isbell, 1952; Jaffe et al., 1970 and 1971). The purpose of this study was to investigate the potential of levomethadyl acetate (LAAM) in a maintenance program for narcotic addicts and to define dose levels. duration of action, secondary effects; and degree of blockade to heroin.

EXPERIMENTAL DESIGN

Subjects

Subjects were 20 male narcotic addicts age 21 or over with at least a two-year addiction history and one treatment failure. Ten were randomly assigned to the experimental (LAAM) group and ten to the control (methadone) group. The two groups did not differ from each other in age, years of drug abuse, or social class. They were detoxified and drug free at least one week before the study.

Methodology

The duration of the study was six months. Subjects in the experimental group received medication on Mondays, Wednesdays, and Fridays. Dose levels were built up as in-patients; the subjects were discharged when dose levels were attained. Two dose levels of LAAM were established:

Four patients at low dose, 30-40 mg twice weekly and 50 mg on Fridays

Five patients at high dose, 80 mg three times a week

One subject was discontinued because of of a prior seizure disorder

Subjects in the control group were built up to 100 mg methadone hydrochloride daily in the hospital and discharged. After the first month, they attended the clinic twice weekly and received take-home medication.

Criteria For Effectiveness

Subjects were evaluated for changes in vocational and social rehabilitation on a scale from 0 (no change) to 2 (marked improvement).

Substance abuse was monitored by twice weekly urine testing for the presence of morphine, heroin, barbiturates, and amphetamines.

Cross-tolerance to 25 mg heroin was established while drug free and to 25 and 50 mg heroin after induction at 24 hours after treatment for all subjects and 48 hours after for one high-dose LAAM subject. The quality

of the euphoria, voice change, and pupillary constriction were observed; subjects were interviewed and completed an Addiction Research Center Inventory (ARCI) questionnaire.

Adverse Experiences Look For

Laboratory studies of liver function, fasting blood glucose, blood urea nitrogen, uric acid, blood cell caunt, and urinalysis were made prior to and weekly during the study.

RESULTS

Dropouts

One of the nine LAAM subjects dropped out at three months; two of the ten methadone patients dropped out, one at two months and one at four months. Eight LAMM and eight methadone patients remained in the study at six months.

Behavioral Change Ratings

Ratings of change in vocational and social functioning were similar in the two groups; 1.4 for the LAAM group and 1.2 for the methadone group.

Dose Levels

Withdrawal symptoms were experienced by three of the four low-dose LAAM group, 40-48 hours following their last dose.

At the 80 mg LAAM dose level, no withdrawal symptoms or craving for heroin were reported.

Cross-Tolerance To Heroin

Three low-dose LAAM subjects responded to challenge with 50 mg heroin with mild, transient euphoria; blockade was complete in the fourth subject.

All five high-dose LAAM subjects demonstrated complete blockade to 50 mg heroin.

The high-dose subject challenged at 48 hours demonstrated complete blockade to heroin.

All 10 100 mg methadone subjects demonstrated complete blockade to 50 mg heroin.

Urine Tests

The LAAM group had 8.9 percent positive tests for morphine compared to 2.0 percent for the methadone group. High- and low-dose LAAM subjects had 2.8 percent and 18.9 percent, respectively.

The LAAM group had 2.0 percent positive tests for barbiturates and amphetamines compared to 7.9 percent for the methadone group.

Adverse Experiences And Side Effects

The methadone group did not complain of side effects; constipation at the beginning of treatment was acknowledged by four subjects when asked.

Three of nine LAAM subjects complained of irritability; one of these also complained of anxiety. Tranquilizers were prescribed to two patients.

Two of the LAAM subjects complained of involuntary, jerky movements of the extremities preceding sleep, persisting intermittently throughout the study.

Results of all laboratory tests were normal for both groups except liver function tests. All subjects manifested intermittent elevated transaminase levels which were sporadic and not dose related.

This chapter and the following present summaries of the Phase II clinical studies of LAAM. A8 discussed in the introductory chapter, both of these studies were initiated by SAODAP to detenmine safety and effectiveness of LAAM. The clinical trials in each of the Phase II studies were carried out simultaneously in multiple participating clinics utilizing a common protocol. This procedure ensured attainment of adequate sample sizes within a reasonable time and of a more geographically representative sample of addicts than possible in a single clinic. Also, this procedure permits analysie of variation in outcome between different clinics. Organization, execution, monitoring of both studies and data compilation, analysis, interpretation and reporting were performed by C. James Klett, Chief VA Central Neuropsychiatric Research Laboratory and Cooperative Studies Program Support Center. The following summaries of the VA and SAODAP Cooperative Studies of LAAM and Methadone were prepared from progress reports submitted by Dr. Klett to FDA as sponsor of the Phase II IWD.

SUMMARY OF VETERANS ADMINISTRATION PHASE II COOPERATIVE STUDY FOR LAAM AND METHADONE

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Although early studies tend to substantiate the observation of the clinical usefulness of acetylmethadol, the number of patients studied was quite small. The present study attempted to maximize subject availability by means of multihospital participation in a common double blind protocol. The goals of the study were to evaluate the safety and toxicity of a fixed dose of acetylmethadol (80 mg TIW) and to compare its relative efficacy with two doses of methadone, a high (100 mg) and a low (50 mg) daily dose. Safety and toxicity were evaluated by a multilayer clinical and laboratory monitoring system. Relative efficacy was measured in terms of a number of outcome variables, including positive urines, clinic attendance, employment, and social rehabilitation. A secondary goal of the study was to compare the two methadone doses with regard to these same outcome variables, since the desirability of high dose versus low dose methadone maintenance remains an issue of controversy. Originally, Dole and Nyswander (1) had advocated a rather high methadone dose. It was felt that this would produce a physiological "blockade" against the effect of heroin and would thus discourage further experimentation with illicit drugs. Others have questioned the need for this high (80-120 mg) dosage. Garbutt and Goldstein (2), for instance, have found an average of 50 mg to be just as effective as 100 mg with respect to survivorship in the program and cessation of heroin use.

METHOD

Patients

Patients were eligible for the study if they met all of the criteria for admission to methadone maintenance programs as defined by the FDA and were males between the ages of 18 and 60. Patients were excluded for incapacitating or life-threatening conditions, disease requiring regular repeated medication, frankly psychotic states, epilepsy, current severe alcoholism, and pending criminal charges. It was further specified that any addicted spouse or relative in the same household must be under treatment and that there be a reasonable expectation that the patient would continue to reside in the vicinity of the clinic and be able to attend for the full duration of the trial. Eligible patients who signed an informed consent for voluntary participation in the study were then given a general physical examination with neurologic and

psychiatric evaluation and including chest x-ray, electrocardiogram, urinalysis, and blood studies. Patients began treatment on the following Monday.

Drug Administration

Patients were randomly assigned to levo-alpha-acetylmethadol or one of two dose levels of methadone. The two methadone groups received active medication daily but the acetylmethadol group received active medication on Monday, Wednesday, and Friday with placebo (dextromethorphan plus quinine) on all other days. Take-home doses (of the Tuesday, Thursday, Saturday, Sunday doses only) were permitted at the physicians' discretion after the twelfth week of treatment. Take-home doses of acetylmethadol were not permitted; any take-home dose in this group was placebo. All doses were dispensed in a masking-diluting liquid such as Tang or grapefruit juice.

The first dose in all three groups was 30 mg which was incremented by 10 mg on each succeeding Monday until the patient achieved his target dose of 50 mg of methadone (M-50), 100 mg of methadone (M-100), or 80 mg of acetylmethadol (L-80). All doses were dispensed double-blind with the sequence of dosage increments and placebo doses controlled by bottle number. Duration of treatment was 40 weeks (280 days).

Psychotrophic drug use was permitted only for occasional nighttime sedation. All use of supplemental medication during the trial was recorded.

Clinical Evaluations

Patients were evaluated immediately before and every four weeks during their tenure in the study. The evaluation included a brief history, a current status record of their employment activity, legal involvement, interpersonal relationships and drug use during the preceding four weeks, a supplementary medication record of all drugs prescribed during the preceding four weeks, and a symptom-sign checklist. The complete physical examination was repeated at the twelfth week and at the end of the study, with abbreviated physical exams at all other four week evaluations. Vital signs (blood pressure, temperature, pulse) and weight were recorded on these occasions and fluid samples were obtained for laboratory tests.

In addition, daily entries were required on a treatment record of each patient's adherence to the clinic schedule of visits and details of medication dispensed. Urine samples were collected weekly following a random testing sequence supplied centrally. Specimens were sent to the clinical laboratory at the Sepulveda VA Hospital where they were tested for morphine, barbiturates, amphetamines, and a variety of other substances. Whenever a patient concluded treatment, an attempt was made to repeat all evaluations and the staff recorded their consensus judgment of outcome in a number of different areas.

RESULTS

Characteristics of Sample

The sample consisted of 430 men whose median length of addiction to opiates was 7.2 years. They were reasonably young (58% were below the mean age of 31 years) and reasonably well educated 62% had graduated from high school and 21% had gone on to do some college work. Mast had been married at one time but 37% were still single. Racially, 46% were black, 39% white, and 11% had Spanish surnames. Other characteristics were consistent with expectation in an addict group.

Early Termination

Only 42% of the starting sample completed the full 40 weeks of the study. If all reasons for termination are combined, 69% terminated early from the L-80 group (N=142), 58% from the M-50 group (N=146), and 48% from the M-100 group (N=142). This difference between the L-80 and M-100 groups is statistically significant. Not all of these patients terminated for drug related reasons but since the nondrug related terminators should have been equally distributed among groups except for chance, it has to be concluded that high-dose methadone maintenance (M-100) was superior in retention to the L-80 group. It does not necessarily follow that high-dose methadone is the superior maintenance drug, however, because there are other dimensions of outcome that must be considered.

The average length of stay in the study before early termination was remarkably similar for the three groups: 82 days for the two methadone groups and 81 days for the L-80 group. Of the 251 early terminations, 45% occurred by the end of the seventh week (which marked the end of the induction period for the M-100 group). A greater number of terminations had occurred

in the L-80 group by this time but when the groups were adjusted for their total number of dropouts, there was no apparent trend for patients to drop earlier from one group than another.

Table 1 presents the number of patients in each group who terminated early for a variety of reasons. The only significant differences between groups for specific categories of dropout were: a greater number for side effects in the L-80 group than in the M-50 group, and a greater number of "No shows" in the L-80 group than the M-100 group. (Note: In these and all subsequent analyses, $p<.05$ was accepted as the level of statistical significance.)

TABLE 1

Reasons for Early Termination

Reaons	M-50	M-100	L-80	Total
Jail	11	5	10	26
Side effects	0	3	8	11
No show for 7 days	4	1	8	13
Moved from area	11	11	12	34
Medication not holding	11	8	16	35
Dose too high	4	10	5	19
Disciplinary discharge	7	3	3	13
Didn't like study	16	11	14	41
Didn't like drug	1	1	2	4
Detoxification	6	8	7	21
Couldn't attend clinic	5	1	3	9
Psychiatric	6	4	5	15
Miscellaneous	2	1	4	7
Excessive drug use (illicit)	1	1	1	3
Total	85	68	98	251

Safety

There were no deaths of study patients, nor were there any serious adverse reactions reported. There were 11 patients terminated primarily for side effects. Four L-80 patients terminated because of inability to ejaculate and another L-80 patient who terminated because of swelling of joints listed decreased sexual interest along with heartburn, nodding, and constipation. The other L-80 terminators were: a patient who couldn't keep medication down (nausea, vomiting); another who complained of being tired and dizzy with chest and arm pain; and one who experienced jerking of extremities at bedtime and some nausea. The three high-dose methadone patients were terminated because of: a pruritic maculo-papular rash that developed on a second day while the patient was still on 30 mg; abnormally high liver function tests which were present before treatment but showed only minor trends toward stabilization at a lower level; and an apparent case of hone marrow suppression.

The symptom-sign data were collected by a research assistant, nurse, or primary therapist before the Monday dose every week for the first eight weeks and every four weeks thereafter. The schedule consisted of 30 symptom-signs and an "OTHER" category. Specific symptom-signs were not enumerated, but when their presence was elicited by general questioning, their severity was judged as mild, moderate, or severe.

Initially each symptom-sign was monitored independently as well as in a priori clusters. When sufficient data had accumulated, the schedule was factor analyzed and a three factor solution accepted as the best representation of the data. The first factor (14 items) is clearly an Underdosing withdrawal factor. It consists of Aching Bones and Joints, Yawning, Runny Nose, Watery Eyes, Muscle Cramps, Goose Bumps, Loss of Appetite, Abdominal Cramps, Nausea and Vomiting, Diarrhea, Insomnia, Excessive Sweating, Irritability, and Anxiety (tension, nervousness). The second factor (five items) is an Overdosing factor which consists of Feeling High, Nodding, Dizziness on Standing, Poor Concentration, and Impotence. The remaining 11 items made up a third factor which was termed Somatic: Heartburn-Gastric Distress, Constipation,Bad Dreams and Nightmares, Drowsiness, Blurring of Vision, Urinary Frequency, Decreased Sexual Interest, Delayed Ejaculation, Numbers of Hands and Feet, Involuntary Jerking Movements of Lower Extremities, and Edema of Extremities. These three factors and their sum which was referred to as Total Symptomatology were subsequently monitored along with the individual symptom-signs.

As a general statement, reporting of any symptom-signs was infrequent and of a low level of severity when reported. All three factor scores and total symptomatology had their highest level in the first week or two of treatment but rapidly decreased to nearly absent levels. There were no differences between drugs worth noting. Because of special interest in several specific symptom-signs, this analysis was supplemented by another approach which used the patient as the unit of analysis and examined individual symptom-signs (rather than dealing with the mean level of a cluster). For each symptom-sign separately, a patient was tallied as "severe" if he had even one such rating at any time during his tenure in the study. A patient who was never rated as "severe" but had at least one rating of "moderate" was tallied in that category and if a patient was never rated as "moderate" or "severe" but had at least one rating of "mild", he was tallied in that category. Patients tallied under "none" were those rated as asymptomatic throughout. In this particular approach, the pretreatment rating was ignored completely. To be tallied somewhere in the table, a patient had to have at least one rating during treatment; patients who completed the study could have as many as 16. This approach defines the highest rating obtained during treatment per patient as a unit of analysis. Table 2 presents these data for all three drug regimens combined.

TABLE 2

Number and Percent of Patients in Terms of Highest Severity Rating Obtained During Treatment

	None		Mild		Moderate		Severe	
	N	%	N	%	N	%	N	%
Aching bones and joints	152	37	130	32	108	27	18	4
Yawning	171	42	152	37	75	18	10	2
Runny nose	136	33	163	40	97	24	12	3
watery eyes	160	39	158	39	79	19	11	3
Musle cramps	212	52	118	29	60	15	17	4
Goose bumps	221	54	106	26	70	17	10	2
Loss of appetite	117	29	156	38	117	29	18	4
Abdominal cramps	181	45	134	33	76	19	17	4
Nausea or vomiting	160	39	141	35	84	21	23	6
Diarrhea	288	71	81	20	37	9	2	0
Insomnia	113	28	139	34	129	32	27	7
Excessive sweating	92	23	111	27	177	44	28	7
Irritability	124	30	144	35	123	30	17	4
Anxiety (tension, nervousness)	91	22	136	33	150	37	31	8
Feeling high	298	74	74	19	25	6	3	1
Nodding	260	65	96	24	38	10	6	2
Dizziness on standing	297	74	75	19	24	6	4	1
Poor concentration	252	63	107	27	31	8	10	2
Impotence	297	74	44	11	44	11	15	4
Heartburn-gastric distress	221	54	123	30	54	13	9	2
Constipation	78	19	129	32	167	41	34	8
Bad dreams or nightmares	205	50	110	27	81	20	12	3
Drowsiness	162	40	156	38	83	20	7	2
Blurring of vision	286	70	84	21	32	8	5	1
Urinary frequency	244	60	101	25	54	13	9	2
Decreased sexual interest	164	40	116	29	97	24	30	7
Delayed ejaculation	185	45	98	24	84	21	40	10
Numbness of hands or feet	231	57	114	28	46	11	16	4
Involuntary jerking movements of lower extremities	180	44	136	33	83	20	8	2
Edema of extremities	335	82	47	12	23	6	2	0
Other	253	62	46	11	81	20	27	7

The data shown in Table 2 were also generated separately by drug regimen and differences between groups evaluated by 2 x 3 chi-square or Fisher's exact probability test. For these tests, rating was dichotomized as None-Mild and Moderate-Severe. In only three instances was there a significant drug difference: Aching Bones and Joints for which the M-50 group had a significantly higher frequency of moderate-severe ratings than either of the other groups; and Anxiety for which M-50 significantly exceeded L-80 in terms of moderate-severe ratings.

Although Delayed Ejaculation (and possibly other problems in sexual function) seemed to be associated with the L-80 patients in the early termination data, this was not supported by the symptom-sign data where ratings of moderate and/or severe on Impotence, Decreased Sexual Interest, and Delayed Ejaculation are all more frequent (but not significantly so) in the methadone groups. Irritability is another symptom-sign of special interest because of observations of animals on acetylmethadol in the preclinical studies. In this study, irritability is represented in higher frequency in the methadone groups but not significantly so.

The "Other" category included a wide array of symptom-signs, many of which seem to be either trivial or clearly nondrug related, most of which were reported at a single rating period only rather than persistently and some of which were elaborations of one or more of the 30 symptom-signs on the checklist.

The laboratory studies were conducted before treatment and every four weeks thereafter. Hematologic tests consisted of total WBC, total RBC, neutrophils, lymphocytes, eosinophils, monocytes, basophils, hematocrit, and hemoglobin. Blood chemistry was the usual SW-12 panel, specifically calcium, FBS, BUN, uric acid, total protein, albumin, total bilirubin, alkaline phosphatase, LDH, and SGOT. (Globulin was calculated as the difference between total protein and albumin.) Urinalysis included albumin, sugar, WBC, and RBC. Vital signs recorded at the same intervals included blood pressure, pulse and temperature, plus weight.

The hematologic tests, blood chemistries, vital signs and weight provided 25 comparisons for each of the 10 test periods (weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40)--a total of 250 analyses of covariance with initial level as the covariate. Only six of these were statistically significant. Three of these occurred on a single variable--weight. The others represented a difference between groups at one period only: WBC at week 20, calcium at week 36, and alkaline phosphatase at week 16. Sample sizes for these tests ranged from slightly over 300 cases for the pre- to four-week analyses to around 160 cases for the 40th week analyses.

Two cohorts of patients were established to look specifically at changes over time rather than cross-sectionally. The 24-week cohort consisted of patients who had a complete set of data on a variable at pretreatment and every test period for the first 24 weeks. Usually this consisted of 60 M-50 patients, 57 M-100 patients, and 45 L-80 patients. The 40-week cohort usually consisted of 39 M-50 patients, 45 M-100 patients and 31 L-80 patients. Although the statistical testing provided a variety of information about within-group and between-group differences, the primary interest was in two tests of between-drug regimen difference. One of these was essentially in terms of the average of all tests periods--the height of the curve. The other tested the variation of means across time between drug groups (the drug by time interaction). In the analysis of the 25 variables using the 24-week cohort, there was a single significant finding--the interaction of drug and time on weight. In the analysis of the same variables using the 40-week cohort, there was a significant interaction for total WBC, total RBC, hematocrit, hemoglobin, and weight. In addition, there was a significant difference between groups for SGOT when all values were collapsed across time.

In another series of analyses, a cohort of 128 patients from three hospitals who had a complete set of values over a 20-week period were used to provide similar but somewhat different information. In these analyses, the pretreatment value was included as a covariate and all subsequent values were adjusted for initial level. Hospital was included as a factor in the design which permitted a comparison of hospitals and the various interactions of hospital with drug and time. Both of these changes in design were introduced to provide greater sensitivity for the analyses of drug difference, although it was accomplished by reduction in time to 20 weeks, a reduction of sample size and a restriction to the three hospitals that had sufficient data to be included. In these analyses, the only main effects of treatment that reached significance were on weight and pulse. There were significant interactions between drug and time on hematocrit, hemoglobin, and SGOT.

A final attempt to gain precision and extract information about any drug group changes present in the data consisted of a series of multivariate analyses of covariance. The following hematologic tests were analyzed simultaneously: WBC, RBC, neutrophils, lymphocytes, hematocrit, and hernoglobin. The pretreatment values on all six variables were used as covariates and the values at each test point were used as dependent variables. Hospital was included as a factor, and in each analysis as many patients and as many hospitals were included

as possible. There were no significant differences involving treatment group in these analyses. The renal tests (calcium, BUN, and uric acid) were analyzed in the same manner and with the same result. In the analysis of liver function tests (total bilirubin, alkaline phosphatase, LDH, SGOT and an index defined as albumin divided by globulin), there was a significant difference between groups at the 16th week only. The multivariate test of vital signs and weight was significant at the 4th week only.

These different analyses each supply somewhat different information and need to be further examined and integrated. In the hematologic tests, there is reason to look closer at WC, RBC, hematocrit, and hemoglobin. In the covariance analyses of WC, a significant difference between groups was obtained at week 20. The adjusted means were M-50 7180, M-100 7720, and L-80 8060. In addition there were significant differences in unadjusted post means at week 16 and 20. In a total of 30 tests of pre-post within-groups change (three drug groups times 10 time periods), only the change from pre- to week 8 in the L-80 group was significant. Furthermore, all means at all test points were within the normal range (all means varied from 7260 to 8020). In both the 24 and 40-week cohorts, there was significant within-group variation of means across time in the L-80 group but this variation represented considerable scatter in values from one test period to the next rather than an increasing or decreasing trend in WBC. The same scatter was present but not significantly so in the two methadone groups. In the 40-week cohort analysis, this variation across time was significantly greater in the L-80 group than in the two methadone groups (significant interaction) and there were significant differences between drugs at week 16, 20 and 28. The drug by time interaction was not significant in the 24-week cohort. At each of these test points (week 16, 20, 28) the L-80 mean was highest and the M-50 mean was lowest. All means were in the normal range. There were no drug differences in the 20-week cohort analysis. In summary, there is a suggestion that something might have been happening with WBC in at least some patients during the middle weeks but it is difficult to give clinical meaning to it because it did not persist, all means are comfortably in the normal range and a review of individual patient's data did not identify anything remarkable about this part of the treatment period. RBC, hematocrit, and hemoglobin surfaced as possibly significant (in a clinical sense) on the cohort analyses only. The evidence for RBC is not convincing. There appeared to be a predominately linear downward trend particularly in the two methadone groups over the first 20 to 24 weeks but the trend did not continue and in fact seemed to reverse itself. It may be more accurate to say that there was some initial decline which then leveled off. The only between-groups difference was the drug by time interaction in the 40-week cohort, and even in this analysis only at week 8 was there a significant difference between drugs (M-100 highest, L-80 lowest, all means within normal values). It is difficult to conclude that there is anything clinically significant in RBC. The situation is much the same for hematocrit and hemoglobin. The trend analyses suggest an initial decline in all three groups and then a leveling off after about the eighth week. There is no clear and consistent separation of groups across time. Finally, considering also the results of the multivariate tests that included all of these variables, it seems reasonable to conclude that the occasional between-groups differences that did emerge as statistically significant have no clinical importance. In no case were the blood changes sufficient to necessitate termination from the study.

The evaluation of renal and liver function tests was similarly reassuring from a clinical point of view. SGOT was noteworthy for the fact that the means of all three drug groups before and throughout treatment were well above the usual normal range (from a low of 56 to 107) and the pretreatment values for many individual patients were high enough to be of serious concern in a nonaddict sample. The main finding for SGOT is that the L-80 curve is at a somewhat higher level at pretreatment and throughout the 40 weeks than the methadone groups. All three groups show essentially no change across time on SKIT. The significant difference between groups at week 16 in the multivariate analysis of the liver function tests is paradoxical and not likely to be of clinical importance because there is so little supporting evidence of differences at other weeks either in the univariate or multivariate tests.

The analysis of vital signs and weight had a generally low yield, except for weight, which is clearlv affected bv all three drug regimens, and particularly acetylmethadol. There is clearly an upward trend in all groups, and somewhat more substantially so in the L-80 group. There was no morbid obesity reported.

Efficacy

This study was not designed to evaluate efficacy in the usual manner, i.e., there is no placebo or nontreatment group. However, acetylmethadol has previously been shown to be pharmacologically effective in suppressing the abstinence syndrome and there is abundant evidence in this study that both drugs will maintain addicted individuals without their having to resort to supplementary (illicit) narcotic use to avoid withdrawal. It seems reasonable to assume efficacy in this sense and turn to the question of the relative efficacy of the three drug regimens.

There are a number of variables that individually or collectively could be used to deal with the issue of relative efficacy. All of these are imperfect indices. The amount of discomfort indicated on the Underdosing factor of the Symptom-Sign Record provides a measure of efficacy but would need to be evaluated sirmultaneously with illicit drug use to be unambiguous as an outcome index. Early termination is obviously related to efficacy in some complex manner but is less than ideal as an indicator for some equally obvious reasons. A patient who completes 40 weeks of treatment but tests positive for morphine at every week cannot be considered more of a treatment success than a patient who is clean for 32 weeks and then moves to another part of the country Both kinds of patients are represented in this study. Conformity to scheduled clinic visits is equally ambiguous. Some patients who faithfully attend clinic show a heavy illicit drug use pattern. It is not even safe to assune that missed clinic visits are accompanied by illicit drug use. Many other outcome variables are clearly secondary, i.e., have no direct pharmacological relationship to the drug. Examples are employment variables, encounters with the law, and interpersonal relationship variables. It is the hope and the expectation that patients being adequately maintained will show improvement in these areas and it may be appropriate to use such variables to evaluate a total program of rehabilitation including the whole array of supportive services but it seems unjustified to use them as criteria of primary drug effect. They seem, instead, to be contingency variables. The use of these variables as outcome indicators of maintenance treatment is contingent upon achievement of the primary goal which is to decrease illicit drug use.

Urine test data is considered to be the key to evaluation of the results of this study. Unfortunately, even illicit drug use is not a simple variable. The amount of drug use is, of course, important but the pattern is probably even more so. A patient who completed the study with 50% urines positive for morphine could have been entirely clean in the first or the last 20 weeks. The latter seems to be a clearly superior outcame.

An index of illicit morphine use has been derived which takes into account total use and pattern of use. With a single exception to be noted later, this index was developed completely independent of the study data and was therefore not biased by knowledge of drug group outcomes. This index has some arbitrary features end some defects but experience with its use has not revealed serious distortions. The rules are entirely objective and do not require clinical judgment . The entire operation can be performed by the computer.

Rule 1: A score cannot be derived for a patient who is in the study for less than 50 days (seven weeks).

Rule 2: Urine tests Positive for morphine are given a weight of five if they occur in the last 8 weeks of a patient's tenure in the study, a weight of four if they occur in the next to last 8 weeks, three if they occur in the next block of 8 weeks and so on.

Rule 3: A missing urine test result is handled in exactly the same manner as a positive urine except that it is not weighed as heavily. A positive urine in the last 8 weeks would be weighted 5 x 1 = 5; a missing value would be weighted 5 x .22 = 1.1. The value .22 is not totally arbitrary but is derived from the data. It represents the percent of all urine samples collected in the study that tested positive for morphine and its use for missing value introduces some notion of the probability that a missing value would have been positive.

Rule 4: All scores derived by the rules above are adjusted to a comparable range of 0 to 120. Patients who have 40 negative urines would be scored 0; patients with 40 positive urines would be scored 120.

Although the index seems to have the desired characteristic in an abstract sense, the test of its value must be in terms of actual data. Preliminary attempts to establish construct validity have been encouraging. It was predicted that the drug use index would correspond to staff judgments of outcome made at the time of termination of a patient's participation in the study. The patients rated

as being better or much better had a mean urine index of 17.5, the patients rated unchanged had a mean of 38.3, and the patients who were worse or much worse had a man of 39.9. The F was 24.16 ($p < 001$). A similar relationship was predicted for percent clinic attendance. Patients who had a perfect attendance record had a mean urine index of 17.7, those patients that had a near perfect attendance record (96-99.9%) had an index of 20.5, the patients who attended 90 to 95.9% of the time had an index of 33.0 and patients whose attendance was below 90% had an index of 36.3. The F was 7.82 ($p < .001$). A series of more carefully planned analyses will need to be conducted to further define the index. However, using this index to compare the three drug regimens gave the following results: 110 M-50 patients had a urine index of 33.3, 111 M-100 patients had an index of 22.6, and 96 L-80 patients had an index of 20.8. The F was 6.19 ($p < .005$). The M-50 group is significantly higher on the urine index than either M-100 or L-80.

Urine test data were analyzed in other ways as well. For each patient, the number of urines positive for morphine was divided by the number of his specimens tested. This gave a "percent dirty for morphine" score for that patient which was then used in a comparison of groups. A similar score was calculated for barbiturate positive, amphetamine positive, and "something" positive, the latter being the number of specimens positive for either morphine, barbiturates, amphetamines, or cocaine (tested randomly) at any one week divided by the total number of specimens for that patient. The results of these analyses showed the L-80 group less likely to use illicit barbiturates than the M-50 group.

Another kind of outcome index is program conformity, which was defined as each patient's number of actual scheduled clinic visits divided by his total number of expected scheduled visits for however long he was in the study. The M-50 group had an average of 92% attendance, M-100 95%, and L-80 90%. The difference between M-100 and L-80 on this clinic visit index was significant. However, since the acetylmethadol patients only received active medication on MWF, the analysis was redone comparing the three groups on percent attendance for those days only. L-80 still had a lower average attendance rate than M-50 or M-100 but the difference is not significant.

Still another evaluation of relative efficacy was possible using the global rating of outcome, which was a combined staff judgment made shortly after a patient's termination, taking into account all known information about the patient. This was a five-point scale: much improved, improved, changed, worse, and much worse. The M-50 group was judged to be significantly less improved than either the M-100 group or the L-80 group.

Preliminary review of secondary (contingent) outcome variables such as number of arrests, hours of employment, income, etc. has not yielded evidence of advantage of any one group over another but a conclusive summary of these variables will have to be deferred until more definitive analyses have been done. Similarly, there are many other aspects of the data that will have to await subsequent publication.

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SUMMARY OF SAODAP PHASE II COOPERATIVE STUDY OF LAAM VS. METHADONE

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The primary purpose of the trial was to compare the efficacy and safety of LAAM and methadone for treating heroin addicts in a maintenance program. The program was designed to be conducted with uniformity, supervision and coordination based upon adherence to three common protocols. Data were recorded on a uniform set of forms and submitted to a central data coordinating center for analysis. Safety was evaluated by monitoring patients for symptoms, signs and laboratory evidence of toxicity. Although the primary endpoint for statistical evaluation of efficacy was use of illicit drugs, changes in social adjustment, arrest rate, employment and retention in treatment were also considered indications of effectiveness.

METHOD

Patients

Patients were eligible for the study if they were currently in a methadone maintenance program as defined by the FDA and were males ages 18 or older. Patients were excluded for incapacitating or life-threatening conditions, disease requiring regular repeated medication, frankly psychotic states, epilepsy, current severe alcoholism, and pending criminal charges. It was further specified that any addicted spouce or relative in the same household must be under treatment and that there be a reasonable expectation that the patient would continue to reside in the vicinity of the clinic and be able to attend for the full duration of the trial. Eligible patients who signed an informed consent for voluntary participation in the study were then given a general physical examination with neurologic and psychiatric evaluation and including chest x-ray, electrocardiogram, urinalysis, and blood studies. Patients began treatment on the following Monday.

Drug Administration

Patients were randomly assigned to LAAM or methadone. Methadone patients were continued on their regular daily dosage of methadone, unless an adjustment was required. Patients assigned to LAAM received a first dose equal to their previous methadone dose. After the initial dose, adjustments could be made but in no case could the dosage exceed 100 mg TIW. Psychotropic drug use was discouraged except for occasional sedation. All use of supplemental medication during the trial was recorded.

Initially the following three protocols were used for the study: Protocol 1. Random assignment to LAAM or methadone. LAAM group receives LAAM three times a week at the clinic. Methadone group receives methadone daily, with take-home privileges as determined by the clinic; Protocol 2. Same as Protocol 1, but no take-home privileges for methadone group; Protocol 3. Random assignment to LAAM or methadone. Methadone group receives methadone daily. LAAM group receives methadone MTWTH, LAAM on Friday, no medication Saturday or Sunday.

Twelve investigators chose Protocol 1, three close Protocol 2, and three chose Protocol 3 (one investigator chose both 1 and 3). however, changes in clinic policy and the resultant small number of subjects in Protocol 2 led to the combined analysis of patients in these protocols.

Clinical Evaluations

Evaluation was essentially identical to that of the VA cooperative study described in the preceding chapter except that urine testing was done locally rather than in a central laboratory.

Characteristics of the Sample

(Protocols 1 and 2)--The sample consisted of 636 men, with 308 maintained on methadone and 328 maintained on LAAM 61% of the sample had been addicted to opiates for more than five years. The mean age was 28.8 years 54% of the sample had graduated from high school and 25% had gone on to college. 61% of the sample were, or had been, married. 55% of the sample was white, 28% black and 15% had Spanish surnames. Almost two-thirds of the sample was employed, and 54% worked full-time. 73% had been in some form of voluntary treatment program previously, but only 20% had been in some form of involuntary drug treatment program. There were no significant differences between the LAAM and methadone groups.

The sample for Protocol 3 consisted of 136 men, 71 of whom were assigned to methadone and 65 of whom were assigned to LAAM This sample was somewhat older (mean age 31.3) than the sample in Protocols 1 and 2, but the other demographic characteristics were similar. There were no significant differences between the LAAM and methadone groups.

Early Termination

(Protocols 1 and 2)--49% of the starting sample completed the full 40 weeks of the study. If all reasons for termination are combined, 61% terminated early from the LAAM group (N = 200) and 40% from the methadone group (N = 122). This difference is statistically significant. Not all of these patients terminated for drug related reasons but since the nondrug related terminators should have been equally distributed between groups except for chance, it has to be concluded that methadone maintenance was superior to LAAM in retention, at least under the conditions of an open comparison of an approved and an experimental drug.

There was also a difference between the length of stay in the study before early termination. The average drop-out in the LAAM group occurred after 72 days, whereas the early terminator in the methadone group dropped out after 122 days. 43% of the drop-outs occurred before the ninth week, with the LAAM group drop-outs occurring earlier as well as more frequently than methadone group drop-outs.

Protocol 3. The pattern of drop-out was remarkably similar for Protocol 3, although there was a higher drop-out rate for both groups. 44% of the total sample conpleted the full 40 weeks of the study. 48% (N=34) of the methadone group and 65% (N=42) of the LAAM group dropped out early. This difference is statistically significant. The average drop-out in the LAAM group occurred after 81 days in the study, whereas the average methadone drop-out occurred after 141 days.

It should be noted that there was a great deal of variation in percentage and timing of drop-outs between clinics, which suggests that factors other than the drugs themselves contributed to drop-out rates.

Table 1 presents the number of patients in each group who terminated early for a variety of reasons under Protocols 1 and 2. Table 2 presents the same data for Protocol 3.

The major differences between groups for reasons for early termination were Medication Not Holding (all three protocols) and Side Effects, Psychiatric, Medical unrelated, irritability, detoxification, and did not like drug (protocols 1 and 2). In each instance, there were more LAAM drop-outs than methadone drop-outs.

SAFETY-TOXICITY

Protocols 1 and 2

Laboratory data, vital signs and weight were obtained before treatment and every four weeks during treatment. At each of ten test

TABLE 1

Reasons for Early Termination
(Protocols 1 and 2)

Reasons	M	L	T
Medication not holding	0	62	62
Jail	28	19	47
Moved from area	21	18	39
Detoxification	29	9	38
Did not like study	15	7	22
Disciplinary discharge	12	5	17
Psychiatric	0	14	14
No show for 14 days	8	4	12
Excessive drug use	4	8	12
Side effects	0	11	11
Medical unrelated	1	9	10
Irritability	0	9	10
Did not like drug	0	7	7
Miscellaneous	0	5	5
Excessive alcohol use	2	3	5
Dose too high	0	4	4
Could not attend clinic	1	3	4
Abnormal laboratory value	1	2	3
Not eligible for inclusion	0	2	2
Death	0	1	1
Total	122	200	322

TABLE 2

Reasons for Early Termination
Protocol 3 (Friday only LAAM)

Reasons	Meth	LAAM	Total
Medication not holding	0	20	20
Detoxification	11	5	16
Jail	6	4	10
Moved from area	6	1	7
Disciplinary discharge	5	1	6
No show for 14 days	4	0	4
Medical unrelated	1	3	4
Excessive alcohol use	0	3	3
Did not like drug	0	2	2
Did not like study	1	0	1
Side effects	0	1	1
Psychiatric	0	1	1
Irritability	0	1	1
Total	34	42	76

paints differences between the means of the methadone and acetylmethadol groups were evaluated by analysis of covariance with adjustments for pretreatment value. Out of 250 such analyses (25 variables x 10 occasions) there were 35 significant differences between adjusted means: WBC at week 8; RBC at weeks 16, 20 and 24; basophils at week 8 and 12; hematocrit at weeks 8, 16, 20, 24, 28, 36, 40; hemoglobin at weeks 8, 16, 20, 36; calcim at week 28; RBS at week 16, uric acid at week 32; albumin at weeks 4, 32 end 40; weight at week 4; systolic blood pressure at weeks 8, 12, 16, 24, 28, 32, 36; diastolic pressure at weeks 8, 20, 24. and 28. Most impressive of those are hematocrit and hemoglobin and perhaps RBC end basophils. The blood pressure results are of less interest as far as LAAM is concerned because the changes are essentially all due to increased blood pressure in the methadone group with little or no change in LAAM patients. The other scattered differences between groups (WBC, RBS, uric acid, albmin and weight) are probably not of much clinical consequence.

On each of the ten occasions that blood was drawn during treatment, the LAAM group showed a statistically significant reduction in hematocrit compared to their baseline average. These changes were very small. The largest average change was a drop of 1.53. None of the tests of pre-post changes in the methadone group were significant but except for one test (week 40) the post mean was always lower then the pre mean. These changes were also small. In other words, both groups showed reduction of hematocrit values during treatment but the changes were a little larger in the LAAM group. With sample sizes of 100-200 in a group for all tests, even very small differences can be statistically significant. All of the mean values of both groups at all times were within the normal range. The LAAM group tended to have somewhat higher values at pre than the methadone group and this could contribute to the observed difference in adjusted means. The changes across time are not progressive, i.e., there is no discernable trend for continuing decrease in hematocrit as treatment progresses. Instead there appeared to be an initial drop in the first 4-8 weeks of treatment and a restabilization of average hematocrit at a somewhat lower level then pretreatment. Essentially, the same things can be said for the differences in hemoglobin.

The decrease in average hematocrit (or hemoglobin) could be caused either by large drops in a few patients or by smaller drops in a larger number of patients. Review of individual patients records did not identify patients with dramatic and systematic changes in these tests but there does seem to be a pattern of small decreases by a fairly large number of patients. Similar trends were noted in both the methadone and LAAM groups in the VA study. The current speculation is that the introduction of a new drug (methadone or LAAM in the VA study or LAAM but not methadone in the SAODAP study) causes some initial physiologic disturbance which then stabilizes. It may be that there is an association with weight gain i.e., fluid retention, or some other simple explanation. In any case, there is no corresponding clinical evidence of drug toxicity and unless additional data (or new analyses of existing data) are forthcoming, these changes do not seem to be at all alarming.

SAFETY-TOXICITY

Protocol 3

In Protocol 3, laboratory values were obtained only at pre, week 12 and week 40. Differences between the means of methadone and acetylmethadol on these tests at week 12 were evaluated by analysis of covariance with adjustments for pretreatment level using all patients that had pretreatment and 12th week values. Differences at week 40 were evaluated in the same manner. Out of 40 such analyses (20 lab tests x 2 occasions), there were four significant differences between adjusted means: WBC at week 40, Random Blood Sugar at week 12, Globulin at week 12, SGOT at week 12.

Vital signs and weight were obtained at pre and every four weeks thereafter. These five variables were analyzed in the same manner at each of 10 occasions yielding 50 more analyses of covariance. Only one of these tests of adjusted means was statistically significant: weight at week 20. These variables were also analyzed by trend analysis across the 40 weeks as described in the summary of the main study. There were no between groups differences in any of these analyses that reached a significant level.

SYMPTOM-SIGN RECORD

Protocols 1 and 2

Symptom-signs were examined individually in a number of ways and in scoring clusters established by factor analysis. In one approach to individual evaluation of symptom-signs, the highest rating obtained during treatment per patient was used as a unit of analysis as described in the VA

study. To test differences between drug groups, rating was dichotomized as None-Mild andModerate-Severe. The following symptoms were significantly different between groups.

	None		Mild		Moderate		Severe	
	METH	LAAM	METH	LAAM	METH	LAAM	METH	LAAM
Yawning	181	147	84	110	40	58	3	12
Runny nose	151	126	107	109	47	80	3	12
watery eyes	170	128	95	110	40	77	3	12
Muscle cramps	169	128	91	112	42	75	6	12
Goose bumps	182	150	93	109	29	60	4	8
Abdominal cramps	177	122	80	106	44	80	7	19
Nausea or vomiting	186	127	74	102	43	82	5	16
Insomnia	118	73	69	94	97	119	24	41
Excessive sweating	114	93	85	75	92	126	17	33
Irritability	134	108	92	84	69	105	13	30
Anxiety (tension, nervousness)	118	86	82	87	87	109	21	45
Nodding	262	255	35	47	9	21	2	4
Impotence	255	249	42	52	8	21	3	5
Drowsiness	195	191	79	80	29	45	5	11
Other	203	180	36	40	40	62	29	45

Efficacy

The Discussion of issues involved in establisting eficacy of LAAM in the VA Cooperative Study applies equally well to the SAODAP Cooperative Study. There are a number of criteria of efficacy that can be used but all have certain limitations or defects.

Generalization about efficacy from the VA study has to be qualified because of the fixed dose design and the induction schedule which may have been too slow. In theory, the SAODAP study does not suffer from this particular problem because dosage was flexible after the first dose. However, any suggestion that LAAM is a less effective maintenance drug then methadone has to consider how effectively this option to adjust dose was exercized by the clinicians, most of whom were initially inexperienced in the use of LAAM. To the extent that dosage was not individually optimized, LAAM could be expected to appear somewhat less effective than methadone which is not only a more familiar drug but was the drug on which all patients were stabilized prior to the study. Furthermore, the price paid in the design of this study to provide for flexible dosage was to drop the double-blind control. Patients and staff were aware of the treatment assignment and this allowed for the full effect of psychological factors associated with treatment with an unfamiliar experimental drug. Even if the effect of psychological factors is discounted, retention rates on LAAM had to be influenced by the fact that there was a clinical choice possible with LAAM patients--they could stay on LAAM or be switched back to methadone--but this choice did not exist for methadone patients--their only choice was to drop out of maintenance altogether. Because of these problems, the SAODAP cooperative study provides almost no useful information about efficacy relative to methadone. The exception may be the urine index as defined in the VA study. In protocols 1 and 2, 28 methadone patients had a urine index of 15.0 while 227 LAAM patients had an index of 14.9. In protocol 3, 71 methadone patients had a urine index of 19.9 while 65 LAAM patients had an index of 16.2. Thus, in both instances, LAAM had a slightly better (non-significant) index of illicit opiate use.

Another kind of outcome index is program conformity, which is defined as each patient's number of actual scheduled clinic visits divided by his total expected scheduled visits for however long he was in the study. In Protocols 1 and 2 the percentage of clinic visits were essentially the same with averages of 97.75% and 97.71% for the methadone and LAAM groups, respectively. In protocol 3, the methadone patients attended 97.24% of their scheduled clinic visits while the LAAM group attended 97.49% of the time.

Still another evaluation of relative efficacy was possible using the global rating of outcome, which was a combined staff judgment made shortly after a patient's termination, taking into account all known infomation about the patient. This was a four point scale: much improved, unchanged, worse and much worse. In protocols 1 and 2, the mean score for both groups was 2.96. In protocol 3, the mean scores were 3.00 and 2.90 for the methadone and LAAM groups, respectively.

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PHASE III CLINICAL STUDY OF LEVO-ALPHA-ACETYLMETHADOL

John A. Whysner, M.D., Ph.D.

INTRODUCTION

The purpose of the Phase III trial of levo-alpha-acetylmethadol (LAAM) is to establish efficacy of this medication for the maintenance of persons addicted too opioids. Also during the course of the Phase III trials additional data relating to the safety of LAAM will be obtained. It is the intended purpose of the Phase III clinical trials to provide sufficient information to alllow the FDA to grant a New Drug Application for LAAM.

The administrative stucture which has been developed for these Phase III clinical trials is intended to provide for a centralized drug supply, data collection, and adminstrative system with a maximun national clinical participation. Whysner Asscciates is the prime contractor for NIDA and is responsible for the Coordination of the Study which includes filing of the IND application, medical supervision, review of results, administration of all subcontractors, and development of the final NDA application. Subcontractors include the Vitarine Company, who will be the formulator of the liquid concentrate, Friends Medical Science Research Center, Inc., who will provide data managemement and analysis support, and approximately 50 methadone clinics who will perfom the clinical trials and provide the data for analysis. A Medical Advisory Panel has been established which is responsible for approval of the study protocol, analysis of any adverse reactions, and review of the conclusions of the study.

The subject population will be approximately 6,000 men and woman over the age of 18 who meet the current criteria for entrance into methadone maintenance programs or who are currently clients of such proqrarm. The clinical trial will last up to 40 weeks for each patient. Each clinic will participate in one of two studies whichcc are being conducted as part of these Phase III trials. In one study all patients will be put on LAAM. In a second a random assignment of patients will be made to LAAM or methadone providing a comparative analysis of efficacy and safety measures.

MEASURES OF EFFICACY

The proof of efficacy for maintenance of persons addicted to opioids may be defined as the relief of abstinence over a prolonged period of time when the drug is given on a regular basis. There are three aspects of the abstinence syndrome: drug seeking behavior, physiological, and psychological changes. A drug such as LAAM must prevent the development of abstinence inall three areas. Therefore, measures of efficacy must be aimed at measuring the signs and symptoms of the develpment of abstinence in these three areas.

The measure of drug seeking behavior can be attempted through history taking, direct measurement of illicit drugs in body fluids, or assessment of the consequences of taking

illicit drugs. During the past several years our ability to measure illicit drugs in body fluids has been developed to the point where these methods are both reliable and are a regulaar part of the methadone program routine. Therefore, in the Phase III studies this will be the most important measure of drug seeking. Assessment of the use of illicit drugs through history taking or an independent measure of the consequences of heroin use such as number of arrests, employment, etc. is not reliable or easy quantitrate.

Physiological signs of abstinence will be measured through the analysis of a synptomsign checklist. The components of the checklist are well known parts of the physical abstinence syndrome; for example, sweating, gooseflesh, and rinorrhea.

For the psychological componence patients may became anxious, hostile, irritable, require other drugs such as traquilizers, develop other patterns Of drug abuse such as polydrug abuse, or adjust poorly to the social and work environment. Many of these aspects of psychological abstinence may be difficult to measure; however, measures will be attempted. The Profile of Mood States will be used to measure anxiety, hostility, and irritability. Also questions involving hours of emp1oyment, number of arrests, and a global assessment Of client's progress will be made.

There are no fixed scales against which efficacy can be measured. It is not known what is an acceptable level of abstinence or what are acceptable drug seeking, physiolcgical or psychological changes. Therefore, a heavy reliance must be made on comparative measures with a control group.

The only applicable control group for this study would be persons who are currently on methadone maintenance therapy. Comparisons of the efficacy and safety measures will be made between the methadone and LAAM patients in part of the Phase III study.

Another determinant of an acceptable level of abstinence would be the willingness of the participant to stay on the drug. If one can make the assumption that remaining on the drug is the equivalent of efficacy, dropout rates are very useful. The reason for dropout and a judgment by the clinic of wheter such a dropout is drug related will be determined. Only those dropouts which are drug related such as side effects, feelings of under medication on weekends,etc. will be used as efficacy measures. However, dropping out of the study to attempt detoxificationn would be viewed as a positive result.

SAFETY MEASUREMENTS

Previous Phase II clinical studies have indicated that for a 40 week period LAAM does not cause any consistent abnormalities in the CBS, SMA-12, urine analysis, EKG, or EEG which would be cause for concern. However, these Phase II studies have only been accomplisked on 170 males for 40 weeks. Therefore, it is desirable to test a large number of males and femailes to determine if there are any untoward reactions which occur on a low frequency basis. It is hoped that the Phase III studies will include approximately 2,000 patients om LAAM for 40 weeks. This should test enough individuals to give an estimate of the incidence of adverse reactions to the medication.

Another problem which must be studied during Phase III is the use of other medication concurrently with LAAM. It is known that drug interactions may occur which would either potentiate or preventthe effective action of narcotics. me use of both prescription and illicit drugs may have untoward interactions effects. Although it has been suspected that certain other drugs my interact favorably, not enough patients have been studied to gather any quantificable data. In the Phase III studies the use of all medications will be documenteds and the possibility of any drug interactions will be investigated thoroughly.

OPEN VERSUS BLIND STUDY

The use of any maintenance drug for the treatment of heroin addiction has a strong subjective component to its effectiveness for both the patient and the physician. A double-blind study is designed to eliminate the impact of these subjective effects om the outcome of the study. Double-blind studies have been used in the past to compare the effectiveness of LAAM to methadone and the results of these studies have been described elsewhere. There are several reasons for which the Phase III study has been designed as an open rather than a double-blind study. These are the following:

1. The primary advantage of using LAAM instead of methadone is the need for only three day a week pickup. If a double-blind study was done a schedule of either daily pickup or of three day a week pickup would be necessary in both LAAM and methadone groups. This would negate the scheduling effect of LAAM.

2. The large number of patients needed for the phase III study and the use of multiple clinic sites makes the logistical problems associated with such a study very difficult.

3. A double-blind study may adversely effect the efficacy of either methadone or LAAM in an unpredictable way. The patient population is very anxious concerning the medication they are receiving and about participation in a clinical study. One of the greatest difficulties encountered in the PhaseII study was that the efficacy results had a large number of patients who dropped out because of the nature of the study rather than the drug

4. The blind is difficult to keep because patients and physicians would be able to break the code due to the subjective effects of the drug.

USE OF LAAM IN FEMALES

The Phase III study will be the first large-scale use of this drug in femles. A small group of famales was tested before the FDA restrictions on the use of LAAM. During the course of the Phase II studies there was a study of seventeen females of non-childbearing potential. The use of LAAM in females at this stage is essential,otherwise another large-scale study in females would need to be canstructed. It is currently being decided whether or not some females should be given LAAM througout pregnacy or whether all woman who become pregnant while on LAAM should be switched to methadone. The arguments on both sides of this question are valid. The use of LAAM through pregnancy would mean exposing pregnantfemales and neonates to a new drug with which the medical community is unfamiliar. However, LAAM may prove to be a drug with fewer problems in the pregnant female and the neonate than does methadone. The long duration of action of LAAM may make the neonatal withdrawal syndrome less severe.

CURRENT STATUS OF THE STUDY (MARCH, 1976)

The current planning for the Phase III study of LAAM has been almost completed. The final study design, forms, data management system, formulation of the drug, and analysis have all been in progress and should be completed within a couple of months. It is anticipated that the Phase III study will begin in the Spring of 1976 and that induction of these patients will be completed by the Fall of 1976. An additional 40 week period will be needed for the follow-up of the last patients included in the Study and time will need to be available for the final data analysis and collection. Therefore, it is anticipated that the Phase III study will be completed late in 1977. Hopefully by that time of the other animal and human data will be comleted to allow the award of a NDA for LAAM. Therefore, beginning in 1978 there may be another maintenance treatment modality available for the treatment of heroin addiction.

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Dr. Cooper is Special Assistant to the Director of NIDA's Division of Commmunity Assistance (DCA). He has been its liason to the Division of Research during Phase II and III of the LAAM studies. Beyond Phase III DCA will continue to oversee NIDA-funded LAAM treatment programs. Like methadone, LAAM will be dispensed only through licensed narcotic maintenance programs. Once LAAM's New Drug Application is approved, responsibility for continous monitoring of treatment programs will pass from NIDA's Division of Research to the Division of Community Assistance.

THE USE OF LAAM IN TREATMENT

James Cooper, M.D.

The purpose of this chapter is to present the National Institute of Drug Abuse, Division of Community Assistance's (DCA), perspective on the usefulness of LAAM as a maintenance drug in the treatment and rehabilitation of opiate addicts. One of the major responsibilities of the DCA is to administer, monitor, evaluate and establish treatment standards for all National Institute of Drug Abuse funded treatment programs. It will become the Division's responsibility to oversee those Federal programs which will administer and dispense LAAM once the drug has received a New Drug Application (NDA) and is marketed.

In order to understand our current thinking regarding the utility of a maintenance drug in the treatment of narcotic dependence, it is important to review, from a historical perspective, methadone maintenance treatment over the last ten years. Initially, there was a tendency to view the addict simply as a person afflicted with a metabolic problem or disease. Methadone was prescribed to treat the symptoms of this chronic metabolic disease. In this model, methadone was analagous to insulin for diabetes and so perceived as a life-saving treatment. In the same model, LAAM would be similar to a long-acting form of insulin that relieved the patient of the need for frequent dosing.

In the early stages of development, the methadone clinic emphasized the physician/client relationship and cast the physician in a primary decision-marking role. The medication was considered the primary treatment and the understanding of its properties and actions was deemed of utmost importance to staff and the client.

However, it was appreciated from the beginning that although methadone corrected a biological condition by medically stabilizing the addict, this was only one part of the treatment. Pharmacological treatment was only one factor in a program which should include counseling as well as supportive services such as legal vocational and educational counseling. These supportive services were believed necessary to provide the addict with the skills he may never have developed or had lost during his addiction.

In the following years there was a rapid proliferation of methadone maintenance clinics, due to the heroin epidemic of the late 60's and the success of this prototype treatment. Unfortunately, the speed of proliferation and the great number of addicts needing treatment overwhelmed the treatment capacity. The need for supportive services also outstripped available resources, as a result, treatment effectiveness declined.

In the last several years more knowledge has accumulated from treating larger and more diverse populations of addicts. The model

has been made more comprehensive with awareness that individualized treatment is needed which recognizes the unique psychological characteristics of each addict. Most clinicians have come to view methadone as a stabilizing treatment tool which can be effectively used to engage the client in broader rehabilitation. Once this engagement occurs, an individualized evaluation and provision of appropriate treatment services can proceed. Many, now believe that these services are the primary rehabilitative tool for most clients.

This gradual shift in emphasis was a result of our better understanding of the diversity of the people applying for treatment. The only common trait shared by all is that they are narcotic users and are dependent upon opiates. Those who make up this population have different reasons for initiating drug use, exhibit different patterns of drug use, relapse for different reasons and have widely differing experiences as a result of their drug using behavior. The Division's experience has demonstrated that the etiologies of addiction are diverse and complex. While under-education, unemployment, racial or ethnic discrimination and environmental stress may result in drug-taking behavior for some, other psychodynamic factors including excessive dependency needs, a compulsive desire to escape from reality and a lack of poor coping mechanisms for stress play an important role in addiction for others. Further, total abstinence from drugs may not be a realistic goal for all drug abusers. Thus, the objectives of treatment have become more complicated and achievement of the goals sometimes become more elusive.

With the knowledge gained from experience, DCA is currently encouraging all maintenance programs to develop the resource capabilities for treating a diverse population. Such a heterogeneous group requires a number of distinct treatment, rehabilitative and resocialization approaches. Pragmatically this entails that a program have the capabilities of providing legal, vocational, educational, psychological and medical services either within the program or through referral sources.

The diversity in the treatment population has resulted in wide variation as to the length of time an individual receives methadone and the intensity of the counseling intervention. Some patients only want detoxification or short-term maintenance, while others may need or request long periods of maintenance and services. The well-run clinic usually will have some clients who are receiving methadone and very low-key programming either because the initial assessment of the client revealed that they could not tolerate intensive psycho-social intervention or because there was no indication of need for such service. However, many other clients will require varying degrees of psycho-social and vocational intervention based on the client's past and current behavioral performance.

Each program has been encouraged to view each patient as a unique individual with his own personal combination of strengths and weaknesses which must be continually assessed in order to tailor a treatment regimen appropriate for each patient.

The Federal Funding Criteria for Drug Treatment Services was developed in part to insure that this individualized approach be incorporated by all Federally-funded programs. One section of the Federal Funding Criteria requires that an individualized treatment plan be developed for each patient and that periodic evaluation of the plan occur. Such a requirement should provide the staff with an instrument to insure that (1) each patient's strengths and weaknesses are assessed, (2) a determination is made of the appropriate types of supportive services needed (if any) and (3) the extent of counselor involvement necessary to meet the objectives of the treatment plan is ascertained. The ongoing individual evaluative process will provide the staff with a periodic testing and redefining of the patient's progress (or lack of progress) and encourage the counselor to search for the contributing dynamics of the patient's success or failure.

Although the advent of LAAM may not introduce treatment changes, for some patients and programs, LAAM may provide some distinct pharmacologic and therapeutic advantages to methadone based on existing clinical studies.

The 1975 White Paper on Drug Abuse produced by the Domestic Council Drug Abuse Task Force recommends "switching from methadone to LAAM...in treating opiate-dependent persons as soon as its safety and efficacy have been determined." This recommendation is based on the potential benefits to programs and patients of three times a week dosage. Some of these benefits are: less drug diversion into illicit channels; more cost-effective treatment; and less interference with patients' daily work schedules, education and rehabilitation efforts or responsible homemaking.

Several other potentially advantageous therapeutic characteristics of LAAM have been observed. Among them are that LAAM helps change the individual's and clinic's focus from daily preoccupation with drugs and drug-taking to an emphasis upon human relationships and development of alternative activities, life style and peer group relationships. Furthermore, LAAM's smoother, sustained, drug effect apparently allows some individuals to feel more alert, more emotionally level, less "high", and less habituated. It's longer duration of action may allow LAAM to be used for detoxification from methadone maintenance or heroin. Clinicians have noticed that some patients appear to be able to detoxify from LAAM maintenance easier than from methadone maintenance. This Division will watch the Phase III LAAM Studies closely to determine if these observations/findings are substantiated in the larger population to be studied in Phase III large scale clinical trial.

The availability of two maintenance agents may provide for increased treatment flexibility. For example, Sequential Treatment Employing Pharmacologic Support (STEPS) has been proposed by Dr. Avram Goldstein as an alternative treatment method. STEPS is characterized by sequential use of a variety of pharmacologic agents each progressively decreasing narcotic induced euphoria and increasing social rehabilitation. The STEP from daily methadone to three times weekly LAAM would represent a safe and very stable opiate dependence with virtually no subjective euphoria and less dependence on the clinic. This novel approach would naturally have to be investigated with a limited number of individuals to determine its effectiveness but does provide a potential alternative, particularly for those who have been unsuccessful in remaining abstinent following a particular maintenance regime.

The Division of Commmunity Assistance does not currently anticipate that LAAM implementation will lead to dramatic alteration in the current Federal opiate addiction treatment policy or philosophy. LAAM appears to be an alternative to, rather than a replacement for, methadone. Some individuals do better on one or the other drug, probably due to either pharmacological, psychological or social factors not yet understood. Furthermore, LAAM is not viewed as a pharmacologic panacea for all opiate addicts. No known drug, including LAAM, can cure or alleviate psychosocial and economic impoverishment. For some opiate addicts, LAAM, like methadone, may be the primary treatment. For others, temporary pharmacotherapeutic stabilization will act merely as a tool to engage the narcotic-dependent individual into participation in a comprehensive treatment program, concomitantly utilizing extensive psychological socio-economical and vocational rehabilitation services. And others may require no pharmacological support at all. LAAM provides one more choice in tailoring treatment to each individual's needs.

The following article is from a transcript of remarks given by Dr. Avram Goldstein at NIDA, Rockville, Maryland, May 19, 1976.

A CLINICAL EXPERIENCE WITH LAAM

Avram Goldstein, M. D.

I would like to discuss our clinical experience with LAAM. Several years ago we did a pilot trial with LAAM in the Santa Clara County Methadone Program with about 60 patients. Some of them were Put directly onto LAAM, off the street, so we had that experience; and others crossed over from methadone to LAAM. Now in the last year we have put 165 addicts directly off the street onto LAAM. So that my remarks here are based on this accumulation of experience.

PHARMACOLOGY

There is the pharmacology issue. That's turned out, I think, to be the most interesting part of our experience with LAAM. Let me start by stating that: I think LAAM is a better drug than methadone, from a pharmacological point of view. I think patients know that and understand it too. Let me describe what I mean.

Now, in pharmacology, quite apart from any regulatory questions or the issue of diversion, in the development of any drug, one of the important objectives is to get a lasting stable effect. I need only refresh your memory about the history of insulin. As you know the early insulins had to be admininistered several times a day. It was a very tricky operation, because when you gave the insulin, you got too much insulin effect; then it wore off and you had too little insulin effect. The problem was to stablize things so that there would be a lasting effect of insulin in the patient. Tremendous effort was directed toward developing a long-acting insulin which you could give once a day to get stable coverage. Finally that was achieved. For almost every drug there is the same problem of developing stability of action, so that there will not be fluctuation up into the toxic range and then down below the therapeutic range.

Now, let's look at methadone in those terms. Methadone is a tremendous improvement over heroin! which has to be administered four or five tunes a day, giving continual highs and lows. That's why methadone was introduced, of course. Nevertheless, you all know that when patients come in, in the morning, for their methadone, many are at the very edge of withdrawal; they feel "icky" (as they say). You also know that after they take their methadone, within the next hour or so, they feel it hit them; they feel a sense of warmth that starts in the abdomen and spreads through the body. They're getting partially "loaded" every morning with methadone, and they're partially

"sick" every morning before they get their methadone. That's not a comfortable condition to be in, but they're a lot better off than they were when they were using heroin.

The lasting effect that LAAM produces makes the patients feel better. Every patient I've spoken to who has been on both methadone and LAAM remarks on this--how he feels just generally better--more under control, more stable less of this up and down. And they don't feel sick at the end of the period.

Now, if patients have enjoyed the feeling of methadone relieving an incipient withdrawal! and if that's been an important part of their daily pattern, transferring their getting high on heroin to getting drug-induced satisfaction once a day on methadone, then they're not going to like LAAM; there is no question about it. Some patients really want that feeling on methadone, so that in the long run we're probably not going to just replace methadone with LAAM. There are going to be patients who need that feeling and it may take them a long time before they're ready to-give it up. But there are also a lot of patients who don't want that. who are really willing to make the transition and give up that sensation, and those patients much, much prefer to be on LAAM.

The So-Called "Week-end Problem"

Let me give you an example of a pseudoproblem that turned out not to exist with LAAM. In some places LAAM was introduced as "48-hour methadone". The patients, who are by no means stupid, immediately thought, "Well, if it's a two-day methadone, then how will I get through the weekend? I'll be sick on Monday morning." And they were sick on Monday morning ! But LAAM actually has a very long duration of action, at least over a three- to four-day period. Without going into the complicated pharmacokinetics, that means if you get the dose of LAAM on Monday you're in a stable state when you come in Wednesday morning. That Monday dose hasn't disappeared; it is picked up and carried along by the Wednesday dose and that is picked up and carried along by the Friday dose, and on Monday morning the effect of the Friday dose is still there. In other words, you're getting a stable effect. We have some very interesting data on that.

To have you understand the data, I will have to tell you the way we control dosage. Dosage is self-controlled by patients, who follow the same principle we described in that article about patient control of methadone dosage (J. Amer. Med. Ass. 234:734, 1975). The absolute ceiling is 75 mg. of LAAM on Monday and Wednesday, 100 mg. on Friday. Now up to that ceiling patients can set their own dosages. Our rule is that on Friday the patient is allowed to increase, if he wants to, by about 30%. Thus, if he is taking 75 he can increase to 100, if he is on 50 he can raise it to 65, and so on.

The question is, with that opportunity, do patients actually do it? Now, obviously, if they felt sick on Monday morning, they would raise their Friday dose to try to take care of that feeling of being sick. The interesting thing we found is that the great majority of patients do not make any increase in their Friday dose; in other words, they're voting that the LAAM takes care of them over the weekend. About one-third of the patients do make a Friday increase of varying degree. The average increase on Friday is very small, but some patients do take full advantage of the opportunity. This result tells us that the "weekend problem" is largely a non-problem, as long as anxiety is minimized. If the staff is worried that LAAM is not going to last through the weekend, and conveys their anxieties to the patient, then you get this tremendous psychological effect.

Patient Reaction to LAAM

If you ask our patients: "How do you like LAAM," they vote affirmatively. I have not known an exception to that. Some of the patients who have experienced methadone in the past prefer LAAM; others have never experienced methadone and have nothing to compare it to but they feel that it "holds" them in a stable way. Our experience with the laboratory data has been the same as in the Phase II study. We don't find any significant abnormalities in all of the careful checks that we have been making. Efficacy is very good, as measured by suppression of heroin use. It's as good or better than seen in methadone clinics in our area.

Finally, we have been pleasantly surprised to to find, at least in some patients, that LAAM can be discontinued with less discomfort than we were used to with methadone withdrawal. There is still the problem of anxiety exacerbating withdrawal problems for some patients, and there are certainly patients who have the usual problems with withdrawal (especially insomnia, as with methadone withdrawal). We have observed some patients, however, who simply stopped taking LAAM at a dosage of 50 mg or above, and experienced no withdrawal symptoms at all. It is possible that the long duration of action and the long persistence of the LAAM metabolites in the body produce a situation in which the drug detoxifies itself (so to speak), tapering itself over a long

enough time to minimize any acute withdrawal distress. This requires more research, however; we are not now claiming that most patients can detoxify more easily from LAAM than from methadone.

TAKE-HOME POLICY

The third point is a very significant one. In our clinic we, of course, have no takehome -- ever. Patients understand from the outset that takehome just doesn't arrive; it's not in the cards. We never use any methadone on the premises--exclusively LAAN consumed right there. For patients who are to be away for a while, we have had no difficulty at all in substituting methadone (e.g., by arrangement at a clinic in another city) and then resuming LAAM when they return.

There is a remarkable consequence of this policy. You may not realize how much of the unpleasantness and hassle in your clinic operation is related to the issue of takehome privileges, and how much of the deceit and gameplaying, manipulation and wasted staff time and energy and argumentation is related to that issue of takehome. It corrupts the urine collection system. As long as takehome depends on clean urines, you really cannot trust the urine collection, because it pays to cheat. It doesn't make any difference if it's called an "observed" urine collection or not. The potential for cheating and corruption is always there. With LAAM, suddenly, all that disappears. There is a quite incredible change in the whole attitude of the clinic. There is just no more argumentation about things like that. Patients level with their counselors about their drug use, and urines can be believed. I think it's fair to say that an awful lot of staff time and energy is wasted otherwise. This time and energy can now be devoted to patient welfare and to effective counseling, once you eliminate the takehome business and everything that goes with it. Unfortunately, I don't know how to measure these effects; they are major effects; everybody on our staff is convinced of that, but I don't know how to produce objective data to prove it, so I can only report it anecdotally to you. I think it is one of the major advantages of LAAM.

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