A Medical Treatment for Diacetylmorphine (Heroin) Addiction

A Clinical Trial With Methadone Hydrochloride

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

A group of 22 patients, previously addicted to diacetylmorphine (heroin), have been stabilized with oral methadone hydrochloride. This medication appears to have two useful effects: (1) relief of narcotic hunger, and (2) induction of sufficient tolerance to block the euphoric effect of an average illegal dose of diacetylmorphine. With this medication, and a comprehensive program of rehabilitation, patients have shown marked improvement; they have returned to school, obtained jobs, and have become reconciled with their families. Medical and psychometric tests have disclosed no signs of toxicity, apart from constipation. This treatment requires careful medical supervision and many social services. In our opinion, both the medication and the supporting program are essential.

The question of "maintenance treatment" of addicts is one that is often argued but seldom clearly defined. If this procedure is conceived as no more than an unsupervised distribution of narcotic drugs to addicts for self-administration of doses and at times of their choosing, then few physicians could accept it as proper medical practice. An uncontrolled supply of drugs would trap confirmed addicts in a closed world of drug taking, and tend to spread addiction. This procedure certainly would not qualify as "maintenance" in a medical sense. Uncontrolled distribution is mentioned here only to reject it, and to emphasize the distinction between distribution and medical prescription. The question at issue in the present study was whether a narcotic medicine, prescribed by physicians as part of a treatment program, could help in the return of addict patients to normal society.

No definitive study of medical maintenance has yet been reported. The Council on Mental Health of the American Medical Association, after a thorough review of evidence available in 1957,1 concluded that "The advisability of establishing clinics or some equivalent system to dispense opiates to addicts cannot be settled on the basis of objective facts. Any position taken is necessarily based in part on opinion, and on this question opinions are divided." With respect to previous trials of maintenance treatment, the Council found that "Assessment of the operations of the narcotic dispensaries between 1919 and 1923 is difficult because of the paucity of published material. Much of the small amount of data that is available is not sufficiently objective to be of great value in formulating any clear-cut opinion of the purpose of the clinics, the way in which they operated, or the results attained." No new studies bearing on the question of maintenance treatment have appeared in the eight years since this report was published. Meanwhile, various medical and legal committees have called for additional research.2

See also page 673.

The present study, conducted under the auspices of the departments of health and hospitals, New York city, has yielded encouraging results; patients who before treatment appeared hopelessly addicted are now engaged in useful occupations and are not using diacetylmorphine (heroin). As measured by social performance, these patients have ceased to be addicts. It must be emphasized that this paper is only a progress report, based on treatment of 22 patients for periods of 1 to 15 months. Such limited study obviously does not establish a new treatment for general application. The results, however, appear sufficiently promising to justify further trial of the procedure on a larger scale.

Procedure

The patients admitted to the program to date were men, aged 19 to 37, "mainline" diacetylmorphine users for several years with history of failures.
TREATMENT FOR DIACETYLMORPHINE—DOLE & NYSWANDER

Maintenance Therapy of Ex-Addicts With Methadone Hydrochloride, Summary of First 15 Months (February 1964 to May 1965)

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Age, Years</th>
<th>Previous Treatments</th>
<th>Status Before Admission to Program</th>
<th>Status Since Admission</th>
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<tr>
<td></td>
<td>FD</td>
<td>A F S M P</td>
<td>Education</td>
<td>Best Job</td>
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<tr>
<td>E 16 22</td>
<td>3 3 3</td>
<td>6 8th grade</td>
<td>Truck driver</td>
<td>...</td>
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<td>3 3 2</td>
<td>8 1 year high school</td>
<td>Odd jobs (few months each)</td>
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<td>2 years high school</td>
<td>Office clerk</td>
<td>...</td>
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<tr>
<td>E 20 30</td>
<td>1 2 3 1</td>
<td>1 Graduated high school</td>
<td>Store manager</td>
<td>A 3</td>
</tr>
<tr>
<td>E 17 22</td>
<td>6</td>
<td>2 years college</td>
<td>Shipping clerk</td>
<td>...</td>
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<tr>
<td>E 21 25</td>
<td>12 2</td>
<td>12 2 years college</td>
<td>Musician</td>
<td>...</td>
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<tr>
<td>E 18 25</td>
<td>1</td>
<td>6 Graduated high school</td>
<td>Radio operator in military service</td>
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<tr>
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<tr>
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<td>3 years high school</td>
<td>Truck driver</td>
<td>A 4</td>
</tr>
<tr>
<td>P 15 23</td>
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<td>1 year high school</td>
<td>Head usher</td>
<td>A 3</td>
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<tr>
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<td>1 year high school</td>
<td>Stock clerk</td>
<td>A 5</td>
</tr>
<tr>
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<td>3 2</td>
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<td>Mason</td>
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<td>1 4</td>
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<td>Supervisor of shipping department</td>
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<tr>
<td>N 18 30</td>
<td>2 6</td>
<td>3 years high school</td>
<td>Shipping clerk</td>
<td>AF 4</td>
</tr>
<tr>
<td>E 18 24</td>
<td>10 0</td>
<td>8th grade</td>
<td>Installing window screens</td>
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<td>2 2</td>
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<td>M 3</td>
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<td>AF 2½</td>
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<tr>
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<td>0 Graduated high school</td>
<td>None</td>
<td>...</td>
</tr>
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<td>...</td>
</tr>
<tr>
<td>E 19 26</td>
<td>2 8</td>
<td>2 years high school</td>
<td>Construction laborer</td>
<td>AF 4</td>
</tr>
<tr>
<td>N 14 30</td>
<td>2 8</td>
<td>2 grade</td>
<td>Shipping clerk</td>
<td>AF 4</td>
</tr>
</tbody>
</table>

*For comparison with other treatment series, patients classified into three groups: Western European ancestry (E), Puerto Rican and Cuban (P), and Negro (N).

†Age first used diacetylmorphine (FD): age at admission (A).

‡Number of admissions to Federal Hospital—Lexington, Ky (F), state hospitals—Manhattan General, Metropolitan, Riverside (M), private clinics and groups, including Synanon (P).

§All but two patients were employed at time of admission. Job indicated is best position ever held.

∥Time in Army (A), Navy (N), Marines (M), or Air Force (AF).

№Phases of treatment: 1a—four patients, residents on metabolic ward of Rockefeller Institute; 1—new patients being stabilized on methadone therapy, they sleep in hospital but may leave during day for school, shopping, or job; 2—patients newly discharged, living at home or rooming house, needy social support; 3—ambulatory patients who are self-supporting.

###High school equivalency status: If not a high school graduate, each patient was encouraged to enroll in night school to prepare for high school equivalency certificate. Those who have completed this course, passed examination, and received certificate are indicated by "Cert." Those now in night school indicated by "NS."

of withdrawal treatment. They have reported no substantial addiction to other agents (although most of them had used barbiturates or tranquilizers when narcotic drugs were unavailable), and they were not psychotic. Patients came from the streets, from drug withdrawal units, from referrals by social agencies and physicians who had heard of the program, and from recruitment of addicted friends by patients under treatment. Further details of their history are given in the Table.

**Division of Program Into Three Phases—PHASE 1.—**The addict patients were stabilized with methadone hydrochloride in an unlocked hospital ward, given a complete medical workup, psychiatric evaluation, a review of family and housing problems, and job-placement study. After the first week of hospitalization, they were free to leave the ward for school, libraries, shopping, and various amusements—usually, but not always, with one of the staff. Patients lacking a high school diploma started in classes that prepare students for a high school equivalency certificate. For the present study the time in this initial phase was arbitrarily set at six weeks.

During this phase of hospitalization, the treatment unit was kept small (four to nine patients). This was felt necessary because most patients started the treatment with serious anxieties and doubts. The limitation of patient load allowed the staff to individualize the daily ward activities and deal with the special problems of each patient.

**PHASE 2.—**This began when subjects left the hospital and became outpatients, returning every day for methadone medication. They were asked to
drink their medication in the presence of a clinic nurse, and to leave a daily urine specimen for analysis. When indicated, this rule has been relaxed; reliable patients who have been on the program for several months have been given enough medication for a weekend at home or a short trip. Continued contact with the hospital staff was provided as required. The most important services needed during this phase of treatment were help in obtaining jobs, housing, and education.

Phase 3.—This phase is the goal of treatment, the stage in which an ex-addict has become a socially normal, self-supporting person. The two patients who are considered to have arrived at this phase are still receiving maintenance medication since the physicians in charge of their treatment feel that withdrawal at this time would be premature. Supervision of their medication is as careful as in phase 2; the only distinction between patients in phases 2 and 3 is in the degree of social advancement.

Phase 1A.—This phase designates a special group of four patients who are being maintained on high doses under close and continuing observation to reveal any delayed toxic effects of methadone (Table). So far, none have been found. These patients live on a metabolic ward, and so are still classified in phase 1, but as measured by social adjustment they have progressed to phase 2 or 3, since all are either employed or going to school. The ward serves mainly as their residence, which they are free to leave as they wish subject only to the general routine of hospital activities.

Narcotic Medication.—Patients have differed markedly in tolerance to narcotics at the beginning of treatment, and in the rate with which they have adapted to increasing doses of medication. Individualization of treatment thus has been necessary. A rough estimate of initial tolerance was made from each new patient’s history of drug usage, with allowance for exaggeration since addicts coming to a maintenance program usually fear that physicians will not prescribe enough medication, and with recognition of the fact that the number of “bags” used by an addict is not a reliable measure of narcotic tolerance. The diacetylmorphine content of a “bag” obtained on the street today is low and variable. This estimate provided a guide to initial dosage, but the only sure way to measure tolerance is to observe the reaction to test doses of narcotic drugs. The schedule, therefore, differed for each patient.

On admission patients usually have shown mild or moderately severe symptoms of abstinence, the last shot of diacetylmorphine having been taken some hours before. These patients were relieved promptly by one or two doses of morphine sulfate (10 mg) or dihydromorphine (Dilaudid) hydrochloride (4 mg), given intramuscularly, and then started on oral methadone hydrochloride therapy (10 to 20 mg, twice daily). Patients coming to treatment without symptoms were started on a regimen of methadone without other medication, but were watched carefully for appearance of symptoms after admission. After the first 24 hours most patients could be maintained comfortably on the oral medication alone. The dose of methadone hydrochloride was increased gradually over the next four weeks to stabilization level (50 to 150 mg/day). Two patients in whom tolerance at the expected rate failed to develop have been held at lower doses (Table). With some patients, treated early in the study, the buildup of dosage was too rapid; they became overly sedated for a few days, and two of them had transient episodes of urinary retention and abdominal distention. Other patients, given too little, have become abstinent, exhibiting malaise, nausea, sweating, lacrimation, and restlessness. With more accurate prescription, patients have not become euphoric, sedated, or sick from abstinence at any stage of treatment. They have simply felt normal, and have not asked for more medication.

After the patients reached maintenance level, the morning and evening doses were combined by progressive reduction of the evening medication with an equal addition to the methadone taken in the morning. After discharge from the hospital patients could thus be maintained by a single daily visit to the outpatient clinic. The patients who have had difficulty in spanning a 24-hour period with a single dose have been given medication to take at home; this has been a minor problem, limited to those who could visit the clinic only in the evening. In all cases it has been made clear to the patients (and accepted by them as a condition of treatment) that the amount of medication and the dosage schedule were the responsibility of the medical staff. Physicians did not discuss dosage with the patients, although of course they listened carefully to any report of symptoms that might suggest excess or lack of medication.

Laboratory Control.—The urine of every patient was collected daily in the hospital and at each clinic visit, to be analyzed for methadone, morphine (the chief metabolite of diacetylmorphine), and quinine (a regular constituent of the street “bag”). The thin layer chromatographic method of Cochlin and Daly” was used, after preliminary extraction of the alkaloids from urine with cation exchange resin. The sensitivity of the procedure was such that it would give a definite positive if a patient had taken an average “bag” of diacetylmorphine during the preceding 24 hours.

Results

The most dramatic effect of this treatment has been the disappearance of narcotic hunger. All of the patients previously had made efforts to remain drug-free after withdrawal, but were unable to resist the craving. Drug hunger became intolerable for most of them shortly after discharge from a withdrawal unit and return to their neighborhood. It became especially severe when they were ex-
posed to emotional stress. With methadone mainte-
nance, however, patients found that they could meet addict friends, and even watch them inject
diacetylmorphine, without great difficulty. They
have tolerated frustrating episodes without feeling
a need for diacetylmorphine. They have stopped
dreaming about drugs, and seldom talk about drugs
when together. Patients have even become so in-
different to narcotics as to forget to take a sched-
uled dose of medication when busy at home.

The extent to which the patients have ceased to
behave as addicts, and their reliability in reporting
illegal drug use, were verified by the results of
urinanalysis. Negative results in almost all analyses
showed that use of diacetylmorphine has been rare
and sporadic, although the patients have had ample
exposure to addict friends and pushers. Remark-
ably, the episodes of drug taking were reported by
the patients spontaneously, and their reports have
correlated with the laboratory evidence.

An interesting phenomenon, which has been seen
in several patients, was the production of symp-
toms typical of drug deficiency by acute emotional
stress. Anxiety in some susceptible patients caused
malaise, nausea, yawning, and sweating, indistingui-
shable from the effects of abstinence, even
though the patients were being maintained on large
doses of medication. After experiencing relief with
reassurance but without additional medication, sus-
ceptible patients have become less alarmed by
these symptoms, and the episodes have occurred
less frequently. In two other patients symptoms
suggesting abstinence have appeared in the course
of mild respiratory-tract infections. These symp-
toms, not associated with anxiety, were difficult to
evaluate, but in any event disappeared in a few
days without need for increase in medication. These
observations suggest that the effectiveness of
methadone can vary with changes in psychological
and metabolic state.

The degree of tolerance established by metha-
done was titrated in six patients by giving diacetyl-
morphine, morphine, dilaudid, or methadone intrave-
rously in a double-blind study. The drugs were
given in randomized order and various doses every
hours after the last administration of methadone.
Stabilization with methadone, as here described,
was found to make patients refractory to 40 to 80
mg diacetylmorphine (which would cost $10 to
$25 if purchased on the street). Larger amounts
were not systematically tested; probably blocking
would extend to greater doses since two patients
with high tolerance showed little reaction to in-
travenous injection of 200 mg of diacetylmor-
phine—a huge amount, possibly enough to kill a
nontolerant individual.

Unscheduled, but perhaps necessary, experi-
ments in drug usage were made by four patients.
These subjects found that they did not “get high”
when “shooting” diacetylmorphine with addict
friends on the street. Both the patients and their
friends were astounded at their lack of reaction
to the drug. They discontinued these unrewarding
experiments without need for disciplinary measures,
and have discouraged other patients from repeating
the experiment. So long as patients take methadone
as scheduled, they apparently cannot feel the
euphoria of an addict taking a street bag of
diacetylmorphine.

Complications.—The chief medical problem has
been constipation. The tonus of the sigmoid and
the defecation reflex remain depressed even in
patients with high tolerance to the narcotic effects
of methadone, while the motility of the upper
gastrointestinal tract appears to be unaffected.
Five patients, given a barium sulfate meal and
followed with daily x-ray examinations for a week,
showed normal or only slightly delayed passage
of barium through the small intestine, but in
three of the five, the evacuation of barium from
the colon was abnormally slow. Fecal impaction
has occurred when patients have made no effort
to defecate for several days. Patients therefore
were instructed to take a hydrophilic colloid every
day, and a supplementary laxative or enema if
bowels have not moved for three days. With
these precautions patients have had no further
difficulty.

Apart from constipation, patients have shown no
major ill effects ascribable to use of methadone.
The tendency of addicts to leukocytosis (9,000 to
14,000 white blood cells/cu mm with 60% to 80%
polymorphonuclear cells" continued, apparently un-
affected by this medication. Bone marrow biopsies
in four patients after eight months of treatment
were normal. No effect of methadone on renal
function was disclosed by repeated urinanalyses.
Lever-function tests, when originally normal, re-
maind so. Results of basal metabolic rate, thyroid
uptake of sodium iodide I 131, red blood cell up-
take of labelled triiodothyronine, and plasma pro-
tein-bound iodine were normal in three patients who
had been stabilized on methadone hydrochloride
(100 to 150 mg/day) for four to six months. Some
patients have reported excess sweating in hot
weather, but no one has been unable to work for
this reason.

Mental and neuromuscular functions appear un-
affected. Patients have performed well in school
and at various jobs. Studies of motor skill (accuracy
in tracking moving targets) showed normal co-
ordination. We have not yet been able to find a
medical or psychological test capable of distinguish-
ing patients on methadone therapy from normal
controls. They can, of course, be distinguished by
urinanalysis.

There has been no problem so far in holding
patients. Only two of the patients who started
treatment have been discharged. These uncooper-
active and disruptive psychopaths were transfered
to withdrawal units. Two others who were admitted
specifically for tolerance tests at an early stage of
the study were returned (as originally planned)
to the withdrawal unit from which they came;
both subsequently have asked to return to the program. A fifth patient signed out after only four days on the ward, and also asked to return.

Comment

Previous efforts to treat addict patients with narcotic medication have been handicapped by lack of sufficiently long-acting agents. The Council's report noted that in 1919 to 1923 experience, "in all instances it was eventually found necessary to give drugs to addicts for self-administration." This is inherent in the pharmacology of parenterally administered morphine, which was used in these clinics and would probably apply to other agents with short periods of action such as diacetylmorphine, dihydromorphine, or meperidine. If addict patients are to be maintained with any of these drugs, they would need several injections per day; otherwise they would return to the street for additional drugs.

Projected into large-scale treatment, a medical use of short-acting narcotic drugs would require dispensaries staffed to give thousands of injections per day, with rooms or park benches in the neighborhood for addicts to wait between shots. Alternatively, physicians would have to yield control of drug administration to the addicts themselves. Neither alternative is acceptable. With methadone, however, the situation is much different since patients can be stabilized with a single daily dose, taken orally, under medical control. Maintenance of patients with methadone is no more difficult than maintaining diabetics with oral hypoglycemic agents, and in both cases the patient should be able to live a normal life.

We believe that methadone has contributed in an essential way to the favorable results, although it is quite clear that giving of medicine has been only part of the program. This drug appears to relieve narcotic hunger, and thus free the patient for other interests, as well as protect him against readdiction to diacetylmorphine by establishing a pharmacological block. A previous attempt by one of us (M.N.) to treat addict patients without narcotic medication ended in failure.16 Other clinics, attempting to rehabilitate patients after withdrawal, have had equally poor results. These, however, are indirect arguments. When the treatment program is sufficiently well established, the necessary control studies with social support, but without medication, must be made.

This study was supported by the Health Research Council grant U-1501 of New York city, and by the National Association for Prevention of Addiction to Narcotics.

Major contributions to this investigation were made by the following: Mary Jeanne Kreek, MD, bone marrow biopsies and tests of narcotic tolerance; Joyce Lowinson, MD, and George Lowen, MD, expansion of the program at Manhattan General Hospital; Nathan Poker, MD, measurements of intestinal motility; David Becker, MD, and Eugene Furth, MD, tests for thyroid function; and Norman Gordon, MD, Alan Warner, and Ann Henderson, measurements of motor skills of patients, and ratings with intelligence tests and mood scales.

Generic and Trade Names of Drug


References


Critique and Cavil

A REFERENCES AND REVIEWS item entitled "Is There a Toxoplasmic Pericarditis?" (JAMA 181, Feb 1, 1965, adv p 195) answers its own question by telling of what is claimed to be the first report of toxoplasmic pericarditis" (Presse Med 72:3047-3048 [Nov 28] 1964). Just to keep the record straight, I should direct the attention of those interested to a communication entitled "Pericarditis and Myocarditis Caused by Toxoplasma," which describes a case from the Third Medical Clinic, University of Helsinki (Amer Heart J 55:758 [May] 1958). The authors of this communication cite a previous case report on toxoplasmic pericarditis by Guimaraes (Mem Inst Cruz 38:257-320, 1943).

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