

# Forum

THE QUARTERLY NEWSLETTER FOR CLINICAL HEALTH CARE PROFESSIONALS ON ADDICTION TREATMENT

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**Research suggests higher doses may be required for "adequate" methadone maintenance dosing.**

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## MMT & Beyond

### Redefining "Adequate" Methadone Dose

The first article in this series [1] proposed that past research studies exploring allegedly adequate methadone maintenance doses have rarely ventured above a 100 mg/day threshold and that such investigations might be characterized as "defining the science of methadone *undermedication*." Next, it was demonstrated that the 100 mg/d "glass ceiling" was determined purely arbitrarily without any basis in science.[2]

This current article presents newer research revealing how higher doses than previously examined might serve to redefine the limits of "adequate" methadone maintenance dose.

### Contrary Attitudes

Today, many methadone maintenance treatment (MMT) programs appear to prescribe inadequate daily doses of methadone more for philosophical, moral, or psychological reasons than being guided by sound pharmacologic and medical principles.[3] Many clinicians also assume that lower doses automatically prevent methadone overmedication and eventually lead to opioid abstinence.[4]

Such attitudes and practices are contrary to recent scientific evidence suggesting that even doses in the 80 mg/d to 120 mg/d range once recommended by some guidelines [5] would be inadequate for a great many patients.

### Methadone Complexities

Although the concept of MMT is straightforward, methadone itself is a

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## Treatment Trends

### CSAT Launches Innovative Initiative

With an estimated 13 to 16 million Americans needing treatment for alcohol or drug abuse in any given year, and only 3 million receiving treatment, the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (CSAT) has taken steps to end the currently fragmented system of care for substance abuse.



### National Treatment Plan

#### Changing the Conversation

A new consensus report, called "Changing the Conversation: Improving Substance Abuse Treatment: The National Treatment Plan Initiative" (NTP Initiative), proposes developing accepted standards for what constitutes *effective* addiction treatment in the U.S. It also recommends that insurers adopt standardized benefits allowing for a continuum of treatment services and reimbursements appropriate to patients' needs, similar to what is available for other illnesses.

The report was prepared by a CSAT-organized consensus group comprised of 5 expert panels, including researchers, treatment providers, and members of the recovery community. A series of public hearings to gather input also was held.

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## Events to Note

For additional postings & information,  
see: [www.atforum.com](http://www.atforum.com)

### APRIL 2001

#### ASAM Annual Conference

April 19-22, 2001

Los Angeles, CA

Contact: 301-656-3920; [www.asam.org](http://www.asam.org)

### MAY 2001

#### American Psychiatric Association

May 5-10, 2001

New Orleans, LA

Contact: 202-682-6000; [apa@psych.org](mailto:apa@psych.org)

#### NAATP Annual Conference

(Nat. Assn. Addiction Treatment Prov.)

May 20-22, 2001

Scottsdale, AZ

Contact: 717-581-1901; [www.naatp.org](http://www.naatp.org)

#### 1st Intl. Conf. - Lindesmith

#### Center/Drug Policy Foundation

May 30- June 2, 2001

Albuquerque, NM

Contact: 212-548-0695;

[conference@drugpolicy.org](mailto:conference@drugpolicy.org)

### LATER 2001...

#### American Psychological Society

June 14-17, 2001

Toronto, Ontario, Canada

Contact: 202-783-2077

#### American Methadone Treatment Assn.

October 7-10, 2001

St. Louis, MO

Contact: 856-423-7222 ext. 360;

[www.americanmethadone.org](http://www.americanmethadone.org)

[To post your event announcement in A.T. Forum and/or our Web site, fax the information to: 847/413-0526 or submit it via e-mail from <http://www.atforum.com>]

A.T.F.

## Straight Talk... from the Editor

### When is "Good" Not Good Enough?

How should success in methadone maintenance treatment (MMT) be measured? What sort of results should be expected?

Two objective measures of success are treatment retention and illicit-drug abstinence. Those who stay longer in MMT and avoid illicit opioids do best.

However, it is a concern that certain research studies appearing in major medical journals (referenced in *Addiction Treatment Forum* articles during the past 2 years) have reported treatment "success" with dropout rates ranging up to 40%, despite the short-term nature of most investigations. Continued opioid abuse was found in up to 62% of patients

Such lackluster results may have hinged on a single factor: less than adequate daily doses of methadone for many, if not most, patients. This, even though the researchers claimed those patients were receiving "adequate" doses.

#### Greater Expectations

There may be reason for greater expectations.

Clinical studies described in this edition of *AT Forum* demonstrated that continued opioid abuse, even in recalcitrant patients, could be reduced to as little as 3%. Theoretically, 100% abstinence might be achieved in previously unresponsive patients by increasing methadone doses to optimal levels.

Furthermore, one-year retention rates of up to 86% were demonstrated with higher methadone doses, which was roughly a 50% improvement compared with control group patients. Statistically, the implication here is that for every two patients increased to a truly adequate dose, one *additional* patient would remain in treatment for a year or more who otherwise might have dropped out.

#### Therapeutic Pessimism

There are also counter arguments. For example, Wayne Hall (*Addiction*, 1993;88:1181-1182) warned, "[W]e may set such high criteria for what counts as successful outcomes that we predispose ourselves to therapeutic pessimism." He proposed that an insistence on abstinence as the most acceptable outcome of treatment could lead to an underestimation of the therapeutic benefits of MMT. Reducing drug-related

harm and improving patient health and well-being also are valid recovery goals, he urged.

Ward advised against "the best being an enemy of the good" when appraising the therapeutic effectiveness of MMT. Although he conceded that settling for lower expectations "will affect our standards of what counts as a successful treatment outcome." This is an especially important point as the formal accreditation of MMT programs continues.

#### Better Outcomes

We wonder if "good" is *good enough*. Or, should programs strive for the best possible outcomes achievable?

Are average treatment results or those demonstrated by unremarkable research studies acceptable, or should goals for MMT be set higher? Are clinicians willing to become better educated and modify their methadone dosing practices to achieve superior results? After all, patients do not seek treatment for their addictions to get just a *little bit* better.

#### Survey – Realistic Goals?

As usual, we want to know what our readers think. Please respond to the following questions:

What percentage of patients in MMT should be able to achieve complete abstinence from illicit opioids? \_\_\_\_\_%

What percentage of patients should still be retained in MMT after at least one year? \_\_\_\_\_%

Or, are other outcomes more important? Such as: \_\_\_\_\_.

There are several ways to respond:

**A.** Provide your answers on the postage-free feedback card in this issue; **B.** Write or fax us [see info below]; or **C.** Visit our Web site to respond online. As always, your *written comments* are important to help us discuss the results in our next issue.

Stewart B. Leavitt, PhD, Editor  
[stew202@aol.com](mailto:stew202@aol.com)

#### Addiction Treatment Forum

1750 East Golf Rd., Suite 320

Schaumburg, IL 60173

FAX: 847-413-0526

Internet: <http://www.atforum.com>

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## Part 7: The Hijacked Brain Revisited

Notes from the ASAM Review Course in Addiction Medicine

Part 3 of this series [1] observed that substances of abuse and dependency appear to “hijack” the brain’s natural pleasure/reward system and alter certain aspects of its normal functioning. This same concept was further explored at the American Society of Addiction Medicine’s (ASAM) Review Course in Addiction Medicine, October 2000, in Chicago, IL. More than 18 distinguished speakers and 425 attendees participated in the Course as preparation for the certification exam in addiction medicine. This article focuses on several of the presentations and associated reference materials.

### The Power of SPAM

Carlton Erickson, PhD – of the University of Texas College of Pharmacy, Austin, TX – observed that until relatively recently the field of addiction treatment and prevention drifted aimlessly due to insufficient research evidence. There also has been much misinformation about just how addicting drugs work in the brain.

Persisting negative attitudes have harmed the quality of patient care and have hindered funding for prevention, education, and research in addiction. Erickson portrayed these negative influences as “SPAM” – Stigma, Prejudice, And Misunderstanding. Among other damaging outcomes, SPAM leads to unfairness toward certain treatment options, belittling of patients, and lack of insurance coverage.

He said that the picture is rapidly changing thanks to scientific research indicating that the brain’s *pleasure/reward pathway* – consisting of cells and structures deep within the brain – is affected by *all* addictions. However, addiction does not automatically occur with a particular drug; rather, individual factors of genetics, environment, and chronic drug use play key roles in *susceptible* persons.

### Pirating Pleasure

Eliot Gardner, PhD – Senior Research Scientist at NIDA’s Intramural Research Program, Washington, DC – observed how one might consider the addictive power of certain drugs as an accident of nature. He has written,[2] for example, that the poppy and coca plants quite unintentionally produce chemicals (morphine and cocaine) capable of “pirating” the pleasure pathways of the brain. Alcohol, a byproduct of natural fermentation, acts similarly, as does practically every other addicting substance.

The brain’s pleasure/reward pathway is necessary for survival since it motivates important activities such as food seeking and eating, mating, and parenting. Unfortunately, those same parts of the brain that are stimulated by natural pleasures and rewards are also stimulated by addicting substances.

Both Gardner and Erickson stressed that a key characteristic of drug addiction is impaired control over the compulsion to use drugs and the inability to stay away from them if the person tries to stop. This is probably caused by abnormal functioning of pleasure/reward structures.

The important point here is that, since these sites of addicting drug action are located well inside the brain, and *not* in the cerebral cortex – which is the outermost, thinking part of the brain – addictions are not primarily under conscious control.

That is, *addictive behaviors are not simply problems of weak willpower, poor judgment, or corrupt morals. Furthermore, a person cannot simply think his/her way out of addiction.*

**Addictive behaviors are not simply problems of weak willpower, poor judgement, or corrupt morals.**

### Brain Chemistry Disease

According to Erickson, addiction is essentially a brain chemistry disease and addicting drugs seem to “fix” chemical disturbances in the brain, at least briefly. Gardner observed that different addictive drugs enter the brain’s pleasure/reward centers at different sites and affect the brain in different ways. The various effects of addicting drugs are due to the way in which a given drug can disrupt brain functioning.

Gardner further proposed that vulnerability to drug addiction may be caused by unusually low levels of certain natural chemicals in the pleasure/reward system. People with such chemical imbalances get a greater “kick” from certain addicting drugs than persons with normal brain chemistry. In fact, those drugs actually may produce unpleasant feelings in “normal” persons, motivating them to avoid the drugs.

Erickson similarly suggested that when an addictive substance stimulates certain brain centers, it may satisfy an unfulfilled chemical need in the brains of susceptible persons. It’s as if their brains respond to the drug, “Welcome. You’re just exactly what I’ve been waiting for!”

### “Getting Straight”

Stress and depression can trigger relapse to drug-taking, Gardner explained. Environmental cues – people, places, things – also play crucial roles.

With chronic use of certain drugs, like opioids, the depression, anxiety, and restlessness that follow drug use become unbearable. Under these circumstances, Gardner has written, [2] the addicted person no longer uses drugs to get a “rush” or “high,” but simply to get back to feeling what they consider as better or “normal” (to “get straight” in street parlance).

Erickson suggested that a goal of addiction treatment is to improve function in the proper brain areas. The success of methadone maintenance is evidence that many people need and benefit from pharmacologic therapy for a prolonged period to overcome abnormal brain chemistry.

He also has written that the emotional, interactive, sometimes stressful process of recovery via behavioral therapy programs and/or 12-step groups also may be associated with at least temporary positive changes in brain chemistry. And such changes may eventually engender a decreased need for the addictive substance.[3]

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## Physical Dependence

Gardner emphasized that the brain pathways producing desired effects of addictive drugs are *entirely separate* from those causing physical dependency (and subsequent drug withdrawal or abstinence syndrome). Some drugs, such as cocaine, are very addicting, yet they produce no physical dependence.

Furthermore, research has clearly demonstrated that drug-taking behavior cannot be explained simply in terms of the ability of addicting drugs to ease or overcome the withdrawal discomfort as drug effects wear off. That is, *the need to constantly avoid unpleasant withdrawal effects does not account for continued drug addiction.*

Withdrawal can be basically understood as a physiological “rebound” effect, Gardner explained. If chronic drug administration and/or intoxication causes one bodily effect, withdrawal from the drug will typically cause an opposite reaction.

For example, opioids may produce constipation, whereas opioid withdrawal produces diarrhea. Withdrawal from sleep medications (sedative-hypnotics) often produces insomnia.

Of course, unpleasant withdrawal effects can be quickly ended by more drug-taking. However, the importance of physical dependence and the need to overcome withdrawal effects in drug addiction should not be overstated, Gardner cautioned. Explanations of continued drug taking merely based on tolerance, physical dependence, and/or avoidance of withdrawal symptoms do not paint the whole picture.

## Multiple Disorders Typical

Focusing on psychiatric issues, James David, MD – Associate Professor of Clinical Psychiatry, Albert Einstein College of Medicine, Bronx, NY – stressed that multiple disorders are the rule, rather than the exception, for patients coming into addiction treatment.

At the least, most patients use multiple addicting substances and each drug is worthy of diagnosis as a separate disorder. However, he claimed, even in patients only using a single addictive drug there are likely to be a number of disorders.

For example, disorders associated with any form of substance abuse may include intoxication hallucinations, withdrawal syndrome, memory problems,

mood or anxiety disorders, sleep disorder, sexual dysfunction, and other maladies. These diagnoses were updated by the American Psychiatric Association in its DSM-IV-Text Revision, fall 2000.[4]

Among other benefits of multiple diagnoses, David asserted that a patient’s progress and improvement during treatment can be more easily seen when a more complete list of disorders is tracked. It also helps some patients to understand that their depression, anxiety, restlessness, sexual dysfunction, or insomnia, for example, are among well-known disorders associated with the particular drug(s) they are abusing.

A more broadly and behaviorally defined set of criteria for addiction are now in force, independent of the concepts of “tolerance” and “withdrawal.” A patient can be given a diagnosis of *substance dependence* (DSM-IV-TR does not use the term “addiction”) with neither tolerance nor withdrawal in the clinical picture. Key markers of dependence are *unsuccessful attempts to reduce drug/alcohol use, along with incurring the repeated consequences of such use, whether they are legal, financial, health, family, job, or school related.*

## Role of Thinking

A major unresolved question is how input from the thinking, outer portion of the brain might come into play in addiction and recovery. As noted above, Gardner and Erickson suggested that during active addiction more primitive brain centers in the pleasure/reward pathway dominate and drug-taking becomes involuntary or, at the least, not entirely under conscious control.

In this regard, Gardner has acknowledged early 19th century descriptions of drug addictions as being impulse control disorders: “Voluntary control is profoundly impaired. The patient is compelled to perform acts which are dictated neither by his reason nor his emotions – acts of which his conscience disapproves of, but over which he no longer has willful control....”[5]

**The notion of addiction being related to OCD might open new doors for therapeutic strategies.**

Along similar lines, Erickson wondered whether addictions might be appropriately considered obsessive-compulsive disorders (OCD). That is, those afflicted think about the substance or behavior all the time (obsession) and end up repeatedly taking the drug or behaving uncontrollably (compulsion).

For example, David observed that OCD occurs 2 to 3 times more often in alcoholics and other drug-dependent persons than in the general population. The notion of addiction being related to OCD might open new doors for therapeutic strategies of interest to psychologists and counselors.

## Overcoming Hurdles

A series of seemingly insurmountable hurdles appear to be erected in the path of drug-dependent persons wishing to recover and stay abstinent. What is the solution?

Gardner has written [5] that there are surprisingly few clearly effective and FDA-approved medicines for treating drug addiction, including methadone and LAAM maintenance for opioid addiction (with buprenorphine awaiting approval); naltrexone and disulfiram for alcoholism; and nicotine substitution therapy and bupropion for tobacco dependence. Strategies solely based on talk therapy, group therapy, behavior modification, and economic incentives have had limited success.

The many presentations at the ASAM Course made it clear that better solutions will be found through continuing scientific research.

1. The hijacked brain. *Addiction Treatment Forum*. Winter 2000;9(1):3-5. Available online at [www.ATForum.com](http://www.ATForum.com).
2. Gardner EL, David J. The neurobiology of chemical addiction. In: Elster J, Skog O, eds. *Getting Hooked - Rationality and Addiction*. Cambridge University Press;1999:93-136.
3. Erickson CK. Voices of the afflicted [commentary]. *Alcohol Clin Exp Res*. 1997;21(3):567-568.
4. *Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text revision.* [DSM-IV-TR.] Washington DC: American Psychiatric Association; 2000.
5. Gardner EL. The neurobiology and genetics of addiction: implications of the “Reward Deficiency Syndrome” for therapeutic strategies in chemical dependency. In: Elster J, ed. *Addiction: Entries and Exits*. New York: Russel Sage Foundation;1999:57-119.

*For information on courses and other events, ASAM may be contacted at 301-656-3920; [www.asam.org](http://www.asam.org).*

# Reader Survey Results - "Patient" or "Client"?

In the summer 2000 edition of *AT Forum* (Vol. 9, No. 3) readers were asked whether persons in addiction treatment programs should be referred to as "patients" or "clients."

An accompanying "From the Editor" column noted that, although *client* might be intended as a respectful term, there were concerns as to whether health insurers and/or legislators might be willing to pay for or fund programs caring for clients as opposed to *patients*. There is also the question of which term better reflects the disease concept of addiction, as supported by scientific research. During a several-month period readers submitted their opinions via feedback cards or at the *AT Forum* Web site ([www.ATForum.com](http://www.ATForum.com)).

## "Patient" Favored

There were 308 survey responses: 80 from medical staff (physicians, nurses); 119 from nonmedical staff (administrators, psychologists, counselors, social workers, etc.); 109 from patients (persons in treatment). Although medical staff and patients seemed largely in agreement that persons in treatment should be called *patients*, nonmedical personnel were highly equivocal in their opinions. See chart.

Overall, 61% of respondents favored using the term *patient*, including 71% of medical staff and 67% of patients. Nonmedical staff were about evenly split (49% vs 51%) between using patient or client. As usual, reader comments reflected a diversity of well-considered opinion on both sides of the issue.

## Medical Staff Speak Out

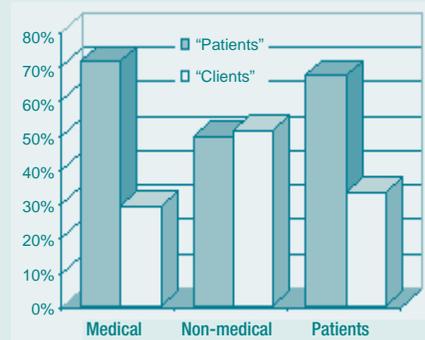
"With all of the research pointing to physiologic reasons for addiction, the term patient is more appropriate."

"The word client lacks the connotation of illness; seeking the services of a professional because of illness is the fundamental concept [of addiction treatment], and that is embodied in the word patient. While the definition of client includes the idea of employing a professional, it also carries the connotation of patronage and dependency that does not succeed in reducing possible stigma."

"Client implies working together. Patient implies a dependent, nonparticipatory status."

"Client is better because patient refers to a person who is ill or sick with a disease."

"I use 'patient' in an inpatient setting and 'client' in an office setting."



## Patients' Perspectives

"Opiate addiction is a disease. Methadone is a medication. Therefore, I am a patient."

"The term client only feeds the stigma surrounding MMT. I'm a patient receiving medical treatment."

"I think it hurts MMT by calling us clients. People with other illnesses are not called clients."

"Patient should be used because it is an affirmation of the fact that we are 'sick' and have a disease, rather than 'bad' and have no morality."

"Being referred to as a patient implies sickness. I am healthy now and plan to stay that way."

"We begin treatment as patients striving to get better and end as clients striving to work a program [of recovery]."

"Client is a less stigmatizing term. Any way we can reduce stigma in MMT should be encouraged."

"Insurance companies may be reluctant to pay for MMT if patients are called clients."

"I've been on methadone for 29 years. A patient goes to a doctor and that's what we do. What else can we be called but patients - no shame in that."

## Nonmedical Staff Voice Opinions

"A patient is a person receiving medical care. A client is a customer. Receiving addiction treatment is different from retaining a lawyer or buying a car."

"If addiction is a disease (and I believe it is) then don't we treat patients?"

"I believe using patient is consistent with the medical model of addiction treatment. Words are very powerful and using patient will help destigmatize addiction."

"Using client 'demedicalizes' the treatment process."

"Some clients I have served resent being called client."

"I use the term patient for clients who aren't paying."

"I have found that when individuals in treatment are asked, they prefer client."

"Although substance abuse is classified as a disease, I feel client is more appropriate. We are providing a service."

"Not all addiction treatment programs are medical. Those that are should use the term patients; others should use different terms (e.g., residents or clients)."

## Confusion Continues

The survey results raise several concerns. For one thing, there appears to be some ambivalence regarding this issue, especially among nonmedical staff. One wrote, "Who really cares? My clients/patients just want help." And a patient commented, "As long as we are treated with dignity and respect, I don't care either way."

Secondly, there is still the question of what treatments insurance will pay for and what programs legislators will fund. Perceived nonmedical approaches serving "clients" - for example, therapeutic communities or family counseling - could be left out in the cold. Yet, one reader insisted, "Fully understanding the insurance implications, as a nonmedical professional, I'm uncomfortable with the term patient."

Third, the disease concept of addiction does not appear to be universally accepted by professionals or patients. Hence, uncertainty by the public logically follows. As one patient observed, "The public doesn't look at addiction as a disease. I wish the public were more educated regarding MMT and would look at it as a medical treatment program."

As one counselor noted, "This is an important issue and applies to all substance abuse treatments." However, it seems apparent from the comments that there are no easy answers to the question of terminology. In fact, another confusing buzzword has emerged to describe persons in addiction treatment: "consumer."

*AT Forum*, with an emphasis on the science of addiction and medical approaches to treatment, will continue to feature the term *patient*. And, it was gratifying to receive one staff member's comment, "I've always used 'client,' however, [your editorial] made sense; I'll now use 'patient.'"

## “MMT & Beyond”

### Continued from Page 1

more complex medication than many appreciate.

The formulation typically used in MMT programs is a mixture of two chemical forms, called “enantiomers.” Only one of these forms, specified as “R-methadone” and making up half the mixture, is active at the *mu*-opioid receptors in the brain,[6,7] which is where methadone does its work in preventing withdrawal symptoms and stemming drug craving.

Furthermore, methadone is largely metabolized or “digested” in the liver, and before it even reaches the liver the medication is partially digested in the gut. So, only a relatively small portion of any given dose ends up freely circulating in the blood to the brain.[6]

Levels of methadone circulating in the blood should be sufficient to maintain “normalcy” over a 24-hour period, without the patient feeling drugged or “high,” or experiencing withdrawal symptoms (called “abstinence syndrome”).[8] It is important to note that methadone’s blood level and its rate of elimination from the body may be influenced by numerous factors, such as poor absorption in the gut, changes in urine acidity, continued drug abuse, diet, physical condition, pregnancy, medications or herbal remedies, and even vitamins.[6]

Genetic factors also account for differences among individuals in how their bodies “digest” methadone.[9] New research suggests that there may be genetic differences influencing how a person’s brain responds to methadone.[10,11].

As a result of these many influences, in patients given exactly the same dose of methadone, actual concentrations of active methadone reaching their brains can be greatly different.[7,9] This helps explain the many cases of so-called “fast metabolizers” who repeatedly complain, “My methadone dose is not enough to hold me.”

In most circumstances, considerable flexibility in methadone dosing may be required to stabilize patients in MMT.

### How Much is Enough?

Methadone circulating in the blood can be measured by a laboratory test and is expressed in nanograms per milliLiter(ng/mL). A methadone blood level of 400 ng/mL (measured just prior to dosing and called the “trough” level) has been considered necessary by many for successful stabilization in MMT. However, no clinical research had actually demonstrated the existence of such a requirement.

Eap and colleagues [7] in Switzerland studied 180 patients in MMT to evaluate this and also to demonstrate the blood concentration of the active R-methadone component that works best. They looked at differences between treatment responders and nonresponders. *Response* was defined as the absence of illicit opioid-positive urine tests during a 2-month study period.

Eap et al. did find that a methadone blood level of 400 ng/mL and, in particular, an R-methadone concentration of 250 ng/mL were the most favorable levels for adequate treatment response. However, due to individual differences in methadone metabolism, individual patients required daily methadone doses ranging anywhere from 55 mg to 921 mg to achieve those adequate blood levels.

In the case of nonresponders (i.e., those with continuing illicit opioid-positive urine screens), almost all patients required much greater than 100 mg/d of methadone for treatment success. Furthermore, in patients receiving medications in

addition to methadone, the range of effective methadone blood-level concentrations was extremely broad. There was more than a 40-fold difference between the smallest and largest optimal levels.

Of particular interest, as blood levels of the active R-methadone component in these patients approached 400 ng/mL, a 100% positive response rate was achieved. That is, these difficult patients completely stopped using illicit opioids.

This research helps explain why some previously unresponsive patients may require and benefit from relatively high doses of methadone. Especially in those receiving additional medications for physical or psychiatric illness.

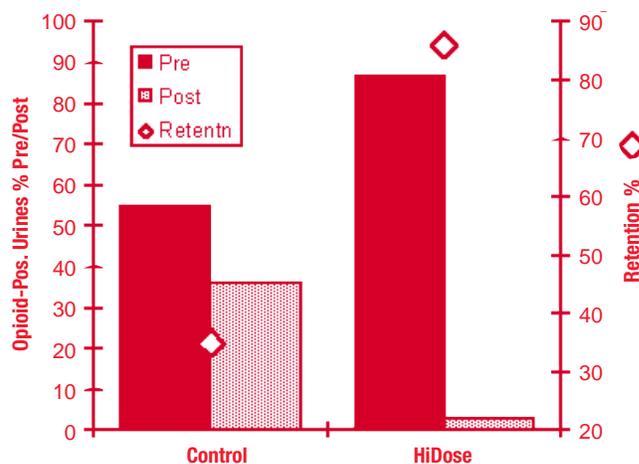
### Raising the Bar

What might constitute adequately “high” methadone dosing in everyday clinical practice?

To explore that question, Maxwell and Shinderman [12] identified a group of 164 patients who, despite methadone doses up to 100 mg/d, had excessive rates of continuing illicit opioid use. These patients, assigned to a “high dose” (HD) condition, received clinically-guided dose increases, resulting in an average dose of 211 mg/d (range 120-780 mg/d). This group was compared to a control group of patients receiving an average dose of 69 mg/d randomly drawn from a large clinic population.

Patients in the HD group differed in 2 significant ways from the control group. They were taking more prescribed psychotropic medications and they had more severe addictions (taking larger amounts of daily heroin) prior to entering treatment.

In the HD group, opioid-positive urine samples decreased from 87% before the dose increase (Pre) to 3% after the dose increase (Post). This compared with a decline only from 55%-Pre to 36%-Post in the control group. Furthermore, the one year or more retention-in-treatment rate for the HD group was 86%, compared with only 35% for the control group. *See graph.*



The higher methadone doses necessary in the HD group might have been predicted from their larger heroin habits prior to MMT. Also, their greater intake of prescription psychotropic medicines might have interacted to speed up methadone metabolism and reduce blood levels of the medication.

Maxwell and Shinderman proposed that “medical evaluation of objective signs and subjective symptoms [of abstinence syndrome] is a sensitive, reliable, and cost-effective method of dose titration.” Furthermore, the authors stressed that, as long

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as the patient does not exhibit signs/symptoms of methadone overmedication, adequate methadone dose may be quite high in a truly individualized treatment milieu.

**Provided the clinical picture does not suggest opioid overmedication, adequate methadone dose may be quite high in a truly individualized treatment milieu.**

### International Evidence

Recently, Maremanni et al. [13] in Italy reported on 90 opioid-dependent patients. About half of the patients required methadone doses greater than 110 mg/d, and a quarter required 160 mg/d or much more. Those patients with psychiatric illness in addition to opioid addiction required significantly higher doses for stabilization on methadone.

The authors observed that effective doses for patients with psychiatric comorbidity typically average higher than 200 mg/d and may exceed 400 mg/d. This is important, considering that various psychiatric diagnoses in addition to opioid dependence have been reported in up to 90% of some MMT clinic populations.[14]

Byrne [15] reported from Australia on 56 patients who were unstable (using illicit opioids) despite receiving up to 150 mg/d of methadone. Trough methadone blood levels in these patients ranged from only 35 ng/mL to 330 ng/mL. Methadone dose increases up to 350 mg/d resulted in considerable improvements, with a reduction or elimination of heroin use and enhanced self-reported patient well-being.

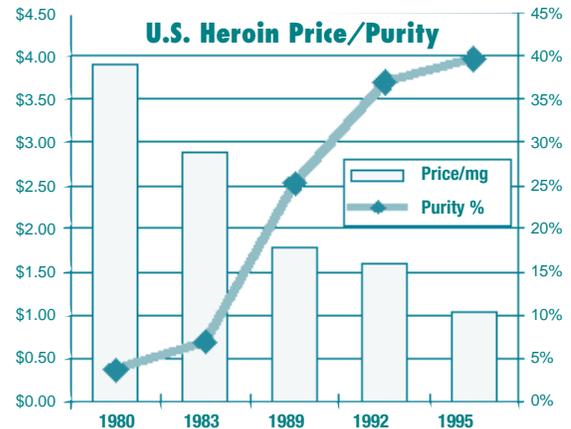
Adelson et al. [16] reported on 212 patients in an MMT clinic newly established in Israel. Average methadone doses reached 114 mg/d by the conclusion of the study. More than half the patients received methadone doses greater than 100 mg/d.

A one-year retention rate of 72.5% and a 71.2% abstinence rate from illicit opioids were achieved in this successful program. Although, based on the other research reported above, it seems possible that further dose increases might have improved results in the nearly 30% of patients who dropped out of treatment or continued abusing opioids.

### Exceptions Becoming “Rule”

Contributing to the necessity for higher methadone dosing is the likelihood that the drug environment and the opioid-addicted population of today are different from an earlier era of MMT.

Over the years, street heroin has become purer in quality and lower in price, making it more potent and more economically appealing. A report of the U.S. Drug Enforcement Agency noted that from 1980 to 1995, the price of a milligram of street heroin decreased from \$3.90 to \$1.04, while its purity increased from 3.6% to 39.7%.[17] See graph.



Higher-purity, lower-cost street heroin has led to increased use, since it can be smoked or snorted, avoiding the need for intravenous injection. Persons snorting or smoking heroin increased from about half of users in 1994 to 82% in 1996, and this has especially attracted first-time users.[18,19]

Borg et al.[20] and others [21] have proposed that the increasingly higher levels of heroin purity and greater use contribute to addiction severity and, consequently, the need for increased methadone doses. This was demonstrated in the Shinderman/Maxwell research described above.[12]

Hence, environmental factors – combined with psychiatric comorbidity and individual differences in methadone metabolism – suggest that today’s increasing numbers of opioid addicts may have more refractory or complicated drug dependencies, which often necessitate appropriately higher doses of methadone during MMT. There have been cases of patients requiring in excess of 2000 mg of daily methadone, sometimes associated with organic illness.

For example, recent investigations from the U.S. and Eastern Europe have reported that MMT patients with hepatitis C had a 30% to 50% higher requirement for methadone than uninfected patients. This increased need is contrary to what might be expected with liver disease; however, it is very noteworthy, since up to 96% of the populations in some clinics have tested positive for hepatitis C.[22]

In this era of hepatitis, HIV/AIDS, tuberculosis, and other infectious diseases, along with more aggressive pharmacotherapy for physical and psychiatric comorbidity in substance abusing populations, it appears that past interpretations of adequate methadone dose and the prescribing practices of many clinicians are no longer valid. The “exceptional” MMT patient requiring what was once considered an exceptionally high methadone dose may be more of a “rule” for defining *truly adequate dose* than is presently appreciated.[6]

1. Shifting paradigms & slippery slopes. *Addiction Treatment Forum*. Summer 2000;9(3):1. Available online at [www.atforum.com](http://www.atforum.com).
2. The 100 mg/d methadone glass ceiling. *Addiction Treatment Forum*. Fall 2000;9(4):1. Available online at [www.atforum.com](http://www.atforum.com).
3. Loimer N, Schmid R. The use of plasma levels to optimize methadone maintenance treatment. *Drug Alcohol Depend*. 1992;30(3):241-246.
4. Kell JM. Utilization of plasma and urine methadone concentrations to optimize treatment in maintenance clinics: I. Measurement techniques for a clinical setting. *J Addict Dis*. 1994;13(1):5-26.
5. Dole VP, Nyswander ME. Rehabilitation of heroin addicts after blockage with methadone. *New York State J Med*. 1966;66(15):2011-2017.
6. Leavitt S, Shinderman M, Maxwell S, Eap CB, Paris P. When “enough” is

## “MMT & Beyond” Continued from Page 7

- not enough: new perspectives on optimal methadone maintenance dose. *Mt Sinai J Med.* 2000;67(5-6):404-411. Available online at [www.mssm.edu/msjournal/](http://www.mssm.edu/msjournal/).
7. Eap CB, Bourquin M, Martin J-L, et al. Plasma concentrations of the enantiomers of methadone and therapeutic response in methadone maintenance treatment. *Drug Alcohol Dep.* 2000;61(1):47-54.
  8. Why measure methadone blood levels? *Addiction Treatment Forum.* Summer 1999;8(3):1. Available online at [www.atforum.com](http://www.atforum.com).
  9. Eap CB, Déglon J-J, Baumann P. Pharmacokinetics and pharmacogenetics of methadone: clinical relevance. *Heroin Add & Rel Clin Probl.* 1999;1(1):19-34.
  10. Noble EP, Lawford BR, Ritchie T, Young RM, Zhang X. The D2 dopamine receptor (DRD2) gene and methadone treatment outcome of opioid-dependent patients [abstract]. Presented at: 1998 Annual Meeting of the Society for Neuroscience; November 7-12, 1998; Los Angeles, CA.
  11. Lawford BR, Young RM, Noble EP, et al. The D(2) dopamine receptor A(1) allele and opioid dependence: association with heroin use and response to methadone treatment. *Am J Med Genet.* 2000;96(5):592-598.
  12. Maxwell S, Shinderman M. Optimizing response to methadone maintenance treatment: higher-dose methadone. *J Psychoactive Drugs.* 1999;31(2):95-102.
  13. Maremmani I, Zolesi O, Aglietti M, Marini G, Tagliamonte A, Shinderman M, Maxwell S. Methadone dose and retention during treatment of heroin addicts with Axis I psychiatric comorbidity. *J Addict Dis.* 2000;19(2):29-41.
  14. Dual diagnosis & MMT: a chicken-egg enigma. *Addiction Treatment Forum.* Winter 1998;7(1):1. Available online at [www.atforum.com](http://www.atforum.com).
  15. Byrne A. Use of serum levels for optimizing doses in methadone maintenance treatment. *J Maint Addict.* 1998;1(3):13-14.
  16. Adelson MO, Hayward R, Bodner G, Bleich A, Gelkopf, Kreek MJ. Replication of an effective opiate addiction pharmacotherapeutic treatment model: minimum need for modification in a different country. *J Maint Addict.* 2000;1(4):5-13.
  17. O'Dea P. Domestic monitor program. Presented at: Heroin: It Never Went Away; the National Heroin Conference, February 1997. Washington, DC: US Department of Justice, Drug Enforcement Administration.
  18. Nadelman E, McNeely J. Doing methadone right. *The Public Interest.* 1996;123:83-93.
  19. Office of National Drug Control Policy (ONDCP). *Policy Paper: Opioid Agonist Treatment.* Washington, DC: Office of National Drug Control Policy; March 1999.
  20. Borg L, Broe DM, Ho A, Kreek MJ. Cocaine abuse sharply reduced in an effective methadone maintenance program. *J Addict Dis.* 1999;18:63-75.
  21. Bach PB, Lantos J. Methadone dosing, heroin affordability, and the severity of addiction. *Am J Pub Health.* 1999;89(5):662-665.
  22. HCV paradoxically increases methadone dose requirement. *Addiction Treatment Forum.* Fall 2000;9(4):1. Available online at [www.atforum.com](http://www.atforum.com).

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## “Treatment Trends” Continued from Page 1

### Five Principles

The report makes 5 major recommendations for change:

- greater investment to close the gap between treatment need and availability,
- ensure that treatment can be accessed across all systems, including primary care medicine and criminal justice,
- commit to high-quality treatment that is science-based and delivered by well-trained health care professionals,
- change attitudes to combat stigma,
- build partnerships between consumers and the treatment system.

The consensus group especially felt that quality care must include better links between research and practice, so that proven and innovative treatment methods are widely adopted.

### No “Wrong Door”

According to H. Westley Clark, MD, CSAT director, fighting stigma is among the most important tasks. It affects everything from attitudes regarding treating addiction as a public-health problem to reimbursement rates.

An essential underlying principle is that there should be “no wrong door for treatment.” When a substance abusing person presents for treatment for any condition at any point in the health care system, he or she should be guided toward appropriate treatment. To achieve this goal, the NTP Initiative also stresses the inclusion of the recovery community, including patient advocacy groups, in all discussions.

*NTP Initiative documents can be obtained online at [www.natxplan.org](http://www.natxplan.org).*

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### ADDICTION TREATMENT

## Forum

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