

# Forum

THE QUARTERLY NEWSLETTER FOR CLINICAL HEALTH CARE PROFESSIONALS ON ADDICTION TREATMENT

Vol. IX, #4 • FALL 2000

***“Despite methadone treatment’s extensive history, controversy regarding optimal dosing persists.”***

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## MMT & Beyond

### The 100 mg/d Methadone Glass Ceiling

#### Controversy Persists

The first article in this MMT & Beyond series, “Shifting Paradigms & Slippery Slopes,”[1] proposed that much research to date exploring allegedly adequate methadone dosing practices actually might be characterized as defining the science of methadone undermedication. Of note, time and again, in one research study after another (many very recently reported), 100 mg of daily administered methadone has been presented as the upward limit of “optimal” dose; an impenetrable glass ceiling of sorts.

In practice, most patients engaged in research investigations have received maximum daily doses far below that ceiling threshold, even in those study conditions portrayed as “high dose.” Many researchers have qualified their sometimes lackluster results by observing that the methadone doses in their studies were modest, not individualized, or simply not high enough to achieve their therapeutic objectives.

Strain et al.[2] noted in their dose-comparison study reported in 1999 that, “Despite methadone treatment’s extensive history, controversy regarding optimal dosing persists.” Indeed, they related how by the late 1980s surveys found some MMT clinics had average daily doses of less than 30 mg. In their study, Strain and colleagues allowed daily doses in a “high dose” condition of 80 to 100 mg/d, yet the average was 89.5 mg/d, staying well below the ceiling threshold.

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## Clinical Concepts

### HCV Paradoxically Increases Methadone Dose Requirement

#### Lurking Crisis

Past articles in AT Forum [1,2] have discussed the hepatitis C virus (HCV) crisis lurking around MMT programs like a massive iceberg with only its tip exposed to view. The virus, first detected in 1989, infects up to 90% of heroin addicts, with more than 60% of cases due to injection drug use.

In the general population, HCV has infected twice as many people as HIV and deaths from HCV, which can lead to cirrhosis and liver cancer, are expected to be more than double those from AIDS within 20 years.

Among patients in methadone maintenance treatment (MMT) programs, up to 96% of the population has tested positive for HCV in some clinics. Now comes word that, besides treatment for their HCV infection, these patients also may have special needs when it comes to their methadone dose.

#### High Prevalence

Speaking last May at a conference of the European Opiate Addiction Treatment Association,[3] Marc Shinderman, MD and Sarz Maxwell, MD, both of the Center for Addictive Problems (CAP) in Chicago, Illinois, presented some rather surprising research involving their MMT patients with HCV.

They tested 558 MMT patients, representing 46% of their clinic population, for HCV antibodies. Overall prevalence of HCV in the sample was 60%; that is,

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## Events to Note

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

### DECEMBER 2000

#### National Leadership Forum XI

December 6-8, 2000

Washington, DC

Contact Ronald Dixon:

703-706-0560 x231

[rdixon@cadca.org](mailto:rdixon@cadca.org); [www.CADCA.org](http://www.CADCA.org)

#### 4th Pain Management & Chemical Dependency Conference

December 7-9, 2000

Washington, DC

Contact: 770-751-7332

### JANUARY 2001

#### Addictive Disorders & Behav. Health;

#### 27th Annual Winter Symposium

January 29 - February 2, 2001

Colorado Springs, CO

Contact Gary Forrest: 719-594-9304

[addicteduc@aol.com](mailto:addicteduc@aol.com)

#### APA 2nd Multicultural Conference

January 25-26, 2001

Santa Barbara, CA

Contact: 202-336-5500

### FEBRUARY 2001

#### American College of Psychiatrists

February 21-25, 2001

Tucson, AZ

Contact: 510-704-8020

### LATER 2001...

#### ASAM Annual Conference

April 20-22, 2001

Los Angeles, CA

Contact: 301-656-3920;

[email@asam.org](mailto:email@asam.org)

#### American Psychiatric Association

May 5-10, 2001

New Orleans, LA

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

#### American Psychological Association

August 24-28, 2001

San Francisco, CA

#### American Methadone Treatment Assn.

October 7-10, 2001

St. Louis, MO

[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

### War on Words Continued - "Detox" or "MSW"

In the last edition of *A.T. Forum* (Summer 2000) we posed the question of whether persons in addiction treatment should be called "patients" or "clients." Results of the reader survey will appear in our next edition.

Having launched that "war on words" so to speak, we received a query from Duncan McGonagle, RN, MMTP Administrator at St. Barnabas Hospital, Bronx, NY, asking if we'd consider use of the term "tapering" rather than "detoxification" when a patient's methadone dose is being decreased.

#### Therapeutic Reduction

McGonagle makes the point that to *detoxify* or "detox" means to remove a poison or toxin, or to render the substance harmless. Certainly, this wouldn't properly pertain to methadone, which is an opioid agonist medication with proven safety when appropriately used. This is quite unlike alcohol detoxification, for example, which genuinely seeks to eliminate a noxious, harmful substance from the body.

On the other hand, McGonagle observes, patients are *tapered* from a medication, when it is indicated on medical grounds, via gradually lowering the dose over time. This essentially is what is meant, rather than detoxification, when patients have their methadone doses therapeutically reduced.

#### Detox Mindset

The Institute of Medicine (IOM) had similar thoughts in its 1995 report "Federal Regulation of Methadone Treatment." The distinguished committee authoring the report noted that, in the 1950s, methadone only was used to "detoxify" heroin addicts by substituting the medication for heroin, then tapering the dose to zero to minimize withdrawal symptoms.

Originally, this methadone "detox" was limited to 21 days. The rule later was changed and distinctions were made between a short-term (up to 30 days) and long-term (31 to 180 days) process.

The IOM committee noted, however, that those time periods were not supported by scientific or clinical data. Of great concern, research demonstrated that treatment based on such arbitrary

time limits often resulted in patients relapsing to illicit opioid use. Perhaps most disconcerting today is a detox mindset focusing on temporary methadone treatment based on nonclinical, administrative decisions; rather than indefinite methadone maintenance, which has proved the most effective approach for most patients coming into opioid addiction treatment.

#### MSW Rationale

The IOM committee recommended that "medically supervised withdrawal (MSW)" be substituted for the term "detoxification." Their intention was to place decisions regarding longevity of treatment back in the hands of clinicians, based on medical guidelines. However, that goal has yet to be accomplished.

Certainly, progress moves slowly at best. The IOM committee also recommended in 1995 that "methadone maintenance treatment (MMT)" be changed to "maintenance pharmacotherapy (MPT)"; but that's another story.

#### Survey - MSW Limits & Reasons

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

What is the ideal time to allow for medically supervised withdrawal from methadone?  Up to 30 days;  90 days;  180 days;  No limit; Other: \_\_\_\_\_

What is the primary reason for withdrawing a patient from methadone? \_\_\_\_\_

Are you responding as:  a patient;  a healthcare worker? (check only one.)

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.

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A.T.F.



## Part 6: The Shifting Sands of Opioid Addiction & Treatment

*Every form of addiction is bad, no matter whether the narcotic be morphine or idealism. – Carl Jung, 1963*  
*The wise know that foolish legislation is a rope of sand, which perishes in the twisting. – Ralph Waldo Emerson, 1844*

Throughout history and in most societies drugs of some sort have been used to alter consciousness. It has been suggested that, of all the mistakes repeated time and again, the most serious fallacy is trying to free society of drugs via legislation and regulation.[1] Such acts may reflect American society's frustration with past failings of medical science and, consequently, there has been unprecedented control over the medical treatment of opioid addiction in particular for nearly a century. Opioid addiction and treatment perspectives have changed like shifting sands.

### Iatrogenic Addiction

During the 19th century, physicians faced with a host of ineffective nostrums to treat diseases about which little was known turned to palliative substances. Opium was one of the most widely prescribed substances in the medical pharmacopeia in the United States, followed by oral preparations of morphine (synthesized from opium in 1815) and laudanum (a tincture of alcohol and opium).[2]

Such prescriptions frequently resulted in iatrogenic addiction (i.e., induced by medical treatment). Older white women from the middle and upper socioeconomic classes constituted about two-thirds of persons addicted to opioids. Another medically-addicted group consisted of Civil War veterans who had been treated for pain. Opioid addiction in these persons was viewed as an unfortunate medical condition eliciting tolerance and empathy.[3]

Smoking of opium was primarily common among Chinese immigrants, in whom a weak will and immoral behavior were considered the basis of continued addiction. Opium smokers became stigmatized and faced restrictive legislation, which drove up the price of opium but did little to stem its use.[2,4]

### Narcotic Dilemma

Soon, the door was opened to a new generation of addicts as waves of young European immigrants arrived and crowded into tenements. Adoption of the hypodermic needle (invented in the mid-1800s), and the synthesis of heroin from morphine in 1898, exacerbated the situation.[2]

Use of opium, heroin, and cocaine (grouped together as "narcotics"), along with burgeoning drug-related crime, were of concern to social, religious, and political leaders during the early 20th century. The stigma once foisted upon Chinese opium smokers was transferred to new groups of addicts, and chronic addiction to narcotics was attributed to a moral degeneracy that would destroy American social values.[2]

### Distorted Legislation

Passage of the Harrison Narcotics Act in 1914 marked a turning point in policies and attitudes regarding narcotics in America. Superficially, it was an effort to generate revenue and exercise control over the flow of narcotics. It did not impose punishments on drug users or appear to deter medical practitioners from treating addicts with opioids.[4]

However, this legislation became distorted as government

agencies adopted the position that addiction was not a disease and addicts were not legitimate patients requiring narcotics for maintenance purposes. Medical practitioners and clinics dispensing opioid medications for drug withdrawal or maintenance purposes were vilified. Through a series of revised interpretations of the Harrison Act and legal decisions, clinics were shuttered and thousands of physicians were arraigned on narcotics charges, with many serving penitentiary sentences.[3,4]

A pivotal swing in the other direction involved a Supreme Court decision in 1925, which recognized drug addiction as being a disease and drug addicts as proper subjects for medical treatment.[4]

However, Payte has observed [4] that this decision was too little and too late. There was residual fear among physicians of becoming involved in addiction treatment and little motivation to do so. The medical profession rapidly faded from the addiction treatment picture and would remain absent for decades.

After World War II, the Boggs Bill of 1951, the Narcotic Drug Control Act of 1956, and many other laws were efforts to accelerate arrests, convictions, and harsher penalties for anyone involved with narcotics.[4] This occurred at a time when there was a mass migration of African-Americans from southern cities to the north and immigration of Hispanics from outside the U.S. These groups moved into tenements vacated by European immigrants and inherited the preexisting problems of drug trafficking and narcotics addiction.[3]

### Scientific Vacuum

Government actions, reflecting public sentiments, may have been driven at least in part by failures of medical science to deal with addiction.

Herman Joseph has observed [2] that medical knowledge and technology were simply not available during the first half of the 20th century to test hypotheses confirming or negating the premise that narcotic addiction was a physical disease or had a physiologic basis at all. Consequently, psychological theories of addiction filled the vacuum and addicts were stigmatized as having addictive character disorders or psychopathic personalities.

### Opioid Maintenance

By the 1960s, the heroin epidemic was rampant and a new generation of middle-class addicts had emerged. The time was ripe for reconsideration of medical treatments for addiction, particularly pharmacologic maintenance, even though such approaches had been resisted by policymakers and the medical establishment was still cowering from their earlier reproaches.[4]

Breakthroughs in neuroscience research beginning in the 1950s helped change the direction of addiction treatment. Meticulous observations of derangements in physiologic functioning wrought by substances of abuse and the neuropharmacologic properties of the drugs themselves were used to challenge purely psychological theories.

It was in this atmosphere, in 1963, that Vincent Dole, MD, was awarded a research grant to begin his work on what would

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## “Brainstorms: Part 6” Continued from Page 3

become methadone maintenance treatment (MMT). Although this therapy proved successful and effective, it was under the scrutiny and control of federal authorities from the outset.

In the late 1960s, federal officials and treatment providers saw methadone as a quick fix for reducing demand for heroin and its associated problems. MMT programs expanded rapidly, the media called methadone a “Cinderella drug” and a “magic bullet,”[5] and policymakers viewed it as a panacea that could cure addiction.[6] Expectations were unrealistically high and methadone may have been oversold.

Policymakers persisted in stressing abstinence as the treatment goal of MMT rather than rehabilitation, which might require indefinite maintenance just as for any other chronic disease.

In the 1970s, as public funding of MMT programs waned, private entrepreneurs interested more in monetary profit than patient welfare moved in and quality of care deteriorated. MMT took on a patina of disrepute that would take several decades to fade away.

During the 1980s and 90s, political and ideological agendas still ruled MMT. For the most part, the mainstream medical community remained wary of this practice specialty in which federal regulations dictated who could be treated, how much medication could be prescribed, and for how long.

### Rational Outlooks

Eventually, in the late 1990s, the federal Office of National Drug Control Policy (ONDCP) acknowledged that the regulations governing MMT “reflect the political and social climate of [earlier times] rather than rigorous study.” Furthermore, ONDCP conceded that there often were attempts to accomplish via federal regulation matters that should have relied more on medical discretion.[7]

A consensus panel convened by the National Institutes of Health concurred that, “However well intended the [government] regulations were when written... they are no longer helpful,” and, “we know of no other area where the federal government intrudes so deeply and coercively into the practice of medicine.”[8]

Most recently, the House of Representatives approved a bill [9] allowing “qualified” physicians to dispense schedule III, IV, or V narcotic drugs to patients for opioid maintenance treatment or medically supervised withdraw-

al. It represents the first time since passage of the Harrison Narcotics Act that general practitioners would be allowed to treat an opioid-dependent patient with a narcotic, provided the drug has been approved for such use by the FDA. This appears tantamount to congressional approval for the widespread practice of addiction medicine... albeit, still with certain strings attached.

**“Vigorous and effective leadership is needed to inform the public that addiction is a medical disorder that can be effectively treated with significant benefit for the patient and society”**

### Persistent Demagoguery

To this day, however, a segment of public opinion opposes the use of methadone for treating opioid addiction and another segment is ambivalent to its use. Periodically, municipal,[10] state,[11] and federal [12] initiatives have been enacted or proposed to thwart access to methadone treatment by all who might benefit.

For example, in 1998, New York City Mayor Rudolph Giuliani proclaimed that drug addicts should learn to recover without the help of medication and he lobbied to eliminate MMT programs.[10] A year later, U.S. Senator John McCain introduced “The Addiction Free Treatment Act of 1999.” The bill would have limited methadone maintenance to 6 months and immediately terminated treatment for any patient testing positive for an illegal substance. The text of the legislation stated that methadone “results in the transfer of addiction from one narcotic to another” and that the government should adopt a zero-tolerance, nonpharmacologic policy to achieve “independence from drug addiction.”[12]

Neither proposed action became law; however, the underlying attitudes and convictions attest to the persistence of old ideologies. Even the debate over the extent to which addiction is a medical disease versus a moral failure remains unsettled.[13]

### Difficult Challenge

The problem has not been so much in addictive substances themselves as in people. Perceptions of who is addicted have influenced attitudes toward addiction and its treatment.[3] From compassionate support for the iatrogenically-addicted victims of the 19th century there has been a paradigm shift toward the criminalization and stigmatization of addicts and their substances of abuse. Even more insidious, these outlooks, fueled by legislation, negatively affected the practice of addiction medicine.

Times have not changed that much. The NIH consensus panel conceded in 1997 that “Many people believe that addiction is self-induced or a failure of will and also believe that efforts to treat it will inevitably fail. Vigorous and effective leadership is needed to inform the public that addiction is a medical disorder that can be effectively treated with significant benefits for the patient and society.”[8]

The challenge before addiction medicine today has never been more difficult, or of more critical importance.

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### **Regulated Inadequacy**

As other researchers have conceded in the past, Strain and colleagues[2] stated, “It is possible that dosages in excess of 100 mg/d may be required for optimal benefit in some patients.” And then they added, “However, current federal regulations in the United States discourage methadone dosages greater than 100 mg/d.”

Indeed, regulations have long required clinics to apply for and receive a special exemption to provide higher doses. Although most clinicians acknowledge that such requests merely involve extra paperwork and are rarely denied, the requirement also creates a mindset that any dose above 100 mg is probably unnecessary or inappropriate, else why would the government have established that limit?

Furthering that perception, in 1999, the U.S. government issued a proposed rule encompassing best practice guidelines for MMT clinic accreditation.[3] This was expected to allow greater clinical discretion in treatment decisions, including appropriate medication regimens. Yet, the rule states, “The administering physician shall assure that any time a daily dose greater than 100 milligrams is provided to a patient, the justification for such a daily dose is stated in the patient’s record.” Might this be interpreted by many clinicians as implying that any dose greater than 100 mg should be considered an infrequent exception, and possibly raising red flags during the accreditation process if a clinic has too many “exceptional” patients?

Furthermore, one of the options concerning take-home doses in the proposed clinic accreditation rule [3] sets a maximum of roughly 100 mg per day during any 2-week period. Again, the magic 100 number appears without a rationale or justification.

Additionally, state MMT-regulatory authorities have the option to, and frequently do, mandate more rigid requirements than federal regulations.

### **Back to the Future**

A look at history may help delineate origins of the dose ceiling conundrum that has persisted to this day.

When Drs. Vincent Dole, Marie Nyswander, and Mary Jeanne Kreek were developing the protocol in the early 1960s for what would become MMT, their very first 2 patients required 150 to 180 mg of

**“There is really no empirical, theoretical, or commonsense justification for the 100 mg/d dose limit.”**

oral methadone daily to avert abstinence syndrome and achieve normal functionality. The treatment modality evolved rapidly through a growing series of successes and, by 1968, 1,139 patients were in the research program.[4] In the earliest publication of their work, Dole and Nyswander recommended daily doses averaging between 80 and 120 mg.[5] That range often has been suggested as optimum for most patients, with the caveat that certain patients may need higher doses.[6,7]

Interestingly, the average of those 2 average recommended doses is 100 mg/d. However, those were, indeed, merely average doses; so possibly more than half of patients would require above 100 mg and at the upper end of the range many patients might need much more than 120 mg/d. This is often overlooked.

Dole has noted that by the early 1970s, instead of further expansion, the objectives of MMT were reversed by federal agencies and the authority of physicians was limited; abstinence rather than rehabilitation became the goal of treatment and doses were lowered to levels that were frequently inadequate. “The punitive attitudes of moralists hardened into regulatory law, subjecting clinics to an unprecedented degree of control over every detail of their operation,” he recently wrote.[8]

Cooper [9] has observed that, by the early 1980s, more than 40% of MMT patients were administered allegedly stabilized doses of less than 40 mg/d. In 1983, the National Institute on Drug Abuse (NIDA) convened a group of clinicians and researchers to review the wealth of data compiled over the prior 15 years and arrive at recommendations for appropriate methadone dose. Their consensus was that the most effective dose would be between 50 and 100 mg/d, in contrast to the earlier-recommended higher doses of Dole and his research team.

Dosing regimens did not improve over time. Even with the 100 mg/d ceiling established, a survey in 1990 by NIDA found that almost 25% of MMT patients were still receiving less than 40 mg of

methadone daily and half the treatment population was receiving less than 55 mg/d. A nationwide survey in the late 1980s of 172 randomly-selected MMT programs by D’Aunno and Vaughn [10] found that the average daily methadone dose was less than 60 mg in almost all (97%) of programs surveyed. A more recent update by D’Aunno and his team [11] found that in 1995 more than half (53%) of MMT patients were still receiving average doses of less than 60 mg/d. Two thirds of the programs had absolute maximum dose limits of 80 to 100 mg/d, while 22% of patients were receiving progressively smaller doses.

### **Why a Dose Ceiling?**

According to several sources, selection of 100 mg/d as a dose ceiling, or any threshold limit for that matter, was arbitrary and inappropriate.

Robert Newman, MD, a leader in the MMT field and originator of a New York City MMT program that had 12,000 active patients in the early 1970s, told *AT Forum* (e-mail communication, July 2000): “The determination [of 100 mg/d] was purely arbitrary and without any substantive basis. ...a bunch of ‘experts’ (sorry to say it frequently included me) would meet in [Washington] DC and someone would say something like, ‘nobody should get more than 40 mg/d,’ and someone else would insist that dose was ridiculously low and it should be much higher.”

“No one, as I recall, said it was absurd to stipulate ANY dosage limit at all. Finally, the number 100 was a compromise, with exceptions above that permitted, but only for consumption in the clinic. Exceptions above 120 required prior approval on an individual basis by some bureaucrat in Washington. There is really no empirical, theoretical, or commonsense justification for the 100 mg/d dose limit or refusing to give take-home methadone greater than a certain amount. The reason 100 mg was agreed to was that the threat of 40 mg was vastly worse!”

Similarly, Dole recalls (e-mail communication, July 2000): “The 100 mg ceiling was not based on any research data. Like many other arbitrary restrictions, it was imposed in the 1970s by bureaucrats who assumed that this dose was more than enough for addicts (who, they said, would be tempted to sell any excess medication). It has not been seriously challenged in modern times, since, unfortunately, many clinicians still see detoxification as the goal of treatment and wrongly

**"There can be no agreement on 'adequacy' of dose if the reason for prescribing methadone is in dispute."**

assume that prescription of inadequate doses increases the probability of ultimately achieving drug-free status."

### The Enemy is Us

The question suggested by Newman is, why is there a dose ceiling at all?

As the comic strip character Pogo once said in despair, "We have met the enemy and they is us." Or, as Cooper [9] observed, "...certain societal issues, such as reluctance to view some medical and psychiatric disorders as legitimate illnesses, misunderstanding of the difference between drug dependence and addiction, and disproportionate fears of diversion, are unique to the prescription of psychoactive substances. These problems are most evident when narcotics are used to treat narcotic addicts."

Along the same lines, Dole told AT Forum, "The concern of the low-dose proponents stems from a philosophy that equates addiction with moral weakness, and therefore a conviction that a narcotic drug [methadone] cannot be considered legitimate medicine for what, to them, is misuse of essentially the same kind of drug. .... From this perspective, methadone maintenance is merely appeasement. They say that, if prescribed for treatment of heroin addiction, methadone should be given at the lowest acceptable dose and for the shortest time needed for psychotherapists to deal with the 'fundamental problems.'"

"Or, as a distasteful compromise in dealing with refractory patients," Dole continued, "they abandon any effort to cure the patient (i.e., achieve permanent abstinence) and accept maintenance as a harm-reduction measure. This unfortunately is still the opinion of many physicians, perhaps the majority, and even of some physicians who are employed by methadone clinics. In other words, there can be no agreement on 'adequacy' of dose if the reason for prescribing methadone is in dispute."

Dole expressed his regret that the

dosage of methadone has become a political issue and that the medical profession has tolerated the unique restrictions that have been placed on the legitimate prescription of this well-tested medication. "Will the next generation of physicians be wiser?" he wondered.

In his correspondence, Newman suggested a simple principle to guide MMT best practices: "Do what you would do with the treatment of any other chronic disease, and with any other medication. This applies to the level of dose, its duration, and patient compliance with the treatment regimen. I've never come across a single issue in methadone treatment that can't be resolved sensibly by applying this 'guideline.'"

On a note of optimism, Dole observed that many physicians – especially in Europe – have come to view addiction as a medical disease and are studying the beneficial effects of much higher methadone doses. In that regard, the next article in this MMT & Beyond series will examine the handful of research investigations that have penetrated and ventured beyond the 100 mg/d glass ceiling.

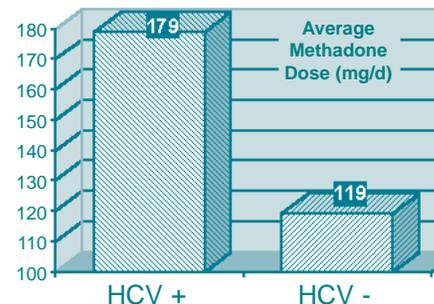
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[Disclosure: This article was sponsored by an educational grant from Mallinckrodt Inc, a manufacturer of methadone.]

335 tested positive (HCV+), 223 were HCV negative.

HCV+ patients were more likely than those HCV negative to be Caucasian (79.7% vs 61%) and much older (mean 40.8 years vs 29.4 years). A significantly greater proportion of HCV+ patients (87%) had a history of IV drug use (as opposed to only insufflation of opioids) compared with HCV negative patients (35%). There were no significant differences in gender between groups, although there were more male patients in both groups (63% HCV+ vs 59% HCV-).

Besides being older, patients with HCV had longer addiction histories than the HCV negative patients. The majority of HCV+ patients at CAP had been stable and drug-free in methadone treatment for years. Testing for HCV had not been available when most of these patients were admitted and their viral infections went undetected on the basis of obvious signs and symptoms.



### "Eating Methadone"

Of particular interest, the patients that turned out to be HCV+ were less likely to be abusing illicit drugs and were receiving significantly higher doses of methadone than those without the virus. Average daily methadone dose was 179 mg (range 7-1300 mg) in those with HCV compared with 119 mg (range 10-600 mg) in patients who were HCV negative ( $P < 0.001$ ). See figure. Overall, patients with HCV appeared to have a 50% greater requirement for methadone. This higher dose level, however, also may help account for their longer, and illicit-drug-free, tenure in treatment.

Maxwell described a case example that first alerted them to the clinical trend of a higher dose requirement associated with HCV. The patient, a 63-year-old male, had been stable and drug-free in MMT for 17 years when he complained that his 100 mg daily dose was no longer holding him. The man's primary care physician simply

noted in the chart, "... [patient's] liver is eating the methadone."

During a several-year period, this patient's dose was gradually increased to 900 mg/d and was finally stabilized at 1300 mg divided into 5 to 6 doses daily. "He has recently concluded a 12-month course of interferon-ribavirin," Maxwell commented, "his liver function tests are normal and the viral load is undetectable."

### **Paradoxical Effects**

Shinderman and Maxwell noted that most hepatic diseases impair metabolic function, usually by inhibition of cytochrome P450 enzymes, particularly CYP2D6. This effect would be routinely managed in part by decreasing doses of medications, such as methadone, that are intensely metabolized by this enzyme system.

Indeed, research to date suggests that disease states with hepatic involvement, such as HCV, would disrupt hepatic metabolic function, downregulate CYP450 enzymes, and result in slower rates of drug clearance.[4] Viral infections also stimulate cytokine production, which has been associated with suppressed CYP enzyme activity.[5] There also are indications from research that CYP450 activity normally is less in men than women and decreases further with age.[6,7] All of these effects would have been expected to produce higher-than-anticipated methadone levels in the CAP HCV+ patients, rather than lower, and require dose reductions rather than increases.

Paradoxically, however, the clinical data from CAP appear to suggest that HCV infection may actually induce components of the CYP450 system, resulting in increasingly rapid metabolism of methadone leading to higher methadone dose requirements. "This clinical phenomenon is so prominent in our patient population," Maxwell stated, "that when a stable patient reports the maintenance dose is no longer holding we routinely recommend testing for HCV antibodies."

Shinderman commented that they expected patients developing advanced cirrhosis due to HCV would have decreased methadone requirements, but they have not yet observed that phenomenon. "One HCV+ patient's dose requirement was lowered by half after liver transplantation, but it gradually increased again over 18 months."

## **Paradoxically, the clinical data suggest that HCV infection may induce the CYP450 enzyme system, resulting in more rapid metabolism of methadone.**

Shinderman told AT Forum (e-mail correspondence, June 2000) that, after the May conference, he received reports from colleagues in Europe that they observed similar dose increase requirements of up to 50% in MMT patients with HCV.

A confirming report from Eastern Europe [8] retrospectively examined dosing records of 105 patients who were in MMT more than 1 year. Patients found to be HCV+ had a significantly higher average methadone dose requirement of 136 mg/d ( $\pm 60$  mg;  $n = 46$ ) compared with 105 mg/d ( $\pm 56$  mg;  $n = 59$ ;  $P < 0.01$ ) for patients who were HCV negative. In this study, patients were younger than those in the CAP population (average age 26 years), were predominantly male (79%), and had less time in treatment (roughly 3 years on average). The authors concurred with Shinderman and Maxwell that induction of CYP450 enzymes by HCV possibly might account for higher dose requirements.

### **Testing, Adequate Dose Critical**

Maxwell says their research in this area has continued and they have accumulated data on more than 1000 patients. They expect to prepare a paper for journal publication.

Certainly, further research is needed to solve the mystery of why HCV might increase methadone dose requirement. There do not appear to be any reports as yet of research specifically measuring the effects of HCV on methadone serum levels. In this regard, it would be important to determine whether viral infection specifically alters metabolism of the active R-enantiomer of methadone. It is possible that overall serum methadone levels might increase as expected due to impaired hepatic function; however, the active R-methadone component might be

more rapidly metabolized due to HCV effects, causing the previous daily dose to become inadequate for the patient.

There normally can be a high degree of interindividual variability in CYP450 activity, up to 30-fold or more, and this may become more pronounced in the presence of viral infections.[7] It is also possible that the hepatitis C virus might in some way influence higher metabolic activity of CYP450 isoenzymes and P-glycoprotein in the gut, thereby accelerating methadone clearance before it even reaches the impaired liver.[9]

The above are but several hypothetical possibilities. Meanwhile, the implications of this preliminary research by the CAP team and confirmed by others are that it is important to test all patients coming into MMT for HCV, and that those testing positive might be expected to have higher methadone dose requirements. Furthermore, when previously stable patients appear to unexpectedly require methadone dose increases, it may be advisable to immediately test them for HCV.

AT Forum would welcome, and will publish, further information or commentary from clinicians and researchers in the field on this paradoxical phenomenon. See the contact information at the end of "From the Editor" on page 2.

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## Where To Get Info...

### Video Paints Positive MMT Portrait

*The Joy of Being Normal* is a short (7-1/3 minutes) video that skillfully illustrates the benefits of methadone as a medication allowing people to live normal and productive lives. Several vignettes reveal examples of "secret successes" that have so often been hidden from public view – MMT patients flourishing in everyday life, with responsible jobs and loving families.

The film is excellently produced, culturally diverse, attention-grabbing, and suitable for any audience. It is certain to generate further interest and set a very positive tone for discussions with community groups, healthcare professionals, families and prospective patients, and others. Indeed, this innovative production can be a powerful tool to help spark the sort of open dialogue that may help abolish the enduring, unjustified stigma surrounding this vital treatment modality.

Copies of *The Joy of Being Normal* can be ordered from Danya International: 8737 Colesville Rd., Suite 1200; Silver Spring, Maryland 20910. Phone: 301-565-2142. Web site: <http://www.danya.com/methadone>. Cost is \$14.95 plus \$3.00 shipping & handling.

### Guide to Treating Drug Emergencies

In *Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment; 5th ed.*, Marc A. Schuckit, MD provides an overview of drug classifications and mechanisms, and covers the pharmacology and mental/physical effects of alcohol, depressants, stimulants, opioids, hallucinogens, cannabis, and more. Most critical, there is an emphasis throughout the book on how to deal with emergency medical problems related to drug abuse, addiction, and overdose.

This new edition of the book, which dates back to 1979, includes a 70% updating of reference material with a focus on recent developments in pharmacotherapy, plus an all-new chapter on prevention. Schuckit recommends skimming all of the chapters covering the many drug classes. From there, the book can serve as a handbook, kept nearby for easily-accessed advice on dealing with drug-related crises or confirming suspected drug-induced symptomatology appearing in clinical settings.

*Drug and Alcohol Abuse: A Clinical Guide to Diagnosis and Treatment; 5th ed.* is from Kluwer Academic/Plenum Publishers; New York (ISBN 0306462303,

January 2000, 380 pp). Available online from [www.amazon.com](http://www.amazon.com) (\$49.95 + shipping) and at other booksellers.

### Recovery Options Examined

*Recovery Options: The Complete Guide* by Joseph Volpicelli, MD, PhD and Maia Szalavitz provides an in-depth look at the many ways to view alcoholism and other drug addictions, and an overview of addiction treatment research, modalities, and pharmacotherapies.

The outlook in this book is extremely well-balanced, without lobbying for any particular treatment approach as a one-size-fits-all solution. In fact, the "Penn Paradigm," which Volpicelli advocates, stresses that "it is what the patient considers important, not what the treatment program is pushing, that matters." The underlying posture of the entire book is, "Patients given a menu of treatment options do significantly better than those who are simply told what to do."

Patients, or prospective patients, also will greatly benefit from this book, as denoted by its subtitle: *How You and Your Loved Ones Can Understand and Treat Alcohol and Other Drug Problems*. Case studies and anecdotes, used liberally throughout, vividly illustrate important principles in the book and make for very interesting reading.

*Recovery Options: The Complete Guide* from Wiley books is available at local bookstores (ISBN 0-471-34575-X, June 2000, paperback, 300 pp, \$15.95), or from [www.amazon.com](http://www.amazon.com) (\$12.76 + shipping) and other online booksellers.

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ADDICTION TREATMENT

## Forum

is published quarterly by:

Lanmark Group, Inc.  
1750 East Golf Road, Suite 320  
Schaumburg, IL 60173

Editor: Stewart B. Leavitt, Ph.D.

Publisher: Sue Emerson

Art Director: Julia Lee

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Addiction Treatment Forum is made possible by an educational grant from Mallinckrodt Inc., a manufacturer of methadone and naltrexone. All facts and opinions are those of the sources cited. The publishers are not responsible for reporting errors, omissions or comments of those interviewed.

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