

# Forum

THE QUARTERLY NEWSLETTER FOR CLINICAL HEALTH CARE PROFESSIONALS ON ADDICTION TREATMENT

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**Sound medical practices can help overcome concerns about methadone affecting heart health or its use during pregnancy.**

## Clinical Concepts

### FDA Advisory Raises Concerns About Methadone

Last November, 2006, the U.S. Food & Drug Administration (FDA) issued a Public Health Advisory (PI) announcing that it had revised the package insert (PI) for oral methadone because of concerns about a sharp increase in overdose deaths attributed to prescribed methadone. Although the FDA concerns were focused on methadone used as a pain reliever, product labeling changes featuring new "black box" warnings will apply to all methadone medications, including formulations used in methadone maintenance treatment (MMT).



An alleged effect of particular concern noted by the FDA is dangerous changes in heartbeat in patients prescribed methadone. Specifically they warned of cases of cardiac electrical conduction disturbances, including QT interval prolongation and a serious arrhythmia, torsade de pointes (TdP) [see *Box 1* for an explanation of these conditions]. Concerned MMT providers were wondering what to do to minimize cardiac risks.

Additionally, the patient information portion of the new PI suggests that methadone may not be safe during pregnancy, and that it should not be taken if the woman chooses to breastfeed after delivery. Naturally, this raised fears among female MMT patients.

This article examines those two issues – cardiac concerns and use during pregnancy – that are of critical importance for MMT providers and patients. Internet links to the respective FDA documents are provided in a box at the very end of this article.

### Is Methadone Harmful to Heart Health?

A particularly alarming aspect of the FDA Advisory was the strong warning that oral methadone may influence "life-threatening changes in heart beat." However, the possibly harmful cardiac effects of methadone in a relatively small number of patients, and under certain circumstances, were already known and several *AT Forum* special reports have addressed this very complex subject [see, Leavitt 2001, 2002; Leavitt and Krantz 2003].

Still, the FDA Advisory and "black box" warning raised the question of whether MMT providers would need to conduct repeated electrocardiograms (ECGs) on all patients to monitor their heart rhythm. Or, what other measures should they institute?

capacity to inhibit cardiac electrical conduction and prolong the QTc interval [see references in Leavitt 2001]. However, such laboratory research – essentially, case examples – does not necessarily translate to clinical significance in human patients.

There have been various case reports of QTc interval prolongation and serious arrhythmia, TdP, in patients prescribed methadone [see for example, Krantz et al. 2002]. These cases often, but not always, appear to be more commonly associated with higher-dose treatment (> 200 mg/day) [Pearson and Woosley 2005].

Some cases involve patients being treated for pain with large, multiple daily doses of methadone, although many reports have been in patients receiving doses commonly used once daily for MMT. In most of those involving typical

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### Case Reports Inadequate

Early laboratory studies, both in animals and isolated tissue samples, demonstrated that excessive methadone has a

*Continued on page 4*

## Events to Note

For additional postings, including international meetings, see: [www.atforum.com](http://www.atforum.com)

### April 2007

#### Ruth Fox Course for Physicians

April 26, 2007  
Miami, Florida  
Contact: 301-656-3920 or [www.ASAM.org](http://www.ASAM.org)

#### ASAM 38th Annual Meeting & Medical-Scientific Conference

April 27-29, 2007  
Miami, Florida  
Contact: 301-656-3920 or [www.ASAM.org](http://www.ASAM.org)

#### 12th National Conference: Management of Drug User in Primary Care

April 19-20, 2007  
Birmingham, UK  
Contact: [www.healthcare-events.co.uk](http://www.healthcare-events.co.uk)

### May 2007

#### The UK/European Symposium on Addictive Disorders (UKESAD)

May 17-19, 2007  
Central London, UK  
Contact: [www.ukesad.org](http://www.ukesad.org)

#### NAATP 2007 Annual Addiction Treatment Leadership Conference

May 19-22, 2007  
San Diego, California  
Contact: 717-392-8480 or [www.naatp.org/conferences/annualconference.php](http://www.naatp.org/conferences/annualconference.php)

#### American Psychiatric Association (APA) 160th Annual Meeting

May 19-24, 2007  
San Diego, California  
Contact: 703-907-7300 or [www.psych.org/](http://www.psych.org/)

### June 2007

#### National Association of State Alcohol/Drug Abuse Directors (NASADAD) Annual Meeting

June 7-10, 2007  
Burlington, Vermont  
Contact: 202-293-0090 or [www.nasadad.org](http://www.nasadad.org)

#### The College of Problems on Drug Dependence (CPDD) Annual Conference

June 16-21, 2007  
Quebec City, Quebec  
Contact: 215-707-3242 or [www.cpdd.vcu.edu/Pages/Meetings/FutureMeet.html](http://www.cpdd.vcu.edu/Pages/Meetings/FutureMeet.html)

### Later 2007

#### AATOD (American Association for the Treatment of Opioid Dependence) Conference

October 20-24, 2007  
San Diego, California  
Contact: 212-566-5555 or [www.aatod.org](http://www.aatod.org)

[To post your event announcement in AT Forum and/or our website, fax the information to: 847-392-3937 or submit it via e-mail from [www.atforum.com](http://www.atforum.com)]

## Straight Talk... from the Editor

### Put Methadone Risks in Proper Perspective

#### All Therapies Have Risks

Through the years, methadone maintenance treatment (MMT) in treating opioid addiction often has been compared with insulin in treating diabetes. For one thing, both opioid addiction and diabetes are chronic and potentially deadly disorders that will progressively worsen without treatment. For each disorder, medication is often necessary for a lifetime to keep it under control.

Both therapies, insulin and methadone, have risks of complications, just as do all other pharmacologic therapies. This does not mean that pharmacotherapy should be avoided or discontinued; rather, it is a matter of weighing risks versus benefits for individual patients.

In an interesting monograph addressing risks of opioid therapy, Nathan Katz, MD, compares insulin with opioids for pain. This has been adapted in the *Table below* for methadone prescribed during MMT.

#### Benefits Outweigh Risks

The message here is that the prescribing of methadone is no different than any other medication for which there are benefits as well as risks. Unfortunately, there seems to have been an over-emphasis on methadone risks lately.

As might be expected, occurrences of methadone-related complications, including deaths, have risen along with its increased use in more patients both as a pain reliever and for opioid-addiction treatment. Furthermore, many persons treated with methadone might be considered high risk, and complications are more likely to occur in such individuals. So, it is important to identify those patients at risk and manage their treatment more carefully, as is suggested in this edition of *AT Forum* regarding heart health.

The benefits side of MMT in reducing risks has been emphasized repeatedly through the years in a large body of valid research. Recently, for example, in an exhaustive systematic review of the literature an international team of researchers confirmed previous findings: 1) MMT significantly reduces drug injecting, 2) it reduces sharing of injecting equipment, 3) it reduces high risk sexual behaviors, and consequently 4) this translates into fewer cases of HIV infection [see, Gowing et al. *J Gen Intern Med*, 2006;21(2):193-195]. Furthermore, these investigators concluded that *there is insufficient evidence to determine whether any other forms of pharmacotherapy for opioid addiction provide such significant benefits.*

*Continued on page 3*

#### Insulin Therapy Compared with MMT

Insulin for Diabetes	MMT for Addiction
Insulin should be prescribed when simpler therapies have failed.	MMT should be prescribed when simpler therapies have failed.
Insulin is an effective treatment for appropriate patients.	MMT is an effective treatment for appropriate patients.
Insulin can have complications, such as overdose resulting in hypoglycemia and diabetic coma.	Methadone can have complications, such as overdose, constipation, and others.
Some patients are at greater risk for insulin-related complications than others. Those at higher risk should be identified and managed more carefully.	Some patients are at greater risk for methadone-related complications than others. Those at higher risk should be identified and managed more carefully.
Some patients are so complicated that they should be co-managed with specialty consultants (eg, endocrinologists specializing in diabetes), or managed in a specialty setting.	Some patients are so complicated that they should be co-managed with specialty consultants (eg, mental health or psychiatric specialists), or managed in a specialty setting.
Patients should be screened regularly for complications of insulin therapy, and if a complication is diagnosed, appropriate management instituted.	Patients should be screened regularly for complications of methadone therapy, and if a complication is diagnosed, appropriate management instituted.

Modified from: Katz NP. Patient Level Opioid Risk Management. A supplement to the PainEDU.org Manual. Available at: [http://www.painedu.com/manual/manual\\_supplement.pdf](http://www.painedu.com/manual/manual_supplement.pdf).

## Patients Have Responsibility

Probably, the weakest link in the chain of any medication's effectiveness and safety is patients themselves. Those who do not follow directions, or misuse their medication in some way greatly increase the risks of adverse complications.

As long-term MMT patient Sandy Linton observes in this issue of *AT Forum*, patients must take greater responsibility for their recovery. This could apply to many medical conditions and therapy settings, not just MMT clinics.

Unfortunately, therapeutic noncompliance and accidental or intentional misuse occurs with insulin, methadone, and just about every other medication – often with dire consequences. Of course, an important element is that opioids, such as methadone, are sometimes diverted for illicit use and can pose a threat to innocent individuals and to society.

The medical risks of methadone therapy can and should be greatly minimized by well-trained MMT staff. However, patients in MMT also share a burden of responsibility for risk reduction by following directions, adhering to clinic rules, and safeguarding any take home medication that is provided.

*Stewart B. Leavitt, MA, PhD, Editor*  
ATFeditor@comcast.net

*Addiction Treatment Forum*  
P.O. Box 685; Mundelein, IL 60060  
Phone/Fax: 847-392-3937  
Internet: <http://www.atforum.com>  
E-mail: [Feedback@atforum.com](mailto:Feedback@atforum.com)

### NEW SURVEY: Guarding Heart Health

As a followup to the article on heart health in this issue, *please respond to the following survey questions:*

1. Does your MMT clinic screen all patients for heart health?  Yes;  No;  Don't Know.
2. If an electrocardiogram (ECG) is performed, where is it done?  MMT Clinic;  Outside Facility;  Other (specify) \_\_\_\_\_.
3. Are patients educated on signs and symptoms of heart problems?  Yes;  No;  Don't Know.
4. Are you responding as  an MMT patient, or  MMT clinic staff member or other?

*There are several ways to respond to AT Forum surveys:* **A.** provide your answers on the postage-free feedback card in this issue; **B.** write, fax, or e-mail [info above]; or, **C.** visit our website to respond online. As always, your written comments are important.

## Sidebar

### Are You Registered for E-mail Notifications?

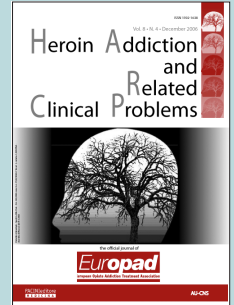
Did you know that you can receive notifications via e-mail of when the *AT Forum* website is updated. Be among the first to know when newly published ATF Newsletters and News Updates are available. Hear about important addiction-related events and new resources of interest. Click on the "Guestbook" button at the [ATForum.com](http://www.atforum.com) home page, or go directly to <http://www.atforum.com/guestbook.shtml> to register.

**Guestbook**  
Receive e-mail notifications when [atforum.com](http://atforum.com) is updated, or to send comments...

### EUROPAD Journal Available Free at ATForum.com

*Heroin Addiction and Related Clinical Problems*, the official journal of EUROPAD (European Opiate Addiction Treatment Association), is a peer-reviewed publication for professionals wanting to stay informed of research and opinion on opioid misuse treatment in Europe and around the world. A particular emphasis is on medication-assisted treatments for opioid addiction, including many articles of importance regarding methadone maintenance treatment (MMT).

Courtesy of EUROPAD, full copies of the journal are now available at the [ATForum.com](http://www.atforum.com) website for free download as PDF documents. Go to: <http://www.atforum.com/europad.html>.



## Reader Feedback

### An Alternate View of Methadone Dose Induction

Your Fall 2006 edition of *AT Forum* (Vol. 15, #4) was excellent, as usual. The feature article on "Safely Starting Methadone in MMT" had much that is consistent with "best practices." However, I have some concerns regarding the table on page 5, "Methadone Induction Protocol."



Clinics throughout the methadone maintenance treatment (MMT) community have through the years established protocols that may differ from the guidance provided in that table. In my opinion, the table should not be followed blindly or accepted as a standard protocol.

I have treated methadone patients since 1967, and I would be surprised if the practices followed in our clinic are an exception. Here are some examples of our well-tested protocol that has been trouble-free for 4 decades:

#### 1) Initiating Dosing...

The table in your article offers good general advice; however, we have an alternative approach that we find useful. If a patient is actively in opioid withdrawal we will give 20 mg of methadone immediately and then an additional 10 mg if, after 2 hours, he/she is still "dope sick."

We have developed a safe procedure for this initial dose escalation. Ironically, patients often say, "My tolerance is high so I'll need more methadone at startup, *but* I want to stay low because I'm *outa here soon!*"

I respond, "We empower you to take over important aspects of your treatment. It is your responsibility to tell us when your maintenance dose is at a sufficient level." When they ask how they will know when the dose is adequate, I say, "When you wake up one day and say to yourself, 'I haven't even thought about doing drugs lately.'"

#### 2) Followup Dose Increases...

Following the above 'startup dosing decision,' we proceed to increase the dose 10 mg per day. We have NEVER found this to be problematic. Making a patient wait 3 or more days for a dose increase, as noted in the article table, is seriously counterproductive.

When patients enter MMT they are interested in relief of their suffering first and foremost. If they must wait 3 days for the next methadone dose elevation, many of the more fragile patients who are impatient to feel better will simply head back to the streets. I have never found that escalating the dose 10 mg per day is dangerous.

Methadone's pharmacology – how it is metabolized and excreted, and how it affects the brain and body – is well known. Physiologic tolerance to methadone develops quickly and a day-to-day dose escalation accommodates the early

requirements of treatment, chief of which is that the patient "stick it out."

Along with that, however, I would be reluctant to give a 15 mg per day dose increase; especially during the early days of methadone induction. The human body is sensitive to percentage not milligram changes; with a 20 mg initial dose, a 15 mg increase is approaching a doubling of the dose, whereas a 10 mg increase is only a 50% change.

### 3) Monitoring, Education Important...

When it comes to monitoring patient response to the methadone dose, I have faith in our experienced nursing staff. They observe patients and respond to signs and symptoms of potential methadone overdose in a reliable way. If they feel a patient needs a methadone dose adjustment because of excessive medication, or alcohol, or other sedating drugs, they tell me immediately.

Also, as noted in the article table, patient education is essential. However, it must be recognized that morning dosing with assessment several hours afterward is not always practical. For example, we have 60 patients attending a "workers' clinic" in the evening that is open until 7:30 PM.

People must be reminded of those other items in the "Patient Education" box in the table, and each one is an important counseling issue. We do urinalyses to detect "forbidden" substances; however, I have convinced our staff that use of the expression 'dirty urine' is scientifically inaccurate and not particularly useful.

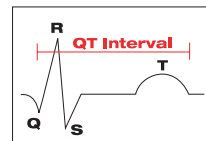
Robert Maslansky, MD  
Medical Director, Addiction Rehabilitation Program; Clinical Professor, Department of Medicine; NYU School of Medicine, Bellevue Medical Center; New York, NY

*[Editor's Note: The approach to methadone dosing described above is no doubt based on Dr. Maslansky's many years of experience and the diligence of his well-trained staff. As noted in our article in the Fall 2006 edition of AT Forum, other practitioners also have developed alternate protocols using variable and relatively high methadone doses during the startup period.]*

*However, caution would be advised when dose increases are implemented more frequently than every 3 to 5 days. Until a steady state methadone level is reached, which can take at least several days after each dose increase, methadone will accumulate in the blood. Depending on the individual patient's opioid tolerance and metabolism of methadone, an excessive build-up of methadone can produce signs/symptoms of over-medication, potentially leading to overdose, so this must be carefully monitored.]*

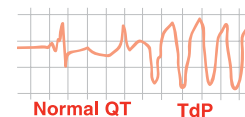
## Box 1: What is the QT and Why Does It Matter?

When the heart contracts it emits an electrical signal, which can be recorded on an electrocardiogram (ECG). On a paper readout strip, the ECG produces a characteristic waveform with the different parts designated by letters – such as Q, R, S, and T (see *Diagram*). The QT interval represents the time for electrical activation and relaxation of the ventricles, which is measured in fractions of a second, or milliseconds (msec). It is an indicator of either healthy or abnormal heart rhythm. The QT interval measurement is affected by heart rate, so it is mathematically adjusted for this to give a QT-corrected number, or QTc.



What is a normal QTc? There is a range of 'normal' QTc values, according to a recent review of the literature [Peles et al. 2006]. Women generally have longer QTc intervals than men, and the upper limit of normal QTc values ranges from 430 msec to 500 msec. Usually, a QTc greater than 500 msec raises clinical concerns about possible heart rhythm disturbance; although, in otherwise healthy persons known to be taking medications that increase QTc (including methadone), some cardiologists consider higher QTc intervals as acceptable. Personal factors affecting a patient's cardiac health also need to be taken into account.

When the QTc becomes significantly prolonged, the person may be at risk of developing a particularly rapid, abnormal heart rhythm, called torsade de pointes, or TdP. This literally means 'twisting of the points' and is represented on the ECG by undulating peaks twisting about a central axis (see *Diagram*). This may signal convulsive twitching of heart muscle, or ventricular fibrillation, which can cause death if emergency care is not provided [see, Leavitt and Krantz 2003].



### Heart Health... continued from page 1

MMT doses, additional medications, illicit drug use, and/or clinical conditions such as low potassium levels were noted as contributing factors.

Although the cases suggest that methadone possesses the potential for adverse cardiac conduction effects in *some* patients, such reports are weak evidence from a scientific perspective. For one thing, cardiac arrhythmias are not uncommon in the overall population, accounting for 10% of all natural deaths, and there is a hereditary form of QT-interval prolongation – the Long QT Syndrome – that may be more common than previously thought [Leavitt 2001]. Therefore, the background prevalence of cardiac problems, unrelated to methadone, must be taken into account.

An examination of all methadone adverse-event cases reported to the FDA spanning more than 3 decades found only a 0.29% incidence of QT prolongation and 0.79% incidence of TdP [Pearson and Woosley 2005]. It is unknown whether this represents an expected frequency of such problems in *any* large population of patients; however, the investigators did note that, besides methadone, 75% of cases also involved complicating factors such as electrolyte deficiencies, prior heart disease, and/or comedications known to cause arrhythmia, among others. They conceded that it was impossible to be "absolutely certain if methadone caused or contributed to the prolonged QT and TdP."

Therefore, while case reports can be of use in signaling a *possible* problem, in themselves they are weak evidence of methadone being a primary or even sig-

nificant contributor to cardiac disturbances. The limitations of case reports as valid evidence, no matter how many in number, are often overlooked.

### Clinical Studies Ambiguous

Through the years, various more scientific clinical investigations in MMT patients have examined the potential influence of methadone dose or serum methadone level (SML) on QT prolongation. Some studies have shown an effect of methadone dose or SML in modestly prolonging the QTc interval, while many others have not shown *any* such influence [references in Schmittner and Krantz 2006; Peles et al. 2007]. It also should be noted that none of the clinical researchers to date have reported incidences of TdP-related deaths in their methadone-treated subjects.

In the typical research setting, patients' methadone doses and/or SMLs are compared with their QTc intervals on ECGs taken at various points in time. The investigators are most interested in determining if there is a direct relationship, or correlation, between QTc and the methadone dose or SML [see *Box 2* for an explanation of statistical correlation].

Quite often in these studies, there are confounding factors that are difficult to control and serve to muddle the results. This is, some of the subjects also may be taking medications or illicit drugs, have physical conditions or lifestyle habits (eg, smoking), or other factors that might influence heart health.

To date, the variously reported correlations of methadone dose or SML and QTc

## Box 2: What is Statistical Correlation and Why is it Misunderstood?

To measure the relationship between two variables – such as methadone dose and QTc – researchers commonly calculate a statistic called the *correlation coefficient*, usually designated as *r*. When one variable increases along with increases in the other one, this indicates that there is a positive relationship.

The *r* can vary from 0 to +1.0, with 0 indicating no correlation and +1 denoting a perfectly positive 100% correlation. In between, there can be a range, with less than .20 being a slight correlation, .20-.40 being a low correlation, .40-.70 being moderate, and more than .70 being high to very high [Glantz 1997; Williams 1968].

Most of the studies demonstrating methadone affecting the QTc interval have found positive correlation coefficients to suggest that as methadone increases so does the QTc; *however*, these *r* values generally fall within the lower ranges indicating weak or, at best, modest associations. Despite the rather low *r*'s, some have been reported as being 'statistically significant' (with appropriately low probability or *P* values).

The confusion here is that a statistically significant *r* may still not be *clinically significant* in predicting harm to patients. The *P* value merely expresses how likely the association is to have come about by chance. Hence, a *P* < .01, for example, indicates there is less than a 1% probability that the result was merely a fluke [Greenhalgh 1997].

In the case of, say, a reportedly significant *r* of .30 for methadone dose and QTc, *P* < 0.01, the researchers are in essence saying, "We found a low relationship, which didn't come about purely by chance." This often is misunderstood by readers who interpret the statistically significant result as indicating a stronger and more clinically important effect of methadone than actually exists.

An important measure, though rarely reported in the literature, is the *coefficient of determination*. This is simply the square of the correlation coefficient, or *r*<sup>2</sup>, which is quite easy to calculate [Glantz 1997; Williams 1968]. Of interest here, this would represent the proportion of the observed QTc prolongation that is influenced by methadone.

In the example above, an *r* = .30 translates to an *r*<sup>2</sup> of .09 or 9%. In other words, only 9% of the QTc prolongation is attributable to methadone dose. In this light it can be seen that, while methadone may have *some* influence, there are other even more important factors at work that should be considered and also taken into account to help insure patient safety. Merely attributing the cardiac disturbance to methadone would be inappropriate and neglectful medical practice.

*Heart Health... continued from page 4*

prolongation have ranged from practically nonexistent to rather low, for example *r* = 0.01 to 0.37 [references in, Schmittner and Krantz 2006; Peles et al. 2007]. Many of these data have been found to be statistically significant; however, this *does not* necessarily equate to clinical significance in actually harming patients [see Box 2].

Interestingly, one of the highest significant correlations to date (*r* = 0.40, *P* = 0.03) between methadone dose and QTc increases was recently reported by Peles et al. [2007] *specifically* in a subgroup of MMT patients abusing cocaine, which is well-known to be cardiotoxic. There was practically no correlation at all in those MMT patients *not* abusing cocaine (*r* = 0.04, *P* = 0.4).

This brings into question how well-controlled other research studies have been that reported significant correlations of methadone and QTc; that is, have all extraneous factors been fully accounted for and excluded? Furthermore, it must be considered that, even in the most rigorous studies reporting significant correlations, methadone itself would statistically account for only a relatively small proportion – usually less than 15% – of the QTc prolongation; other factors, many of them unknown, account for the vast majority of the effect [see Box 2].

All of this is not to belittle the body of research to date seeking to demonstrate methadone's potential influence on cardiac conduction disturbances. However, many of the data are suggestive rather than positively confirming a relationship, and the emphasis on methadone as the culprit may be diverting attention from finding and controlling more critical causal factors.

Other contributing factors may become activated in the presence of methadone; that is, methadone might act as a "triggering mechanism" of some sort; however, this is speculative, and whether higher doses of methadone exert a greater influence in this regard is still largely undetermined. Meanwhile, limiting methadone doses is unlikely to be a successful strategy for preventing TdP in susceptible patients, according to some distinguished researchers [Pearson and Woosley 2005].

### What the Experts Advise

Expert opinions expressed by various researchers [for example, Schmittner and Krantz 2006; Leavitt and Krantz 2003; Maremmani et al. 2005; Pearson and Woosley 2005; Peles et al. 2007] are consistent with FDA recommendations and have proposed an approach adhering to best medical practices. Their advice may be combined and briefly summarized as follows:

*The risks of opioid addiction are considerable, and MMT programs are generally life-saving interventions for many patients. Conversely, the risk of TdP is likely to be quite small and should not deter providers or patients from MMT. Generally, benefits of methadone therapy greatly outweigh any risks.*

*Further research and guidelines are needed; consequently, it would be premature to recommend routine requirements for ECGs in all patients before or during MMT. However, it would be prudent for MMT providers to conduct a careful medical examination and history taking in each patient, screening for known cardiac risk factors. Baseline and followup ECGs might only be recommended for patients found to be at high risk for adverse cardiac events. Furthermore, due to potentially additive effects, the co-prescribing of methadone and drugs known to prolong the QT interval should be avoided whenever possible.*

Further suggestions for sound medical practice to optimize cardiac safety during MMT are presented in Box 3.

### More Objective Perspective Needed

The question of whether oral methadone itself causes harmful cardiac conduction disturbances and, if so, the extent of this effect remains unanswered. Case studies are of limited value, and for every clinical trial showing that methadone alone prolongs the QTc interval or influences TdP another study demonstrates no effect at all. In some instances, methadone therapy actually lowered the QTc in specific groups of patients [Cruciani et al. 2005], and other research has suggested that long-term methadone might protect patients from certain harmful cardiac conditions [Leavitt 2001; Marmor et al. 2004].

Some of the research and commentary stressing methadone's negative influence on cardiac health may express an underlying anti-methadone bias. This is reflected in an over-emphasis of case reports and an over-reliance on weak statistical data from clinical studies. The literature should be cautiously scrutinized.

Yet, cardiac concerns regarding methadone cannot be ignored and sound medical practices to help safeguard the heart health of methadone treated patients should be employed. Hopefully, the existing body of clinical evidence will be examined more objectively in the near future and/or larger, more definitive clinical trials will be conducted to resolve unanswered questions.

### Box 3: Optimizing Cardiac Safety During MMT

None of these suggestions is intended to deter the use of methadone in any patient who would otherwise benefit. [Modified from Schmittner and Krantz 2006; Leavitt and Krantz 2003.]

- ❑ Patients entering MMT should be screened for cardiac risk factors and medical records for all patients should be periodically updated.
- ❑ Records should note prior and current cardiac problems, family history of cardiac conditions, past and present substances abused (including tobacco), and current medications (including OTC and herbal products).
- ❑ A 12-lead ECG might be considered in...
  - new patients with a history of arrhythmia or prolonged QTc, a family history of premature sudden death, and/or other significant arrhythmia risk factors (eg, cardiac hypertrophy, hypokalemia, hypomagnesemia, diuretic use, cocaine or benzodiazepine abuse);
  - ongoing MMT patients suspected of having arrhythmia risks, and especially before starting QT-prolonging medications or methadone metabolism inhibitors in those patients. Practitioners should become familiar with drugs that may interact with methadone.
- ❑ A followup ECG should be performed in such patients to detect significant changes from baseline.
- ❑ Patients with QTc prolongation during MMT should be evaluated for modifiable risk factors, such as concomitant medications that affect cardiac repolarization, inhibit methadone metabolism, or are known to cause electrolyte imbalance, etc.
- ❑ Closer monitoring (and/or consultation with experts) might be considered in patients with...
  - known or detected conditions affecting heart rhythm (such as, CHF with reduced ventricular function);
  - unexplained syncope (fainting) or seizure episodes;
  - QTc > 460 msec (in males or females);
  - significant increase in QTc (>60 msec) from baseline;
- ❑ Patients at risk of arrhythmia should be educated on symptoms to watch for – e.g., "racing" heartbeat, dizziness, seizures, or fainting spells – and encouraged to contact the clinic immediately. Clinic staff should be trained in handling such calls from patients: eg, appropriately encouraging those with severe symptoms to call 911, facilitating referrals to urgent care, or arranging for ECGs.

### Where to Access FDA Documents



The FDA Public Health Advisory is available at:

<http://www.fda.gov/cder/drug/advisory/methadone.htm>.

Information for Healthcare Professionals is at:

<http://www.fda.gov/cder/drug/InfoSheets/HCP/methadoneHCP.pdf>

The revised PI for methadone tablets is at:

<http://www.fda.gov/cder/foi/label/2006/006134s028lbl.pdf>

### Is Methadone Safe During Pregnancy & Breastfeeding?

The patient information section of the new PI for methadone states that women who are pregnant or plan to become pregnant should notify their physicians, since "methadone may harm your unborn baby." Additionally, if a woman is breastfeeding her newborn, the PI says that methadone "passes through your breast milk and may harm your baby." Women should choose to use methadone or breastfeed, but not both, it recommends.

This advice may cause great alarm among MMT providers and their female patients. And, it is contrary to prior research and recommendations concerning MMT during and after pregnancy [CSAT 2005].

In response, the Director of the Center for Substance Abuse Treatment (CSAT) – H. Westley Clark, MD, JD, MPH, CAS, FASAM – issued a "Dear Colleague" letter in December 2006. He noted that methadone is considered "Pregnancy Category C," like most other medications. According to the FDA definition of this Category, it means that controlled studies for establishing safety of methadone use in pregnant women are inadequate. Although, in this case, there have been a number of studies demonstrating a favorable safety profile of methadone in pregnant women on MMT, and it is approved by the FDA for MMT during pregnancy.

Clark went on to state in his letter, "SAMHSA/CSAT is not aware of evidence that an unborn baby has been harmed from the mother's use of methadone. Furthermore, neonatal abstinence syndrome (NAS) has been well described and is easily treated with no long-term consequences on child development."

"Methadone is still considered 'probably safe' for lactation (breastfeeding)," he continued. "About 2-3% of methadone might pass through to breast milk, with peak dose 4-5 hours post administration."

Clark advised that the newly revised patient information sheet for methadone is most applicable to women considering methadone for pain management, "for whom treatment might be temporary and for whom there might be several alternative treatments. However, for pregnant women and new mothers who are opioid dependent and have adhered to methadone maintenance treatment, the desire to breast feed should be encouraged unless there is another medical or psychological reason that serves as a contraindication to breastfeeding."

This was a significant clarification by CSAT of the FDA Advisory, which should be carefully noted by MMT providers. Clark's letter reaffirms the considerable research and recommendations already favoring the benefits over risks of methadone maintenance during and after pregnancy in opioid-addicted women [see CSAT 2005, pp 211-224].

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# Patient's Perspectives

## Lifelong MMT Can Mean a Lifetime of Happiness

by Sandy Linton

### Opportunity for a More Normal Life

I am a 60 year old woman and have been on methadone maintenance treatment (MMT) since 1969. That's right, more than 37 years.

My husband, Peter ('Pete'), and I both grew up in suburban Essex County in New Jersey, enjoyed happy childhoods, and both became intravenous heroin users. Pete began using heroin first, and I was horrified when I first saw him injecting himself. However, after awhile I also began using heroin. I likened it to being a golf widow; either I stayed home alone, or I took up the game.

After several imprisonments and other problems associated with drug addiction, we decided that was not a viable lifestyle. We had two small children and wanted better not only for them, but for us as well. A friend of ours steered us to a doctor who was prescribing methadone, and that medication became instrumental in affording us the opportunity to live more-normal lives.

We both became gainfully employed, purchased a home, and basically lived the American dream. We successfully raised four children, were active in local scouting groups, served in PTA organizations and other groups.

### Good Days, Bad Days – One Day at a Time

In the beginning of our MMT 37 years ago, we were given a prescription by a local doctor for a week's worth of methadone at a time and had it filled at a pharmacy. As MMT became more widespread, the government put tighter restrictions on methadone. It could only be prescribed and dispensed at specially licensed clinics.

My husband and I pretended that taking our methadone was similar to someone taking insulin. We needed it every day – we didn't feel it when we took it, but we certainly felt it if we missed our dose. If methadone is used correctly, it can change your life.

After a few years, the methadone tablets we had been taking were replaced by the biscuits, and then by methadone in a liquid form. Some clinics had the clear methadone mixed with water and others had the thick, red, syrupy mixture. We found that the methadone seemed to work best for us when taken with a hot beverage.

We had our good days and a lot of bad days. We talked ourselves through it by taking it one day at a time. Each evening, we would say, "well, one more day under our belts."

One tool we used was to list 'goals.' Every time we achieved a goal, we checked it off. When you are able to see in black and white that progress is being made, you can feel good about yourself.

Pete and I were competitive and we used that as a tool, also. Each of us would think that if the other could do it, then so can I. Neither of us wanted to be the quitter.

During the early days of MMT, and in some areas today, neighborhoods didn't want methadone clinics nearby. All drug addicts were envisioned as vicious criminals. My clinic had a group of us go to several community meetings to address them.

We convinced them that a drug addict can be anyone, including their teachers, firemen, policemen, lawyers, etc. It was difficult getting certificates of need for MMT clinics because local

I remember hearing  
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"getting high on life,"  
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I don't anymore.

communities didn't even want to admit that they had drug problems.

### Patients Must Assume Responsibility

My personal opinion is that some people in MMT are not taking full responsibility for their sobriety. Responsibility is a big word and encompasses a lot. There is responsibility for admitting you have a problem, responsibility for taking steps to correct it, and responsibility for staying with your decision for sobriety.

Some clinics, through public aid funding, will arrange to get you to the clinic,

medicate you, counsel you, and deliver you back home to your door – all courtesy of the government. This is wrong. After all, you didn't need to be taken by the hand before to buy your drugs, and the government certainly wasn't paying for it – so why do you need it now?

Everyone is different. What helps one, may not help another, and some people do need more help than others. However, sometimes things matter most to us when they are earned through hard work. If you don't participate in the process, it is being done for you.

Is it easy? NO!

However, most things worthwhile are not gotten easily. If you want something – like sobriety – badly enough, it is definitely worth the work. Unfortunately, too many patients use methadone on top of other drugs, and that works against their recovery.

### Getting High on Life

A lot of drug addicts need to rebuild the trust of their families and friends. This cannot be done overnight – just as trust wasn't lost overnight.

We all need to take the small steps necessary to show our families that we're staying on the road to recovery. Pete and I always felt blessed in recovery. Our daughter, now 41, thinks she had the best parents and life ever. Evidently, we were good actors. We also have three sons, ages 24 to 39, and three grandchildren, ages 10 to 19.

When our children were young, we only told them what was necessary at the time. Generally we said we were getting medicine at a clinic. As they got older and asked more questions, we told them that we took bad drugs many years ago and now we're taking medicine to help us keep from ever doing that again.

We didn't want to lie to them. We always thought that once a child catches you in a lie, you lose your credibility. As they became adults, we told our children the whole story.

I remember hearing for years about "getting high on life," and I used to snicker at that. I don't anymore.

It's nice to have your family together and being proud of yourself, instead of being the "odd man out." Life truly is wonderful. It is a lot more fun being healthy, owning a home, going on nice vacations, and being financially solvent than living day to day on drugs.

*[Editor's Note: In early November 2006, Sandy's husband, Pete, passed away after a long life of sobriety in MMT and a brief battle with cancer.]*

## Survey Results: Contracts in MMT?

As a followup to the editorial on "Treatment Contracts for MMT Patients" in *AT Forum* Summer 2006 (Vol. 15, No. 3), readers were surveyed on methadone maintenance treatment (MMT) clinic practices and their opinions in this regard.

The editorial noted that the concept of an "MMT Contract" extends beyond the usual informed consent for participation in MMT. In a "Contract" both parties – clinic and patient – commit to a plan of action and share common visions for treatment success. It typically spells out patients' responsibilities, patients' rights, and clinic staff responsibilities.

### Contracts Widely Used

There were 155 responses to the survey, two-thirds from clinic staff and a third from MMT patients. Nearly 60% indicated that their MMT clinics have such patient contracts, and 20% do not. Another 20% responded that they did not know if their clinics required patient contracts.

Two-thirds of respondents believed that treatment contracts are helpful, while 28% felt they are unnecessary [see *Graph*]. Only 6% indicated that contracts are harmful.

One healthcare provider wrote, "Three of the biggest problems with patient contracts are: 1) they are too often punitive and are written in language that is negative or patronizing, 2) they are one-sided, rarely examining the clinic's commitment and obligations, and 3) there are no provisions for remedies if the clinic does not follow through on its part of the agreement."

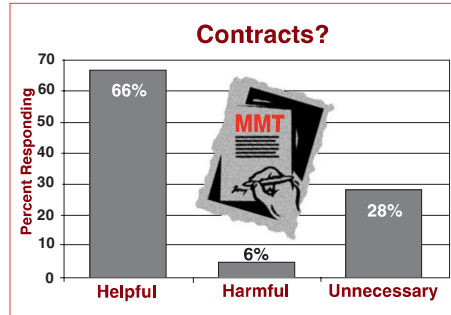
A staff member said: "Any contract can be bad if it is used as a weapon. But, when used to establish a clear understanding of both parties' needs and obligations it can be very useful."

A patient responded: "I think that a treatment contract is good, if the patient clearly understands what must be done to fulfill the requirements and agrees with them. It cannot merely favor the clinic in all regards."

### When Are Contracts Signed?

Readers were asked when treatment contracts should be signed. Most – one third – indicated "during admission to MMT," while a quarter said "after stabilization on methadone." The remaining 42% indicated "never," or "other."

The *AT Forum* editorial expressed a concern that during the anxiety-filled atmosphere of entering treatment a patient might not be in a state of mind to carefully consider the contract, and there is an implication that MMT will be refused unless it is signed. As one patient wrote: "Most of us are so



desperate to get accepted into MMT that we would sign anything."

Another patient wrote, "Upon entering MMT 9 years ago I remember signing something, I don't know if it was a contract. It would be better if a treatment contract was signed during admission and then revised appropriately and signed again after stabilization."

### Supporting Mutual Obligations

There may be some confusion between the government-required informed consent for methadone treatment and a treatment contract, as described in the editorial. The former, mandatory upon admission, should explain confidentiality issues, risks and benefits of methadone, and MMT program policies and services.

The "contract," which many respondents also likened to a "treatment plan," is about expectations and performance by both clinic staff and patients. As a staff member indicated, "At our clinic, contracts are usually specific to issues that could hinder recovery."

However, one MMT-patient advocate noted, "I have witnessed the use of 'contracts' as a device to get rid of problematic patients." Nobody wins when a patient is dismissed from treatment. A good contract supports the mutual obligations shared by providers and patients.

#### ADDICTION TREATMENT

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