



Methadone Analgesia Safety Overview & Patient Instructions Handout

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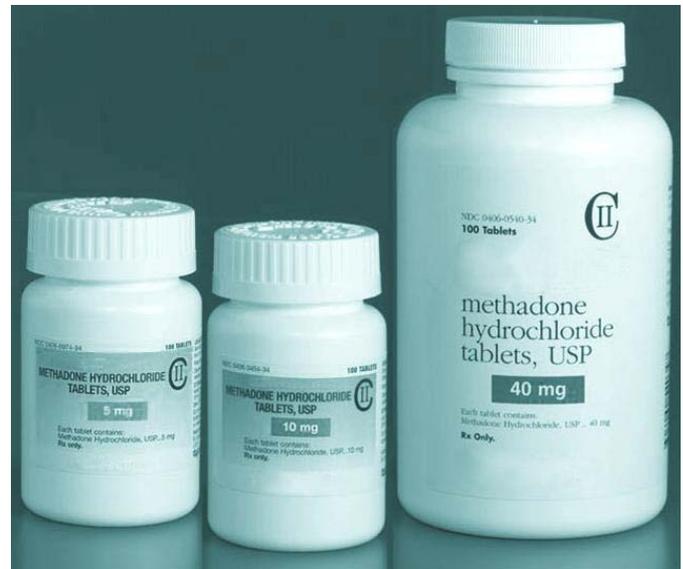
Oral methadone has demonstrated an excellent record of effectiveness and safety during the more than 60 years since its development. Although millions of patients have been successfully treated daily with the medication, reports of methadone-associated overdoses and fatalities continue to appear in sensational news headlines, describing methadone as a widely abused and dangerous drug. This has caused apprehension among healthcare providers and patients alike and, consequently, has burdened methadone with an unwarranted tarnished reputation.

Yet, when properly prescribed and used, oral methadone can provide effective and economical pain relief even when other analgesics – opioid or non-opioid – fail to do so. It is suitable for treatment of even the most severe acute or chronic pain (CSAT 2004a).

Most of the tragedies surrounding the misuse and abuse of oral methadone, typically in tablet form, could be prevented by a greater understanding of prescribing the medication among healthcare providers and by better education of patients and their families or caretakers (CSAT 2004a, 2004b). *Pain Treatment Topics* has created several guidance documents – described and linked below – that can assist healthcare providers and a special handouts for patients (in English and Spanish, at the end of this Overview). All of these documents are available for free download at: <http://www.pain-topics.com>.

Understanding Methadone

Methadone is a well-established opioid medication. It was synthesized in Germany as an analgesic and spasmolytic in the late 1930's, and a patent application was filed in September 1941. Methadone was found to be more potent than morphine; however, the pharmacology of methadone was different than other opioids, and little was known about how to best prescribe the new agent (Leavitt 2006; Toombs 2006).



Please see Update Note on page 12.

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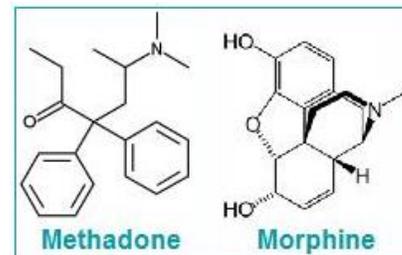
Consequently, methadone was not effectively used as an analgesic during the war years, reportedly because the very high initial doses typically administered at that time produced intolerable side effects. Oral methadone was approved in the US in 1947 as an analgesic and antitussive indicated for migraine, dysmenorrhea, labor pain, painful nerve disorders, advanced cancer or tuberculosis, tetanus, and other disorders (Leavitt 2006).

Methadone Safety Requires Proper Prescribing

Methadone's chemical structure is quite different from opium-derived alkaloids like morphine (Peng et al. 2005, see **Figure**) and, in the early days, methadone's pharmacology was not well understood. Due to improper prescribing and/or misuse, there were deaths associated with methadone in the late 1940's and 1950's, with a number of those fatalities reported in young children exposed to the drug in cough syrups (CSAT 2004b; Leavitt 2006).

Similar deaths in adults, or cases of near-fatal respiratory depression, soon occurred. Consequently, due to its perceived toxicity and the potential for methadone to produce physiologic dependence, it fell into disuse in general medicine as an analgesic by the early 1960's (CSAT 2004b). Soon thereafter, however, it was revived for use as a maintenance therapy for managing opioid addiction (Leavitt 2003, 2006).

During more than 40 years clinical use as methadone maintenance treatment (MMT) for opioid addiction, hundreds of studies have examined the pharmacology and efficacy of oral methadone. With a greater understanding of methadone and its proper prescribing, it has proven to be a well-tolerated medication, without serious adverse reactions or associated organ damage, even in patients taking the drug for more than 20 years (Leavitt 2003, 2006). As a result, methadone also has re-emerged as an important opioid analgesic.



Unique Pharmacology of Methadone

Aside from its agonist activity at mu-opioid receptors, typical of opioid-class analgesics, methadone exerts antagonistic (blocking) activity at N-methyl-d-aspartate (NMDA) receptors (Gorman et al. 1997). This helps counteract opioid tolerance development (Davis and Inturrisi 1999; Eap et al. 2002; Manfredi et al. 2003) and attenuates opioid abstinence syndrome (Lugo et al. 2005).

The NMDA receptor is a target for glutamate, a primary excitatory neurotransmitter in the brain, and blockade of this receptor can decrease neuronal excitability, attenuate hypersensitivity, and reduce seizure activity (Davis and Inturrisi 1999; Woolf and Salter 2000). These qualities are often evident in agents used as adjuvant analgesics, of special importance in treating neuropathic pain (Brown et al. 2004, CPSO 2004), so beneficial effects of methadone in modulating the glutamate system may be significant (Mannino et al. 2006).

Of further interest, methadone inhibits the reuptake of both norepinephrine and serotonin (Codd et al. 1995; Eap et al. 2002), and medications with this effect have been important in treating depression and as adjuvant analgesics. Some authors have commented specifically on methadone's beneficial effects on depression (Humenuik et al. 2000; Payte et al. 2003; Rounsaville et al. 1983), and research in MMT populations has shown that, at adequately high doses, methadone helps stabilize mood (Leavitt 2004), which also might benefit patients with chronic pain.

Toxic Effects in Overdose

As with other opioids, the primary toxic effects of excessive methadone are respiratory depression and hypoxia, sometimes accompanied by pulmonary edema and/or aspiration pneu-

Methadone has unique properties that also are typical of adjuvant medications used in pain management.

monia. Among patients in addiction treatment, the largest proportion of methadone-associated deaths have occurred during the drug's induction (start up) phase, usually when treatment personnel overestimate a patient's degree of tolerance to opioids, or a patient consumes opioids or other central nervous system (CNS) depressant drugs in addition to prescribed methadone (CSAT 2004b).

When deaths occur during later stages of methadone therapy, other drugs besides methadone usually are detected at postmortem examination. In particular, researchers have called attention to the "poison cocktail" resulting from the intake of multiple psychotropic drugs such as alcohol, benzodiazepines, and other opioids in conjunction with methadone. When used alone, many of these substances are relatively moderate respiratory depressants; however, when combined with methadone, their additive or synergistic effects can be lethal (CSAT 2004b).

Clearly, the implication is that oral methadone is a unique opioid analgesic, which can be safe and effective if properly managed. Better education of healthcare providers, as well as patients and their families or caretakers, is necessary for ensuring methadone safety (CSAT 2004a, 2004b) and the reports described below are designed to achieve that end.

Methadone-associated deaths usually involve multiple drugs in a "poison cocktail."

Proper Methadone Dosing

Methadone has emerged as a good choice for the management of chronic non-cancer or cancer pain, both as a first line medication and as a replacement opioid (Fishman et al. 2002; Toombs 2006). Also, compared with other opioids, methadone offers very significant cost advantages (CSAT 2004b).

Particular cautions must be observed, as methadone's pharmacokinetics and pharmacodynamics are unique among opioids (as noted above). Milligram for milligram, methadone is more powerful than morphine; however, there is significant interindividual variability in the response to methadone (Fishman et al. 2002; Toombs 2006).

Oral methadone has good bioavailability and a long duration of action (CPSO 2004). Its analgesic effects begin within 30 to 60 minutes or less, generally peak within 2 hours, and last from 3 to 6 hours, but can extend longer with repeated dosing (Brown et al. 2004; Ettinger et al. 1979; Peng et al. 2005). The manufacturer-recommended adult dosage for methadone analgesia is 2.5 mg to 10 mg every 3 or 4 hours as necessary (Mallinckrodt 1995; Roxane 2000); however, it was observed some time ago that the higher-end analgesic dose (80 mg/day) could be excessive and potentially lethal unless opioid tolerance is already well-established in the patient (Ettinger et al. 1979). Dosage is adjusted gradually according to the severity of the pain and the response of the patient.

The terminal elimination half-life of methadone analgesia ranges from 5 to 130 hours, with a mean of 20-35 hours. There can be considerable variability in time to steady-state blood concentrations – typically 3 to 5 days, but possibly up to 10 days – depending on half-life in the particular patient, during which time methadone accumulates even when maintained at a constant dose (Eap et al. 2002; Leavitt 2003; Lugo et al. 2005; see **Graph**). After each dose increase, another period of days is required to again reach steady state.

Therefore, frequent methadone dose increases, or the addition of

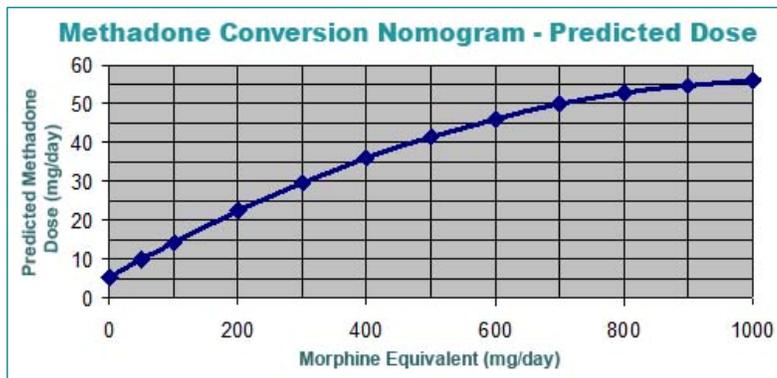


Even at a constant dose, methadone accumulates during a number of days until a steady state level is achieved. (Adapted from Lugo et al. 2005.)

other opioid medications, can incur hazardous opioid blood levels. Furthermore, methadone has a potential to interact with a large number of medications, and drug-drug interactions must be considered (see below, Leavitt 2006; Toombs 2006).

As with many potent medications, the general dosing rule with methadone is *to start low, go slow, and titrate gradually to effect* (CPSO 2004; Toombs 2006). There is no ceiling effect for opioids like methadone, and increased analgesia may be produced with each dose escalation (Thompson and Ray 2003).

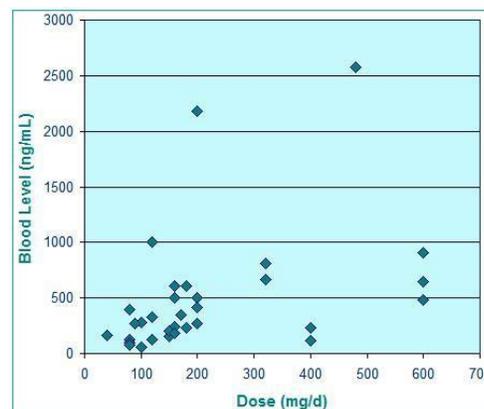
However, when initiating opioid therapy with methadone or transitioning from a different opioid, standard “equivalency tables” for calculating methadone dose can be unreliable (CPSO 2004). It is important to note that, in converting to methadone from morphine or morphine-equivalent dose, methadone dose determination does not follow a linear trend as doses increase. This relationship is shown in the nomogram *at right*, which can be helpful in calculating methadone dosing (see Toombs 2006, linked below, for instructions on using this).



When dosing methadone analgesia, start low, go slow, and titrate gradually to full effect.

Limiting factors in methadone dosing include the appearance of toxicity or adverse effects. However, concerns of respiratory depression with chronically administered high doses of *properly titrated* opioids like methadone may be unwarranted, and cases of individual patients receiving thousands of milligrams of opioid medication per day without such complications have been reported (Thompson and Ray 2003).

Additionally, available evidence suggests that during its use for analgesia, methadone blood concentration may not relate directly to the dose, possibly due to individual variations of absorption and/or metabolism. In a study of 32 patients receiving chronic oral methadone for pain, total daily doses ranged from 40 mg to 600 mg (mean 218, SD +/- 161), while blood levels ranged from 80 ng/mL to 2580 ng/mL (mean 495, SD +/- 555). A modest but significant correlation ($r = 0.40, p = 0.018$) was influenced primarily by strong dose vs blood level associations at lower doses (Tennant 2006b; see **Graph**). Higher methadone doses do not necessarily produce correspondingly high blood levels.



Methadone analgesia dose (mg/d) vs. blood level (ng/mL). (Pain Treatment Topics analysis of data from Tennant 2006b.)

A number of the blood levels in that study greatly exceeded what some would consider toxic amounts (CSAT 2004b), yet all patients were ambulatory and functional. This same phenomenon, and lack of a dose-to-blood-level correlation at higher doses, is observed in patients maintained on oral methadone for opioid addiction (CSAT 2004b; Leavitt 2003).

The following report available from *Pain Treatment Topics* provides further evidence-based guidance for effective and safe oral methadone dosing. Click on the link or copy and paste the URL into an Internet browser. (*The Adobe® Acrobat® Reader is required for all reports.*)

For detailed dosing information, see...

Methadone Dosing for Chronic Pain in Ambulatory Patients

James D. Toombs, MD, February 2006.

PDF available at: http://www.pain-topics.com/pdf/Methadone_Dosing_Chronic_Pain_2006.pdf (260 KB; 12 pp). Access checked 10/8/06.

Avoiding Methadone-Drug Interactions

Each year in the U.S. there are innumerable adverse drug reactions, broadly defined as any unexpected, unintended, undesired, or excessive response to a medicine. Such reactions may require discontinuing or changing medication therapy. Furthermore, greater than 2 million of those are serious reactions resulting in hospitalization and/or permanent disability, and there are more than 100,000 deaths annually attributed to reactions involving prescribed medications (Leavitt 2006).

Three-fourths of those adverse reactions relate to *drug interactions*, which occur when the amount or action of a drug in the body is altered, usually increased or decreased, by the presence of another drug or multiple drugs. Avoiding these can be difficult; for example, there are more than 100 substances – medications, illicit drugs, OTC products, etc. – that potentially can interact in some fashion to affect a patient's response to oral methadone (see Leavitt 2006). However, many of these interactions have not been rigorously studied clinically (Brown et al. 2004), and just because an interaction is possible does not mean it will occur or have clinical significance if it does.

Possible methadone-drug interactions sometimes can be difficult to predict and they may be harmful and/or can lead to treatment failures. Methadone is metabolized to inactive forms via cytochrome P450 (CYP450) enzymes in the intestine and the liver, which serves as the principle means of elimination. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6 (Leavitt 2006; Lugo et al. 2005; see **Table**).

Another agent that affects methadone elimination is P-glycoprotein (P-gp), which is found in the intestine, along the blood-brain barrier, and in other tissues. P-gp functions as a “pump,” transporting methadone out of cells lining the intestinal wall and back into the lumen for excretion (Leavitt 2006; Lugo et al. 2005).

Drugs that induce CYP enzymes or P-gp responsible for methadone metabolism and elimination may lower methadone blood levels. Conversely, inhibition of those agents would serve to increase methadone, possibly to toxic blood levels. Additionally, certain drugs that are antagonists or mixed agonists-antagonists of mu-opioid receptors can reverse opioid effects, leading to painful withdrawal symptoms, and must be avoided (Brown et al. 2004; Eap et al. 2002; Lugo et al. 2005 – see *Leavitt 2006, below, for complete interacting drug tables*).

Healthcare providers should be aware of potential interactions with methadone and the agents that might cause them. Along with that, they must know of all substances – including prescribed drugs, illicit substances, alcohol, over-the-counter products, etc. – that a patient prescribed methadone is using.

The following report available from *Pain Treatment Topics* discusses methadone metabolism in more detail and provides extensive tables of substances that may interact with methadone to influence its effectiveness and safety. Click on the link or copy and paste the URL into an Internet browser



CYP450 Enzymes Metabolizing Methadone	
CYP3A4	Important methadone metabolizer (can also be induced by methadone during the early start-up phase of therapy).
CYP2B6	Relatively recently discovered as an important methadone metabolizer.
CYP2D6	Secondary role (methadone can inhibit this enzyme in some cases, and this enzyme is particularly involved in the metabolism of the active R-methadone enantiomer).
CYP1A2	Possibly involved (clinical significance still under investigation).
<p>Note: Previously, CYP2C9 and 2C19 were thought to be involved, but this has not been confirmed. (Leavitt 2006.)</p>	

For methadone safety and effectiveness, healthcare providers must be aware of agents that may cause potential interactions.

For complete information and interacting-drug tables, see...

Methadone-Drug* Interactions (*Medications, illicit drugs, & other substances)

Stewart B. Leavitt, MA, PhD, January 2006.

PDF available at: http://www.pain-topics.com/pdf/Methadone-Drug_Intx_2006.pdf (700 KB; 33 pp).
Access checked 10/8/06.

Cardiac Considerations and Precautions

Some patients with chronic pain may have conditions associated with increased risks of arrhythmia, including cardiovascular disease, electrolyte imbalances, and prescribed medications or abuse of cardiotoxic substances that may foster cardiac repolarization disturbances (Leavitt and Krantz 2003). Furthermore, there is some evidence that severe, chronic, undertreated pain itself may produce cardiac complications (Tennant 2006a).

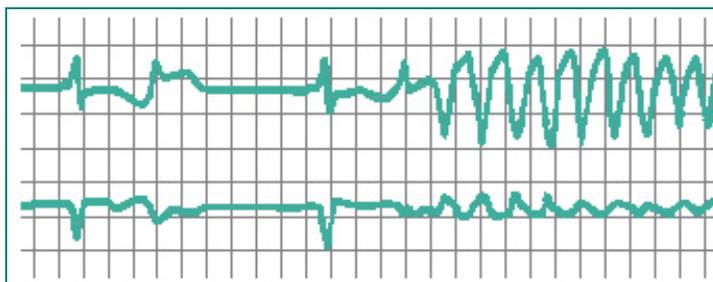
Additionally, studies primarily in patients receiving MMT for opioid addiction suggest that in some individuals, methadone – alone or, more commonly, in combination with other drugs and/or cardiac risk factors – can prolong the cardiac QT interval. This may contribute to development of the serious arrhythmia torsade de pointes (TdP) in susceptible patients (see **Figure**; Eap et al. 2002; Leavitt and Krantz 2003).

While effects of methadone on cardiac rhythm are still under investigation, healthcare providers should be aware of this potential complication, and heart health assessments prior to and during methadone analgesia therapy can be an important preventative measure. Some sources have recommended electrocardiographic (ECG) monitoring in patients receiving oral methadone doses greater than 200 mg daily (CPSO 2004; Rhodin et al. 2006).

Current evidence, however, does not support altering methadone analgesia dosing practices or requiring ECGs for *all* patients beginning or continuing methadone therapy and should not deter the appropriate use of methadone. The relatively small potential risk of adverse cardiac events induced by methadone should be weighed against the significant benefits of this analgesic (Leavitt and Krantz 2006).

The following report available from *Pain Treatment Topics* summarizes the published research concerning methadone effects on cardiac repolarization and TdP. Clinical suggestions are offered for identifying individual patient cardiac risk factors and for optimizing cardiac safety during methadone therapy. Click on the link or copy and paste the URL into an Internet browser.

Methadone alone or, more commonly, in combination with other drugs and/or cardiac risk factors can affect cardiac rhythm.



Prolonged QTc on ECG waveform transitioning to polymorphic ventricular tachycardia, called torsade de pointes. (From Leavitt and Krantz 2003.)



For complete information on cardiac safety during methadone therapy, see...

Methadone Cardiac Concerns

Stewart B. Leavitt, MA, PhD; Mori J. Krantz, MD, FACC - from *Addiction Treatment Forum*, Oct. 2003.

PDF available at: http://www.pain-topics.com/pdf/Methadone_Cardiac_Concerns.pdf (200 KB; 6 pp).

Access checked 10/8/06.

Other Pain Treatment Topics Reports of Assistance...

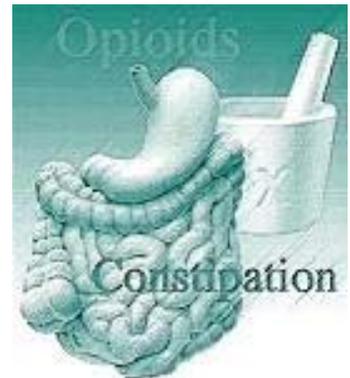
Managing Constipation

Constipation is a frequent side effect of opioid therapy, including with methadone, since these agents decrease peristaltic activity in the gastrointestinal tract. Because of the mechanisms involved in opioid-induced constipation, some treatments that may be applicable for common, functional constipation are inappropriate for ambulatory-care patients prescribed methadone (Goodheart and Leavitt 2006).

The distress of constipation in these patients may add to the discomfort already present from pain, and they might decrease or discontinue opioid therapy to avoid constipation. So, motivating such patients to comply with their opioid regimen also requires a special approach for managing constipation.

Certain popular beliefs about treating constipation have little or no evidence to support them. For example, merely adding fluids or fiber to the diet, and increasing activity, may not be helpful in patients with opioid-induced constipation. Bulk-forming laxatives may be harmful and, in most cases, other laxative therapy will be needed for prevention or for treatment of existing constipation (Goodheart and Leavitt 2006).

The following report from *Pain Treatment Topics* reviews the causes and consequences of opioid-induced constipation and provides guidance for its effective management.



Managing Opioid-Induced Constipation in Ambulatory-Care Patients

Clyde R. Goodheart, MD, MBA, MS; Stewart B. Leavitt, MA, PhD, August 2006.

PDF available at: http://www.pain-topics.com/pdf/Managing_Opioid-Induced_Constipation.pdf (180 KB; 9 pp). Access checked 10/8/06.

Safely Tapering Opioids

There are many reasons for considering opioid analgesic tapering, both from healthcare provider and patient perspectives. Whereas guidance for starting opioid analgesics can be obtained from product package inserts and reference sources, it is much more difficult to find reliable information about switching or stopping these medications. Some practitioners have their own protocols for managing conversions or tapers; although, there is no single strategy that can be applied to all patients, and each situation must be handled on an individual basis.

The following report from *Pain Treatment Topics* discusses the many factors to consider when discontinuing opioid analgesics, and it presents specific and practical clinical guidance for establishing protocols that maximize patient safety and comfort during the process. Important advice for patients regarding emergency tapering – such as after natural disasters or other crises when medication is inaccessible – also is provided.

OPIOID TAPERING

Opioid Tapering: Safely Discontinuing Opioid Analgesics

Lee A. Kral, PharmD, BCPS, March 2006.

PDF available at: http://www.pain-topics.com/pdf/Safely_Tapering_Opioids.pdf (140 KB; 7 pp). Access checked 10/8/06.

Patient Education – An Absolute Necessity

Most patients and their families or caretakers find the medication information provided by pharmacies, or product package inserts (if provided), difficult to read and understand. Hence, these are of little help in fostering patient compliance. Additionally, opioids medications must be especially safeguarded by patients.

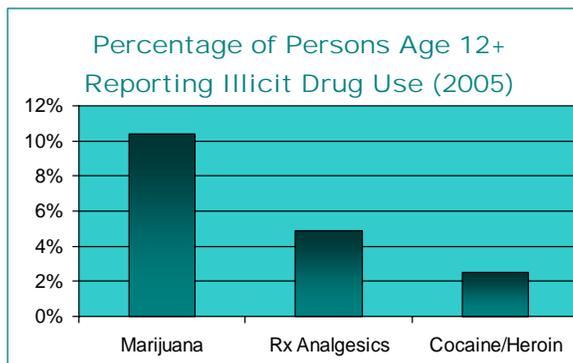
Recent data suggest that pilferage of prescription opioids from patients’ medicine cabinets and their illicit use is a continuing and growing problem (CSS 2006). The latest U.S. household survey found that the nonmedical, illicit use of prescription pain relievers was second only to marijuana abuse and was twice that of cocaine and heroin use combined (see **Graph**), and it also exceeded abuse of any other illicit substance (CESAR 2006a). In all, approximately 7.25 million persons age 12 and older used prescription pain relievers for nonmedical purposes in 2005, and the alarming trend was rising rapidly.

Furthermore, opioid analgesics are more likely than such agents as cocaine or heroin to be the cause of unintentional drug-poisoning fatalities in the U.S. In an analysis of data from 2002, opioid analgesics accounted for more than a third (36.5%) of drug-poisoning deaths, with methadone mentioned in nearly a third (32%) of those opioid cases (CESAR 2006b). Three ways that oral methadone may induce fatalities have been noted and have implications for patient education (adapted from CPSO 2004):

- **Single Overdose** – In this case, the first dose is fatal and occurs most often via accidental or illicit ingestion of a toxic dose by an individual without *any* opioid tolerance, or in a previously tolerant user who has not taken opioids for a considerable period of time and resumes methadone at a previously high dosage.
- **Accumulated Toxicity** – This can develop during several days as methadone blood levels build up excessively. It is seen most commonly with overly aggressive methadone initiation protocols or in patients taking more doses than prescribed.
- **Drug-drug Interactions** – As noted above, methadone can be lethal when used with alcohol, other opioids, and other CNS depressants. Furthermore, substances that inhibit methadone metabolism can result in methadone accumulation and toxicity.

In the drug-poisoning data above, it is not known how many deaths involved *illicit nonmedical* opioid use (eg, recreational) versus those resulting from *medical misuse* (eg, noncompliance with the dosing regimen or mixing with other medications), or from *misprescribing*. It seems logical that better patient education regarding therapeutic compliance might help prevent unintentional medical misuse of methadone, and more rigorous safety precautions could help avert methadone from falling into the hands of persons who might use the drug for illicit, nonmedical purposes.

Yet, a recent observational study (Tarn et al. 2006; see **Table**) found that busy healthcare providers often failed to adequately instruct patients and communicate critical information



Prescription opioid analgesics are more likely than illicit drugs to be involved in drug-poisoning fatalities.

Communication Failures When Prescribing a New Medication (243 various prescriptions; 45 prescribers)	
Missing Information	% Failures
General directions for taking the medication not stated.	66%
– Specific dosing not indicated.	45%
– Frequency/timing of dose not indicated.	42%
Adverse effects not addressed.	65%
Name of medication not mentioned.	26%
Purpose of medication not described.	13%

(Adapted from Tarn et al. 2006.)

regarding various prescribed medications. This might expectedly contribute to misunderstandings by patients leading to noncompliance and/or medication misuse, which could be harmful or fatal in the case of opioids like methadone.

About the *Patient Instructions Handout*

To assist healthcare providers in their vital patient education responsibilities, *Pain Treatment Topics* developed the special “Patient Instructions” handout, in English and Spanish and attached on the last 4 pages. This can be reproduced and given to patients at the time methadone analgesia is prescribed (*see permission to reproduce the handout below*). Ideally, the handout also would be used as a discussion guide for face-to-face education of patients – and their families or caretakers – and a notation of this education might be made in the patient’s record.

Development of the handout was based on the literature cited in this overview and the reviews of *Pain Treatment Topics* clinical medicine advisors. The emphasis is on **safety**, to help prevent misuse and avoid adverse events potentially associated with methadone (Fishman et al. 2002; Patient Ed 2006).

The handout does not necessarily include *all* information in the methadone package insert or that might be provided by medical staff, and it is not intended to take the place of such guidance. However, unlike traditional communications of this sort, the handout stresses several points that often are overlooked:

- Patients (along with their families or caretakers) must be specifically cautioned that methadone can be lethal if it is misused.
- Methadone is unlike other opioid medications, and absolute compliance with the prescribed regimen is essential; unauthorized extra doses should *never* be taken.
- Patients must keep careful track of when they take methadone, enlisting the help of others in this if necessary.
- Patients need to understand the importance of reporting all substances that they are using – medications, drugstore products, alcohol, or other drugs – and that unauthorized use of these with methadone can be harmful or even fatal.
- Methadone must be safeguarded from pilferage and illicit use by others. It should not be casually stored as many other medications might be.
- Family members or caretakers must know of methadone overdose warning signs and be instructed to immediately seek emergency help if any occur.
- Patients’ fears of true addiction to methadone should be dispelled. Along with that, they must be cautioned against reducing methadone dosing on their own.

The handout provides more detail regarding these essential messages and very specific recommendations. It is hoped that healthcare providers will take the extra time necessary for communicating such information and instructions that can help promote the effective and safe use of methadone analgesia. The old adage, “Better to be safe than sorry,” was never more appropriate.

Patient Instructions

Safely Taking Methadone for Pain

Please read this handout carefully and share it with family members or caretakers. It does not take the place of your healthcare provider's guidance or the medicine package insert.

Your healthcare provider has prescribed methadone to help control pain. Methadone (meth-uh-done) is a strong pain reliever that has been used successfully for more than 60 years in millions of persons worldwide. It is a man-made, or synthetic, opioid (oh-pee-oid) drug with actions similar to natural opioids like morphine or codeine that come from the opium poppy; except, methadone is more potent.

Methadone is a very effective and economical medication. When used properly, it can help safely relieve pain even when other medications fail. However, since it is a long-acting and powerful drug, its improper use or abuse can be harmful and even fatal (causing death). Therefore, it is very important that you read, understand, and follow all of the safety instructions below.

- Always take methadone exactly as directed.
- Taking extra methadone or combining it with other drugs, alcohol, or over-the-counter products, unless approved by your healthcare provider, can be harmful or fatal.
- Make sure the methadone prescriber knows of all healthcare products and drugs (prescribed or not) that you are using and your complete medical history.
- You must take only the prescribed amount of methadone and at the specified time intervals, such as every 6 or 8 hours (that is 4 or 3 times per day).
- If you were told to split methadone tablets for the proper dose, ask your healthcare provider or pharmacist how to do that accurately.
- Methadone builds up in the body over time, often taking a week or longer to achieve full effect. During that time, pain relief may be incomplete. However, unless told to do so by your healthcare provider, never take extra methadone doses or other pain relievers, as this could be harmful or fatal.
- If you forget to take your usual methadone dose on time, you can take it very soon thereafter. Otherwise, wait until it is time for the next dose and take only that. Do not take extra methadone to make up for what was missed.
- To help avoid missing doses or taking extra ones, use a dosing chart or medication log to keep track of when you take each dose of methadone.
- If you are forgetful, have someone else give you each dose of methadone and keep a record of it.
- Do not take methadone with grapefruit or grapefruit juice. It can block digestion of methadone, causing a harmful excessive amount to accumulate.
- Tell all of your healthcare providers that you are taking methadone. Unless they know of this, they might prescribe medications that alter methadone's effects. They should contact the methadone prescriber if there are questions.

Taking extra methadone, more often, or with other drugs or alcohol can be harmful or even fatal.

Keep careful track of when you take your methadone.

The handout may be freely reproduced and distributed to all patients prescribed methadone.

It is hoped that healthcare providers will take the extra time to convey necessary safety information and instructions to patients.

Permission to reproduce the “Patient Instructions” handout – In the interest of open access for the benefit of patient care, the *Patient Instructions* handout for methadone analgesia safety that follows, in English and Spanish, may be freely reproduced and distributed, provided the copyright notice is maintained. It may *not* be distributed in any way for which there is a cost for the handout to the recipient without prior notice to and approval of *Pain Treatment Topics*. If a customized version of this handout is created, and the contents are significantly modified from the original, the copyright recognition notice should be removed.

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Stewart B. Leavitt, MA, PhD, is the Publisher/Editor-in-Chief of *Pain Treatment Topics* and has served as the Editor of *Addiction Treatment Forum* since its founding in 1992. During that time he has extensively researched and written on methadone in the treatment of opioid addiction and for analgesia. He has served as a consultant to the U.S. Center for Substance Abuse Treatment and was researcher/writer for the landmark reports on methadone-associated mortality issued by CSAT in 2004 (and referenced below). Dr. Leavitt also has served as an officer in the US Public Health Service, stationed at the National Institutes of Health, and has more than 25 years experience as a medical researcher/writer.

Medical reviewers:

The qualifications of *Pain Treatment Topics* medical advisors/reviewers for this document may be viewed at:

http://www.pain-topics.com/contacts_aboutus/index.php.

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Release Date: October 2006. Modified November 2006 to include the handout for patients in Spanish.

See the *Patient Instructions* handouts attached on the next 4 pages.



IMPORTANT UPDATE NOTE:

In late November 2006, the Food & Drug Administration (FDA) announced that it had approved new prescribing information for methadone products approved for pain control, based on a review of the scientific literature.

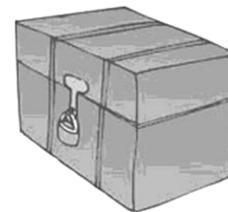
Accordingly, a revised package insert (PI, October 2006) for methadone tablets, including patient information, was released and is available at Pain-Topics.com for download (136KB, 21 pages):

http://www.pain-topics.com/pdf/MethadoneTabs_PI_Oct2006.pdf.

Pain Treatment Topics documents -- including this "Methadone Safety Overview," the "Patient Instructions Handouts," and the other documents linked in this Overview -- were developed prior to release of the revised methadone PI. However, they all have been reviewed and found to be in compliance and consistent with FDA-approved findings and recommendations.

❑ Store methadone safely.

- ❑ Methadone *absolutely must be kept in a safe place* where others – children or adults – cannot gain access to it. A single tablet of methadone can be harmful, or even fatal, in an individual who is not used to the medication.
- ❑ Do not keep methadone on kitchen counters, in bathroom cabinets, or other obvious places. If necessary, store methadone in a locked box or cabinet and in an out of the way location.
- ❑ Remember, persons you may least suspect, family members or visitors, might look for drugs like methadone to use for illegal purposes.
- ❑ Never share your methadone with anyone else, since it could do them great harm.



❑ What are methadone side effects to watch for?

- ❑ Alert your family members or caretakers of **important warning signs** to watch for that may indicate you are reacting badly to methadone and are in distress. If you experience any of the following, they should call for emergency help:
 - Trouble staying awake. ■ Difficult or slow breathing.
 - Loud or unusual snoring at night and difficulty being awakened.
 - Fast heartbeat, unusual dizziness, or loss of consciousness (fainting).
- ❑ Methadone, like all other opioids, may cause constipation. Your healthcare provider or pharmacist can recommend approaches for preventing or treating this. Reducing the methadone dose will *not* help.
- ❑ Certain side effects, if they occur at all, usually become milder or go away with time, such as a lightheaded feeling, nausea, stomach upset, or mild drowsiness. Possible others may be more long-lasting, including: itching, dry mouth, flushing, or increased sweating. Contact your healthcare provider if any of these continue or worsen.
- ❑ Uncommon side effects include confusion, mood changes (depression or agitation), shaking, blurred vision, or difficulty urinating. If you experience any of these, tell your healthcare provider.
- ❑ Allergic reactions to methadone – including rash, hives, or swelling – are rare but require prompt medical attention.
- ❑ You should refrain from driving and other activities requiring balance or focused concentration until the effects of methadone are known, typically a week or longer.



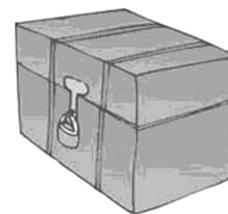
❑ Will you become dependent on or addicted to methadone?

- ❑ After awhile, methadone causes *physical dependence*. That is, if you suddenly stop the medication you may experience uncomfortable withdrawal symptoms, such as diarrhea, body aches, weakness, restlessness, anxiety, loss of appetite, and other ill feelings. These may take several days to develop.
- ❑ This is not the same as *addiction*, a disease involving craving for the drug, loss of control over taking it or compulsive use, and using it despite harm. Addiction to methadone in persons without a recent history of alcohol or drug problems is rare.
- ❑ If you ever want to stop taking methadone, do not do so on your own. Gradually reducing the methadone dose as directed by your healthcare provider will help prevent uncomfortable withdrawal reactions.

Do not reduce or stop taking methadone on your own.

Guarde la metadona en un lugar seguro.

- La metadona *debe guardarse en un lugar absolutamente seguro* al que las demás personas, tanto niños como adultos, no puedan tener acceso. Una sola tableta de metadona puede ser perjudicial, e incluso mortal, en un individuo que no esté habituado al medicamento.
- No guarde la metadona en los armarios de la cocina, del baño, ni en otros lugares fácilmente accesibles. Si es necesario, guarde la metadona en una caja o gabinete con llave y en un lugar fuera de alcance.
- Recuerde, las personas de las que menos lo pueda esperar, miembros de la familia o visitas, podrían buscar fármacos como metadona para usar con fines ilegales.
- Nunca comparta su metadona con los demás, ya que podría causarles un gran daño.



¿Cuáles son los efectos secundarios de la metadona a los que debería prestar atención?

- Alerta a los miembros de su familia o cuidadores sobre los **síntomas importantes** a los que deben estar atentos, ya que pueden indicar que usted está reaccionando mal a la metadona y que está en peligro. Si sufre alguno de los siguientes efectos, las personas que estén a su alrededor deberían llamar para pedir ayuda de emergencia:
 - Dificultad para mantenerse despierto. ■ Dificultad para respirar o respiración lenta.
 - Ronquido fuerte o inusual por las noches y dificultad para despertarse.
 - Ritmo cardíaco rápido, mareos inusuales, o pérdida de la conciencia (desmayos).
- La metadona, como todos los demás opioides, puede causar estreñimiento. Su profesional de la salud o farmacéutico puede recomendar formas de prevenirlo o de tratarlo. El reducir la dosis de metadona *no dará resultados*.
- Algunos efectos secundarios, en caso de ocurrir, a menudo se vuelven más leves o desaparecen con el tiempo como los mareos, náuseas, malestar estomacal o somnolencia. Otros posibles efectos secundarios pueden durar más, incluyendo: comezón, sequedad bucal, enrojecimientos o aumento de la transpiración. Póngase en contacto con su profesional de la salud si alguno de estos efectos continúa o empeora.
- Los efectos secundarios anormales pueden incluir confusión, cambios de humor (depresión o agitación), temblores, visión borrosa o dificultad para orinar. Si sufre alguno de estos efectos, dígaselo a su profesional de la salud.
- Las reacciones alérgicas a la metadona, incluyendo erupciones, urticaria o hinchazón, son poco frecuentes, pero requieren de atención médica inmediata.
- Debería evitar conducir y otras actividades que requieren equilibrio o demasiada concentración hasta familiarizarse con los efectos de la metadona; generalmente una semana o más.



¿Se volverá dependiente o adicto a la metadona?

- Después de un tiempo, la metadona provoca *dependencia física*. Es decir, si usted deja de tomar el medicamento en forma repentina, puede sufrir síntomas molestos del síndrome de abstinencia, como diarrea, dolor en el cuerpo, debilidad, inquietud, ansiedad, pérdida del apetito y otras sensaciones de malestar. Estas sensaciones pueden demorar varios días en aparecer.
- Esto no es lo mismo que *adicción*, una enfermedad que implica un ansia por el fármaco, la pérdida de control al tomarlo o el uso compulsivo, y el uso a pesar del daño. La adicción a la metadona en personas sin antecedentes recientes de problemas de alcohol o drogas es muy poco común.
- Si alguna vez desea dejar de tomar metadona, no lo haga por su cuenta. La reducción gradual de la dosis de metadona según se lo indique su profesional de la salud lo ayudará a evitar reacciones incómodas por la abstinencia.

No reduzca ni suspenda la metadona por su cuenta.