

e-Briefing

Access to Clinical News, Information, Research, and Education

In This Issue

- From Editor... News Reports, FDA Advisory Should Not Deter Use of Methadone 1
- Discard “Dependence”; Get Serious About “Addiction” 3
- Methadone Safety Stressed by FDA; Report from *Pain Treatment Topics* Provides Clinical Guidance 5
- Conversion Ratios for Rotation from Methadone to Other Opioids.. 10
- Pain & Addiction: Common Threads ...Seminar Notes 11
- Events Calendar 13
- Pain-Topics.com Launches Pain-Art Gallery 14

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From Editor...

News Reports, FDA Advisory Should Not Deter Use of Methadone

In their late-November 2006 advisory on methadone, the U.S. Food and Drug Administration used the dramatic headline: “Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat.” As it was no doubt intended to do, this sounded an alarm throughout the pain management community; however, it is hoped this will not inspire an overreaction that deters the continued use of this very effective analgesic.

Concerns Were Well Known

Cases of potentially hazardous methadone side effects have been extensively reported through the years and should be well known. In fact, ever since methadone’s development in the late 1930s there have been concerns about misprescribing or inappropriate use of methadone leading to sometimes fatal respiratory depression. More recently, there have been reports of methadone cardiotoxicity fostering arrhythmias in a relatively small number of patients.

The news media have reported increases in methadone-related deaths, including among patients who allegedly adhered to the prescribed therapeutic regimen. However, it is difficult, if not impossible, to know for certain in such cases if the patients were indeed compliant with the prescribed methadone dosing schedule, were taking unauthorized medications on the side, or if other factors came into play that unexpectedly and suddenly altered methadone serum levels.

(Continued on page 2)

It is often difficult, if not impossible, to know the exact causes of fatalities allegedly related to methadone.

(From Editor... continued from page 1)

Still, this is not to minimize the tragedy of these deaths. And, it must be conceded that the methadone prescribing information in the package insert (PI) was somewhat vague and could be interpreted as allowing hazardous methadone analgesia startup doses of up to 80 mg per day in opioid naïve patients. No doubt, the news reports and the previously known inadequacies of dosing instructions spurred the FDA into action.

Pain Treatment Topics Was Proactive

Since the beginning of the Pain-Topics.com website last January, well in advance of the FDA initiatives, we have posted evidence-based reports on using methadone more safely. Topics include: preventing methadone-drug interactions, proper methadone analgesia dosing, and managing arrhythmia concerns with methadone, among others. These were brought together last October in our “Methadone Analgesia Safety Overview” report, which also included a first-of-its-kind “Patient Instructions Handout” in English and Spanish (see article on page 5 in this e-Briefing).

Those documents have been reviewed and found to be in accordance with the new FDA-approved methadone-safety guidance. In fact, our documents go a step further by providing citations of the scientific-evidence sources behind our recommendations.

Although the FDA notes that “information in the new prescribing information is based on a review of the scientific literature,” the PI contains no references and prescribers cannot determine how current, complete, or accurate the information might be. In fact, some of the information appears to be incomplete and dosing recommendations, either for startup or transitioning from another opioid to methadone, still seem subject to interpretation and clinical judgment.

Therefore, the *Pain Treatment Topics* reports can be consulted for added understandings of the safety issues in question, and for helpful guidance in instructing patients on properly using methadone. As always, we will be updating those documents as new information becomes available, and feedback from readers is welcome.

New Feature Targets Miscommunication in the Pain Field

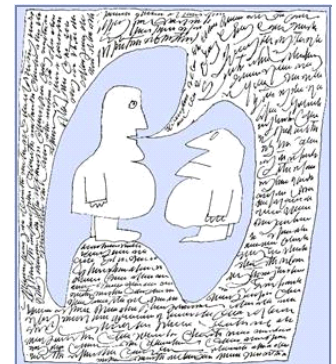
In this edition of the e-Briefing we introduce a new feature called “Language Matters” (see page 3). Its purpose is to explore how the terminology used during clinical interactions in the pain field affects perceptions that ultimately influence the quality of patient care.

First, we consider an important discussion that appeared in the *American Journal of Psychiatry* on differences between opioid “addiction” and “dependence,” a subject that still seems to confuse many in the field. In a future edition we will explain why such terms as “narcotic” and “detox,” while ubiquitous, serve to stigmatize patients and lead to the mistreatment of their pain conditions. We also will explore how opioid-use problems have been mischaracterized due to poorly defined clinical terminology, leading to faulty reporting of problem prevalence and the inappropriate treatment of patients with pain.

Be sure to register for e-Notifications of when Pain-Topics.com is updated to be informed via e-mail about e-Briefing newsletter publication. Go to: <http://www.pain-topics.com/register.php>.

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***Pain-Topics.com
reports can be
consulted for added
understandings of
the safety issues in
question, and for
helpful guidance in
instructing patients
on properly using
methadone.***



Discard “Dependence”; Get Serious About “Addiction”

The chart reads, “Pain persists and the patient has become dependent on morphine.” What does that mean, and how might it affect continued prescribing of opioid analgesia?

“Dependence” has multiple connotations and despite all that has been written and said there is still confusion among healthcare providers. In particular, misinterpretations of “dependence” versus “addiction” have served as barriers to the effective treatment of pain.

“Dependence” a Serious Mistake

Last May, the *American Journal of Psychiatry* featured an editorial providing an important clarification of these terms and how “dependence” came to be used instead of “addiction” in the first place (O’Brien et al. 2006). The authors observed that much of the confusion stems from definitions developed for the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, a widely used and authoritative reference from the American Psychiatric Association (APA 2000).

Among committee members responsible for developing that reference, starting with the 3rd edition (*DSM-III*), there was general agreement in defining addiction as a psychiatric diagnosis; however, there was disagreement about the label to use (O’Brien et al. 2006). Proponents of the term “addiction” believed it would convey the appropriate meaning of a compulsive drug-taking condition and would distinguish it from *physical dependence* (referring to adaptations resulting in drug tolerance, and in withdrawal symptoms when certain drugs are discontinued).

Those who favored the term “dependence” in lieu of addiction felt that it was a more neutral term. They argued that “addiction” was pejorative and would add to the stigmatization of people with substance-use disorders. During a final poll, the word “dependence” won over “addiction” by merely one vote. The editorialists note, “Experience over the past two decades has demonstrated that this decision was a serious mistake” (O’Brien et al. 2006).

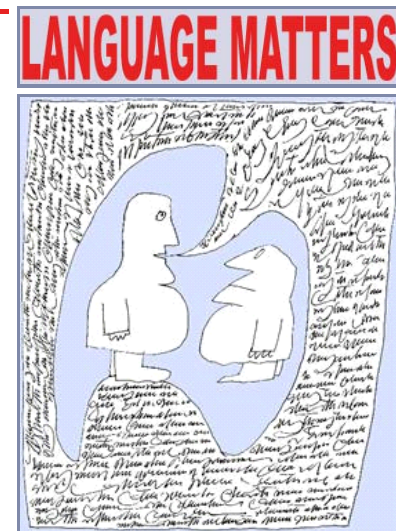
Dependence Not Necessarily Addiction

In the latest edition of the *DSM* (APA 2000, *DSM-IV-TR*) the word “addiction” is nowhere to be found, and “substance dependence” is used instead. Yet, within that diagnosis, “physiological dependence” – encompassing drug tolerance and withdrawal – represents 2 of 7 criteria for substance dependence. Confusing matters further, the *DSM* notes that substance dependence can occur with or without physiological dependence.

Physiological dependence would be an expected and natural effect of all opioids. When healthcare providers perfunctorily note that a patient is dependent on opioids, it could be interpreted as physiological dependence or substance dependence. Just as confusing, “addiction” might be casually used, when physiologic dependence (tolerance, withdrawal) is intended.

Addiction is a Psychiatric Diagnosis

“Addiction” is most properly synonymous with “substance dependence”; however, a full understanding of its ramifications is often lacking. Addiction has been defined as a “primary, chronic, neurobiological *disease*, with genetic, psychosocial, and environmental factors influencing its development and manifestations.” It is a serious psychiatric diagnosis, characterized by behaviors that may include impaired control over drug use, compulsive use, continued use despite severe harms, and/or craving for the drug (APA 2000, Consensus 2001). A thorough patient history and careful clinical evaluation are required to accurately determine this diagnosis.



Experience has demonstrated that the decision to use “dependence” rather than “addiction” was a serious mistake



Last May, the American Journal of Psychiatry featured an editorial providing an important glimpse into the tenuous circumstances under which “dependence” came to be used instead of “addiction” in the first place.

(Continued on page 4)

(Language Matters... continued from page 3)

Like many disease states, it takes time for addiction to develop. Persons administered opioids short-term would be highly unlikely to develop *de novo* addiction as a result; although, this does not rule out possible exacerbation of a prior addictive disorder that is in remission. Even chronically administered opioid analgesics would not be expected to engender the psychiatric disease state of addiction, unless there also were predisposing factors.

Misunderstandings Harm Patients

Misunderstandings of “dependence” can have serious consequences. As O’Brien and colleagues (2006) note in their editorial, practitioners (and their patients) who encounter evidence of opioid tolerance and withdrawal symptoms (dependence) often assume this means addiction, and patients are sometimes denied the additional pain medication that they need. Similarly, pain patients who would benefit from opioid medications may forgo proper treatment because they fear dependence, which they equate with addiction.

The authors further suggest that the medical world drastically needs a change. “Addiction is a perfectly acceptable word,” they write. “It is clear that any harm that might occur because of the pejorative connotation of the word ‘addiction’ would be completely outweighed by the tremendous harm that is now being done to the patients who have had needed medication withheld because their doctors believe that they are addicted simply because they are dependent.”

Discard “Dependence”; Return to Common Sense

It would serve all concerned much better if “dependence” as synonymous with addiction were struck from medical lexicon; although, not everyone agrees. A letter in response to the editorial argued that, “‘addiction’ is unscientific, overused, misunderstood (e.g., addicted to my cellphone), and clinically inaccurate (e.g., addicting antidepressants)” (Erickson and Wilcox 2006). They claim that, in common use, “addiction” is highly stigmatized and does not differentiate between the medical (brain) disease, with over-involvement in drugs (substance abuse), or obsessions with everyday activities.

The correspondents concede that the term “physiological dependence” is unhelpful, outmoded, and should be phased out. Still, they assert that “dependence” is still valid with regard to addiction, provided a qualifier is used – such as “*chemical* dependence” – and it is understood that this refers to an adapted disease state (Erickson and Wilcox 2006).

However, this offers no real improvement over the current *DSM* label of “substance dependence.” And, it does not overcome the need for better education in understanding and properly diagnosing the psychiatric disease state better known as “addiction.” It is hoped that a revised edition of the *DSM* currently in development (*DSM-V*) will discard “dependence” and return to a more sensible approach that will foster better understanding and improved patient care.

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Opioid tolerance and withdrawal – physiological dependence – are often assumed to denote addiction, and patients are sometimes denied the additional pain medication that they need.

It is hoped that a revised edition of the DSM will discard “dependence” and return to a more sensible approach that will foster better understanding and improved patient care, rather than further confuse practitioners and patients.

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[December 4, 2006]*

Pain-Topics Methadone Update

Methadone Safety Stressed by FDA; Report from *Pain Treatment Topics* Provides Clinical Guidance



In a public health advisory on November 27, 2006, the U.S. Food and Drug Administration (FDA 2006) notified healthcare professionals of reports of death and life-threatening side effects in patients taking methadone. These occurred in patients newly starting methadone for pain control and in patients who switched to methadone after being treated for pain with other strong opioid pain relievers.

The adverse events are the possible result of unintentional methadone overdoses, drug interactions, and methadone's alleged cardiac toxicities (QT prolongation and Torsades de Pointes). The FDA emphasized the importance of knowing methadone's toxicities and unique pharmacologic properties, including dosing and monitoring recommendations. Along with its advisory, the FDA released revised prescribing information (PI) for 5 mg and 10 mg methadone tablets (Roxane 2006; **also see the end of this article for access link to the PI**).



Methadone Safe When Properly Prescribed

During the more than 60 years since its development, millions of patients have been successfully and safely treated daily with methadone. Yet, reports of methadone-associated overdoses and fatalities have caused apprehension among healthcare providers and patients alike.

However, 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 analgesia, 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)

In advance of the FDA advisory, *Pain Treatment Topics* issued a “Methadone Analgesia Safety Overview & Patient Instructions Handout” (Leavitt 2006a; **see access link at the end of this article**). This 16-page *Overview* document provides essential background information and serves as a gateway to the several evidence-based documents created by *Pain Treatment Topics* that can guide healthcare providers in more safely and effectively prescribing methadone analgesia. A special handout for patients and their families or caretakers (at the end of the *Overview*, and in English and Spanish) offers vital instructions for treatment compliance and safety. Following are some important highlights from the *Overview*.

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). 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.

Recent cautions aside, millions of patients have been successfully and safely treated with methadone during more than 60 years.



(Continued on page 6)

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

According to the FDA advisory (FDA 2006), pain relief from a dose of methadone lasts about 4 to 8 hours; however methadone stays in the body much longer – from 8 to 59 hours after it is taken. Other sources have noted that methadone's 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 average half-life of methadone analgesia ranges from 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; Lugo et al. 2005; see **Graph**). After each dose increase, another period of days is required to again reach steady state.

Cautious Methadone Dosing Needed

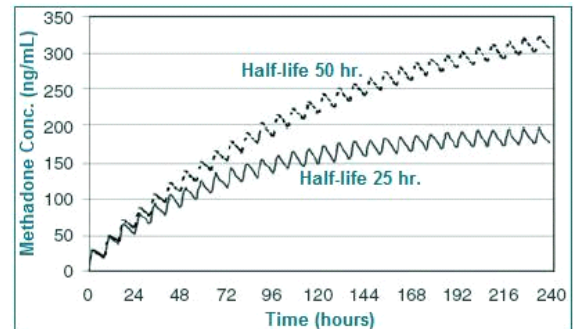
As a result of methadone's pharmacokinetics, the FDA notes that patients may feel the need for more pain relief before methadone is gone from the body. Consequently, methadone may build up to toxic levels if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements (FDA 2006).

The general dosing rule with methadone is *to start low, go slow, and titrate gradually to effect* (CPSO 2004; Toombs 2006). Prior to the latest PI revision (Roxane 2006), the manufacturer-recommended adult dosage for methadone analgesia was 2.5 mg to 10 mg every 3 or 4 hours as necessary (Mallinckrodt 1995; Roxane 2000); however, this could result in startup analgesic doses ranging up to 80 mg/day that are excessive and potentially lethal unless opioid tolerance is already well-established in the patient (Ettinger et al. 1979; Leavitt 2006a).

The revised FDA-approved PI (Roxane 2006) recommends a usual oral methadone analgesia starting dose in opioid-naïve patients of 2.5 mg to 10 mg every 8 to 12 hours, slowly titrated to effect. It is further noted that “more frequent administration may be required during methadone initiation in order to maintain adequate analgesia, and extreme caution is necessary to avoid over dosage, taking into account methadone's long elimination half-life.”

However, the revised PI also notes a number of caveats for consideration, such as the patient's age, medical status, concurrent medications, and other factors. In some patients the recommended 30 mg (10 mg x 3) maximum first-day dosing of oral methadone analgesia could be overly aggressive and more conservative approaches might be appropriate (see Toombs 2006).

When transitioning to methadone from a different opioid, the revised PI (Roxane 2006) notes, as have others (CPSO 2004; Leavitt 2006a; Toombs 2006), that standard “equivalency tables” for calculating methadone dose can be unreliable. It is important to consider that, in converting to methadone from morphine or morphine-equivalent dose, methadone dose determination does not



Even at a constant dose, methadone accumulates during a number of days until a steady state level is achieved. Variable half-life affects time to steady state and methadone level.
(Adapted from Lugo et al. 2005.)

Changes to the recommended startup dosing for methadone analgesia in the revised PI are significant.

(Continued on page 7)

(Methadone Safety... continued from page 6)

follow a linear trend as doses increase. The revised PI includes a conversion table illustrating the concept, with the caveat that “methadone dosing should not be based solely on [the table].” A more convenient and appropriately conservative scheme that is consistent with FDA recommendations for calculating methadone dosing is presented in Toombs (2006).

Avoiding Methadone-Drug Interactions

The FDA advisory mentions the potential for other substances – medications, supplements, etc. – to interact harmfully with methadone (FDA 2006), and the revised PI (Roxane 2006) notes that methadone is metabolized to inactive forms via cytochrome P450 (CYP450) enzymes. The most important enzymes in methadone metabolism are CYP3A4 and CYP2B6 (Leavitt 2006a, 2006b); although, others may play secondary roles.

Drugs that induce CYP enzymes responsible for methadone metabolism and elimination may lower methadone blood levels. Conversely, inhibition of those enzymes could serve to increase methadone concentrations, possibly to toxic levels (Brown et al. 2004; Eap et al. 2002; Lugo et al. 2005).

Healthcare providers should be aware of potential interactions with methadone and the agents that might cause them. The revised PI lists some of the more prominent methadone-drug interactions reported in the literature, although that discussion might not be considered all inclusive. (See Leavitt 2006b for more extensive methadone-drug interaction tables.)

Cardiac Considerations and Precautions

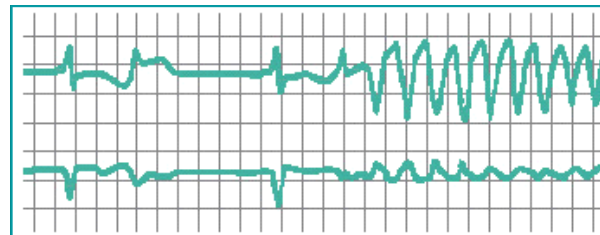
The FDA advisory (FDA 2006) stressed concerns about methadone’s purported cardiotoxic effects, and a black box warning in the revised PI (Roxane 2006) notes that cases of QT prolongation and serious arrhythmia (torsade de pointes) have been observed during methadone therapy.

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

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 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).

Equianalgesic dosing tables should be used cautiously when calculating methadone dosing.



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

Current evidence does not support requiring ECGs for all patients or discontinuing the use of methadone.

(Continued on page 8)

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/or understand. So, these are of limited help in fostering patient compliance.

To assist healthcare providers in their vital patient education responsibilities, *Pain Treatment Topics* developed a special “Patient Instructions” handout, in English and Spanish, which is attached to the “Methadone Analgesia Safety Overview” document (Leavitt 2006a). This can be reproduced and given to patients at the time methadone analgesia is prescribed. 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.

The emphasis in the handout is on *safety*, and it does not necessarily include *all* information in the methadone package insert or that might be provided by medical staff. 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 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 becoming “addicted” to methadone should be dispelled. Along with that, they must be cautioned against reducing methadone dosing on their own.

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.

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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 methadone package insert.

Your healthcare provider has prescribed methadone to help control pain. Methadone (methyadone) is a strong pain reliever that has been used successfully for more than 40 years in millions of persons worldwide. It is a man-made, or synthetic, opioid (opiate-type) drug with actions similar to natural opiates 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.

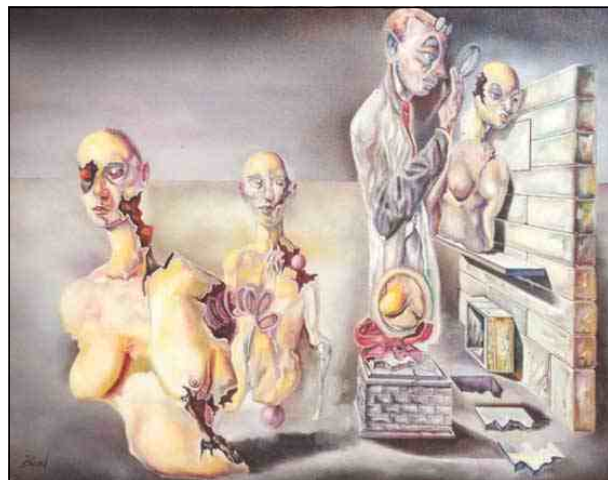
Keep careful track of when you take your methadone.

The Patient Instructions handout may be freely reproduced by healthcare providers and distributed to all patients who are prescribed methadone analgesia.

(Continued on page 9)

(Methadone Safety... continued from page 8)

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*Broken People by Robert S. Beal.
See back page for news of the
Pain-Topics.com "Pain Art" Gallery.*

Researcher/Writer: Stewart B. Leavitt, MA, PhD [December 1, 2006]

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Methadone Analgesia Safety Overview & Patient Instructions Handout

By: Stewart B. Leavitt, MA, PhD, released in October 2006, updated November 28, 2006.



PDF at: http://www.pain-topics.com/pdf/Methadone_Safety_Overview&Handout.pdf (1.2 MB; 16 pp)

Note: All *Pain Treatment Topics* methadone-related documents linked in this report have been reviewed and found in compliance and consistent with FDA-approved recommendations and the revised methadone PI.

Revised Methadone 5 mg and 10 mg Tablets Prescribing Information (PI)

Revised October 2006, released November 27, 2006.



PDF at: http://www.pain-topics.com/pdf/MethadoneTabs_PI_Oct2006.pdf (136 KB; 21 pp)

Conversion Ratios for Rotation from Methadone to Other Opioids

Despite the many advantages of methadone analgesia, in certain cases it may be desirable to rotate patients from methadone to another opioid. However, there have been few clinical studies in this area, so definitive guidance is lacking when it comes to making the transition. However, recently reported research suggests that oral methadone is nearly 5 times more potent than the oral morphine equivalent, and IV methadone may be 13.5 times more potent than oral morphine.

At the 2006 annual meeting of the American Society of Clinical Oncology, researchers from the University of Texas M.D. Anderson Cancer Center in Houston presented preliminary conversion ratios for switching from oral or intravenous methadone to an oral morphine equivalent, and their results also were subsequently published in the *Journal of Clinical Oncology* (Walker et al. 2006). A supplemental report appeared in *Pain Medicine News* (Sheiszer 2006).

The investigators conducted retrospective records reviews of 29 qualifying patients (10 female, mean age 48) who had received methadone for at least 3 days before being switched to another opioid, and then reached a stabilized dose of the alternate opioid(s) for a period of 7 days following conversion. A stable dose was defined as $\leq 30\%$ change in opioid dose from one day to the next. Doses of methadone and opioids other than morphine were converted to morphine-equivalent daily doses (MEDD) using standard equianalgesic tables [the exact tables used were unspecified].

There was nearly a 3-fold difference in analgesic potency between oral and IV methadone, and IV methadone was found to be many times more potent than the oral morphine equivalent (see **Table**). Along with that, the mean time period for achieving a stable dose of opioid analgesic converted from IV methadone was very similar to that for oral methadone.

Switching patients with difficult-to-manage pain syndromes from methadone to another opioid may not be as difficult as previous literature has suggested.

Methadone to Oral Morphine-Equivalent Daily Dose Conversion

	Oral Methadone to Oral MEDD	IV Methadone to Oral MEDD
Estimated conversion ratio (95% CL)	1:4.7 (3.0 - 6.5) mg/d	1:13.5 (6.6 - 20.5) mg/d
Days to achieving stable MEDD (mean \pm SD)	2.6 \pm 0.3 days	2.5 \pm 0.2 days
MEDD = Morphine-Equivalent Daily Dose; CL = Confidence Limit; SD = Standard Deviation. <i>Data from Walker et al. 2006.</i>		

The authors propose that these findings seem to indicate that successfully switching patients with difficult-to-manage pain syndromes from methadone to another opioid analgesic may not be as difficult as previous literature on the subject has suggested. However, it should be noted that this was a small retrospective study, with consequently wide confidence limits for the conversion ratios. Therefore, clinical discretion would be advised in applying these data in everyday practice until more extensive research is conducted and reported.

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*Pain-Topics Researcher/Writer:
Stewart B. Leavitt, MA, PhD
[December 6, 2006]*

Pain & Addiction: Common Threads ...Seminar Notes

Late last October, the American Society of Addiction Medicine (ASAM) launched the 7th generation of its popular 1-day seminar, "Pain & Addiction: Common Threads." A new faculty of 11 presenters, led by co-chairs Donald Kurth, MD, and Herbert Malinoff, MD, conducted an intensive program attended by about 125 healthcare professionals. Following are notes from the day's lectures and case studies.

Doing Opioid Analgesia "Right"

Jennifer Schneider, MD, a pain practitioner from Arizona, discussed opioid therapy for chronic pain, which might be defined as pain that no longer serves as a physiological warning sign and persists for 3 to 6 months or longer. It is a multifaceted experience, also negatively affecting emotions, thinking, memory, and other aspects of functioning.

Chronic pain management includes using medications to decrease pain and increase function. However, medications are but one part of an overall approach, which may also include physical therapy, acupuncture, massage, hypnosis, and other modalities.

Schneider observed that there are many barriers to the use of opioid analgesics. Prescribers may be concerned about: opioid toxicity; causing or worsening addiction; being "scammed" by patients; or regulatory agency scrutiny. Similarly, patients may fear opioid side effects and the possibility of addiction (or addiction relapse). However, she noted, in persons with a history of substance abuse or addiction, undertreated pain itself poses a risk of drug relapse.

Tolerance to the pain-relieving effect of opioid analgesics is uncommon, she said. Unless there is a change in underlying disease, many patients continue the same opioid dose for years.

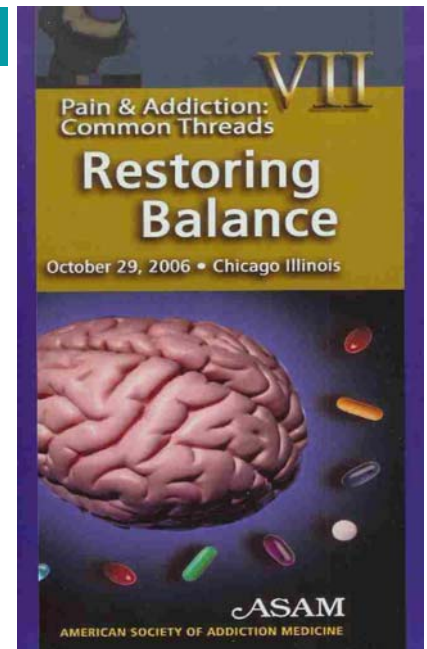
In chronic pain, she suggested that there are several advantages of long-acting opioid analgesics: 1) they are "single entity" without acetaminophen or aspirin to increase their toxicity, 2) they achieve smoother blood levels, providing stable pain relief, 3) a longer duration of action is provided at lower overall doses, and 4) patients may experience better sleep.

Schneider emphasized that opioid analgesic therapy should be initiated with conservative doses and titrated upward appropriately. For breakthrough pain, short-acting opioids can be prescribed as needed. In patients with a history of substance abuse/addiction, Schneider said the research indicates that those without polysubstance abuse, with good family support, and actively participating in recovery groups (e.g., 12-step programs) have better outcomes. She stressed that pain practitioners should provide increased structure and patient monitoring, and encourage the patient's ongoing participation in a recovery program.

Opioids Not Always the Solution

Jianren Mao, MD, PhD, of Harvard University, observed that even after decades of research no new categories of pain relievers have been discovered and opioid analgesics are still very essential. Most opioids, with a few exceptions, do not have a ceiling effect; that is, increasing doses produce greater pain relief without any upper limit. However, Mao proposed that hyperalgesia (increased pain sensitivity) during opioid therapy is possible; therefore, when little additional pain relief is achieved, tapering the opioid dose actually may improve pain control.

However, Edward Covington, MD, with the Cleveland Clinic Foundation, conceded that there are almost no clinical studies of opioid analgesic tapering or weaning strategies. Additionally, few trials report on the benefits of this, so most of what is known is based on "recipe swapping" among healthcare providers.



Chronic pain management includes using medications to decrease pain and increase function.

But medications are one part of an overall approach, which may include physical therapy, acupuncture, massage, hypnosis, and other modalities.

(Continued on page 12)

(Seminar Review... continued from page 11)

Covington agreed with Mao that when opioids no longer provide benefits for a patient – e.g., desired analgesia and functionality improvements – they might be stopped, just as any other drug would be. But he acknowledged that there is no “best way” to wean patients from opioids and, in all cases, withdrawal symptoms should be expected and treated with adjunctive medications.

CPS Conundrum

Throughout the day, much concern was expressed about patients abusing their opioid medications or exhibiting addiction behaviors. This was related to “Chronic Pain Syndrome (CPS)” in which the patient develops a preoccupation with body functioning, a lifestyle centered on seeking pain relief, negative behaviors despite adverse consequences, and psychosocial dysfunctions that the patient blames on pain (e.g., anger, depression, anxiety, social isolation, etc.). Similarities with the signs and symptoms of drug addiction are striking.

While CPS was presented during the lectures and case study discussions as a bona fide diagnosis, there are some concerns. Attendees were cautioned about leaping too quickly to a diagnosis of opioid addiction in patients exhibiting seemingly undesirable behaviors regarding their medication that might be associated with a vague diagnosis of CPS.

In actuality, these patients may be reacting to pain that has been undertreated or mistreated. Rather than CPS or addiction, their perceived aberrant behaviors might reflect patients’ dealings with a healthcare system that has been unresponsive to their needs, resulting in frustration, anger, and behavioral problems.

“Hedonic Tone” Connection

To complete the day, Edwin Salsitz, MD, from Beth Israel Medical Center, New York, presented his interesting concept of the relationship between pain, addiction, and hedonic tone. The term “hedonic” relates to one’s sense of pleasure. Good hedonic tone provides feelings of well being, happiness, and contentment. Conversely, poor hedonic tone deprives the person of a sense of joy, comfort, or satisfaction.

Of importance, anatomical centers of hedonic tone in the human brain encompass both the circuits for pleasure that may drive addiction and those that process and interpret pain sensations – the “mesolimbic” area. Salsitz proposes that some persons have inherently low hedonic tone and they find that certain addictive substances or medications raise the level to where they feel more ‘normal’ or comfortable. At the same time, chronic pain can lower whatever natural hedonic tone the person might have, until their pain becomes a daily struggle with suffering.

For these reasons, treating persons experiencing both addiction and chronic pain can be challenging. Salsitz suggests that the complex actions and interactions of medications used to treat each condition can be difficult to anticipate and manage. Furthermore, the recovery process for both chronic pain and addiction requires attention to psychosocial, spiritual, and other life factors in addition to physical health.

Although this approach proposed by Salsitz is somewhat theoretical and further research would be appropriate there is currently some support in the neurobiological literature. And, it takes into account the necessity of a holistic approach to the care of patients with pain and addiction, which may be more compassionate and effective in the long run.

The next ASAM-sponsored “Pain & Addiction: Common Threads” seminar will be April 26, 2007 in Miami, Florida. For information see <http://www.asam.org>, or call 301-656-3815.



Perceived aberrant behaviors in patients with chronic pain might reflect their dealings with a healthcare system that has been unresponsive to their needs, resulting in frustration, anger, and behavioral problems.

This article was adapted from Leavitt SB. Notes from ASAM's Pain & Addiction Course. Addiction Treatment Forum. 2006;15(4).

EVENTS CALENDAR

For a complete listing of events see: http://www.pain-topics.com/events_calendar/index.php

February 2007

AAPM 23rd Annual Meeting

Sponsor: American Academy of Pain Medicine

February 7-10, 2007

New Orleans, LA

Contact: <http://www.painmed.org/annualmeeting/>

AAHPM and the Hospice and Palliative Nurses Association Annual Assembly

Sponsor: Amer. Acad. Hospice and Palliative Med.

February 14-17, 2007

Salt Lake City, Utah

Contact: <http://www.aahpm.org>

ACP 2007 Annual Meeting

Sponsor: The American College of Psychiatrists

February 21-25, 2007

Palm Springs, CA

Contact: <http://www.acpsych.org>

March 2007

17th Annual HCNE Headache Symposium

Sponsor: Headache Cooperative of New England

March 2-3, 2007

Stowe, VT

Contact: <http://www.hacoop.org>

AHS Winter Headache Symposium

Sponsor: American Headache Society

March 9-11, 2007

Miami, FL

Contact: 856-423-0043; <http://www.ahsnet.org>

Palliative Medicine 2007: The 11th Annual Intl. Symposium

Sponsor: The Cleveland Clinic

March 15-17, 2007

Fort Myers, FL

Contact:

<http://www.clevelandclinicmeded.com/pm2007>

AACN Spring Annual Meeting

Sponsor: Amer. Assn. of Colleges of Nursing

March 17-20, 2007

Washington, DC

Contact:

<http://www.aacn.nche.edu/conferences/confsche.htm>

Hospital & Palliative Care Study Seminar in Britain

Sponsor: Hospice Education Institute

March 18-30, 2007 (13 days)

London, England

Contact: <http://www.hospiceworld.org/>

ELNEC – Pediatric Palliative Care

Sponsor: End of Life Nursing Education Consortium

March 29-31, 2007

Washington, D.C.

Contact: <http://www.aacn.nche.edu/ELNEC>

April 2007

APS Annual Scientific Meeting

Sponsor: Australian Pain Society

April 1-4, 2007

Adelaide, Australia

Contact: <http://www.apsoc.org.au/>

22nd Management and Leadership Conference NHPCO

Sponsor: Natl. Hospice & Palliative Care Org.

April 19-21, 2007

Washington, D.C.

Contact: <http://www.nhpco.org>

ASRA 2007 Annual Pain Medicine Meeting

Sponsor: Amer. Soc. of Reg. Anesth. and Pain Med.

April 19-22, 2007

Vancouver, British Columbia, Canada

Contact: <http://www.asra.com>

BPS Annual Scientific Meeting

Sponsor: British Pain Society (IASP Chapter)

April 24-27, 2007

Glasgow, United Kingdom

Contact: meetings@britishpainsociety.org

<http://www.britishpainsociety.org>

Later 2007

7th Intl. Conference on Pain & Chemical Dependency

Sponsor: IAPCD (Intl. Assoc. for Pain & Chemical Dependency)

June 21-24, 2007

New York City

Contact: 1-800-370-9293 or <http://www.iapcd.com/>

AAPM Annual Clinical Meeting

Sponsor: American Academy of Pain Management

September 27-30, 2007

Las Vegas, Nevada

Contact:

<http://www.aapainmanage.org/conference/Conference.php>

AATOD National Conference

Sponsor: American Association for the Treatment of Opioid Dependence

October 20-24, 2007

San Diego, California

Contact: <http://www.aatod.org>

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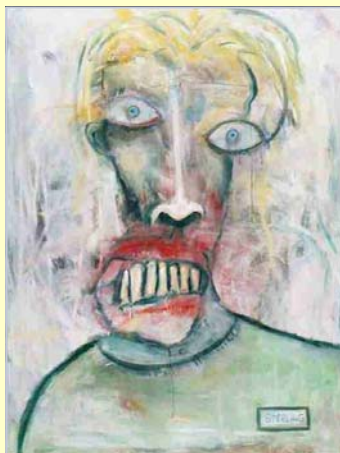
Pain-Topics.com Launches Art Gallery “Portraying the Personal Side of Pain”

Just as pain is a very personal experience, so is its portrayal through creative expression. *Pain Treatment Topics*, in affiliation with the “Chronic Pain Visual Arts Project,” has created a special gallery of artwork developed by patients, depicting a broad and vibrant pallet of pain conditions.

According to these patients, their artistic endeavors have often made them feel more in control of their pain and have lessened their suffering as a result. Healthcare providers can learn much from such works, for they express emotions, thoughts, and perspectives that patients often cannot put into words.

As one patient/artist, Sterling Witt, stated, “Pain is the beginning and the end of every day for me. I have suffered from chronic pain for so long that I cannot imagine life without it anymore. I found myself painting an increasing number of self-portraits, and through them I try to express feelings that cannot be put into words, attempting to explain the torment I am going through.”

“For me, creating art is just something I do to help me survive a life of constant pain. It’s as if the paintings have become a record of my pain, giving a face to an otherwise face-less enemy.”



*Self Portrait, Green Shirt
Sterling Ajay Witt*



*The Despair in Pain
Ariella Yaron*

According to Mark R. Collen, originator of the Chronic Pain Visual Arts Project and the associated PainExhibit.com website, he began this venture in 2001 as a response to years of pain that he had endured himself. His desire to help end the undertreatment of chronic pain, coupled with an understanding of the power of art to educate, were seminal factors in his starting the nonprofit Project.

Pain art has been received from around the world. Although many of the artworks depict great suffering, many also express great hope and faith in a future without pain.

Visit the Pain-Topics.com Art Gallery at:

<http://www.pain-topics.com/gallery.php>

*Patients interested in having their own artwork displayed in the gallery
should send an e-mail inquiry to Info@Pain-Topics.com*