The Evidence Against Methadone as a "Preferred" Analgesic:

A Position Statement from the **American Academy of Pain Medicine**

The use of methadone as an analgesic for severe chronic pain has expanded in recent years. It is effective for some patients, but has unique pharmacologic properties that call for caution and expertise in administering it. Methadone shows up in mortality reports with greater frequency than should be expected given the small number of prescriptions written compared with other opioids. Despite this evidence of risk, most states have designated methadone as a preferred analgesic, presumably because its low cost results in savings for publicly-funded health plans. The American Academy of Pain Medicine (AAPM) takes the position that methadone should not be designated as a preferred analgesic by any insurance payer, whether public or private, unless special medical education is provided. In taking this position, AAPM concurs with the Centers for Disease Control and Prevention (CDC) that methadone should not be considered a drug of first choice for chronic pain and should only be prescribed by health-care professionals experienced in its use who follow consensus, prescribing guidelines. Though methadone is invaluable in the treatment of heroin addiction and also belongs in the armamentarium of pain medications, specific medical education is necessary for prescribing and consuming it safely, and prescriber certification to do so should be considered.

Introduction

Methadone was developed in 1937 as a synthetic opioid analgesic and introduced into the United States in 1947. It has been proven to have a role in the treatment of otherwise refractory chronic pain [Toombs & Kral 2005]; however, its clinical management can be challenging. Several of its unique properties highlight the need for special caution in the use of methadone for chronic pain.[1] Reflecting its relatively long and unpredictable half-life, methadone stays in circulation longer than many other pain medications [US FDA 2006]. Methadone's analgesic benefits last 4 to 8 hours on average; however, methadone

[1] This position paper is focused on the use of methadone for pain relief only. Nothing in this document should be taken to question the value of methadone maintenance as a treatment for opioid addiction, for which there is very strong evidence of effectiveness. Citation: Strang J, Babor T, Caulkins J, Fischer B, Foxcroft D, Humphreys K. Drug policy and the public good: Evidence for effective interventions. Lancet 2012;379(9810):71-83.

can remain in the body much longer: normally, between 8 and 59 hours [US FDA 2006] and even up to 130 hours due to variations in individual metabolism [Eap et al 2002]. Because of this variation, correct individual dosages are difficult to calculate *a prioi*. Furthermore, the waning analgesic effect as it is cleared can tempt users to take more drug than prescribed, increasing the risk for overdose due to the cumulative respiratory-depressant effect. Further risks are posed by a large number of potential drug interactions, some of which are poorly understood [Weschules et al 2008].

Methadone contributes disproportionately to opioid-related deaths. Opioids were involved in 16,651 overdose deaths in 2010, most of them unintentional [Jones et al 2013]. Methadone represents only about 2% of opioid prescriptions written but is associated with one-third of deaths, as reported by the CDC [CDC Vital Signs 2012]. By 2009, methadone-related deaths had risen six-fold over the previous decade. During that same year, nearly 4 million methadone prescriptions were written for pain.

Methadone is less expensive relative to other opioids prescribed for pain (see Table 1)[Consumer Reports 2012], a circumstance that may contribute to its frequent appearance on formularies as a drug of first choice. Payer policies that promote methadone as a preferred treatment option for chronic pain were among the factors identified by an expert panel as potential contributors to methadone mortality when prescribed for pain [Webster et al 2011]. The panel included national pain experts, regulators, health-care policy makers, and epidemiologists. In describing the risk associated with methadone prescribing, the CDC has written that methadone should not be considered a drug of first choice for chronic pain and further proposed that methadone should only be prescribed by health-care professionals experienced in its use who follow consensus prescribing guidelines [CDC MMWR 2012].

States Listing Methadone as "Preferred"

State preferred drug lists (PDLs) are approved by Pharmaceutical and Therapeutics (P & T) Committees to guide the prescribing of and reimbursement for specific prescription name-brand and generic drugs by therapeutic class. In 2003, the Centers for Medicare & Medicaid Services (CMS) first approved PDLs for use when prescribing medications for fee-for-service, publicly-funded, programs, specifically Medicaid [Hinkley & Cauchi 2012]. In general, PDLs divide drugs into two categories: drugs that are *preferred* and drugs that are *non-preferred*. (Some states divide categories of drugs into tiers in order of preference). Preferred drugs have been selected with the goal of delivering clinically appropriate medications in a cost-effective fashion. If a drug does not appear on the preferred list, an extra step such as prior authorization by the state agency or certification by the prescribing physician typically is needed before dispensing through the program can occur. In some states, the same or similar PDLs apply to other types of state-funded health coverage – such as public-employee health plans -- as well as to Medicaid [Hinkley & Cauchi 2012]. In the

state of Washington, the state PDL was compiled with the assistance of the Department of Labor & Industries, which handles workers' compensation, and the Health Care Authority, which oversees state employee benefits [Washington State Social & Health Services 2007]. As the nation increases the number of insured individuals provided through Accountable Care Organizations, this transition to less expensive opioids may increase.

Table 2 shows the 33 states that list some formulation of methadone as a preferred analgesic and the 15 states that do not list it as preferred, including two (West Virginia and Nevada) that designate it as non-preferred and 13 that do not mention methadone. Two states have not published current PDLs.

State policies toward preferred or covered drugs vary. Some states that list methadone as preferred for pain offer several additional options, while others limit preferred medications more strictly. Note that Massachusetts lists methadone as covered, and New Mexico lists it as preferred; however, both states also require a prior authorization to prescribe it (Table 2).

The Risk of Methadone

A risk with methadone is incurred when payers such as Medicaid require methadone to be a preferred therapy for pain. A Pulitzer Prize-winning investigation by *The Seattle Times* detailed the experience of Washington state after listing methadone as a preferred drug in 2004 [Berens & Armstrong 2011]. By 2006, the number of deaths linked to methadone had doubled in the state, mainly concentrated in lower income areas. The newspaper reported that although Medicaid recipients made up only 8 percent of the state's adult population, they accounted for 48 percent of the 2,176 methadone deaths since 2003. After the publication of this series of news articles, state officials in Washington took a number of steps to alert doctors to the special risks of methadone via educational presentations and a public-health advisory [Berens & Armstrong 2012]. Regardless, as of Nov. 1, 2013, generic methadone remained on the state's Medicaid PDL. Washington's Labor & Industries PDL, which lists drugs preferred for workers' compensation benefits, did not include methadone as of July 1, 2013 [Washington State L & I 2013]. As the Affordable Care Act expands the number of people receiving Medicaid benefits, the pressure to reduce health expenditures can be expected to increase as well, along with risk for methadone toxicity if it continues to be categorized as a preferred drug.

The Position of AAPM

AAPM is opposed the use of methadone as a preferred treatment option for chronic pain and calls for manufacturers and payers to underwrite professional educational programs to educate prescribers of opioids on safe practices. A continuing medical education and certification program could serve this purpose with providers demonstrating that they

know how to use methadone and other opioids, and how to counsel patients before prescribing them.

As scientists and specialists dedicated to helping patients with pain and to furthering the practice of pain medicine, AAPM calls for payers, manufacturers and professional medical societies to commit resources nationally to resolving a knowledge deficit in prescribing practices surrounding opioids and methadone in particular. The first step in this commitment is to acknowledge that methadone's unique pharmacologic properties make it risky to prescribe by clinicians without special training. This does not mean that other opioids are without risk and should not be interpreted as such. All opioids demand caution and training in their use for pain, and all opioids can be harmful if abused, misused, or combined with other substances that include but are not limited to other medications that depress the central nervous system, medications to treat anxiety, alcohol, and illegal street drugs.

The goal of AAPM is not to remove methadone from the armamentarium of pain medications. If methadone is chosen to treat chronic pain, all methadone prescribers should complete an education program specific to the medication.

Minimum Methadone Education Program Components

Educational programs to increase safety in the use of opioids for chronic pain, particularly extended-release and long-acting forms and methadone in particular, should include mention of primary problems identified in methadone prescribing. These include [Webster et al 2011; CDC MMWR 2012; Price et al 2014]:

- Initiating methadone at too high a dose
- Inflexibly applying published equianalgesic conversion tables when converting to methadone, thus failing to titrate cautiously according to the individual patient's response
- Underestimating the risk of respiratory depression in patients with prior opioid use
- Titrating too rapidly
- Failing to identify and monitor patients at risk for substance misuse or abuse
- The risk of QT interval prolongation and possible risks with sleep apnea
- Failure to use caution with co-prescribing of benzodiazepines, tricyclic antidepressants, and other sedatives
- Knowledge deficits of common drug-drug interactions

Every provider who prescribes methadone for chronic pain should demonstrate proficiency on the following points [Toombs & Kral 2005; Webster & Dove 2007; Chou et al 2009; Albert et al 2011; CDC MMWR 2012]:

- Be familiar with methadone's unique pharmacology, e.g., long elimination half-life compared to analgesia, before prescribing it
- Use methadone only when pain is severe enough to warrant it and when alternative treatment options are inadequate, and only after conducting a thorough risk-benefit analysis
- Assess patients thoroughly for risk of substance abuse and mental-health comorbidities that could increase the risk of non-adherence to medical direction
- Initiate, titrate, and rotate methadone dose conservatively, even in opioid-tolerant patients, and closely monitor patient response, particularly during dose changes
- Monitor patients for adherence, analgesic response, effect on daily activities, and adverse effects
- In particular, watch for and address aberrant drug-related behaviors and psychosocial issues that could compromise therapy
- Monitor patients for potential cardiac toxicities and possible drug interactions, particularly with other central nervous system depressants, such as benzodiazepines and alcohol
- Counsel patients to adhere strictly to medical direction and never to take an extra dose of methadone without checking with the prescribing clinician
- Prepare an appropriate strategy to taper and discontinue methadone if needed
- Receive information on naloxone kits that may be prescribed along with methadone to reduce overdose deaths

Because of variations in individual patient metabolism, including speed of distribution and vulnerability to respiratory-depressant effects, methadone calls for an individualized approach to prescribing and close monitoring. No physician should prescribe methadone unless specifically trained or advised by an expert in methadone prescribing.

Summary

Methadone's affordability as a long-acting opioid analgesic is an advantage; however, public policies that designate methadone as a preferred analgesic for chronic pain may inadvertently contribute to toxicity and overdose. Methadone's pharmacologic properties make it unpredictable due to a long half-life, short analgesic window relative to respiratory-depressant effect, potential for drug-drug interactions, and other issues. Payers should not designate methadone as preferred, and should support detailed and expert medical education to make the administration of all opioids, particularly extended-release and long-acting opioids and methadone in particular, safer.

About AAPM

With over 2,500 members, the American Academy of Pain Medicine is the premier medical association for pain physicians and their treatment teams. Now in its 31st year of service, the Academy's mission is to optimize the health of patients in pain and eliminate pain as a major public health problem by advancing the practice and specialty of pain medicine through education, training, advocacy and research. Information is available on the Academy's website at www.painmed.org.

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Table 1. Methadone Cost Compared With Other Long-Acting Opioids [Consumer Reports 2012]

Long-acting Opioids – Dosing and Costs*				
Generic Name and Strength	**Brand Name(1)[1]**	**Frequency of use Per Day[2]**	**Total Daily Dose[3]**	**Average Monthly Cost[4]**
Buprenorphine patches				
Buprenorphine patch 5 mcg/hour	Butrans	One patch every 72 hours	120 mcg	$189
Buprenorphine patch 10 mcg/hour	Butrans	One patch every 72 hours	240 mcg	$276
Buprenorphine patch 20 mcg/hour	Butrans	One patch every 72 hours	480 mcg	$495
Fentanyl patches				
Fentanyl extended-release 25 mcg/hour	Duragesic	One patch every 72 hours	600 mcg	$303
Fentanyl extended-release 25 mcg/hour	Generic	One patch every 72 hours	600 mcg	$126
Fentanyl extended-release 50 mcg/hour	Duragesic	One patch every 72 hours	1200 mcg	$666
Fentanyl extended-release 50 mcg/hour	Generic	One patch every 72 hours	1200 mcg	$205
Hydromorphone pills				
Hydromorphone sustained-release 8 mg	Exalgo	1	8 mg	$349
Hydromorphone sustained-release 12 mg	Exalgo	1	12 mg	$520
Hydromorphone sustained-release 16 mg	Exalgo	1	16 mg	$520
Methadone pills				
Methadone 5 mg	Generic	3	15 mg	$17
Methadone 10 mg	Generic	3	30 mg	$20
Morphine pills				
Morphine extended-release 15 mg	Generic	2	30 mg	$48
Morphine extended-release 30 mg	Avinza	1	30 mg	$177

Morphine extended-release 30 mg	**Kadian**	**1**	**30 mg**	**$247**
Morphine extended-release 30 mg	**MS-Contin**	**2**	**60 mg**	**$270**
Morphine extended-release 30 mg	**Generic**	**2**	**30 mg**	**$72**
Morphine extended-release 60 mg	**Avinza**	**1**	**60 mg**	**$313**
Morphine extended-release 60 mg	**Kadian**	**1**	**60 mg**	**$433**
Morphine extended-release 60 mg	**Generic**	**2**	**120 mg**	**$101**
Morphine extended-release 90 mg	**Avinza**	**1**	**90 mg**	**$456**
Morphine extended-release 100 mg	**Kadian**	**1**	**100 mg**	**$692**
Oxymorphone pills				
Oxymorphone sustained-release 10 mg	**Opana ER**	**2**	**20 mg**	**$290**
Oxymorphone sustained-release 15 mg	**Opana ER**	**2**	**30 mg**	**$343**
Oxymorphone sustained-release 15 mg	**Generic**	**2**	**30 mg**	**$319**
Oxymorphone sustained-release 20 mg	**Opana ER**	**2**	**40 mg**	**$509**
Oxymorphone sustained-release 40 mg	**Opana ER**	**2**	**80 mg**	**$955**
Oxycodone pills				
Oxycodone sustained-release 10 mg	**OxyContin**	**2**	**20 mg**	**$164**
Oxycodone sustained-release 20 mg	**OxyContin**	**2**	**40 mg**	**$306**
Oxycodone sustained-release 40 mg	**OxyContin**	**2**	**80 mg**	**$529**
Oxycodone sustained-release 80 mg	**OxyContin**	**2**	**160 mg**	**$1,031**

* Selected doses. There are dozens of pill strengths for most of the medicines listed in this table. For space reasons, we have limited our list to selected strengths of both brand and generics.

1. "Generic" indicates it's the generic version of this drug.
2. As typically and generally prescribed. Means number of pills unless otherwise noted.
3. Total daily dose of opioid only.

Prices reflect nationwide retail average for July 2012, rounded to the nearest dollar. They are derived by *Consumer Reports Best Buy Drugs* from data provided by Wolters Kluwer Pharma Solutions, which is not involved in our analysis or recommendations.

Table 2. Methadone on State Medicaid Preferred Drug Lists

State	Date Effective	Methadone on Preferred Drug List	Methadone Non-preferred	Methadone Neither Preferred/Non-Preferred
Alabama[1]	10/01/13	X		
Alaska	07-09-12	X		
Arizona	01-01-13	X		
California	10-2013	X		
Colorado[2]	01-01-14	X		
Connecticut	12-06-13	X		
Delaware	08-23-13	X		
Florida	10-15-13	X		
Georgia	11-01-13			X
Hawaii	10-01-13	X		
Idaho	07-02-13	X		
Illinois	10-01-13	X		
Indiana	07-11-13	X		
Iowa	01-01-14	X		
Kansas	2-01-14			X
Kentucky	11-25-13	X		
Louisiana	01-01-12	X		
Maine	11-22-13	X		
Maryland	07-24-13	X		
Massachusetts[3]	10-14-13	X		
Michigan	10-15-13	X		
Minnesota	11-2013			X
Mississippi	10-01-13	X		
Missouri				X
Montana	11-01-13			X
Nebraska	07-24-13	X		
Nevada	08-05-13		X	
New Hampshire	09-04-13			X
New Jersey	10-01-13	X		
New Mexico[3]	06-2013	X		
New York	12-04-13			X
North Carolina	06-20-13			X
North Dakota	No Preferred Drug List Published			
Ohio	04-01-13	X		
Oklahoma	2012	X		
Oregon	05/01/13	X		
Pennsylvania	07/24/13	X		
Rhode Island	09/25/13			X
South Carolina	07/22/13			X
South Dakota[4]	No Preferred Drug List Published			
Tennessee	10-2013	X		
Texas	07-22-13			X

Utah	10-01-13	X		
Vermont	10-23-13	X		
Virginia	01-01-14	X		
Washington	11-01-13	X		
West Virginia	01-01-14		X	
Wisconsin	12-01-13	X		
Wyoming	11-01-13			X
District of Columbia	09-19-13			X

[1]All generic opioid agonists covered

[2]Specifies patient not required to switch to methadone from non-preferred agent

[3]Prior authorization required

[4]The South Dakota Department of Social Services issued a Request for Information in February 2012, and decided, as of January 2013, that it is not financially viable to proceed with a preferred drug list.