Methadone As an Analgesic: A Review of the Risks and Benefits

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Abstract

While methadone has been available for over 50 years, its use in opiate dependence has overshadowed its use as an analgesic. Within the last 10-15 years, though, methadone has been increasingly used to manage neuoropathic pain and cancer pain, but its use is causing an alarming number of deaths in the U.S. Last June, *The Charleston Gazette* ran a series titled *"The Killer Cure"* by Scott Finn and Tara Tuckwiller that found that the number of Americans whose deaths were caused by methadone rose from 790 in 1999 to 2,992 in 2003. The series also reported other statistics from the National Center for Health Statistics that revealed that West Virginia ranked first per capita in methadone overdose deaths, and that methadone was more likely involved in overdose deaths than any other prescription drug. Methadone has several unique properties that can be beneficial in the treatment of neuropathic pain and cancer pain unresponsive to other opioids, but some of these properties make it very dangerous and difficult to prescribe properly. As a result of these factors, methadone should not be the first-choice drug for pain and it should not be used in opioid-naive patients. The goal of this article is to provide a review of the properties and protocols for safe prescribing of methadone to help physicians recognize situations where this drug offers the greatest advantage as an analgesic.

Introduction

Even though it has been available for use in the United States since 1947, methadone has never widely been used as an analgesic until the last 10-15 years because there was not a wide understanding of its unique properties. Methadone is a potent μ-agonist with generally similar efficacy and side effects when compared to morphine, but it does possess several unique properties that distinguish it from other opiates. Some of these properties are advantageous in treating chronic pain with a neuropathic component (1-3), but some of its characteristics can make it an extremely dangerous and difficult drug to prescribe properly (Table 1).

As the use of methadone has increased during the last decade, there has been an unfortunate increase in the amount of diversion and abuse of this drug during this same time period (4). Furthermore, there has been an increase in the number of methadone-related fatalities, and many of these patients obtained their methadone through legitimate prescriptions (5-13). As noted in the series of articles *The Killer Cure* by Scott Finn and Tara Tuckwiller which started on June 4, 2006, in *The Sunday Gazette-Mail*, deaths certificates showed that nationally 2,992 Americans were killed by methadone in 2003, nearly quadrupling from 790 in 1999 (8). A total of 82% of those fatalities were declared accidental (8). In addition, Finn and Tuckwiller found that West Virginia's rate of accidental methadone overdose deaths in 2003 was four times the national rate, and that one in five methadone overdose victims had no other drug in their systems (8).

One major problem Finn and Tuckwiller discovered was that the usual adult doses listed on the packaging and approved by the U.S. Food and Drug Administration were much too high to be safe and could cause an accidental overdose (8, 9). Until recently, the package insert read under the heading "For Relief of Pain" as follows, "The usual adult dosage is 2.5 mg to 10 mg every three or four hours as necessary" (9, 14). Someone reading that label could believe it is safe for an adult to consume up to 80 milligrams of methadone a day. But 50 milligrams of methadone or less can kill a patient not used to strong painkillers, studies say (9, 15).

As a result of *The Sunday-Gazette Mail* series, U.S. Senators Chuck Grassley of Iowa, and Jay Rockefeller of West Virginia called on the FDA to respond to the thousands of overdose deaths blamed on methadone (16). In November 2006, the FDA announced that it had revised the package insert for methadone so it now recommended a dosing interval of every 8-12 hours as necessary (17, 18). The FDA also released a public health advisory titled *"Methadone Use for Pain Control May Result in Death"* (18, 19). It warned of methadone's unique properties – how it slows breathing, how it can stay in the body for days, and how taking an extra pill can kill a patient (20). Simultaneously, the FDA released an information sheet for healthcare professionals that included these points, as well as further discussion of the potential for QT prolongation and Torsades de Pointes (21). In addition, prior to these FDA actions, the U.S. Substance Abuse and Mental Health Services Administration began developing a strategy with the White House Drug Czar and the Drug Enforcement Administration to reduce the number of overdose deaths (22).

In West Virginia, response to the series has resulted in a lecture on the safe use of methadone at a continuing education conference in September (23), and other organizations are planning discussions on this subject. In addition, a live Internet training session on the safe use of methadone was recently conducted for hospitals and clinics throughout the state by the Appalachian Pain Foundation (24).

This article reviews the properties and protocols for safe prescribing of methadone to help physicians recognize situations where methadone offers the greatest advantage as an analgesic.

Properties of Methadone

In many ways, methadone can be considered a typical opiate. It is available in injectible (10 mg/ml) and oral (5, 10, and 40 mg tablets, as well as 1, 2, and 10 mg/ml oral solutions) dosage forms, and can be compounded into suppositories. It provides effective analgesia in moderate to severe pain, and it causes the usual opiate side effects, such as sedation, nausea, and constipation. In addition, it is a Schedule II drug with a high potential for abuse, and can be lethal in overdose, usually as a result of respiratory depression. However, methadone does have some differences.

One of the most distinctive qualities of methadone relative to other opiates is its long half-life. This is estimated to range anywhere from 4-130 hours, with typical steady state averages running between 22-35 hours (25). This property yields mixed outcomes. On the one hand, it allows methadone to be dosed one to three times a day in most patients without having to resort to more expensive extended release formulations. At the same time, the duration of analgesic effect is significantly shorter than what the half-life would suggest. Thus, the dose interval of methadone required to maintain a therapeutic level of pain relief is usually shorter than one half-life, resulting in accumulation of serum levels over several days. If titrated too rapidly, these rising levels can lead to toxicity, respiratory depression, and occasionally death (15). For example, while fatalities can occur with as little as a single dose, the period of greatest risk for fatalities in patients of methadone maintenance programs is in the first 1-2 weeks (26, 27).

As previously mentioned, the half-life of methadone is not only long, but highly variable (2, 25). There are many factors that play into this. Methadone is metabolized by both Cytochrome P450 (CYP) 3A4 and 2D6, though the former can be considered the primary enzyme. However, metabolism of methadone by CYP3A4 is relatively easily inhibited. Metabolism by CYP2D6, while somewhat less important, is not negligible, and remains a source of interindividual variability. Patients receiving potent CYP2D6 inhibitors or who are poor CYP2D6 metabolizers show significant methadone accumulation. Other factors that will affect serum levels include variable absorption, protein binding, and tissue distribution (2, 25).

Interestingly, in spite of its high interpatient variability, and in contrast to most other opiates, metabolism of methadone appears to remain relatively stable in the elderly, in those with chronic renal failure, and those with moderate liver disease. Furthermore, it yields inactive compounds that are primarily excreted in the feces. Thus, it is one of the safer opiates to use in these patients, once a stable dose has been achieved (28). It should be noted that these patient groups are often more sensitive to side effects, and thus the titrations should start lower, and progress slower to maintain appropriate margins of safety.

The wide variety of drug interactions that can occur with methadone are shown in Table 2. Inhibitors and inducers of both CYP3A4 and CYP2D6 may change serum concentrations (2, 25). Some drugs such as verapamil or quinidine and probably grapefruit juice may alter methadone's absorption. Other drugs, such as propranolol, tricyclic antidepressants, or certain phenothiazines, may influence protein binding by methadone through various mechanisms (2). Pharmacodynamic interactions are also present. Obviously, agents with opioid antagonist properties will be problematic. In addition, agents that potentiate the respiratory depression from opiates pose a significant danger. Specifically, concomitant use of alcohol and/or benzodiazepines has been identified as a risk for methadone-associated death (15). Concomitant use of these agents should be discouraged.

While an extensive review of medications that have a low likelihood of interacting with methadone is beyond the scope of this article, certain options do suggest themselves among those drug classes likely to be co-prescribed in pain patients. Among antidepressants, venlafaxine and mirtazepine probably offer the lowest potential for interaction. With anticonvulsants, gabapentin is the preferred agent. Finally, most NSAIDs or acetaminophen could be combined with methadone without causing additional adverse effects.

Another highly distinctive property of methadone is its ability to antagonize the N-methyl-D-aspartate (NMDA) receptor (29). Stimulation of the NMDA receptor is thought to play a role in lowering activation thresholds and central sensitization seen in neuropathic pain. Blocking the NMDA receptor may provide methadone additional pain reducing properties over typical opiates. Furthermore, there is some

Table 1. Potential Advantages and Disadvantages of Methadone As an Analgesic.

Advantages	Disadvantages
Extended dose interval	Interpatient variability of half-life
Low cost	Duration of analgesia shorter than half-life
Use in renal dysfunction	Numerous drug interactions
No active metabolites	Variable dose equivalence to other opioids
NMDA receptor antagonism	Social stigma

Table 2. Selected Drugs That Potentially Interact With Methadone.

Increase methadone levels	Decrease methadone levels	Block methadone effects	Additive effects with methadone
Azole antifungals	Barbiturates	Naloxone	Ethanol
Macrolides	Phenytoin	Naltrexone	Benzodiazepines
Grapefruit juice	Carbamazepine	Buprenorphine	Anticholinergic drugs
Quinidine	Rifampin	Pentazecine	Muscle relaxants
Verapamil	Risperidone	Nalbuphine	
Fluvoxamine	Protease Inhibitors	Butorphanol	
Fluoxetine	Efavirenz		

evidence to suggest that blocking the NMDA receptor may attenuate the process of developing opiate tolerance (30). Thus, methadone doses should be more stable over time relative to other opiates. Also, evidence suggests that this mechanism underlies the difficulties in determining an equipotent dose between methadone and other opiates. The higher the dose of conventional opiate, the more potent methadone appears upon switching. Theoretically, NMDA antagonism may be reversing the tolerance associated with the high dose of the previous opiate.

One other important property of methadone has nothing to do with its chemistry. It is the stigma that methadone carries as the drug of choice in the treatment of opiate dependence. The lay public is well aware of this, and patients may not want to take this drug out of fear of being perceived as an addict. Even if the patient initially takes the drug with relief of pain, he/she may receive pressure from family and friends to change medications. Physicians too may be affected by the stigma. They may not prescribe methadone for pain, under the assumption that it requires special licensing, as it does for maintenance purposes. Alternatively, physicians who attempt to prescribe methadone for pain may only prescribe it once daily, as typically done in maintenance therapy, rather than the two to three times daily usually required for optimal pain management.

Usage of methadone for pain

Methadone is not commonly used for short-term treatment of acute pain, and given its potential for drug accumulation, this is probably appropriate. Use of methadone for acute pain should be reserved for specialists in pain management who have expertise in using the drug. However, it can prove extremely useful in the treatment of chronic pain, including pain of both cancerous (3, 31) and non-cancerous (32) etiology.

Placebo-controlled trials have demonstrated that methadone has efficacy in the treatment of neuropathic pain (32). However, there are no trials available that compare methadone to more standard therapies (i.e. tricyclic antidepressants, anticonvulsants) or to other opiates in this patient population.

Table 3. Two Examples of Methadone Conversion Ratios.

Ayonrinde and Bridge[20]		Ripamonte, et al.[19]	
Daily morphine dose	Conversion ratio (morphine:methadone)	Daily morphine dose	Conversion ratio (morphine:methadone)
<100 mg	3:1	30-90 mg	3.7:1
101-300 mg	5:1	90-300 mg	7.75:1
301-600 mg	10:1	>300 mg	12.25:1
601-800 mg	12:1		
801-1000 mg	15:1		
>1000 mg	20:1		

For this reason, it cannot be recommended as a routine first-line agent. It does remain an option in those who fail or cannot afford the typical treatments.

Methadone has been tested as part of several opiate switching trials. These were included in a recent systematic review of opioid switching (33). Unfortunately, none of the trials were conducted in a randomized, controlled manner. Also, the vast majority of trials included in the review were conducted in cancer patients. As a result, it can't be stated unequivocally that methadone offers clear benefits, especially in non-cancer pain. However, it should be noted that the vast majority of trials did report opioid switching resulted in improved pain control and/or reduced opioid-related side effects.

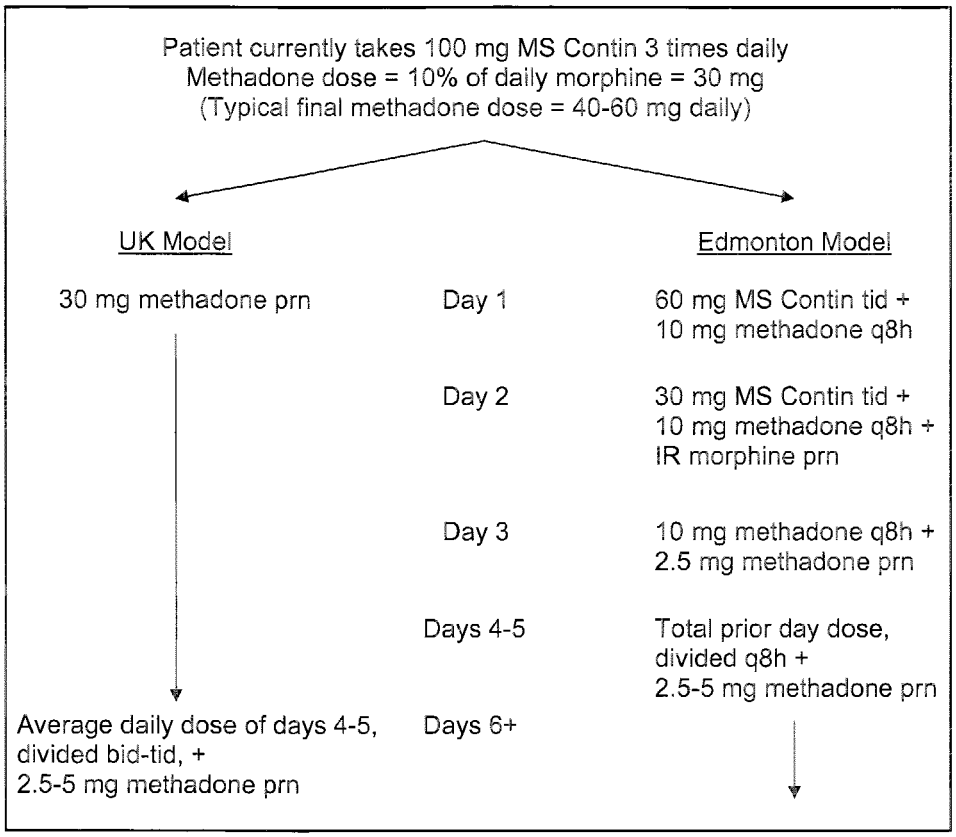
Due to all of the factors mentioned, a picture of the patients most likely to benefit from methadone begins to appear (1, 34). These patients will have long-standing severe pain, usually with a significant neuropathic component. They will have tried and failed multiple recommended agents. Unless it is a pure neuropathic pain, this means that more common opiates (i.e. morphine, oxycodone) will have been tried and documented to provide inadequate analgesia and/or intolerable side effects.

In the unusual case of methadone prescribing in opiate naïve patients, dosing is relatively straightforward, and based on the proviso that initial doses should be low and titration should be slow (1, 2). Typically, recommended doses are 2.5-5 mg methadone dosed every 12 hours. The total daily dose can be increased by 5 mg every 3-7 days until sufficient analgesia is obtained. One can consider shortening the dose interval to every 8 hours if symptoms dictate, though a few patients will only require once daily dosing. During titration, daily contact between the patient (or his/her representative) and the physician's office is recommended. Dosages should only be increased during physician visits.

The process of switching from another opioid to methadone is complex, and numerous modalities have been published (3, 31). The main point of contention is the equipotent dosing of morphine and methadone. Single dose studies in opioid naïve patients suggest a 3-4:1 ratio (3-4 mg morphine equal to 1 mg methadone) to be equianalgesic. However, in opiate tolerant patients, the ratio will increase with increasing morphine dose. Two of the most common conversion tables are presented in Table 3 (35, 36). These conversion rates, it should be noted, are not target doses. They merely allow the physician to evaluate if the given patient's dose is above or below the population norm.

The process is further complicated by a lack of consensus between an immediate switch versus a more gradual shift. Several of these variations were reviewed by Ripamonte and Bianchi (3). One example of a rapid switch is the United Kingdom model (37) (Figure 1). In this, patients would stop their opiate and have it replaced by a replacement methadone dose, calculated at 10 mg morphine to 1 mg methadone, based on their total daily morphine (or morphine equivalent) intake. This same dose of methadone could be repeated as needed, but at intervals no shorter than three hours. Dosing would be expected to be more frequent in the first day or two, but the interval between doses should increase as the drug accumulates. As an added safety factor, some experts recommend a limit of no more than 30 mg methadone per day. The methadone would continue to be dosed in this manner for five full days, at which time the average daily dose over the last two days is

Figure 1. Examples of methods of switching to methadone.



calculated. This is then divided into two doses at 12-hour intervals starting on day six.

Figure 1 also shows the Edmonton model (38), an example of a slower shift. In this model, the morphine dose is reduced by 30% on the first day. Simultaneously, a replacement dose of methadone based on a 10:1 ratio of morphine:methadone is calculated. This is divided into 2-3 doses at 8-12 hr. intervals. On the second day, the morphine is reduced by a further 30%. The methadone dose is increased only in the presence of moderate to severe pain. A short-acting opiate can be used for breakthrough pain. On the third day, the morphine is discontinued and the previous day's methadone dose continued. A rescue methadone dose of 10% of the total daily dose can be given as needed. Methadone can then be titrated daily based on the number of rescue doses utilized. Regardless of whether the slow or fast method is utilized, careful monitoring is required during the transition, and for several days after a stable dose is achieved. In particular, one should monitor for excess sedation or cognitive impairment because these are signs of accumulation.

Conclusions

Methadone has a long history of use in the treatment of opiate dependence, but only recently has it begun to be used for its analgesic properties. While its relatively long duration, low cost and adjunctive analgesic properties make it appealing, its potential for accumulation in the body and large number of drug interactions complicates its use. As a result of these factors, methadone should not be the first-choice drug for pain and it should not be used in opioid-naive patients.

Physicians who choose to use methadone as an analgesic must be aware of both the benefits and risks, and should monitor patients closely, especially upon initiation of methadone therapy. They should also not hesitate to consult with colleagues who are more experienced in prescribing methadone for pain, especially for patients whose treatment may be complex.

References

1. Toombs JD, Kral LA. Methadone treatment for pain states. *Am Fam Physician.* 2005; 71:1353-1358.
2. Brown R, Kraus C, Fleming M, Reddy S. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. *Postgrad Med J.* 2004;80:654-659.
3. Ripamonti C, Bianchi M. The use of methadone for cancer pain. *Hematol Oncol Clin N Am.* 2002;16:543-555.
4. Cicero TJ, Inciardi JA. Diversion and abuse of methadone prescribed for pain management. *JAMA.* 2005; 293:297-298.
5. Centers for Disease Control and Prevention. Unintentional and undetermined poisoning deaths - 11 states, 1990-2001. *MMWR.* 2004;53:233-238.
6. Centers for Disease Control and Prevention. Increase in poisoning deaths caused by non-illicit drugs - Utah, 1991-2003. *MMWR.* 2005; 54:33-36.
7. Ballesteros MF, Dudnitz DS, Sanford CP, Gilchrist J, Agyekum GA, Butts J. Increase in deaths due to methadone in North Carolina. *JAMA.* 2003; 290:40.
8. Finn S, Tuckwiller T. The killer cure: deaths tied to methadone escalate across state, nation. *The Sunday Gazette-Mail.* June 4, 2006.
9. Finn S, Tuckwiller T. The killer cure: a deadly dose. *The Sunday Gazette-Mail.* June 4, 2006.
10. Finn S, Tuckwiller T. The killer cure: federal overdose report written by industry insider. *The Sunday Gazette-Mail.* June 5, 2006.
11. Finn S, Tuckwiller T. The killer cure: despite deaths, methadone prescriptions multiply. *The Charleston Gazette.* June 5, 2006.
12. Finn S, Tuckwiller T. The killer cure: one pill can kill. *The Charleston Gazette.* June 6, 2006.
13. Finn S, Tuckwiller T. The killer cure: dangerous medicine. *The Charleston Gazette.* June 6, 2006.
14. Dolophine HCl [package insert]. Columbus, Ohio: Roxane Laboratories, Inc.; 2001.
15. Corkery JM, Schifano F, Ghodse AH, Oyefeso A. The effects of methadone and its role in fatalities. *Hum Psychopharmacol Clin Exp.* 2004; 19:565-576.
16. Finn S, Tuckwiller T. The killer cure: patients are "the ones at risk." *The Sunday Gazette-Mail.* June 11, 2006.
17. Dolophine HCl [package insert]. Columbus, Ohio: Roxane Laboratories, Inc.; 2006.
18. Finn S, Tuckwiller T. The killer cure: new warning issued on methadone. *The Charleston Gazette.* November 28, 2006.
19. Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat. November 27, 2006. Food and Drug Administration. Available at: www.fda.gov/cder/drug/advisory/methadone.htm Accessed March 5, 2007.
20. Finn S, Tuckwiller T. The killer cure: a deadly double standard. *The Sunday-Gazette Mail.* December 3, 2006.
21. Methadone Hydrochloride. November 27, 2006. Food and Drug Administration. Available at: www.fda.gov/cder/drug/InfoSheets/HCP/methadoneHCP.pdf Accessed March 5, 2007.

22. Finn S, Tuckwiller T. The killer cure: Feds act on methadone deaths. *The Sunday-Gazette Mail.* July 23, 2006.
23. Finn S, Tuckwiller T. Methadone to be topic at W.Va. health conference. *The Sunday-Gazette Mail.* August 13, 2006.
24. Finn S. Gazette series inspires methadone training. *The Charleston Gazette.* September 19, 2006.
25. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. *Clin Pharmacokinet.* 2002; 41:1153-1193.
26. Zador D, Sunjic S. Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. *Addiction.* 2000; 95:77-84.
27. Buster MC, van Brussel GH, van den Brink W. An increase in overdose mortality during the first two weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction.* 2002; 97:993-1001.
28. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage.* 2004; 28:497-504.
29. Gorman A, Elliott K, Inturrisi C. The d- and l- isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. *Neurosci Lett.* 1997; 223:1263-1270.
30. Davis A, Inturrisi C. d-Methadone blocks morphine tolerance and N-methyl-D-aspartate (NMDA)-induced hyperalgesia. *J Pharmacol Exp Ther.* 1999; 289:1048-1053.
31. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. *J Palliative Med.* 2002; 5:127-138.
32. Morley JS, Bridson J, Nash TP, Miles JB, White S, Makin MK. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliative Med.* 2003;17: 576-587.
33. Quigley C. Opioid switching to improve pain relief and drug tolerability. The Cochrane Database of Systematic Reviews. 2004: CD004847.
34. Manfredi PL, Houde RW. Prescribing methadone, a unique analgesic. *J Supportive Oncol.* 2003; 1:216-220.
35. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavratkis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol.* 1998;16:3216-3221.
36. Ayonrinde O, Bridge D. The rediscovery of methadone for cancer pain management. *Med J Austr.* 2000; 173:536-540.
37. Morley JS, Makin MK. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev.* 1998; 5:51-58.
38. Lawlor P, Turner K, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer.*1998;82: 1167-1173.