TITLE: Methadone for the Management of Pain in Patients with Opioid Addiction: A Review of the Evidence and Guidelines for Dosing Recommendations

DATE: 28 July 2009

CONTEXT AND POLICY ISSUES:

Methadone is a synthetic long-acting opioid indicated for the relief of severe pain (Metadol, Paladin Labs Inc.)\(^1\) and for the treatment of opioid addiction to heroin or other morphine-like drugs (Metadol-D, Pharmascience Inc.).\(^2\) Methadone is available in tablet, oral solution, and injectable dosage forms.\(^1,2\) Under Canadian legislation, methadone is a controlled substance that may be prescribed only by physicians who have an exemption from Health Canada to treat chronic pain or opioid addiction.\(^3\) The exemption is granted on the recommendation of the province’s College of Physicians and Surgeons.

In recent years, interest in using methadone for the management of chronic pain has increased in Canada.\(^4\) Methadone’s properties of high oral bioavailability, rapid onset of analgesic effect, long half-life (resulting in less frequent dosing schedules), lack of active metabolites, and low cost have resulted in its increasing use for the management of pain.\(^5\) The total number of physicians in Canada actively prescribing methadone for pain was 1,368 in 2003 compared with 398 physicians in 1998.\(^4\) However, less desirable characteristics of methadone include highly variable inter-individual pharmacokinetics, a high potential for accumulation leading to delayed toxicity including respiratory depression, and possible drug interactions.\(^6,7\) Furthermore, there is evidence that methadone may be associated cardiac arrhythmias, especially at higher doses.\(^6,8\) Therefore, a careful and individualized approach is required for methadone dosing.\(^9\)

Chronic pain is common in patients enrolled in methadone maintenance treatment programs (MMTPs) for opioid addiction with an estimated prevalence ranging from 37% to 60%.\(^10-12\) However, individuals with a history of opioid addiction, including those enrolled in MMTPs, are at risk of inadequate management of various types of pain including acute pain, cancer-related pain, and chronic pain of non-cancer origin.\(^13-15\) This may be due to several factors including physician concern over increased risk for adverse effects, prescription drug diversion,
withdrawal symptoms with opioid cessation, and a belief that maintenance dosing of methadone for opioid addiction provides adequate pain relief.\textsuperscript{14,15} In addition, there is evidence that patients on long-term methadone therapy have a lower pain threshold and are less sensitive to the analgesic effects of other opioids.\textsuperscript{1,13,16-18} For patients enrolled in MMTPs, there are some recommendations that methadone dose remain unchanged and short-acting narcotics be administered at higher and more frequent doses for patients with acute pain.\textsuperscript{1,3,19} However, increasing the methadone dose may be an option for treatment of chronic pain.\textsuperscript{3,20,21}

There has been some discussion as to whether a maximum allowable dose for methadone should be established for managing pain in patients with a history of opioid addiction. In order to help support coverage decisions, this report reviews evidence and guidelines assessing methadone dosing for the management of pain in opioid addicted patients.

**RESEARCH QUESTIONS:**

1. Is there evidence to support a maximum dose of methadone for the management of pain in opioid addicted patients?

2. If there is evidence to support a maximum dose, what is the maximum dose?

**METHODS:**

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2009), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2004 and June 2009. No filters were applied to limit the retrieval by study type. This search was supplemented by hand searching the bibliographies of selected papers to include background information from clinical and epidemiological studies not retrieved in the original literature search.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, controlled clinical trials, observational studies, and evidence-based guidelines.

**SUMMARY OF FINDINGS:**

One observational study conducted in patients with opioid dependence\textsuperscript{22} and one observational study conducted in patients enrolled in MMTPs\textsuperscript{14} were identified. Five evidence-based guidelines\textsuperscript{3,20,21,23,24} discussing methadone dosing were retrieved. No health technology assessments, systematic reviews, randomized controlled trials, or controlled clinical trials were identified.

**Health technology assessments**

No literature identified.

**Systematic reviews and meta-analyses**

No literature identified.

**Randomized controlled trials**
Zero literature identified.

Controlled clinical trials
No literature identified.

Observational studies

One center in Sweden published a retrospective study assessing if a long-term methadone treatment program could improve pain relief in patients with non-malignant pain suffering from iatrogenic opioid dependency. The inclusion criteria were that patients had to be over 20 years of age, have severe chronic non-malignant pain, have insufficient pain relief, have poor quality of life, and have over a year of iatrogenic opioid dependency. Records of 60 patients included in the methadone program between 1994 and 2002 were studied. The mean duration of pain before methadone treatment was 13 years (range 1 year to 20 years), and the mean length of opioid treatment was 7.1 years (range 1 year to 20 years). The most common sources of pain were low back pain and musculoskeletal disorders. The most commonly misused opioids were ketobemidone (an opioid mostly used in Scandinavia with a potency equivalent to that of morphine) and codeine. All patients were switched to and stabilized on oral methadone. Due to significant inter-individual variability, dose titration was conducted as an inpatient procedure over two to six weeks. Once stabilized, daily doses of methadone for analgesia ranged from 10 mg to 350 mg (mean of 99.5 mg). Patients were followed for a mean of 34 months (range 1 month to 94 months) after the initiation of methadone treatment to assess pain relief, quality of life, and adverse effects using the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC-QLQ 30 C). The EORTC-QLQ 30 C incorporates several multi-item scales to measure functional status, symptoms, global health, and quality of life.

At the end of 2002, 42 of the 60 patients were still in the program. Of the 18 patients that had left the program, pain had resolved in three patients, four patients had intractable nausea, one patient discontinued due to cardiac arrhythmia, four were excluded due to addiction or diversion, one did not experience pain relief, and five died of somatic diseases unrelated to methadone use. The patient who suffered from cardiac arrhythmia was receiving a high dose of methadone (270 mg per day). However, the cardiac arrhythmia episode resolved upon discontinuation of methadone. Four patients suffered from a pulmonary embolism during methadone treatment. While these patients required higher than average daily methadone doses (i.e., 150 mg, 270 mg, 345 mg, 350 mg), they were also at higher risk for pulmonary embolism due to factors such as, being smokers, having activated protein C-resistance, and having sedentary lifestyles. Between 40% and 60% of patients complained of sedation, loss of energy, weakness, weight increase, sweating, and sexual dysfunction. The side effects more commonly associated with opioids such as constipation, somnolence, nausea, and pruritus occurred in less than 20% of patients. Approximately 30% of patients complained of dyspnea and 10% reported edema.

Pain relief was rated as “good” by 75% of the patients, and the remaining 25% rated pain relief as “moderate”. Those patients who had rated their pain relief as “good” had a mean daily methadone dose of 81.5 mg (range 10 mg to 230 mg). In comparison, the patients who rated their pain relief as “moderate” were receiving higher daily doses of methadone with a mean of 157.5 mg (range 50 mg to 350 mg). The authors did not conduct statistical analyses to show whether the dose differences between “good” and “moderate” pain relief patients were statistically significantly different. After receiving methadone, improvements were noted in quality of life, as measured by physical function, role function (e.g., ability to work, perform hobbies, leisure activities), emotional function (e.g., depression, anxiety), cognitive function...
Blinderman et al. evaluated the clinical-effectiveness and safety of initiating and maintaining additional methadone for chronic pain in HIV/AIDS patients enrolled in MMTPs. A retrospective chart review of 53 HIV/AIDS patients was conducted to determine the range of safe, effective doses of methadone required for analgesia during a 12-month follow-up. The inclusion criteria were that patients had to be between the ages of 18 years and 75 years, have HIV-positive status, have a diagnosis of at least one chronic pain syndrome, have a history of heroin addiction, be enrolled in an MMTP for longer than one month, and have undergone treatment in an HIV pain clinic for at least one year. MMTP doses remained unchanged and were administered once daily. Patients also received methadone for analgesia every six to eight hours from the pain clinic. The primary outcome measure was the numeric rating scale (NRS), a validated pain assessment tool in cancer patients. Pain severity was assessment by asking the patient to rate their “average pain in the last two weeks”, or “current pain at this visit” based on the NRS. The method of questioning was not standardized. Illicit substance use measured by urine toxicology was the secondary outcome measure.

The mean and standard deviation (SD) for methadone maintenance dose for addiction treatment was 102 ± 34 mg daily. The mean and SD methadone dose for analgesia at the initial visit was 61 ± 34 mg daily. Over the 12-month retrospective observation period, the methadone dose for analgesia was titrated according to analgesic effect, side effect profile, and cognitive function to 200 ± 139 (SD) mg daily. The total mean methadone dose for opioid addiction and analgesia at 12 months was 302 ± 173 (SD) mg per day. Side effects associated with the additional methadone required for analgesia included worsening of fatigue in three patients (6%) and worsening of constipation in three patients (6%). Although patients were not routinely evaluated for cardiac arrhythmias, no cardiac events, death, or other serious adverse events were reported over the 12 month follow-up period. There was a significant reduction in mean pain scores versus baseline scores after one, three, six, and 12 months of treatment with methadone for analgesia (all follow-up periods, p < 0.001). Furthermore, the number of patients abusing drugs was statistically significantly reduced after 12 months of methadone treatment for analgesia (9 patients versus 53 patients at baseline, p < 0.0001). The authors concluded that HIV/AIDS patients with chronic pain enrolled in MMTPs achieved improved analgesia with no serious side effects when additional methadone was administered for pain relief.

**Guidelines and recommendations**

Guidelines from the College of Physicians and Surgeons of Nova Scotia for the use of methadone in chronic non-cancer pain were released in 2006. No details are provided regarding the development of this guideline. The authors recommend that the dose of methadone can be increased until analgesia is achieved in the absence of side effects; stating that the usual dose-limiting side effect is sedation. The authors of the guidelines also note that doses of methadone exceeding 120 mg daily are unlikely to be effective if low-to-moderate doses do not provide partial analgesia. However, these recommendations are not specific to individuals with opioid addiction.

The College of Physicians of Ontario published guidelines for the use of methadone in pain in 2004 based on a systematic review of the literature and consensus in the absence of supporting
The guidelines state that given the pharmacokinetic peculiarities and inter-individual variability for response to this drug, careful titration to effect is recommended and the optimal dose is that which relieves pain symptoms without sedation or other significant side effects. Although the guidelines acknowledge that there is no consensus as to what constitutes a high dose, practitioners are advised to be cautious with doses in excess of 200 mg per day and use electrocardiography (ECG) to monitor for cardiac arrhythmias. For patients enrolled in MMTPs, guidelines published by the same college in 2005 based on a non-systematic literature review and consensus recommend that as an alternative to adding a short-acting opioid for the management of acute pain, a temporary increase of 10 mg to 15 mg in the methadone dose may be considered when administered as a temporary split dose that is discontinued once the pain has resolved.

Provincial guidelines from Alberta (2005, based on a literature review and consensus), Ontario (2005, based on a literature review and consensus), and Saskatchewan (2008, development process not described) for methadone maintenance treatment of opioid addiction indicate that there is no defined maximum daily dosage of methadone but patients receiving doses over 120 mg should be monitored for cardiac arrhythmias using ECG.

The Canadian product monograph also recommends a maximum daily dose of 120 mg daily for methadone maintenance treatment.

Limitations

Two retrospective studies have been published in the past five years assessing methadone for the management of chronic pain in patients with a history of opioid addiction. These studies did not control for several factors that may have influenced the results, including inconsistencies in provider charting, lack of standardization of tools for assessing pain relief and quality of life, selection bias, and the evaluation of low numbers of patients. Furthermore, studies with a lack of randomization and a control group made it difficult to assess the clinical-effectiveness of methadone at higher doses for the management of pain versus lower doses of methadone or other opioids in this population. No studies were identified assessing methadone for acute pain in patients with opioid addiction. Although current Canadian guidelines provide dosing recommendations for the management of pain using methadone, only one guideline is specific for patients with a history of opioid addiction. The literature search for this report was restricted to information published in the past five years. Given the fact that methadone has been available for over four decades, useful dosing information from older references may have been missed.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

No information was identified from studies or guidelines to support a defined maximum daily dose for methadone when used for the management of pain in patients with a history of opioid addiction. Results from observational studies indicate that the optimal analgesic dose of methadone varies widely among participants when titrated according to analgesic effect and can be significantly higher than the maximum dose recommended for methadone maintenance treatment of opioid addiction.

Current guidelines indicate that individuals receiving doses of methadone greater than 120 mg per day should be monitored for cardiac arrhythmias and other adverse effects. However, results from observational studies suggest that the risk of serious adverse effects including...
cardiac arrhythmias and respiratory depression is low in patients with a history of opioid addiction, even at higher doses of methadone.

Further studies are needed to establish dosing recommendations and long-term feasibility of methadone for chronic pain in patients with opioid addiction as well as possible situations that may warrant its use in acute pain. In conclusion, dosing and administration of methadone for the management of pain in patients with a history of opioid addiction, including those enrolled in MMTPs, should be individualized and take into account the nature and severity of pain, degree of tolerance to the analgesic effects of methadone, and risk factors for adverse effects including cardiac arrhythmias and respiratory depression.

PREPARED BY:
Sarah Ndegwa, BScPharm, Research Officer
Raymond Banks, MLS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


