

# Use of methadone in treating chronic noncancer pain

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Chronic, noncancer pain is often very difficult to treat. Opioids continue to be the most effective analgesics in relieving severe pain, and recently their long-term use has gained wider acceptance because patients report benefits related to improved comfort and/or enhanced function. There is no best choice of opioids, but rather analgesics are chosen according to individual needs and response. It may be beneficial to trial various opioids because of the possibility that opioid responsiveness may vary from drug to drug. The authors' clinical experiences using oral methadone and the switchover process from the previously used opioid to methadone are reported. This potent analgesic has a wide variation in elimination half-life and clearance. Consequently, there are inherent risks, such as severe sedation, in using opioid equianalgesic charts when switching to methadone from alternate opioids. Therefore, it is imperative that treatment be individualized, and that practitioners be familiar with prescribing opioids and have a good understanding of their pharmacokinetics. The authors' experiences are with an outpatient population, and the gradual changeover process that they use demonstrate safety without loss of pain control. This method may also be useful in those suffering terminal illness.

**Key words:** *Chronic pain, Methadone, Opioids*

## Utilisation de la méthadone pour traiter la douleur chronique non cancéreuse

**RÉSUMÉ :** La douleur chronique non cancéreuse est souvent difficile à traiter. Les opioïdes restent les analgésiques les plus efficaces pour soulager la douleur sévère, et récemment leur utilisation sur une base prolongée est mieux acceptée parce que les patients rapportent des bénéfices liés à une amélioration de leur fonction et de leur bien-être. Il n'y a pas un opioïde meilleur qu'un autre, mais on choisit plutôt les analgésiques selon les besoins individuels et la réponse du patient. Il peut être bénéfique d'essayer plusieurs opioïdes puisque la réponse aux opioïdes peut varier d'un médicament à un autre. Les expériences cliniques des auteurs portant sur la méthadone par voie orale et sur le processus de substitution d'un opioïde utilisé antérieurement à la méthadone sont rapportées. Cet analgésique puissant démontre une grande variation dans la demi-vie d'élimination et dans sa clairance. En conséquence, il existe des risques inhérents tels qu'une sédation sévère, à l'utilisation de tableaux d'équivalence des opioïdes, en substituant la méthadone aux autres opioïdes. En conséquence, il est important de personnaliser le traitement, que les praticiens soient familiers avec la prescription d'opioïdes et qu'ils en comprennent bien leur pharmacocinétique. Les expériences des auteurs ont été menées dans une population non hospitalisée, et le processus de substitution graduelle qu'ils utilisent, démontre une certaine sécurité sans perte de maîtrise de la douleur. Cette méthode peut aussi s'avérer utile chez les patients souffrant d'une maladie en phase terminale.

Opioids are the most effective medications used to relieve severe pain, regardless of its etiology (1). Because chronic pain can be so debilitating, some experts believe that patients should be given a trial of opioids in an attempt to relieve the suffering from pain (2-6). Wall (4) believes that "No patient in pain should be deprived of an open trial of the analgesic effectiveness of narcotics, even if it conflicts with the social, political, religious or scientific beliefs of the physician." Use of these medications to treat chronic pain has been traditionally frowned upon because of the risks

of addiction, tolerance, toxicity and side effects. However, this view is being re-examined because of two sets of observations: opioids have been used effectively for the treatment of cancer pain and these risks have not been problematic, and opioid regulations have contributed to the undertreatment of pain (5).

In our practice, patients who suffer with chronic noncancer pain of varying pathogenesis (nociceptive, neuropathic and/or idiopathic) are treated following the College of Physicians and Surgeons of Alberta guidelines for the man-

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**TABLE 1**  
Patient profile

Patient	Sex	Age (years)	Pain diagnosis
1	F	40	Kyphoscoliosis
2	F	49	Progressive arachnoiditis
3	F	32	Chronic symphysis pubitis, sacroiliac pain
4	F	36	Degenerative disc disease
5	F	40	Myofascial pain syndrome
6	M	48	Degenerative disc disease
7	F	52	Fibromyalgia
8	F	51	Spinal stenosis, disc herniation
9	F	42	Progressive arachnoiditis
10	F	41	Chronic nerve entrapment
11	M	27	Osteomyelitis
12	M	48	Dysaesthetic pain related to exenteration for bladder cancer

F Female; M Male

agement of chronic nonmalignant pain (7). Various pharmacological agents, including nonopioid analgesics, adjuvant analgesics and opioids, are trialed, and, if beneficial in enhancing function and/or providing comfort, are used in the long term.

When determining the effectiveness of opioids, Portenoy et al (8) recommend applying the term 'opioid responsiveness', defined as the degree of analgesia obtained following dose escalation to an end point determined by either analgesia or the development of intolerable and unmanageable side effects. They have recognized that both patient-related and pain-related factors determine the response to analgesics and that opioid responsiveness may vary with different opioids.

We have recently treated a group of patients who were referred with chronic, noncancer pain who had been managed on a long-term basis with the use of high doses of opioids. These patients were switched to methadone from their previous opioid because of inadequate pain control, unacceptable side effects and/or as a cost saving measure. This paper reports our experiences with methadone, including the switch over process.

Methadone is a synthetic opioid that binds preferentially to the mu-type opioid receptor. It has been used to treat cancer pain, chronic nonmalignant pain and as a maintenance drug for heroin addicts (9). Numerous researchers have reported on the pharmacokinetics of methadone (10-13). Its oral bioavailability is excellent at about 85% to 90% (11). It has a long half-life, varying from 13 to 58 h, and a large variation in clearance so that it may take from two to nine days to approach stable serum levels (12). Consequently, because of the wide interpatient variability, prescribing metha-

**TABLE 2**  
Previous opioid in oral morphine equivalents compared with methadone

Patient	Previous opioid (dose/day, route)	Morphine equivalents (mg/day)	Methadone (mg/day)
1	Hydromorphone 280 mg sc	2800	480
2	Hydromorphone 480 mg sc	4800	800
3	Hydromorphone 1520 mg po	9140	680
4	Hydromorphone 576 mg po	2880	440
5	Hydromorphone 384 mg po	1920	440
6	Morphine 540 mg po	540	500
7	Morphine 930 mg po	930	930
8	Hydromorphone 72 mg po	360	600
9	Hydromorphone 336 mg sc	3360	360
10	Hydromorphone 384 mg po	1920	400
11	Hydromorphone 192 mg po	960	60
12	Hydromorphone 72 mg sc	720	105

sc Subcutaneously; po Orally

done must be done cautiously and on an individual basis, balancing patient response to analgesia and side effects (13).

### PATIENTS AND METHODS

The 12 patients (nine women, three men), ranging in age from 27 to 52 years (Table 1), had been treated with strong opioids for a duration of three months to 10 years (average treatment time four years).

The process of switching patients from their previous opioid to methadone took from two to four weeks. All patients were managed at home, and the authors remained in close contact with them by telephone daily; later every two to three days. Patients were assessed at these times; they rated their pain, drowsiness and any other reported symptoms on a scale of zero to 10, with zero defined as no pain/drowsiness and 10 defined as severe pain/drowsiness.

On treatment day 1, liquid methadone 10 mg every 6 to 8 h was ordered in addition to the other regularly scheduled opioid. On treatment day 2, the dose of methadone was increased to 20 mg every 6 to 8 h. Generally, by day 3 or 4 patients reported a decrease in pain by two to three points on the numerical scale and/or reported drowsiness at about 2 to 3 on a scale of 10. At this time, the dose of methadone was usually increased by 30 mg/day, but the dose of the other opioid was decreased by about 8% to 15% of that daily dose. If patients reported an increase in pain, methadone was increased by 30 mg/day, without decreasing the dose of the other opioid on that particular day. If drowsiness was a problem, the process of increasing methadone was usually halted for that day. Increasing one opioid and decreasing the other opioid continued until methadone was the sole opioid used.

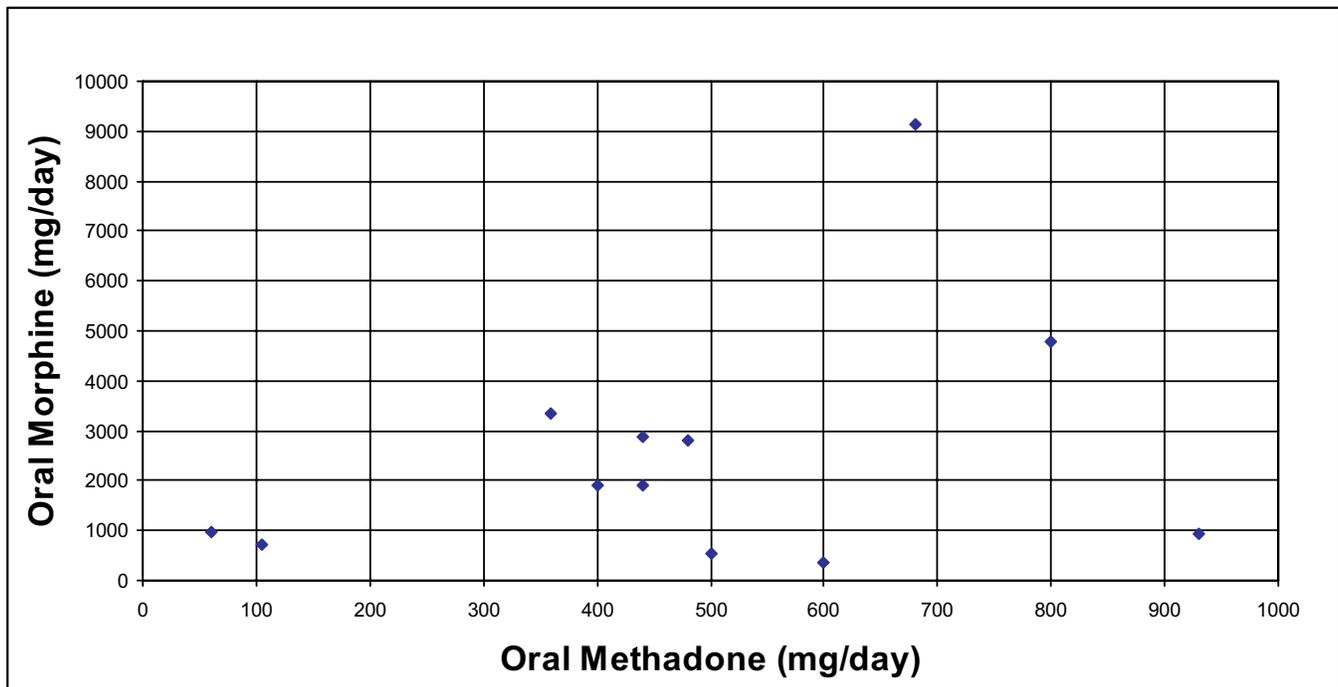


Figure 1) Comparison of methadone and morphine doses

## RESULTS

Patients were switched to methadone from other opioids over a period of two to four weeks, except patients 11 and 12 who were switched directly to methadone because they were previously taking only small doses of other opioids. None of the patients experienced severe adverse events such as excessive drowsiness. However, patient 11 developed itchiness, and the treatment was discontinued. Doses were individualized according to patient reports of pain and drowsiness. Table 2 reviews total daily doses of oral methadone compared with previous opioid in total daily oral dose of morphine equivalents. Symptoms attributable to withdrawal were not reported by patients. Figure 1 illustrates that no consistent equianalgesic dose for methadone was found when patients were switched from their previous opioid.

### Benefits

Eleven of the 12 patients reported improved pain control while on methadone. The other patient was not as comfortable on methadone, but did not wish to switch to his previous analgesic because of the cost savings. Three patients reported more even pain control without the peaks and troughs experienced with other opioids, including long-acting oral analgesics.

Two patients who previously reported myoclonus were now relieved of this side effect. Two other patients, who were obese, experienced a reduction in peripheral edema and, consequently, had substantial weight loss. These same two patients had improved function and have been able to be more active; for example, attending hockey games and walking with a cane rather than using a wheelchair.

### Side Effects

Patients reported the common side effects of opioids such as constipation, nausea and mild drowsiness. However, these symptoms were controlled with proper management. Nausea and drowsiness dissipated when patients were on regular, stable doses of methadone. Two patients were troubled with very dry mouth, but this also subsided after a few weeks. These patients were also on amitriptyline, which may cause dry mouth. Two other patients reported diaphoresis and were treated with clonidine 0.05 mg bid with some success.

## DISCUSSION

Patients with chronic noncancer pain are often a challenge to treat. It may be beneficial to trial various opioids because of the possibility that opioid responsiveness may vary from drug to drug (8). For our group of patients on high doses of opioids, the switch to methadone provided an improved level of comfort with side effects that were manageable. Gardner-Nix (14) also reported that methadone can sometimes provide better pain control than high doses of other opioids. This may be explained by the fact that methadone possesses properties of *N*-methyl-D-aspartate (NMDA) antagonism and incomplete cross-tolerance (15).

The process of changing to methadone was individualized and very gradual because of the large interindividual variations in pharmacokinetics. Indeed, it was interesting to compare the difference in dose of the previous opioid to the stable dose of methadone required for each patient for acceptable pain control. For example, patient 3 used the equivalent of 9140 mg oral morphine/day and was switched to 680 mg oral methadone/day, whereas patient 2, who was taking the

equivalent of 4800 mg of oral morphine/day, was changed to 800 mg oral methadone/day. Other studies (13-15) have also reported the possible difference in the analgesic equivalence between morphine and methadone, usually quoted as one to one (16). Therefore, because of these factors relating to inter-individual variations in pharmacokinetics and dose equivalencies, it is imperative to use caution when ordering methadone to prevent patients from being obtunded. Patients must be assessed carefully each day for level of sedation.

During this switching process, liquid methadone (10 mg/mL) was used so that the dose could be easily changed. Patients were instructed on the importance of precise measurement with a syringe and also to mix methadone in a sweetened drink because it is very bitter. After the switch was completed, methadone was ordered in formulated capsules to match the strength of the ordered dose. This has been particularly convenient and safe for these patients, one of whom was counting 32 pills for each dose, ordered every 4 h on schedule. Patients were cautioned to keep all analgesics in a safe place, preferably in a locked cupboard, out of the reach of children.

This group of patients has continued to remain on stable doses of methadone. Occasionally, an individual requests a temporary increase for an exacerbation of pain. Permission is generally granted to increase methadone by an additional dose per day, for a short interval, and then return to the baseline dose.

Patients have been satisfied with their pain control while taking methadone. Additionally, the three patients on continuous subcutaneous medications have been given freedom from a portable pump and concerns related to needle-site problems.

Methadone has been well tolerated by these patients. Myoclonus has not been reported at these high doses, and confusion and drowsiness have not been a problem. Five patients in the group have undergone periodic cognitive studies. Although there has not been any deterioration in cognitive functioning since trialing methadone, these patients score 'low-average' to 'average' on functions such as memory, attention and reaction time.

For elderly patients and patients who are opioid naive or using lower doses of other opioids, methadone is ordered very cautiously to avoid oversedation. Indeed, Fainsinger (13) suggests that the two most important guidelines for the clinical use of methadone are to use this drug cautiously and to tailor the dose to individual patient response (13). In our

clinical experience, methadone 5 mg every 12 h is generally initiated. Both the doses and the appropriate dose intervals for administering the medication are adjusted on an individual basis, mindful that steady-state serum levels may not occur for up to nine days. Consequently, doses may only need to be adjusted every three to nine days. Some patients do not require more than 15 to 20 mg/day in divided doses, and one elderly patient tolerates only 5 mg/day in divided doses.

Breakthrough analgesics are not ordered routinely for patients with noncancer pain when using methadone because of its long-acting property. Occasionally, some patients, especially those with cancer pain, require a short-acting analgesic such as hydromorphone for incident pain.

Physicians in Canada who order methadone for analgesic purposes in nonaddicted persons must have special authorization, which is obtained by contacting the Health Protection Branch, Bureau of Drug Surveillance (Ottawa).

### CONCLUSIONS

Recent research has supported the long-term use of opioids in the treatment of noncancer pain when conventional treatments have failed to provide improved comfort or function. Opioid responsiveness may vary from drug to drug, and, consequently, some patients may experience better pain control when switched to an alternate opioid. Methadone, a long-acting opioid, may be a good choice for patients requiring high doses of opioids. The process of switching from a particular opioid to methadone should be gradual and individualized to avoid excessive sedation. It is imperative that out-patients be monitored closely on a daily basis. In our group of patients, there have been no serious adverse effects with the use of methadone, and side effects have been manageable. We continue to order methadone for other patients with chronic pain. Elderly patients and patients who are opioid-naive or on low doses of other opioids should be started on methadone 5 mg every 12 h, and the dose should be adjusted cautiously according to individual progress. Patients with terminal cancer who are very ill and frail may require hospitalization for closer observation during the switchover process to methadone if the current opioid is being ordered at a high dose. Physicians ordering methadone should have a good understanding of the pharmacokinetics of this particular opioid and should be very familiar when prescribing opioids. More research is required to assess cognitive function for patients using opioids in the long term.

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