

# Use of Methadone for the Treatment of Diabetic Neuropathy

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*Editor's comment: This is the second Commentary of those that will appear from time to time describing treatments that may not have been validated by appropriate clinical trials but seem to be effective in diabetic patients based on small studies and/or extensive clinical experience. This one describes effective opioid treatment for those diabetic patients failing nonopioid therapies for painful neuropathy.*

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**M**ethadone, a schedule II opioid, was developed in Germany in the 1940s as a spasmolytic and was not used as an analgesic agent until many years later. In the 1960s, methadone was researched and tested as a medical treatment for the growing crisis of heroin addiction and since then has been primarily used as a medication to prevent withdrawal in drug-addicted patients. In 1976, the American Pharmaceutical Association won a suit allowing providers to dispense methadone as an analgesic agent. Since that time, any provider with a schedule II license can prescribe methadone for the treatment of pain (1). Twenty-eight years later, there continues to be little literature on the use of this analgesic agent and methadone continues to be rarely prescribed, if at all, by most health care providers.

In her *New England Journal of Medicine* editorial, Foley (2) emphasized that “given our lack of data about how to manage chronic neuropathic pain, we must focus urgent attention on the needs of suffering patients.” It has been recognized that a main indication for methadone use in palliative medicine is the treatment of neuropathic pain. Two small studies (3,4) have demonstrated the analgesic efficacy of methadone in the treatment of neuropathic pain. One study demonstrated that patients with peripheral neuropathy seem

to be more opioid responsive than those with pain from central nervous system lesions (5). Of the more than 2 million Americans affected by chronic neuropathic pain, a significant subset is comprised of individuals with diabetic peripheral neuropathy. In a small report, Bergmans et al. (6) concluded that methadone may be of particular value in the treatment of phantom limb pain and advocated for controlled clinical trials to verify their observations.

Methadone, a potent  $\mu$  (mu) agonist, has a number of unique properties that we feel, based on our clinical experience, make it the first line “opioid of choice” for the treatment of persistent neuropathic pain. Fishman et al. (7) noted that “administering methadone to opioid naïve individuals may possess a greater margin of safety than after exposure to other opioids” and that “methadone may be better as a first-line opioid than as a traditional second or third line choice.” The properties of methadone that set it apart from other opioids include the following.

1). Antagonism to NMDA (*N*-methyl-D-aspartate) receptors, known modulators of neuropathic pain and important in the attenuation of the development of morphine tolerance (1). NMDA is an excitatory amino acid that has been implicated in the development of neuropathic pain and opioid tolerance (8). Due to this

property, methadone, in theory, appears to be the ideal opioid for neuropathic pain and may account for the demonstration that the need for opioid escalation was significantly less in patients treated for pain with methadone than in those treated with morphine (7,9).

2). Inhibition of the reuptake of nor-epinephrine and serotonin. Facilitates improved analgesia in neuropathic pain. Tricyclic antidepressants have traditionally been used to accomplish this task (2,10).

3). Trimodal metabolism/excretion. Metabolism in the liver via the cytochrome P-450 system, fecal, and, to a lesser extent, renal excretion (other opioids are excreted renally) (1).

4). No active metabolites. This decreases the incidence of side effects such as confusion, sedation, myoclonus, seizures, and a variety of other adverse reactions related to build up of toxic metabolites (1).

5). Highly lipophilic. Leads to excellent absorption, rapid crossing over of the blood-brain barrier, and marked drug distribution in both muscle and fat, leading to high bioavailability (considered to be about three times that of other oral opioids). This allows methadone to be administered orally, in liquid and tablet form, as well as rectally, intravenously, epidural, intrathecally, and subcutaneously (1,11). Among the long-acting opioids, only methadone is available as a liquid and can be given sublingually (concentrate) or via a g-tube. Methadone works both as a sustained-release and immediate-acting medication. With chronic dosing, methadone analgesia lasts an average of approximately 10 h (12). Upon acute administration, analgesia begins within 20 min and peaks in 3–4.5 h, allowing it to be used for breakthrough pain, and a single dose lasts 4–6 h (12).

6). Very inexpensive. Methadone is available only as a generic agent, making it very inexpensive when compared with the cost of all the newer brand name long-acting opioids and nonopioids used in treating pain.

The combination of trimodal elimination and absence of active metabolites translates clinically to the fact that methadone dosing does not have to be adjusted

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**Abbreviations:** HNS, Hospice of the North Shore.

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**Table 1—Daily oral morphine dose equivalents followed by the conversion ratio of oral morphine to oral methadone**

<100 mg	3:1 (i.e., 3 mg morphine:1 mg methadone)
101–300 mg	5:1
301–600 mg	10:1
601–800 mg	12:1
801–1,000 mg	15:1
>1,001 mg	20:1

Due to incomplete cross-tolerance, it is recommended that the initial dose be 50–75% of the equianalgesic dose (1).

in the face of renal insufficiency/failure. This gives methadone another very distinct advantage over the other opioids in the treatment of the neuropathy commonly seen in dialysis patients, many of whom have diabetes and diabetic neuropathy but some of whom have neuropathy exclusively on the basis of their renal failure. This fact lends support to the argument that methadone should be strongly considered for use as the first-line opioid analgesic for treatment of neuropathy, particularly in the face of chronic renal insufficiency (1).

Hospice of the North Shore (HNS) and the Palliative Care Consult Service of HNS have treated large numbers of patients successfully and gained significant clinical experience in using methadone in the treatment of persistent neuropathic pain, with particular success in treating diabetic neuropathy. Much of the time, we will recommend starting with adjuvants, such as gabapentin and/or tricyclic antidepressants, for those patients with mild pain (1–3 on 0–10 scale) from diabetic peripheral neuropathy who have not had trials on these medications. For those patients already being treated with adjuvants, we will evaluate the current dose and, if subtherapeutic, will maximize the doses and reassess the response. For patients whose pain is moderate to severe ( $\geq 4$  on 0–10 scale), and who are symptomatic despite maximizing the adjuvant medication, we will initiate methadone if they are opioid naïve or, if they are on an opioid other than methadone, we will convert their currently prescribed opioid to methadone.

Opioid-naïve, frail, or elderly patients are initiated on low doses: 0.5–1 mg every 8 h; the general population is started on 2.5–5 mg every 8 h. Breakthrough pain can also be treated with methadone, and

breakthrough pain dosing should be at least 10–20% of the total daily dosage, given every 3–4 h as needed. Dosing does not need to be symmetric, and since the pain of diabetic neuropathy oftentimes worsens at night, we frequently give a larger dose at bedtime or at any other time of the day when pain tends to increase, such as when individuals are up and about. Titration of the scheduled doses may occur every 4–7 days, as needed, depending on the analgesic response and requirements for breakthrough dosing, with the scheduled doses titrated up to reflect the total dose of methadone received over 24 h (scheduled plus breakthrough doses). Occasionally, we will need to select 6-h dosing in those few patients who do not get a full 8 h of analgesia from their scheduled methadone doses. As the total daily opioid dose increases, the breakthrough dose should also be increased to remain at  $\sim 10$ –20% of the total daily dose.

When converting a patient from another opioid to methadone, the clinician should first convert the current opioid to morphine-equivalent doses using an equianalgesic table. The current morphine equivalent dose then needs to be converted to methadone using a methadone conversion table. It is also important to reduce the initial starting dose of methadone by  $\sim 25$ –50% because cross-tolerance to the new opioid may be incomplete. Table 1 is the conversion table used by our team.

Side effects are generally less common and less severe in association with methadone use when compared with other opioids. If the side effects that develop are significant, we recommend dose reductions of  $\sim 25$ % (usually withholding a single daily dose if the patient is receiving their methadone every 8 h). If the side effects are just undesirable, we recommend closely observing the patient, since they will usually resolve within a few days. Constipation, the most common side effect of any opioid, needs to be managed with an aggressive bowel regimen. Other side effects associated with methadone use include nausea, vomiting, sweating, pruritus, and, rarely, respiratory depression. Discontinuation of methadone should be carried out similar to stopping any long-acting opioid, with a slow taper over a period of days to weeks to prevent withdrawal symptoms and cessation of the taper if pain reappears.

### Case example

Charlie is a 74-year-old male with a complex medical history that includes type 2 diabetes, coronary artery disease, chronic renal insufficiency, and advanced chronic obstructive pulmonary disease. He lived independently at home but was experiencing progressive difficulty performing activities of daily living due to his bilateral foot pain. He described his pain as persistent burning pain that “felt like fire.” It was exacerbated by prolonged standing, got worse late in the day, and was somewhat improved with rest and elevation. He rated this pain as 5 of 10 at best and 10 of 10 at worst. Based on the description of his pain, his long-standing diabetes, and his physical exam, which demonstrated the classic findings of peripheral neuropathy, i.e., decreased light touch and pinprick in a stocking-glove distribution, the diagnosis of diabetic peripheral neuropathy was made. The Palliative Care Team of HNS was consulted to help manage his pain after multiple analgesic regimens/combinations, including oxycodone SR, oxycodone IR, gabapentin, amitriptyline, and transdermal Fentanyl, were unsuccessful in subduing the pain. He took various other medications, including inhalers, aspirin, prednisone, lisinopril, and senna. His opioid analgesic regimen was converted from 25  $\mu$ g fentanyl to 2.5 mg methadone every 8 h and 2.5 mg q3h prn. Four days after methadone was initiated, the patient noted that he needed an average of one breakthrough dose per day and felt more alert. After 10 days, the methadone dose was changed to 5 mg b.i.d. with 2.5 mg q3h prn. He was able to optimally perform his activities of daily living, was sleeping better, and noted that his breathing had improved. He did not experience sedation, had less constipation, and was able to discontinue his bedtime Gabapentin. His clinical status has remained unchanged for months now.

In conclusion, it has been our clinical experience that methadone is a unique opioid analgesic that we have found to provide consistently superior analgesia for the treatment of diabetic neuropathy/persistent neuropathic pain, when compared with the other opioids currently available, without sacrificing safety or tolerability. Our initial therapy for diabetic peripheral neuropathy still includes the use of tricyclic antidepressants, anticonvulsants, or combinations of those drugs. However, when we do not get an adequate clinical response in a patient to the use of

these adjuvants and the pain intensity the patient is experiencing is moderate to severe, we will quickly turn to methadone as our opioid of choice. In our experience, concerns regarding methadone's significant interindividual variability in potency and long and variable half-life have been minimally problematic with proper dosage initiation and subsequent appropriate dose titration. The treatment of persistent pain, in general, and specifically the treatment of painful diabetic peripheral neuropathy, should not be left to be treated exclusively by pain specialists. There are too many patients living with persistent pain and too few noninvasive pain specialists to deal with all of these patients. Referrals to pain specialists for painful diabetic peripheral neuropathy should be primarily limited to those cases that have remained refractory to the reasonable therapeutic interventions of their primary care physicians or endocrinologists. Many practitioners, with appropriate education and some practice using methadone, will find that they will reach a real

level of comfort prescribing this unique drug to their patients.

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