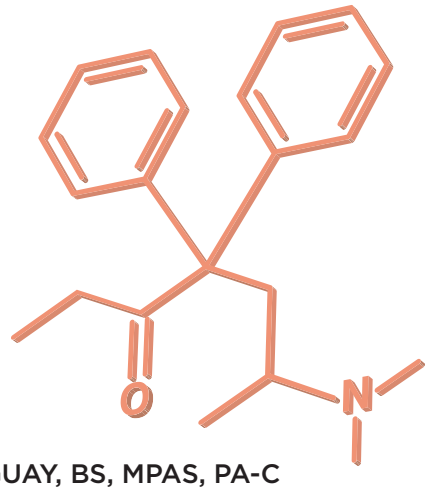

Methadone

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The image at top is an illustration of the structural formula of methadone.

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Pain is a common problem in patients with cancer, and advanced practitioners in oncology are frontline managers of cancer-related pain and other deleterious symptoms. Opioids are the mainstay of cancer pain treatment, and methadone is one opioid analgesic available for management of this symptom. Methadone has been available for over 50 years and used historically in addiction maintenance. More frequently, it is being used for cancer pain management due to its low cost, pharmacologic profile, and efficacy.

While methadone has several advantages, its unique pharmacologic profile can lead to fatal overdose when not accurately prescribed. The number of deaths from methadone rose from 790 in 1999 to 2,992 in 2003 (Terpening & Johnson, 2007). This alarming data prompted the Food and Drug Administration to revise its package insert for methadone in 2006 with clearer dosing guidelines. In addition, professional organizations such as the American Pain Society have developed dosing recommendations to increase safety and assist in appropriate dosing (American Pain Society, 2008). This column will provide information for prescribers of methadone including mechanisms of action, pharmacologic properties, dosing recommendations, and potential adverse effects.

Mechanisms of Action

Methadone is a potent opioid analgesic that binds to mu and delta receptors at the dorsal horn of the spinal cord. It also demonstrates N-methyl-D-aspartate (NMDA) antagonism in animal studies which has a role in the prevention of opioid tolerance and central nervous system desensitization. Therefore, methadone's NMDA antagonism has stimulated interest in the management of neuropathic pain syndromes (Mannino, Coyne, Swainey, Hansen, & Lyckholm, 2006). While some studies report favorable results for the management of neuropathic cancer pain, a recent Cochrane review indicated that methadone was not superior to morphine (Nicholson, 2009). Additional comparison studies are needed.

Pharmacologic Properties

Methadone is a lipophilic opioid with high bioavailability and a wide tissue distribution. It is available in liquid, tablet, capsule, rectal, and parenteral preparations. Clinical trials using a sublingual methadone are underway and this route may serve an advantage because of the fast onset of 5 minutes (Gupta, Duckles, & Giordano, 2010; Hagen, Fisher, & Stiles, 2007). Metha-

Table 1. Pharmacokinetic properties of methadone

Absorption	Onset Oral 30 minutes Sublingual 5 minutes Parenteral 10–20 minutes Peak – 1–2 hours, levels decline 24 hours after dosing Oral Bioavailability – 85% Duration – up to 8 hours
Distribution	Large volume distribution Only 1% in blood Tightly bound to protein with sequestration in extravascular binding sites Half-life average 24 hours, range 13–100 hours
Metabolism	Lacks active metabolites
Elimination	Renal compromise does not alter clearance Mediated by hepatic biotransformation Increased metabolite to methadone ratios with chronic dosing suggesting autoinduction of hepatic enzymes

Note: Sources: Toombs & Kral (2005), American Pain Society (2008).

done can also be given subcutaneously; however, this route may cause some local irritation. Changing the injection site and limiting doses to 30 mg per site have been shown to satisfactorily manage local irritation (Centeno & Vara, 2005).

One distinctive quality of methadone is its high affinity for protein and subsequent long half-life that varies from 5 to 130 hours. The advantage of the long half-life is the extended analgesic effect and longer dosing interval; however the agent can also accumulate and contribute to over-sedation and respiratory depression. The variability in the half-life of methadone is dependent on host factors such as albumin level, absorption, and distribution. Interestingly, it is not dependent on renal or liver function and can be a wise choice in the elderly and those with renal and hepatic insufficiency. The most significant variable is that methadone is metabolized by cytochrome P450 (CYP) 3A4 and 2D6. Metabolism may be inhibited in some individuals including those who take other foods and medications that inhibit metabolism (e.g., antifungal agents, grapefruit juice, fluoxetine), contributing to significant drug accumulation. Others may be extensive metabolizers or may take medications that increase the metabolism of methadone (e.g., phenytoin, carbamazepine) resulting in decreased blood levels (Terpening & Johnson, 2007). Extensive review of the patient's medication list is essential in safely prescribing methadone. Methadone's pharmacologic profile is included in Table 1. Advantages and disadvantages of use are summarized in Table 2.

Dosing Recommendations

When dosing methadone, practitioners must be cognizant of the patient's opioid history, medical history and current medications prior to initiation of therapy. In the opioid naïve patient, the general rule is to start low and go slow.

A typical regimen recommended to start for an opioid naïve patient is 2.5-5 mg every 12 hours. The total daily dose may then be increased by 5 mg every 3-7 days until pain control has been met. Some patients may demonstrate symptom control with once daily dosing (e.g., the elderly) (Terpening & Johnson, 2007). While some patients may have relief with every 12 hour dosing, some guidelines recommend the dosing interval be

Table 2. Advantages and disadvantages of methadone use

Advantages	Disadvantages
Global distribution in body tissues NMDA antagonism—potential to alleviate neuropathic pain and decrease tolerance High oral bioavailability Repeated administration results in greater potency Rapid onset Long half-life resulting in less frequent dosing schedules Lack of active metabolites Low rate of tolerance Cost	High potential for accumulation leading to delayed toxicity Complex dosing regimen based on previous opioid amount Pharmacokinetic variability between individuals Potential food and drug interactions Inducers Inhibitors Social stigma

Note: Based on Terpening & Johnson, 2007.

Table 3. Opioid Conversion to Methadone

Author or guideline	Daily morphine dose	Conversion ratio morphine to methadone
Ayonrinde & Bridge, 2000	< 100 mg	3:1
	101–300 mg	5:1
	301–600 mg	10:1
	601–800 mg	12:1
	801–1,000 mg	15:1
	> 1,000 mg	20:1
Ripamonti & Bianchi, 2002	30–90 mg	3.7:1
	91–300 mg	7.75:1
	> 300 mg	12.25:1
American Pain Society, 2008	< 90 mg	1:4
	90–300 mg	1:8
	> 300 mg	1:12

shortened to every 8 hours (American Pain Society, 2008). Dosing titration should be performed with close monitoring, and daily contact between the patient and the provider.

In the opioid tolerant patient, opioid rotation from other opioids to methadone requires calculating the patient's current daily morphine equivalent dose. This will include both the long acting and breakthrough medications. Several conversion ratios have been developed from retrospective data. Each study or guideline calculates the final equianalgesic dose ratio or EDR between morphine and methadone. For example, single dose studies have shown (in opioid naïve patients) that 3-4 mg of morphine is equal to approximately 1 mg of methadone. However, in the tolerant patient, this ratio will increase as methadone becomes more potent with increasing doses. This correlates to the daily opioid dose prior to switching to methadone. Conversion ratios listed in the literature are included in Table 3 (American Pain Society, 2008; Ayonrinde & Bridge, 2000; Ripamonti & Bianchi, 2002).

When titrating a patient to an appropriate methadone dose, dosing increases should not be made more frequently than every 5-7 days due to the potential for delayed accumulation (Toombs & Kral, 2005). Methadone dosing can safely occur in the outpatient setting (Parsons et al., 2010), but daily communication between the office and patient is important to monitor any change in status. Immediate release opioids can be used for breakthrough pain while the methadone is being titrated to an efficacious and safe dose. One titration example is included in Table 4.

Table 4. Methadone titration example

Week	Dose	Total dose/day
1	5 mg po TID	15 mg
2	10 mg po TID	30 mg
3	15 mg po TID	45 mg
4	20 mg po TID	60 mg
5	25 mg po TID	75 mg

Note: Sources: Toombs & Kral (2005).

Adverse Effects

Adverse effects of methadone include respiratory depression, sedation, nausea, and constipation. At higher doses, adverse effects may include myoclonus and hallucinations. More recently concerns of Q-T interval prolongation and torsades de pointes have been identified (Reddy et al., 2010). It is critical that patients are monitored for these adverse effects, especially during the initiation and rotation to methadone.

One of the most distinctive qualities of methadone relative to other opiates is its long half-life. When titrated too rapidly, these rising levels can lead to respiratory depression and sedation (Terpening & Johnson, 2007). It should be noted that methadone's peak respiratory depressant effect usually occurs later and will persist longer than the analgesic effect. Even when doses have been correctly calculated, the risk of overdose remains (Toombs & Kral, 2005).

The half-life of methadone is not only long, but highly variable. This can create the potential for drug accumulation. Careful dose titration, thorough history for medical risk factors, and cognizance of medication interactions should be a standard approach. Extensive review of medications is essential in safely prescribing methadone. Familiarity with the side effect profile of methadone will aid in the appropriate titration of a methadone regimen.

As mentioned previously, the use of methadone has drawn concerns of Q-T interval prolongation. In 2006, the FDA issued an alert that highlighted the potential for serious cardiac conduction effects and the need to carefully weigh methadone's risk (Stringer, Welsh, & Tommasello, 2009). Current research to better assess the risk factors associated with Q-T prolongation has been reviewed. A list of factors has been compiled

that may increase the risk of patients developing Q-T prolongation, including female gender, hypokalemia, history of drug interactions, underlying cardiac conditions, and unrecognized congenital long Q-T syndrome. The American Pain Society recommends an electrocardiogram (ECG) before initiating methadone and when the doses become relatively high, specifically those greater than 200 mg/day (American Pain Society, 2008). A thorough patient history and ECG monitoring are essential for patients treated with methadone, and obtaining this baseline information would provide insight into the potential development of this life threatening conduction abnormality.

Summary

The use of methadone has been increasing steadily for cancer pain management. The increased use can be attributed to its low cost, pharmacologic profile, and efficacy. While methadone has several advantages, the adverse effects that come with it should be carefully considered. The advanced practitioner can safely prescribe methadone with careful assessment of opioid adverse effects, which can be particularly challenging in patients with advanced illness due to the existence of the disease state or comorbidities. Balancing both the benefits and risks of its use and individualizing treatment is essential for success.

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