Methadone: applied pharmacology and use as adjunctive treatment in chronic pain

R Brown, C Kraus, M Fleming, S Reddy

This article reviews the unique pharmacological properties of methadone and outlines its appropriate clinical application, with focus upon its use in the treatment of chronic pain. Although methadone is most widely known for its use in the treatment of opioid dependence, methadone also provides effective analgesia. Patients who experience inadequate pain relief or intolerable side effects with other opioids or who suffer from neuropathic pain may benefit from a transition to methadone as their analgesic agent. Adverse effects, particularly respiratory depression and death, make a fundamental knowledge of methadone’s pharmacological properties essential to the provider considering methadone as analgesic therapy for a patient with chronic pain.

Methadone is a synthetic opioid medication best known for its use in the treatment of opioid dependence. Methadone is also an effective analgesic agent, potentially with increased efficacy in the setting of neuropathic pain. Patients experiencing inadequate analgesia or adverse effects while on other opioids may also benefit from a transition to methadone. Additionally, unique pharmacological properties make methadone a useful addition to the care provider’s arsenal of prescription analgesic agents.

Methadone’s excellent oral bioavailability and mucosal absorption, effectiveness as an analgesic agent, low cost, long half-life, and availability in oral, parenteral, and suppository forms make it an excellent alternative for the treatment of both cancer and non-cancer pain. Medication interactions and the potential for serious adverse effects (particularly central apnoea and death, which have received recent attention in the popular press) make an understanding of methadone’s pharmacological profile essential to the prescribing provider.

Many individuals participating in methadone maintenance treatment for opioid dependence seek medical care in the community outside of their addiction treatment facility. An understanding of potential adverse effects and medication interactions is important when caring for this population as well, so that the provider can avert untoward events resulting from medication interactions.

In this article, we discuss the pharmacology of methadone and briefly comment upon its use in the treatment of opioid dependence and withdrawal. We then focus upon an approach to the prescription of methadone for the treatment of chronic pain conditions. Finally, we discuss the adverse effects of and potential drug interactions with methadone which may occur with usual clinical use.

PHARMACOLOGY

Methadone occurs in R-enantiomeric and S-enantiomeric forms, with essentially all of its activity due to activity of R-methadone. Methadone exerts its activity through binding to and activating μ opioid receptors centrally and in the periphery. This activity produces the effects common to all μ opioid agonists: analgesia, euphoria, constipation, sedation, respiratory depression, nausea, and miosis. Additionally, methadone antagonises N-methyl-D-aspartate receptors, which may increase its effectiveness in the treatment of neuropathic pain compared with other opioids.

Pharmacokinetics

Methadone is a fat soluble drug which is rapidly absorbed after oral administration. Time to peak concentration, however, varies from one to five hours. Methadone induced slowing of gastric emptying may account for longer time to peak concentration in chronic users. Oral bioavailability of tablets is approximately 60%–70%, but wide variation among patients exists. The analgesic effect of a dose begins within 30 to 60 minutes after administration and generally lasts for four to six hours.

Methadone is highly bound to plasma proteins. In particular, α1-acid glycoprotein is important, because disease states, like cancer, may induce a rise in the concentration of this protein and, as a result, affect the concentration of free methadone. Certain drugs may influence α1-acid glycoprotein concentrations and, in turn, methadone concentrations. Methadone may be displaced from plasma proteins by drugs like propranolol, certain phenothiazines, and imipramine. Other drugs may decrease plasma protein and, theoretically, increase free methadone levels. Examples of such drugs are carmustine and mechlorethamine. Finally, drugs may also selectively compete for protein binding sites, resulting in situations where their own free levels might increase. The tricyclic antidepressants, progesterone, and lidocaine are a few examples. Although animal data suggest that dose adjustments based on protein binding may be necessary, there are no data in humans to suggest these interactions are clinically significant.
Methadone is also widely distributed to tissue, and, with continuous use, tissue levels may exceed levels in plasma. This extensive protein and tissue binding is responsible for the long plasma half life of the drug, particularly with continuous use. Metabolism of methadone to inactive forms is the principle means of elimination. Less than 10% of an oral dose is extracted by the liver during first pass. The drug is metabolised both by the liver and by intestinal CYP 3A4 and, to a lesser extent, by CYP 2D6. Some of the variability of enzyme activity in different people likely accounts for the large differences in clearance and half life of methadone seen within a population. For example, due to a polymorph of CYP 2D6, a subset of the white population, less than 10%, are considered to be poor metabolisers of methadone. Estimates of methadone half life vary from 15 to 55 hours. In addition to metabolic inactivation, parent drug and metabolites are also eliminated in the faeces and urine.

Age does not appear to have a large influence on clearance and generally no change in dose is required for persons over age 65 years. For patients with impaired renal function, methadone clearance via faeces will increase and no dose adjustment is necessary. For patients with end stage renal disease, some experts suggest a 50% reduction in methadone dosing. Because methadone is highly protein bound, little is expected to be removed from the plasma with dialysis. Patients with chronic, stable liver diseases may be able to tolerate usual methadone maintenance doses. For patients with acute hepatitis and elevated liver enzymes, higher doses of methadone may be required.

No relationship has been established between plasma concentration and analgesic effect. For the treatment of chronic pain, treatment should be titrated to clinical effect rather than a drug level.

**CLINICAL APPLICATIONS**

**Methadone for opioid dependence**

Since the enactment of the Narcotic Addicts Treatment Act in 1973, methadone prescription in the United States for opioid dependence or opioid withdrawal has been (and continues to be) legal only in the setting of a federally licensed methadone maintenance facility. Resources for the care of health issues unrelated to substance abuse are often limited in these facilities. Methadone maintained individuals, therefore, frequently seek medical care from community providers. Over 150,000 opioid dependent individuals are enrolled in methadone treatment centres in the United States. The United States Office of National Drug Control Policy estimates that these services reach one in 10 to one in eight actively opioid dependent individuals in the United States.

Methadone maintenance treatment has been shown to decrease use of heroin and other drugs; reduce the acquisition and transmission of HIV; hepatitis B, and hepatitis C; reduce criminal behaviour; and has been shown to be a cost effective treatment for opioid dependence. Most of the benefits of methadone maintenance have been shown to be related to methadone dose and to duration of treatment.

**Methadone for chronic pain**

Federal and state regulations restricting the use of methadone in the setting of opioid dependence and withdrawal to specially licensed facilities do not apply to the prescription of methadone for chronic pain. Therefore, the care provider may consider the use of methadone as an analgesic agent for the treatment of chronic pain.

In addition to being effective treatment for opioid dependence, methadone provides effective analgesia with several unique properties. Patients experiencing adverse effects (constipation, euphoria, nausea/vomiting) or inadequate analgesia with other prescribed opioids may benefit from a transition to methadone. Additionally, methadone often provides analgesia superior to other opioids in the setting of neuropathic pain syndromes. Furthermore, a reduced level of tolerance to analgesic effects and less constipation has been reported for methadone as opposed to other opioids.

Given the short duration of analgesia (4–6 hours) relative to methadone’s half life, the use of methadone as an analgesic agent requires a more frequent dosing regimen than the daily dosing used for the treatment of opioid dependence. Usual analgesic treatment regimens with methadone require dosing every eight to 12 hours. The long half life of methadone in the setting of more frequent dosing creates the potential for drug accumulation and adverse effects. Many protocols for a transition to methadone from other opioid analgesics have been put forward in the literature. These methods are of two basic types: (1) a rapid transition in which the previously prescribed opioid is completely discontinued with institution of methadone analgesic therapy, and (2) a slow transition in which the previously prescribed opioid is tapered in conjunction with titration of methadone dosing. Equianalgesic doses of the most commonly prescribed opioids are provided in table 1.

Boxes 1 and 2 provide examples of each protocol (slow and rapid) for transition to methadone using morphine milligram equivalents.

Though not generally a first line agent, methadone may be considered early on in the treatment of neuropathic pain and/or in situations where cost issues are compelling. This situation mandates caution because, in the opioid naïve patient, methadone may precipitate respiratory arrest. A history of sleep apnoea, severe asthma or respiratory failure, right heart failure, morbid obesity, or the concurrent use or abuse of sedative drugs (for example, alcohol, muscle relaxants) increase the risk of respiratory depression or arrest with methadone. The first visit with the care provider should, therefore, include a detailed medical history to screen for these high risk situations. A methadone regimen for chronic pain in the opioid naïve patient may then begin with a low dose (5 mg or less twice daily) and be gradually (an additional 5 mg daily every 72 hours) titrated upward to pain relief. Total daily doses exceeding 120 mg are rarely required to provide adequate 24 hour analgesia. As needed doses of short acting analgesics, such as oxycodone, hydrocodone, or short acting morphine preparations, may be considered for the treatment of breakthrough pain.

An optimal concentration of methadone for maintenance therapy for opioid dependence is considered to be 400 μg/l, although in some studies, designed to determine an effective concentration, a threshold was not found. On the other hand, some patients will have a reasonable clinical response with lower serum concentrations and other factors such as receptor sensitivity, social support, and psychological issues may also play a part. Therefore, therapeutic drug monitoring is indicated.

### Table 1: Opiate milligram equivalents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equianalgesic doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>180–200 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25 μg transdermal</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30 mg</td>
</tr>
<tr>
<td>Morphine</td>
<td>30–60 mg oral</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

*Equianalgesic doses are not included due to varying conversion ratios at varying prior doses of other opiates. See boxes 1 and 2 for appropriate conversion to methadone based upon morphine milligram equivalents."
is not recommended routinely for all patients receiving methadone maintenance.15 No relationship has been established between plasma concentration and analgesic effect.9 For the treatment of chronic pain, therefore, treatment should be titrated to clinical effect rather than a drug level.3

CESSATION/TAPER OF METHADONE
Should cessation of methadone treatment be indicated, gradual tapering will minimise withdrawal symptoms. The taper generally should not exceed 1 mg/day.31 A 5 mg/week taper is convenient given methadone’s availability in 5 mg and 10 mg tablet forms.

Aching muscles and joints, insomnia, nausea, and mood changes may indicate opioid withdrawal.16 If the patient begins to experience opioid withdrawal effects, symptomatic treatments on an as-needed basis may assist in the management of a continued taper if necessary. Clonidine or a β-blocker may alleviate sympathomimetic symptoms (tachycardia, lacrimation, stuffy nose, sweats). These medications

<table>
<thead>
<tr>
<th>Box 1: United Kingdom model for switching from morphine to methadone (rapid transition)1</th>
</tr>
</thead>
<tbody>
<tr>
<td>● The use of the previous opiate is stopped and replaced by a fixed dose of methadone. A patient who was receiving 300 mg or less of morphine milligram equivalents daily would have the dose replaced at a ratio of 10 mg morphine: 1 mg methadone. A patient receiving greater than 300 mg of morphine milligram equivalents daily would receive a fixed dose of 30 mg methadone. This dose is then used at intervals of not less than three hours as needed for analgesia.</td>
</tr>
<tr>
<td>● On day 6, the amount of methadone administered over the previous two days is converted to a regimen delivered regularly at 12 hour intervals.</td>
</tr>
<tr>
<td>● Methadone requirements should be expected to decrease during days 2 and 3 and reach steady state on days 4–5.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box 2: Edmonton model for switching from morphine to methadone (slow transition)2</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Day 1: Decrease morphine dose by 30% and replace with oral or rectal methadone every eight hours using titration equianalgesic morphine-to-methadone dose ratio of 10:1.</td>
</tr>
<tr>
<td>● Day 2: If pain control is adequate, decrease the original dose of morphine by another 30%. Increase the dose of methadone only if the patient experiences moderate to severe pain. Treat transient pain with rescue doses of short acting opioids.</td>
</tr>
<tr>
<td>● Day 3: Discontinue the last 40% of the original morphine dose and maintain the patient on regular methadone administered every eight hours plus about 10% of the daily methadone dose administered as a rescue dose for breakthrough pain.</td>
</tr>
</tbody>
</table>

Table 2 Drug interactions associated with enhanced methadone effects

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Pharmacokinetic effects</th>
<th>Clinical effects</th>
<th>Type of evidence</th>
<th>Possible mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>● 35% ↑ AUC; 27% ↑ peak, 48% ↓ trough, 24% ↓ clearance methadone</td>
<td>Sedation/respiratory depression/confusion</td>
<td>Single case report; ciprofloxacin reintroduced with same outcome</td>
<td>Inhibition of CYP1A2 and/or CYP3A4</td>
<td>39</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>• Day 3: morphine to methadone (rapid transition) 1</td>
<td>● No signs/symptoms of methadone overdose reported</td>
<td>Randomised, double blind, placebo controlled trial; 13 participants received fluconazole 200 mg/day</td>
<td>Inhibition of CYP3A4, possibly others</td>
<td>38</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Fluoxetine</td>
<td>Some patients had moderate ↑ plasma level, but this was less marked than with fluvoxamine in the two patients</td>
<td>None reported</td>
<td>Nine case reports of serum levels of methadone after addition of fluoxetine; two participants had also use fluoxetine previously</td>
<td>Inhibition of CYP2D6</td>
</tr>
<tr>
<td>Sertraline</td>
<td>↑ serum methadone level</td>
<td>Hypoxemia, hypercapnia</td>
<td>Single case</td>
<td>Inhibition of one of several enzymes: CYP3A4, CYP1A2, CYP2C9, CYP2C19</td>
<td>41</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>↑ R-methadone plasma levels in CYP2D6 extensive metabolisers but not in poor metabolisers</td>
<td>No side effects reported by patients and no signs of intoxication were noted</td>
<td>Prospective administration of paroxetine in 10 methadone-using patients (two poor metabolisers, eight extensive metabolisers)</td>
<td>Inhibition of CYP2D6; also possibly CYP1A2, CYP2C9, CYP2C19, and CYP3A4</td>
<td>43</td>
</tr>
<tr>
<td>Sertraline</td>
<td>↑ methadone plasma level 26% with addition of sertraline</td>
<td>No significant difference in side effects between groups</td>
<td>Prospective, 12 week, randomised, placebo controlled trial; 12 patients received up to sertraline 200 mg/day</td>
<td>Inhibition of several isoenzymes (CYP2D6, CYP3A4, CYP1A2, CYP2C19)</td>
<td>44</td>
</tr>
</tbody>
</table>


AUC, area under the curve.
may also alleviate some of the subjective irritability common in opioid withdrawal. Prochlorperazine or promethazine assist in the management of nausea and vomiting. Loperamide will alleviate diarrhoea. Dicyclomine calms abdominal cramping; and a limited supply of a benzodiazepine such as lorazepam, might be considered to assist in the control of insomnia and irritability/anxiety.

**SIDE EFFECTS OF METHADONE**

Familiarity with the side effect profile of methadone will assist the practitioner in the appropriate titration of a methadone regimen, will obviate the unnecessary laboratory investigation of signs and symptoms known to be common medication side effects, and may assist the practitioner in the management of these side effects.

Methadone acts upon central opioid receptors, as do the other opioid drugs. This action may reduce hypercapnoeic and hypoxic ventilatory drives resulting in respiratory depression. The most severe potential consequence of this effect is central apnoea. Many cases of mortality due to this effect have been reported. In most situations, medication interactions were missed, medical risk factors ignored, or doses increased too quickly. Methadone toxicity can also result from inadequately spaced dosage regimens (dosing more frequently than every eight hours) due to the drug’s long half life and consequent drug accumulation. Careful

### Table 3 Drug interactions associated with diminished methadone effects

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Pharmacokinetic effects</th>
<th>Clinical effects</th>
<th>Type of evidence</th>
<th>Possible mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusidic acid</td>
<td>Total clearance antipyrine ↑ in group using fusidic acid × 28 days</td>
<td>No side effects were reported by patients; some patients in 28 day group developed signs of underdosage</td>
<td>Randomised, prospective trial, placebo controlled. Ten patients received fusidic acid 500 mg/day × 14 days; 10 patients with same dose × 28 days; 10 patients received no additional meds. Antipyrine clearance used to assess effect on CYP450 system</td>
<td>Induction of CYP450 enzymes</td>
<td>46</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↓ methadone plasma level</td>
<td>Methadone withdrawal symptoms</td>
<td>Case</td>
<td>Induction of CYP3A4</td>
<td>12, 47</td>
</tr>
<tr>
<td>Antivirals/non-nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Marked ↓ maximum plasma methadone concentration, ↓ AUC</td>
<td>Nine patients described symptoms of methadone withdrawal</td>
<td>Prospective trial of 11 patients using methadone and beginning therapy with efavirenz</td>
<td>Induction of CYP3A4</td>
<td>48</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Three of seven records had a documented decrease in methadone trough level or subtherapeutic level 36% reduction in maximal concentration of methadone, significant ↓ AUC</td>
<td>All seven records had evidence of opiate withdrawal</td>
<td>Retrospective chart review of 800 records of HIV-infected patients</td>
<td>Induction of CYP3A4</td>
<td>49</td>
</tr>
<tr>
<td>Antivirals/nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Administration of both abacavir and amprenavir associated with median 65% decrease in methadone concentration</td>
<td>Two patients of the five reported symptoms consistent with withdrawal</td>
<td>Prospective administration of abacavir and amprenavir to five patients using methadone</td>
<td>Abacavir not expected to induce CYP3A4 activity; the protease inhibitor, amprenavir, is a known inducer of CYP3A4 and more likely the cause of ↓ methadone concentration</td>
<td>51</td>
</tr>
<tr>
<td>Antivirals/protease inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amprenavir (see abacavir statement)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>40% ↓ AUC in S-methadone and 32% ↓ AUC in R-methadone</td>
<td>No evidence of withdrawal reported</td>
<td>Single case report nelfinavir 750 mg three times a day added to drug regimen Prospective pharmacokinetic study of 12 patients using methadone who began 400 mg nelfinavir and 400 mg saquinavir twice daily</td>
<td>Induction of CYP3A4; possible induction of P-glycoprotein</td>
<td>52, 53, 54</td>
</tr>
<tr>
<td>Ritonavir/ saquinavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Adapted with permission from Eap CB, Buclin T, Baumann P. Interindividual variability of clinical pharmacokinetics of methadone. Clin Pharmacokinet 2002;41:1153–93. AUC, area under the curve.
dose titration, a thorough history for medical risk factors, and
cognisance of medication interactions should avert this
temporally catastrophic effect.

Due to central opioid receptor activation, somnolence is
quite common during the first weeks of treatment before
tolerance to this drug effect is gained. Methadone may also
interfere with rapid eye movement sleep and sleep stages 3
and 4. When these changes persist during chronic treatment,
insomnia may occur. Patients experiencing this side effect
have lower sleep efficiency, less rapid eye movement, and less
slow wave sleep accompanied by sleep disordered breathing.
Additionally they spend more time in sleep stage 2.19

Methadone maintenance patients may also experience
subjective cognitive slowing. Objective, controlled data on
this phenomenon are scare. Tolerance would be expected to
this side effect as has been demonstrated with the chronic
use of other opioid medications. A European study examining
the cognitive effects of chronic methadone therapy concluded
that methadone treatment was not, in itself, predictive of
impairment in cognitive psychomotor skills; inferior perfor-
man ce on tests was more strongly related to sociodemo-
graphic factors. A second study demonstrated that
psychophysical performances and driving aptitude are not
significantly related to methadone dose.14

Weight gain is a commonly reported side effect among
patients on methadone maintenance. The precise aetiology is
unclear but may involve appetite increase and/or non-
cardiogenic peripheral oedema. Previous studies have indi-
cated an onset of weight gain three to six months after
initiation of methadone maintenance treatment or after a
sharp dosage increase.32 35

Sexual dysfunction is also a common complaint of
individuals on chronic methadone. In men, orgasm dysfunc-
tion and a decrease in libido are the most common concerns.
Spermatic dysmotility has also been described.16 17 Whether
or not fertility is adversely affected has yet to be firmly
established. Several studies that indicate subnormal levels
of plasma testosterone in men maintained on methadone may
account for these side effects, though a dose effect relation-
ship has yet to be discovered.16 44 Women may experience
dysfunction of libido as well as oligomenorrhoea or amenor-
rhoea.32 The aetiology of and potential treatments for these
effects are unclear.

Up to 65% of patients report constipation as a direct effect
of methadone.44 Tolerance to this peripheral opioid effect may
not develop, often necessitating a scheduled bowel regimen
during treatment with methadone.45

DRUG INTERACTIONS WITH METHADONE

There are many potential drug interactions with methadone. However, it is difficult to study drug interactions because
methadone has a long half life, and time to steady state
concentration after a change due to a drug interaction may
require up to 10 days. Many of the drug interactions cited in
the literature have not been rigorously investigated.19 In
addition, even though statistically significant change in
methadone concentration may occur as a result of a drug-
drug interaction, the clinical outcome may not be significant,
since methadone’s half life varies significantly between
individuals. In the setting of a potential drug interaction,
therefore, it is reasonable to institute a dosing regimen as
described in tables 2 or 3, and monitor the patient closely for
signs of supratherapeutic dosing (sedation, euphoria).

Drug interactions with methadone most commonly occur
due to inhibition or induction of liver enzymes. Although
drugs like older macrolide antibiotics (troleandomycin),
ketocazole, and diazepam are able to inhibit CYP3A4
metabolism of methadone to its inactive metabolite by up to
80% in vitro, many of these agents do not exhibit the same
degree of inhibition in vivo.25 A summary of medications
associated with increased concentrations of methadone are
found in table 2.44–50

Drugs which induce enzyme systems responsible for
methadone metabolism may result in lowering of methadone
levels. It is thought that chronic abuse of alcohol may
increase liver enzymes and reduce methadone levels.21 22
Seizure medications like phenytoin, phenobarbital, and
carbamazepine are classic examples of CYP3A4 enzyme
inducers that may lower methadone concentrations.21 22 Of
the antibiotics, rifampin has been shown to interfere with
methadone. Of the antiviral medications used for the
management of HIV, the non-nucleoside reverse transcriptase
inhibitors increase the metabolism of methadone. Drug
interactions resulting in lowered methadone concentrations
can be found in table 3.17 52–60

Methadone levels may be affected by competition for
enzyme metabolism. For example, some feel that binge
drinking of alcohol may prevent appropriate metabolism of
methadone, temporarily increasing concentrations.29 One
example of preferential metabolism of methadone is its
interaction with zidovudine, where increased zidovudine
levels have been described.16 On the other hand, methadone
appears to decrease the concentration of stavudine and
didanosine by apparently decreasing their absorption.19
Finally, both alcohol and benzodiazepines have been associ-
ated with increased risk for respiratory depression in
patients using opioids.14

CONCLUSION

In summary, methadone has important therapeutic applica-
tions beyond methadone maintenance for opioid depend-
dence. It is a viable choice for patients with neuropathic pain,
for pain resistant to treatment with other opioid analgesics,
and for situations where dose limiting side effects occur from
other opioid agents. Practitioners who prescribe methadone
need to be familiar with its unique pharmacokinetic profile,
side effects, and potential drug interactions to ensure safe,
effective use of this agent.

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