Opioids and Methadone Equivalents for Clinicians

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Settings in which clinicians are likely to prescribe narcotics and opioids include those that manage chronic pain, methadone maintenance programs, and primary care. More commonly, clinicians prescribe psychotropic medications that may potentiate opioid-associated respiratory depression.

The terms *narcotics* and *opioids* are commonly used interchangeably. These substances bind to the μ receptors for their euphorigenic, mood-altering, and dependence-producing properties.[1] These agents also may depress respiration via the μ receptors in the pons and medulla oblongata. Positron emission tomography (PET) scan of μ receptors shows them to be located in the (1) thalamus (highest concentrations and involved in pain), (2) cerebral cortex (intermediate concentrations), (3) basal ganglia (intermediate concentrations and involved in movement and emotions), and (4) visual cortex (lowest concentrations).[2] PET scanning has also located μ receptors in the pons and medulla, but semiquantitative estimates are not available.

The respiratory center is located in the pons and medulla oblongata. This center is a part of the reptilian brain when separating the central nervous system into (1) brain stem (midbrain, pons, and medulla oblongata) and cerebellum (reptilian), (2) limbic system (mammalian), and (3) cortex and neocortex (human) divisions.[3] Because the respiratory center arose in the brain stem more than 200 million years ago with primitive vertebrates, it is hardier than more recent brain structures. Thus, lower doses of narcotics and opioids may provide pain relief as agonists for μ receptors. At higher doses, narcotics and opioids may cause respiratory depression.

Clinicians work with patients suffering from both acute and chronic pain. Long-term pain management is more problematic, particularly in the mental health field. Long-acting opioids include methadone, sustained-release preparations of morphine, and fentanyl patches. Of these 3 opioids, clinicians in the mental health field tend to be most familiar with methadone. It is important that clinicians be conversant with methadone-equivalent doses of various opioids that their patients may be taking because of the potential respiratory-depressing effects of nonopioid psychotropic drugs coupled with opioid psychotropic drugs.

There is no clear linear relationship between methadone dose and respiratory depression because of several factors. Subjects receiving long-term opioid treatment usually develop tolerance to the respiratory-depressant effects of these drugs. Respiratory depression may occur when pain is abruptly relieved and the sedative effects of opioids are no longer opposed by the stimulating effects of pain. This is a rare event.

In methadone maintenance programs, effective methadone doses today generally fall in the 60- to 100-mg/day range.[4,5] Methadone doses greater than 40 to 50 mg/day in subjects entering a methadone maintenance program may be associated with respiratory depression.

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Table 1. Commonly Used Medications That May Inhibit Cytochrome P450 3A4 Metabolism and Increase Blood and Tissue Levels of Methadone[a]

Fluconazole	Erythromycin
Itraconazole	Clarithromycin
Ketoconazole	Diltiazem
Ritonavir	Verapamil
Nelfinavir	Paroxetine
Amiodarone	Fluoxetine

[a]Based on Lacy et al.[6]

In terms of drug interactions, methadone is a minor substrate of cytochrome P450 (CYP) 2C8/9, 2C19, and 2D6; it is a major substrate of CYP3A4.[6] Methadone moderately inhibits CYP2D6 and weakly inhibits CYP-3A4.[6] Concomitant administration of drugs inhibiting the CYP3A4 isoenzyme may contribute to methadone overdose by increasing methadone accumulation. Table 1 lists commonly used medications that may inhibit CYP3A4 metabolism.

CONVERSION TABLE

We provide an opioid conversion table (Appendix 1)[7–10] for commonly used opioid preparations to help clinicians better understand the relationship between these agents and methadone. Conversion must take into consideration clinical issues that affect translation of equivalents to and from methadone.

Concomitant drugs affecting the metabolism of the nonmethadone drug may not similarly affect the metabolism of methadone and vice versa during and after conversion.[11] Similarly, organ disease, particularly liver disease, may confound the conversion process. Also, the nonmethadone drug may have a different effect than methadone on such psychiatric conditions as anxiety and depression. In a perfect world, the clinician would have serial plasma levels of the nonmethadone drug before conversion and then serial plasma levels of methadone during and after conversion. However, even here there may not be a linear relationship between plasma level and clinical effect. Methadone plasma levels are most useful when the patient's current state does not agree with the expected state of methadone treatment. Ultimately, clinicians must depend on the patient's report and their own assessment and experience when making medical judgments. This principle most certainly applies when converting from a nonmethadone narcotic to methadone.

In *The American Psychiatric Publishing Textbook of Substance Abuse Treatment,*[12] Gunderson and Stimmel dedicate a section of their chapter on treating pain in drug-addicted patients to the conversion from one opioid to another. They emphasize the importance of using equivalence doses. Because of incomplete cross-tolerance, Gunderson and Stimmel[12] recommend dividing the calculated equivalent dose in half followed by adjusting that dose upward for the first 24 hours of conversion to optimize analgesia. For patients dependent on methadone in a methadone treatment program, prescription of an opioid analgesic in excess of baseline requirements is recommended—initially prescribe two thirds of the calculated total dose and adjust upward as needed. When changing from other opioids to methadone for pain control, clinicians should start methadone at a dose much lower than the equi-analgesic dose—down to one tenth the calculated dose—and then monitor the patient closely over the ensuing 3 to 6 days.

Drug names: amiodarone (Cordarone, Pacerone, and others), clarithromycin (Biaxin and others), diltiazem (Cardizem, Tiazac, and others), erythromycin (Eryc, PCE, and others), fluconazole (Diflucan and others), fluoxetine (Prozac and others), itraconazole (Sporanox and others), ketoconazole (Ketozole, Nizoral, and others), nelfinavir (Viracept), paroxetine (Paxil and others), ritonavir (Norvir), verapamil (Calan, Isoptin, and others).

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Appendix 1 appears on page 88.

Appendix 1. Opioid Conversion Data: Equi-Analgesic Dosing Guide Equivalency Table

Chemical Name	Trade Name (examples)	FDA Schedule	Onset	Duration	Half-Life of Parent Drug	Typical Dose Ranges	Example Daily Dosing Regimen	Equivalent Morphine Dose (po) (mg/d) to Example	Equivalent Methadone Dose (po) (mg/d) to Example
Fentanyl patch	Duragesic	II	12–24 h	60–72 h	7 h	25–300 µg (transdermal) q 72 h	50 µg q 72 h	150–200	60–80
Fentanyl transmucosal	Actiq	II	5–15 min	4–8 h (dependent on blood levels)	17 h	200–1600 µg q 8–12 h (only for chronic opiate users)	400 µg q 8 h	45–60	18–24
Hydromorphone oral	Dilaudid	II	15–30 min	4–6 h	2–4 h	2–8 mg po q 6–8 h	4 mg q 6 h	64	26
Meperidine oral	Demerol	II	10–15 min	2–4 h	3–4 h; liver disease patients = 7–11 h; active metabolite = 15–30 h	50–100 mg po q 4–6 h	100 mg q 6 h	40	16
Methadone oral	Dolophine, Methadose	II	30–60 min	4–8 h > 8 h (chronic)	15–29 h	10–100 mg q 6–8 h	20 mg q 8 h	150	60
Morphine oral	MSIR, Roxanol	II	15–60 min	3–6 h	2–4 h	5–20 mg q 4–6 h (as adjunct)	10 mg q 4 h	60	24
Morphine oral (long-acting)	Avinza, Kadian, MS Contin, Oramorph	II	2–3 h (Avinza = 30 min)	8–14 h (Avinza = 18–24 h)	2–4 h	15–100 mg q 8–12 h	60 mg q 12 h	120	48
Oxycodone oral	OxyFast, Percocet, Percodan, Roxicet, Roxicodone, Tylox	II	15–30 min	4–6 h	3–4 h	5–15 mg q 4–6 h (as adjunct)	10 mg q 6 h	80	32
Oxycodone oral (long-acting)	OxyContin	II	1–2 h	6–10 h	3–4 h	10 mg–80 mg q 12 h	40 mg q 12 h	160	64
Hydrocodone oral	Anexsia, Lorcet, Lortab, Norco, Vicodin, Vicoprofen, Zydone	III	30–60 min	4–8 h	3–4.5 h	5–15 mg q 3–8 h	10 mg q 6 h	No data (in practice, 40, approximately)	No data (in practice,16, approximately)
Codeine oral	Tylenol #3 (combination)	II (alone), III, V in combinations	30–60 min	4–8 h	3–4 h	15–60 mg q 4–6 h	30 mg q 6 h	20	8
Propoxyphene oral	Darvocet, Darvon	IV	30–60 min	4–6 h	3–15 h	50–100 mg q 4–6 h	100 mg q 6 h	60	24

Abbreviation: FDA = U.S. Food and Drug Administration.
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