Dosage

Available as morphine sulfate; dosage usually expressed as the sulfate.[b]

Should be given in the smallest effective dose and as infrequently as possible in order to minimize the development of tolerance and physical dependence.[b]

In patients with severe, chronic pain, dosage should be adjusted according to the severity of the pain and the response and tolerance of the patient.

In patients with exceptionally severe, chronic pain or in those who have become tolerant to the analgesic effect of opiate agonists, it may be necessary to exceed the usual dosage.

Pediatric Patients

Pain

Moderate to Severe Pain

Oral

Infants and children: 0.2–0.5 mg/kg every 4–6 hours (conventional tablets, oral solution).[197]

IM or Sub-Q

Neonates: 0.05–0.2 mg/kg every 2–4 hours as necessary.[197]

Infants and children: 0.1–0.2 mg/kg every 2–4 hours.[197]

Single pediatric doses should not exceed 10 mg.[196]

IV

Neonates: 0.05–0.2 mg/kg every 2–4 hours as necessary.[197] For continuous IV infusion, 0.025–0.05 mg/kg per hour.[197]

Infants and children: 0.1–0.2 mg/kg every 2–4 hours.[197]

Adolescents >12 years of age: 3–4 mg; may repeat in 5 minutes if needed.[197]

Single pediatric doses should not exceed 10 mg.[196]

PCA (usually IV) via controlled-delivery device: Loading doses of 0.05 mg/kg (preferably titrated by clinician or nurse at bedside, up to 0.05–0.2 mg/kg total) used.[200] Maintenance doses (administered intermittently) of 10–20 mcg/kg, usually no more frequently than every 6–12 minutes as a device-programmed lockout period used for developmentally mature pediatric patients ≥7 years of age.[200] [201]

Epidural or Intrathecal

Safety and efficacy in children not established.[192] [b]

Cancer Pain (Severe, Chronic)

IV

Maintenance dosages of 0.025–2.6 mg/kg per hour (median: 0.04–0.07 mg/kg per hour) have been infused IV in children.[b]

Sub-Q

Maintenance dosages of 0.025–1.79 mg/kg per hour (median: 0.06 mg/kg per hour) have been infused sub-Q in a limited number of children.[b]

Sickle Cell Crisis (Severe Pain)

IV

Maintenance dosages of 0.03–0.15 mg/kg per hour have been infused IV in children.[b]

Postoperative Analgesia

IV

Maintenance dosages of 0.01–0.04 mg/kg per hour have been infused.[b]

Adults

Pain (Oral Treatment)

Most manufacturers suggest that it is preferable to initiate and stabilize oral morphine sulfate therapy with a conventional (immediate-release) preparation and then switch the patient to an extended-release preparation (Avinza, Kadian, MS Contin, Oramorph SR) since titration of dosage may be more difficult with the latter preparations.[169] [170] [172]

Dosing regimen must be individualized based on the patient's prior analgesic therapy.[169] [170] [171] [172]

Initial dosage of extended-release preparations should be based on the total daily dosage, potency, and specific characteristics of the current opiate agonist.[169] [170] [171] [172]

Other considerations should include the reliability of relative potency estimates used in calculating the equivalent morphine sulfate dosage, the degree of opiate experience and tolerance, the medical condition of the patient, concomitant drug therapy, and the nature and severity of the patient's pain.[169] [170] [171] [172]

It is preferable to underestimate the initial dosage of extended-release preparations than to inadvertently cause an overdosage of morphine sulfate.[171] [172]

Supplemental doses of a short-acting opiate agonist can be considered if breakthrough pain occurs with dosing regimens employing extended-release preparations.[169] [170] [171] [172]

When converting to another oral extended-release morphine sulfate preparation or to other oral or parenteral opiate analgesics, the manufacturer's labeling information should be consulted.[169] [170171] [172]

Oral Solutions or Conventional Tablets

Oral

Usually, 10–30 mg every 4 hours as necessary or as directed by a physician.[197] [200]

Extended-release Capsules (Avinza)

Oral

Individualize dosage according to patient response and tolerance; do not exceed 1.6 g daily.[171](See Fumaric Acid under Cautions.)

Administer Avinza no more frequently than once every 24 hours.[171] The 60-, 90-, and 120-mg Avinza capsules should be used only in opiate-tolerant patients.[171]

Switching from other oral morphine preparations to Avinza: Use the prior total daily oral dosage and administer once every 24 hours.[171] Supplemental doses of a short-acting opiate analgesic may be required for up to 4 days until the patient's response to Avinza has stabilized.[171]

Switching from parenteral morphine or other non-morphine oral or parenteral opiate therapy to Avinza: Calculate the opiate analgesic requirements during the previous 24 hours and convert to an equianalgesic dosage of Avinza.[171] Use conservative dosage conversion ratios to avoid toxicity.[171]

When used as the initial opiate in patients who do not have a proven tolerance to opiates: Usual initial dosage is 30 mg once daily; increase dosage by no more than 30 mg every 4 days.[171]Dosage increases should be conservative in opiate-naive patients.[171]

Extended-release Capsules (Kadian)

Oral

Individualize dosage according to patient response and tolerance; do not increase dosage more frequently than every other day.[172]

Administer Kadian no more frequently than every 12 hours.[172] Patients receiving once-daily Kadian who experience excessive sedation or inadequate analgesia prior to the next dose should be switched to a twice-daily regimen.[172] The 100- and 200-mg Kadian capsules should be used only in opiate-tolerant patients.[172]

Switching from other oral morphine preparations to Kadian: Use the prior total daily oral dosage and give in 2 divided doses every 12 hours or once every 24 hours.[172] First dose of Kadian may be administered concurrently with the last dose of immediate-release opiate therapy because of the delayed peak plasma morphine concentrations produced by Kadian.[172]

Switching from parenteral morphine or other non-morphine oral or parenteral opiate therapy to Kadian: Calculate the opiate analgesic requirements during the previous 24 hours and convert to an equianalgesic dosage of Kadian.[172] Use conservative dosage conversion ratios to avoid toxicity.[172]

When used as the initial opiate in patients who do not have a proven tolerance to opiates: Initially 10 or 20 mg of Kadian; increase by no more than 20 mg every other day.[172]

Extended-release Tablets (MS Contin)

Oral

Individualize dosage according to patient response and tolerance.[170]

Interval between doses of MS Contin should not exceed 12 hours in order to avoid administration of large single doses.[170]

Use 15-mg tablets when total daily dosage is expected to be <60 mg daily; use 30-mg tablets when total daily dosage is expected to be 60–120 mg daily.[170] The 100- and 200-mg tablets of MS Contin should be used only in patients who are opiate tolerant and require dosages of ≥200 mg daily.[170]

Switching from an immediate-release oral morphine preparation to MS Contin: Use the prior total daily oral dosage and give in 2 divided doses every 12 hours or in 3 divided doses every 8 hours.[170]

Switching from parenteral morphine or other oral or parenteral non-morphine opiate to MS Contin: Calculate the opiate analgesic requirements during the previous 24 hours and convert to an equianalgesic dosage of MS Contin.[170] Use conservative dosage conversion ratios to avoid toxicity.[170]

Extended-release Tablets (Oramorph SR)

Oral

Individualize dosage according to patient response and tolerance.[169]

Dosing interval for Oramorph SR should not exceed 12 hours because administration of large single doses may lead to acute overdosage.[169] If pain is not controlled for the entire 12-hour interval, then the dosing interval may be decreased, but doses should be administered no more frequently than every 8 hours.[169]

Use 30-mg tablets if morphine sulfate requirement is ≤120 mg daily.[169] Use 15-mg tablets if morphine sulfate requirement is low.[169]

Switching from other oral morphine preparations to Oramorph SR: Use the prior total daily oral dosage and give in 2 divided doses every 12 hours.[169]

Switching from parenteral morphine or other oral or parenteral non-morphine opiate to Oramorph SR: Calculate the opiate analgesic requirements during the previous 24 hours and convert to an equianalgesic dosage of Oramorph SR.[169] Use conservative dosage conversion ratios to avoid toxicity.[169]

Pain (Other Routes)

Rectal

Suppositories: Usually, 10–20 mg every 4 hours as necessary or as directed by a physician.[b]

IV

May administer 2.5–20 mg every 2–6 hours as needed[196] [197] or via continuous infusion at a rate of 0.8–10 mg per hour.[197]

Can be administered at a rate of 2–4 mg every 5 minutes, with some patients requiring as much as 25–30 mg before pain relief is adequate.[140]

IM or Sub-Q

May administer 2.5–20 mg every 2–6 hours as needed[196] [197] or via continuous infusion at a rate of 0.8–10 mg per hour.[197]

Epidural (Morphine Sulfate Injection [preservative-free])

Usual initial dose for intermittent injection is 5 mg.[b]

Inadequate pain relief within 1 hour after administration of the initial dose: Additional epidural doses may be given carefully in 1- to 2-mg increments at intervals sufficient to assess efficacy; no more than 10 mg total daily dose.[b]

Pain relief generally occurs within 6–30 minutes and persists for about 16–24 hours (range: 4–36 hours) after a single, effective epidural dose of morphine.[b]

Continuous epidural infusion, device not implanted surgically: Initial dosage of 2–4 mg per 24 hours has been recommended; epidural dosage may be increased by 1–2 mg daily if adequate relief is not achieved initially.[b]

If an implantable microinfusion device is to be employed for continuous epidural infusion, efficacy and adverse effects of initial dosage should be assessed for each patient using serial, intermittent epidural doses of the drug prior to implantation surgery.[b]

Most adults who are not tolerant to opiates achieve adequate relief with initial epidural dosages of 3.5–7.5 mg daily.[b]

Administer with extreme caution and in reduced dosage epidurally or intrathecally in geriatric or debilitated patients.[b]

Epidural (Morphine Sulfate Extended-release Liposomal Injection [DepoDur])

Administer as a single dose.[192]

Major orthopedic surgery of a lower extremity: 15 mg prior to surgery.[192] Some patients may benefit from 20-mg dose; however, the incidence of serious adverse respiratory events was dose related in studies.[192]

Lower abdominal or pelvic surgery: 10–15 mg prior to surgery.[192] Some patients may benefit from 20-mg dose; however, the incidence of serious adverse respiratory events was dose related in studies.[192]

Cesarean section: 10 mg after the umbilical cord is clamped.[192]

Intrathecal

The intrathecal dose of morphine sulfate is about $^{1}/_{10}$ the epidural dose.[b]

A single 0.2- to 1-mg intrathecal dose may provide adequate relief for up to 24 hours in adults who are not tolerant to opiates.[b]

Repeated intrathecal doses of the drug are not recommended except to establish initial intrathecal dosage when continuous intrathecal infusion is to be employed; if additional morphine therapy is necessary for patients who are not candidates for continuous intrathecal infusion, alternative routes of administration should be considered.[b]

Naloxone may be infused IV at a rate of 0.6 mg/hour for 24 hours after intrathecal morphine administration to decrease potential opiate-induced adverse effects.[b]

If an implantable microinfusion device is to be employed for continuous intrathecal infusion, efficacy and adverse effects of initial dosage should be assessed for each patient using serial, intermittent intrathecal doses of the drug prior to implantation surgery.[b]

Intrathecal dosages exceeding 20 mg daily should be employed with caution since they may be associated with an increased likelihood of serious toxicity, including myoclonic spasms.[b]

Administer with extreme caution and in reduced dosage epidurally or intrathecally in geriatric or debilitated patients.[b]

Pain (MI)

To relieve pain and associated anxiety and provide potentially beneficial cardiovascular effects in adults with AMI, dosages of 2–15 mg have been administered parenterally.[b]

IV

Preferred route since absorption following sub-Q or IM injection may be unpredictable, and repeated doses (up to every 5 minutes if necessary) in small increments (e.g., 1–4 mg) generally are preferred to larger and less frequent doses in order to minimize the risk of adverse effects (e.g., respiratory depression).[b]

Occasionally, patients may require relatively large cumulative doses (e.g., 2–3 mg/kg).[b]

Patients should be advised to notify their caretakers (e.g., nurse) immediately when discomfort occurs and describe its severity on a numeric scale (e.g., 1–10).[b]

Cancer Pain

Individualize dosage according to the response and tolerance of the patient for sub-Q or continuous IV infusions.[b]

Continuous IV

Initially 0.8–10 mg/hour and then increase to an effective dosage as necessary; an IV loading dose of ≥15 mg can be administered for initial relief of pain prior to initiating continuous IV infusion of the drug.[b]

Maintenance doses have ranged from 0.8–80 mg/hour infused IV, although higher (e.g., 150 mg/hour) maintenance dosages occasionally have been required.[b]

Patient-controlled Analgesia (PCA)

IV

Adjust dosage according to the severity of the pain and response of the patient; consult the operator’s manual for the patient-controlled infusion device for directions on administering the drug at the desired rate of infusion.[b]

Exercise care to avoid overdosage, which could result in respiratory depression, or abrupt cessation of therapy with the drug, which could precipitate opiate withdrawal.[b]

PCA via controlled-delivery device: Standard protocol uses loading dose of 1 mg,[198] [199] [200] time between doses of 6 minutes (lockout period), and limit of 10 doses per hour.[198] [199] Loading doses of 2–4 mg every 10 minutes, preferably titrated by clinician or nurse at bedside, up to 6–16 mg total have been used for rapid control of pain.[200] [204] Maintenance doses (self-administered intermittently) of 0.5–2 mg, usually no more frequently than every 6–12 minutes as a device-programmed lockout period used.[200] [203] [204]

Unstable Angina (Unresponsive to 3 Sublingual Doses of Nitroglycerin)

IV

2–5 mg (repeated every 5–30 minutes as needed to relieve symptoms and maintain patient comfort) has been used.[b]

Analgesia during Labor

Sub-Q or IM

10 mg.[b]

a. Endo Pharmaceuticals. DepoDur (morphine sulfate extended-release liposome injection) prescribing information. Chadds Ford, PA; 2006 Jul.

b. AHFS drug information 2006. McEvoy GK, ed. Morphine Sulfate. Bethesda, MD: American Society of Health-System Pharmacists; 2006;2117-24.

e. AHFS drug information 2006. McEvoy GK, ed. Opiate agonists general statement. Bethesda, MD: American Society of Health-System Pharmacists; 2006:2096-101.

169. Xanodyne Pharmaceuticals. Oramorph SR (morphine sulfate) sustained release tablets prescribing information. Newport, KY; 2006 Feb.

170. Purdue Pharma. MS Contin (morphine sulfate) controlled-release tablets prescribing information. Stamford CT; 2005 Nov 3.

171. Ligand Pharmaceuticals. Avinza (morphine sulfate) extended-release capsules prescribing information. San Diego, CA; 2005 Dec.

172. Actavis Kadian. Kadian (morphine sulfate extended-release capsules) prescribing information. Morristown, NJ; 2009 Feb.

173. Baxter. Morphine sulfate injection prescribing information. Deerfield, IL; 1999 Apr

174. Society of Critical Care Medicine and American Society of Health-System Pharmacists: Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Am J Health-Syst Pharm.* 2002; 59:150-78.

175. Purdue Pharma L.P. OxyContin (oxycodone HCl controlled release) tablets patient information. Stamford, CT; 2002 Jan.

176. USP DI: drug information for the health care professional. 23rd ed. Greenwood Village, CO: Thompson Micromedex; 2003;1:2063-8.

177. American Geriatric Society Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soci*. 2002; 50(suppl):S205-24.

178. Freedman GM. Clinical management of common causes of geriatric pain. *Geriatrics*. 2002; 57:36-41. [IDIS 480380] [PubMed 12040592]

179. Sanofi-Synthelabo. Demerol (meperidine hydrochloride) tablets and syrup prescribing information. New York, NY; 2002 May.

180. Anon. Principles of analgesic use in the treatment of acute pain and cancer pain. 4th ed. Glenview, IL: American Pain Society; 1994.

181. Jacox A, Carr DB, Payne R et al. Management of cancer pain: clinical practice guideline. No. 9. Rockville, MD: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR publication No. 94-0592.

182. Food and Drug Administration. 2003 safety alert: Roxanol (morphine sulfate) concentrated oral solution. Rockville, MD; June 2003. From FDA website ().

183. Schobelock MJ. Dear healthcare professional letter: Product discontinuation notice—Orlaam (levomethadyl hydrochloride acetate) oral solution, 10 mg/mL, CII. Columbus, OH: Roxane Laboratories; 2003 Apr 23.

184. aaiPharma, Inc. Methadone hydrochloride injection prescribing information. Wilmington, NC; 2004 Feb.

185. Anderson R, Saiers JH, Abram S et al. Accuracy in equianalgesic dosing: conversion dilemmas. *J Pain Symptom Manage*. 2001; 21:397-406. [IDIS 463769] [PubMed 11369161]

186. Roxane Laboratories, Inc. Methadone hydrochloride tablets prescribing information. Columbus, OH. 2000 Dec.

187. Layson-Wolf C, Goode JV, Small RE. Clinical use of methadone. *J Pain Palliat Care Pharmacother*. 2002; 16:29-59. [PubMed 14650449]

188. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer*. 2001; 9:73-83. [PubMed 11305074]

189. Kharasch ED, Hoffer C, Whittington D et al. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther*. 2004; 76:250-69. [IDIS 521156] [PubMed 15371986]

190. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003; 349:1943-53. [IDIS 506512] [PubMed 14614170]

191. Principles of analgesic use in the treatment of acute pain and cancer pain. 5th ed. Glenview, IL: American Pain Society; 2004:14,17.

192. Endo Pharmaceuticals. DepoDur (morphine sulfate extended-release liposome injection) prescribing information. Chadds Ford, PA. From Skye Pharma web site (). Accessed 19 Oct 2005.

193. Baxter. Duramorph (morphine sulfate injection) preservative free prescribing information. Deerfield, IL; 2004 Dec.

194. Medtronic. Tools for safe patient management. Minneapolis, MN; 2006 Jan.

195. Alpharma. Kadian: important safety information health care professionals. From Kadian website .) Accessed 2006 Nov 29

196. Faulding Pharmaceutical Co. Morphine sulfate injection prescribing information. Paramus, NJ; 2003 Mar.

197. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson textbook of pediatrics. 17th ed. Philadelphia: Saunders; 2004:2469.

198. Viscusi ER, Schechter LN. Patient-controlled analgesia: finding a balance between cost and comfort. *Am J Health-Syst Pharm*. 2006; 63 (suppl 1):S3-13. [PubMed 16598071]

199. Strassels SA, McNicol E, Suleman R. Postoperative pain management: a practical review, part 1. *Am J Health-Syst Pharm*. 2005; 62:1904-16. [PubMed 16141110]

200. Bailey PL. Clinical Pharmacology and Applications of Opioid Agonists. In: Bowdle TA, Horita A, Kharasch ED. The pharmacologic basis of anesthesiology. New York: Churchill Livingstone; 1994:83-119.

201. Berde CB, Lehn BM, Yee JD et al. Patient-controlled analgesia in children and adolescents: a randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. *J Pediatr*. 1991; 118:460-6. [PubMed 1999793]

202. aai Pharma. Roxanol and Roxanol-T (morphine sulfate) oral solution prescribing information. Wilmington, NC. 2004 Jul.

203. Hudcova J, McNicol E, Quah C et al. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev. 2006; 4:CD003348. DOI: 10.1002/14651858.CD003348.pub2.

204. Ginsberg B, Latta KS. Acute pain management. In: Lipman AG, ed. Pain management for primary care clinicians. Bethesda, MD; American Society of Health-System Pharmacists; 2004:123-38.

متادون:

در دردهای شدید ۲/۵ تا ۱۰ میلی گرم به صورت خوراکی، عضلانی و زیر جلدی تجویز خواهد شد که هر ۳ تا ۴ ساعت یکبار قابل تمدید است.

نکته قابل توجه در مصرف متادون دوز انباشته آن است که در صورت تکرار آن بعد از ۳ تا ۵ روز به وجود می آید که احتیاج به تعدیل دوز در این زمان خواهیم داشت که به صورت تجویز دوز ها در ۸ تا ۱۲ ساعت صورت خواهد گرفت .

دوز ضد دردی متادون:۲/۵ تا ۱۰ میلی گرم هر ۳ تا ۸ ساعت یکبار در صورت لزوم ۵ تا ۲۰ میلی گرم هر ۶ تا ۸ ساعت یکبار صورت میگیرد.

Administration

Administer orally or by sub-Q, IM, or IV injection.[217] [222] [225] [226] [261] [262]

Oral Administration

Tablets, dispersible tablets, oral solution, and oral concentrate solution are for oral administration only and *must not* be injected.[217] [225] [226] [261] [262]

Dispersible Tablets

Disperse dose in 120 mL of water, orange juice, Tang, citrus-flavored Kool-Aid, or other acidic fruit beverage immediately prior to oral administration.[261] [262] Complete tablet dispersion occurs within 1 minute; dispersion time is slightly increased when a cold and/or acidic vehicle is used.[a] If any residue remains in cup after initial administration, add a small amount of liquid and administer the resulting mixture.[261] [262]

The 40-mg dispersible tablets are used in detoxification and maintenance of opiate dependence;[261] [262] [271] this preparation should *not* be used for the treatment of pain.[261] [262] [270] [271]

Dispersible tablets contain insoluble excipients and must *not* be used to prepare solutions for injection.[261] [262]

Each 40-mg dispersible tablet can be divided in half or in quarters.[261] [262]

Because dispersible tablets can be administered only in 10-mg increments, this dosage form may be inappropriate in many patients for initial dosing during detoxification and maintenance treatment or for gradual dosage reduction following detoxification or a period of maintenance treatment.[261] [262]

Oral Concentrate Solution

Dilute the dose with water or other suitable liquid (e.g., Kool-Aid, Tang, apple juice, Crystal Light[with aspartame]) to ≥30 mL prior to administration.[255] [256]

IM or Sub-Q Administration

Absorption following sub-Q or IM injection may be unpredictable and has not been fully characterized; local tissue reactions may occur.[222]

IV Administration

Administer by IV injection.[222]

For solution and drug compatibility information, see Compatibility under Stability.

Dosage

Available as methadone hydrochloride; dosage expressed in terms of the salt.[217] [222] [225] [226] [261] [262] [263]

Careful dosage selection and titration are essential to avoid overdosage.[217]

Adults

Pain

When selecting an initial dosage, consider the type, severity, and expected duration of the patient's pain; the age, general condition, and medical status of the patient; concurrent drug therapy (see Interactions); and the acceptable balance between pain relief and adverse effects.[217][222]

Give the smallest effective dose in order to minimize development of tolerance and physical dependence.[a]

Oral

Opiate-naive patients: Initially, no more than 2.5–10 mg every 8–12 hours.[217] Titrate dosage to provide adequate analgesia; increase dosage slowly to avoid accumulation and potential toxicity.[217]

Dosage interval may range from 4–12 hours, since the duration of analgesia is relatively short during the first days of therapy but increases substantially with continued administration.[217] [223] [227]Use caution to avoid overdosage.[217]

Patients being switched from parenteral methadone: Initiate oral methadone at an oral-to-parenteral dosage ratio of 2:1 (e.g., 10 mg of oral methadone hydrochloride in patients previously receiving 5 mg of parenteral methadone hydrochloride).[217]

Adjust dosage at intervals of 1–2 days with close monitoring.[217] If breakthrough pain occurs, adjust dosage or administer small dose of rescue (immediate-release) analgesic.[217] If adverse effects are excessive, reduce the next dose; if adverse effects are intolerable, adjust dose or dosing interval.[217]

If discontinuance of opiates is required, taper dosage every 2–4 days to avoid manifestations of abrupt withdrawal.[217]

IV

Opiate-naive patients: Initially, 2.5–10 mg every 8–12 hours.[222] Titrate dosage to provide adequate analgesia; increase slowly to avoid accumulation and potential toxicity.[222] More frequent administration may be required during initiation of therapy to maintain adequate analgesia; however, use caution to avoid overdosage.[222]

Patients being switched from oral methadone: Initiate parenteral methadone at a parenteral-to-oral dosage ratio of 1:2 (e.g., 5 mg of parenteral methadone hydrochloride in patients previously receiving 10 mg of oral methadone hydrochloride).[222]

Conversion from Other Opiate Therapy

For patients being transferred from therapy with other opiate agonists, dosage may be estimated based on comparisons with morphine sulfate.[217] [222] Select dosage carefully (see General: Conversion from Other Opiate Analgesic Therapy under Dosage and Administration).[217] [222]

For patients being transferred from therapy with opiate agonists other than morphine, a comparative opiate agonist dosage table may be consulted to determine the equivalent morphine dosage.[217] [222]

Oral

Dosage estimates obtained from Table 1 must be individualized (e.g., based on prior opiate use, medical condition, concurrent drug therapy, anticipated use of analgesics for breakthrough pain).[217] [222]

Administer the total daily dosage in divided doses (e.g., at 8-hour intervals) based on individual patient requirements.[217] [222]

Table 1. Conversion from Oral Morphine Sulfate to Oral Methadone Hydrochloride (for Chronic Administration)217222

Baseline Total Daily *Oral*Morphine Sulfate Dosage	**Estimated Daily *Oral* Methadone Hydrochloride Dosage (as % of Total Daily Morphine Sulfate Dosage)**
<100 mg	20–30%
100–300 mg	10–20%
300–600 mg	8–12%
600–1000 mg	5–10%
>1000 mg	<5%

IV

Dosage estimates obtained from Table 2 and Table 3 must be individualized (e.g., based on prior opiate use, medical condition, concurrent drug therapy, anticipated use of analgesics for breakthrough pain).[222]

Administer the total daily dosage in divided doses (e.g., at 8-hour intervals) based on individual patient requirements.[222]

Table 2. Conversion from Oral Morphine Sulfate to IV Methadone Hydrochloride (for Chronic Administration)222

Baseline Total Daily *Oral*Morphine Sulfate Dosage	**Estimated Daily *IV* Methadone Hydrochloride Dosage (as % of Total Daily Morphine Sulfate Dosage)**

<100 mg	10–15%
100–300 mg	5–10%
300–600 mg	4–6%
600–1000 mg	3–5%
>1000 mg	<3%

Derived from Table 2 assuming a 3:1 oral-to-parenteral morphine ratio.[222]

Table 3. Conversion from Parenteral Morphine Sulfate to IV Methadone Hydrochloride (for Chronic Administration)

Baseline Total Daily *Parenteral*Morphine Sulfate Dosage	**Estimated Daily *IV* Methadone Hydrochloride Dosage (as % of Total Daily Morphine Sulfate Dosage)**
10–30 mg	40–66%
30–50 mg	27–66%
50–100 mg	22–50%
100–200 mg	15–34%
200–500 mg	10–20%

Detoxification and Maintenance of Opiate Dependence

Detoxification

Oral

Initiate when there are substantial opiate-agonist abstinence symptoms.[217]

A single dose of 20–30 mg will often suppress withdrawal symptoms.[217] Initial dose should not exceed 30 mg;[217,263] use lower initial dose in patients whose tolerance is expected to be low.[217]Additional doses may be necessary if withdrawal symptoms are not suppressed or if they reappear.[217] If same-day dosage adjustments are to be made, reevaluate the patient 2–4 hours after the previous dose.[217] If an additional dose is needed to suppress withdrawal symptoms, administer an additional 5–10 mg.[217] Total daily dose for the first day generally should not exceed 40 mg[217,263] unless it is documented that this total dose does not suppress withdrawal symptoms.[263]

During the first week, adjust dosage based on control of withdrawal symptoms at times of expected peak activity of methadone (2–4 hours after a dose).[217] Use caution to avoid overdosage.[217] With continued dosing, symptoms are suppressed for a longer time.[217]

Usual stabilizing dosage is 40 mg daily in divided doses.[217] When the patient has been stabilized (i.e., substantial symptoms of withdrawal are absent) for 2 or 3 days, gradually decrease dosage daily or at 2-day intervals.[217] Individualize and adjust dosage to keep withdrawal symptoms at a tolerable level.[217] In hospitalized patients, reduce dosage by 20% daily; a more gradual reduction may be required in ambulatory patients.[217]

Parenteral

Patients unable to receive methadone orally: Hospitalize patient and convert oral dose to parenteral dose using accepted criteria.[217] [222] [a] Patients being switched from oral methadone usually initiate parenteral methadone at a parenteral-to-oral dosage ratio of 1:2 (e.g., 5 mg of parenteral methadone hydrochloride in patients previously receiving 10 mg of oral methadone hydrochloride).[222]

Maintenance

Oral

A single dose of 20–30 mg will often suppress withdrawal symptoms.[217] Initial dose should not exceed 30 mg;[217] [263] use lower initial dose in patients whose tolerance is expected to be low.[217]Additional doses may be necessary if withdrawal symptoms are not suppressed or if they reappear.[217] If same-day dosage adjustments are to be made, reevaluate the patient 2–4 hours after the previous dose.[217] If an additional dose is needed to suppress withdrawal symptoms, administer an additional 5–10 mg.[217] Total daily dose for the first day generally should not exceed 40 mg[217] [263] unless it is documented that this total dose does not suppress withdrawal symptoms.[263]

During the first week, adjust dosage based on control of withdrawal symptoms at times of expected peak activity of methadone (2–4 hours after a dose).[217] Use caution to avoid overdosage.[217] With continued dosing, symptoms are suppressed for a longer time.[217]

Titrate dosage to a level at which opiate withdrawal symptoms are prevented for 24 hours, drug craving is reduced, euphoric effects of self-administered opiates are blocked or attenuated, and patient is able to tolerate the sedative effects of methadone.[217] Usual stabilizing dosage is 80–120 mg daily.[217] Review maintenance dosage requirements regularly and reduce as indicated.[a]

Once-daily dosing usually is adequate; there generally is no apparent advantage to divided doses.[a] However, rapid metabolizers may not maintain adequate plasma concentrations with usual dosing regimens.[206] [207] [208] [210]

Withdrawal from methadone maintenance: Considerable variability in appropriate rate of dosage reduction; one regimen involves reducing the dose by <10% of established tolerance or maintenance dosage at intervals of 10–14 days.[217] All patients in a maintenance program should be given careful consideration for discontinuance of methadone therapy, especially after reaching a dosage of 10–20 mg daily.[a]

Parenteral

Patients unable to receive methadone orally: Hospitalize patient and convert oral dose to parenteral dose using accepted criteria.[217] [222] [a] Patients being switched from oral methadone usually initiate parenteral methadone at a parenteral-to-oral dosage ratio of 1:2 (e.g., 5 mg of parenteral methadone hydrochloride in patients previously receiving 10 mg of oral methadone hydrochloride).[222]

216. Reckitt Benckiser Pharmaceuticals, Inc. Suboxone (buprenorphine hydrochloride and naloxone hydrochloride dihydrate) sublingual tablets and Subutex (buprenorphine hydrochloride) sublingual tablets prescribing information. Richmond, VA.

217. Roxane Laboratories, Inc. Dolophine (methadone hydrochloride) tablets prescribing information. Columbus, OH; 2012 Jul.

218. Raisch DW, Fye CL, Boardman KD et al. Opioid dependence treatment, including buprenorphine/naloxone. *Ann Pharmacother*. 2002; 36:312-21. [IDIS 476846] [PubMed 11847954]

219. Boatwright DE. Buprenorphine and addiction: challenges for the pharmacist. *J Am Pharm Assoc*. 2002; 42:432-8.

220. Fiellin DA, O'Connor PG. New federal initiatives to enhance the medical treatment of opioid dependence. *Ann Intern Med*. 2002; 137: 688-92.

221. Schobelock MJ. Dear healthcare professional letter: Product discontinuation notice—Orlaam (levomethadyl hydrochloride acetate) oral solution, 10 mg/mL, CII. Columbus, OH: Roxane Laboratories; 2003 Apr 23.

222. Xanodyne Pharmaceuticals Inc. Methadone hydrochloride injection prescribing information. Newport, KY; 2006 Mar.

223. Anderson R, Saiers JH, Abram S et al. Accuracy in equianalgesic dosing: conversion dilemmas. *J Pain Symptom Manage*. 2001; 21:397-406. [IDIS 463769] [PubMed 11369161]

225. Roxane Laboratories, Inc. Methadone hydrochloride Intensol (oral concentrate) prescribing information. Columbus, OH. 2012 Jul.

226. Roxane Laboratories, Inc. Methadone hydrochloride oral solution prescribing information. Columbus, OH. 2012 Jul.

227. Anon. Principles of analgesic use in the treatment of acute pain and cancer pain. 5th ed. Glenview, IL: American Pain Society; 2003.28-31.

228. Nicholson AB. Methadone for cancer pain. Cochrane Database Syst Rev. 2004; 3:CD003971.

250. Wines JD, Weiss RD. Opioid withdrawal during risperidone treatment. *J Clin Psychopharmacol*. 1999; 19:265-7. [IDIS 428397] [PubMed 10350033]

251. Kharasch ED, Hoffer C, Whittington D et al. Role of hepatic and intestinal cytochrome P450 3A and 2B6 in the metabolism, disposition, and miotic effects of methadone. *Clin Pharmacol Ther*. 2004; 76:250-69. [IDIS 521156] [PubMed 15371986]

252. Dale O, Sheffels P, Kharasch ED. Bioavailabilities of rectal and oral methadone in healthy subjects. *Br J Clin Pharmacol*. 2004; 58:156-62. [IDIS 520428] [PubMed 15255797]

253. GlaxoSmithKline. Retrovir (zidovudine) tablets, capsules, syrup prescribing information. Research Triangle Park, NC. 2003 Apr.

254. Ballantyne JC, Ma J. Opioid therapy for chronic pain. *N Engl J Med*. 2003; 349:1943-53. [IDIS 506512] [PubMed 14614170]

255. USPDI: drug information for the health care professional. Greenwood Village, CO: Thomson/Micromedex; 2004:2149-50.

256. Lauriault G, LeBelle MJ, Lodge BA et al. Stability of methadone in four vehicles for oral administration. *Am J Hosp Pharm*. 1991; 48:1252-6. [PubMed 1858805]

257. Lawlor PG, Turner KS, Hanson J et al. Dose ratio between morphine and methadone in patients with cancer pain. *Cancer*. 1998; 82:1167-73. [IDIS 404009] [PubMed 9506365]

258. Ripamonti C, Groff L, Brunelli C et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol*. 1998; 16:3216-21.

259. Reviewers' comments (personal observations).

260. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. *Pain*. 1997; 70:109-15. [PubMed 9150283]

261. Roxane Laboratories, Inc. Diskets (methadone hydrochloride) dispersible tablets prescribing information. Columbus, OH; 2009 Feb.

262. Mallinckrodt Inc. Methadose (methadone hydrochloride) and methadone hydrochloride dispersible tablets prescribing information. Hazelwood, MO; 2009 May.

263. Department of Health and Human Services, Public Health Service. Certification of opioid treatment programs. (42 *CFR* Part 8). 2004; 42:62-70. From Government Printing Office website via GPO Access. Accessed 2005 May 3.

بوپره نورفین و نالوکسان:

در بیماران دوز نگهدارنده در محدوده ۴ تا ۲۴ میلی گرم در روز و به صورت متوسط ۱۶ میلی گرم در روز خواهد بود.

Administration

Administer by IM or IV injection for relief of pain.[1,2,3] Administer transdermally for management of chronic pain only.[213] Administer sublingually as a single agent or in fixed combination with naloxone for management of opiate dependence.[202,214]

Also administered by continuous IV infusion†,[32,33,34] by IM[103] or IV[76,79] injection using a patient-controlled infusion device†, and by epidural injection† for pain relief.[23,24,25,26,28,29,30,31,50,78,92,192]

For drug compatibility information, see Compatibility under Stability.

Sublingual Administration

Administer as a single daily dose.[202,214]

Sublingual Tablets

Place tablets under the tongue and allow to dissolve; swallowing the tablets reduces bioavailability.[202] Drinking warm fluids prior to administration may aid dissolution.[204]

For doses requiring >2 tablets, all the tablets may be placed under the tongue at once.[202]Alternatively, patients may place 2 tablets under the tongue at a time if they are unable to place >2 tablets comfortably.[202]

To ensure consistent bioavailability, patients should adhere to the same manner of dosing with continued use.[202]

Sublingually Dissolving Strips

Place up to 2 strips under the tongue (on either side near the base of the tongue) in a way that minimizes overlapping, and allow to dissolve; patient should not talk while the strip is dissolving, chew the strip, or swallow the strip; these activities may alter absorption.[214,219] Drinking water prior to administration may aid dissolution.[214,219]

For doses requiring >2 strips, place additional strip(s) under the tongue after the first 2 strips have completely dissolved.[219]

IV Injection

Rate of Administration

Administer over ≥2 minutes.[1,2,3]

Continuous IV Infusion

Dilution

Dilute to a concentration of 15 mcg/mL in 0.9% sodium chloride.[32]

Rate of Administration

Administer via a controlled-infusion device.[32]

Epidural Injection†

Dilution

Has been diluted to a concentration of 6–30 mcg/mL in 0.9% sodium chloride.[23] [24] [25] [26] [28] [29] [30] [31] [78] [92] [192]

Transdermal Administration

To expose the adhesive surface of the system, peel off and discard the protective-liner covering just prior to application.[213]

Apply the transdermal system to a dry, intact, nonirritated, hairless or nearly hairless surface on the upper chest, upper back, side of chest, or upper outer arm by firmly pressing the system by hand for 15 seconds with the adhesive side touching the skin and ensuring that contact is complete, particularly around the edges.[213] [220]

Clip, not shave, hair at the application site prior to application if needed.[213]

Only water should be used if the site must be cleaned before transdermal application;[213] do *not* use soaps, oils, lotions, alcohol, or abrasive devices that could alter absorption of the drug.[213] [220]

Do *not* use transdermal system if the seal of the package is broken or if the system is altered in any way (e.g., cut, damaged).[213]

Each transdermal system is intended to be worn continuously for 7 days; apply subsequent systems to a different site after removal of the previous system.[213] [220] At least 21 days should elapse before reusing any single application site.[213]

If a system should inadvertently come off during the period of use, apply a new system to a different skin site and leave in place for 7 days.[213] [220] The edges of the system may be taped in place with first-aid tape if the patient experiences difficulty with system adhesion.[213] If adhesion problems persist, an adhesive film dressing (e.g., Bioclusive, Tegaderm) may be applied over the system.[220] [221]

Restricted Distribution Program

The Drug Addiction Treatment Act (DATA) of 2000 allows qualifying physicians to prescribe and dispense opiates in schedules III, IV, and V of the Federal Controlled Substances Act that have been approved by FDA for detoxification or maintenance treatment of opiate dependence.[205] Prior to passage of this law, opiate dependence treatment could be provided only at specially registered clinics.[203] Under DATA 2000, prescription use of buprenorphine and buprenorphine/naloxone fixed combination in the treatment of opiate dependence is limited to physicians who meet certain requirements and have notified the Secretary of the US Department of Health and Human Services of their intent to prescribe these preparations for this indication.[202]

Pharmacists may utilize the DATA physician locator (at) or contact 866-287-2728 or info@buprenorphine.samhsa.gov to verify whether a physician is in compliance with the provisions of DATA.[203] [225]

Dosage

Available as buprenorphine (transdermal systems) and buprenorphine hydrochloride (injection and sublingual tablets); dosage expressed in terms of buprenorphine.[1,2,213]

Also available as fixed combination of buprenorphine hydrochloride and naloxone hydrochloride (sublingual tablets, sublingually dissolving strips); dosage generally expressed in terms of the buprenorphine content.[202,214]

Pediatric Patients

Pain

Adjust dosage according to the severity of pain, physical status of the patient, and other drugs that the patient is receiving.[1,2]

IV or IM

Children 2–12 years of age: 2–6 mcg/kg every 4–6 hours; however, longer dosing intervals (e.g., every 6–8 hours) may be sufficient.[1] Do not use a fixed around-the-clock dosing interval until an adequate dosing interval has been established by clinical observation of the patient.[1]

Children ≥13 years of age: 0.3 mg given at intervals of up to every 6 hours as necessary.[1,2,3] Repeat initial dose (up to 0.3 mg) once in 30–60 minutes, if needed.[1]

Exercise particular caution with IV administration, especially with initial doses.[1]

Decrease dosage by approximately 50% in patients who are at increased risk of respiratory depression.[1] (See Respiratory Depression under Cautions.)

Circumcision-related Pain

IM

Children 9 months to 9 years of age† undergoing circumcision: Initial dosage of 3 mcg/kg as an adjunct to surgical anesthesia, followed by additional 3-mcg/kg doses as necessary to provide analgesia postoperatively, has been used.[27]

Adults

Pain

Adjust dosage according to the severity of pain, physical status of the patient, and other drugs that the patient is receiving.[1,2]

IV or IM

0.3 mg given at intervals of up to every 6 hours as necessary.[1,2,3] Repeat initial dose (up to 0.3 mg) once in 30–60 minutes, if needed.[1] A dosing interval longer than 6 hours may be adequate in some patients.[71,72,97,99]

It may be necessary to administer single doses of up to 0.6 mg, but the manufacturer recommends that such relatively high doses *only* be administered IM and *only* to adults who are not at increased risk of respiratory depression.[1]

A regimen including an initial dose of 0.3 mg followed by another 0.3-mg dose repeated in 3 hours is as effective as a single 0.6-mg dose in relieving postoperative pain.[129]

Exercise particular caution with IV administration, especially with initial doses.[1]

Decrease dosage by approximately 50% in patients who are at increased risk of respiratory depression.[1] (See Respiratory Depression under Cautions.)

Continuous IV Infusion†

Dosages of 25–250 mcg/hour have been used for the management of postoperative pain.[33] [34]

Epidural Injection†

Dosages of 0.15–0.3 mg have been administered in the management of severe, chronic pain (e.g., in terminally ill patients) as frequently as every 6 hours, up to a mean total daily dosage of 0.86 mg (range: 0.15–7.2 mg).[31]

60 mcg as a single dose, up to a mean total dose of 180 mcg administered over a 48-hour period, has been used for the management of postoperative pain.[23]

Supplement to Surgical Anesthesia

Epidural Injection†

Dosage of 0.3 mg has been used as a supplement to surgical anesthesia with a local anesthetic.[24192]

Chronic Pain

Transdermal

When selecting the initial transdermal dose, consider the dose, potency, and characteristics of previous opiate regimens and the reliability of the potency estimate used to calculate an equivalent buprenorphine dosage; the patient's degree of tolerance to adverse effects; the patient's age and medical status; type and severity of pain; concurrent therapy; the acceptable balance between efficacy and adverse effects; and the patient's risk factors for abuse, addiction, or diversion.[213] Fatal overdosage possible with the first transdermal dose if the dose is overestimated.[213]

Manufacturer considers the following dosage recommendations to be suggested approaches to the individual management of each patient.[213]

Opiate-naive patients: Initiate with buprenorphine 5 mcg/hour.[213]

Patients previously receiving <30 mg daily of morphine sulfate (or equivalent): Initiate with buprenorphine 5 mcg/hour.[213]

Patients previously receiving 30–80 mg daily of morphine sulfate (or equivalent): Taper current opiate regimen for up to 7 days to a total 24-hour dosage of ≤30 mg of morphine sulfate (or equivalent) and initiate with buprenorphine 10 mcg/hour.[213]

Titration: Increase at minimum intervals of 72 hours to a level providing adequate analgesia and acceptable adverse effects, taking into account patient's requirement for supplemental short-acting analgesics.[213] Maximum transdermal dosage is 20 mcg/hour (see Cardiac Effects under Cautions).[213]

Discontinuance: Periodically reassess need for continued around-the-clock opiate therapy.[213] When discontinuing therapy, taper dosage to prevent manifestations of withdrawal.[213] Consider use of a short-acting opiate during tapering process.[213]

Opiate Dependence

Induction

Sublingual

Initially, buprenorphine 8 mg on day 1 and 16 mg on day 2.[202] From day 3 onward, administer buprenorphine in fixed combination with naloxone at the same buprenorphine dose as on day 2.[202]

To avoid precipitating withdrawal, give the first dose when objective and clear signs of opiate withdrawal are evident.[202] [214]

Manufacturer recommends that an adequate maintenance dosage, titrated to clinical effectiveness, be achieved as rapidly as possible to prevent undue opiate withdrawal symptoms.[202]

Maintenance

Sublingual

Target dosage of buprenorphine in fixed combination with naloxone is 16 mg daily; however, dosages as low as 12 mg daily may be effective in some patients.[202] [214] Adjust dosage in increments/decrements of 2 or 4 mg daily to a dosage that suppresses opiate withdrawal symptoms and ensures that the patient continues treatment.[202] [214]

Usual dosage: 4–24 mg daily depending on the individual patient.[202] [214]

If switching between buprenorphine/naloxone sublingual tablets and sublingually dissolving strips, continue same dosage.[214] However, not all doses and dose combinations are bioequivalent; monitor for efficacy and tolerability and adjust dosage if needed.[214] (See Bioavailability under Pharmacokinetics.)

Discontinuance

Sublingual

The decision to discontinue therapy after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan.[202] [214] Both gradual and abrupt discontinuance have been used; the best method for tapering dosage at the end of treatment has not been established.[202] [214]

100. Brown DH, Kasuya A, Leiken JB. Endotracheal administration in the critical care setting. *J Emerg Med*. 1987; 5:407-14. [PubMed 3312392]

101. Ward JT Jr. Endotracheal drug therapy. *Am J Emerg Med*. 1983; 1:71-2. [PubMed 6393996]

102. Tandberg D. Endotracheal naloxone. *Am J Emerg Med*. 1983; 1:366-7. [PubMed 6680644]

103. Tandberg D, Abercrombie D. Treatment of heroin overdose with endotracheal naloxone. *Ann Emerg Med*. 1982; 11:443-5. [PubMed 7103164]

104. Greenberg MI. The use of endotracheal medication in cardiac emergencies. *Resuscitation*. 1984; 12:155-65. [PubMed 6096940]

105. Hahnel J, Lindner KH, Ahnefeld FW. Endobroncial administration of emergency drugs. *Resuscitation*. 1989; 17:261-72. [PubMed 2548271]

106. Greenberg MI, Roberts JR, Baskin SI. Endotracheal naloxone reversal of morphine-induced respiratory depression in rabbits. *Ann Emerg Med*. 1980; 9:289-92. [PubMed 7386953]

107. Raehl CL. Endotracheal drug therapy in cardiopulmonary resuscitation. *Clin Pharm*. 1986; 5:572-9. [IDIS 217499] [PubMed 3527527]

108. American Academy of Pediatrics Committee on Drugs. Emergency drug doses for infants and children. *Pediatrics*. 1988; 81:462-5. [PubMed 3422026]

109. American Academy of Pediatrics Committee on Drugs. Emergency drug doses for infants and children and naloxone use in newborns: clarification. *Pediatrics*. 1989; 83:803. [IDIS 254337] [PubMed 2717301]

110. American Academy of Pediatrics Committee on Drugs. Naloxone dosage and route of administration for infants and children: addendum to emergency drug doses for infants and children. *Pediatrics*. 1990; 86:484-5. [IDIS 273346] [PubMed 2388800]

111. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. *JAMA*. 1992; 268:2171-302. [PubMed 1404767]

112. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA*. 1998; 279:229-34.

113. Endo Pharmaceuticals. Narcan (naloxone hydrochloride injection, USP) prescribing information. Chadds Ford, PA; 2003 Jul.

114. Reckitt Benckiser Pharmaceuticals, Inc. Suboxone (buprenorphine hydrochloride and naloxone hydrochloride dihydrate) sublingual tablets and Subutex (buprenorphine hydrochloride) sublingual tablets prescribing information. Richmond, VA. Accessed 2005 Nov 7.

115. Sanofi-Synthelabo Inc. Talwin NX (pentazocine and naloxone hydrochlorides) prescribing information. New York, NY; 2003 May.

116. The American Heart Association. Guidelines 2005 for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2005; 112(Suppl I): IV1-211.

117. Eigel B. (American Heart Association, Dallas, TX): Personal communication; 2006 Dec 18.

118. field JM, Hazinski MF, Gilmore D, eds. Handbook of emergency cardiovascular care for healthcare providers. Dallas, TX: American Heart Associaiton; 2005:95.

b. AHFS drug information 2004. McEvoy GK, ed. Naloxone. Bethesda, MD: American Society of Health-System Pharmacists; 2004:2093-5.

c. AHFS drug information 2004. McEvoy GK, ed. Buprenorphine. Bethesda, MD: American Society of Health-System Pharmacists; 2004:2067-74.

d. AHFS drug information 2004. McEvoy GK, ed. Opiate agonists general statement. Bethesda, MD: American Society of Health-System Pharmacists; 2004:2030-35.

e. Goldfrank LR, Flomenbaum NE, Lewin NA, et al. Goldfrank's toxicologic emergencies. 7th ed. New York: McGraw-Hill; 2002: 909.

f. Behrman RE, Kliegman RM, Jenson HB. Nelson textbook of pediatrics. 17th ed. Elsevier Publishing: 2470.

g. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2002: 969.

PDH. Schilling McCann JA, Publisher. Pharmacists drug handbook. 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins and American Society of Health-System Pharmacists; 2003.