Handbook of Methadone Prescribing and Buprenorphine Therapy

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ISBN 978-1-4614-6973-5 ISBN 978-1-4614-6974-2 (eBook)
DOI 10.1007/978-1-4614-6974-2
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2013936725

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

This volume describes the evolving role of methadone and buprenorphine—pharmacologically distinct opioids that share clinical utility in the management of both pain and addiction. It is a timely work given the attention now focused on the effort to improve the safety of long-term opioid therapy for pain, in part by better management of drug abuse outcomes. By highlighting the role of two drugs with complex pharmacologies that have the potential for both liability and benefit in two types of challenging disorders, it explores larger issues that have profound importance for the broader use of opioids in practice.

Opioids have been used therapeutically for millennia and it is difficult to imagine a class of substances that has had a more tumultuous history. During the past 50 years, the medical community has repeatedly revised standards and practices related to opioid therapy in response to new information, experience, or risk-related concerns. Practice guidelines have appeared repeatedly, but become outdated quickly.

Changes in the perception of opioid drugs and their clinical use in the treatment of pain or addiction have diverse and complicated drivers. To some extent, changes over time reflect the emergence of a large basic science literature related to endorphin physiology, nociception and brain reward mechanisms, and opioid pharmacology. Perhaps more important from the clinical vantage, however, is a large literature comprising mainly short-term trials and epidemiologic studies that have supported the efficacy of opioid therapy in heterogeneous patient populations while delineating a complicated risk profile that includes overt and occult side effects and toxicities, and the potential for abuse, addiction, and overdose. Although the latter data may be criticized for their questionable relevance to long-term opioid therapy in populations of patients with pain or addictive disease, they demonstrate the types of responses that must be assessed and managed if clinical use of these drugs is to be safe and effective.

The complexity inherent in the clinical use of opioid drugs means that it is possible to frame a deeper discussion from any of a very broad array of directions. The literature focused on pain, for example, can variably address the clinical pharmacology of the agents available or the challenges posed by specific populations.

There are very stark differences in the information presented if the narrative focuses on acute pain in inpatient settings, opioid management of pain related to advanced illness, or the controversial use of long-term opioid therapy to treat chronic pain. In the same way, the literature on opioid agonist therapy for addiction reveals large differences in tone and content if the focus is on methadone therapy or office-based therapy using buprenorphine.

These issues, which are touched upon in this volume, are less pressing now than the emerging literature on opioid risk assessment and management, which promotes the need for risk-related knowledge and skills irrespective of the specific drugs, indications, or populations receiving care. The essential nature of risk management has become increasingly clear with evidence that drug abuse outcomes and unintentional overdose have increased greatly with the rising prevalence of long-term opioid treatment of chronic pain. With millions of patients exposed to these compounds in an effort to provide analgesia and hundreds of thousands more receiving them in an effort to suppress addiction, the skills necessary to minimize risk and manage adverse outcomes are an obligation of every prescriber, in every context.

Methadone and buprenorphine each has characteristics unique among clinically used opioids. They both deserve critical analysis from this perspective, particularly as it relates to their expanding use for analgesia. Methadone has long been viewed as a drug that offers a relatively inexpensive alternative to other pure mu agonists for the treatment of pain, and one that can offer surprising efficacy and potency when initiated on rotation from another opioid. Increased prescribing for pain during the past decade, however, has highlighted its challenges. It is now evident that methadone is more likely to yield serious adverse effects when prescribed for pain than other mu agonists. This potential for adverse effects, which may be related to the long and variable half-life, the unpredictable high potency when started after another mu agonist has been on board, or the potential for QTc prolongation, must be understood and managed to minimize adverse outcomes. Only clinicians familiar with these issues should undertake prescribing for pain. The concern about toxicity should not limit the use of this drug in the management of addiction, but should still inform guidelines for initiating and monitoring therapy.

There is also extensive experience in the use of buprenorphine for pain, particularly in transdermal formulations now available in Europe and the United States. In the United States, the dose of this formulation is low and the use of oral transmucosal formulations approved for addiction also could be considered for analgesic purposes. Analgesic uses of this drug may be complicated, however, by the potential for withdrawal when it is started during treatment with a pure mu agonist, and the potential for a ceiling effect in practice. The management of withdrawal is appreciated by those who are treating addiction, but guidelines for converting opioid-treated pain patients to buprenorphine have yet to be tested. This challenge notwithstanding, buprenorphine may be a drug with a broader potential as an analgesic given favorable characteristics, such as a ceiling effect for respiratory depression and lesser inhibition of the gonadal function.

Opioids are essential drugs and the problems they address are among the most common and challenging in medicine. Risk assessment and management are critical

elements in their use, irrespective of context. Methadone and buprenorphine are accepted as effective treatments for addiction, and offer options for pain management that may have advantages in selected patients. This volume describes the pharmacology and clinical use of these agents and provides information that can assist in ensuring safe use for addiction and effective integration of these drugs into pain management.

New York, NY, USA Russell K. Portenoy, MD

Preface

I am a great believer in luck. The harder I work, the more of it I seem to have.
Attributed to Thomas Jefferson and F.L Emerson. The Yale Book of Quotations, ed.
Fred R. Shapiro (New Haven, CT: Yale University Press, 2006).

The opening quote on the relation between work and luck is clever but although attributed to one of the Founding Fathers for many years it seems that Emerson might have been who said it. Not surprisingly the "level of evidence" is intermediate on this topic so we reference the Year Book of Quotations by Fred R. Shapiro that is considered to be the most reliable source [1]. This situation, where the level of evidence is not strong, is not uncommonly seen in the opioid field where evidence tends to be limited and recommendations often rely on expert opinions and best practice guidelines [2]. Being aware of these limitations we invited to participate of this book experts, world-renowned researchers, and clinicians that made the commitment to present only information that is based on the highest level of evidence or that what is considered to be the best practice.

Only two opioids, methadone and buprenorphine, are indicated for the management of both pain and opioid-related drug addiction and, interestingly, both present unique pharmacodynamic and pharmacokinetic challenges to the general practitioner and pain specialist, justifying a separate analysis from the rest of the drugs in the same family.

Methadone, first synthesized as an analgesic in the period that preceded WWII, in the 1960s became the drug of choice for maintenance therapy in patients with opioid-related drug addiction. Due to the "stigma" associated to this drug its use as an opioid analgesic became less popular, but about 20 years ago due to its very good analgesic properties, long half life and low cost, became a viable option to the newly commercialized long acting opioid formulations [3].

With the increase in methadone prescribing emergency room visit and deaths attributed to methadone showed a sharp increase. Indeed, according to the Center

for Disease Control and Prevention (CDC) between 1999 and 2009, the rate of fatal overdoses involving methadone increased more than fivefold as its prescribed use for treatment of pain increased [4]. Although the significance of these findings is not clear due to issues related to reporting and data collection that makes the denominator uncertain, in the year 2006 the FDA issued a methadone black box warning. The warning box addresses the following issues [5]. Appropriate use: should only be prescribed by healthcare professionals knowledgeable in use of potent opioids for chronic pain management; proper dosing and titration essential to decrease respiratory depression risk; Abuse Potential: opioid agonist Schedule II controlled substance; assess opioid abuse or addiction risk prior to prescribing; increase opioid abuse risk if personal or family substance abuse or mental illness history; monitor all patients for misuse, abuse, and addiction; Respiratory Depression: life-threatening and fatal cases may occur even with recommended use; monitor for respiratory depression especially during treatment start or after dose increase; methadone peak respiratory depressant effects typically occur later and last longer than peak analgesic effects, especially during initial dosing period; QTc interval prolongation: life-threatening QTc interval prolongation and serious arrhythmias including torsades de pointes have occurred; most cases involve pain treatment with large multiple daily doses, but also reported with doses commonly used for opioid addiction maintenance treatment; monitor for ECG changes during treatment start or after dose increase; accidental exposure: accidental ingestion, especially by children, can result in fatal methadone overdose; opioid addiction treatment: methadone used for detoxification and maintenance of opioid dependence should be administered in accordance with treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration.

The pain management community along with substance abuse specialists has also taken significant steps towards safe opioid prescribing as denoted by several recent publications on opioid safety and best evidence-based expert guidelines on opioid prescribing [6, 7].

Methadone is substrate of the cytochrome P450 isoenzymes CPY3A4, CPY2D6, and CPY2B6. Other drugs that are commonly utilized in patients with chronic pain or enrolled in methadone maintenance programs are also substrates and hence compete with methadone resulting in an elevation of plasma levels that in occasions can cause toxicity [8]. Since the report by Morris Krantz on predisposition for *Torsades de Pointes* (TdP) in patients on methadone, attention shifted towards cardiac toxicity [9]. In vitro studies have shown that methadone can block potassium channels responsible for the delayed rectifying current that brings depolarized fibers to its resting potential. When this current is blocked repolarization is delayed predisposing to potentially fatal cardiac arrhythmias, including TdP [10].

Buprenorphine is also a peculiar drug as its pharmacodynamics is different from most mu opioid agonists that are commonly utilized in pain management. Buprenorphine is a highly lipophilic semisynthetic derivative of thabaine that has a potent partial agonistic effect at the mu receptor while having an antagonistic effect at the kappa receptors [10]. In addition it is more potent than morphine (approximately 30 times when given parenterally), is absorbed through the oral mucosa

allowing sublingual delivery of the drug, has a mean duration analgesic action that can last 8 h, and a better profile of side effects than the rest of the mu agonists. Interestingly it presents a "bell shaped" dose response meaning that once analgesia is achieved further dose escalation results in complete luck of analgesic effect [11]. Indeed, PET scan studies with displacement of [11] carfentanil binding to mu opioid receptors in human brain 3–4 h after sublingual administration of buprenorphine have suggested full receptor occupancy with 32 mg, and for that reason this is the recommended maximal dose [12]. The new technology for administration of buprenorphine by the transdermal route has opened up new opportunities of care resonating with the concept of anticipating pain and treating it before it reoccurs.

The above-described characteristics of methadone and buprenorphine make them more challenging to utilize for those practitioners that are not aware that these two drugs are not the same than the rest of the opioid agonists. Indeed, despite of the fact that mu agonists have differences in their pharmacology that becomes relevant when rotating to another compound due to the possibility of incomplete cross-tolerance, the differences between methadone and buprenorphine and the other mu agonist are more significant. When rotating from one mu agonist to another the recommendation is to reduce the calculated equianalgesic dose by 20 % for incomplete cross-tolerance, while when switching to methadone the recommendation by some authors is to reduce the calculated dose by up to 90 % [13]. When the opioid rotation is to be done to buprenorphine the mu agonist has to be discontinued and completely before buprenorphine can be started as it can precipitate withdrawal symptoms [14].

By collecting the information on methadone and buprenorphine in one volume we are hoping that the reader will have the opportunity to consult on two drugs that are perceived to be challenging. Becoming familiar with methadone and buprenorphine will allow adding to the practitioner's armamentarium two drugs that can provide excellent analgesia and that can be excellent options when opioid rotation is required.

References

1. Shapiro FR, editors. The Yale book of quotations. New Haven, CT: Yale University Press; 2006.
2. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113–30.
3. Cruciani RA. Methadone: to ECG or not to ECG…That is still the question. J Pain Sym Manag. 2008;36(5):545–2.
4. Centers for Disease Control and Prevention. Vital signs: risk for overdose from methadone used for pain relief—United States. MMWR Morb Mortal Wkly Rep. 2012;61(26):493–7.
5. http://www.fda.gov/cder/foi/label/2006/006134s028lbl.pdf
6. Webster LR, Cochella S, Dasgupta N, Fakata KL, Fine PG, Fishman SM, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med. 2011;12 (Suppl 2):S26–35.

7. Martin JA, Campbell A, Killip T, Kotz M, Krantz MJ, Kreek MJ, et al. QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. J Addict Dis. 2011;30(4):283–306.
8. Skjervold B, Bathen J, Spigset O. Methadone and the QT interval: relations to the serum concentrations of methadone and its enantiomers (R)-methadone and (S)-methadone. J Clin Psychopharmacol. 2006;26(6):687e–689e.
9. Katchman AN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, et al. Influence of opioid agonists on cardiac human ether-a-go-gorelated gene K(+) currents. J Pharmacol Exp Ther. 2002;303:688–94.
10. Lewis JW. C-bridged derivatives of thebaine and oripavine. Adv Biochem Psychopharmacol. 1974;8:123–36.
11. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol. 1977;60(4):537–45.
12. Greenwald MK, Johanso C-E, Moddy DE, Woods JH, Wilbourn MR, Koeppe RA, et al. Effects of buprenorphine maintenance dose on μ-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin dependent volunteers. Neuropsychopharmacol. 2003;28:2000–9.
13. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. J Pain Symptom Manage. 2009;38(3):426–39. Review.
14. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. J Pharmacol Exp Ther. 1988;247:47–53.

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Chapter 1
Prescribing Methadone Safely

Eliezer Soto, Joy Hao, Helena Knotkova, and Ricardo A. Cruciani

Introduction

Methadone, a very useful analgesic and the most utilized drug for replacement therapy in patients with opioid-related addiction, is now also widely used for the management of chronic pain. Methadone was synthesized in Germany before the WWII and imported to the USA by Lilly after the war and was utilized for several years as an opioid analgesic but lost popularity in the 1950s. In the early 1960s, Dole and Nyswander proposed that patients abused opioids to compensate for an endogenous opioid deficiency, and it was introduced as a maintenance medication to control craving in patients treated for drug addiction [1]. Due to the widespread use in Methadone Maintenance Treatment Programs (MMTPs), it became a social stigma associated with drug addiction; consequently, chronic pain patients often refuse methadone as a possible analgesic option, and practitioners often avoid

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_1,

prescribing it for chronic pain management. Nonetheless due to its long half-life (although variable), low cost, and good analgesic properties, it resurged as a good alternative in patients requiring long-term opioid therapy [2].

Importance of Methadone Pharmacokinetic in Safe Prescribing

Methadone has several unique pharmacokinetic characteristics that set it apart from other opioids, and some of these characteristics have raised concerns about its safety. First, the half-life of methadone is variable and ranges from 15 to 150 h depending on the individual. The prolonged half-life is an advantage for the management of chronic nonmalignant pain in patients that require opioid analgesia with a long-acting agent, but the variability can result in unpredictable dosing and drug accumulation [3]. Second, the main mechanism for methadone metabolism is hepatic through the cytochrome P450, specifically isoenzymes 2B6, 3A4, and 2D6 [4]. Methadone can be displaced by other substrates for the same enzymatic complex, resulting in an elevation of free drug concentration, thereby increasing the risk for side effects and toxicity. In addition the isoenzymes can be inhibited or induced by a variety of substances contributing to the changes in plasma levels [5]. The degree to which other opioids are metabolized by this set of isoenzymes varies, and while hydromorphone, oxymorphone, and morphine are not significant substrates, hydrocodone, codeine, oxycodone, and methadone are widely metabolized [2]. This is important because patients with chronic pain are often treated with multiple medications (a phenomenon known as "polypharmacy") that are also metabolized through this pathway.

There is a wide variety of medications for the treatment of chronic pain, including adjuvant analgesics used to treat chronic neuropathic pain such as antidepressants and anticonvulsants, among others. In addition depression is a common comorbidity among chronic pain patients. Indeed several surveys have shown that up to 50 % of patients have dual diagnoses [6]. Some of the antidepressants are also substrate of the cytochrome P450 and may compete with methadone resulting in an increase in free drug concentration of methadone, predisposing the patient to side effects and toxicity.

Methadone Safety and the QTc Interval Duration

Another characteristic of methadone is its ability to block the delayed rectifying potassium current. This current is responsible for the repolarization of the action potential bringing the electrical activity of the fibers back to their resting membrane potential. The blockade of the potassium channels results in a prolongation of the depolarized state predisposing to ventricular arrhythmias including Torsades de Pointes (TdP). Interestingly, in vitro studies have shown that other opioids have also the ability to block this delayed rectifying current, including LAAM, fentanyl, methadone, buprenorphine, and codeine (in descending order of potency) [7]. From

Table 1.1 Risk factors for QTc prolongation and Torsades de Pointes (TdP)

- Elderly women
- Advanced heart disease
- Congenial and acquired long-QT syndromes
- Concomitant use of drugs with potential to prolong QTc
- Family history of sudden death
- Hypokalemia
- Hypomagnesaemia
- CYP 3A4 inhibitors
  - Potent inhibitors
    - Protease inhibitors: ritonavir, nelfinavir, indinavir
    - Macrolide antibiotics: erythromycin, clarithromycin, troleandromycin
    - Antifungal agents: ketokonazole, itraconazole
  - Less potent inhibitors
    - Saquinavir, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, clotrimazole
- Potential of commonly used medications in HIV/AIDS and chronic pain patients to produce QT prolongation
  - Very probable: quinidine
  - Probable: pimozide, ziprasidone
  - Possible: clarithromycin, erythromycin, pentamidine, chlorpromazine, haloperidol, olanzepine, risperidone, amitriptilyne, desipramine, imipramine, sertraline, venlafaxine
  - Improbable: fluconazole, levofloxacin, trimetropin-sulfamethoxazole, fluoxetine, paroxetine, sumatriptan, zolmitriptan, methadone
  - Very improbable: azythromycin, ciprofloxacin, clindamycin
- Drugs associated with TdP
  - Amiodarone, arsenic trioxide, bepridil, chlorpromazine, cisapride, clarithromycin, disopyramide, dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, mesoridazine, methadone, entamidine, pimozide, procainamide, quinidine, sotalol, sparfloxacin, thioridazine

the clinical prospective, however, since fentanyl is about two log units more potent than methadone, the plasma concentration required to produce analgesia in vivo is lower than the concentration required to interfere with the delayed rectifier potassium current. Lastly, recent data suggest that prolongation of the depolarization state could be clinically relevant with oxycodone but more studies are necessary to clarify this point [8].

The blockade of the rectifier current by methadone can be even more significant when administered concomitantly with other drugs that also have the ability to block the same current. For instance, the HIV/AIDS patient population often requires polypharmacy, and may receive multiple medications with potential to block the rectifying potassium currents. Indeed, patients with HIV/AIDS may be taking a variety of agents including antibiotics (e.g., trimetroprim-sulfamethoxazole), antipsychotics (e.g., haloperidol), antifungals (e.g., ketoconazole), and antidepressants (e.g., venlafaxine), all of them with the potential to predispose to arrhythmias such as TdP through the blockade of the potassium rectifier current (Table 1.1) (full list available at www.torsades.org).

Understanding Racemic Methadone and Methadone Enantiomers

In the USA, methadone is commercialized as a racemic mixture where 50 % of the molecules deviate polarized light to the left (levorigirous) and 50 % of the molecules deviate polarized light to the right (dextrogirus). The two enantiomers (*R* and *S*) have some differences in terms of efficacy, receptor affinity, and effect on the delayed potassium rectifying current. The *R*-enantiomer has higher affinity for the mu opioid receptors while the *S*-enantiomer has lower affinity for the mu opioid receptors but blocks the delayed rectifier potassium current more efficiently, thus predisposing to cardiac toxicity [9]. Indeed, Ansermot et al., replaced (*R*,*S*)-methadone by (*R*)-methadone (half-dose) in 39 opioid-dependent patients receiving maintenance treatment for 14 days. (*R*)-methadone was then replaced by the initial dose of (*R*,*S*)-methadone for 14 days ($n=29$). The QTc interval decreased when (*R*,*S*)-methadone was replaced by a half dose of (*R*)-methadone by a mean of −3.9 ms per week ($P=0.04$) and increased when (*R*)-methadone was replaced by the initial dose of (*R*,*S*)-methadone for 14 days. These observation needs to be replicated, but suggests that (*R*)-methadone is safe to treat patients in need of substitution therapy [10].

Reports of Increased Deaths and ED Visits Attributed to Methadone

In 2006, the FDA placed a warning box on methadone to alert the public about the observed increase in death rates attributed to this drug. The increase in popularity of methadone as an analgesic resulted in higher number of prescriptions written for the management of chronic pain. The CDC reported that the number of deaths that were attributed to methadone climbed from 800 in 1999 to close to 5,000 in 2006 [11]. These surveys, however, have significant flaws, and in many cases the results are difficult to interpret. The most common weaknesses in these reports include variable sources for data gathering, reliance on retrospective data collection, difficulties defining the denominator, and coexistence of other drugs in the system at the time of death (e.g., cocaine, benzodiazepines). Despite the limitations in these reports, the absolute increase in number of deaths where methadone was present at the time of death raises concerns about safety.

In 2002, Krantz and coworkers published a case series of sudden deaths occurring in the ICU setting, in which many of these patients were on methadone at the time of death [20]. Although most of the 17 patients in the case series had other findings that could have been responsible for the poor outcome (e.g., electrolyte abnormalities), this study has the merit of raising awareness in the pain and drug

addiction community about the possibility of cardiac toxicity related to methadone. This study was followed by a wide range of publications that included cross-sectional, retrospective, prospective, and controlled studies and a number of case series and case reports, but the issue is not yet fully understood.

Methadone Induced QTc Prolongation and TdP

Several mechanisms have been proposed to explain methadone toxicity: (1) QTc prolongation leading to fatal arrhythmias including TdP; (2) PR interval prolongation; (3) non-obstructive sleep apnea (more prominent with the coadministration of benzodiazepines); (4) syncope. TdP is caused by prolonged depolarization that leads to a ventricular arrhythmia with a characteristic pattern for which the condition is named [12]. The upper limit of the normal range for the QT interval has been established at 450 ms for men and 470 ms for women, and QTc prolongation over 500 ms is considered to be high risk for TdP regardless of the sex [13].

There is significant controversy on the role of ECG to help prevent cardiac toxicity induced by methadone. While some clinicians take the position that an ECG should be performed on every patient on methadone, addiction specialists argue that requiring ECGs on patients attending MMTP could result in abandonment of treatment and an increase in morbidity and mortality. Indeed, after an increase in death attributed to methadone was detected in Wales, the dispensation of maintenance methadone was discontinued. Shortly afterwards, deaths related to methadone decreased, but a concomitant increase in deaths related to heroin abuse was reported. The death rate related to heroin abuse was higher than that observed with methadone before it was discontinued. Once the methadone programs were reinitiated, death rates decreased again and eventually reached baseline levels [14].

The literature on the role of routine ECG monitoring in prevention of cardiac toxicity attributed to methadone is controversial, and the recommendations range from “never necessary” to “do ECG on every patient on methadone,” [15] while other groups recommend performing ECGs on patients receiving doses over 100 mg/day [16]. However, in the guidelines soon to be published by the American Pain Society (APS) and the College on Problems of Drug Dependence (CPDD), no dose limit is included (Table 1.2).

The observation that methadone can increase the duration of the QTc interval was first noted by Stimmel and coworkers in a study published in 1973. In this study, an increase in the duration of the QTc interval was observed in 34 % of patients, but no TdP was reported [17]. Some investigators questioned the relevance of this observation in view of the 27-year gap during which no other study on this phenomenon was published, until the more recent observations were reported by

Table 1.2 ECG recommendations to decrease risk of cardiac toxicity

"Vigilant for doses >600 mg/day"	Walker [35]
"Patients on high doses"	Almehmi [36]
"Never necessary"	Krook [37]
"Consider ECG in patients on high doses"	Martell [38]
"Consider ECG before starting QT-prolonging medications"	Maremmani [39]
"Repeat ECG after every change in drug regime"	Sticherling [40]
"ECG screening in patients at risk, especially after starting CYP2A4 inhibitors or increase in dose"	Ehret [41]
"ECG for patients on >120 mg/day" "ideally every patient at entering treatment"	Peles [42]
"For HIV-infected patients receiving drugs with QTc prolongation potential"	Chinello [43]
"ECG for high risk patients"	Krantz [44]
"ECG in methadone users … with inhibitors of methadone metabolism"	Rothier [45]
"An ECG is a convenient way with little cost to screen for an increased risk of TdP"	Ehret [46]

Krantz and coworkers on a possible association between methadone use and TdP [20]. It is important to highlight that at the time the Stimmel study was done, a typical dose of methadone in MMTPs was 40–60 mg a day, and it was not a popular opioid analgesic. Furthermore, during the 1970s, opioids including methadone were under-prescribed even for the management of malignant pain. More recently, however, it was shown in MMTP that higher doses of methadone resulted in lower morbidity and mortality rates [18].

In recent years, pain specialist started prescribing methadone more readily, and at higher doses than prescribed in MMTPs in the 1960s, often up to 120–140 mg/day. Indeed, there are reports of doses of up to 1,200 mg/day [19] and even higher, prescribed for the management of malignant and nonmalignant pain. As a result, the doses of methadone prescribed in the last 10 years are overall significantly higher than the doses prescribed when the first observations about the effect of methadone on cardiotoxicity were reported. Since the study by Krantz et al. in 2002 [20], many reports addressing the same topic resurfaced. However, most of the studies did not provide convincing data to favor one position over the other.

"Windows" for Risk of Toxicity

Overall methadone is a safe drug when utilized according to current guidelines; however, it is important to become familiar with instances when patients can be prone to more marked side effects and toxicity. A common denominator to these possible scenarios is the discontinuation and re-initiation of methadone therapy at the same dose that the patient was taking before discontinuing therapy. Although the

level of evidence is low, the current recommendation is to consider patients to be "opioid naïve" if methadone is to be reinitiated, when methadone has been discontinued for more than a week [22]. The rationale is that during that period of time, patients may lose tolerance to the drug secondary to lack of exposure, and they might become relatively "naïve" or at least recover some of the original sensitivity to the drug both for analgesia and side effects. The time course to become "naïve" to methadone after discontinuation is not clear but siding on caution is recommended. The reasons that may account for methadone discontinuation are multiple, some of them are patient-related but others are imposed on them. Patient-related causes are: losing the medication, taking more than prescribed and running out of the medication early and not having refills, taking methadone "only when the pain gets worse," dropping out of a methadone clinic and reinitiating therapy in other facility, and drifting from a methadone clinic to a pain clinic. Taking methadone "only when the pain is worse" is equivalent to taking it for breakthrough pain. But prescribing methadone in this fashion has been less popular due to the possibility of toxicity. Situations that are imposed on the patient may include opioid rotations, imprisonment (where the medication may be discontinued), or discharge from an MMTP or pain clinic.

Opioid Rotation

This is one of the scenarios that a practitioner may encounter where methadone might be initiated at a higher dose than what is now considered safe. In general when opioids are rotated (except for methadone), the recommendation is to add all the doses of the opioid that the patient is taking, including extended release and breakthrough medication, convert the amount into the new opioid utilizing the available conversion tables, then cut down 25 % of the estimated dose for incomplete cross-tolerance, prescribe 80 % of the total dose as a long acting formulation of the new opioid, and 20 % in divided doses for breakthrough pain [21]. The evidence that supports this practice is not strong but it has been adopted by many practitioners in the pain management community. One of the criticisms of this approach is the limitations of the conversion tables [22, 23] as they have been developed based on single comparative doses rather than on full dose–response curves [24].

When an opioid rotation to methadone is done, the usual recommendation is to calculate the equianalgesic dose to the opioid that the patient has been taking, and then cut down by 75–90 %. However in patients that are taking high doses of an opioid (e.g., 500 mg a day), even the most conservative conversion to methadone (cutting down by 90 %), would result in 50 mg a day, and that is over what some experts consider to be a safe starting dose in opioid tolerant patients (i.e., 10 mg 3 times a day) [22]. A more sound strategy would be to do a stepwise conversion where every incremental step would be kept below 30 mg a day of methadone. In patients without a baseline ECG, one should be performed after four half-lives of methadone (4–7 days). Although the level of evidence for these recommendations is low, there is enough clinical experience that justifies this algorithm.

Resuming Methadone Prescribing After Imprisonment

One of the circumstances in which patients are vulnerable to increased risk of side effects due to inappropriate methadone dosage is imprisonment. Inmates do not always receive appropriate opioid substitution therapy or opioids for the management of chronic pain during the period of incarceration. After release from prison, patients may inadvertently be restarted at the previous dose that they were taking before it was discontinued, even though they should now be considered "opioid naïve." Indeed, one study showed a high risk for mortality associated with decreased tolerance to heroin during the transition period from inmate back into the community [25]. There is no data on chronic pain management, but the assumption of inadequate treatment during incarceration is reasonable (as extrapolated from the data on maintenance therapy), and these patients should be considered "opioid naïve" at the time of reinitiating of opioids.

Importantly, it has been noted that continuing patients that are on opioid substitution therapy on the same dose of medication during incarceration seems to correlate with better outcomes than when it is discontinued [25]. It has also been observed that patients who reached a moderate-to-high methadone dose for opioid substitution therapy during incarceration had higher rates of reporting to community MMTPs vs. those on lower doses [26], and the likelihood of re-incarceration was reduced by 20 % in those inmates that received opioid substitution therapy during incarceration [27]. In addition, treatment of inmates with opioid substitution therapy during incarceration has been correlated with decreased rates of blood-born infectious diseases, including HIV [28, 29]. A call for restructuring the system and allocating more funding to support opioid substitution therapy during incarceration has been made [30].

Missing Doses at the Methadone Clinic

Another scenario is that of patients missing doses of methadone at the methadone programs. It has been recognized at MMTP clinics that missing doses have to be taken into consideration in determining the dose of medication that will be prescribed at the time of return to the clinic. The recommendations are the following: (1) if the patient missed 1–2 doses, give the usual dose; (2) if missed 3–5 doses, give half of the usual dose, assess tolerance, then increase 15 mg/day back to the usual dose; (3) if missed >5 doses, start at 30 mg or less, assess tolerance, and increase 15 mg/day back to usual dose. Except in the case of extenuating circumstances, consider the client to have withdrawn from the program after three consecutive missed doses. However, extenuating factors should be taken into consideration when discontinuation of methadone is entertained [31]. Other variations of this algorithm are used at other MMTPs with the same underlying concept of restarting at a reduced methadone dosage after a period of missed doses.

Exit Strategy as an Intervention for Safe Prescribing

This is a concept that has been introduced recently to assist practitioners in addressing circumstances in which opioids need to be discontinued for various reasons: it is no longer safe to prescribe to a particular patient [32], benefits of the drug do not outweigh the risks, or the opioid is not effective despite titration of the dose. The exit strategy is embedded in the overall algorithm of frequent reassessment during the course of opioid treatment. When the patient is initially evaluated and a plan of care developed, different possibilities for the management of the pain should be considered. Possible treatments are outlined in Table 1.3.

The strategy should be tailored to individual patient preferences. The armamentarium includes pharmacology, interventional approaches, alternative, complementary, and behavioral strategies. Non-opioid analgesics should be considered first. Opioids are part of the pharmacological strategy, and are usually introduced after non-opioid medications have shown to be insufficient to manage the pain. The selection of a specific opioid depends on analgesic efficacy and the side effect profile. Some clinicians and researchers choose to include opioids at the beginning of the

Table 1.3 Strategies for the management of chronic pain

- Interventional approaches
  - Injections
  - Neurostimulation
  - Neuroaxial infusion
  - Neuroablative
- Pharmacotherapy
  - Non-opioid analgesics
  - Adjuvant analgesics
  - Opioid analgesics
- Others
  - Rehabilitative
  - Psychological
  - Complementary and alternative strategies
  - Lifestyle changes
  - TENS
- Neurostimulation
  - Invasive
    - Motor cortex stimulation
    - Deep brain stimulation
  - Noninvasive
    - rTMS
    - tDCS

TENS transcutaneous electrical nerve stimulation; *rTMS* repetitive transcranial magnetic stimulation; *tDCS* transcranial direct current stimulation

Table 1.4 Domains to be assessed during the patient visits to decrease risk of opioid diversion and proper opioid prescribing

• Assess and document level of **Analgesia** and modify therapy if necessary
• Assess and document drug-related **Adverse effects** and, if present, modify therapy
• Assess and document **Activity** (level of function) and consider modification of therapy if not improved
• Assess and document drug-related **Aberrant behavior** and modify therapy if present

treatment when other alternatives have failed previously [33]. Appropriate patient selection is crucial if opioids are used, and patient characteristics such as history of drug abuse should be considered (see next section for further discussion).

Once a decision is made to use an opioid, a trial is initiated. During the trial, the patient should be assessed for level of analgesia, the presence of side effects, level of function, and the presence of drug-related aberrant behavior. These domains, based on earlier observations, have been coined by Passik as the four "As" and they assist the clinician in making a decision on the safety and efficacy of opioid therapy [34] (Table 1.4).

At the time of every reassessment (follow-up visit), the patient should be evaluated for alternative strategies to treat the pain, and when indicated, they should be added to the plan of care. If the patient experiences intolerable side effects or reports no improvement in the level of function, or if the clinician notes aberrant drug-related behaviors, then the trial should be discontinued and emphasis should be placed on alternative strategies to treat the pain. The dilemma is that when we "exit" the use of opioids, the patient may not have effective alternatives to address the pain. Further research is clearly needed to explore alternative approaches (Fig. 1.1).

General Recommendations for Successful Methadone Prescribing

The practitioner should evaluate risk related to methadone-prescribing for every patient before embarking on a medication trial. During this assessment special attention should be paid to the patient's social history as it can provide information on predictors of aberrant drug-related behavior, including current or past drug or alcohol abuse and history of sexual abuse (a more relevant predictor in women). Clinicians should also be aware of patient behaviors that may suggest opioid abuse. These "red flags" include running out of medications early, having multiple prescribers for opioid medications, and utilizing multiple pharmacies for opioid prescriptions. Stratification of risk level will assist in structuring the visits, including length of follow-up intervals, the institution of an opioid treatment agreement, limiting the amount of medication prescribed, or pill counting.

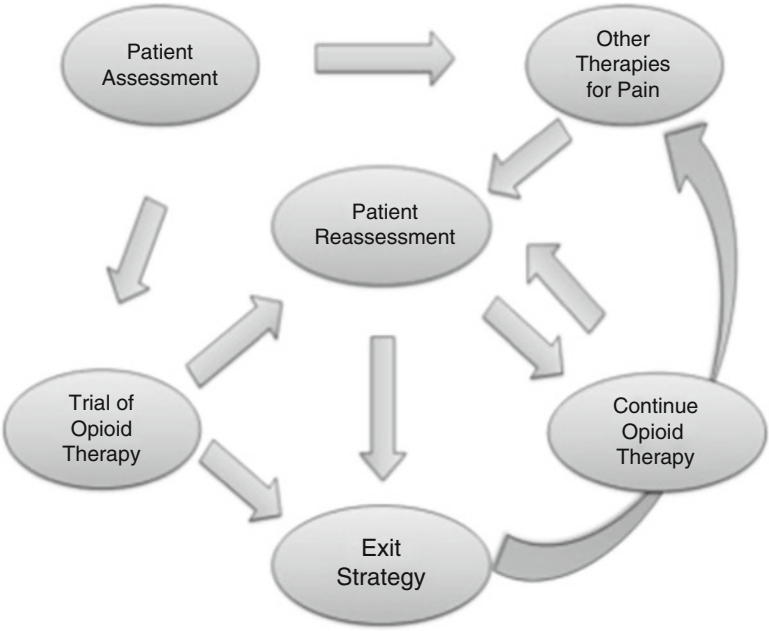

Fig. 1.1 Algorithm to assist reassessment of opioid prescribing over time

Table 1.5 Strategies that can help increase successful opioid prescribing

Implementing the strategy
• Stratify risk in every case
• Structure therapy commensurate with risk
• "Dose for success"
• Repeatedly assess an array of outcomes
• Make changes in dosing or risk management based on outcomes
• Document and communicate

The result of this assessment will help the practitioner determine whether or not this patient will benefit from continued opioid therapy. Should the treatment with opioid medications continue, then at every visit the dose should be adjusted for analgesia and side effects, and an evaluation for the addition of adjuvant therapy should also be done. Documentation of the rationale behind each decision is very important as there is no consensus on how chronic opioid therapy should be conducted. If aberrant drug-related behavior is detected, then a referral to addiction psychiatry is strongly recommended (Table 1.5).

Conclusions

Methadone is a very useful analgesic and the most widely utilized medication for opioid substitution therapy. However, recent data suggest an increase in methadone-related deaths, likely due to methadone-induced QTc prolongation, thereby leading to fatal arrhythmias. Therefore, understanding certain principles of safe opioid prescribing is paramount. This entails an understanding of the "windows" of risk for toxicity, including patient-related factors such as missing doses or appointments, and external circumstances such as imprisonment. The strategy for safe prescribing involves taking a detailed patient history, noting behaviors that are "red flags" for opioid abuse, and instituting appropriate management strategies such as short follow-up intervals, an opioid treatment agreement, or pill counting. If used appropriately, methadone can be very effective as opioid substitution therapy and for the treatment of chronic pain. Further research is needed to explore alternative therapies for patients for whom the risk of methadone outweighs the benefits.

References

1. Dole VP, Nyswander ME. The use of methadone for narcotic blockade. Br J Addict Alcohol Other Drugs. 1968;63(1):55–7.
2. American Pain Society. Principles of analgesic use in the treatment of acute pain and chronic cancer pain. 5th ed. Skokie, IL: American Pain Society; 2003.
3. Skjervold B, Bathen J, Spigset O. Methadone and the QT interval: relations to the serum concentrations of methadone and its enantiomers (R)-methadone and (S)-methadone. J Clin Psychopharmacol. 2006;26(6):687–9.
4. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Phys. 2008;11(Opioid Special Issue):S133–53.
5. Leavitt SB. Addiction treatment forum: methadone-drug interactions. 2005. www.atforum.com/SiteRoot/pages/rxmethadone/methadonedruginteractions.Shtml.
6. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev. 2012. Jun 28 [Epub ahead of print].
7. Katchman AN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther. 2002;303:688–94.
8. Fanoe S, Jensen GB, Sjøgren P, Korsgaard MP, Grunnet M. Oxycodone is associated with dose-dependent QTc prolongation in patients and low-affinity inhibiting of hERG activity in vitro. Br J Clin Pharmacol. 2009;67(2):172–9.
9. Eap CB, Crettol S, Rougier J-S, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. Clin Pharmacol Ther. 2007;81(5):719–8.
10. Ansermot N, Albayrak O, Schläpfer J, Crettol S, Croquette-Krokar M, Bourquin M, et al. Substitution of (R, S)-methadone by (R)-methadone: impact on QTc interval. Arch Intern Med. 2010;170(6):529–36.
11. Centers for Control Disease and Prevention. Vital signs: risk for overdose from methadone used for pain relief—United States, 1999–2010. Morb Mortal Wkly Rep. 2012;61(26):493–7.
12. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004; 350(10):1013–22.

13. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA. 2003;289(16):2120–7.
14. Morgan OW, Johnson H, Rooney C, Seagroatt V, Griffiths C. Changes to the daily pattern of methadone-related deaths in England and Wales, 1993–2003. J Public Health (Oxf). 2006;28(4):318–23.
15. Cruciani RA. Methadone: to ECG or not to ECG…That is still the question. J Pain Symptom Manage. 2008;36(5):545–52.
16. Martin JA, Campbell A, Killip T, Kotz M, Krantz MJ, Kreek MJ, et al. QT interval screening in methadone maintenance treatment: report of a SAMHSA expert panel. J Addict Dis. 2011;30(4):283–306.
17. Stimmel B, Lipski J, Swartz M, Donoso E. Electrocardiographic changes in heroin, methadone and multiple drug abuse: a postulated mechanism of sudden death in narcotic addicts. Proc Natl Conf Methadone Treat. 1973;1:706–10.
18. Maremmani I, Nardini R, Zolesi O, Castrogiovanni P. Methadone dosages and therapeutic compliance during a methadone maintenance program. Drug Alcohol Depend. 1994;34(2):163–6.
19. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic methadone therapy. J Pain Symptom Manage. 2005;29:385–91.
20. Krantz MJ, Lewkowiez L, Hays H, et al. Torsade de pointes associated with very-high-dose methadone. Ann Intern Med. 2002;137(6):501–4.
21. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table [review]. J Pain Symptom Manage. 2009;38(3):426–39.
22. Webster LR, Fine PG. Review and critique of opioid rotation practices and associated risks of toxicity. Pain Med. 2012;13(4):562–70.
23. Webster LR, Fine PG. Overdose deaths demand a new paradigm for opioid rotation. Pain Med. 2012;13(4):571–4.
24. Fine PG, Portenoy RK, Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation. Establishing “best practices” for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage. 2009;38(3):418–25.
25. Merrall EL, Kariminia A, Binswanger IA, Hobbs MS, Farrell M, Marsden J, et al. Meta-analysis of drug-related deaths soon after release from prison [review]. Addiction. 2010;105(9):1545–54.
26. Harris A, Selling D, Luther C, Hershberger J, Brittain J, Dickman S, et al. Rate of community methadone treatment reporting at jail reentry following a methadone increased dose quality improvement effort. Subst Abus. 2012;33(1):70–5.
27. Larney S, Toson B, Burns L, Dolan K. Effect of prison-based opioid substitution treatment and post-release retention in treatment on risk of re-incarceration. Addiction. 2012;107(2): 372–80.
28. Farnia M, Ebrahimi B, Shams A, Zamani S. Scaling up methadone maintenance treatment for opioid-dependent prisoners in Iran [review]. Int J Drug Policy. 2010;21(5):422–4.
29. Larney S. Does opioid substitution treatment in prisons reduce injecting-related HIV risk behaviours? A systematic review [review]. Addiction. 2010;105(2):216–23.
30. Horton A. Heroin users: the need for improved treatment for incarcerated women. Soc Work Public Health. 2011;26(2):176–88.
31. Methadone maintenance treatment, policies and procedures for New Brunswick addiction services. 2009.
32. Gourlay DL, Heit HA. Pain and addiction: managing risk through comprehensive care [review]. J Addict Dis. 2008;27(3):23–30.
33. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline [review]. J Pain. 2009;10(2):131–46.
34. Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: overcoming obstacles to the use of opioids. Adv Ther. 2000;17:70–80.

35. Walker PW, Klein D, Kasza L. High dose methadone and ventricular arrhythmias: a report of three cases. Pain. 2003;103(3):321–4.
36. Almehmi A, Malas AM, Yousufuddin M, Rosencrance JG. Methadone-induced torsade de pointes in a patient with normal baseline QT interval. W V Med J. 2004;100(4):147–8.
37. Krook AL, Waal H, Hansteen V. Routine ECG in methadone-assisted rehabilitation is wrong prioritization. [Norwegian]. Tidsskr Nor Laegeforen. 2004;124(22):2940–41.
38. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005;95(7):915–8.
39. Maremmani I, Pacini M, Cesaroni C, et al. QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur Addict Res. 2005;11(1):44–9.
40. Sticherling C, Schaer BA, Ammann P, Maeder M, Osswald S. Methadone-induced torsade de pointes tachycardias. Swiss Med Wkly. 2005;135(19e20):282–5.
41. Ehret GB, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. Arch Intern Med. 2006;166(12):1280–7.
42. Peles E, Bodner G, Kreek MJ, Rados V, Adelson M. Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: a crosssectional study. Addiction. 2007;102(2):289–300.
43. Chinello P, Lisena FP, Angeletti C, et al. Role of antiretroviral treatment in prolonging QTc interval in HIV-positive patients. J Infect. 2007;54(6):597–602.
44. Krantz JM, Martell BA. Medications that prolong the QT interval. JAMA. 2007;29(8):1025.
45. Routhier DD, Katz KD, Brooks DE. QTc prolongation and torsades de pointes associated with methadone therapy. J Emerg Med. 2007;32(3):275–8.
46. Ehret BG, Desmeules JA, Broers B. Methadone- associated long QT syndrome: improving pharmacotherapy for dependence on illegal opioids and lessons learned for pharmacology. Expert Opin Drug Saf. 2007;6(3):289–303.

Chapter 2
Use of Methadone in Opioid Maintenance Treatment

Randy M. Seewald

Introduction

Addiction is a chronic relapsing disease of the brain and pharmacotherapies that effectively treat opioid dependence are acknowledged to be first-line treatment with significant benefits for the patient [1]. Methadone is the most widely used and effective evidence-based medication for the treatment of opioid dependence [2, 3]. This chapter is intended to assist prescribing professionals in making medical decisions for patients on methadone maintenance treatment (MMT). Methadone is most effective when used as a maintenance agent at optimal dosing with supportive counseling [4, 5]. In the United States, approximately 260,000 persons are treated in more than 1,100 opioid treatment programs (OTP) [6]. The clinics are extensively regulated by the federal and state governments. Federal regulations are found in the federal register code of federal regulations (CFR), 42 CFR Part 8, and the prescriber needs to be familiar with the individual regulations of the state in which they practice, as the strictest standard regulating treatment is the one adhered to if there is discordance.

The desired clinical effects of methadone in MMT include the relief of physical withdrawal, the elimination of craving, and blocking of the euphoric effects of illicit opioid use [7, 8]. The primary function of MMT is to reduce (and ideally stop) illicit opioid use, reduce harmful substance misuse, and to improve the patients' health and psychological wellbeing. Methadone has been established to be efficacious, decreasing high risk behaviors associated with drug use including unsafe injection and sexual practices, decreasing the risk of HIV, hepatitis, and other infections [9–14]. Methadone has also been shown to decrease mortality, criminal activity, incarceration, overdose, and societal costs related to illicit heroin use [15, 16].

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_2,

Federal Criteria for Admission to MMT in an OTP

Methadone can only be dispensed (and not prescribed) for addiction treatment in the setting of an OTP in the United States. Patients must meet the diagnostic criteria of opioid dependence as set forth in the Diagnostic and Statistical Manual, Fourth Edition (DSM–IV) [17]. Patients who meet the DSM diagnostic criteria for Opioid Abuse but not Opioid Dependence are not eligible for treatment with methadone. Federal regulations require documentation of at a minimum, opioid addiction for 1 year to qualify for admission. Current physical dependence is not required if patients have been incarcerated and are admitted within 6 months of release, in pregnant patients who can document a past history of addiction and are at current risk of relapse, and in former MMT patients admitted within 2 years of discharge from MMT. Parental consent and two failed detoxification attempts in the 12 months prior to admission for MMT are required of minors. Treatment must be voluntary, and may not be mandated. An informed consent regarding the risks and benefits of methadone treatment must be documented prior to admission for MMT. Individual states have varying guidelines, which may be more stringent and must be adhered to. A waiver from regulation may be obtained if withholding treatment is a risk to the patient's health. Patients who do not meet the criteria for MMT may be considered for methadone detoxification by the OTP. Patients may not be admitted to an OTP for pain management.

Admission History and Physical Exam

An initial comprehensive history and physical exam is required on admission to confirm current physical dependence on opioids, to determine patient eligibility and fitness to participate in MMT. Laboratory tests and screening for infectious disease (federal regulations require screening for tuberculosis and syphilis), and toxicology screening for opioids and drugs of misuse are performed. The Clinical Opiate Withdrawal Scale (COWS) may be used to document the presence and quantify the severity of opioid withdrawal on admission [18] (Table 2.1).

The patient should be in withdrawal prior to the first dose of methadone (the exceptions to this are stated as above). It is important to obtain an illicit drug and medication history. Some patients may need a medical detoxification from sedatives, such as alcohol and benzodiazepines. Medical conditions and mental health issues are identified in order to coordinate care with outside medical providers. The patient must sign an authorization for release of information prior to any communication. A general form for the release of medical information is not adequate, specific requirements for release of information when a patient is in treatment for addiction are found in 42 CFR Part 2 [19].

A caring, respectful, nonjudgmental manner is necessary to establish a therapeutic relationship with the patient and to encourage the full disclosure of important

Table 2.1 Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score

Patient's Name: _____ Date and Time ____/_____/____:_____

Reason for this assessment: _____

Resting Pulse Rate: _____beats/minute
Measured after patient is sitting or lying for one minute
0 pulse rate 80 or below
1 pulse rate 81–100
2 pulse rate 101–120
4 pulse rate greater than 120

Sweating: *over past ½ hour not accounted for by room temperature or patient activity.*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Restlessness *Observation during assessmen*t
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 Unable to sit still for more than a few seconds

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny nose or tearing *Not accounted for by cold symptoms or allergies*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

GI Upset: *over last ½ hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 Multiple episodes of diarrhea or vomiting

Tremor *observation of outstretched hands*
0 No tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Yawning *Observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh skin
0 skin is smooth
3 piloerrection of skin can be felt or hairs standing up on arms
5 prominent piloerrection

Total Score _____
The total score is the sum of all 11 items
Initials of person completing Assessment: _____
_____

Score: 5–12 = mild; 13–24 = moderate; 25–36 = moderately severe; more than 36 = severe withdrawal

information regarding their drug use history and risk behaviors. It is important for the interdisciplinary team to develop a treatment plan addressing the patients' overall health issues and addiction-related problems, not just their opioid dependence.

Determining the Methadone Dose

Methadone, a synthetic opioid, is normally administered once daily in an oral liquid formulation (1 mg/mL) in MMT. It is a racemic mixture of the (R)- and (S)-methadone enantiomers. It is well absorbed from the gastrointestinal tract into the blood stream and is distributed in body fats. The bioavailability of methadone varies depending on the patient's individual metabolism, age, gender, ethnicity, body mass, and prior drug and health history. Pharmacokinetics is different in opioid-dependent compared to non-opioid-dependent individuals. Different doses are often needed to create the same serum methadone level (SML), but the average half-life of methadone is 24–36 h, which leads to a long duration of action and generally allows for once daily dosing. Some patients may need more frequent or divided dosing schedules to remain asymptomatic. This coupled with a slow onset of action (30–60 min, the peak effect of one dose is from 2 to 6 h after ingestion) blunts its euphoric properties making it unattractive as a principal drug of abuse. Tissue stores build up over time and steady state plasma levels are achieved after 4–5 days, therefore any given dose of methadone produces higher blood levels each day for the first 4–5 days of treatment. Accumulation continues and finally reaches a steady state by around 10 days [20, 21]. There is a risk of overdose during the induction period if the starting dose of methadone is too high or is increased too quickly. Assessment of the response to the previous day's dose is necessary to determine subsequent doses and frequent patient observation and evaluation is required after a dose change until a steady state has been achieved. A literature review by Ball and Ross [3] cited an adequate dose of methadone to usually be between 60 and 100 mg/day, but some may need more some less depending on individual factors.

Tolerance

The maximum initial dose of methadone on admission cannot exceed 30 mg by regulation, but after a period of observation a follow up dose may be given on the same day. The maximum total dose administered on the first day must not exceed 40 mg. There is no way to determine a patient's current level of tolerance. The mantra "start low, go slow" reflects safety concerns. A conservative induction approach, waiting 5 days between dose adjustments, can be risky in that it may contribute to continued illicit drug use by delaying relief from physical withdrawal and craving. When assessing tolerance consider that patients may over report or under report their level of daily drug use and intravenous use generally produces greater levels

of tolerance. After a period of abstinence, tolerance may be absent; therefore after release from incarceration, hospitalization, or residential drug-free treatment, in the absence of opioid medication patients may have low tolerance, if any [22]. Opioid equi-analgesic dose tables are not used to determine the starting and maintenance dose of methadone for patients taking prescription opioids. If there is any question of the level of tolerance or a low level of tolerance is likely, an initial dose of 5–15 mg may be given with follow up doses as clinically indicated. Patients generally start at 20–40 mg of methadone. Patients in whom the first dose suppresses withdrawal completely for a full 24 h may experience sedation as tissue stores accumulate and exhibit symptoms of overmedication. Daily evaluation during the induction period as the dose builds to therapeutic levels is the safest route to take. If patients do not experience complete suppression of withdrawal 3–4 h after dosing on the preceding day, it is safe and reasonable to increase the dose by 5–10 mg. Patients must be counseled to report symptoms of overmedication, and the dose reduced immediately if sedation or other symptoms are detected to prevent fatal overdose. Severe physical withdrawal should be suppressed in a day or two, and complete suppression after a week or two [23].

Several missed doses may produce a decrease in tolerance. It is common practice in MMT for a 3 day consecutive miss to lead to a dose review with a possible dose reduction. Five days or more missed consecutively should lead to a dose reassessment and re-titration of the methadone upwards, even if the patient reports continued opioid or methadone use during this period. The tolerance of patients on MMT is an important protective factor against overdose and patients are far less likely to overdose than opioid users not in treatment.

Optimal Dosing

A given methadone dose which suppresses opioid withdrawal may or may not be a therapeutic or adequate dose. The optimal dose of methadone will not only control the physical signs and symptoms of opioid withdrawal but will also control cravings for opioids (the desire to use, frequent thoughts or dreams of using) with the avoidance of sedation and the minimization of other adverse effects (sweating, constipation, and loss of libido), which may be dose-dependent. Cravings are the result of the inability of the patient to produce natural endogenous opioids and methadone is effective at suppressing them. Conditioned cravings or “tiggers” occur with patient exposure to persons, places, and things associated with using opioids. A patient constantly exposed to triggers may continue to use and require a higher blocking dose of methadone to block the euphoric effects of opioids used in addition to the methadone. Not all patients require a blocking dose to achieve abstinence from illicit drug use. Some patients do not want to stop using and/or suffer methadone side effects and choose to keep their methadone dose low allowing for continued opioid use. Outcomes are better when a therapeutic dose is achieved and illicit opioid use ceases; however, even on low doses of methadone patients with continued

illicit opioid use remaining in treatment have been shown to be substantially improved in terms of decreasing heroin consumption, arrests, and employment [24]. An interdisciplinary model of care with all disciplines—counselors, nurses, and clinicians working together, supports the patient's adherence to treatment and acceptance of an adequate dose.

The benefit of maintenance treatment is correlated with retention in treatment and the adequacy of the methadone dose [5, 25]. Once stabilized a patient may stay on the same dose for years. More often the dose needs to be adjusted due to changes in the patient's health, medications, schedule, life circumstances, stress, and exposure to triggers. Increasing or decreasing the dose by 5–10 mg and waiting 4–5 days for a new steady state to be achieved before any further changes are made may be all that is needed in the case of extreme oversedation, the dose decrease is more aggressive. It is important to ask the patient at regular intervals if they are comfortable on their current methadone dose. Patients may not be using illicit drugs but can still experience cravings which otherwise would go unreported. Decisions to change the methadone dose should be individualized and made with patient input.

Relapse may account for a loss of stability on the current methadone dose. If continued illicit opioid use (heroin or prescribed medications) is still causing euphoria, a methadone dose increase should be offered to block this effect and to suppress drug cravings. Misuse of centrally acting psychotropic medications, commonly benzodiazepines and alcohol, may require a methadone dose decrease as the additive effects may cause sedation, respiratory depression, and coma. The methadone dose required to treat opioid dependence may prove inadequate if decreased to counter oversedation from polysubstance use. It is important for the patient to receive their methadone but it may be unsafe to medicate patients that are observed to be sedated, particularly after taking the methadone in combination with other drugs prescribed or not. A supervised withdrawal from the sedative or alcohol is often necessary: if the patient is willing to decrease their use where and how detoxification will be accomplished needs to be established. The patient needs to be counseled regarding the risks polysubstance use on MMT. Care coordination and communication with outside prescribing professionals is essential.

A dose increase may be indicated in response to a patient reporting cravings or withdrawal when facing increased life stressors. Conversely, after a patient has been stabilized on a blocking dose of methadone and is no longer confronted by daily triggers a decreased dose may be well tolerated and adequate for maintenance treatment.

New medications may precipitate withdrawal. Incremental dose increases may not be adequate and a split dose may be necessary to restabilize from the increased metabolism of methadone. Partial opioid agonists (buprenorphine, Nubain) and antagonists (naltrexone, naloxone) will acutely precipitate withdrawal in methadone maintained patients and may be severe and potentially dangerous to patients. Medications that decrease methadone metabolism may require a methadone dose decrease.

Some medical conditions may change the metabolism of methadone, produce symptoms that mimic withdrawal or produce life stress which trigger craving and

will require a methadone dose adjustment. Minor colds and flu often feel like withdrawal to patients, but an increase in the methadone dose is not needed.

Anxiety not related to withdrawal, but which is related to an anxiety disorder or underlying depression will not respond to a methadone dose increase and the underlying condition needs to be treated with appropriate psychotropic medication and/or counseling.

Insomnia may result from many causes, so first rule out stimulant use and educate the patient regarding good sleep hygiene. The patient may have a sleep disorder not related to opioid use or treatment. If the methadone dose is too low, the patient will wake in the night with withdrawal mediated insomnia and after being medicated in the AM fall asleep appearing over sedated in spite of subtherapeutic nighttime methadone levels. A thorough patient history is required to assess the cause and treatment of insomnia.

In pregnancy methadone blood levels may be significantly lowered particularly in the first and third trimester. Split dosing may be required to restabilize patients, with an increase of the methadone dose. Any dose decrease needs to be discussed with the patient so that she is aware of the risks of withdrawal to the fetus in utero. Tapering is best done in the second trimester if the patient chooses to do so. An informed consent regarding the risks of tapering the methadone dose during pregnancy is documented before initiating a taper during pregnancy.

Split Dosing

If a patient is clinically overmedicated several hours after dosing but experiences withdrawal before it is time for the next dose, they may request a split dose. Most patients can be stabilized on a single daily dose but patients who are rapid metabolizers of methadone may require split dosing to alleviate withdrawal symptoms between doses. Additional once-a-day dose increases will not make the dose last longer and would only elevate the peak level, not the trough level. Peak and trough plasma levels of methadone can be utilized to evaluate the adequacy of a dose, but should not replace clinical judgment. Increasing the once-a-day dose for rapid metabolizers results in greater overmedication during the early hours but continued opioid withdrawal later [26]. There is no standard therapeutic blood level: blood levels vary from patient to patient. The R isomer of methadone is active in the treatment of opioid dependence [27, 28]. Serum blood levels however do not distinguish between the active (R) and inactive (S) isomers of methadone. The methadone dose is significantly correlated with SMLs, but evaluating the trough level in a patient is less useful than comparing the peak and trough levels. The peak level should be less than twice the trough level. If the peak SML is more than twice the trough level (P:T ratio > 2.0), splitting the daily methadone dose should be considered as a peak level that is more than twice the trough level suggests a rapid metabolizer of methadone. Methadone blood levels are obtained when a patient has reached a steady state on a given dose after 5–7 consecutive daily doses. The trough level is drawn

approximately 24 h after the previous dose and before the daily dose is taken. The patient is asked to remain in the clinic and needs to be observed so no other methadone is ingested during the interim 3–4 h before the methadone peak level is drawn. The therapeutic benefit to the patient of split dosing and a take-home dose must outweigh the risks of possible methadone diversion. Split dosing is recommended in pregnancy when the metabolism of methadone is increased and may be helpful for patients with pain because patients report some analgesic effect from the methadone after dosing.

Possible Side Effects of MMT

Oral methadone has proven to be well tolerated with minimal adverse reactions when prescribed in appropriate doses in MMT [29, 30]. Most adverse effects from methadone are general opioid effects, such as nausea, vomiting, constipation, and drowsiness, and most improve over time. Higher doses of methadone may produce respiratory depression and hypotension. Dry mouth, sweating, and decreased libido may also commonly occur.

Drug Interactions with Methadone

Methadone is metabolized in the liver by the CYP enzymes. Other medications may induce enzyme activity, accelerate its breakdown, increase its rate of clearance, lower the SML, and possibly precipitate an abstinence (withdrawal) syndrome or inhibit this enzyme system, slowing methadone metabolism, raising the SML, and possibly causing methadone toxicity from oversedation and/or respiratory depression [31]. Medications that alkalinize the urine (bicarbonate) decrease the rate of methadone excretion and medications that acidify the urine (vitamin C) increase the rate of excretion. Ciprofloxacin can significantly increase the methadone level resulting in severe sedation, bradycardia, and/or respiratory failure [32]. Tricyclic antidepressants (Elavil) may increase methadone toxicity and plasma levels, and are often misused by patients when prescribed or can be illicitly obtained. Because of the relatively small but statistically significant QT interval increases among MMTP patients it would be prudent not to co-prescribe methadone with other drugs that prolong the QT interval where possible. Many drugs used for HIV interact with each other and their combined effects on methadone can be complex [33].

Most potential drug interactions are not absolute contraindications for co-administration. The clinical response varies widely depending on the medication and the individual patient. Many patients will not develop any clinically significant problems. It is important to be aware of concomitant diseases (e.g., liver disease) that might influence the potential for adverse drug interactions. Substitute alternative medications that do not interact with methadone where possible, or use those

that have the least potential for interaction. Careful monitoring for signs of withdrawal or sedation when the patient is prescribed new medications, with appropriate methadone dose adjustments, is all that may be necessary. A complete list of prescribed OTC and herbal preparations must be obtained and reviewed prior to starting methadone treatment and updated on a regular basis. Patients must inform the clinic when prescribed a new medication and communication with outside providers maintained.

Prolonged QTc and ECG Screening in MMT

In some individuals, methadone—alone, or more commonly, in combination with other drugs and/or cardiac risk factors—can prolong the QTc interval, particularly at higher doses (greater than 100 mg), putting the patient at risk from the potentially life-threatening cardiac arrhythmia torsade de pointes. Current evidence does not support altering methadone dosing practice or requiring electrocardiograms (ECGs) for all patients beginning methadone therapy and should not deter the appropriate use of methadone. There are concerns that recently released guidelines for QT interval screening may jeopardize treatment [34–38]. More research is needed to support routine EKG screening, as the relatively small potential risk of adverse cardiac events with methadone should be weighed against the significant benefits of treatment [39]. Alternatives, such as buprenorphine, which has not been shown to prolong the QTc in vivo, may be considered after evaluating the risks/benefits of methadone treatment for a particular patient. It is important to inform patients of the risks associated with MMT, identify those patients who may be at an increased risk of adverse reactions, counsel at-risk patient regarding treatment options and coordinate care for at-risk patients with other treating physicians.

Ongoing Care

After admission to the MMT and methadone dose stabilization, physicians in an OTP provide ongoing medical oversight of the patients overall treatment [23]. Activities include:

- Reviewing each patient's treatment plan to ensure that it meets regulatory criteria and addresses current recovery, medical and social needs.
- Provide medical counseling as needed and ensure that the patient receives appropriate addiction-related counseling at the program.
- Evaluates and reevaluates the patients' methadone dose to support him/her in achieving and maintaining abstinence while minimizing side effects and ensuring safety.
- Evaluate patients who appear sick or intoxicated when they present for dosing to determine they may be safely dosed or a dose adjustment needs to be made or if they need acute medical attention.

- Make decisions regarding patients' eligibility for take-home doses.
- Review and interpret drug screen results when necessary.
- Review patients' prescription medications, intervening with the patient and/or prescribing physician when there is a concern.
- Advocacy for patients to ensure that they receive appropriate medical treatment (especially for pain management) and are not penalized for being in MMT.
- Coordinate care with outside medical staff, hospitals or jail medical units, and to provide consultation when needed.

Comorbid Polysubstance Use

Polysubstance use is common in patients admitted to MMT. Some patients quit using all other illicit drugs but many do not. Increasing the methadone dose will often stabilize patients who are only using illicit opioids, but for other non-opioid drugs other interventions are needed. The patient should be assessed for medical and psychiatric conditions contributing to the misuse. Patients should be warned about the dangers of driving and/or operating heavy machinery when using illicit drugs or other medications in combination with methadone. It may be necessary to discontinue methadone treatment if it becomes unsafe for the patient to continue, especially if the patient is missing multiple doses or who appear to be at a risk of overdose, but discharging a patient from treatment may also be detrimental. The physician must weigh the risks and benefits for the patient remaining in treatment vs. discharge, to determine the appropriateness of discharging the patient.

Comorbid Psychopathology

The incidence of comorbid psychopathology in MMT may be as high as 78 % and has been found to have a negative impact on quality of life [40]. On-site mental health services are recommended as it is important to diagnose and treat psychotic, mood and anxiety disorders because when symptoms remain untreated substance use is likely to continue. In dual diagnosis patients good control of their opioid dependence leads to stability and improvements in mental health. Clinical experience suggests that some psychiatric conditions sometime respond to appropriate methadone dosing. Mood disturbance may be a sign of withdrawal and will respond to methadone dose adjustments. If mood problems disappear and recur at trough levels, this is suggestive of withdrawal-mediated mood disturbance [41]. Antisocial behaviors associated with active addiction may disappear when the addiction comes under control. There is a high incidence of physical, sexual, and posttraumatic stress disorder among opioid-dependent patients.

Associated Medical Problems

Urgent conditions and needle-related diseases (abscess and cellulitis, necrotizing fasciitis, botulism, infectious endocarditis, trauma, HIV, hepatitis, tuberculosis) must be screened for intake and as needed, and prompt care arranged when necessary. Medical comorbidities seen in MMT patients related to opioid use are often associated with the method of ingestion (intravenous, inhalation, nasal insufflation, or snorting) and activities related to obtaining the drug. Those comorbidities associated with the non-opioid drugs of abuse (smoking, cocaine, amphetamines, etc.) are frequently directly related to the drug. Chronic diseases include diabetes, asthma, hypertension, chronic obstructive pulmonary disease, and coronary artery disease. It is important to ensure that patients with HIV are aware of the potential interaction between methadone and antiretrovirals and to ensure that prescribing physicians are aware of the patient's methadone treatment and care coordinated with other medical providers. The methadone dose needs to be adjusted in response to the patients' particular reaction and often more rapidly than in usual clinical practice. Many patients smoke cigarettes and are at high risk for cardiac and lung diseases. Methadone can potentially suppress respiration and although tolerance to respiratory depression is expected during MMT, hospital physicians may temporarily decrease the methadone dose in MMT patients. It is important to advocate for and coordinate care when patients are hospitalized.

Chronic and Acute Pain in MMT

Pain in people who use drugs is common, complex, and poorly treated. Pain prevalence estimates in MMT are high and range from 37 % with chronic severe pain (i.e., pain lasting at least 6 months with at least moderate pain intensity or significant pain interference in the past week) to more than 60 % with chronic pain of any intensity [42–45]. Chronic pain in patients attending MMTPs is associated with increased psychopathology, including increased levels of anxiety, depression, personality disorder criteria, suicide attempts, trauma, and disability [42–45]. The fear of diversion and medication misuse may result in opioid users receiving inadequate analgesia. The undertreatment of pain in MMT patients is often based on misconceptions such as MMT provides adequate analgesia, the use of opioids for analgesia may trigger relapse, the additive effects of opioid analgesics in addition to MMT may increase respiratory and central nervous system depression, and requesting pain medication or complaining of pain is seen as drug-seeking behavior.

The usual methadone dose is generally maintained when treating both acute and chronic pain. Non-pharmacological approaches as well as non-opioid analgesics and adjuvants may be useful.

Toxicology Screening

Toxicology screening should never be used punitively, but only as an aid to treatment. Positive screens for heroin and other illicit drugs require a review of the patient treatment plan, of the methadone dose and should not normally lead to discharge from MMT or a dose reduction. Regulations require screening for illicit drug use and to verify that methadone is present. Federal regulations require eight drug tests at a minimum per calendar year and do not specify which drugs, other than methadone, must be included. States have different, often more onerous regulations. The use of toxicology screening is limited in its ability to prevent diversion of methadone in MMT as screening provides only positive or negative results and does not measure consumption. Both urine and oral fluid/saliva tests are now available for use. Mouth swab tests of oral fluid provide the same information about recent drug use as testing urine. Saliva tests however are not as sensitive as they have a shorter detection window than urine but can be observed more easily, preserving patient dignity and can be used in patients unable to produce urine. Clonazepam, ativan, and other sedatives, such as muscle relaxants and synthetic opioids, are not reliably screened for using the current toxicology tests available. Specific requests need to be made for the lab to perform these tests. Screening tests may be confirmed by GC/MS to ensure that results are accurate if necessary.

Take-Home Privileges

Patients must be assessed to see if they meet the eight federal criteria for considering eligibility for take-home doses of methadone. These are:

1. Absence of recent abuse of drugs (opioid or non-narcotic) including alcohol
2. Regularity of clinic attendance
3. Absence of serious behavioral problems at clinic
4. Absence of recent criminal activity, e.g., drug dealing
5. Stability of the patient's home environment and social relationships
6. Length of time in comprehensive maintenance treatment
7. Assurance that take-home medication can be safely stored within the patient's home
8. Determination that the rehabilitative benefit to the patient derived from decreasing frequency of clinic attendance outweighs the potential risk of diversion

Take-home medications can support a patient's progress in MMT and be of therapeutic benefit. Federal regulations permit up to 1 month of take-home doses after 9 months in treatment but state regulations are often much stricter. Any patient may receive a take-home medication dose of methadone for days when the treatment facilities are closed, including Sundays and holidays if they can safely and responsibly handle medication. No patient in short-term detoxification or interim

maintenance may receive take-home maintenance medication. Patients who are ill may be provided take-home medication and a designee approved to pick up medication in emergencies, but regular reassessment by a physician is then necessary.

Pregnancy

MMT is recommended to treat opioid dependence in pregnancy. It appears to benefit fetal growth and survival. Improved outcomes may be due to improved antenatal care, health, and nutrition (even if the woman continues to use illicit drugs) and not to the methadone alone [46–48]. The withdrawal of methadone and other opioids in pregnant women puts the woman, the pregnancy, and the baby at risk. MMT on an adequate dose of methadone is recommended rather than a dose reduction due to the high risk of relapse and subsequent harm to the fetus. If the patients are physically dependent on alcohol and sedatives, methadone treatment should be started prior to hospitalization so opioid withdrawal does not complicate the detoxification [23].

Dose determination in pregnancy unfortunately remains controversial and some obstetricians insist on low doses or even methadone tapers to avoid the risk of NAS. The literature on the relationship of dose to withdrawal is inconclusive but it is well established that therapeutic doses of methadone are associated with decreased illicit drug use, more prenatal care and longer retention in treatment. Babies exposed to ongoing illicit drug use are at greater risk of adverse outcomes. It is not established if higher doses of methadone produce adverse outcomes. Recent studies have shown no association between the severity of withdrawal and dose. After initial stabilization many women required dose increases as the pregnancy progresses due to the reemergence of signs and symptoms of withdrawal. Current recommendations are to treat pregnant women according to the same dosing guidelines as the nonpregnant patient without any upper methadone dose limit. Rarely urine drug screens may become negative for methadone and the methadone metabolite because of the increased clearance in pregnancy. When breastfeeding, the amount of methadone passed into the breast milk is negligible. MMT or the methadone dose should not be used as a contraindication to breastfeeding in women.

Detoxification and Discharge from MMT

Evidence shows outcomes are better with long-term MMT; however, patients are discharged from programs for many reasons both voluntary and involuntary [49]. Patient-led detoxification can be successful with adequate support, but enforced reductions are associated with poor outcomes. Research has shown the all-cause mortality is 3–4 times lower in patients continuing in MMT compared with those who discontinue treatment [50]. Discharge from MMT requires appropriate discharge planning because of the high risk of relapse, the loss of tolerance, and the

risk of overdose and death. The patient should be counseled that few patients are able to maintain abstinence after tapering off methadone and that a successful outcome of tapering is ongoing, sustained abstinence from illicit opioid use, even if the patient needs to remain on MMT. To prevent destabilizing a patient, it is best to proceed very slowly, starting and stopping to control symptoms of withdrawal and/or craving. Cravings and slips are indications to stop the taper and restabilize the patient on a higher dose. There is no evidence to indicate the superiority of any one dose reduction approach, a comfortable taper rarely takes less than 2 months and often will take months to years, if ever. Tapers are more likely to succeed if the patients have stability of physical and mental health, and the social environment. Careful monitoring of increased drug and alcohol use during methadone dose tapers is advisable. Psychotic or depressive symptoms may emerge as the methadone concentration decreases and a relapse into depression carries a risk of relapse to drug use [41]. The risk of suicide is increased if the patient relapses after a long period of abstinence.

References

1. Effective medical treatment of opiate addiction. NIH Consensus Statement Online 17–19 Nov 1997 [cited 17 March 2012].
2. Dole VP, Nyswander ME. Methadone maintenance: a ten year perspective. JAMA. 1976;193:646–50.
3. Ball JC, Ross A. The effectiveness of methadone maintenance treatment: patients, programs, services, and outcomes. New York: Springer; 1991.
4. D'Aunno T, Pollack H. Changes in methadone treatment practices. JAMA. 2002;288(7):850–6.
5. Blaney T, Craig R. Methadone maintenance: does dose determine differences in outcomes. J Subst Abuse Treat. 1999;16(3):221–8.
6. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. National survey of substance abuse treatment services (N-SSATS); 2007.
7. Maremmani I, Barra M, Bignamini E, et al. Clinical foundations for the use of methadone. Italian consensus panel on methadone treatment. Heroin Addict Relat Clin Probl. 2002;4(2):19–32.
8. Maremmani I, Pacini M, Lubrano S, Lovrecic M. When "enough" is still not "enough": effectiveness of high-dose methadone in the treatment of heroin addiction. Heroin Addict Relat Clin Probl. 2003;5(1):17–32.
9. Schoenbaum E, Hartel D, Selwyn P. Risk factors for human immunodeficiency virus infection in intravenous drug users. N Engl J Med. 1989;321:874–9.
10. Ward J, Hall W, Mattick R. Role of maintenance treatment in opioid dependence. Lancet. 1999;353:221–6.
11. Metzger D, Woody G, McLellan T, et al. Human immunodeficiency virus seroconversion among intravenous drug users in- and out-of-treatment: an 18-month prospective follow-up. J Acquir Immune Defic Syndr. 1993;6:1049–56.
12. Institute of Medicine. No time to lose: making the most of HIV prevention. Washington, DC: National Academy Press; 2000.
13. Hagan H, Des Jarlais DC. HIV and HCV infection among injecting drug users. Mt Sinai J Med. 2000;67:423–8.

14. Pollack HA. Cost-effectiveness of harm reduction in preventing hepatitis C among injection drug users. Med Decis Making. 2001;21:357–67.
15. Gronbladh L, Ohland M, Gunne L. Mortality in heroin addiction: impact of methadone treatment. Acta Psychiatr Scand. 1990;82:874–9.
16. Marsch L. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behaviour and criminality: a meta-analysis. Addiction. 1998;93:515–32.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: Author; 2000.
18. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale. J Psychoactive Drugs. 2003;35(2):253–9.
19. Code of Federal Regulations 42 CFR chapter 1, part 8.12 (i) (2) (i)–(viii).
20. Benet L, Kroetz D, Sheiner L. Pharmokinetics. In: Hardman J, Limbird L, editors. The pharmacological basis of therapeutics. 9th ed. New York: McGraw-Hill; 1996. p. 3–27.
21. Stine SM, Greenwald MK, Kosten TR. Pharmacologic therapies for opioid addiction. In: Graham AW et al., editors. Principles of addiction medicine. 3rd ed. Chevy Chase, MD: American Society of Addiction Medicine; 2003. p. 735–50.
22. Strang J, McCmbridge J, Best D, et al. Loss of tolerance and overdose mortality after inpatient opiate detoxification: follow up study. BMJ. 2003;326:959–60.
23. California Society of Addiction Medicine (CSAM). Guidelines for physicians working in California Opioid Treatment Programs; 2009.
24. Craig RJ. Effectiveness of low dose methadone maintenance treatment for the treatment of inner city heroin addicts. Int J Addict. 1980;15:701–10.
25. Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow up results from the National Treatment Outcomes Research Study. Drug Alcohol Depend. 2001;62:255–64.
26. Tenore PL. Guidance on optimal methadone dosing. Addict Treat Forum. 2003;12(3):1, 6–7.
27. Loimer N, Schmid R. The use of plasma levels to optimise methadone maintenance treatment. Drug Alcohol Depend. 1992;30(3):241–6.
28. Mitchell TB, Dyer KR, Newcombe D, Salter A, Somogyi AA, Bochner F, et al. Subjective and physiological responses among racemic–methadone maintenance patients in relation to relative (S)- vs. (R)-methadone exposure. Br J Clin Pharmacol. 2004;58:609–17.
29. Kreek MJ. Medical safety and side effects of methadone in tolerant individuals. JAMA. 1973;223:665–8.
30. Novick DM, Richman BL, Friedman JM, et al. The medical status of methadone maintained patients in treatment for 11–18 years. Drug Alcohol Depend. 1993;33:235–45.
31. Leavitt S. Methadone-drug interactions. Addict Treat Forum. Nov 2005.
32. Herrlin K, Segerdahl M, Gustafsson LL, Kalso E. Methadone, ciprofloxacin, and adverse drug reactions. Lancet. 2000;356(9247):2069–70.
33. Faragon JJ, Piliero P. Drug interactions associated with HAART: focus on treatments for addiction and recreational drugs. AIDS Read. 2003;13(9):433–50.
34. Byrne A. Concerns about consensus guidelines for QTc interval screening in methadone treatment. Ann Intern Med. 2009;151(3):216.
35. Cohen SP, Mao J. Concerns about consensus guidelines for QTc interval screening in methadone treatment. Ann Intern Med. 2009;151(3):216.
36. Girgis G. Concerns about consensus guidelines for QTc interval screening in methadone treatment. Ann Intern Med. 2009;151(3):216.
37. Bart G. Concerns about consensus guidelines for QTc interval screening in methadone treatment. Ann Intern Med. 2009;151(3):216.
38. Gourevitch M. First, do no harm… reduction? Ann Intern Med. 2009;150:417–8.
39. Carpentier PJ, Krabbe PF, van Gagh MT, Knapen LJ, Buitelaar JK, de Jong CA. Psychiatric comorbidity reduces quality of life in chronic methadone maintained patients. Am J Addict. 2009;18(6):470–80.

40. Dyer RK, White JM, Foster DJR, Bochner F, Menenlaou A, Somogyi A. The relationship between mood state and plasma methadone concentration in maintenance patients. J Clin Psychopharmacol. 2001;21(1):78–84.
41. Barry DT, Beitel M, Garnet B, Joshi D, Rosenblum A, Schottenfeld RS. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. J Clin Psychiatry. 2009;70:1213–8.
42. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. J Pain Symptom Manage. 2000;19:53–62.
43. Peles E, Schreiber S, Gordon J, Adelson M. Significantly higher methadone dose for methadone maintenance treatment (MMT) patients with chronic pain. Pain. 2005;113:340–6.
44. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA. 2003;289:2370–8.
45. Winklbaur B, Kopf N, Ebner N, Jung E, Thau K, Fischer G. Treating pregnant women dependent on opioids is not the same as pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates. Addiction. 2008;103:1429–40.
46. Finnegan LP. Women, pregnancy and methadone. Heroin Addict Relat Clin Probl. 2000;2(1):1–8.
47. Suffett F, Brotman R. A comprehensive care programme for pregnant addicts: obstetrical, neonatal and child development outcomes. Int J Addict. 1984;19:199–219.
48. Sees K, Delucchi K, Masson C, et al. Methadone maintenance vs 180-day psychosocially enriched detoxification for treatment of opioid dependence. JAMA. 2000;283:1303–10.
49. Bell J, Zador D. A risk-benefit analysis of methadone maintenance treatment. Drug Saf. 2000;22(3):179–90.

Chapter 3
Treating Pain in Patients Receiving Methadone Maintenance for Opioid Dependence

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Misconceptions About Pain in Patients Receiving Methadone for Opioid Dependence

The clinical conditions of pain and opioid dependence are related phenomena [1]. Opioids, whether administered for analgesic or addiction treatment purposes, activate opioid receptors that provide both analgesia and euphoria [2]. The presence of one condition seems to influence the expression of the other. Clinical examples of this include how the presence of acute pain seems to decrease the euphoric qualities of an opioid [3] and how the presence of opioid dependence seems to worsen the experience of pain [4]. In patients with addictive disorders, the experience of pain is worsened by subtle withdrawal syndromes, intoxication, sleep disturbances, and affective changes.

Common misconceptions held by healthcare providers result in the undertreatment of pain in patients receiving methadone maintenance for opioid dependence [5]. These include: (1) methadone maintenance provides analgesia; (2) use of opioids for analgesia may result in addiction relapse; (3) the additive effects of opioid analgesics and methadone maintenance may cause respiratory and central nervous system (CNS) depression; and (4) the pain complaint may be a manipulation to obtain opioid medications, or drug-seeking, in a patient with opioid dependence. We address each of these individually.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_3,

There are pharmacokinetic and pharmacodynamic explanations for why patients do not receive adequate analgesia from methadone used in the treatment of opioid dependence. Not only do the analgesic and addiction treatment profiles of methadone differ, but the neuroplastic changes associated with long-term opioid exposure (i.e., tolerance, opioid-induced hyperalgesia) may effectively diminish its analgesic effectiveness [6]. Methadone, a potent analgesic, has a duration of action for analgesia (4–8 h) that is substantially shorter than its suppression of opioid withdrawal (24–48 h) [7]. Because patients receiving methadone to treat opioid dependence receive a dose every 24 h, the period of even partial pain relief is short. Opioid tolerance and narcotic blockade are other factors that explain why patients derive little pain relief from their daily methadone maintenance dose [8]. One study found that patients receiving methadone maintenance were cross-tolerant to the analgesic effects of morphine and that pain relief, when obtained, did not last as long as expected [9]. Therefore, cross-tolerance between methadone used for treating opioid dependence and other opioids used for analgesia may explain why these patients often require higher and more frequent doses of opioid analgesics to achieve adequate pain control.

A second concern is that the use of opioid analgesics in patients receiving methadone maintenance may result in relapse to illicit opioid use. There is no evidence that exposure to opioid analgesics in the presence of pain increases rates of relapse in such patients. A small retrospective study of patients receiving methadone maintenance who received opioid analgesics after surgery did not find a difference in relapse indicators compared with matched patients [10]. Similarly, no evidence of relapse was seen in patients receiving methadone maintenance who received opioid analgesics for cancer-related pain [11]. In fact, relapse prevention theories would suggest that the stress associated with unrelieved pain is more likely to be a trigger for relapse than adequate analgesia. In one study patients receiving methadone maintenance therapy stated that pain played a substantial role in their initiating and continuing illicit opioid use [12].

A third concern is that the addition of opioid analgesics to methadone maintenance will cause severe respiratory or CNS depression. This is a theoretical risk, which has not been clinically demonstrated. Tolerance to the respiratory and CNS-depressant effects of opioids occurs rapidly and reliably [13]. Patients with worsening cancer-related pain who require dose escalations typically do not exhibit respiratory and CNS-depressant effects when additional opioids are administered [14, 15]. It has been suggested that acute pain serves as a natural antagonist to opioid-associated respiratory and CNS depression [16].

Finally concern about being manipulated by a drug-seeking patient is a powerful influence underlying physicians' reservations to prescribe or order opioid analgesics for pain to patients receiving methadone for opioid dependence. Pain is always subjective, making assessment of its presence and severity difficult. While this may be a concern, it is important to note that patients receiving methadone maintenance typically receive methadone doses that block most euphoric effects of co-administered opioids, theoretically decreasing the likelihood of opioid analgesic abuse.

Treating Acute Pain in Patients Receiving Methadone

The appropriate treatment of acute pain in methadone maintained patients includes addressing the patient's baseline opioid requirement for their opioid dependence along with aggressive pain management. As with all patients who have acute pain, nonpharmacologic and nonopioid analgesic pain-relieving interventions should be aggressively implemented. However, patients with moderate to severe acute pain will often require opioid analgesics. To decrease the total amount of opioid provided to these patients, multimodal analgesia (i.e., nonsteroidal anti-inflammatory drugs and acetaminophen) and use of adjuvant analgesics that enhance opioid effects (i.e., tricyclic antidepressants) may be co-administered [17]. If patients are hospitalized, acute opioid withdrawal causing worsening pain symptoms can be avoided by continuing the usual daily dose of methadone, after the important step of verification with the patient's opioid treatment program (methadone maintenance provider). It is important to decrease the patient's anxiety by reassuring them that their methadone maintenance will be continued and that their pain will be aggressively treated. When the increased pain sensitivity and cross-tolerance with methadone are considered, adequate pain control will generally necessitate higher doses of opioids administered at shorter intervals. Analgesic dosing should be continuous or scheduled, rather than "as needed" when treating acute pain. Allowing pain to reemerge before administering the next dose causes unnecessary suffering and anxiety and increases tension between the patient and the treatment team.

The pharmacologic properties of opioids must be considered when selecting an opioid analgesic for the methadone-maintained patients. Mixed agonist and antagonist opioid analgesics, such as pentazocine, nalbuphine, and butorphanol, must be avoided because they will likely displace methadone from the μ-opioid receptor, thus precipitating acute opioid withdrawal in these patients [18]. Combination products of opioid analgesics containing fixed doses of acetaminophen and an opioid should be limited to patients not requiring large doses to avoid acetaminophen-induced hepatic toxicity.

Treatment of Chronic Pain in Patients Receiving Methadone

Chronic pain is common in patients receiving methadone maintenance [19, 20]. For example, among patients receiving methadone maintenance, estimates of chronic pain prevalence range from 37 % with chronic severe pain [21, 22] to more than 60 % with chronic pain of any intensity [23, 24]. Many patients seek admission to opioid treatment programs because of opioid analgesic dependence (and not because of heroin dependence) and the majority of those presenting with dependence on prescription opioids report that their primary reason for beginning prescription opioid use was to relieve pain (and not for its euphoric effects [24–26]).

While debate exists about the reasons for the elevated rates of chronic pain in opioid agonist-maintained patients (e.g., opioid-induced hyperalgesia, shared biological vulnerability), it is widely accepted that chronic pain in opioid addicted and non-addicted patients can have multiple deleterious consequences, including health complications, such as sleep and appetite problems; psychological complications, such as trauma, anxiety, and depression; increased attempts to self-medicate (e.g., illicit substance use); and medical/psychosocial problems associated with increased drug seeking behaviors [22, 27–39]. For example, studies have found that in comparison to patients receiving methadone maintenance without pain, those with chronic severe pain are more likely to meet clinical cutoffs for somatization (75 % vs. 6 %, $p<0.001$), anxiety (52 % vs. 17 %, $p<0.005$), overall psychiatric distress (63 % vs. 17 %, $p<0.001$), personality disorder criteria (66 % vs. 31 %, $p<0.01$), and screened symptoms of posttraumatic stress disorder (45 % vs. 14 %, $p<0.05$) [22, 30].

The high prevalence of psychiatric and medical comorbidity among patients with co-occurring chronic pain and opioid dependence can pose clinical management challenges for providing methadone maintenance [24, 40–42]. In one study, physicians and physicians assistants caring for patients receiving methadone maintenance who reported chronic pain tended to fall into one of the two categories, those who prioritized addiction treatment by emphasizing the adverse consequences of using illicit drugs or prescription medications to address pain complaints and those who prioritized pain management and focused on the adverse consequences of untreated pain [42]. Unfortunately, there are no clinical trials to help guide management in this area of medicine and much research is needed [43].

Small experimental studies constitute the state of the science on the role of methadone in contributing to a pathologic chronic pain response in those receiving the medication over a long period of time. A study comparing controls to 31 subjects receiving low dose ($n=13$, mean dose = 41 mg/day) and high dose ($n=18$, mean dose = 188 mg/day) methadone maintenance, some with ($n=18$) and without ($n=6$) chronic pain, used noxious and innocuous thermal and mechanical stimuli to examine pain thresholds [44]. The results indicated that compared to controls, pain thresholds in those receiving methadone maintenance differed based on the presence or absence of chronic pain. Those receiving methadone maintenance who had chronic pain demonstrated higher pain thresholds than pain-free subjects (hypoalgesia) yet had lower pain thresholds compared with controls (hyperalgesia). Patients receiving methadone maintenance who had chronic pain demonstrated higher suprathreshold pain ratings than those without pain and controls. Methadone dose modified the findings. Patient receiving high dose methadone had lower suprathreshold pain ratings than those receiving low dose methadone and controls [44].

These experimental findings correlate with an observational study noting higher daily methadone doses in opioid treatment programs among patients with chronic pain compared to those with pain of shorter duration and those without pain [24]. Similarly, a case series study tracked the dose of methadone prescribed to 53 HIV-infected patients receiving methadone maintenance who had supplemental methadone titrated up in response to patients complaints of pain [45]. The patients mean

dose of supplemental methadone was initially 67 % of their maintenance dose of methadone and mean pain ratings were 9.4 ± 1.03 (10 point scale). At 12 months, mean dose of supplemental methadone was 200 % of the mean maintenance dose, and mean pain ratings were 4.2 ± 1.4 ($p < 0.01$).

Due to limited empiric evidence, consensus guidelines provide the best guidance on treatment of chronic pain in those receiving methadone for the treatment of opioid dependence. Standard recommendations include (1) thorough examination to determine the cause of pain, (2) non-pharmacologic treatments (e.g., cognitive behavioral therapy, physical therapy), (3) use of non-opioid medications, (4) close monitoring for relapse, (5) open discourse between opioid treatment program and pain treatment provider including medications prescribed and urine toxicology results, (6) avoidance of providing opioids that were previously abused by the patient, (7) continuing maintenance doses of methadone, (8) increasing methadone dose frequency (e.g., split dosing), (9) adding immediate release opioid formulations, (10) consideration of increasing maintenance doses in situations where immediate release formulations are frequently required, and (10) referral to specialty pain treatment providers for a full spectrum of pain management [46].

Conclusion

The challenges outlined in this chapter reflect the complexity of these co-occurring conditions. Safe management of patients receiving methadone maintenance for opioid dependence who have pain requires a good understanding of underlying pathology, psychiatric comorbidity, and pharmacology. Trials of combination therapies guided by close patient monitoring and frequent assessments are most likely to result in appropriate treatment of patients and improved outcomes in both pain and addiction.

References

1. Schnoll SH, Weaver MF. Addiction and pain. Am J Addict. 2003;12(Suppl 2):S27–35.
2. Compton P, Gallagher RM, Mardini IA. The neurophysiology of pain and interfaces with addiction. In: Ries RK, Fiellin DA, Miller SC, Saitz R, Ries RK, Fiellin DA, Miller SC, Saitz R, editors. Principles of addiction medicine. Philadelphia, PA: American Society of Addiction Medicine; 2009. p. 1277–96.
3. Zacny JP et al. The effects of a cold-water immersion stressor on the reinforcing and subjective effects of fentanyl in healthy volunteers. Drug Alcohol Depend. 1996;42(2):133–42.
4. Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. J Pain Symptom Manage. 1994;9(7):462–73.
5. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127–34.
6. White JM. Pleasure into pain: the consequences of long-term opioid use. Addict Behav. 2004;29(7):1311–24.

7. Fishman SM et al. Methadone reincarnated: novel clinical applications with related concerns. Pain Med. 2002;3(4):339–48.
8. Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. Arch Intern Med. 1966;118:304–9.
9. Doverty M et al. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. Pain. 2001;93(2):155–63.
10. Kantor TG, Cantor R, Tom E. A study of hospitalized surgical patients on methadone maintenance. Drug Alcohol Depend. 1980;6(3):163–73.
11. Manfredi PL et al. Methadone analgesia in cancer pain patients on chronic methadone maintenance therapy. J Pain Symptom Manage. 2001;21(2):169–74.
12. Karasz A et al. The experience of chronic severe pain in patients undergoing methadone maintenance treatment. J Pain Symptom Manage. 2004;28(5):517–25.
13. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain. 2002;18(4 Suppl):S3–13.
14. Bruera E et al. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. Pain. 1989;39(1):13–6.
15. Walsh T, Baxter R, Bowerman K, Leber B. High-dose morphine and respiratory function in chronic cancer pain. Pain. 1981;11(S39).
16. Eriator I. Narcotic analgesics for chronic pain management. Curr Pain Headache Rep. 1998;2:193–200.
17. Botney M, Fields HL. Amitriptyline potentiates morphine analgesia by a direct action on the central nervous system. Ann Neurol. 1983;13(2):160–4.
18. Scimeca MM et al. Treatment of pain in methadone-maintained patients. Mt Sinai J Med. 2000;67(5–6):412–22.
19. Barry DT et al. Pain and associated substance use among opioid dependent individuals seeking office-based treatment with buprenorphine-naloxone: A needs assessment study. Am J Addict (in press).
20. Barry DT et al. Pain and substance-related pain reduction behaviors among opioid dependent individuals seeking methadone maintenance treatment. Am J Addict. 2009;18(2):117–21.
21. Rosenblum A et al. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA. 2003;289(18):2370–8.
22. Barry DT et al. Relations among psychopathology, substance use, and physical pain experiences in methadone-maintained patients. J Clin Psychiatry. 2009;70(9):1213–8.
23. Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. J Pain Symptom Manage. 2000;19(1):53–62.
24. Peles E et al. Significantly higher methadone dose for methadone maintenance treatment (MMT) patients with chronic pain. Pain. 2005;113(3):340–6.
25. Brands B et al. Prescription opioid abuse in patients presenting for methadone maintenance treatment. Drug Alcohol Depend. 2004;73(2):199–207.
26. Cicero TJ et al. Co-morbid pain and psychopathology in males and females admitted to treatment for opioid analgesic abuse. Pain. 2008;139(1):127–35.
27. Chapman CR, Gavrin J. Suffering: the contributions of persistent pain. Lancet. 1999;353(9171):2233–7.
28. Rosenblum A et al. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. J Am Med Assoc. 2003;289(18):2370–8.
29. Peles E, Schreiber S, Adelson M. Documented poor sleep among methadone-maintained patients is associated with chronic pain and benzodiazepine abuse, but not with methadone dose. Eur Neuropsychopharmacol. 2009;19(8):581–8.
30. Barry DT et al. Exploring relations among traumatic, posttraumatic, and physical pain experiences in methadone-maintained patients. J Pain. 2011;12(1):22–8.
31. Trafton JA et al. Treatment needs associated with pain in substance use disorder patients: implications for concurrent treatment. Drug Alcohol Depend. 2004;73(1):23–31.

32. Currie SR, Wang JL. Chronic back pain and major depression in the general Canadian population. Pain. 2004;107(1–2):54–60.
33. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry. 2003;60(1):39.
34. Bair MJ et al. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163(20):2433.
35. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain. 2003;106(1–2):127–33.
36. Jensen MP et al. The relationship of changes in pain quality to pain interference and sleep quality. J Pain. 2010;11(8):782–8.
37. Asmundson GJG, Katz J. Understanding the co-occurrence of anxiety disorders and chronic pain: state-of-the-art. Depress Anxiety. 2009;26(10):888–901.
38. Tsang A et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain. 2008;9(10):883–91.
39. Fischer-Kern M et al. The relationship between personality organization and psychiatric classification in chronic pain patients. Psychopathology. 2010;44(1):21–6.
40. Barry DT et al. Counselors' experiences treating methadone-maintained patients with chronic pain: a needs assessment study. J Addict Med. 2008;2(2):108–11.
41. Barry DT et al. Opioids, chronic pain, and addiction in primary care. J Pain. 2010;11(12):1442–50.
42. Berg KM et al. Providers' experiences treating chronic pain among opioid-dependent drug users. J Gen Intern Med. 2009;24(4):482–8.
43. Cruciani RA et al. MMTP patients with chronic pain switching to pain management clinics. A problem or an acceptable practice? Pain Med. 2008;9(3):359–64.
44. Peles E et al. The differential effect of methadone dose and of chronic pain on pain perception of former heroin addicts receiving methadone maintenance treatment. J Pain. 2011;12(1):41–50.
45. Blinderman CD et al. Methadone as an analgesic for patients with chronic pain in methadone maintenance treatment programs (MMTPs). J Opioid Manag. 2009;5(2):107–14.
46. Anonymous. Medication-assisted treatment for opioid addiction in opioid treatment programs. Treatment improvement protocol (TIP) Series 43. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.

Chapter 4
Methadone Side Effects: Constipation, Respiratory Depression, Sedation, Sleep-Disordered Breathing, and the Endocrine System

Lynn R. Webster

Introduction

Methadone is an effective analgesic for the relief of moderate-to-severe pain unresponsive to non-opioid treatments [1]. However, candidates for methadone therapy must be carefully selected and closely monitored for side effects. The primary risk with methadone is death from respiratory depression, particularly when initiating therapy or changing doses, and clinicians who prescribe methadone should understand its unique pharmacologic properties. Nowhere are educated prescriber practices and precise patient adherence to medical direction more vital than in methadone therapy for chronic pain.

Adverse effects of methadone are common to all opioids. Many resolve as therapy progresses, including sedation, vomiting, confusion, and dizziness; others, such as constipation and endocrinopathies, persist throughout the treatment period and may require concurrent therapy [2, 3]. Sleep-disordered breathing, particularly if it remains undiagnosed, may contribute to respiratory depression in methadone-treated patients on moderate-to-high doses or with pertinent risk factors [4].

All patients should receive counseling on potential adverse effects along with the risks and benefits of therapy and give informed consent before beginning opioid therapy [5]. Intolerable side effects drive many patients from opioid therapy, but many respond to dose reduction, opioid rotation, a change in the route of administration, or treatment of the symptoms [3].

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_4,

Constipation

Opioid-induced constipation (OIC) is so common with opioid administration that it is best to assume some degree of OIC will occur and take preventive measures. Between 14 and 70 % of opioid-treated patients report symptoms of bowel dysfunction, which may include infrequent and hard stools, abdominal pain and bloating, and decreased appetite [6]. Optimal therapy should improve bowel-movement frequency and stool consistency as well as reduce incidence of straining and incomplete evacuation. Patients vary widely in the quantity and severity of symptoms and in response to treatment, thus highlighting the importance of individual dosing and monitoring for effect.

Tolerance to OIC rarely develops; therefore, co-therapy to prevent or control constipation is necessary [5]. The usual treatment is to advise patients to start immediate nonpharmacologic measures such as increasing liquids, dietary fiber, and physical activity in addition to prophylactic treatment with a laxative [3]. A stool softener is helpful to ease passage of stool when prescribed in combination with a laxative but is usually insufficient as monotherapy [3]. Senna, a stimulant laxative that increases intestinal motility, is effective and often considered a first-line therapy for patients treated chronically with opioids [3], although tolerance can develop and colonic tone can lessen with long-term use [6]. Osmotic laxatives, which increase the amount of water in the gut, provide another option. Dehydration is a risk with osmotic laxatives that can be minimized with electrolytes [6]. Bulk laxatives are not recommended for the treatment of OIC [6].

Laxatives and stool softeners treat the symptoms and must be continuously used. If they are not effective, more invasive therapies with suppositories or enemas may be necessary. In patients with ongoing problems with constipation, consider rotating to another opioid with a less constipating effect [3].

Peripherally active opioid antagonists comprise a new class of medications that target the underlying mechanism of OIC. They work by displacing opioids from the opioid receptors in the gastrointestinal (GI) tract without loss of centrally activated analgesia [6–8]. Several drugs in this class are undergoing development, but the only one currently approved for OIC is methylnaltrexone.

Methylnaltrexone is specifically indicated for OIC in patients with advanced illness who are receiving palliative care when response to laxative therapy has been insufficient. Methylnaltrexone has been investigated in randomized, controlled, double-blind trials and found to be significantly effective in inducing bowel movements over placebo in patients with advanced illness and OIC [7, 8]. No withdrawal or changes in pain scores accompanied the GI effects. The most common drug-associated adverse effects were abdominal pain, flatulence, and nausea. The medication's effect beyond short-term use has not been studied.

Methylnaltrexone is commonly used off label for OIC in patients on chronic opioid therapy for noncancer pain. In the author's clinical experience, patients on methadone demonstrate high sensitivity to peripheral opioid antagonists, thus a reduced dose of methylnaltrexone is usually effective and reduces the incidence of uncomfortable side effects from its use.

In the near future we should see more peripherally active opioid antagonists approved for the treatment of OIC. At this time, the evidence is still too inconclusive to inform standard clinical practice [5].

Respiratory Depression

The largest risk with methadone is respiratory depression. This is true of all opioids, but it appears that prescribing clinicians and patients sometimes underestimate the risk of respiratory depression with methadone, and fatal outcomes have risen with the increased availability of methadone to treat pain [9]. Methadone deaths increased almost sevenfold from 790 in 1999 to 5,420 in 2006, rising faster than deaths from heroin or other opioids [10]. In 2006, the U.S. Food and Drug Administration (FDA) issued warnings of deaths and life-threatening adverse events, including respiratory depression and drug interactions, in methadone-treated patients [1, 11].

Methadone is abused recreationally, but some of the deaths occurred during clinical practice of pain therapy [12]. The Government Accountability Office, which analyzed methadone deaths, determined that insufficient knowledge among healthcare providers and patients on how to prescribe and consume methadone safely contributed to the increase in deaths [12]. Risks arise during initiating, titrating, and converting from other opioids; from drug–drug interactions; from patient nonadherence in escalating doses; and from mixing with unauthorized substances, among other sources [13].

Expert consensus in the pain field says opioid-related respiratory-depressant effects occur principally in opioid-naïve patients and resolve quickly [14]. However, methadone-specific evidence suggests that the course of tolerance is unpredictable. Patients enrolled in methadone maintenance treatment for heroin addiction and who took daily methadone at an average dose of 75 mg demonstrated differing ventilatory responses based on the duration of treatment [15]. Patients who had taken methadone for <2 months demonstrated reduced ventilatory response to carbon dioxide and hypoxia, in contrast with patients who had taken methadone for >5 months who demonstrated ventilatory tolerance to carbon dioxide but failed to demonstrate complete tolerance to hypoxia.

Clinicians should follow conservative prescribing practices due to methadone's unique pharmacokinetic and pharmacodynamic profile. It is vital that prescribing clinicians understand that a disparity exists between methadone's respiratory-depressant and analgesic effects and equally vital that they counsel patients accordingly. Methadone analgesia typically lasts 4–8 h; however, methadone lingers in the body, depressing respiration for 8–59 h on average [11]. Furthermore, the speed at which methadone is eliminated is unpredictable, ranging from 5 to 130 h due to individual variations in metabolism [16].

Genetic contributions may influence vulnerability to respiratory depression and overdose, and patients vary considerably in how quickly or well they metabolize opioids. For example, a CYP2B6 gene variant has been linked to the slow

Table 4.1 Suggested guidelines for initiating methadone for pain

	Starting methadone dose	
Total daily morphine equivalents	Healthy adults age <70 years (mg tid)	Adults with chronic illness or age >70 years (mg bid)
Opioid naïve	5	2.5
60–100 mg	5	5
>100 mg	5	5

Source: [19]

metabolism of methadone resulting in high concentrations and, possibly, to methadone-related mortality [17]. The same study also found a significant correlation in methadone-related mortalities between postmortem benzodiazepine concentrations and an OPRM1 A118G allele [17].

Patients are particularly vulnerable to overdose when initiating opioid therapy, converting from other opioids, and increasing doses. Medical records of 20 patients with chronic pain who died from opioid-related overdose showed methadone to be the primary opioid in 10 (50 %) of cases [18]. In 13 (65 %) of all cases, the death occurred within the first week following an opioid dose change. These results underscore the imperative of starting all patients on a low dose and titrating slowly to effect, even if converting from high doses of other opioids. This often means that the starting dose will not control all pain.

It is safest to treat all new methadone patients as opioid naïve, regardless of prior opioid dose. This is because tolerance to the respiratory-depressant effect of methadone is slow to develop, and cross-tolerance is incomplete between methadone and other opioids [11]. Safe practice supports starting methadone with a ceiling dose of no more than 15 mg a day (Table 4.1) [19]. Starting doses should be even more conservative in vulnerable patients including seniors, obese patients, patients with respiratory, renal, or hepatic compromise, and patients taking concomitant central nervous system depressants. The initial dosing guidelines shown in Table 4.1 are consistent with those published by the FDA [11] and by a physician-specialist consensus panel [5].

Titrating to an effective dose requires close and individual monitoring. Methadone analgesia may require 3–5 days to reach peak effect. Meanwhile, methadone accumulates in the liver, kidneys, and other tissues with repeated dosing, maintaining serum levels between doses, and posing a risk for toxicity and respiratory depression [20]. In some patients who are slow metabolizers, the respiratory-depressant effect continues to accumulate for 7–10 days. Therefore, it is important to wait *at least* 7 days before increasing dose again.

Do not be tempted to give higher-than-recommended doses or to accelerate the titration process to control all pain. Patients should be warned that analgesia may not be immediately effective with methadone and counseled never to take an additional dose on their own. If patients being started on methadone continue to suffer uncontrolled moderate-to-severe pain, consider providing a short-acting opioid to control painful episodes until the methadone titration process can be completed. Clinicians must balance risk with benefit, and patients whose severe pain continues unabated may be at risk for dangerously increasing their own methadone doses [12].

Table 4.2 Counsel patients as follows to avoid methadone-related respiratory depression

1. Never take a prescription pain medication unless it is prescribed for you
2. Never adjust your own doses
3. Never take pain medication with alcohol
4. Mixing pain medications with sedative or antianxiety medications can be dangerous. Follow doctor directions carefully and avoid using pain medication to facilitate sleep
5. Always tell your healthcare provider about all medications you are taking from any source
6. Keep track of when you take all medications
7. Keep your medications locked in a safe place
8. Dispose of any unused medications

Source: [24]

Certain drugs may intensify or inhibit methadone's respiratory-depressant effect. Methadone is metabolized in the liver by CYP enzymes, and drug interactions can occur when methadone is administered together with other medications that induce or inhibit the same enzymes [21]. Drugs that inhibit CYP 3A4 metabolism could slow methadone metabolism, leading to an increase in methadone's effects. Medications in this category include certain antifungal agents (e.g., ketoconazole, fluconazole), antibiotics (e.g., erythromycin, ciprofloxacin), selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, fluvoxamine, and fluoxetine), benzodiazepines, and cimetidine [21, 22]. Patients co-administered CYP inhibitors should be monitored for toxicity.

Benzodiazepines may contribute additive or synergistic respiratory effects and raise the risk of an adverse respiratory event with methadone [4, 20]. The "safe dose" of benzodiazepines in combination with methadone is uncertain. In general, it is inadvisable to co-administer benzodiazepines with methadone. If unavoidable, the starting dose of methadone should be lowered and titration slowed.

One should also monitor for the effect of CYP inducers, which may speed methadone metabolism and lower methadone concentration. Insufficient analgesia could result, posing the risk of patient nonadherence to medical dosing directions. Examples of CYP inducers include phenobarbital, phenytoin, rifampin, and possibly carbamazepine [21].

Variations in DNA sequencing may render some people more vulnerable than others to the effects of drug combinations, and methadone may reach toxic levels more easily [17]. Drug–drug interactions are a particular concern in geriatric patients because age brings its own metabolic changes [23].

Respiratory suppression leading to death is a risk that prescribers of methadone should take seriously and impress upon their patients. Tables 4.2 and 4.3 contain eight points for patient counseling and eight prescribing guidelines for clinicians to increase methadone safety [24, 25]. Counseling should stress the prohibition against mixing methadone with alcohol, benzodiazepines, or illicit drugs, and warn against escalating doses without medical authorization. Most methadone deaths involved additional substances; frequent co-intoxicants include benzodiazepines, antidepressants, other opioids, illicit drugs, and alcohol [12]. Many methadone deaths occur as a result of diversion for nonmedical use [26], but patients are also at risk from the additive effect of mixing central nervous system depressants with daily doses of methadone.

Table 4.3 Follow these guidelines to prevent harm when prescribing methadone and other opioids

1. Assess your patients for risk of misuse before opioid therapy and manage accordingly
2. Watch for and treat comorbid mental health disorders when they occur
3. Use conventional conversion tables cautiously when rotating (switching) from one opioid to another
4. Avoid combining benzodiazepines with opioids, especially during sleep hours
5. Start methadone at a very low dose and titrate slowly regardless of whether your patient is opioid-tolerant or not
6. Assess for sleep apnea in your patients on high daily doses of methadone or other opioids and in those with a predisposition
7. Tell your patients on long-term opioid therapy to reduce opioid dose during upper respiratory infections or asthmatic episodes
8. Avoid using long-acting opioid formulations for acute, postoperative, or trauma-related pain

Source: [25]

Clinicians must monitor patient respiratory response, particularly when initiating methadone and during dose increases. Checking in with the patient and family every other day is optimal during the first week of therapy. To guard against drug interactions, patients must report all concurrent prescription and other-the-counter medications. As part of monitoring, it is important to counsel patients and their family members to watch for sedation, to recognize the warning signs of respiratory depression, and to respond quickly by summoning medical assistance.

Sedation

Sedation is common with any opioids, particularly during the first few weeks of therapy and during dose changes until the body has developed tolerance [3]. The effect is usually transient, and medical treatment is seldom necessary unless sedation or cognitive disturbances are persistent or severe. Once most patients are stabilized on opioid doses, the cognitive and sedative effects of opioids lessen considerably and do not impair functions of daily life [27, 28].

Again, however, methadone-specific pharmacologic properties require special caution. Clinicians must pay particular attention to signs of patient sedation, not merely as a level of consciousness but as a possible warning sign of respiratory depression. This is because a patient who is initiated on methadone may experience a high level of sedation but still not achieve sufficient analgesia. When this occurs, sedation may signal toxicity.

The prudent clinical method is to avoid sedation with methadone dosing, reducing the dose if sedation occurs. The body must have time to develop tolerance, even to a non-analgesic dose, before methadone can be titrated upward.

Sleep-Disordered Breathing

Fatal or nonfatal respiratory depression is a risk, particularly during sleep. Certain evidence has suggested a relationship between opioids and sleep-disordered breathing, although consensus about how to address the problem is not complete, and further research is needed [4, 29, 30]. One study found a positive correlation between methadone dose and central sleep apnea in patients with chronic pain, an effect that was heightened with benzodiazepines [4]. The same study reported that up to 75 % of patients on chronic opioid therapy had sleep-disordered breathing, although no opioid other than methadone demonstrated a specific dose relation. In a separate study, 30 % of patients in treatment for addiction who were on clinically stable methadone doses were found to have central sleep apnea [31].

The clinical implication is that sleep-disordered breathing should be considered a risk for patients on methadone or other opioids [32]. Prior to initiating methadone therapy for pain, clinicians should:

- Question all new methadone patients about history, signs, and symptoms of sleep apnea.
- Conduct a sleep study in any patient with signs of sleep-disordered breathing.
- Consider a sleep study for all patients to be treated with moderate-to-high doses of methadone.

Research has not yet determined a set dose of methadone that should trigger an initial sleep study. A conservative, "safety first," approach would be to perform a sleep study for patients who are currently taking >50 mg methadone a day or >150 mg of morphine equivalents or whose total daily opioid dose is expected to exceed that quantity. Sleep studies are indicated, regardless of dose, if patients exhibit risk factors, such as obesity, diabetes, neurological disorders, or a history of known sleep apneas.

The two main types of available sleep studies are a polysomnography performed in a sleep laboratory and a home sleep study. Home sleep evaluations do not allow for electroencephalogram (EEG) assessments; however, this is not necessary for diagnostic purposes. A problem with in-laboratory sleep studies is that they are not always covered by insurance payers and are expensive. Home sleep studies cost a fraction of what laboratory tests do, are approved by Medicare, and are often more easily arranged than an in-lab study.

Tables 4.4 and 4.5 show risk stratification and management procedures for sleep-disordered breathing developed at the author's pain clinic [33]. Most healthcare providers are not specially trained in interpreting sleep studies and, therefore, should consult with a sleep specialist for assistance in choosing the appropriate therapy. Patient adherence to medical direction is important to the success of therapy.

Therapeutic options vary and include:

1. Supplemental oxygen for central sleep apnea
2. Continuous positive airway pressure (CPAP) with supplemental oxygen for combined central and obstructive sleep apnea
3. Bi-level positive airway pressure (BiPAP) with backup rate, with or without supplemental oxygen

Table 4.4 Patient risk stratification after initial sleep study

Level 3 (highest risk)	• Taking around-the-clock opioids with CAI ≥5 events per hour • Taking around-the-clock opioids with AHI ≥30 events per hour
Level 2 (moderate risk)	Taking around-the-clock opioids with AHI ≥5 events per hour
Level 1 (lowest risk)	Patients with AHI <5 events per hour

CAI Central apnea index, defined as the number of central sleep apneas per hour of sleep; *AHI* apnea–hypopnea index, a measure of overall severity of sleep apnea, defined as the number of apneas and hypopneas per hour of sleep
Source: [33]

Table 4.5 Sleep apnea management based on risk stratification

Risk level	Timing	Clinical actions
Level 3 (highest risk)	Every 120 days	Check patient adherence with therapy (minimum 4 h per night, 7 nights per week) Repeat home sleep study in patients with • AHI <10 events per hour • CAI <5 events per hour
Level 2 (moderate risk)	Every 6 months	Check patient adherence (minimum 4 h per night, 5 nights per week) Repeat home sleep study in patients with: • AHI <10 events per hour • CAI <5 events per hour
Level 1 (lowest risk)	Annually	Repeat home sleep study in patients with: • AHI <5 events per hour

CAI central apnea index, defined as the number of central sleep apneas per hour of sleep; *AHI* apnea–hypopnea index, a measure of overall severity of sleep apnea, defined as the number of apneas and hypopneas per hour of sleep
Source: [33]

Based on the author's clinical experience, about half of patients diagnosed with central sleep apnea respond to oxygen alone. In some cases, CPAP alone has worsened central sleep apnea, highlighting the importance of consulting with a sleep specialist in choosing the best possible therapy. The treatments require individualization. If the sleep apnea does not respond, it may be necessary to reduce the methadone dose.

Endocrine Effects

The normal production of sex hormones in men and women takes place through activation of the hypothalamic–pituitary–gonadal axis. Opioid administration has been shown to suppress this mechanism [34]. Patients who consume opioids to treat

nonmalignant pain have demonstrated lower levels of estrogen, testosterone, cortisol, luteinizing hormone (LH), gonadotropin-releasing hormone (GnRH), and other hormones when compared with controls [2, 35, 36]. Results of depressed hormone production can include sexual dysfunction, loss of libido, depression, lowered energy, reduced cortisol response to stress, and—in women—amenorrhea and possible loss of bone mineral density [2, 35]. Adrenal insufficiency is another side effect of opioid administration [34]. Patients may suffer diminished quality of life as a result of these effects, and individual monitoring of patient response is necessary during the course of opioid therapy.

Methadone has been associated with hypogonadism, primarily through studies of methadone maintenance therapy in people with opiate dependence [34, 37]. In general, suppression of sex hormone production is an effect methadone shares with all opioids. In contrast, patients maintained on buprenorphine rather than methadone have shown testosterone levels similar to healthy controls and reported significantly less sexual dysfunction [37].

Patients on long-term opioids should be periodically tested for sex-hormone abnormalities [38]. Rotation to another opioid can be helpful; however, patients who do not respond may be considered for hormone supplementation [34, 38]. Men taking opioids for chronic noncancer pain who completed an open-label trial of testosterone replacement therapy showed increases in hormone levels and improvements in mood and sexual function [39]. Prior to initiating testosterone therapy, patients should be screened for prostate cancer. Patients who receive testosterone must be monitored clinically and tested periodically for response. It is advisable to test for effect on prostate-specific antigen levels 2 months after initiating testosterone and to adjust to the lowest effective dose as needed [34].

Few studies have addressed potential adjuvant therapies for women on long-term opioid therapy, although testing to measure bone density, estradiol, and free testosterone have been suggested as guides to therapy [35]. Hormonal testing may be performed, but diagnostic criteria are uncertain and interpretation difficult in women whose menstrual cycles are irregular [34]. Supplemental therapy with dehydroepiandrosterone (DHEA) has been reported to improve energy, libido, and weight control in opioid-treated women, although clinical evidence is limited [34]. Testosterone-replacement therapy in women may raise the risk of breast cancer and is controversial [34].

Concluding Remarks

Clinicians who prescribe methadone for moderate-to-severe chronic pain should be vigilant in preventing, tracking, and treating adverse events. Respiratory depression is the primary risk, and clinicians who prescribe methadone must be familiar with the unique pharmacologic profile and take necessary safety precautions. Constipation is common and is best managed by prophylactic treatment of symptoms. Sedation usually resolves as treatment progresses; however, this effect should be closely

monitored as it may foretell respiratory depression. The effects of methadone related to sleep-disordered breathing have been studied but should be better understood. Current data indicate that sleep apnea and hypoxemia may be underdiagnosed in methadone-treated patients, and respiratory compromise appears to increase with coadministration of benzodiazepines. Patients who display symptoms of hormone suppression should be further tested and considered for hormone replacement therapy. Clinicians should counsel patients as to risks, benefits, and available testing and treatment options before initiating methadone therapy and obtain informed consent.

Acknowledgment Dr. Webster acknowledges the contribution of medical writer Beth Dove of Dove Medical Communications in Salt Lake City, Utah, in the preparation of this manuscript.

References

1. United States Food and Drug Administration. Public health advisory: methadone use for pain control may result in death and life-threatening changes in breathing and heart beat. Rockville, MD: United States Food and Drug Administration; 2006.
2. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105–20.
3. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician. 2006;74(8):1347–54.
4. Webster LR, Choi Y, Desai H, Grant BJB, Webster L. Sleep-disordered breathing and chronic opioid therapy. Pain Med. 2008;9(4):425–32.
5. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113–30.
6. Fakata KL, Cole BE. Peripheral opioid antagonists: a therapeutic advance for optimizing opioid gastrointestinal tolerability. J Fam Pract. 2007;56(6 Suppl Peripheral):S3–12.
7. Slatkin N, Thomas J, Lipman AG, et al. Methylnaltrexone for treatment of opioid-induced constipation in advanced illness patients. J Support Oncol. 2009;7(1):39–46.
8. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med. 2008;358(22):2332–43.
9. Center for Substance Abuse Treatment. Summary report of the meeting: Methadone mortality—a reassessment. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2007.
10. Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999–2006. NCHS Data Brief. 2009;22:1–8.
11. United States Food and Drug Administration. Information for healthcare professionals: methadone hydrochloride. Rockville, MD: United States Food and Drug Administration; 2006.
12. GAO. (Government Accountability Office). Methadone-associated overdose deaths: factors contributing to increased deaths and efforts to prevent them. GAO-09-341. Washington, DC; March 2009.
13. Webster LR, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. Pain Med. 2011;12(S2):S26–35.
14. The use of opioids for the treatment of chronic pain: A consensus statement from American Academy of Pain Medicine and American Pain Society. Glenview, IL, 2007. http://www.ama-assn.org/ama1/pub/upload/mm/455/opioidschronicpain.pdf. Accessed October 28, 2011.

15. Santiago TV, Pugliese AC, Edelman NH. Control of breathing during methadone addiction. Am J Med. 1977;62(3):347–54.
16. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41(14):1153–93.
17. Bunten H, Liang WJ, Pounder D, Seneviratne C, Osselton MD. CYP2B6 and OPRM1 gene variations predict methadone-related deaths. Addict Biol. 2011;16(1):142–4.
18. Rich BA, Webster LR. A review of forensic implications of opioid prescribing with examples from malpractice cases involving opioid-related overdose. Pain Med. 2011;12(S2):S59–65.
19. Webster LR. Methadone-related deaths. J Opioid Manage. 2005;1(4):211–7.
20. Toombs JD. Oral methadone dosing for chronic pain: a practitioner's guide. *Pain Treatment Topics*. (http://pain-topics.org/). March 12, 2008.
21. Toombs JD, Kral LA. Methadone treatment for pain states. Am Fam Physician. 2005;71(7):1353–8.
22. Dolophine side effects and drug interactions. RxList.com. Owned and operated by WebMD. 2011. http://www.rxlist.com/dolophine-drug.htm. Accessed October 31, 2011.
23. Cavalieri TA. Pain management in the elderly. J Am Osteopath Assoc. 2002;102:481–5.
24. Six opioid safety (SOS) steps. PainSAFE. American Pain Foundation. http://PainSAFE.org. Accessed October 27, 2011.
25. Eight prescribing guidelines. PainSAFE. American Pain Foundation. http://PainSAFE.org. Accessed October 27, 2011.
26. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. Addiction. 2009;104(9):1541–8.
27. Ersek M, Cherrier MM, Overman SS, Irving GA. The cognitive effects of opioids. Pain Manag Nurs. 2004;5(2):75–93.
28. Fishbain DA, Cutler RB, Rosomoff HL, Rosomoff RS. Are opioid-dependent/tolerant patients impaired in driving-related skills? A structured evidence-based review. J Pain Symptom Manage. 2003;25(6):559–77. Review.
29. Teichtahl H, Wang D. Sleep-disordered breathing with chronic opioid use. Expert Opin Drug Saf. 2007;6(6):641–9.
30. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioid use is a risk factor for the development of central sleep apnea and ataxic breathing. J Clin Sleep Med. 2007;3(5):455–61.
31. Wang D, Teichtahl H, Drummer O, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest. 2005;128:1348–56.
32. Utah Department of Health. Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain. Salt Lake City, UT: Utah Department of Health; 2009.
33. Webster LR. Examining the relationship between long-term opioid therapy and sleep-disordered breathing. Pract Pain Manage. 2008;8(9):56–62.
34. Colameco S, Coren JS. Opioid-induced endocrinopathy. J Am Osteopath Assoc. 2009;109(1):20–5.
35. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain. 2008;9:28–36.
36. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002;3:377–84.
37. Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmüller D. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab. 2005;90(1):203–6.
38. Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain. 2009;25(2):170–5.
39. Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. J Pain. 2006;7(3):200–10.

Chapter 5
Cardiovascular Effects of Methadone

Miguel A. Leal and Craig T. January

Introduction

Methadone is a synthetic opioid commercially available as methadone hydrochloride. Its main therapeutic use is as an analgesic typically reserved for management of patients with moderate to severe pain. Its other therapeutic use is in the treatment of narcotic addiction where it is the most widely used agent for opioid maintenance. It was initially synthesized during the Second World War as a remedy for then ongoing shortages of opiate medications for the management of severe pain. According to the United States Controlled Substances Act, it is a Schedule II classification, a category reserved for medications that have a high potential for abuse. Abuse of Schedule II drugs may lead to severe psychological or physical dependence. Its pharmacokinetic profile includes a relatively long elimination half-life, which allows for once daily use, a feature that makes it attractive for heroin detoxification and maintenance programs.

As with other opiate analgesics, methadone has important effects on major organ and systems, including the cardiovascular system, and patients who start or continue chronic therapy with methadone require careful management and monitoring in order to identify and correct undesirable side effects or adverse reactions.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_5,

Mechanism of Action

Cardiac arrhythmias and sudden death in otherwise healthy persons using drugs such as cocaine have been widely described [1, 2]. It was thought that cocaine had two principal pharmacological properties that affect the heart and vascular systems. Cocaine blocks the reuptake and increases the release of catecholamines from central and peripheral stores, causing catecholamine accumulation at postsynaptic receptors and intense sympathomimetic stimulation. In addition, cocaine interacts with ion channels. It exerts local anesthetic effects by blocking sodium (Na^+) channels to slow cardiac action potential conduction. More recently, cocaine has also been shown to block repolarizing potassium (K^+) channels. In isolated cardiac myocytes, cocaine blocks the delayed rectifier K^+ current, which prolongs the ventricular action potential duration and may trigger early after depolarizations [3, 4], which in humans can induce long QT syndrome and the potentially lethal arrhythmia known as *torsades de pointes* [5–7], a form of polymorphic ventricular tachycardia. It does this by blocking selectively the rapidly activating delayed rectifier K^+ channel, I_{Kr} (hERG or Kv11.1 channels encoded by the *human Ether-a-go-go-related gene* or *KCNH2*) without affecting the slowly activating channel, I_{Ks} (KvLQT1+mink channels encoded by the *KCNQ1* and *KCNE1* genes) [8], and cocaine has multiple active metabolites [9].

As a therapeutic agent, methadone works primarily as an agonist on opiate receptors in the central nervous system and in organs composed of smooth muscle tissue. Because methadone is a synthetic narcotic, it shares the potential to cause drug addiction with psychological dependence, physical dependence, and tolerance. Major hazards related to drug overdose include respiratory depression, circulatory depression, respiratory arrest, shock, and cardiac arrest. These risks are enhanced if other central nervous system depressants are co-administered, such as general anesthetic agents, other narcotic analgesics, tranquilizers, sedative-hypnotics, and tricyclic antidepressants.

Cardiovascular Effects: Epidemiological Observations

The risk of cardiac arrest secondary to methadone use is well described in the medical literature. A landmark clinical study, focused on this issue, was published in 2008 and included patients from the metropolitan area around Portland, Oregon [10]. It was based on an evaluation of all sudden cardiac deaths recorded in that metropolitan area between 2002 and 2006 where detailed autopsies were performed. The analysis was based on a comparison of two case groups. One group consisted of 22 sudden cardiac deaths in which toxicology screens demonstrated recent methadone use as detected by the presence of therapeutic drug levels. These cases were compared with a second group of 106 cases where no evidence of recent methadone use was found. Seventeen individuals of the first case group (77 % of the sample)

had no significant cardiac abnormalities, while five had evidence of significant coronary artery disease. However, a total of 60 % of individuals in the group where no methadone was present had identifiable evidence of cardiac disease or structural abnormalities, all of which representing established potential causes of sudden cardiac death. The unexpectedly high proportion of otherwise unexplained sudden deaths in the therapeutic methadone group suggested that there could be a significant contribution of this drug toward the occurrence of sudden cardiac death among these patients. In the pivotal Oregon study data, when stratified by drug indication, more than half of the individuals in the first case group (14 out of 22) were using the drug for pain control, three for management of opiate drug addiction, and three for recreational use. The mean age of the group was 37 years, and 68 % were males. The mean age of the non-methadone group was 42 years, and 69 % were males.

Other additional case series and case reports have indicated that methadone use is associated with *torsades de pointes* resulting from a prolonged QT interval on the surface electrocardiogram. The QT interval primarily represents the duration of ventricular depolarization from underlying myocardial cell action potentials. Significant prolongation of the QT interval increases the probability of initiating early after depolarizations, which have been postulated to be the triggering mechanism for *torsades de pointes*, and this arrhythmia can then result in symptoms ranging from palpations to syncope to seizure. If *torsades de pointes* is sustained or degenerates into ventricular fibrillation, the result can be sudden cardiac death.

In a meta-analysis performed by researchers in the University of Arizona, from a total of 5,503 reports of adverse events associated with methadone, 43 (0.78 %) noted the occurrence of *torsades de pointes*, and 16 (0.29 %) demonstrated objective evidence of QT interval prolongation. Doses were reported in 42/59 (71 %) of cases: the mean dose was 410 ± 349 mg/day (median 345, range 29–1680). The dosages for 10 of the 42 cases (29 %) were within the typical recommended range for methadone maintenance treatment (60–100 mg/day). Female gender, interacting medications, hypokalemia, hypomagnesemia, and the presence of structural heart disease, risk factors previously identified with other drugs known to cause *torsades de pointes*, were found in 44 (75 %) cases. Most adverse events required hospitalization or resulted in prolonged hospitalization (28/59, 47 %) and 5/59 (8 %) were fatal.

Cellular Basis: Methadone and the Prolongation of the Myocardial Cell Action Potential

In the heart, cardiac action potentials initiate each beat. The cardiac action potential is unique and differs from the neuronal and skeletal muscle action potentials by having a long duration with an extended plateau phase (Fig. 5.1). From the resting potential (phase 4), depolarization (phase 0) is carried out by the rapid inflow of positive charge through the transient opening of voltage-gated Na^+ channels. From the action potential peak voltage, there is a small repolarization (phase 1) due to the

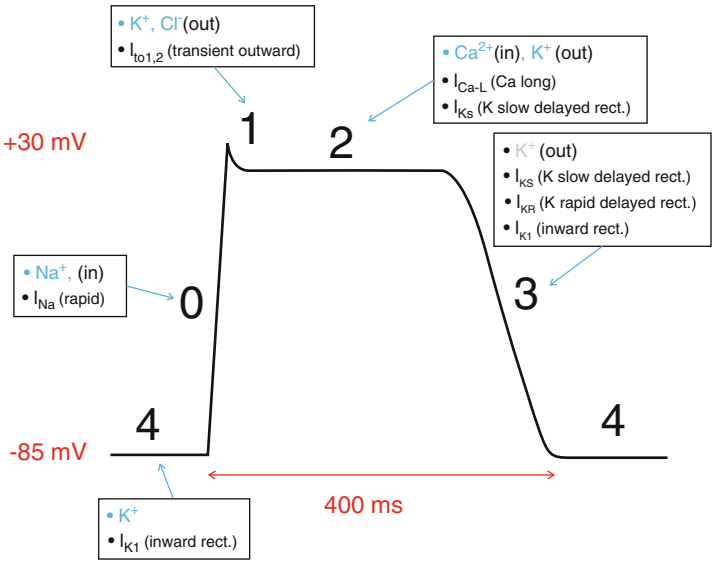

Fig. 5.1 The cardiac ventricular action potential and its different phases. The key ion channel types and their currents are indicated in each phase

activation of the transient outward current, and this is followed by the plateau voltage (phase 2). The plateau phase is governed by the slower opening and closing of calcium (Ca^{2+}) channels that allow for Ca^{2+} entry counterbalanced by the gradual opening of delayed rectifier K^+ channels (I_{Ks} and I_{Kr}) that allow for K^+ ions to leave the myocytes to initiate repolarization. During phase 3, the K^+ current becomes dominant and additional inward rectifier K^+ channels (I_{K1}) open to rapidly return the cell membrane to its resting potential.

Anomalies in the cardiac action potential, whether due to a congenital ion channel gene mutation or acquired circumstances such as drug effects on ion channels, hypothermia, electrolyte abnormalities, or myocardial ischemia and injury, can sometimes lead to lethal cardiac arrhythmias. Drug block of cardiac ion channels can have both desirable and untoward effects. Drugs primarily targeting Na^+ channels, such as anti-arrhythmic drugs like flecainide and propafenone, can decrease the velocity of myocardial cell-to-cell conduction of action potentials (by decreasing the amplitude and upstroke of the phase 0), and can, therefore, prolong the duration of the QRS complexes as seen in the surface electrocardiogram. These drugs also can worsen arrhythmias (a pro-arrhythmic effect), especially in patients with structural heart disease. Drug targeting K^+ channels, particularly those involved in action potential repolarization, can prolong the action potential duration and the QT interval, to cause t*orsades de pointes*.

A major cardiac ion channel target for drugs is the hERG K^+ channel (Fig. 5.2). This ion channel, which was originally cloned from fruit flies, encodes I_{Kr}. It gradually opens with depolarization and its current is maximal during phase 3 of the

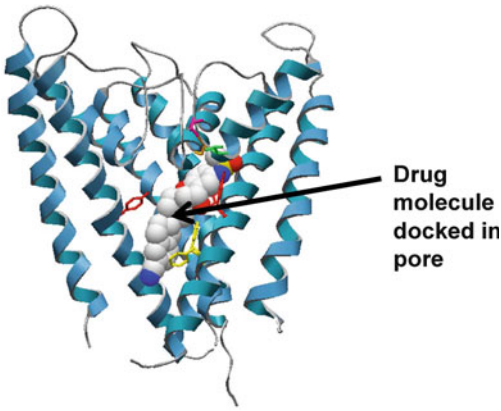

Fig. 5.2 Schematic "ribbon" cartoon of the pore-region of the hERG K^+ channel formed by the co-assembly of four hERG proteins (the fifth and sixth transmembrane domains of each hERG subunit protein are shown). The pore is located in the center and a representative drug molecule is shown binding to and blocking the channel pore

cardiac action potential. Blocking it potentially causes drug-induced (acquired) long QT syndrome. The channel protein is structurally distinct from other K^+ channels, thus it is a "promiscuous" binder of many classes of cardiovascular and non-cardiovascular drugs, such as anti-arrhythmic drugs (quinidine, sotalol, dofetilide, ibutilide, flecainide, amiodarone, etc.), antihistaminics (terfenadine, astemizole), antibiotics (erythromycin, ciprofloxacin, grepafloxacin, chloraquine, moxifloxacin, halofantrine, etc.), GI prokinetic drugs (cisapride), antipsychotic drugs (haloperidol, droperidol, risperidone, etc.), calcium channel antagonist drugs (verapamil, mibefradil, bepridil), miscellaneous agents (sildenafil, cocaine, HIV protease inhibitors, several herbal products), and opiate agonists such as methadone. Several of the drugs above have been removed from the market or had their use restricted due to untoward hERG channel associated K^+ channel block to cause long QT syndrome.

Methadone appears to have its highest affinity to block hERG K^+ channels, although it can interact with multiple channel types [11]. Figure 5.3 shows summarized results of the effect of various opioid agonists, including methadone, L-α-acetylmethadol (LAAM), fentanyl, meperidine, codeine, morphine, and buprenorphine, on hERG current amplitude (for experimental detail, see Katchman and colleagues) [12]. Next only to LAAM, methadone (IC_{50} value of 9.8 μM) was shown to be a potent blocker of the hERG channel. Furthermore, when the ratio between IC_{50} and the maximal plasma concentrations (C_{max}) reported after therapeutic dosing was analyzed, LAAM and methadone had the smallest IC_{50}/C_{max} values (2.2 and 2.7, respectively), indicating that, of all the compounds tested, LAAM and methadone may have the greatest potential for causing hERG channel block in patients.

Methadone exists as the chiral mixture of the (R-) and (S-) isomers. The R-methadone isomer has a 50-fold greater analgesic potency than the S-methadone isomer. In contrast, S-methadone has a 3.5-fold greater ability to block hERG

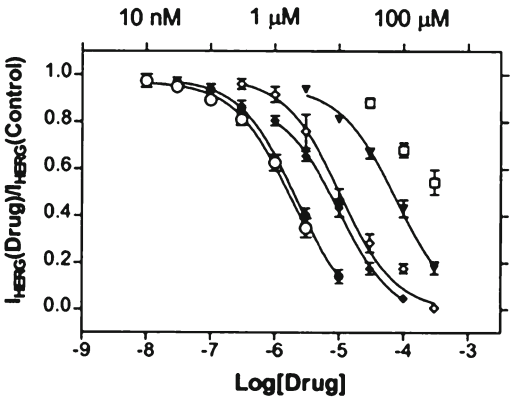

Fig. 5.3 Dose-response curves for the inhibitory action of various opioid agonists on hERG current (I_{hERG}) studied in stably transfected human embryonic kidney cells. *Circle* fentanyl; *filled diamond* methadone; *filled triangle* meperidine; *filled square* codeine; *filled circle* LAAM; *diamond* buprenorphine [12]

channels. In a prospective, non-randomized clinical trial with 39 patients, Ansermot and colleagues demonstrated a small (~4 ms, $p = 0.04$) decrease in the rate corrected QT interval (Fredericia method) with the R-isomer compared to the chiral R-, S-mixture, and the increase in the QTc with re-initiation of the chiral mixture was greater in patients with serum K^+ concentration <4.6 mEq/L [13].

Clinical Example: Long QT Syndrome and Methadone

A 40-year-old female collapsed with minimal warning ("I am going to pass out") while at work. Emergency medical services personnel were activated and found ventricular fibrillation to be her underlying cardiac rhythm during the event. She received two DC shocks to restore normal rhythm and she was intubated. On arrival to the hospital, she was found to be severely hypokalemic (serum K^+ level of 2.3 mEq/L) and acidotic (pH 7.0). Her medications had included hydrochlorothiazide 25 mg once daily with no concomitant KCl supplementation, and methadone 20 mg 3 times daily taken for chronic pain management. She also had recently been given a prescription for ciprofloxacin (for treatment of a urinary tract infection), another drug capable of causing QT interval prolongation. Her past medical history was notable for hypertension and she had recently had a normal transthoracic echocardiogram and a normal stress test with a baseline QTc (Bazette method) was 410 ms. On admission to the hospital she initially was comatose and her electrocardiogram demonstrated marked QT interval prolongation (Fig. 5.4).

Methadone screening was positive. The patient experienced recurrent *torsades de pointes* requiring more than ten subsequent DC shocks, and was treated with K^+ replacement, magnesium supplementation, intravenous lidocaine, and overdrive ventricular pacing. Figure 5.5 shows a representative episode of *torsades de pointes*.

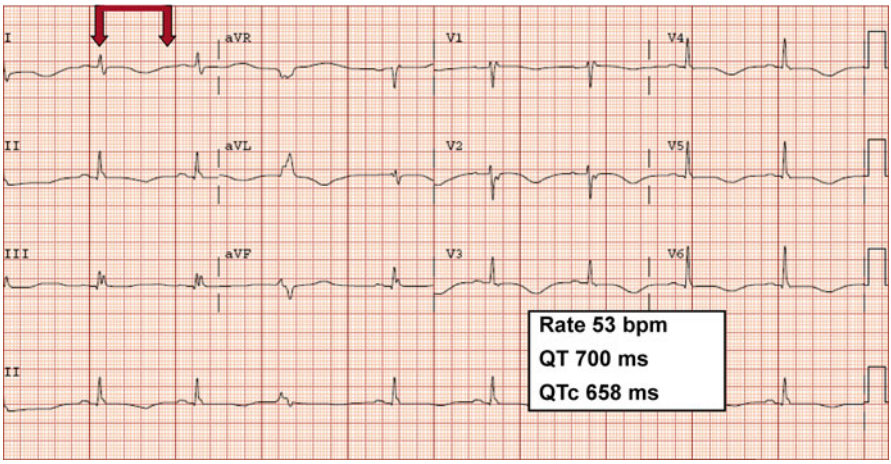

Fig. 5.4 12-lead ECG obtained on hospital admission shows sinus rhythm at 53 bpm with one PVC, and marked QT interval prolongation. The uncorrected QT interval (*red arrows*) is 700 ms with a QTc (Bazette method) of 658 ms, and there are widespread T wave abnormalities

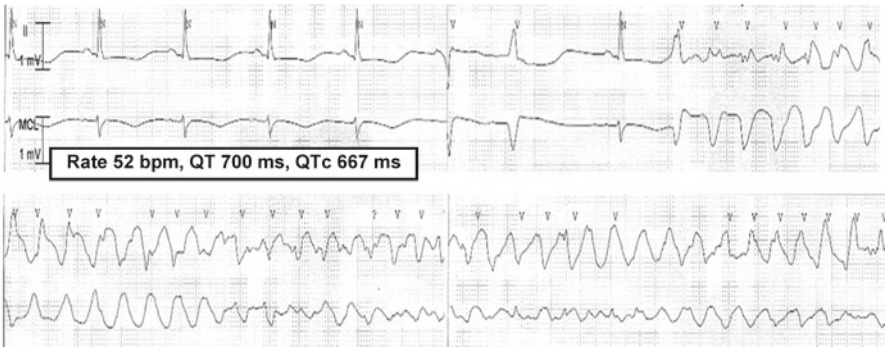

Fig. 5.5 ECG trace depicting PVCs and Torsades de Pointes. Rhythm strip initially shows normal sinus rhythm at 52 bpm with a markedly prolonged QT interval, followed by PVCs with long-short coupling cycles and the initiation of torsades de pointes

Conclusion

The therapeutic use of methadone, a synthetic opiate, is increasing not only for drug addiction but also among patients who suffer chronic pain syndromes. It is less costly than other available alternatives and has a favorable pharmacokinetic profile (rapid onset of action and long elimination half-life). It also has important cardiac and

cardiovascular effects, in part secondary to intense sympathomimetic stimulation along with block of important cardiac ion channels, which can result in QT interval prolongation and potentially lethal cardiac arrhythmias.

As with any QT interval prolonging drug, it seems prudent to obtain periodic surveillance electrocardiograms in patients that use this medication. Electrolyte disturbances, particularly hypokalemia, should be avoided, thus diuretics must be used with care. Patients taking methadone are commonly taking additional drugs. The risk of adverse drug–drug interactions mandates the careful review of the medication history for any patient in whom methadone therapy is considered. Patients and their health care team should be informed of available resources, such as the website www.azcert.org [14], regarding avoidance of drugs that share the risk of QT interval prolongation.

Acknowledgment The authors thank Ms. Thankful Sanftleben for expert assistance with manuscript preparation.

References

1. Bauman JL et al. Cocaine-related sudden cardiac death: a hypothesis correlating basic science and clinical observations. J Clin Pharmacol. 1994;34(9):902–11.
2. Kloner RA et al. The effects of acute and chronic cocaine use on the heart. Circulation. 1992;85(2):407–19.
3. Kimura S et al. Early after depolarizations and triggered activity induced by cocaine. A possible mechanism of cocaine arrhythmogenesis. Circulation. 1992;85(6):2227–35.
4. Clarkson CW et al. Analysis of the ionic basis for cocaine's biphasic effect on action potential duration in guinea-pig ventricular myocytes. J Mol Cell Cardiol. 1996;28(4):667–78.
5. Khan IA et al. Torsades de pointes: a case with multiple variables. Am J Emerg Med. 1999;17(1):80–5.
6. Perera R, Kraebber A, Schwartz MJ. Prolonged QT interval and cocaine use. J Electrocardiol. 1997;30(4):337–9.
7. Schrem SS et al. Cocaine-induced torsades de pointes in a patient with the idiopathic long QT syndrome. Am Heart J. 1990;120(4):980–4.
8. Zhang S et al. Cocaine blocks HERG, but not KvLQT1+minK, potassium channels. Mol Pharmacol. 2001;59(5):1069–76.
9. Ferreira S et al. Effects of cocaine and its major metabolites on the HERG-encoded potassium channel. J Pharmacol Exp Ther. 2001;299(1):220–6.
10. Chugh SS et al. A community-based evaluation of sudden death associated with therapeutic levels of methadone. Am J Med. 2008;121(1):66–71.
11. Kuryshev YA et al. Increased cardiac risk in concomitant methadone and diazepam treatment: pharmacodynamic interactions in cardiac ion channels. J Cardiovasc Pharmacol. 2010; 56(4):420–30.
12. Katchman AN et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K(+) currents. J Pharmacol Exp Ther. 2002;303(2):688–94.
13. Ansermot N et al. Substitution of (R, S)-methadone by (R)-methadone: impact on QTc interval. Arch Intern Med. 2010;170(6):529–36.
14. Woosley, R.L. Arizona CERT: Center for Education and Research on Therapeutics. 2012 02/29/2012]; Available from: www.torsades.org/medical-pros/drug-lists/drug-lists.htm.

Chapter 6
Methadone Pharmacodynamics and Pharmacokinetics

Gavin Bart and Sharon L. Walsh

Background

Methadone (6-dimethylamino-4, 4-diphenyl-3-heptanone) was first synthesized in 1937 by Bockmühl and Ehrhart as part of a larger pharmaceutical program synthesizing atropine derivatives as spasmolytics [1]. This program led to the development in 1939 of meperidine, which not only had spasmolytic properties but also acted as an analgesic. Subsequent testing of methadone found that it had a 5–10-fold greater analgesic effect than meperidine but its further development was limited by wartime supply shortages and potential adverse effects, such as nausea, experienced in a small group of human subjects [1, 2].

Following World War II, 6-dimethylamino-4, 4-diphenyl-3-heptanone was brought to the United States where it was soon given the generic designation methadone [2, 3]. Methadone is a Drug Enforcement Agency Schedule II controlled substance approved for the treatment of severe pain and opiate dependence and is available in 5 and 10 mg tablets, 40 mg dispersible tablet, 5 mg/5 mL, 10 mg/5 mL, 10 mg/mL liquid, and 10 mg/mL injectable formulations. Because there are no significant differences in methadone pharmacokinetics or pharmacodynamics between the various oral formulations, they will be addressed as a single group [4]. When administered intravenously, the injectable formulation has 100 % bioavailability and reaches peak plasma levels immediately following injection. No formal pharmacokinetic studies of subcutaneous or intramuscular methadone injection exist, although bioavailability is likely to approach 100 %, and its pharmacokinetics are expected to

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_6,

be similar to intravenous or orally administered methadone aside from the lag in absorption into the vascular space. Pharmacodynamic differences between the oral and intravenous routes of administration will be discussed.

Acute Pharmacodynamic Actions

Acute methadone administration, regardless of route of administration, produces dose-dependent physiological effects typical of mu opioid agonists, including pupil constriction (i.e., miosis), decreased gastrointestinal motility, and decreased respiratory rate (along with associated changes in other respiratory indices, such as increased expired CO_2 and decreased oxygen saturation). Acute effects of methadone on cardiovascular response (i.e., heart rate, blood pressure) are not generally of clinical significance (but see later chapter in this volume discussing evidence of methadone effects on cardiac QTc prolongation). Pupil constriction is a hallmark sign of mu opioid action and can be used to assess the time-action profile of methadone. Respiratory depression after treatment with methadone and other mu opioid agonists results from decreased chemoreceptor sensitivity to circulating CO_2 concentrations in the medullary brain stem. Thus, relatively low doses of methadone in opiate-naïve individuals and sufficiently high doses of methadone in opioid-tolerant individuals can lead to fatal overdose consequent to respiratory depression and cardiopulmonary failure. The risk for methadone (and opioid) overdose is exacerbated when used in combination with other opioids and/or sedatives, including alcohol and benzodiazepines [5].

The onset of the pharmacodynamic action of intravenous methadone is evident within minutes of administration, and peak effects occur within the first hour after infusion [6]. Pharmacologic activity after parenteral administration of acute doses (intravenous or subcutaneous) persists for approximately 12 h with complete dissipation by 24 h post dosing [6, 7]. Observer ratings of opiate signs and study participant self-report of "liking" for the drug (and other associated abuse liability measures) generally follow this time-action curve when evaluated in experienced opioid abusers without physical dependence; however, miosis may be evident 24 h after a single dose of methadone in the absence of other signs and symptoms. As with miosis, other studies have reported a longer duration of methadone action on respiratory depression after subcutaneous and oral administration. This can be a significant safety concern as illicit opioid users may perceive the absence of psychoactive effects and use additional opioids without recognizing the more persistent effect on respiratory depression. With respect to its qualitative subjective profile of mood effects, intravenous methadone was indistinguishable from morphine or heroin when all were tested within a group of opioid-experienced volunteers [6].

When given parenterally, methadone and morphine (the prototypic euphorigenic comparator) are considered to be equipotent. However, because of the superior oral bioavailability of methadone, this ratio of methadone: morphine changes from 1:1 to approximately 1:2 for oral conversions. [7] Oral methadone administration is

associated with a slower onset of action compared to parenteral administration, with dose-dependent pharmacodynamic responses appearing within the first hour after ingestion and peak subjective responses occurring between 3 and 4 h after oral dosing [7–9]. As with parenteral administration, the subjective effects of methadone (measures of euphoria and sedation) are generally undetectable at 12 h post-dosing, while miosis may persist for 24 h after a single acute dose.

Studies have examined the effect of methadone on a broad array of psychomotor performance and other cognitive function measures. Studies on the acute effects of methadone (and other opioids) generally have reported slowed response time in the absence of significant performance deficits (see Zacny et al. [10] for critical review); however, tolerance is reported to develop to some of these effects with chronic dosing. Numerous studies have reported no differences between methadone-maintained individuals when compared to control subjects on psychomotor and cognitive performance tasks, while others employing a broader range of tests have found some performance decrements in methadone-maintained patients in comparison to former heroin abusers [11] and nondrug using controls [12]. However, as these impairments are frequently described relative to incompletely matched control groups (e.g., nondrug using controls), the observed effects cannot be directly attributed to methadone alone because prior history of drug use, ongoing drug use, and other consequences of a drug-using lifestyle may play a role in the observed outcomes (e.g., prior and ongoing illicit opioid and other drug use, nutritional status, prior head injury) [13] that differentiate the methadone-maintained patients from control subjects.

Pharmacodynamic Effects: Chronic Administration

Isbell and colleagues (1948) conducted the seminal human studies on the response to repeated or chronic administration of methadone and methadone physical dependence properties at the United States Public Health Service Administration Narcotics Hospital in Lexington, Kentucky [14]. In individuals with heroin use histories who were chronically maintained on morphine (4 times per day) these studies demonstrated that parenteral methadone could suppress opioid abstinence signs and symptoms in physically dependent individuals during periods when their daily morphine injections were withheld. Moreover, the substitution of methadone for the regularly scheduled morphine dose prevented the emergence of withdrawal signs and symptoms. These authors also noted that methadone produced euphoria that persisted for a longer duration of action than that produced by morphine and that tolerance developed to the sedative and euphoriant effects with chronic dosing. Later studies of daily maintenance on methadone reported that chronic administration led to small but reliable reductions in respiratory rate, blood pressure, and heart rate along with increased body temperature when compared to either the period prior to maintenance or to a control group [7, 11]. During chronic treatment with methadone, pupil diameter will vary as function of time since dosing, but typically there is some

degree of miosis evident throughout the 24-h dosing period [15]. Finally, chronic administration of methadone with dosing for periods of 28–186 days at high daily doses up to 240 mg (60 mg 4 times daily, s.c.) led to a dependence profile very similar to that seen with morphine, including the (1) development of tolerance with requests for dose escalation, and (2) emergence of an opioid withdrawal syndrome following cessation of dosing (but this emerged later and persisted longer than that seen after morphine discontinuation).

Pharmacodynamics in Treatment of Pain

Methadone is a racemic mixture whose R-entantiomer is a high affinity (Ki 0.6 nM) full agonist at the mu opioid receptor and both R- and S-entantiomers are N-methyl-D-aspartic acid (NMDA) receptor antagonists. It is commonly thought that both of these neuropharmacological actions may contribute to the efficacy of methadone as an analgesic because selective mu opioid agonists and NMDA antagonists produce pain relief in acute and chronic pain conditions. Affinity and/or efficacy at other receptors, such as delta and kappa opioid or monoamine receptors, are sufficiently low to rule out clinical significance. Methadone can be used by the oral, parenteral, or rectal routes of administration for pain relief. Methadone has a long history of use as an analgesic since its early development; however, its use in clinical practice in the United States has increased significantly in recent years due to its (1) efficacy, (2) high oral bioavailability, (3) relative low cost for patients, and (4) an overall increase in prescribing of opioids for pain conditions subsequent to the mandate to assess pain as the fifth vital sign and recommendations for broader usage of opioids for pain control by medical professional societies.

The onset of analgesia occurs within approximately 30–60 min after oral dosing and within the first half-hour after parenteral administration with peak analgesic responses occurring around 1 h of dosing by both routes. While methadone is efficacious as an analgesic, its duration of action is less than would be predicted by its estimated half-life as the duration of pain relief is approximately 3–6 h. This has been shown in the laboratory with experimental models of acute pain and clinical conditions of acute and chronic pain. Although the same principal of "start low and go slow" applies to initiating therapy with methadone for analgesia as induction onto methadone for opioid dependence, starting doses for pain relief are typically much lower than dosing for opioid dependence. Recommendations vary but contemporary clinical practice guidelines generally recommend starting with an initial low oral dose (e.g., 2.5 mg every 8 h) for opiate-naïve patients and up to 5 mg for patients rotating from other opioids and titrating slowly. While numerous relative potency tables for opioid conversions are available, caution is recommended when rotating to methadone (1) because of its long half-life, and (2) because the conversion from some opioids onto methadone is not bidirectionally equivalent. Specifically, the mg/mg conversion from one opioid rotating onto methadone may not be equivalent to conversion from methadone rotating onto that opioid [16].

As with other responses to methadone, tolerance can develop to the analgesic effects faster than to the respiratory suppressive effects and, therefore, dosing may need to be titrated upward under careful supervision in order to assure safe and appropriate clinical response. A lengthier discussion on methadone dosing recommendations for analgesia appears in another chapter of this volume.

Pharmacodynamics in Opioid Maintenance Treatment

The early observations by Isbell and others on the long duration of opioid action produced by methadone and its efficacy in suppressing withdrawal in opioid-dependent individuals led to the seminal work of Dole and Nyswander in which they proposed and tested the use of methadone as a maintenance treatment for heroin addiction in the 1960s [17]. While methadone has now been in use for more than 40 years in the United States for the treatment of opioid dependence, its use for this indication occurs only under very the tight regulatory authority of the Federal government and in very restricted settings. Moreover, it is unlawful to prescribe methadone for opioid addiction outside of the context of specific inpatient circumstances or a federally licensed methadone outpatient treatment program. Most commonly methadone treatment is provided using oral liquid or the dispersible tablet, formulations which may not be used for the treatment of pain.

Because of its long half-life and tendency to accumulate during the early stage of treatment (see below for further details), patients with opioid dependence are usually initiated onto methadone at a dose of 30 mg or less daily. Federal law provides an option for an additional 10 mg on Day 1 of dosing for those patients who are not receiving relief from a 30-mg dose. Various induction schedules have been employed, and while none are mandated, the guiding principle is to "start low and go slow" in order to avoid adverse outcomes resulting from accumulation and overdose. As induction is initiated at relatively low doses, it is not unusual for patients with high levels of physical dependence to experience withdrawal symptoms during the period of induction and stabilization prior to reaching steady-state; these patients should be educated about the harmful risks of continuing illicit opioid use on top of their methadone dosing to avoid overdose. Fatal overdose in a patient receiving methadone is most likely to occur within the first 2 weeks of initiating treatment because of these risks [18].

Once stabilized, most patients achieve adequate relief with once daily dose despite the rise and fall in plasma concentrations of methadone over the 24-h dosing period. In certain instances, however, as with rapid metabolizers or in pregnancy, split dosing can be employed (but this is the exception rather than the norm). Its long duration of action accounts for the ability of methadone to suppress withdrawal signs and symptoms with only once daily dosing. In dose omission studies (or placebo substitution), a missed 24-h dose can be detected through physiological changes but does not typically lead to frank withdrawal symptomatology under double-blind conditions across a range of methadone maintenance doses [19, 20].

In addition to suppression of withdrawal symptoms, another critical therapeutic benefit of methadone maintenance is the development of cross-tolerance to other opioids. Opioid cross-tolerance is the phenomenon whereby chronic maintenance on one opioid can lead to a diminished response to another opioid. The ability of methadone to produce cross-tolerance was reported in a seminal study in which subjects maintained on various doses of methadone were challenged under double-blind, placebo-controlled conditions with heroin, hydromorphone, morphine, and methadone [21]. This study reported that there was significant "narcotic blockade" (i.e., cross-tolerance) to the euphoriant effects and observable signs of the various opioid challenges in the presence of methadone maintenance, and that the degree of blockade was greater with longer exposure to methadone, suggesting increased development of cross-tolerance over the course of stabilization. In another early study, inpatient subjects who had a history of opioid dependence but were not physically dependent at the start of the study were given the opportunity to work (e.g., by riding a stationary bicycle for a prescribed period of time) to earn injections of hydromorphone [22]. Over the course of the study, subjects were initiated onto daily methadone and the maintenance increased to successively higher daily doses such that at the end of the 6-week study 100 mg/day was given. This study demonstrated that the willingness to work for hydromorphone decreased as methadone maintenance dose increased and work effort corresponded to the degree to which the subjects reported "liking" for the hydromorphone, thereby indicating a link between the subjective response to the drug and self-administration behavior. Subsequent studies have expanded these findings on the dose-related effects of methadone cross-tolerance and have (1) demonstrated that the degree of blockade is significantly less at 48 h after methadone compared to 24 h after methadone, supporting the need for daily dosing to achieve optimum response, and (2) revealed that, while lower doses of methadone (30 mg) may be sufficient to produce suppression of opioid withdrawal signs and symptoms, higher doses are needed to produce robust cross-tolerance and to suppress heroin self-administration in the laboratory [20, 23]. Historically, average methadone maintenance doses in the United States were lower but have risen in response to a growing evidence base for the superior efficacy of higher maintenance doses (e.g., 80–120 mg daily) [24, 25] that is likely attributable, in part, to greater cross-tolerance.

In practice, it is commonly thought that patients are able to detect small variations in dose (as some clinic practices reduce doses for infractions—i.e., appearing intoxicated for daily dosing, etc.). Studies reveal that subjects are readily able to detect the effects of their regular methadone dose in comparison to a placebo substitute within the initial hours after dosing and discriminate active methadone from placebo [15]. When controlling for taste cues, it was found that subjects could detect both large increases and decreases in their regular dose but there was substantial interindividual variability in the ability to detect these differences [26]. In another study, subjects maintained on either 30 or 60 mg methadone daily and challenged 40-h after their last dose reported significant and dose-dependent increases on ratings of positive mood effects and opioid agonist-like symptoms after 30 and 60 mg (but not 15 mg) of oral methadone administered under double-blind conditions; these effects were more robust for those maintained on the lower dose of methadone [27].

General Pharmacokinetic Properties

Following oral administration, methadone is rapidly absorbed from the intestinal lumen with an absorption half-life of 15–60 min (Ka 1.4–3.4), with variability likely due to interindividual differences in intestinal motility [28]. For example, patients already on opiates may have reduced gastrointestinal motility leading to slower methadone absorption than opiate naïve patients. While methadone is a substrate for P-glycoprotein transporters and cytochrome P-450 3A metabolizing enzymes, their presence in the intestine has little effect on methadone absorption [29]. Once absorbed across the intestinal lumen, methadone enters the portal circulation and then the liver. Although methadone is primarily metabolized in the liver, in humans it has a low hepatic extraction ratio meaning, in part, it is subject to little first-pass metabolism or alteration in bioavailability caused by changes in hepatic blood flow. Thus, methadone apparent oral bioavailability is between 80 and 90 % [29]. Methadone levels in bile are sufficiently low to exclude a significant effect of enterohepatic recirculation on plasma methadone levels [30].

Methadone has a pKa of 8.25 and an n-octanol:water partition coefficient of 117 at a physiological pH of 7.4, making it highly lipophilic. Methadone is approximately 90 % bound to plasma proteins such as albumin, globulin fragments, and α_1-acid-glycoprotein and 10 % is unbound and available for transit across tissue membranes (e.g., hepatic membranes for metabolism, glomerular membranes for urinary elimination, and across the blood–brain barrier where most of its pharmacodynamic effects are mediated) [31]. Because α_1-acid-glycoprotein is an acute phase reactant, there has been concern that fluctuations in levels of this protein could increase levels of unbound methadone leading to increased adverse effects, such as sedation and respiratory suppression, but also to increased elimination and overall reduced methadone exposure. It does not appear, however, that differences in α_1-acid-glycoprotein binding result in clinically apparent symptoms [32].

Methadone is distributed throughout various tissues such as the liver, intestine, lung, muscle, and brain with an apparent volume of distribution during steady state of 3.6 L/kg. The rate of distribution into and out of the tissue is different than that of elimination, thus methadone displays biexponential, or two compartment, pharmacokinetics. Some investigators have found a monoexponential model to be adequate in describing steady-state methadone pharmacokinetics. Aside from significant inter-individual variability in methadone pharmacokinetics, there is wide inter-study variability in estimated parameters that is due, in part, to methodological variability such as evaluation following single dose versus steady-state dosing, mono- vs. bi-exponential models, frequency and length of plasma sampling, and clinical versus research setting [33]. Thus clinicians should be cautious in translating results of any one study into clinical practice.

Table 6.1 Development of steady-state drug levels

	Percent of day's dose remaining					
Day	2	3	4	5	6	Total
2	50					50
3	25	50				75
4	12.5	25	50			87.5
5	6.25	12.5	25	50		93.75
6	3.125	6.25	12.5	25	50	96.875

Assuming methadone terminal half-life is 24 h and once daily dosing at the same dose level it takes 5 days to reach 93 % of steady-state levels. Each subsequent day after the initial dose is represented in columns and rows. The percentage of each day's dose remaining in the body is shown across columns. Cumulative dose levels are represented in rows.

Following oral administration, peak plasma levels are reached within 2–4 h and the terminal half-life at steady state is 24–28 h [33]. Achieving a steady-state plasma level requires dosing over 4–5 half-lives of a drug and, therefore, is not approximated until day 5 of methadone dosing (see Table 6.1 and Fig. 6.1). Increasing dose before steady state is achieved will result in an accelerated increase in plasma levels, which can contribute to the risk of methadone toxicity (e.g., excess sedation or respiratory suppression). Once steady state is achieved, the ratio of peak to trough methadone level is approximately 1.6–2.0 [34]. Exceeding this ratio may be an indication of increased methadone clearance due to changes in elimination and/or metabolism.

Metabolism and Excretion

Methadone is metabolized in the liver predominately by a cytochrome P450 (CYP)-mediated process of N-demethylation. Initial N-demethylation results in the inactive 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), which is N-demethylated into the inactive 2-ethyl-5-methyl-3,3-diphenylpyraline (EMDP). While at least seven other metabolites have been identified, they are produced in such small quantity that they will not be discussed. Both EDDP and EMDP are eliminated in the urine and approximately half of a methadone dose can be recovered in the urine over 96 h as methadone, EDDP, and EDMP. Renal excretion of methadone is correlated to urinary pH; however, overall elimination of methadone in the urine is so small that manipulation of urinary pH is unlikely to have clinical impact or facilitate the treatment of methadone toxicity [35]. Methadone is also eliminated in the feces, although mostly as metabolites and less than 5 % as methadone. Small amounts of methadone can be detected in body fluids such as saliva, sweat, semen, and breast milk, but these fluids do not comprise a significant route of elimination and concentrations are generally very low and, especially in the case of breast milk, are not high enough to impart risk of methadone toxicity if consumed by others.

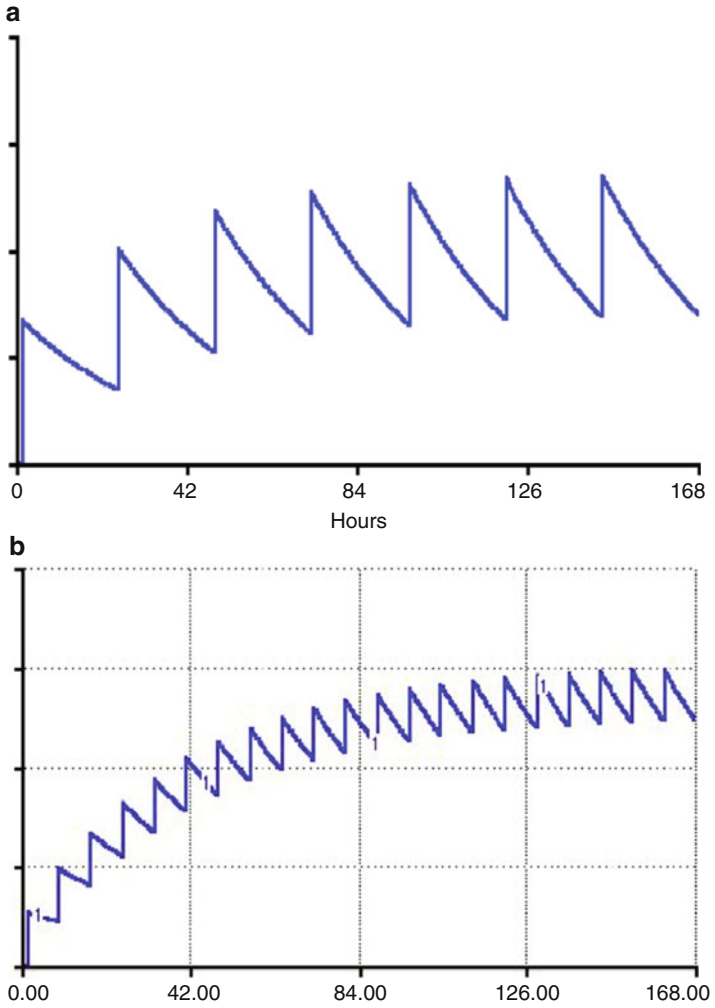

Fig. 6.1 *Upper*: plasma levels of methadone after initiation of daily oral dosing represented by monoexponential model. *Lower*: plasma levels of methadone following initiation of every 8-h oral dosing. Total dose over 24 h is the same in **a** and **b**

Several CYP enzymes are able to metabolize methadone including CYP 3A4, CYP 2B6, CYP 1A2, CYP 2C19, and CYP2D6. Unlike morphine or buprenorphine metabolism, methadone and its metabolites do not appear to undergo a secondary glucuronidation process. Isoenzymes other than CYP 3A4 and CYP 2B6 comprise a small percentage of methadone metabolism and medications or genetic variants known to induce or inhibit their function are not likely to have significant clinical effect on methadone pharmacokinetics or pharmacodynamics. CYP 3A4 is the most abundantly expressed CYP in the liver, comprising approximately 30 %

Table 6.2 Common drug interactions with methadone

Interaction effect	Drug	Effect	Clinical decision-making
Receptor antagonism/ partial-agonism	Naloxone Naltrexone Nalmefene Buprenorphine Nalbuphine Nalorphine Butorphanol Pentazocine	Precipitation of opiate withdrawal, recrudescence of pain	Do not use in methadone patient unless specifically reversing acute life-threatening opiate overdose
Common inhibitors	Ketoconazole Fluconazole Itraconazole Voriconizole	Inhibit methadone metabolism	Observe for clinical signs of opiate toxicity and adjust methadone dose accordingly
Common inducers	Rifampin Phenytoin Ritonavir boosted Anti-retrovirals Nevirapine Efavirenz	Increase methadone metabolism	Observe for clinical signs of withdrawal and adjust methadone dose accordingly through increase or split dosing
Synergism	Benzodiazepines	Increased sedation	Observe for signs of toxicity and adjust dose accordingly
	Barbiturates Tricyclic antidepressants Ethanol (other opiates prior to methadone cross-tolerance)	Increased sedation Decreased Respiratory effort	Cautious dose increases when needed with frequent reassessment

The clinical effect of a drug interaction is highly variable and, therefore, any methadone dose adjustment should be based on clinical response rather than preemptive change.

of all CYP isoforms, and is involved in the metabolism of over half of all prescribed medications. CYP 3A4 has traditionally been thought of as the main isoform responsible for methadone metabolism and prescribers have been cautioned about drug interaction when co-prescribing methadone with other drugs known to induce or inhibit CYP 3A4. For example, CYP 3A4 inducers, such as phenytoin, rifampin, and select antiretroviral therapies, increase methadone elimination and metabolism and can lead to clinically significant symptoms of opiate withdrawal (see Table 6.2). Azole antifungals inhibit CYP3A4 and increase peak plasma levels and area under the time versus concentration curve but rarely do they result in increased sedation or respiratory suppression. However, withdrawal symptoms and increased

methadone elimination/metabolism following nelfinavir, a known CYP 3A4 inhibitor, indicate that drug interactions are more complex than whether CYP 3A4 function is altered [36]. Indeed, there has been increased focus on the role CYP 2B6 plays in methadone metabolism. While in vitro studies support the role of CYP2B6 in methadone metabolism, in vivo studies have been more difficult because many of the medications known to interact with CYP 2B6 also interact with CYP 3A4. Thus prescribers should consider inducers and inhibitors of both CYP 3A4 and CYP 2B6 as having the potential to affect methadone levels with resultant clinical effects.

Because methadone is a racemic mixture, there has been interest in whether there is differential metabolism or pharmacokinetics between the opioid R-enantiomer and the non-opioid S-enantiomer. In human liver microsome studies, it appears that there is no stereoselectivity in CYP 3A4 methadone metabolism but that CYP 2B6 may metabolize S-methadone more rapidly than R-methadone [37, 38]. Clinical studies have shown lower protein binding for R-methadone with subsequent increases in volume of distribution and renal clearance for the unbound enantiomer [32]. There was no difference between enantiomers and total renal clearance, however. It is not clear that enantiomer-specific metabolism or pharmacokinetics translates into clinically significant differences but together they may explain part of the wide interindividual variability in methadone pharmacokinetics.

Special Patient Populations

Several physiological states have the potential to affect methadone pharmacokinetics. For example, since a major component of methadone elimination is renal, there may be concerns that renal failure could result in accumulation of methadone and resultant toxicity. Evaluation of methadone pharmacokinetics in patients on either peritoneal or hemodialysis show that methadone pharmacokinetics remain unchanged, methadone is not removed by dialysis, and fecal elimination compensates for loss of renal function [39]. While large sample pharmacokinetic studies across a range of renal impairment have not been performed, there are no recommendations for dose adjustment in the setting of renal failure.

Patients taking methadone for the treatment of opiate addiction have a higher prevalence of hepatitis C and alcohol dependence than the general population and both conditions increase the risk for developing liver disease and cirrhosis. Although methadone is hepatically metabolized, methadone pharmacokinetics are unaltered in the absence of significant liver disease. In patients with biopsy-proven liver disease, methadone clearance was reduced only in those with decompensated cirrhosis and not those with milder forms of liver disease or cirrhosis. [40] Fluid shifts due to ascites, sodium retention, and decreased levels of circulating proteins increase methadone volume of distribution and decrease its apparent oral clearance. This is in contrast to patients with alcohol-induced liver disease who were noted to have increased volume of distribution but increased apparent oral

clearance. [40] Despite these contrasting findings, both studies found no difference in dose-adjusted area under the curve or dose adjusted mean plasma levels. Therefore, it is currently recommended that in the setting of severe liver disease, methadone dose be adjusted (up or down) based on assessment of symptoms (withdrawal or excess sedation) rather than the mere presence of disease [40, 41]. There are no specific data to guide dosing strategies in the setting of acute liver disease or fulminant hepatitis.

Methadone pharmacokinetics are affected during the course of pregnancy. The placenta is a metabolically active organ with increased blood flow and expression of CYP isoforms as it grows. Therefore, by the second and third trimesters there may be increased methadone clearance via metabolism by placentally expressed CYP19 (aromatase) [42]. Reduction in plasma protein levels and increased plasma volume during pregnancy also may contribute to alterations in methadone pharmacokinetics. In contrast to post-pregnancy conditions, methadone clearance is greater and peak methadone levels lower as pregnancy progresses from weeks 20–40 [43]. This can result in early onset of withdrawal symptoms and may require either an increase in methadone dose or splitting a single daily dose into twice daily dosing.

Conclusion: Relationship Between Methadone Pharmacodynamics and Pharmacokinetics

While randomized clinical trials have demonstrated a dose-dependent relationship between methadone maintenance dose and efficacy at reducing illicit opioid use, there is substantial interindividuality in response to methadone, and, thus, a broad range of doses (e.g., from 30 to 150 mg, p.o.) can be used effectively to treat opioid dependence. The clinical observation of this wide variation in response has prompted numerous studies attempting to relate patient comfort and/or clinical response to circulating concentrations of methadone with the supposition that the interindividual variability was related to individual pharmacokinetic differences. While past recommendations have suggested a therapeutic window for methadone maintenance between 100 and 400 ng/mL in plasma, studies have failed to demonstrate convincing evidence that clinical response to methadone is directly predicted by R,S methadone concentrations or the individual enantiomers (i.e., the concentration–effect relationship) or even methadone dose [44, 45] (and this has been similarly difficult to model with regard to methadone analgesia) [46]. Thus, therapeutic monitoring of plasma drug concentrations is not generally recommended.

Acknowledgment Dr. Gavin Bart (K23 DA024663) and Dr. Sharon Walsh (R01 DA016718) would like to kindly acknowledge the support of the National Institute on Drug Abuse in preparing this chapter.

References

1. Kleiderer EC, Rice JB, Conquest V, Williams JH. Pharmaceutical activities at the I.G. Farbenindustrie plant, Hochst am Main. Washington, DC: Office of the Publication Board Department of Commerce; 1945.
2. Chen K. Pharmacology of methadone and related compounds. Ann N Y Acad Sci. 1948;51:83–97.
3. Council on Pharmacy and Chemistry. *Journal of the American Medical Association.* 1947;134:1483.
4. Kreek MJ. Plasma and urine levels of methadone. Comparison following four medication forms used in chronic treatment. N Y State J Med. 1973;73:2773–7.
5. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999;94(7):961–72.
6. Jasinski DR, Preston KL. Comparison of intravenously administered methadone, morphine and heroin. Drug Alcohol Depend. 1986;17:301–10.
7. Martin WR, Jasinski DR, Haertzen CA, et al. Methadone—a reevaluation. Arch Gen Psychiatry. 1973;28:286–95.
8. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55:569–80.
9. Eissenberg T, Stitzer ML, Bigelow GE, Buchhalter AR, Walsh SL. Relative potency of levo-alpha-acetylmethadol and methadone in humans under acute dosing conditions. J Pharmacol Exp Ther. 1999;289:936–45.
10. Zacny JP. A review of the effects of opioids on psychomotor and cognitive functioning in humans. Exp Clin Psychopharmacol. 1995;3(4):432–66.
11. Gritz ER, Shiffman SM, Jarvik ME, et al. Physiological and psychological effects of methadone in man. Arch Gen Psychiatry. 1975;32:237–42.
12. Mintzer MZ, Stitzer ML. Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend. 2002;67(1):41–51.
13. Darke S, Sims J, McDonald S, Wickes W. Cognitive impairment among methadone maintenance patients. Addiction. 2000;95(5):687–95.
14. Isbell H, Wikler A, Eisenman AJ, Daingerfield M, Frank K. Liability of addiction to 6-dimeth ylamino-4-4-diphenyl-3-heptanone (methadon, “amidone” or “10820”) in man. Arch Intern Med. 1948;82:362–92.
15. McCaul ME, Bigelow GE, Stitzer ML, Liebson IA. Short-term effects of oral methadone in methadone maintenance subjects. Clin Pharmacol Ther. 1982;31(6):753–61.
16. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. J Pain Symptom Manage. 2001;22(2):672–87.
17. Dole VP, Nyswander ME. A medical treatment for diacetyl-morphine (heroin) addiction. J Am Med Assoc. 1965;193:646–50.
18. Buster MC, van Brussel GH, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction. 2002;97(8):993–1001.
19. Goldstein A. Blind comparison of once-daily and twice-daily dosage schedules in a methadone program. Clin Pharmacol Ther. 1972;13:59–63.
20. Donny EC, Walsh SL, Bigelow GE, Eissenberg T, Stitzer ML. High-dose methadone produces superior opioid blockade and comparable withdrawal suppression to lower doses in opioid-dependent humans. Psychopharmacology (Berl). 2002;161:202–12.
21. Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. Arch Intern Med. 1966;118:304–9.
22. Jones BE, Prada JA. Drug-seeking behavior during methadone maintenance. Psychopharmacology (Berl). 1975;41:7–10.
23. Donny EC, Brasser SM, Bigelow GE, Stitzer ML, Walsh SL. Methadone doses of 100 mg or greater are more effective than lower doses at suppressing heroin self-administration in opioid-dependent volunteers. Addiction. 2005;100:1496–509.

24. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Methadone dose and treatment outcome. Drug Alcohol Depend. 1993;33(2):105–17.
25. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Dose–response effects of methadone in the treatment of opioid dependence. Ann Intern Med. 1993;119(1):23–7.
26. Stitzer ML, Bigelow GE, Liebson IA. Single-day methadone dose alteration: detectability and symptoms. Clin Pharmacol Ther. 1984;36(2):244–50.
27. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. Psychopharmacology (Berl). 1995;119(3):268–76.
28. Wolff K, Rostami-Hodjegan A, Shires S, et al. The pharmacokinetics of methadone in healthy subjects and opiate users. Br J Clin Pharmacol. 1997;44(4):325–34.
29. Kharasch ED, Hoffer C, Whittington D, Walker A, Bedynek PS. Methadone pharmacokinetics are independent of cytochrome P4503A (CYP3A) activity and gastrointestinal drug transport: insights from methadone interactions with ritonavir/indinavir. Anesthesiology. 2009;110(3):660–72.
30. Kreek MJ, Kalisman M, Irwin M, Jaffery NF, Scheflan M. Biliary secretion of methadone and methadone metabolites in man. Res Commun Chem Pathol Pharmac. 1980;29:67–78.
31. Olsen GD. Methadone binding to human plasma proteins. Clin Pharmacol Ther. 1973;14:338–43.
32. Boulton DW, Arnaud P, DeVane CL. Pharmacokinetics and pharmacodynamics of methadone enantiomers after a single oral dose of racemate. Clin Pharmacol Ther. 2001;70(1):48–57.
33. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41(14):1153–93.
34. Dole VP, Kreek MJ. Methadone plasma level: sustained by a reservoir of drug in tissue. Proc Natl Acad Sci U S A. 1973;70(1):10.
35. Anggard E, Gunne LM, Homstrand J, McMahon RE, Sandberg CG, Sullivan HR. Disposition of methadone in methadone maintenance. Clin Pharmacol Ther. 1975;17(3):258–66.
36. Kharasch ED, Walker A, Whittington D, Hoffer C, Bedynek PS. Methadone metabolism and clearance are induced by nelfinavir despite inhibition of cytochrome P4503A (CYP3A) activity. Drug Alcohol Depend. 2009;101(3):158–68.
37. Foster DJ, Somogyi AA, Bochner F. Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. Br J Clin Pharmacol. 1999;47(4):403–12.
38. Totah RA, Allen KE, Sheffels P, Whittington D, Kharasch ED. Enantiomeric metabolic interactions and stereoselective human methadone metabolism. J Pharmacol Exp Ther. 2007;321(1):389–99.
39. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. Drug Alcohol Depend. 1980;5(3):197–205.
40. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. Clin Pharmacol Ther. 1981;30(3):353–62.
41. Novick DM, Kreek MJ, Arns PA, Lau LL, Yancovitz SR, Gelb AM. Effect of severe alcoholic liver disease on the disposition of methadone in maintenance patients. Alcohol Clin Exp Res. 1985;9(4):349–54.
42. Nanovskaya TN, Deshmukh SV, Nekhayeva IA, Zharikova OL, Hankins GD, Ahmed MS. Methadone metabolism by human placenta. Biochem Pharmacol. 2004;68(3):583–91.
43. Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exp Ther. 1985;233(1):1–6.
44. Hiltunen AJ, Beck O, Hjemdahl P, et al. Rated well-being in relation to plasma concentrations of l- and d-methadone in satisfied and dissatisfied patients on methadone maintenance treatment. Psychopharmacology (Berl). 1999;143(4):385–93.
45. Dyer KR, Foster JR, White JM, Somogyi AA, Menelaou A, Bochner F. Steady-state pharmacokinetics and pharmacodynamics in methadone mainteance patients: comparison of those who do and do not experience withdrawal concentration-effect relationships. Clin Pharmacol Ther. 1999;65:685–94.
46. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther. 1987;41:392–401.

Chapter 7
Methadone and Opioid Rotation

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Opioid Rotation: Definition and Principle

In many patients treated with opioids for acute or chronic pain, the type of opioid analgesic and/or the route of administration require a change one or more times during the course of treatment in order to optimize therapeutic goals and outcomes or tailor pain treatment to specific clinical circumstances. Opioid rotation (or switching) is "a change in opioid drug or route of administration with the goal of improving outcomes" [1]. The acceptance of this strategy derives from the expectation that a switch to a new drug is likely to yield equivalent or better analgesia and fewer adverse effects. Although the specific mechanisms by which opioid rotation improves the overall response to therapy have not yet been fully understood, the theoretical basis relates broadly to the large individual variation that characterizes the responses to different mu agonist opioids, and more specifically, to the phenomenon of incomplete cross-tolerance to both analgesic and non-analgesic opioid effects [2]. Most recently, Pasternak has stated, "Incomplete cross tolerance

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_7,

provides a mechanism to help explain opioid rotation in that the second drug may be used at far lower doses to achieve pain control, thereby minimizing side effects" [3]. Presumably, any change from one opioid to another is likely to yield a different set of effects, sometimes more favorable and sometimes less, and the impact of incomplete cross-tolerance may bias this change toward relative improvement.

Opioid rotation is usually considered in the following situations: [1, 4–6]

1. The patient experiences severe pain despite repeated opioid dose escalations.
2. Opioid dose escalation has yielded intolerable and unmanageable side effects.
3. A change in clinical status suggests value in an opioid with different pharmacokinetic properties.
4. There may be value in a switch to a different route of administration (e.g., transdermal rather than oral), or drug or formulation (e.g., a formulation with once daily dosing).
5. Problematic drug–drug interactions.
6. Finanical or drug-availability considerations.

When planning opioid rotation, an approximate equianalgesic dose between the current opioid and the new opioid has to be determined. The calculation of an approximate equianalgesic dose is necessary because the analgesic potency (i.e., the dose required to produce a given effect) of the various opioid drugs varies greatly. Therefore, the switch among drugs (or routes of administration) cannot be done safely and effectively unless the relative potencies among them are known. Relative potency, i.e., the ratio of opioid doses necessary to obtain roughly equivalent effects, can be determined through controlled clinical trials that compare different drugs or routes of administration [7–11]. Relative analgesic potency can be converted into equianalgesic doses by applying the dose ratio to a standard. Historically, 10 mg of parenteral morphine has been considered to be the standard for this determination, and doses equianalgesic to this have been calculated by using empirically derived relative-potency estimates. About 40 years ago, findings form a set of relative-potency studies ([12, 13] and others) resulted in construction of the equianalgesic table which since then has served (with some minor variations and additions) as an inevitable tool in the process of opioid rotation. A successful and safe application of opioid rotation in clinical practice requires consideration of numerous methodological issues and limitations when interpreting data obtained from the relative-potency studies [1, 14]. For example:

– The majority of relative-potency trials that yielded the construction of the equianalgesic dose table were short-term studies conducted in patients with acute postoperative pain or in patients with cancer pain receiving low-doses of opioids, and therefore the results may not be directly applicable to patients with chronic noncancer pain or to patients on high doses of opiods.
– Pain measurements used to calculate metrics representing the total amount of pain reduction varied greatly among studies.
– The early studies of relative potency that constituted the equianalgesic dose table did not assess many of the potential influences on potency that have become relevant with subsequent research, including the direction of the switch from one

drug to another, the influence of chronic opioid administration, and the importance of the dose at the time of a change. They could not evaluate formulations and drugs that have come into clinical use since the original equianalgesic table was created nor did they specifically address responses based on ethnicity, advanced age, concommitant medication use, or comorbidities.
- The use of mean data in developing equianalgesic ratios also may pose problems in the clinical setting. For example, a 10:1 ratio listed in the table may actually reflect a ratio of 2:1 in some patients and 20:1 in others [14].
- Relative-potency estimates may be affected by numerous factors that were minimized or overlooked in the clinical trial setting but affect generalizability of the data. For example, major organ dysfunction may change the kinetics of a drug or active metabolites, or alter pharmacodynamics. Race, age, and gender each may also be a potential source of variations in the potency of specific opioids [15–22].

Methadone Characteristics Relevant for Opioid Rotation

Methadone (ME) has many positive attributes that makes it a good candidate when considering opioid rotation [2, 5, 6, 8]. It lacks neuroactive metabolites, clearance is independent of renal function, it has excellent bioavailability, and the cost is minimal compared to other long-acting opioid formulations. Another strong benefit, but also potential problematic characteristic, of ME is that its high degree of incomplete cross-tolerance allows for analgesic effects at relatively small doses. Further, in addition to its mu opioid agonist mechanism of action, ME has a non-opioidaction as noncompetitive antagonist at NMDA receptors [23]. Consequently, ME can enhance analgesia in patients who are not responsive to other opioids and/or present with refractory pain [24].

ME produces analgesic activity within 30–60 min after oral administration with a duration of action of 4–8 h. Although the longer dosing interval can be seen as advantageous for the patient, it requires a great caution in opioid rotation. ME has demonstrated high interindividual variability in pharmacokinetics, which together with long elimination half-life and high bioavailability may increase the risk of accumulation following multiple doses. For this reason, ME is not recommended for opioid rotation in the management of acute pain when pain intensity may change quickly and require prompt changes of dosing.

Further, relative potency is another characteristic significant for opioid rotation. In early single-dose relative-potency assays, the equianalgesic dose ratio for parenteral MS:ME was 1:1 and the ratio between parenteral ME and oral ME was 1:2 [12, 13]. More recent studies, however, have confirmed that the potency of ME when patients are switched from another mu agonist is both dose-dependent and greater than would be anticipated from these early studies [7–10, 25–27]. For example, Ripamonti et al. [9, 10] reported a dose ratio for oral MS:oral ME of 7.75:1 (range between 14.1 and 2.5:1), while a dose ratio for subcutaneous MS vs. oral ME [11, 25] ranged between 5:1 and 7:1. Several studies [7, 9, 10, 25] have found a

significant relationship between the relative potency of ME and the dose of the opioid taken at the time that ME is administered. Oral MS:ME ratio for patients receiving less than 1,165 mg/day was 5.42:1, whereas the ratio for those receiving more than 1,165 mg/day was 16.8:1 [25]. Another study [10] determined the MS:ME ratios to be 3.71:1 if the dose of MS prior to the switch was 30–90 mg/day, 7.75:1 if the MS dose prior to the switch was 90–300 mg/day, and 12.25:1 if the prior MS dose was >300 mg/day. Moreover, a bidirectional difference was noted in the oral MS:ME ratio [7]. The ratio was found to be 8.25:1 when switching from ME to MS, and 11.36:1 when switching from MS to ME [7].

Together, these more recent studies suggest that the conventional equianalgesic dose ratios derived from a single dose studies [12, 13] do not apply to opioid rotation using ME without substantial adjustment. This adjustment may take the form of a standardized reduction in the calculated equianalgesic dose in all cases, or a more specific additional reduction based on the dose of the opioid taken at the time of the switch to ME [1], as discussed below. When considering opioid rotation from another opioid agonist to methadone, it is important to recognize that ME potency and resulting effects in clinical conditions may be influenced by a variety of factors. For example, inducers and inhibitors of enzymes that are involved in ME metabolization can significantly affects the serum level and/or toxicity of ME [28, 29]. Commonly prescribed drugs that inhibit methadone's liver microsomal enzyme metabolic pathways, leading to increases in ME serum levels, include amiodarone, verapamil, cimetidine, or ciprofloxacin. Recently, attention has focused on ME interaction with the antiviral drugs used in the treatment of HIV and AIDS [24]. The nucleoside reverse-transcriptase inhibitors and the non-nucleoside reverse-transcriptase inhibitors have effects on the bioavailability and efficacy of ME, and clinicians considering a switch to ME should be aware of these interactions, and vigilant for potential adverse effects, both immediately and over the course of several days, due to potential dose accumulation.

Clinical Considerations and Guidelines for Opioid Rotation Involving Methadone

The guideline for opioid rotation, as recently delineated by the Expert Panel on Evidence Review and Guidelines for Opioid Rotation [1], suggests using the existing equianalgesic dose tables as a reasonable starting point, but promote safety through dose adjustments based on available evidence and expert opinion, and clinical considerations of the variety of factors that may influence outcomes of the rotation. To reduce a risk of unintentional overdose, the calculated conversion ratio should be adjusted depending on clinical assessment of the risk. Based on the Expert Panel consensus, the strategy for safe use of the equianalgesic dose table in clinical practice should consist of two major steps, each including several activities/clinical considerations (Table 7.1).

Table 7.1 Guideline for opioid rotation (from Fine and Portenoy [1], with permission)

Guideline for opioid rotation
Step 1
• Calculate the equianalgesic dose of the new opioid based on the equianalgesic table
• If switching to any opioid other than methadone or fentanyl, identify an "automatic dose reduction window" of 25–50 % lower than the calculated equianalgesic dose
◦ If switching to methadone, identify this window at 75–90 % lower than the calculated equianalgesic dose. For individuals on very high opioid doses (e.g., 1,000 mg morphine equivalents/day or higher) great caution should be exercised in converting to methadone at doses of 100 mg or greater per day; consider inpatient monitoring, including serial EKG monitoring.
◦ If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the package insert for these formulations.
• Select a dose closer to the lower bound (25 % reduction) or the upper bound (50 % reduction) of this automatic dose reduction window on the basis of a clinical judgment that the equianalgesic dose table is relatively more or less applicable, respectively, to the specific characteristics of the opioid regimen or patient
◦ Select a dose closer to the upper bound (50 % reduction) of the reduction if the patient is receiving a relatively high dose of the current opioid regimen, is not Caucasian, or is elderly or medically frail
◦ Select a dose closer to the lower bound (25 % reduction) of the reduction if the patient does not have these characteristics or is undergoing a switch to a different route of systemic drug administration using the same drug
Step 2
• Perform a second assessment of pain severity and other medical or psychosocial characteristics to determine whether to apply an additional increase or decrease of 15–30 % to enhance the likelihood that the initial dose will be effective for pain, or conversely, unlikely to cause withdrawal or opioid-related side effects
• Have a strategy to frequently assess initial response and titrate the dose of the new opioid regimen to optimize outcomes
• If a supplemental "rescue dose" is used for titration, calculate this at 5–15 % of the total daily opioid dose and administer at an appropriate interval; if an oral transmucosal fentanyl formulation is used as a rescue dose, begin dosing at one of the lower doses irrespective of the baseline opioid dose

Step 1 represents an initial dose reduction automatically applied as a safety precaution; Step 2 is an additional dose adjustment based on an evaluation of additional medical or psychosocial factors.

In practice Step 1 represents an application of an "automatic dose reduction" of the equianalgesic dose within a recommended narrow window. Although for most opioids the window is suggested at 20–50 % lower than the calculated equianalgesic dose, the recommended reduction for ME is much greater, 75–95 % lower than the calculated equianalgesic dose. This is supported by the evidence that ME potency is substantially higher than originally determined by early relative-potency studies, as discussed in the previous section. It is recommended [1] that a dose close to the upper bound of the window should be selected if the patient is receiving a relatively high dose of opioid, is elderly, medically frail or not Caucasian. Although such steep a reduction is probably not needed when switching from a relatively low-dose

opioid regimen, the decision to use a smaller reduction when switching to ME requires careful monitoring of the patient after the change.

Step 2, a dose adjustment in addition to the "automated dose reduction" requires an evaluation of additional medical or psychosocial factors at the time of the switch and may lead to further reduction of the dose. The recommendations are intended to reduce risks associated with opioid rotation. As the application of the dose reduction(s) may lead to initial under-dosing, the plan for opioid rotation must also include a strategy for titration of the dose after the change to a new drug is initiated. Several authors suggest ways to rotate from other opioids to ME, and there are several clinical approaches that may be safe and efficacious [7, 30–33]. The strategies are determined by the comfort level of the clinician, the patient's (or caregiver's) reliability, medical risk factors (e.g., history of obstructive or central sleep apnea), alongside the overall goal of the opioid rotation to improve clinical outcomes and quality of the patient's life [34–41].

Conclusions

Opioid rotation is one of the strategies clinicians implement in order to improve outcomes of opioid treatment. The goal of opioid rotation is to establish an opioid regimen that leads to improved analgesic efficacy and/or lower toxicity, better function, or improved quality of life. An application of opioid rotation in clinical practice requires careful consideration and assessment of a broad spectrum of methodological and clinical factors/limitations that may influence outcomes of the planned rotation.

ME is an opioid agent with several attractive features for opioid rotation. However, ME has demonstrated high interindividual variability in pharmacokinetics, long half-life, and high bioavailability, which together may increase risks of accumulation and adverse effects following multiple doses. Further, recent potency studies indicate that ME has higher potency than originally determined in early studies that led to construction of the conventionally used equianalgesic table. Also, the dose level of a given opioid regimen and duration of opioid exposure prior the switch, as well as the direction of the switch, will affect the equianalgesic ratio between ME and another opioid agent. Therefore, great deal of caution, counseling, ongoing clinical assessment, and a reliable patient/caregiver is required when planning an opioid switch involving ME. In order to promote safety as a primary goal of the overall process of opioid rotation, the Expert Panel [1] issued guidelines (Table 7.1) including a two-step dose-reduction and adjustment, and recommends a substantial reduction of ME dose, as well as an additional dose adjustment and careful clinical assessment and monitoring, when using ME in opioid rotation.

References

1. Fine PG, Portenoy RK. for the Ad Hoc Expert Panel on Opioid Rotation. Establishing "best practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manage. 2009;38(3):418–25.
2. Quigley C. Opioid switching to improve pain relief and drug tolerability. Cochrane Database Syst Rev. 2004;(3):CD004847.
3. Pasternak G. Preclinical pharmacology and opioid combinations. Pain Medicine. 2012; in press.
4. Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. Anesth Analg. 2000;90(4):933–7.
5. Thomsen AB, Becker N, Eriksen J. Opioid rotation in chronic non-malignant pain patients. Acta Anaesthesiol Scand. 1999;43(9):918–23.
6. DeStoutz N, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage. 1995;10:378–84.
7. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and ME in patients with cancer pain: a retrospective study. Cancer. 1998;82(6):1167–73.
8. Gebhardt R, Kinney MA. Conversion from intrathecal morphine to oral ME. Reg Anesth Pain Med. 2002;27:319–21.
9. Ripamonti C, Groff L, Brunelli C, et al. Switching from morphine to oral ME in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol. 1998;16(10):3216–21.
10. Ripamonti C, DeConno F, Groff L, et al. Equianalgesic dose ratio between ME and other opioid agonists in cancer pain: comparison of two clinical experiences. Ann Oncol. 1998; 9:79–83.
11. Gagnon B, Bruera E. Differences in the ratios of morphine to ME in patients with neuropathic pain versus non-neuropathic pain. J Pain Symptom Manage. 1999;18:120–5.
12. Houde RW, Wallenstein SL, Rogers A. Clinical pharmacology of analgesics. 1. A method of assaying analgesic effect. Clin Pharmacol Ther. 1960;1:163–74.
13. Houde R, Wallenstein S, Beaver W. Evaluation of analgesics in patients with cancer pain. Clin Pharm. 1966;1:59–97.
14. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of equianalgesic dose table. J Pain Symptom Manage. 2009;38(3):426–39.
15. Caraco Y, Sheller J, Wood AJ. Impact of ethnic origin and quinidine coadministration on codeine disposition and pharmacodynamic effects. J Pharmacol Exp Ther. 1999;290:413–22.
16. Poulsen L, Brosen K, Arendt-Nielsen L, et al. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. Eur J Clin Pharmacol. 1996;51:289–95.
17. Zhou HH, Sheller JR, Nu H, Wood M, Wood AJ. Ethnic differences in response to morphine. Clin Pharmacol Ther. 1993;54:507–13.
18. Mercadante S, Ferrera P, Villari P, Casuccio A. Opioid escalation in patients with cancer pain: the effect of age. J Pain Symptom Manage. 2006;32:413–9.
19. Hall S, Gallagher RM, Gracely E, Knowlton C, Wescules D. The terminal cancer patient: effects of age, gender, and primary tumor site on opioid dose. Pain Med. 2003;4:125–34.
20. El-Tahtavy A, Kokki H, Reidenberg BE. Population pharmacokinetics of oxycodone in children 6 months to 7 years old. J Clin Pharmacol. 2006;46:433–42.
21. Cook CD, Barrett AC, Roach EL, Bowman JR, Picker MJ. Sex-related differences in the antinociceptive effects of opioids: importance of rat genotype, nociceptive stimulus intensity, and efficacy at the mu opioid receptor. Psychopharmacology (Berl). 2000;150:430–42.
22. Sarton E, Olofsen E, Romberg R, et al. Sex differences in morphine analgesia: an experimental study in healthy volunteers. Anesthesiology. 2000;93:1245–54.
23. Ebert B, Anderson C, Thorkild C, et al. Opioid analgesics as noncompetitive N-methyl-D-aspartate (NMDA) antagonist. Biochem Pharmacol. 1998;56:553–9.

24. Shaiova L. The role of methadone in the treatment of moderate to severe cancer pain. Support Cancer Ther. 2005;2(3):176–80.
25. Bruera E, Pereira J, Watanabe S. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between ME, hydromorphone and morphine. Cancer. 1996;78:852–7.
26. Walker PW, Palla S, Pei BL, Kaur G, Zhang K, Hanohano J, et al. Switching from ME to a different opioid: what is the equianalgesic ratio? J Palliat Med. 2008;11(8):1103–8.
27. Fainsinger R, Schoeller T, Bruera E. Methadone in the management of cancer pain: a review. Pain. 1993;52:137–47.
28. Cherney NJ, Chang V, Franger G, et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. Cancer. 1995;76:1283–93.
29. Nilson MI, Gronbladh L, Widerlow E, et al. Pharmacokinetics of methadone in methadone maintenance treatment: characterization of therapeutic failures. Eur J Clin Pharmacol. 1983;25:497–501.
30. Ripamonti C, Zecca E, Bruera E, et al. An update on the clinical use of methadone for cancer pain. Pain. 1997;70:109–15.
31. Mercadante S. Treatment and outcome of cancer pain in advanced cancer patients followed at home. Cancer. 1999;85:1849–58.
32. Mercadante S, Casuccion A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. J Clin Oncol. 2001;111:2898–904.
33. Indelicato RA, Portenoy RK. Opioid rotation in the management of refractory cancer pain. J Clin Oncol. 2003;21(Suppl):87–91.
34. Mercadante S, Arcuri E. Opioids and renal function. J Pain. 2004;5:2–19.
35. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, ME, morphine, oxycodone). Pain Pract. 2008;8(4):287–313.
36. Benitez-Rosario MA, Feria M, Salinas-Martin A, Martinez-Castillo LP, Martin-Ortega JJ. Opioid switching from transdermal fentanyl to oral ME in patients with cancer pain. Cancer. 2004;101(12):2866–73.
37. Anderson R, Saiers JH, Abraham S, Schlicht C. Accuracy in equianalgesic dosing conversion dilemas. J Pain Symptom Manage. 2001;21:397–406.
38. Cruciani RA, Sekine R, Homel P, et al. Measurement of QTc in patients receiving chronic ME therapy. J Pain Symptom Manage. 2005;29(4):385–91.
39. Davis AM, Inturrisi CE. d-ME blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. J Pharmacol Exp Ther. 1999;289(2):1048–53.
40. Schumacher MA, Basbaum AI, Way WL. Opioid analgesic and antagonists. In: Katzung BG, editor. Basic and clinical pharmacology. New York: McGraw-Hill; 2004. p. 497–516.
41. Manchikanti L, Atluri S, Trescot AM, Giordano J. Monitoring opioid adherence in chronic pain patients: tools, techniques, and utility. Pain Physician. 2008;11(2 Suppl):S155–80.

Chapter 8
Intravenous Use of Methadone: Efficacy and Safety

Sebastiano Mercadante

While oral route is considered the preferred route of administration of opioids, in specific conditions an alternative route of administration is mandatory, especially in patients who are unable to swallow or present gastrointestinal adverse effects precluding the oral route. As the use of subcutaneous methadone has been the subject of many concerns due to its local toxicity [1, 2], intravenous methadone should be the preferred parenteral route, particularly in patients with an intravenous line or implanted with a port-cath.

Pharmacokinetic Issues of the Intravenous Route

Parenteral administration of methadone may be important in some conditions when oral route is unavailable or in specific settings such as in case of use in the perioperative period. Similarly to what has been described for the oral route, however, repeated boluses or continuous administration of intravenous methadone may be problematic, because of its peculiar pharmacokinetics. After a bolus injection, methadone plasma level declines in a bioexponential manner with a half-life of 2–3 h during the initial phase and 15–60 h during the terminal phase. This bioexponential decline with a long terminal half-life may account for the relatively short analgesic action of single doses and the tendency for drug accumulation with repeated dosing [3].

This was demonstrated by some pioneer studies. A prospective, randomized, double-blind trial was designed in advanced cancer patients for 5–6 days to compare

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_8,

the duration of analgesia produced by intravenous morphine and methadone. One-eightth of the patient's daily opioid requirement was supplied as an intravenous infusion of either morphine or methadone over a period of 15 min, when initiated by the patient using a patient-controlled analgesia device. The duration of pain relief when repeated intravenous doses of these analgesics were given was similar throughout the entire study period, although morphine and methadone have different serum half-life (3 h vs. 25 h) [4]. However, the choice of dose bolus is important. Given the lipophilic characteristics and the large distribution volume a sufficient dose of methadone must be administered such that the pain will begin to return during the elimination phase and not during the distribution phase, thereby providing prolonged analgesia as a consequence of the long elimination half-life. It is likely that the brief period of analgesia, similar to that of morphine, is to be attributed to distribution governing duration of action rather than elimination [5]. Unfortunately there is a wide variation in methadone pharmacokinetic parameters among individuals. In some patients methadone appears to have a cumulative effect, resulting in adverse effects, possibly as a consequence of a low clearance, while in some other patients methadone does appear capable of controlling pain, presumably due to high clearance, regardless of pharmacodynamics. Therefore, intravenous infusion of methadone can be planned only on a careful clinical judgment. If no loading dose is used, the steady state of blood methadone concentration is achieved after at least 5 half-lives, from 2 to 9 days [6], a time not always optimal for patients in urgent need to improve analgesia, due to extreme suffering. The consequences of a change in dose regimen are fully realized only after a considerable delay [6]. Due to a long terminal half-life, dose adjustment in the patient with fluctuating pain intensity is more difficult with methadone than with a short half-life drug such as morphine [7]. It has been shown that methadone clearance after an intravenous infusion is highly variable. On the other hand, individual pharmacokinetic studies are unreliable in the clinical setting. According to these observations, an initial intravenous bolus could be of paramount importance to test the analgesic response and its duration, as confirmed by pharmacokinetic models [8]. This is the basis to plan an initial methadone regimen (see section "Clinical Use").

On the other hand, in long-term treatments methadone may induce its own metabolism. This means that accumulation may automatically be self-regulated or a dose regimen which was initially effective might rapidly become inadequate. Alternately a number of substances may influence methadone clearance, including estrogens, verapamil, rifampicine, barbiturates, and aging [8].

Regarding the conversion ratio with the oral route, it should be considered that methadone is highly available by oral route, around 85 %, in comparison with oral morphine, which has a highly variability in availability, which is 20–50 % [9]. This means that the conversion ratio to the parenteral route, subcutaneously or intravenously, should be about 0.8. In a small study doses of subcutaneous methadone, with an availability quite similar to that of the intravenous route, were similar to doses of oral methadone, providing a strict surveillance with a close monitoring [10].

Clinical Use

Methadone is commonly considered an opioid of second choice. The reasons rely on the complex pharmacokinetics which require a certain expertise, rather than on efficacy. In fact methadone provided similar analgesia in comparison with other opioids [11, 12]. On the other hand, opioid switching to methadone in cancer pain has provided excellent results, allowing to improve the balance between analgesia and adverse effect, despite relevant differences in the conversion ratios and technical approaches proposed in the literature. Thus, the main problem is represented by the conversion from other opioids, which is the most challenging aspect of methadone use. Unfortunately, data on intravenous methadone are poor. As the analgesic effect is due to several factors, including pain intensity, previous opioid administration, other than pharmacokinetics of methadone, dose titration with intravenous methadone can guide the subsequent infusion rate. Unlike morphine for which the peak analgesic effect occurs well after the peak serum concentration, the peak of analgesic effect and peak serum concentration following intravenous methadone occur nearly simultaneously.

Some pioneer studies can be helpful to suggest the best approach. Boluses of 5 mg were administered every 10 min until the patient reported satisfactory analgesia. Initial infusion rates were calculated by multiplying the number of boluses required to produce analgesia by 0.3 mg/h. For example if a patient required 20 mg to achieve analgesia, the initial infusion rate was 1.2 mg/h [13]. Overall, the methadone concentrations predicted using pharmacokinetic modelling were in agreement with those measured, and over 95 % of the variance in the data were explained using this model. This approach avoids significant loss of analgesia or problematic adverse effects and by immediately starting the calculated maintenance infusion, allows a rapid conversion.

There are few small reports of conversion from other opiods to intravenous methadone, particularly for cancer pain unrelieved by other opioids. In 13 advanced cancer patients who were switched from morphine to intravenous methadone a conversion ratio of 5.2 was found, with a wide variability [14]. Patients dramatically improved their opioid response after being switched from hydromorpone and morphine to intravenous methadone. As with oral methadone, in high-tolerant patients the conversion ratio is unpredictable, intravenous methadone resulting even 5 times more potent than hydromorphone [15].

A patient-controlled analgesia (PCA) is attractive for the management of severe, intractable cancer pain and may offer some advantages in patients who experienced inadequate pain control and dose-limiting side effects with high-dose intravenous morphine [16]. PCA from intravenous morphine to intravenous methadone indicates was accompanied by a decrease of 30–50 % of PCA demand dose. PCA could reduce the risks of drug accumulation with a continuous intravenous infusion of methadone, particularly when doses are not stabilized, as example when switching from another opioid to methadone. Cancer patients with uncontrolled pain and central adverse effect were switched from intravenous fentanyl to methadone, starting

with a conversion ratio of 0.25, as an initial infusion basal rate. Additional boluses of intravenous methadone were allowed every 20 min. The methadone consumption decreased, as a result of decreased PCA demand use with a hourly infusion rate increasing from 1.5 to 2 mg/h. This suggested that a little bit starting methadone infusion could be started, at least in some patients. The final conversion rate was 0.22 [17, 18]. This ratio appears to be relatively strong in comparison with ratios reported with oral methadone and transdermal fentanyl [18, 19]. While a patient-controlled analgesia method with minimal methadone doses as background analgesia may allow more safety, it also may take longer times before achieving the appropriate balance between analgesia and adverse effects. In fact to obtain analgesia it is necessary to provide initial doses sufficiently large to provide methadone blood levels above a minimal effective concentration for analgesia during both the distribution and elimination phase. This is even more important in patients who are tolerant to opioids [6, 20]. PCA with intravenous methadone presents several challenges, including high cost and limited availability, the required medical expertise for its administration, the need of monitoring patients during infusion, as well as strict regulations by home health agencies regarding the use of intravenous methadone [21].

Using the rapid titration paradigm, one can obtain a reasonable estimate of patient specific analgesic requirements as well as initial infusion requirement for methadone. This concept has been successfully utilized at La Maddalena Cancer Center for years. An intravenous bolus of methadone is given, independently of the previous dose of the previous opioid. Boluses are repeated at 10 min of interval until pain relief is achieved. This is considered a priming dose. The global amount of methadone is converted for a continuous infusion by multiplying by 3. For example an effective dose of 10 mg (two boluses of 5 mg) is converted to an infusion of 30 mg/day (1.25 mg/h). The further doses as needed will be 1/6 of the daily dose (5 mg). Doses are then adjusted according to the clinical response. Once the patient is stabilized, when possible, intravenous route is converted to the oral route by using a conversion ratio of 0.8 [22]. For example, if a patient is receiving 30 mg/day of intravenous methadone, then the daily dose will be 24 mg/day, that is 8 mg every 8 h.

Opioid switching in patients with opioid-induced hyperalgesia (see Chap. 6) is quite difficult, and any calculation of conversion ratios is unreliable [23]. This is even more complex when a rapid opioid titration with intravenous morphine is started in patients who extremely suffering and there is the need to control pain as soon as possible. Titration with intravenous-morphine (IV-MO) may provide fast and efficient pain relief, also providing information about the amount of opioids necessary for a subsequent treatment [24, 25]. Some patients, however, after an initially favourable response, may develop a hyperexcitated state worsened by further dose increments [23]. This state may be reversed by the administration of intravenous methadone in a sort of immediate opioid switching during rapid titration with intravenous morphine. In a clinical experience in an acute pain relief and palliative care unit, 12 patients were switched and re-titrated with IV-ME, because the previous titration with IV-MO failed and produced worsening pain rather than pain

relief [26]. No traditional adverse effects were noticed, except a mild myoclonus in three patients. According to the protocol, patients who did not responded favourably or showing a worsening pain despite increasing doses of morphine within 24 h, even after an apparent pain relief of short duration, were switched to intravenous-methadone (IV-ME). Doses of IV-ME were titrated again to relieve pain, at bedside and under medical supervision, regardless of prior morphine dose. IV-ME titration was stopped when patients reported an adequate pain relief. According to the efficacy of the bolus and patients' response, a continuous infusion of IV-ME was started in doses of approximately 3 times the dose of the effective bolus, as this doses was assumed to provide analgesia for about 8 h (while for IV-MO has been considered 6 times). For example, if the patient responded positively to a bolus of 10 mg of IV-ME, a continuous infusion of 30 mg/day was started. In the subsequent days, doses were changed according to the need. After achieving a dose stabilization providing adequate analgesia and acceptable adverse effects, IV-ME was converted to the oral route-methadone (OR-ME), by using a ratio IV-OR of 0.8–1 [22]. Thus, a patient receiving successfully 30 mg/day of IV-ME can be converted to 36 mg of OR-ME. The dose ratio between the initial bolus of IV-MO and the initial bolus of IV-ME was 2.24. All patients responded to opioid switching-titration with IV-ME, achieving stable analgesia except one patient who required a more complex treatment, including intrathecal administration of morphine and bupivacaine. When excluding the patient who required the spinal treatment, patients were discharged at home after a mean of 5.5 days (range 3–9 days) after starting IV-ME [26].

Substituting another opioid for intravenous methadone in patients with cancer pain has been reported to be unsuccessful [27], as patients would develop resistance to other opioids after a trial with methadone [28]. Given the high doses of opioids administered, it is likely that these patients were in a state of hyperalgesia. Case series have shown that switching from oral methadone to another opioid can be successful [29–31].

Adverse Effects and Safety Issues

Methadone interactions with other drugs are well known (see Chap. 6). Several common adverse effects are associated with methadone and occur with other opioids. Methadone is less constipating and fewer laxatives are required to prevent constipation [9]. While safety issues have been frequently reported with oral methadone, particularly with regard to EKG changes, data regarding the safety of intravenous methadone have been seldom reported in the literature. The preservative chlorobutanol seems to potentiate methadone's ability to block cardiac potassium currents, prolonging the QT interval [32]. Two cases of neurotoxicity induced by intravenous methadone have been reported. In a patient receiving 10 mg/h of hydromorphone, methadone was started at a rate of 5 mg/h. Myoclonus developed at doses of 18 mg/h and subsided with the decrease of dose which was gradually titrated down to 6 mg/h, maintaining adequate analgesia. Another patient was

switched from 240 mg/day of oral methadone to a continuous subcutaneous infusion of 12 mg/h. Due to the development of myoclonus and local skin reactions the patient was converted back to oral methadone. According to the authors' opinion the parenteral route may predispose patients to neurotoxicity mediated through D-receptors in the brain more so than the enteral route, which may allow a slower and steadier redistribution, resulting in less of a bolus effect across the blood–brain barrier [33]. However, these neurotoxic effects have been reported for any category of opioids and for oral methadone. In another article, a patient who developed reversible spastic paraparesis with prominent extensor spasms in the legs while receiving an infusion of intravenous methadone at 100 mg/h was described [34].

Perioperative Use of Intravenous Methadone

Intravenous methadone has been assessed during the perioperative period to provide long-lasting analgesia due to its long-half-life and low clearance, and inexpensiveness. Data are very old and have never been replayed in recent studies. Methadone provided excellent pain control after major surgery. A relationship between methadone pharmacodynamics and pharmacokinetics relating to the treatment of postoperative pain has been found after giving a bolus of 20 mg methadone following induction of anesthesia. About 40 % of patients did not require additional analgesia, and 26 % requested only non-opioid drugs. The median duration of analgesia was 27 h [35]. Methadone or morphine 0.25 mg/kg was given intravenously at induction of anesthesia with further increments in the recovery room for analgesia if required. Total doses of methadone and morphine were similar, but patients in the methadone group had lower pain scores in the subsequent 48 h and required less supplementary opioids. No significant respiratory depression or excessive sedation was observed in either group [36]. Similar data were reported in another study, using a similar protocol. Patients received either methadone or morphine 20 mg intravenously following induction of anesthesia, additional opioids in the recovery room, and subsequent opioids as needed on the postsurgical wards. Patients required less methadone than morphine in the recovery room and requested less methadone than morphine for pain relief on the wards, and reported lower pain intensity with methadone. No toxicity or notable adverse effects were recorded [37]. A bolus of 20 mg of intravenous methadone did not have adverse hemodynamic effects [38]. In another study no significant difference in the amount of analgesic requirement or pain intensity was observed between patients receiving intravenous morphine or methadone at 0.30 mg/kg intraoperatively [39]. In children, methadone or morphine at 0.2 mg/kg was administered and supplemental doses were titrated to achieve comfort in the recovery room. Children in the methadone group required fewer supplemental opioid analgesic drugs and reported lower pain scores. No major adverse effects occurred, no patient had prolonged emergence from anesthesia, and no patents required naloxone or postoperative ventilatory assistance [40].

Conclusion

Intravenous methadone is an important option in the treatment of cancer pain. Given the manageability the use should be reserved to experienced team with methadone use. Intravenous methadone should be started in a specialized setting where careful monitoring is available to prevent the risks of accumulation and to monitor possible EKG changes. Given the unpredictability of conversion ratios, particularly in patients with complex pain situation, a PCA and a continuous assessment of the patient's response could be helpful in minimizing these problems. Although the data are not clear on reported deaths attributed to methadone thought to be caused by prolongation of the QTc interval and interactions with other drugs (e.g., benzodiazepines), methadone should be prescribed with caution.

In the postoperative setting intravenous methadone could be an important option for providing long-lasting systemic analgesia.

References

1. Bruera E, Fainsinger R, Moore M, Thibault R, Spoldi E, Ventafridda V. Local toxicity with subcutaneous methadone. Experience of two centers. Pain. 1991;45:141–3.
2. Mathew P, Storey P. Subcutaneous methadone in terminally ill patients: manageable local toxicity. J Pain Symptom Manage. 1999;18:49–52.
3. Payne R, Inturrisi C. CSF distribution of morphine, methadone and sucrose after intrathecal injection. Life Sci. 1985;37:1137–44.
4. Grochow L, Sheidler V, Grossman S, Green L, Enterline J. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. Pain. 1989;38:151–7.
5. Gourlay G, Plummer J, Cherry D, Cousins M. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? Pain. 1990;42:383–4.
6. Inturrisi C. Pharmacokinetics of methadone. Adv Pain Res Ther. 1986;8:191–8.
7. Inturrisi C, Portenoy RK, Max M, Colburn W, Foley K. Pharmaokinetic-pharmacodynamic relationship of methadone infusions in patients with cancer pain. Clin Pharmacol Ther. 1990;47:565–77.
8. Plummer J, Gourlay G, Cherry D, Cousins M. Estimation of methadone clearance: application in the management of cancer pain. Pain. 1988;33:313–22.
9. Davis M, 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.
10. Centeno C, Vara F. Intermittent subcutaneous methadone administration in the management of cancer pain. J Pain Palliat Care Pharmacother. 2005;19:7–12.
11. Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol. 2004;22:185–92.
12. Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Verna L, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain. 2008;12:1040–6.

13. Denson D, Concilus R, Gregg R, Crews J. The correlation between predicted and measured specific analgesic concentrations after intravenous titration: a guide for initial maintenance requirements with methadone. J Clin Pharmacol. 1990;30:1049–54.
14. Auret K, Roger Goucke C, Ilett K. Pharmacokinetics and pharmacodynamics of methadone enantiomers in hospice patients with cancer pain. Ther Drug Monit. 2006;28:359–66.
15. Manfredi P, Borsook D, Chandler S, Payne R. Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone: clinical observations. Pain. 1998;77:99–101.
16. Fitzgibbon D, Ready B. Intravenous high-dose methadone administered by patient controlled analgesia and continuous infusion for the treatment of cancer pain refractory to high-dose morphine. Pain. 1997;73:259–61.
17. Santiago-Palma J, Khojainova N, Kornick C, Fischberg DJ, Primavera LH, Payne R, et al. Intravenous methadone in the management of chronic cancer pain: safe and effective starting doses when substituting methadone for fentanyl. Cancer. 2001;92:1919–25.
18. Benitez-Rosario MA, Feria M, Salinas-Martin A, Martinez-Castillo LP, Martin-Ortega JJ. Opioid switching from transdermal fentanyl to oral methadone in patients with cancer. Cancer. 2004;101:2866–73.
19. Mercadante S, Ferrera P, Villari P, Casuccio A. Rapid switching between transdermal fentanyl and methadone in cancer patients. J Clin Oncol. 2005;23:5229–34.
20. Inturrisi C, Colburn W, Kaiko R, Houde R, Foley K. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther. 1987;41:392–401.
21. Shaiova L, Berger A, Blinderman C, Bruera E, Davis M, Derby S, et al. Consensus guideline on parenteral methadone use in pain and palliative care. Palliat Supp Care. 2008;6:165–76.
22. Gonzales-Barboteo J, Porta-Sales J, Sanchez D, Tuca A, Gomez-Batiste X. Conversion from parenteral to oral methadone. J Pain Palliat Care Pharmacother. 2008;22:200–5.
23. Mercadante S, Ferrera P, Villari P, Arcuri E. Hyperalgesia: an emerging iatrogenic syndrome. J Pain Symptom Manage. 2003;26:769–75.
24. Mercadante S. Opioid titration in cancer pain: a critical review. Eur J Pain. 2007;11:823–30.
25. Mercadante S. The use of intravenous morphine for cancer pain management. Lancet Oncol. 2010;11:484–9.
26. Mercadante S, Ferrera P, Arcuri E, Casuccio A. Opioid-induced hyperalgesia after rapid titration with intravenous morphine: switching and re-titration to intravenous methadone, in press.
27. Moryl N, Santiago-Palma J, Kornick C, Derby S, Fischberg D, Payne R, et al. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. Pain. 2002;96:325–8.
28. Prommer E. Rotating methadone to other opioids: a lesson in the mechanisms of opioid tolerance and opioid-induced pain. J Palliat Med. 2006;9:488–93.
29. Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and methadone in patients with cancer pain. A retrospective study. Cancer. 1998;82:1167–73.
30. Mercadante S, Ferrera P, Villari P, Casuccio A, Intravaia G, Mangione S. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage. 2009;37:632–41.
31. Walker P, Palla S, Pei B, Kaur G, Zhang K, Hanohano J, et al. Switching from methadone to a different opioid: what is the equianalgesic ratio? J Palliat Med. 2008;11:1103–8.
32. Kornick C, Kilborn M, Santiago-Palma J, Schulman G, Thaler H, et al. QTc interval prolongation associated with intravenous methadone. Pain. 2003;105:499–506.
33. Ito S, Liao S. Myoclonus associated with high-dose parenteral methadone. J Palliat Med. 2008;11:838–41.
34. Manfredi P, Gonzales G, Payne R. Reversible spastic paraparesis induced by high dose intravenous methadone. J Pain. 2001;2:77–9.
35. Gourlay G, Wilson P, Glynn C. Pharmacodynamics and pharmacokinetics of methadone during the perioperative period. Anesthesiology. 1982;57:458–67.
36. Chui P, Gin T. A double-blind randomized trial comparing postoperative analgesia after perioperative loading doses of methadone or morphine. Anaesth Intensive Care. 1992;20:46–51.

37. Richlin DM, Reuben SS. Postoperative pain control with methadone following lower abdominal surgery. J Clin Anesth. 1991;3:112–6.
38. Bowdle A, Even A, Shen D, Swardsstrom M. Methadone for the induction of anesthesia: plasma histamine concentration, arterial blood pressure, and heart rate. Anesth Analg. 2004;98:1692–7.
39. Laur D, Sinkovic J, Betley K. A comparison of intraoperative morphine sulphate and methadone hydrochloride on postoperative visual analogue scale pain scores and narcotic requirements. CRNA. 1995;6:21–5.
40. Berde C, Beyer J, Bournaki M, Levin C, Sethna N. Comparison of morphine and methadone for prevention of postoperative pain in 3 to 7 year old children. J Pediatr. 1991;119:136–41.

Chapter 9
Methadone Hyperalgesia

Peggy Compton

> *He [the morphine addict] is also affected by a hypersensitiveness to pain, or a morbid intolerance of any kind of distress …. He suffers. His suffering is actually great. To his astigmatic inner eye it seems even greater than it is. [1].*

Introduction

It has long been recognized that opioid use brings with it the paradoxical effect of increasing sensitivity to pain, a response that has been explained as the phenomenon of opioid-induced hyperalgesia (OIH). Revered since antiquity for their potent analgesic effects, early observations suggested that opioid administration concurrently sets into motion opponent anti-analgesic processes, prompting that Albutt to ask: "Does morphia [morphine addiction] tend to encourage the very pain it pretends to relieve?" [2].

Largely ignored in the clinical literature for the next century, Martin and Inglis [3] revisited the phenomenon of decreased pain tolerance in persons abusing opioids. Using an adaptation framework, these investigators hypothesized that opioid addicts self-medicate to deal with "an abnormally low tolerance for painful stimuli" (p. 224). They reported significantly increased sensitivity to cold-pressor pain in an incarcerated population of women described as "known narcotic addicts," in comparison to matched "non-addict" controls. Although time since last opioid use and the presence of opioid withdrawal symptoms were not reported in this early trial, the

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_9,

magnitude of the relationships was impressive and supported an opioid-induced mechanism for the hyperalgesic response.

This chapter will review the phenomenon of OIH in general, and specifically what is known about its development and presentation with the use of the long-acting mu-opioid methadone. Primarily used for the last 50 years as a substitution treatment for opioid addiction, appreciation of methadone's effectiveness as an analgesic for the treatment of chronic pain has renewed interest in its hyperalgesic properties. The review will begin with a broad overview of the relevant literature describing and characterizing OIH, including the neurophysiological mechanisms underlying its development, and the role of opioid withdrawal and tolerance in its presentation. Next what is known about the hyperalgesia specifically associated with methadone, both in the treatment of opioid addiction and chronic pain, will be presented. The chapter concludes with suggested strategies to minimize the degree to which methadone hyperalgesia interferes with pain management.

Opioid-Induced Hyperalgesia

As described above, it is suggested that the relative pain intolerance noted in opioid maintained individuals is the result of opioid exposure or OIH (see reviews [4–7]). The time course, opioid dose–response relationship, and opioid pretreatment parameters of OIH have been carefully characterized in preclinical models for over 30 years, such that it is known to arise following single or chronic opioid exposure, increases in intensity with pretreatment opioid dose, and can be detected up to 5 days following subcutaneous injection [8–12]. A biphasic response to opioid administration is described such that analgesia is an early response, followed by the longer lasting hyperalgesic state [13, 14].

More recent work has shown that OIH relies upon mu-opioid receptor activation, can be induced with opioids of differing intrinsic efficacy, and increases in severity with intermittent or naloxone-interrupted opioid dosing [13, 15–17]. Increasingly, OIH is recognized as a variant of central sensitization and, like the hyperalgesia of neuropathic origin [18, 19], can be prevented by *N*-methyl-D-aspartate (NMDA) receptor antagonism and calcium channel blockers [13, 20–24]. Across this literature, it is of note that the degree of hyperalgesic response to opioid administration reported (~30 % of baseline) is so reliable.

Neurophysiologic Mechanisms of OIH

Multiple neurobiological mechanisms have been hypothesized to explain the phenomenon of OIH following opioid exposure (see Fig. 9.1). In a series of early studies, Mao and colleagues [6, 19, 25] suggested that agonist activity at the excitatory ionotropic NMDA receptor on dorsal horn neurons is responsible for the

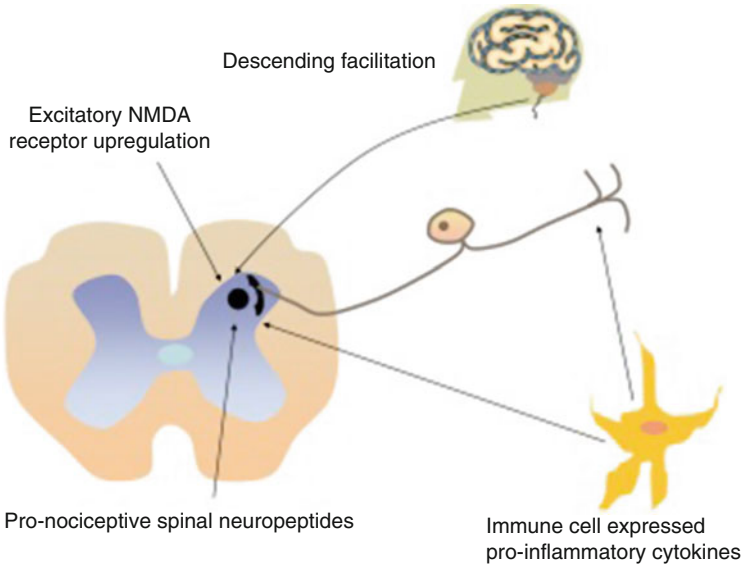

Fig. 9.1 Theorized mechanisms of opioid-induced hyperalgesia [26] (adapted from Angst and Clark [4])

development of OIH. Specifically, they showed that the binding of opioids to receptors on spinal neurons induced changes such that co-localized excitatory NMDA receptors are essentially upregulated, and thus resulting in increased transmission of nociceptive signals.

Various spinal neuropeptides, distinct from excitatory amino acid systems, have also been implicated in the development of OIH. Over a decade ago, Simonnet's laboratory showed that a single dose of parenteral heroin resulted in significant release of the antiopioid neuropeptide FF from the spinal cord in rats, inducing a pain response 30 % below baseline within 30 min, which could be blocked by the subsequent administration of opioid antagonist naloxone [27]. More recent animal work in Porreca's laboratory has demonstrated increased levels of lumbar dynorphin (a kappa opioid agonist with pro-nociceptive activity) following sustained spinal administration of opioid [28, 29]. Interestingly, the hyperalgesic effects of opioids were reversed 15 min following the administration of an antagonist to the neurokinin-1 receptor, the site of activity for the nociceptive neuropeptide substance P [30, 31]. Particularly active in pain of inflammatory origin, substance P involvement suggests a neuro-inflammatory component to the development of OIH [5] (see below).

The work of Porreca and colleagues also provides good preclinical evidence that OIH may be the result of activation of supraspinal descending pain facilitation systems arising from mu-opioid receptor activation [32, 33] in the rostral ventromedial medulla (see [5, 30, 32, 34]). Specifically implicated are increased levels of the pronociceptive peptide cholecystokinin (CCK), which appear to play a role in the

development of opioid analgesic tolerance as well [35]. It is suggested that CCK activity in the medulla drives descending pain facilitatory mechanisms, resulting in spinal hyperalgesic responses to nociceptive stimuli [29, 36].

Increasingly, neuroimmune mechanisms have been implicated in the development of OIH [37, 38]. In this model, exogenously administered opioids bind to mu-opioid receptors located on astrocytes of the blood–brain barrier, and result in the subsequent expression and release of pro-inflammatory chemokines and cytokines. In support of this hypothesis, Song and Zhao [39], and Johnston and Westbrook [40] have demonstrated that the administration of a glial cell inhibitor (fluorocitrate) reversed the hyperalgesic effect of morphine in acute and chronically treated rats up to 2 h following infusion. Further, administration of the cytokine inhibitors interleukin-1β receptor antagonist and interleukin-6 neutralizing antibody reverse and/or block morphine- or methadone-induced hyperalgesia [41–43]. Interestingly, coadministration of the tricyclic antidepressant amitriptyline with morphine in an animal model preserved the opioid's antinociceptive effect for up to 5 days following treatment, theorized to be due to its ability to suppress opioid-induced glial cell activation and subsequent cytokine expression [44]. Although the effects of spinal neuropeptides on OIH are evident acutely (15–30 min following treatment), immune-mediated mechanisms of OIH-reversal have been shown to be relatively enduring (5–6 days following treatment).

As is clear from this literature, characterization of OIH has primarily been established in animal models, making it difficult to extrapolate from preclinical findings to clinical implications. Pain is a much more highly modulated sensory experience in humans, and it is not entirely clear how pain *tolerance* in humans (point of subjective intolerance of pain, an indicator of hyperalgesia) maps onto putative pain *threshold* or perception (point at which animal withdraws tail, jumps on hotplate) in animals. Critical to this review, the development of OIH has been better characterized in animals without pain or with acute pain, thus understanding of its effect and relevance in the setting of chronic pain remains incomplete.

Opioid Withdrawal, Opioid Tolerance, and OIH

Well-recognized neurophysiologic consequences of opioid administration include *tolerance* or the need for increased doses of opioid over time to achieve the same effect, and *physical dependence*, which presents as a distinct withdrawal syndrome when plasma levels of opioid fall. Sharing opioid-induced mechanisms, these phenomena are not unassociated with the clinical presentation of OIH. For example, in preclinical models, hyperalgesia has long been identified as an important symptom of the opioid withdrawal syndrome, and elicited when opioid agonist administration is either abruptly terminated [8, 21, 45–47] or reversed by an antagonist [9, 48–52]. Hyperalgesia is reliably demonstrated to thermal (tail flick, hot plate), electrical (foot shock), and mechanical (pinch) noxious stimuli, and in these animal models, has been demonstrated to arise following single or chronic opioid exposure [10, 11, 53],

can be detected up to 5 days following subcutaneous morphine injection [8, 10, 12], and increases in intensity with pretreatment opioid dose [9, 12].

Subsequent work has confirmed that like OIH, the severity of withdrawal hyperalgesia increases with intermittent or naloxone-interrupted opioid dosing [10, 15, 54] and, like neuropathic hyperalgesia [19, 54, 55], its development can be prevented by NMDA receptor antagonism [13, 20–23]. Further characterization confirms that although it is present during withdrawal, it also exists independent of the withdrawal syndrome, and can, in fact, be detected in the presence of opioid analgesia [5, 56, 57], suggesting that withdrawal from opioids provides an opportunity for underlying OIH to be revealed.

In practice, increased sensitivity to pain during opioid withdrawal is reflected in the DSM-IVR diagnostic criteria for this opioid-induced disorder [57]. Specifically, with respect to this hyperalgesic state, text description of the withdrawal includes "…subjective and consist of complaints of anxiety, restlessness, and an 'achy feeling' that is often located in the back and legs, accompanied by a wish to obtain opioids ('craving') and drug-seeking behavior, along with irritability and increased sensitivity to pain (p. 272)." Better understood in animals than in patients, the DSM criteria acknowledge increased sensitivity to pain as clinical evidence of the opioid withdrawal syndrome.

More recently, withdrawal hyperalgesia to mechanical and thermal stimuli has been characterized in healthy volunteers exposed to opioids commonly used in clinical practice (morphine, hydromorphone, remifentanil). Areas of mechanical hyperalgesia induced by capsaicin and electrical stimulation were demonstrated to increase by 130–180 % beginning within an hour of discontinuation of a 60–90 min IV infusion of remifentanil [58, 59], an effect blocked by the administration of the NMDA receptor antagonist *S*-ketamine 30 min prior to remifentanil administration [58, 59]. Using a model of naloxone-precipitated withdrawal, our own work has shown significant decreases in cold-pressor pain threshold and tolerance following a single acute dose of IV hydromorphone [60]. Thus, an opioid addict is likely to appear hyperalgesic if experiencing opioid withdrawal. This becomes particularly relevant in the case of those patients using heroin or short-acting prescription opioids, as the relatively rapid decrease in opioid blood levels following use allows for the emergence of intermittent withdrawal states.

In that they appear to occur simultaneously by similar mechanisms [33, 61–63], the development of OIH has been conceptualized as integrally related to the development of analgesic tolerance. As eloquently suggested by Colpaert [61, 64] and Celerier et al. [13, 20, 65], that which appears to be opioid analgesic tolerance, and therefore increased opioid need, may in fact be an organismic response to an opioid-induced hypersensitivity to pain. Subsequent work suggests that OIH and tolerance are, in fact, distinct neurophysiologic processes, yet, the role OIH plays in the variable expression of analgesic tolerance in the clinical setting is worthy of consideration. Analgesic tolerance has long been cited as a rationale for withholding opioids in the treatment of chronic pain [66, 67]; reconceptualizing analgesic tolerance as a reflection of underlying OIH may lead to novel insights into the utility of chronic opioid therapy for this patient population.

Methadone Hyperalgesia

Like other opioids, preclinical work has demonstrated that methadone induces hyperalgesia in rats, which resolves within days of discontinuation [68]. Supporting a pro-inflammatory neuroimmune etiology for OIH, methadone has been demonstrated to induce glial cell activation and hyperalgesia to a similar degree as morphine [69], and like morphine, can be reversed by administration of the IL-1 receptor antagonist [43].

Unique to the racemic methadone used in practice is the D-isomer of the compound, which has been demonstrated to have independent NMDA-antagonist activity. In that activation of the NMDA receptor site appears to play a role in the development of OIH (see [6, 19, 25]), it has been theorized that the D-isomer activity of methadone diminishes or blocks hyperalgesia in opioid-exposed individuals. For example, when coadministered with morphine, parenteral and intrathecal D-methadone has been demonstrated to block NMDA-induced hyperalgesia in rat models [70, 71]. Holtman and Wala [72] examined the hyperalgesic properties of racemic methadone (D,L-methadone) and its enantiomers (L-methadone, D-METHADONE) alone and in combination with morphine in rats, and replicated previous reports of a dose-dependent D,L-methadone-induced hyperalgesia. Not only did the D-isomer block morphine hyperalgesia, but the degree of methadone hyperalgesia was greater with L-methadone as compared with the racemic mixture. The D-methadone isomer alone had no hyperalgesic effect, providing further evidence of its anti-hyperalgesic effects.

Methadone Hyperalgesia in Ex-Opioid Addicts

Much of what is known clinically about methadone hyperalgesia (and OIH in general) has been learned from studies of patients receiving methadone for the treatment of opioid addiction. Providing initial evidence for OIH in patients on methadone, Ho and Dole [73] reported in 1979 that methadone-maintained (MM) ex-heroin addicts were significantly more sensitive to pain induced by the cold-pressor test than were drug-free controls. Since that time, mentions of OIH in methadone patients in the scientific literature have steadily increased. Description of hyperalgesia in MM patients is facilitated by the relative stability of the population with respect to opioid use; by virtue of being in methadone treatment, these are individuals for whom opioid dosing, illicit drug use, and withdrawal symptoms are relatively well controlled, providing research subjects who are relatively reliable participants and informants.

Integration of the research on methadone hyperalgesia in ex-opioid addicts is complicated by the use of different pain induction techniques (electrical stimulation, mechanical pressure, cold-pressor); the measurement of pain *threshold* vs. pain *tolerance*; and the effects of methadone blood level (peak vs. trough) on pain

responses. Across all pain stimuli, pain *threshold* (the point at which a non-nociceptive stimulus becomes painful) has most consistently been shown to either be no different or significantly lower for MM patients in comparison to matched normal controls, under both methadone peak and trough conditions [74–79]. Within-group data show that methadone dosing either had no effect on, or improved threshold for both cold-pressor and electrical stimulation pain [26, 77], with the latter finding perhaps reflecting the acute analgesic effect of the medication.

Differences between MM and controls have been more robust on measures of pain *tolerance* (the point at which the subject reports that the pain can no longer be tolerated), which conceptually may be a better representation of a hyperalgesic state. Doverty et al. show decreased tolerance for electrical stimulation pain under both peak and trough methadone conditions [77, 78]. With respect to cold-pressor pain, significantly diminished tolerance has been consistently demonstrated in MM patients in comparison to both matched drug-free addicts [74] and matched controls [75–81], regardless of methadone blood levels. With respect to perceived pain severity, using visual analogue scales, Schall et al. [79] found no difference between MM and control subjects in their perception of mechanical pressure pain, while Pud et al. [81] found a significant higher rating of cold-pressor pain in the former. When evaluated within-subjects, this work indicates a significant analgesic effect for methadone on cold-pressor, electrical stimulation, and mechanical pressure pain tolerance 2–4 h post-dose, an effect correlating with peak methadone blood levels [78, 79].

These cross-sectional data show that MM patients are reliably intolerant of experimental pain, and are on average, between 42 and 76 % less tolerant of cold-pressor pain than are normal controls matched on age, gender, and ethnicity. With appreciable (albeit trough) methadone blood levels, these patients present a case for the *anti-analgesic* (hyperalgesic) effects of chronic methadone therapy. Daily methadone dose however is not significantly related to the degree of hyperalgesia noted [74, 75, 81, 82]. Recent data from our clinic show that heroin addicts entering MM treatment become significantly more hyperalgesic with respect to cold-pressor pain tolerance at trough methadone levels as they stabilized in treatment [83].

That hyperalgesic responses in opioid-dependent patients vary with the type of pain stimulus used has been noted in recent reviews of OIH [7, 84]. Rather than disputing the presence of OIH in opiate-abusing patients, these findings suggest that cold-pressor pain may be a modality particularly sensitive to opioid-induced changes. Recent data from Ruscheweyh et al. [85] show that variance in cold-pressor pain perception is more unique than perception of pain from other sources (heat, pinprick), supporting the position that responses sensitive to the cold-pressor procedure need not be reflected in other modalities. In fact, the genetic factors which underlie cold-pressor pain responses appear to be independent of those influencing phasic heat pain responses [86].

Recent work suggests that chronic pain (which presents in up to 55 % of methadone-maintained patients [87–89]) has a similar effect on experimental pain thresholds and tolerance, such that having concurrent chronic pain increases thermal and mechanical threshold latencies [90] and cold-pressor

tolerance in methadone patients [82]. These findings suggest that the development of hyperalgesia is not only dependent on opiate use, but is also mediated by pain in MM populations. With respect to chronic pain management in MM patients, ambiguity in treatment with opioids persists, with some prescribers minimizing opioid exposure to decrease risk of relapse and others prescribing opioids much more liberally in attempts to minimize pain [91].

Although it appears that OIH is a primary source of decreased tolerance for pain in MM opioid addicts, genetic differences have been posited to mediate its development. Perhaps most compelling is the suggestion that as a population, opioid addicted patients are pain sensitive by nature, and by virtue of their addictive disease, are self-selected for MM. Well-recognized individual differences in pain tolerance and opioid response have long been appreciated at the clinical level, and the genetic factors which underlie these differences are increasingly elucidated. An analysis of the preclinical literature (most notably from the laboratories of Mogil [92, 93] and Elmer [94–96]) reveals that those murine strains that demonstrate poor tolerance to pain are the same as those who are likely to find opioids highly rewarding or "addicting," suggesting a positive relationship between pain sensitivity and opioid addiction. Similarly, genetic differences in opioid response portend individual variability in the propensity to develop hyperalgesia. Interestingly, a strain which developed a high degree of hyperalgesia (87.3 %) following chronic morphine administration (C57BL/6J), was found to be a relatively pain-intolerant mouse [97].

If a genetically determined trait, ex-opioid addicts should evidence poor pain tolerance in comparison to controls, regardless of whether they currently are on methadone or are in drug-free recovery. With respect to pain *thresholds*, however, this does not appear to be the case. A series of studies by Liebmann et al. [98–100] provide evidence that drug-free opioid addicts are less sensitive to pain than are controls, a finding more recently confirmed by Prosser et al. [101] using quantitative sensory testing. A genetic influence on pain *tolerance* is suggested by the data of Pud et al. [81] who found significant hyperalgesia to the cold-pressor in opioid addicts as compared to matched controls, an effect which persisted over of 28 days of opioid abstinence. Interestingly, a distinct subgroup of pain-intolerant ex-opioid addicts was almost three times more likely to relapse within 2 years of treatment entry than were pain-tolerant ex-addicts. Perhaps related to their propensity for relapse, Ren et al. [102] found that cold-pressor pain tolerance in drug-free ex-opioid addicts (mean 5 years of abstinence) negatively correlated to the degree of cue-induced drug craving. Opioid addicts with poor pain tolerance may suffer a more severe form of addiction, or have difficulty tolerating the discomfort (pain) inherent in detoxification and early abstinence, and therefore more likely to present in MM clinics.

Methadone Hyperalgesia in Pain Patients

The degree to which methadone hyperalgesia in ex-opioid addicts generalizes to patients with chronic pain requires description. As noted, in the vast majority of

clinical and preclinical studies characterizing OIH, opioid administration is not paired with pain. Assuming that the nervous system responds differently to opioids when in pain vs. not in pain, it follows that the presentation and implications of OIH may differ as well.

With respect to clinical pain, evidence of OIH has been best described in the setting of acute postoperative pain. Specifically, intra-operative opioids have been shown to increase postoperative reports of pain and opioid consumption. Noted almost exclusively in patients undergoing various abdominal surgeries, putative hyperalgesic effects are described as most robust with administration of intrathecal or intravenous short-acting opioids (fentanyl, remifentanil), and in a dose-dependent fashion. Across a number of case study reports, the emergence of hyperalgesia has been described in patients with malignant chronic pain. In these cases, OIH occurred following large or rapidly escalating doses of morphine or fentanyl, and the pain symptoms resolved by dramatically decreasing or discontinuation of opioid, switching to a weaker opioid, or administration of the potent NMDA-antagonist ketamine.

Further evidence of OIH in chronic pain patients was provided by Chu et al. [103], who showed a significant decrease in cold-pressor pain tolerance following 1 month of opioid therapy (75 mg morphine/day) in a small number of chronic pain patients. Although not employing a pain tolerance measure, patients on chronic opioid therapy for nonmalignant pain reported that the severity of pain associated with a standardized lidocaine injection was positively and significantly correlated with opioid dose and duration of opioid treatment [104], suggesting that opioid-induced hyperalgesic processes may be at play. A methodologic difficulty in providing prospective evidence for OIH in practice is the rarity of opioid-naïve chronic pain patients who present for treatment.

With respect to methadone, even less is known about the degree to which hyperalgesia interferes with pain management. Due to its long half-life, methadone has a more gradual onset and offset of action, avoiding the rapid escalations in opioid plasma levels that have been related to the development of OIH in clinical and preclinical settings. In that the severity of OIH worsens with intermittent opioid dosing or repeated episodes of opioid withdrawal, the relatively stable plasma levels afforded by methadone may help to minimize the emergence of hyperalgesia [59, 105]. Further, and as previously noted [70–72], its partial NMDA-antagonist activity has been posited to counteract OIH development.

Providing evidence for the presence of methadone hyperalgesia in patients with chronic pain, Hay et al. [82] reported that the degree of cold-pressor hyperalgesia in those prescribed methadone for pain control is similar to that of pain-free MM patients, and for both groups, is significantly greater than in matched normal controls. Case reports suggest that methadone may induce less OIH than opioids of higher potency, as pain scores decrease when chronic patients are rotated from traditional opioids (morphine, oxycodone, hydromorphone) to methadone [106, 107]. Further, Gottschalk et al. [108] show that intra-operative methadone improved postoperative pain control to a better degree than intra-operative sufentanil, a finding attributed to the NMDA-antagonist properties of the former.

Strategies for Treating Methadone Hyperalgesia

Although well-designed clinical trials are lacking, certain strategies have been recommended to help avoid or minimize the expression of OIH in general and methadone hyperalgesia specifically [109, 110]. Firstly, the research literature suggests opioid-sparing approaches to the degree possible; hyperalgesia is demonstrated to increase with opioid dose and length of exposure, thus it may help to keep the methadone dose as low as is clinically effective.

The use of adjuvant medications can reduce the dose of methadone required for pain relief. The best-studied agent in this regard is the relatively weak NMDA-antagonist dextromethorphan, although, evidence for its efficacy to offset methadone hyperalgesia in MM patients has been mixed. Acute dextromethorphan administration has been shown to decrease the opioid analgesic requirement in postoperative patients [111, 112] and to reduce OIH in cancer patients [113], but it appears less effective in consistently doing so for patients with chronic nonmalignant pain [114–116]. A 5-week clinical trial of dextromethorphan (titrated to 480 mg/day) in a well-characterized sample of MM patients proved to be no different than placebo in improving cold-pressor and electrical stimulation pain responses both pre- and post-methadone administration [26]. The preclinical data of Chaplan et al. [117] suggest that the lack of dextromethorphan response may be due to its relatively low potency at the NMDA receptor.

The adjuvant medication, gabapentin, a key pharmacotherapy for the treatment of neuropathic pain, has been shown to reverse hyperalgesia in MM patients. Recent work in our clinic evaluated changes in cold-pressor responses following a 5-week trial of gabapentin (titrated to 2,400 mg/day) at peak and trough methadone plasma levels [118]. Analyzing data for those subjects compliant throughout the study, significant improvements in cold-pressor pain threshold and pain tolerance were observed at both dosing time points. Due to its gabaminergic activity, propofol [119] has been identified as another medication potentially useful in minimizing methadone hyperalgesia.

Other adjuvants that have been identified as being potentially helpful in treating OIH in addicts and pain patients include:

- COX-2 inhibitors (e.g., parecoxib, rofecoxib) for their ability to inhibit prostaglandin synthesis [120, 121]
- CCK antagonists (e.g., proglumide) to block descending pain facilitatory processes [122–124]
- α2-Receptor agonists (e.g., clonidine), which appeared to attenuated OIH in a small sample of healthy human subjects [125]

More recently, low-dose opioid antagonists in conjunction with opioid agonists have been used to counteract the development of OIH [126–130]. In two recent randomized clinical trials of pain patients with osteoarthritis [131] and low back pain [132], investigators reported significant benefits for pain relief over time and diminished physical withdrawal with the combination of oxycodone-plus-low-dose

naltrexone (2–4 μg/day) vs. oxycodone alone. It is theorized that the efficacy of low-dose opioid antagonists in preventing OIH is related to the suppression of G-protein switching in the presence of opioid agonist [133]. Although not evaluated specifically for methadone hyperalgesia, the combination of low-dose opioid antagonist with the full opioid agonist may result in decreased analgesic need.

Conclusions

Convergent lines of preclinical and clinical evidence indicate that opioid administration not only provides a rapid and powerful analgesia, but concurrently sets into motion certain anti-analgesic or hyperalgesic opponent processes, which can be observed both during opioid activity and withdrawal. Hypothesized neurophysiological processes with both peripheral and central components underlying its development have been identified. The implications of this altered pain state have become of interest to investigators and clinicians who prescribe methadone for the treatment of opioid addiction and for chronic pain.

Methadone hyperalgesia has been well characterized and reliably demonstrated in patients on MM for the treatment of opioid addiction, which may be related in genetic-imbued differences in opioid responses in reward as well as pain systems. Less is known about the impact of hyperalgesia on the pain of patients prescribed chronic opioid analgesic therapy, but methadone efficacy data suggest that it does not appreciably diminish pain outcomes [134, 135]. Adjuvant medications, including gabapentin, dextromethorphan, and low-dose opioid antagonists may provide anti-hyperalgesic effects for patients prescribed methadone for chronic pain.

References

1. Carter CW. What is the morphine disease? J Inebriety. 1908;30:28–33.
2. Albutt C. On the abuse of hypodermic injections of morphia. Practitioner. 1870;3:327–30.
3. Martin J, Inglis J. Pain tolerance and narcotic addiction. Br J Sociol Clin Psychol. 1965;4:224–9.
4. Angst MJ, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. Anesthesiology. 2006;104:6570–87.
5. Ossipov MH, Lai J, King T, Vanderah TW, Porreca F. Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. Pept Sci. 2005;80:319–24.
6. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. Pain. 2002;100:213–7.
7. Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2007;14:145–61.
8. Grilly DM, Gowans GC. Acute morphine dependence: effects observed in shock and light discrimination tasks. Psychopharmacology (Berl). 1986;88:500–4.
9. Tilson HA, Rech RH, Stolman S. Hyperalgesia during withdrawal as a means of measuring the degree of dependence in morphine dependent rats. Psychopharmacologia. 1973;28:287–300.

10. Bederson JB, Fields HL, Barbaro NM. Hyperalgesia during naloxone-precipitated withdrawal from morphine is associated with increased on-cell activity in the rostral ventromedial medulla. Somatosens Mot Res. 1990;7:185–203.
11. Kim DH, Barbaro NM, Fields HL. Dose response relationship for hyperalgesia following naloxone precipitated withdrawal from morphine. Soc Neurosci Abstr. 1988;14:174.
12. Kim DH, Fields HL, Barbaro NM. Morphine analgesia and acute physical dependence: rapid onset of two opposing, dose-related processes. Brain Res. 1990;516:37–40.
13. Celerier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventative effect of ketamine. Anesthesiology. 2000;92:465–72.
14. Van Elstraete AC, Sitbon P, Trabold F, Mazoit JX, Berhamou D. A single dose of intrathecal morphine in rats induces long-lasting hyperalgesia: the protective effect of prior administration of ketamine. Anesth Analg. 2005;101:1750–6.
15. Ibuki T, Dunbar SA, Yaksh TL. Effect of transient naloxone antagonism in tolerance development in rats receiving continuous spinal morphine infusion. Pain. 1997;70:125–32.
16. Li X, Angst MS, Clark D. Opioid-induced hyperalgesia incisional pain. Anesth Analg. 2001;93:204–9.
17. Gardell LR, King T, Ossipov MH, et al. Opioid receptor-mediated hyperalgesia and antinociceptive tolerance induced by sustained opiate delivery. Neurosci Lett. 2005;396:44–9.
18. Mao J, Price DD, Mayer DJ. Experimental mononeuropathy reduces the antinociceptive effects of morphine: implications for common intracellular mechanisms involved in morphine tolerance and neuropathic pain. Pain. 1995;1:353–64.
19. Mayer DJ, Mao J, Holt J, Price DD. Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions. Proc Natl Acad Sci USA. 1999;96:7731–6.
20. Celerier E, Laulin JP, Larcher A, Le Moal M, Simonnet G. Evidence for opiate-activated NMDA processes masking opiate analgesia in rats. Brain Res. 1999;847:18–25.
21. Dunbar SA, Pulai IJ. Repetitive opioid abstinence causes progressive hyperalgesia sensitive to N-methyl-D-aspartate receptor blockade in the rat. J Pharmacol Exp Ther. 1998; 284:678–86.
22. Dunbar S, Yaksh TL. Concurrent spinal infusion of MK801 blocks spinal tolerance and dependence induced by chronic intrathecal morphine in the rat. Anesthesiology. 1996;84: 1177–88.
23. Larcher A, Laulin JP, Celerier E, Le Moal M, Simonnet G. Acute tolerance associated with a single opiate administration: involvement of N-methyl-D-aspartate-dependent pain facilitatory systems. Neuroscience. 1998;84:583–9.
24. Richebe P, Rivat C, Creton C, et al. Nitrous oxide revisited. Anesthesiology. 2005;105:845–54.
25. Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acids receptors and protein kinase C. J Neurosci. 1994;14:2301–12.
26. Compton PA, Ling W, Torrington MA. Lack of effect of chronic dextromethorphan on experimental pain tolerance in methadone-maintained patients. Addict Biol. 2008;13:393–402.
27. Devillers JP, Boisserie F, Laulin JP, Larcher A, Simonnet G. Simultaneous activation of spinal antiopioid system (neuropeptide FF) and pain facilitatory circuitry by stimulation of opioid receptors in rats. Brain Res. 1995;700:173–81.
28. Gardell LR, Wang R, Burgess SE, et al. Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers. J Neurosci. 2002;22:6747–55.
29. Vanderah TW, Gardell LR, Burgess SE, et al. Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. J Neurosci. 2000;20:7074–9.
30. King T, Gardell LR, Wang R, et al. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. Pain. 2005;116:276–88.
31. King T, Ossipov MH, Vanderah TW, Porreca F, Lai J. Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? Neurosignals. 2005;14:194–205.

32. Vanderah TW, Ossipov MH, Lai J, Malan Jr TP, Porreca F. Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin. Pain. 2001;92:5–9.
33. Gardell LR, King T, Ossipov MH, et al. Opioid receptor-mediated hyperalgesia and antinociceptive tolerance induced by sustained opiate delivery. Neurosci Lett. 2006;396:44–9.
34. Ossipov MH, Lai J, King T, et al. Antinociceptive and nociceptive actions of opioids. J Neurobiol. 2004;61:146–8.
35. Xie JY, Herman DS, Stiller CO, et al. Cholecystokinin in the rostral ventromedial medulla mediates opioid-induced hyperalgesia and antinociceptive tolerance. J Neurosci. 2005;25:409–16.
36. Vanderah T, Suenaga N, Ossipov M, et al. Tonic descending facilitation from the rostral ventromedial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. J Neurosci. 2001;21:279–86.
37. De Leo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. Neuroscientist. 2004;10:40–52.
38. Watkins LR, Maier SF. The pain of being sick: implications of immune-to-brain communication for understanding pain. Annu Rev Psychol. 2000;51:29–57.
39. Song P, Zhao ZQ. The involvement of glial cells in the development of morphine tolerance. Neurosci Res. 2001;39:281–6.
40. Johnston IN, Westbrook RF. Inhibition of morphine analgesia by LPS: role of opioid and NMDA receptors and spinal glia. Behav Brain Res. 2005;156:75–83.
41. Johnston IN, Milligan ED, Wieseler-Frank J. A role for proinflammatory cytokines and fractalkine in analgesia, tolerance, and subsequent pain facilitation induced by chronic intrathecal morphine. J Neurosci. 2004;24:7353–65.
42. Raghavendra V, Rutkowski MD, DeLeo JA. The role of spinal neuroimmune activation in morphine tolerance/hyperalgesia in neuropathic and sham-operated rats. J Neurosci. 2002;22:9980–9.
43. Hutchinson MR, Coats BD, Lewis SS, Zhang Y, et al. Proinflammatory cytokines oppose opioid-induced acute and chronic hyperalgesia. Brain Behav Immun. 2008;22:1178–89.
44. Tai YH, Wang YH, Wang JJ, Tao PL, Tung CS, Wong CS. Amitriptyline suppresses neuroinflammation and up-regulates glutamate transporters in morphine-tolerant rats. Pain. 2006;124:77–86.
45. Ekblom M, Hammerlund-Udenaes M, Paalzow L. Modeling of tolerance development and rebound effect during different intravenous administrations of morphine to rats. J Pharmacol Exp Ther. 1993;266:244–52.
46. Johnson SM, Duggan AW. Tolerance and dependence of dorsal horn neurons of the cat: the role of the opiate receptors of the substantia gelatinosa. Neuropharmacology. 1981;20:1033–8.
47. Laulin JP, Larcher A, Celerier E, Le Moal M, Simonnet G. Long-lasting increased pain sensitivity in rat following exposure to heroin for the first time. Eur J Neurosci. 1998;10:782–5.
48. Donnerer J. Primary sensory neurons and naloxone-precipitated morphine withdrawal. Br J Pharmacol. 1989;86:767–72.
49. Kaplan H, Fields HL. Hyperalgesia during acute opioid abstinence: evidence for a nociceptive facilitating function of the rostral ventromedial medulla. J Neurosci. 1991;11:1433–9.
50. Martin WR, Eades CG. A comparison between acute and chronic physical dependence in the chronic spinal dog. J Pharmacol Exp Ther. 1964;146:385–94.
51. Martin WR, Gilbert PE, Jasinski PE, Martin CD. An analysis of naltrexone precipitated abstinence in morphine-dependent chronic spinal dogs. J Pharmacol Exp Ther. 1987; 240:565–70.
52. Yaksh TL, Harty GJ, Onofrio BM. High doses of spinal morphine produce a nonopiate receptor-mediated hyperesthesia: clinical and theoretic implications. Anesthesiology. 1986;64:590–7.
53. Goldfarb J, Kaplan EI, Jenkins HR. Interaction of morphine and naloxone in acute spinal cats. Neuropharmacology. 1978;17:569–75.

54. Li X, Angst MS, Clark D. A murine model of opioid-induced hyperalgesia. Brain Res Mol Brain Res. 2001;86:56–62.
55. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain. 1995;62:259–74.
56. Chu L, Angst M, Clark D. Opioids in non-cancer pain: measurement of opioid-induced tolerance and hyperalgesia in pain patients on chronic opioid therapy. J Pain. 2004;5:S73.
57. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-IV-TR). 4th ed., Text revision. Arlington, VA: American Psychiatric Association; 2000.
58. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain. 2003; 106:49–57.
59. Hood DD, Curry R, Eisenach JC. Intravenous remifentanil produces withdrawal hyperalgesia in volunteers with capsaicin-induced hyperalgesia. Anesth Analg. 2003;97:810–5.
60. Compton P, Athanasos P, Elashoff D. Withdrawal hyperalgesia after acute opioid physical dependence in nonaddicted humans: a preliminary study. J Pain. 2003;4:511–9.
61. Colpaert FC. System theory of pain and of opiate analgesia: no tolerance to opiates. Pharmacol Rev. 1996;48:355–402.
62. Laulin JP, Celerier E, Larcher A, et al. Opiate tolerance to daily heroin administration: an apparent phenomenon associated with enhanced pain sensitivity. Neuroscience. 1999;89:631–6.
63. Mao J. Opioid-induced abnormal pain sensitivity. Curr Pain Headache Rep. 2006;10:67–70.
64. Colpaert FC. Mechanisms of opioid-induced pain and antinociceptive tolerance: signal transduction. Pain. 2002;95:287–8.
65. Celerier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G. Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process. J Neurosci. 2001;21:4074–80.
66. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005;118:289–305.
67. Foley KM. Opioids and chronic neuropathic pain. N Engl J Med. 2003;348:1279–81.
68. Hay JL, Kaboutari J, White JM, Salem A, Irvine R. Model of methadone-induced hyperalgesia. Eur J Pharmacol. 2010;626:229–33.
69. Hutchinson MR, Lewis SS, Coats BD, Rezvani N. Possible involvement of Toll-like receptor 4/MD-2 activity of opioid inactive isomers causes spinal proinflammation and related behavioral consequences. Neuroscience. 2010;167:880–93.
70. Davis AM, Inturrisi CE. d-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. J Pharmacol Exp Ther. 1999;289(2):1048–53.
71. Inturrisi CE. Pharmacology of methadone and its isomers. Minerva Anestesiol. 2005;71(7–8):435–7.
72. Holtman JR, Wala EP. Characterization of morphine-induced hyperalgesia in male and female rats. Pain. 2005;114:62–70.
73. Ho A, Dole V. Pain perception in drug-free and in methadone-maintained human ex-addicts. Proc Soc Exp Biol Med. 1979;162:392–5.
74. Compton MA. Cold pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. J Pain Symptom Manage. 1994;9:462–73.
75. Compton P, Charuvastra C, Kintaudi K, et al. Pain responses in methadone-maintained opioid abusers. J Pain Symptom Manage. 2000;20:237–45.
76. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. Drug Alcohol Depend. 2001;63:139–46.
77. Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. Pain. 2001;90:91–6.
78. Doverty M, Somogyi AA, White JM, et al. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. Pain. 2001;93:155–63.

79. Schall U, Katta T, Pries E, et al. Pain perception of intravenous heroin users on maintenance therapy with levomethadone. Pharmacopsychiatry. 1996;29:176–9.
80. Athanasos P, Smith CS, White JM, Somogyi AA, Bochner F, Ling W. Methadone maintenance patients are cross tolerant to the antinociceptive effects of very high plasma morphine concentrations. Pain. 2006;120:267–75.
81. Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: new evidence from a study of chronic opioid addicts and healthy subjects. Drug Alcohol Depend. 2006;82:218–23.
82. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. J Pain. 2009;10:316–22.
83. Compton P, Canamar CP, Hillhouse M, Ling W. Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy; J Pain. 2012;13:401–409.
84. Fishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS. Do opioids induce hyperalgesia in humans? An evidence-based structured review. Pain Med. 2009;10:829–39.
85. Ruscheweyh R, Stumpenhorst F, Knecht S, Marziniak M. Comparison of the cold pressor test and contact thermode-delivered cold stimuli for the assessment of cold pain sensitivity. J Pain. 2010;11:728–36.
86. Nielsen CS, Staud R, Price DDJ. Individual differences in pain sensitivity: measurement, causation, and consequences. Pain. 2009;10:231–7.
87. Peles E, Schreiber S, Gordon J, Adelson M. Significantly higher methadone dose for methadone maintenance treatment (MMT) patients with chronic pain. Pain. 2005;113:340–6.
88. Potter JS, Prather K, Weiss RD. Physical pain and associated clinical characteristics in treatment-seeking patients in four substance use disorder treatment modalities. Am J Addict. 2008;17:121–5.
89. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA. 2003;289:2370–8.
90. Peles E, Schreiber S, Hetzroni T, Adelson M, Defrin R. The differential effect of methadone dose and of chronic pain on pain perception of former heroin addicts receiving methadone maintenance treatment. J Pain. 2011;12(1):41–50.
91. Berg KM, Arnstein JH, Sacajiu G, Karaz A. Providers' experiences treating chronic pain among opioid-dependent drug users. J Gen Intern Med. 2009;24:482–8.
92. Mogil JS, Kest B, Sadowski B, Belknap JK. Differential genetic mediation of sensitivity to morphine in genetic models of opiate antinociception: influence of nociceptive assay. J Pharmacol Exp Ther. 1996;276:532–44.
93. Mogil JS, Wilson SG, Bon K, et al. Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. Pain. 1999;80:67–82.
94. Elmer GI. Differences in morphine reinforcement property in two inbred rat strains: associations with cortical receptors, behavioral activity, analgesia and the cataleptic effects of morphine. Psychopharmacology (Berl). 1993;112:183–8.
95. Elmer GI, Pieper JO, Goldberg SR, George FR. Opioid operant self-administration, analgesia, stimulation and respiratory depression in mu-deficient mice. Psychopharmacology (Berl). 1995;117:23–31.
96. Elmer GI, Pieper JO, Negus SS, Woods JH. Genetic variance in nociception and its relationship to the potency of morphine-induced analgesia in thermal and chemical tests. Pain. 1998;75:129–40.
97. Liang DY, Liao G, Lighthall GK, Peltz G, Clark DJ. Genetic variants of the P-glycoprotein gene Abcb1b modulate opioid-induced hyperalgesia, tolerance and dependence. Pharmacogenet Genomics. 2006;16:825–35.
98. Liebmann P, Lehofer M, Schonauer-Cejpek M, et al. Pain sensitivity in former opioid addicts. Lancet. 1994;344:1031–2.
99. Liebmann P, Lehofer M, Moser M, et al. Persistent analgesia in former opiate addicts is resistant to blockade of endogenous opioids. Biol Psychiatry. 1997;42:962–4.

100. Liebmann P, Lehofer M, Moser M, et al. Nervousness and pain sensitivity: II. Changed relation in ex-addicts as a predictor for early relapse. Psychiatry Res. 1998;79:55–8.
101. Prosser JM, Steinfeld M, Cohen LJ, et al. Abnormal heat and pain perception in remitted heroin dependence months after detoxification from methadone-maintenance. Drug Alcohol Depend. 2008;95:237–44.
102. Ren ZY, Shi J, Epstein DH, Wang J, Lu L. Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving. Psychopharmacology (Berl). 2009;204:423–9.
103. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain. 2006;7:43–8.
104. Cohen SP, Christo PJ, Wang S, et al. The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. Reg Anesth Pain Med. 2008;33:199–206.
105. Sweitzer SR, Allen CP, Zissen MH, Kendig JJ. Mechanical allodynia and thermal hyperalgesia upon acute opioid withdrawal in the neonatal rat. Pain. 2004;110:269–80.
106. Axelrod DJ, Reville B. Using methadone to treat opioid-induced hyperalgesia and refractory pain. J Opioid Manag. 2007;3:113–4.
107. Vorobeychik Y, Chen L, Bush MC, Mao J. Improved opioid analgesia effect following opioid dose reduction. Pain Med. 2008;9:724–7.
108. Gottschalk A, Durieux ME, Nemergut EC. Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesth Analg. 2011; 112:218–23.
109. Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE. Acute pain management in opioid-tolerant patients: a growing challenge. Anaesth Intensive Care. 2011;39:804–23.
110. Ramasubbu C, Gupta A. Pharmacological treatment of opioid-induced hyperalgesia: a review of the evidence. J Pain Palliat Care Pharmacother. 2011;25:219–30.
111. Helmy SA, Bali A. The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements. Anesth Analg. 2001;92:739–44.
112. Weinbroum A, Rudick V, Paret G, et al. The role of dextromethorphan in pain control. Can J Anaesth. 2000;47:585–96.
113. Dudgeon DJ, Bruera E, Gagnon B, et al. A phase III randomized, double-blind, placebo-controlled study evaluating dextromethorphan plus slow-release morphine for chronic cancer pain relief in terminally ill patients. J Pain Symptom Manage. 2007;33:365–71.
114. Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG. MorphiDex (morphine sulfate/dextromethorphan hydrobromide combination) in the treatment of chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance. Pain. 2005;115:284–95.
115. Haugan F, Rygh LJ, Tjølsen A. Ketamine blocks enhancement of spinal long-term potentiation in chronic opioid treated rats. Acta Anaesthesiol Scand. 2008;52:681–7.
116. Heiskanen T, Härtel B, Dahl ML, Seppälä T, Kalso E. Analgesic effects of dextromethorphan and morphine in patients with chronic pain. Pain. 2002;96:261–7.
117. Chaplan SR, Malmberg AB, Yaksh TL. Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. J Pharmacol Exp Ther. 1997;280:829–38.
118. Compton P, Kehoe P, Sinha K, Torrington MA, Ling W. Gabapentin improves cold-pressor pain responses in methadone-maintained patients. Drug Alcohol Depend. 2010; 109(1–3):213–9.
119. Singler B, Tröster A, Manering N, Schüttler J, Koppert W. Modulation of remifentanil-induced postinfusion hyperalgesia by propofol. Anesth Analg. 2007;104:1397–403.
120. Joshi W, Connelly NR, Reuben SS, Wolckenhaar M, Thakkar N. An evaluation of the safety and efficacy of administering rofecoxib for postoperative pain management. Anesth Analg. 2003;97:35–8.
121. Tröster A, Sittl R, Singler B, Schmelz M, Schüttler J, Koppert W. Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology. 2006;105:1016–23.

122. Bernstein ZP, Yucht S, Battista E, Lema M, Spaulding MB. Proglumide as a morphine adjunct in cancer pain management. J Pain Symptom Manage. 1998;15:314–20.
123. McCleane GJ. The cholecystokinin antagonist proglumide enhances the analgesic effect of dihydrocodeine. Clin J Pain. 2003;19:200–1.
124. McCleane GJ. Cholecystokinin antagonists a new way to improve the analgesia from old analgesics? Curr Pharm Des. 2004;10:303–14.
125. Koppert W, Angst M, Alsheimer M, et al. Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans. Pain. 2003;106:91–9.
126. Carroll IR, Angst MS, Clark JD. Management of perioperative pain in patients chronically consuming opioids. Reg Anesth Pain Med. 2004;29:576–91.
127. Cepeda MS, Alvarez H, Morales O, Carr DB. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. Pain. 2004;107:41–6.
128. Terner JM, Barrett AC, Lomas LM, Negus SS, Picker MJ. Influence of low doses of naltrexone on morphine antinociception and morphine tolerance in male and female rats of four strains. Pain. 2006;122:90–101.
129. Wang HY, Friedman E, Olmstead MC, Burns LH. Ultra-low-dose naloxone suppresses opioid tolerance, dependence and associated changes in mu opioid receptor-G protein coupling and Gbetagamma signaling. Neuroscience. 2005;135:247–61.
130. Webster LR. Oxytrex: an oxycodone and ultra-low-dose naltrexone formulation. Expert Opin Investig Drugs. 2007;16:1277–83.
131. Chindalore VL, Craven RA, Yu KP, Butera PG, Burns LH, Friedmann N. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex. J Pain. 2005;6:392–9.
132. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. J Pain. 2006;7:937–46.
133. Sloan P, Harmann S. Ultra-low-dose opioid antagonists to enhance opioid analgesia. J Opioid Manag. 2006;2:295–304.
134. Shaiova L, Berger A, Blinderman CD, Bruera E, Davis MP, Derby S, et al. Consensus guideline on parenteral methadone use in pain and palliative care. Palliat Support Care. 2008;6:165–76.
135. Sandoval JA, Furlan AD, Mailis-Gagnon A. Oral methadone for chronic noncancer pain: a systematic literature review of reasons for administration, prescription patterns, effectiveness, and side effects. Clin J Pain. 2005;21:503–12.

Chapter 10
Buprenorphine Analgesia in Chronic Pain

Guy Hans

Introduction

Buprenorphine, a potent centrally acting opioid analgesic, has been used extensively in clinical practice and in wide variety of settings for now 30 years [1]. Buprenorphine is an opioid analgesic with a unique physico-chemical profile. It is a derivative of the morphine alkaloid thebaine. As such, it belongs to the 6, 14-endoethanotetrahydroorivavine class of compounds that include other potent μ agonists such as diprenorphine and etorphine [2]. Buprenorphine is N-dealkylated to norbuprenorphine mainly in the liver by CYP3A4 and to a lesser extent by CYP2D6, but also by the gut wall, producing the major metabolite norbuprenorphine and several glucuronides of less importance [3]. CYP3A4 inducers, such as ritanovir, amiodarone, ketoconazole, erythromycin, but also grapefruit and star-fruit juice, will hereby elevate the serum buprenorphine level. Elimination of buprenorphine occurs independently from the application route predominantly via the gastrointestinal tract (for almost 2/3rd) with the faeces containing mainly unchanged buprenorphine and only to a lesser extent via the urine (remaining 1/3rd), which contains conjugates of the mother compound and norbuprenorphine. Renal impairment is thus not expected to cause increased plasma accumulation of the mother compound. But renal insufficiency could still lead to an increased plasma concentration of norbuprenorphine as the majority of this metabolite is excreted via the urine. Furthermore, one study showed that hemodialysis did not affect buprenorphine plasma levels, leading to stable analgesic effects during such therapy [4]. This was proven by the fact that no differences in pain relief before and after hemodialysis could be observed.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_10,

Oral administration remains still a recommended route of delivery for opioid analgesics. However, some opioids are not amenable to oral administration because of extensive first-pass metabolism and poor oral bioavailability [5]. Furthermore, some oral opioid analgesics, such as propoxyphene, are available only in immediate-release formulations, which require multiple daily doses to maintain around-the-clock pain control in patients suffering from persistent pain. Multiple daily dosing can be inconvenient and may decrease compliance, impair health-related quality of life and fail to provide sufficient around-the-clock analgesia [6–8]. Several delivery formulations of buprenorphine have been investigated over the years. The older sublingual, and intravenous formulations have been supplemented by a new polymer matrix patch system [9]. Because of its noninvasive, easily administered, and has a sustained effect, the transdermal route is beneficial in selected patients, potentially increasing adherence to the analgesic regimen [10, 11]. Transdermal delivery systems are an effective method for drug administration in patients with chronic pain [12]. The transdermal delivery system allows passive transdermal diffusion of medication over a prolonged period, while maintaining a constant therapeutic dose. Buprenorphine is a molecule which is particularly suited for transdermal delivery because of its high potency, high lipophilicity (octanol-to-water partition coefficient of 1,217), and low molecular weight (467 kDa) [13, 14]. In addition, it is able to achieve good permeability through the dermis and deep tissue layers. Hereby problems associated with oral drug formulations, such as poor absorption from the gastrointestinal tract, hepatic first-pass metabolism, and low and variable bioavailability, may be avoided. Thus, transdermal buprenorphine is particularly useful for patients who are not able to swallow properly or who have gastrointestinal disorders or preexisting nausea and vomiting (e.g., elderly, patients treated with chemotherapy, patients on intensive care units). There are currently three buprenorphine transdermal preparations available in different countries. First, a 3-day patch (Transtec®), releasing at one of three defined rates: 35, 52.5, or 70 μg/h (BUP TDS). Dose effectiveness is reached within 12–24 h, and is kept at a constant dose rate control for 96 h. In addition, there are 7-day lower dose buprenorphine patches (Butrans®, Norspan®) which are available in strengths of 5, 10, or 20 μg/h, respectively (LD-BUP TDS). Steady state is achieved by day 3 following the first application. After removal of the low dose buprenorphine transdermal patch, approximately 50 % buprenorphine concentration remains after 12–24 h. In Germany a third transdermal preparation is available, containing a combination of buprenorphine and aloe vera. Therapeutic efficacy of transdermal application of buprenorphine is achieved with daily doses of 0.5–2 mg, making it 25–50 times more potent as an analgesic, per milligram, than morphine. Rather than sitting in a reservoir, buprenorphine is incorporated into an adhesive polymer matrix, with a distinct backing layer of foil that acts as an occluding functioning system.

In recent years, it has become clear that buprenorphine cannot be classified as a typical μ-agonist. Although the emphasis of this chapter lies on the critical evaluation of the clinical effectiveness and applications of buprenorphine formulations, it seems nevertheless essential to start by providing a short overview of the most

important pharmacological features of this unique drug. More comprehensive overviews of buprenorphine's pharmacological profile can be found in recent reviews [15–19].

Buprenorphine: A Unique Receptor Agonist/Antagonist

The complex interaction of a particular opioid with any of the four different opioid receptor types (μ, κ, δ, and σ), found both peripherally and centrally, determines the pharmacological effect of an opioid compound. As mentioned earlier, buprenorphine is a semi-synthetic oripavin-derivative of the morphine alkaloid thebaine with analgesic potency 25–50 times greater than that of morphine [20]. It binds to μ-, κ-, δ-opioid and nociceptin receptors and has a unique analgesic mechanism of action—one quite different from morphine and fentanyl [21]. Buprenorphine's potent analgesic effect results from its partial agonist activity at the μ-opioid receptor, and its high affinity for this receptor results in a long duration of action, making it a possible candidate for the effective management of neuropathic pain [22].

κ_3-Opioid Receptor Antagonist

In addition to being an antagonist at the κ- and δ-opioid receptors, buprenorphine has shown some specific interaction with the κ_3-opioid receptor subtype [23]. Evidence linking this receptor to neuropathic pain shows that serotonin-specific reuptake inhibitors potentiate κ_3-receptor-mediated analgesia, while having no detectable effect on the μ-receptors [24]. Furthermore, κ-opioid agonists are potent antinociceptive agents against formalin-induced pain—both in neonates and adults—with no antinociceptive effect in the tail flick test [25].

K^+-Channel Openers

G-protein-coupled receptor (i.e., μ– and δ–opioid receptor and α_2–receptor) agonists open specific K^+ channels in neurons, namely the K_{ATP} [26, 27] and the G-protein-gated inward rectifier potassium (GIRK) channels [28]. Both types of K^+ channel are involved in opioid-induced antinociception and have been studied extensively. The opening of K_{ATP} channels seems to play an important role in morphine-induced analgesia at supraspinal, spinal, and peripheral levels. While buprenorphine has been shown to open peripheral K_{ATP} channels, it also seems to be sensitive to the effects of K_{ATP} channel openers and blockers [29]. Conversely, morphine- and methadone-induced analgesia is only modestly enhanced or attenuated by K_{ATP} channel openers and blockers, respectively, and fentanyl exhibits no

interactions with K_{ATP} agents. This suggests that at least two subgroups can be distinguished among μ-opioid receptor agonists, each inducing antinociception through different effector mechanisms. K_{ATP} channels represent novel opportunities for enhancing opioid analgesia, particularly in pain syndromes where there is altered expression of these ion channels [30, 31].

Nociceptin/Orphanin FQ Receptors

Buprenorphine exhibits a lower (50–70 %) degree of agonism at the nociceptin receptor, compared with the endogenous ligand nociceptin, which leads to antinociception via opioid receptor-like receptor-1 (ORL-1)-mediated mechanisms, particularly at high doses [32–35]. Following systemic administration of buprenorphine, this analgesic effect can be countered by simultaneous activation of supraspinal ORL-1 receptors [36]. Conversely, sole activation of spinal ORL-1 receptors by buprenorphine may lead to an important antinociceptive effect, which might explain the strong analgesic action observed after intrathecal administration of buprenorphine; [37–40] although some evidence suggests a supraspinal site of action after neuraxial administration [41, 42]. Overall, the clinical result following administration of buprenorphine, by whichever route, is dose-related analgesia and, therefore, the precise involvement of the ORL-1 receptor remains unclear [18].

Review Methodology

For the purpose of this chapter a systematic and extensive literature search was carried out using the PubMed database (from 1988 to February 2012). The search terms included buprenorphine and transdermal, as well as nociceptive pain, neuropathic pain, chronic pain, hyperalgesia, and allodynia. The data consist of double-blind randomized controlled trials (RCTs), open-label studies, retrospective analyses, observational studies, several post-marketing surveillance (PMS) studies, a number of case studies, as well as some recent high-quality reviews on buprenorphine. Some cases of abuse of intravenous buprenorphine as well as publications on administration of buprenorphine in acute pain syndromes have been excluded as they are irrelevant to the subject of this chapter. The Oxford quality scoring system, better known as the Jadad scale, was applied to independently assess the methodological quality of the included trials [43]. The results of this quality scoring are shown in Tables 10.1, – 10.3.

Table 10.1 Studies on the efficacy of BUP-TDS in heterogenous (combined types of pain) populations of pain patients

Study	Design/Methods	Condition(s)	Intervention/Control/Length of treatment	Outcome measures	Results	Quality Grade
Sittl et al., 2003 [44]	RCT (n = 157)	Chronic non-cancer and cancer pain	• BUP TDS or placebo • Up to 15 days	• Number of buprenorphine SL tablets in addition to BUP TDS • Pain intensity, pain relief and duration of sleep	• Significant less SL tablets with BUP TDS • Significant higher response rates for 35 and 55.5μg/h	4
Sorge & Sittl, 2004 [45]	RCT (n = 137)	Severe to very severe chronic non-cancer and cancer pain	• 3 patches BUP TDS (35μg/h) or placebo • 3 sequential patches	• Number of buprenorphine SL tablets in addition to BUP TDS • Pain intensity, pain relief and duration of sleep	• Significant less SL tablets with BUP TDS • No significant difference in intensity and relief of pain	4
Likar et al., 2006 [46]	Open-label follow-up study (n = 239)	Chronic moderate to severe non-cancer and cancer pain	• Long term treatment with BUP TDS (35μg/h) • Mean duration 7.5 months	• Pain relief (on a 4-point scale) • Ease of patch handling • Dose stability and escalation, adherence to therapy	• 90 % of patients with satisfactory pain relief • 78.7 % adherent to therapy	1
Przeklasa-Muszynska et al., 2011 [47]	Multicenter, non-interventional (observational), post-marketing study (n = 4030)	Moderate to severe chronic cancer and non-cancer pain	• Insufficient pain control by non-opioids • BUP TDS (35, 52.5 or 70μg/h) • Follow-up during 3 months	• Pain relief (100mm VAS) • Sleep quality • Need for additional medication • Discontinuation (reason) • Adverse drug reactions	• 73.5% decrease in mean pain intensity after 3 months • 85.9 % rated pain relief as 'very good' or 'good' • Adverse drug reactions in 0.8 % of patients	3
Griessinger et al., 2005 [48]	Open-label observational study (n = 13179)	Chronic moderate to severe non-cancer and cancer pain	• Long term treatment with different doses of BUP TDS • Average treatment time of 60.8 days	• Pain relief (on a 4-point scale) • Evaluation of adverse events	• > 80 % of patients with good or very good pain relief • 10% adverse events related to buprenorphine	1

(continued)

Table 10.1 (continued)

Study	Design/Methods	Condition(s)	Intervention/Control/Length of treatment	Outcome measures	Results	Quality Grade
Tschirner et al., 2008 [50]	Prospective post-marketing study (n = 3654)	Chronic moderate to severe non-cancer and cancer pain	• Long term treatment with different doses of BUP TDS(8 weeks) • Mean treatment time of 50.4 days	• Pain intensity on NRS-11 • Evaluation of adverse events	• Pain relief from 6.1 to 2.6 • Adverse events in 6.7%	1
Likar et al., 2007 [51]	Randomized, open-label, cross-over, comparative study (n =49)	Chronic moderate to severe non-cancer and cancer pain	• Efficacy and tolerability for different durations (3 days versus 4 days) • 12 days treatment	• Rating of treatment quality on 5-point scale • Pain relief on 5-point scale • Pain intensity on NRS-11 and MPQ • Health status, using SF-36	• Adequate quality of treatment in 93.8% • Similar pain ratings in both durations of application • SF-36 scores similar in both groups	3
Barutell et al., 2008 [52]	Retrospective study (n = 1465)	Moderate to severe pain	• Efficacy and tolerability of BUP TDS $\geq$ 52.5μg/h • Median treatment period of 3.7 months	• VAS-score • Rating of treatment quality on 5-point scale	• Absolute reduction of 25.1 points in VAS • Good or Very Good quality by 82.5% • 48.8% drug related AE	1

Table 10.2 Studies on the efficacy of BUP-TDS in neuropathic pain

Study	Design/Methods	Condition(s)	Intervention/Control/Length of treatment	Outcome measures	Results	Quality Grade
Rodriguez-Lopez, 2004 [53]	Retrospective study (n = 237)	Non-malignant neuropathic pain	• Efficacy and tolerability of BUP TDS 35 and 52.5μg/h • Treatment period of 8 weeks	• VAS-score • Sleep score	• 55% reduction in VAS score • Significant improvement in sleep score	1
Penza et al., 2008 [54]	Open-label study (n = 30)	Chronic painful neuropathy (≥ 5 on VAS)	• Efficacy and tolerability of increasing doses of BUP TDS • Treatment period of 42 days	• Number of patients achieving at least 30% pain reduction at day 42	• 13/30 achieved 30% reduction • 9/30 drop-outs, and 8/30 failed to reach outcome	1

Table 10.3 Studies on the efficacy of BUP-TDS in nociceptive (cancerous or non-cancerous) pain conditions

Study	Design/Methods	Condition(s)	Intervention/Control/Length of treatment	Outcome measures	Results	Quality Grade
Aurilio et al., 2008 [57]	Randomized, placebo-controlled study (n = 86)	Patients suffering from ischemic pain	• BUP TDS 35μg/h + epidural infusion to epidural infusion + placebo patch • Treatment period of 4 weeks	• VAS score • Short form McGill Pain Questionnaire • Pain interference with sleep	• Reduction of pain • Increased sleep and • Lower side effects with BUP TDS	5
Steiner et al., 2011 [59]	Enriched, multicenter, randomized, double-blind designs (n = 1024)	Chronic low back pain	• LD-BUP TDS 10μg/h + 20μg/h during open-label run-in period • Afterwards randomization to active or placebo treatment	• Pain score • Incidence of treatment-related events (safety evaluation)	• LD-BUP TDS group showed significant reduction in pain compared to placebo after 12 weeks • Non-significant differences in treatment-related events between active and placebo treatment	5
Karlsson & Berggren, 2009 [60]	Randomized, open-label, parallel group non-inferiority study (n = 134)	Chronic (moderate to severe) osteoarthritis pain of knee and hip	• Low dose 7-day BUP TDS (max. 20 μg/h) versus twice daily prolonged-release tramadol tablets (max 400mg/d) • 12 weeks treatment period	• BS-11 scale • Rescue medication use • Quality of sleep and sleep disturbance • Global assessment of pain relief (patient + investigator)	• Both treatments induced a clinically meaningful decrease in pain • Efficacy of BUP TDS noninferior to tramadol • Comparable incidence of adverse events in both groups	3
Poulain et al., 2008 [63]	Enriched design study (n = 289)	Opioid-tolerant cancer patients	• Efficacy and safety of BUP TDS 70μg/h versus placebo • Maintenance phase of 2 weeks, after 2 weeks run-in	• Mean pain intensity (0–10) • Mean daily sublingual buprenorphine tablet intake	• 131 patients discontinued due to adverse events or lack of efficacy • Lower daily pain intensity with BUP TDS, lower intake of buprenorphine tables and lower drop-outs with BUP TDS	4

Muriel et al., 2005 [94]	Open post-marketing surveillance study (n = 1223)	Chronic moderate to severe cancer pain (unresponsive to non-opioids)	• BUP TDS 35µg/h for majority of patients • Treatment period of 3 months	• Continuation of therapy • Pain relief	• 52% of patients continued the same treatment • 89% of patients were satisfied with treatment	1
Muriel, 2004 [95]	Open, multi-center, retrospective study (n = 164)	Moderate to severe cancer pain	• BUP TDS 35 or 52.5µg/h for majority of patients • Treatment period of 8 weeks	• Pain score	• Significant reductions in pain score after 2 and 8 weeks of treatment	1
Schutter et al., 2008 [58]	Multicenter observational study (n = 4263)	Chronic osteoarthritis pain	• Low dose 7 days buprenorphine patch	• 11-point NRS scale • Aspects of quality of life (QoL) • Need for additional analgesics	• BUP TDS leads to significant decrease in pain • Decrease in additional analgesics and better QoL • 4.5% showed side effects	1
Landau et al., 2007 [62]	Multicenter, double-blind, parallel group study (n = 588)	Non-cancer related pain for which opioid treatment was needed	• Efficacy and safety profile of BUP TDS versus placebo • Acetaminophen 500-mg tablets as rescue medication • 14 days treatment period (after 7- to 21-day run-in phase)	• Proportion of subjects with ineffective treatment • Time to ineffective R/ • Need for rescue medication • Drop-outs	• Significantly higher risk for ineffective R/ with placebo versus BUP TDS • Lower drop-outs with BUP TDS and significantly less rescue medication needed	5
Likar et al., 2008 [71]	Comparative study (n = 82)	Moderate to severe chronic pain in elderly and younger patients	• Compare efficacy and tolerability of BUP TDS • 28-day treatment period	• Pain intensity • Sleep duration • Need for rescue medication	• Significant reduction in pain from BUP TDS, without difference between age-groups • Increase in sleep duration • Need for rescue medication lowest in elderly • Comparable safety profile for all age-groups	2

Buprenorphine: Clinical Efficacy in Chronic Pain Conditions

Published results from a growing number of clinical studies demonstrate the interesting analgesic profile of buprenorphine in the treatment of diverse chronic pain conditions, often previously unresponsive to opioid therapy. Most of the clinically significant studies have been performed by using one of the previously described transdermal delivery systems.

Analgesic Efficacy of Buprenorphine in Heterogeneous Pain Conditions

Several RCTs have previously assessed the effectiveness of buprenorphine transdermal patches (BUP TDS) for the management of chronic cancer and non-cancer pain. One of these randomized, double-blind, multicentre studies, demonstrated the potential analgesic efficacy and tolerability of BUP TDS in patients with chronic pain [44]. In this study of 157 patients, BUP TDS (35 and 52.5 μg/h) was associated with a significantly higher response rate compared with placebo (36.6 % [$p<0.05$] and 47.5 % [$p<0.005$], respectively). A notable, but not significant, improvement in response (33 %) was seen with the 70 μg/h dose. Administration of BUP TDS resulted in a significant reduction (56.7 %; $p<0.005$) in administration of sublingual buprenorphine rescue analgesia as compared with placebo. The improvement in quality of sleep, in addition to the good tolerability profile and reduced need for rescue analgesia, suggests BUP TDS is beneficial for the treatment of diverse chronic pain states. In addition, this study indicated no difference in efficacy of BUP TDS between neuropathic and non-neuropathic pain conditions.

In a second double-blind RCT 137 patients were randomized to receive BUP TDS patches (72 h) or placebo [45]. Rescue therapy in both groups was provided with sublingual buprenorphine. Ninety patients received buprenorphine and 47 were treated with placebo patches. Forty five patients had cancer pain and 92 had non-cancer pain. Patients receiving BUP TDS significantly reduced their consumption of sublingual buprenorphine compared with the control group ($p=0.03$). Patients' assessment of pain intensity and relief suggested better analgesia with BUP TDS, although these results never gained statistical significance during the study protocol ($p>0.05$).

A total of 239 patients from the previously described RCTs participated subsequently in an open-label follow-up study, which demonstrated that BUP TDS was effective in controlling chronic pain over a long period, without the need of significant dose increases (lack of tolerance development) [46]. The maximum study participation was 3.4 years in cancer patients ($n=134$), and 5.7 years in non-cancer patients ($n=105$). In total, 90 % of patients reported at least satisfactory pain relief, measured using a four point verbal scale. Moreover, BUP TDS was generally well tolerated during long-term treatment both in cancer and non-cancer patients, with

the most common side effects being nausea (9.2 %), dizziness (4.6 %), vomiting (4.2 %), constipation (3.8 %), and tiredness (2.9 %). Local adverse reactions with BUP TDS included erythema (12.1 %), pruritus (10.5 %), and exanthema (8.8 %). This study provided some highly interesting clinical findings, since the results indicate the absence of development of tolerance during longer periods of treatment. In addition, incidence of side effects remained low during the prolonged treatment.

More recently, the results of a Polish multicenter, noninterventional, post-marketing study, in which 339 doctors participated, became available [47]. This study evaluated the analgesic efficacy, ease of use, safety profile and adverse drug reaction of BUP TDS during treatment of moderate to severe chronic cancer and non-cancer pain syndromes. A total of 4,030 patients were included, consisting of general practice outpatients, pain therapy center patients, specialist outpatient clinic patients, as well as patients treated in inpatients units. Patients were enrolled if their pain was not well controlled after using non-opioid analgesics. The results of this study showed high efficacy as well as good tolerability of buprenorphine, confirming its usefulness in the treatment of moderate to severe non-cancer and cancer pain that could not be effectively treated with non-opioid analgesics.

Similar results were observed during a large-scale PMS study of 13,179 patients with moderate to severe chronic cancer (25 %) or non-cancer (72 %) pain. The effectiveness and tolerability of BUP TDS were assessed over an average treatment time of 60.8 days [48]. The most frequent diagnoses in non-cancer patients were musculoskeletal disorders (77 %) and neuropathy (23 %), and the majority of patients were treated with BUP TDS 35 μg/h. In total, 80 % of patients reported good or very good pain relief with buprenorphine TDS at the final assessment (median time 63 days), compared with only 6 % at the start of the study. Good or very good pain relief was achieved in 84 % of cancer patients and 80 % of non-cancer patients. At the end of the study, only 4 % of cancer patients and 6 % of non-cancer patients reported poor or no pain relief. This study also revealed that the overall incidence of both systemic and local side effects is lower in clinical practice compared with clinical studies. Patients reported vomiting (1.6 %), nausea (4 %), constipation (1 %), pruritus (0.7 %), erythema (0.5 %), and contact dermatitis (0.8 %). Moreover, compared with PMS data of fentanyl transdermal patch (FEN TDS), long-term use of BUP TDS resulted in a lower incidence of CNS side effects [48, 49].

A more recent, but somewhat smaller, prospective multicenter PMS study obtained comparable results [50]. This study was aimed at obtaining information on the efficacy, tolerability, and safety of a transdermal buprenorphine patch in patients with moderate to severe chronic (cancer and non-cancer) pain. In addition it was evaluated to what extent a fixed change of the patch twice a week (e.g. monday morning and thursday evening) was simplofying the therapy. The evaluation included pain intensity, the dosage of the applied analgesics and additional therapies, the renal function (by serum creatinine), and adverse events. A total of 3,654 patients were treated for a mean of 50.4 days. Using the 11 point Likert-scale the mean pain intensity decreased from 6.3 at the time when patients were switched to the BUP TDS to 2.6 at the last treatment evaluation. The matrix patch was safe and

well tolerated also in patients with advanced renal insufficiency. Adverse events were reported in 6.7 % of the patients. 89.3 % of the physicians quoted to prefer transdermal buprenorphine with the two fixed patch change days per week compared to the pretreatment. From the physicians view the two fixed patch change days per week even facilitated the guidance of therapy.

Concerning this application regimen, Likar et al. investigated the possibility of a 4-day regimen instead of the usual 3-day regimen [51]. The primary recommendation contained in the prescribing information is that transdermal patches be worn for a 3-day period before application of a new patch. This single-center, randomized, open-label, crossover Phase III study was therefore conducted to evaluate the potential for extending the time the buprenorphine patch is worn from 3 to 4 days. Patients suffering from chronic moderate or severe pain of malignant or nonmalignant origin were included. Study participants had already responded to at least 4 weeks of transdermal buprenorphine, and had achieved steady-state conditions for at least 2 weeks before enrollment. The primary end point was patients' rating of the quality of treatment (analgesic efficacy and tolerability, rated on a 5-point scale: very good, good, satisfactory, poor, and inadequate) at the completion of each treatment regimen (12 days each). Also recorded were physicians' ratings of the quality of treatment; pain intensity, rated on an 11-point numerical rating scale (from 0 = no pain to 10 = worst pain imaginable) and on the McGill Pain Questionnaire (MPQ) (maximum pain = 3.0); health status, assessed using the 36-item Short-Form Health Survey (SF-36), expressed as a percentage of the best health condition (100 %); and pain relief (5-point scale: complete, good, satisfactory, slight, and none). Local skin tolerability was evaluated for objective and subjective dermatologic symptoms at the patch-application sites. Patients recorded daily pain intensities at specified times of day and night, pain relief (5-point verbal rating scale), and sleep duration ($\leq$2 h, >2–3 h, >3 to <6 h, or $\geq$6 h) in a diary. The safety profile was evaluated based on standard monitoring of adverse events, vital signs, and routine laboratory tests. Forty-nine white patients (25 women, 24 men) were enrolled; their mean (SD) age was 61.6 (11.5) years, and their mean weight was 74.7 (16.7) kg. The most common source of pain was musculoskeletal disorders (40 patients), followed by nervous system disorders (10), neoplasms (9), injuries (5), and other causes (6). Forty-one patients completed the study; two patients discontinued because of adverse events, one because of lack of efficacy, and five for nonmedical reasons. Thirty-three patients provided data perprotocol. Patients in the perprotocol population received a mean (SD) transdermal buprenorphine dose of 49.9 (38.9) μg/h. The proportion of patients in the perprotocol population rating the quality of treatment as adequate (combined ratings of very good, good, and satisfactory) was 93.9 % (31/33) for both regimens. The physicians' ratings indicated adequate quality of treatment in 93.8 % (30/32) of patients applying four patches for 3 days each and 97.0 % (32/33) of patients applying three patches for 4 days each. Mean (SD) pain intensity scores on the numerical rating scale were similar after completion of the 3- and 4-day regimens (3.73 [1.88] and 3.88 [1.75] points, respectively), as were MPQ scores (0.79 [0.67] and 0.79 [0.78]). The mean (SD) proportion of days with at least satisfactory pain relief was 83.9 % (26.1 %) and 85.6 % (24.4 %) for the

3- and 4-day regimens; the corresponding proportions of nights with at least satisfactory pain relief were 85.2 % (26.6 %) and 88.1 % (21.4 %). Continuously assessed pain intensities at specified times of day and night (numerical rating scale) did not differ significantly between regimens. Mean SF-36 health status scores did not differ significantly between regimens (total score: 37.7 % [17.0 %] and 37.7 % [17.3 %]). Mean rates of nights with good sleep quality were 28.5 % (39.9 %) for the 3-day regimen and 36.0 % (42.6 %) for the 4-day regimen. Local skin tolerability was comparable for the 3- and 4-day regimens, with objective findings (mainly erythema) at the patch-application sites in 17 of 32 and 11 of 33 patients, respectively, and subjective symptoms (mainly itching) in 16 of 32 and 13 of 33 patients. The most common adverse events in the safety population were nausea, dizziness/giddiness, and malaise/fatigue (3/49 [6.1 %] each). On the basis of the above-mentioned results [50, 51] we currently recommend our patients to apply the buprenorphine patches during 3.5 days, resulting in two fixed patch changing days per week (e.g., on Monday morning and Thursday evening). Such a regimen can avoid mistakes or confusion in patch changing.

Spanish pain centers recently completed a retrospective multicenter safety and efficacy study, assessing the effectiveness of BUP TDS in a large number of patients ($n = 1{,}465$) suffering from moderate to severe pain [52]. Pain could have any etiology. All patients suffered from pain ≥50 mm on a 0 to 100 mm visual analog scale (VAS) and were switched to BUP TDS receiving a dose of ≥52.5 μg/h for at least 14 days during the previous months. An absolute reduction of 25.1 points in VAS score was observed over a median period of 3.7 months. In addition, the VAS score was reduced by at least 10 % in 88.4 % of the patients. Incidence of episodic pain also decreased significantly. 82.5 % of the patients rated this treatment as "good" or "very good." Of all patients, 50.2 % experienced an adverse event; which in 48.8 % was drug related, and considered serious in 4.0 %.

Analgesic Efficacy of Buprenorphine in Non-cancer Pain Conditions

While the aforementioned studies assessed the efficacy of buprenorphine in heterogeneous groups of pain conditions, additional studies and reports specifically focused on non-cancer pain conditions, such as painful neuropathic syndromes (see Table 2 for summary and quality scoring). A retrospective study across 20 pain management centers assessed the effectiveness of BUP TDS (35 and 52.5 μg/h), over an 8-week period, in a total of 237 patients suffering from nonmalignant neuropathic pain [53]. Tramadol (75–110 mg/day) was provided for the treatment of breakthrough pain. Significant improvements in VAS scores ($p < 0.001$) were achieved at all endpoints compared with baseline, with a 55 % reduction in mean VAS pain scores being achieved by week 8. Improvements were most notable in those symptoms rated "severe" at baseline. Significant improvements ($p < 0.001$) in

sleep scores provided additional support for the clinical effectiveness of BUP TDS, with increases from 4.9 (±1.5) to 6.2 (±1.39) h. Finally, it was shown that buprenorphine TDS had a good safety and high user compliance profile, which improved even further over the course of the treatment.

An open-label study investigated the efficacy, safety, and tolerability of BUP TDS in 30 patients suffering from moderate to severe chronic painful neuropathies (VAS ≥5) [54]. Starting doses of 35 μg/h were increased in case of unsatisfactory pain control. Primary endpoint was the number of patients achieving at least 30 % pain relief at day 42 (in order to evaluate short- and intermediate-term efficacy). Finally, 13 patients achieved this endpoint. Nine patients dropped out for side effects, and eight patients did not meet the primary outcome. These results seem to indicate that BUP TDS induces clinically meaningful pain relief in about 40 % of the patients suffering from chronic painful neuropathies.

Although of much more limited scientific value, patient case reports often provide a valuable insight into pain management in daily clinical practice. The efficacy of BUP TDS in the treatment of nerve-injury-induced pain is further demonstrated in case reports presented by Likar and Sittl [55]. Two patients with neuropathic pain and two patients with nociceptive pain with a neuropathic component, experienced well-tolerated and prolonged pain relief, and fewer episodes of breakthrough pain with BUP TDS compared with FEN TDS. The patients switched from other opioids to buprenorphine without adverse effects and required a lower level of buprenorphine to match the level of analgesia achieved with previous opioids (70 %). Another interesting report describing two patients suffering from complex painful conditions investigated the efficacy of BUP TDS in the treatment of central neuropathic pain [56]. Results were encouraging in these patients, suggesting that this treatment option might represent a valid alternative to standard approaches for central neuropathic pain, involving for instance the administration of anticonvulsants or antidepressants.

Other studies have been examining the efficacy of buprenorphine in different types of chronic, non-cancer, pain (see Table 3). A randomized study investigated the efficacy of BUP TDS as add-on therapy in the treatment of ischemic pain [57]. This is an interesting protocol from a clinical standpoint since ischemic pain is generally considered as very difficult to treat and often unresponsive to (even strong) analgesics. Eighty-six patients were hereby randomized in two groups. In the first group, a 35 μg/h BUP TDS was applied and an additional peridural infusion of ropivacaine/morphine (200 mg + 2 mg) was established. In the second group, an identical ropivacaine and morphine epidural analgesia was obtained but a placebo patch was added on top. Visual analog scores (VAS) for pain were used as the primary efficacy parameter. In addition, short-form MPQ scores and a score for pain interference with sleep were obtained from the patients every week for a period of 4 weeks. The subjects in the BUP TDS group reported a significant reduction in pain, increased sleep, and even a lower incidence of side effects compared with the control group (all $p < 0.05$).

The efficacy and safety of the 7-day low dose buprenorphine matrix patch (LD-BUP TDS) was recently evaluated in routine clinical practice in a

multicenter observational study in 4,263 patients with chronic osteoarthritis pain [58]. During treatment a significant decrease in mean pain could be observed (6.9 before treatment to 2.9 on an 11-point scale at the end of the observation period). Furthermore, the investigators observed a decrease in need for additional analgesic medication as well as improvements in mobility and quality of sleep. Only 4.5 % of the patients displayed adverse effects, making LD-BUP TDS a safe way of chronic pain relief for osteoarthritis patients.

The clinical features of LD-BUP TDS were also assessed in patients suffering from chronic low back pain in a recently published pivotal phase 3 study (enriched, multicenter, randomized, double-blind study design) [59]. A total of 1,024 patients were initially included. Patients who tolerated and responded to transdermal buprenorphine (10 or 20 μg/h) during an open-label run-in period were randomized to either continue this treatment or receive matching placebo. Patients receiving LD-BUP TDS reported statistically significant lower pain scores at week 12 compared with placebo ($p=0.010$). The incidence of treatment-related adverse events was 55 % for the BUP TDS treatment group and 52 % for the placebo treatment group ($p>0.05$). No unanticipated safety findings were revealed during this study.

In a similar patient population (chronic osteoarthritis pain of the hip and knee) the efficacy and safety of low dose (5, 10, and 20 μg/h, with a maximum strength of 20 μg/h) BUP TDS was compared to prolonged-release tramadol tablets [60]. Eligible patients were adults with a clinical and radiologic diagnosis of OA and moderate to severe pain, while using paracetamol 4,000 mg/day for pain during the screening week. Patients were randomized in a 1:1 ratio to receive either LD-BUP TDS or twice-daily prolonged-release tramadol tablets (tablet strengths of 75, 100, 150, and 200 mg, with a maximum dosage of 400 mg/day) over a 12-week open-label treatment period. Supplementary paracetamol was available as rescue medication throughout the study. The primary end point was the difference in BS-11 scores from baseline to the completion of treatment (noninferiority was assumed if the treatment difference on the BS-11 scale was −1.5 boxes). Secondary efficacy variables were rescue medication use, sleep disturbance and quality of sleep, and patients' and investigators' global assessments of pain relief. One hundred thirty-four patients (69 receiving 7-day buprenorphine patches and 65 receiving tramadol tablets) were randomized and received ≥1 dose of study medication. A respective 98.6 and 100 % of the two treatment groups were white, with mean (SD) ages of 64.4 (11.1) and 64.2 (9.3) years. Both treatments were associated with a clinically meaningful reduction in pain from baseline to study completion. The least squares mean change from baseline in BS-11 scores in the 7-day buprenorphine patch and tramadol tablet groups was −2.26 (95 % CI, −2.76 to −1.76) and −2.09 (95 % CI, −2.61 to −1.58). The efficacy of 7-day buprenorphine patches was noninferior to that of prolonged-release tramadol tablets. The incidence of adverse events (AEs) was comparable in the two treatment groups: 226 AEs were reported in 61 patients (88.4 %) in the 7-day buprenorphine patch group, and 152 AEs were reported in 51 patients (78.5 %) in the tramadol group. The most common AEs in the 7-day buprenorphine patch group were nausea (30.4 %), constipation (18.8 %), and dizziness (15.9 %); the most common AEs in the tramadol tablet group were nausea

(24.6 %) and fatigue (18.5 %). Most patients (47/67 [70.1 %] in the 7-day buprenorphine patch group and 43/61 [70.5 %] in the tramadol tablet group) reported that they would prefer a 7-day patch to a twice-daily tablet for future pain treatment. It can therefore be concluded that in patients with chronic, moderate to severe OA pain of the hip and/or knee, LD-BUP TDS is an effective and well-tolerated analgesic which is noninferior to prolonged-release tramadol tablets.

In addition, LD-BUP TDS has also been identified as an effective and safe treatment option if a previous long-term treatment with tramadol or tilidate/naloxone became insufficient [61]. A German multicenter observational study including data of 310 patients showed that a clinically significant decrease in mean pain intensity during the day from 5.7 to 2.9 (11-point NRS scale) occurred. On physical effort during the day the mean pain intensity decreased from 7.3 to 3.8 and at night from 5.2 to 2.3. In addition, quality of life measurements, such as mobility and self-reliance, improved, including quality of sleep.

Another multicenter, double-blind, parallel-group study compared the efficacy of low dose buprenorphine transdermal 7-day patches and placebo in subjects with persistent non-cancer pain who required opioid analgesics [62]. Five hundred eighty-eight adult subjects with at least a 2-month history of non-cancer-related pain for which they received oral opioid combination agents entered the open-label run-in phase. Subsequently 267 were randomized to the double-blind treatment (129 LD-BUP TDS, 138 placebo). The primary efficacy variable was the proportion of subjects with ineffective treatment during the double-blind evaluation phase. The secondary efficacy variables were the time to ineffective treatment or patients who discontinued for reasons other than ineffective treatment and use of escape medication. The results clearly indicated that the odds of ineffective treatment were 1.79 times greater for placebo than for LD-BUP TDS ($p = 0.022$). Other indicators of effective treatment, such as discontinuation for reason of ineffective therapy, showed also significantly higher results in the buprenorphine treated patient population. The mean amount of escape medication was significantly lower in the LD-BUP TDS group than in the placebo group (1.7 vs. 2.2 acetaminophen tables per day, $p = 0.015$). A limitation of this study is that it did not incorporate direct validated measures of pain control, such as the visual analog scale (VAS).

Analgesic Efficacy of Buprenorphine in Malignant Diseases

Other studies have been focusing on the treatment of cancer pain (see Table 3 for overview) of which some are discussed below. A company sponsored study has investigated the efficacy and safety of BUP TDS in patients suffering from severe cancer pain [63]. Two hundred eighty-nine cancer patients were included in a randomized, placebo-controlled study with an enriched design, making this study the largest placebo-controlled study ever performed in patients with cancer. Treatment with BUP TDS 70 µg/h was compared to placebo in opioid-tolerant cancer patients requiring strong opioid in a dose range of 90–150 mg/day oral morphine

equivalents. All patients first entered a run-in phase during which they were converted to BUP TDS. Those patients who could be stabilized on BUP TDS were then randomized to transdermal buprenorphine patches or placebo patches for a 2-week maintenance phase. Hundred patients discontinued treatment during the run-in phase due to lack of efficacy or adverse events, while 189 patients continued treatment in the maintenance phase (94 BUP TDS vs. 95 placebo). Of these 31 discontinued treatment, a vast majority came from the placebo treatment group (24 vs. 7 BUP TDS). A significantly higher number of patients responded well to the treatment in the buprenorphine group vs. the placebo group (74.5 % vs. 50 %, $p = 0.0003$). These responder results were further supported by lower daily pain intensities, lower intake of rescue medication (buprenorphine sublingual tablets), and lower dropout rates in the BUP TDS group. It should be noted that even during the run-in period, the mean daily pain intensity and the mean daily intake of rescue medication both decreased in 70 % of patients during the first 12 h following active patch application, indicating a rapidly developing distinct analgesic response from BUP TDS.

In recent years, the first reports have been emerging regarding the effective use of BUP TDS in young children (aged 3–5 years) suffering from cancer pain [64]. In all cases distinct decreases in pain scores were observed, with reduction of the overall amount of medications (especially opioids) and improvement of uninterrupted sleep. Although only limited data is available on the use of transdermal buprenorphine in children, these cases indicate that BUP TDS could allow good analgesia without significant side effects in children suffering from severe cancer-related pain.

Recently the findings of an expert panel consensus were published concerning the role of transdermal buprenorphine in the treatment of cancer pain [65]. The consensus was that transdermal buprenorphine has a valuable role to play in the treatment of chronic cancer pain because of its efficacy and good safety and tolerability profile, including a low risk of respiratory depression, a lack of immunosuppression, and a lack of accumulation in patients with impaired renal function. The registered dose range of 35–140 μg/h was considered adequate to achieve sufficient pain relief in most patients although some members of the panel presented data showing that increases beyond this dose range provided improved pain relief if slow titration is used. However, it was generally felt that more evidence was needed before this could become generally acceptable. Nevertheless, a number of general recommendations were made. Large-scale, randomized clinical studies are needed to provide product comparisons on the use of analgesics in the treatment of neuropathic pain although it was recognized that such studies may not be practicable. Physicians should be made more aware of the problem of hyperalgesic effects of some opioids in long-term use. Buprenorphine in contrast has been described to exert an antihyperalgesic effect [66]. The development of analgesic tolerance with some opioids in long-term use and the lack of it with buprenorphine requires further studies.

Finally, in contrast to older beliefs that the use of buprenorphine would prevent future use of opioids (due to an irreversible and permanent blocking of opioid receptors by buprenorphine), it has been shown that use of BUP TDS in cancer patients

does not impede them from future opioid therapies [67]. The aim of this study was to confirm that the concomitant presence of transdermal fentanyl (FEN TDS) and transdermal buprenorphine (BUP TDS) may be feasible without important consequences, using doses presumed to be equianalgesic. A prospective "N of 1" study was carried out in a sample of volunteers with cancer pain receiving stable doses of FEN TDS or BUP TDS, with adequate pain and symptom control. In the study design, each patient provided data before and after a switch from one opioid to the other and then back to the previous one. Sixteen patients receiving daily stable doses of 0.6 or 1.2 mg of FEN TDS were switched to BUP TDS using an FEN-BU ratio of 0.6–0.8. After 3 days, the buprenorphine patch was removed and a fentanyl patch was placed for another 3 days. Six patients receiving buprenorphine were switched to FEN TDS and then rotated back to BUP TDS with the same dosing considerations. No statistical differences in changes in pain and symptom intensity during switching and between the two different sequences were observed. No significant changes in rescue doses of oral morphine were reported at the same intervals. These results clearly indicate that cancer patients receiving stable doses of transdermal fentanyl or buprenorphine can be safely switched to an alternative transdermal opioid. Safe and efficacious opioid rotation from high-dose morphine to BUP TDS has also been demonstrated in different types (musculoskeletal, cancer, and neuropathic) of severe chronic pain [68]. A final study assessed the efficacy and tolerability of an alternative transdermally applied opioid (either fentanyl or buprenorphine) in 32 patients with chronic cancer pain receiving insufficient analgesia using their present treatment [69]. Sixteen patients were switched from FEN TDS to BUP TDS (75 μg/h fentanyl converted to 52.5 μg/h buprenorphine) and 16 from BUP TDS to FEN TDS (70 μg/h buprenorphine converted to 25 μg/h of fentanyl). The dosage applied was 50 % of that indicated in equipotency tables. Pain relief was assessed at weekly intervals for the next 3 weeks. There was no significant difference in either pain relief or rescue medication use between the two patient groups. The number of patients with adverse events decreased during the study. These results clearly indicate that opioid switching at 50 % of the calculated equianalgesic dose produces a significant reduction in pain levels and rescue medication.

Application of Buprenorphine in Special Patient Populations

Buprenorphine is increasingly investigated in special patient populations such as elderly and children. A multicenter, prospective, observational study ($n=93$) evaluated the efficacy and safety of BUP TDS in elderly patients with chronic non-cancer pain [70]. 74.2 % of the patients had suffered pain for more than 12 months before inclusion into the trial, and in most cases pain was due to osteoarthritis. Mean age was 79.7 years. The specific aim of this trial was to assess the cognitive and behavioral status of patients during treatment. For this mean outcomes were assessed using the Mini-Mental State Examination (MMSE), the 17-item Hamilton

Depression Scale (HAM-D17), the Neuropsychiatric Inventory, the Barthel Index, the Short-Form Health Survey (SF-12), a verbal numeric rating scale and the Cumulative Illness Rating Scale (CIRS). The results clearly indicated that BUP TDS treatment was associated with a decrease in pain severity, without negative effects on the central nervous system. On the HAM-D scale reproductions in both the psychological and somatic scores were observed. On the MMSE, comparable findings were observed at the beginning and at the end of the study. SF-12 showed improvements in physical and mental status. CIRS values at baseline and at the end of the study were superimposable, indirectly confirming the tolerability and safety profile of the drug in this population.

An interesting study—in this perspective—compared the analgesic efficacy and tolerability of BUP TDS in patients over and under 65 years of age [71]. A group of elderly were hereby compared to two younger equally sized populations, all requiring analgesic treatment for moderate to severe chronic pain of diverse etiology. During the 28-day treatment period potential differences in responsiveness (pain intensity, rescue medication, and sleep duration) were observed. Two-thirds of the patients completed the study, with similar rates and reasons for premature study termination in all age-groups. Pain intensities significantly decreased from pretreatment until the end of the study without differences between age-groups. At the end of the study period daily mean pain intensities were even significantly lower in elderly patients as compared with both younger age-groups. In addition, need for rescue medication was the lowest in elderly patients. Most prominent side effects were dizziness, nausea, and local skin tolerability issues with comparable percentages in all groups. This study clearly indicated that BUP TDS treatment in elderly patients above the age of 65 years is at least as effective, tolerable, and safe as in younger patients. With the increasing age of patients suffering from pain, the results of this study will undoubtedly have an important clinical impact in the future. As a matter of fact, this good tolerability of BUP TDS in elderly has recently been confirmed by a consensus statement report [72]. Its advantages in elderly have also thoroughly been described in a recent review paper [73].

Analgesic Tolerance of Buprenorphine

Analgesic tolerance is an important factor to consider when choosing the most effective treatment for the management of chronic pain. The risk of dose escalation is higher with full-opioid agonists such as fentanyl because when they bind to μ-opioid receptors down-regulation of these receptors results from the cell surface. Down-regulation of opioid receptors does not seem to occur during buprenorphine treatment [20].

A retrospective data analysis reveals BUP TDS maintains effective pain control in patients with cancer ($n = 446$) and non-cancer pain ($n = 448$), for at least 3 months, without the need to increase dose significantly [74]. Significantly higher increases in mean doses of FEN TDS ($p < 0.05$) were documented compared with BUP TDS,

which suggests a higher risk of analgesic tolerance development with fentanyl as compared with buprenorphine. These results are supported by a more recent study by Sittl et al. [75]. This retrospective analysis used data from the IMS Disease Analyzer-Mediplus database, which contains patient-related data documented by 400 medical practices in Germany. Data from patients with non-cancer pain ($n=631$) or cancer pain ($n=605$) with BUP TDS or FEN TDS for at least 3 months were analyzed. Results showed significantly greater dose stability ($p<0.05$) in patients, with cancer and non-cancer pain, taking BUP TDS as compared with FEN TDS [75]. A significant larger proportion of patients receiving BUP TDS had stable dosages over the entire treatment period compared with patients receiving FEN TDS (non-cancer groups: 56.9 % vs. 41.6 %; cancer groups: 50.0 % vs. 26.2 %; both $p<0.05$). It should be noted however that the results of this study should be analyzed with great care. Indeed, data of this database were primarily reflecting the prescription practice of GPs rather than a clinical phenomenon. Therefore this study only provides circumstantial evidence of the development of analgesic tolerance.

Clinical Safety and Cost-Effectiveness

The safety of buprenorphine has been documented in numerous clinical studies, with the incidence of adverse effects, typical of this drug class, being lower than other opioids used in an identical clinical setting [76]. This is possibly due to buprenorphine's "bell-shaped" dose–response curve being applicable to the spectrum of adverse events [14]. The majority of systemic effects occur in the central nervous system and gastrointestinal tract and include nausea, dizziness, and constipation. Randomized trials have shown that local adverse events, resulting from BUP TDS, occur in <25 % of patients in routine clinical practice [9]. The relatively slow receptor dissociation of buprenorphine may cause fewer symptoms of opioid withdrawal than morphine following cessation of therapy [2] and there appears to be a ceiling to its effects on respiratory function [76, 77]. In a recent study by Dahan et al. [77] the dose–response relationship of intravenous buprenorphine (dose range 0–0.6 mg) was determined in healthy volunteers, and compared to a full μ-opioid receptor agonist with high intrinsic activity, fentanyl (dose range 0–0.5 mg). First, fentanyl, but not buprenorphine, caused immediate respiratory arrest upon infusion at doses greater than 0.3 mg, lasting 3–8 min. Second, when plotting the dose against the time-effect data (expressed as area-under-the-curve, a measure of the overall respiratory effect of the drug) a linear relationship was shown for fentanyl, but nonlinear for buprenorphine with a ceiling at doses of 0.2 mg and greater. These distinctive pharmacodynamic respiratory effects of buprenorphine—lack of apnoea after even high doses and the development of ceiling effect on respiratory function—have evident clinical advantages over other opioids such as fentanyl and morphine, contributing to the concept that buprenorphine is exceptionally safe to use. Moreover, data indicate that ceiling of respiratory effect occurs at a much lower dose (0.1 mg/kg) than the ceiling in analgesic effect (1.0–3.0 mg/kg), which

indicates the relative safety of buprenorphine combined with its ability to produce effective analgesia [76, 77]. Finally, in the unlikely event of buprenorphine-induced respiratory depression, the effect can be fully reversed with continuous administration of naloxone [78] as well as doxapam [79].

Recently several studies have been reviewing or investigating the safety profile of BUP TDS in specific patient populations which are especially vulnerable to drug-induced side effects. As such, a prospective, open-labeled, controlled trial compared the gastrointestinal symptoms of oral sustained-release hydromorphone, FEN TDS, and BUP TDS in patients with cancer pain [80]. Mobility, pain, and gastrointestinal symptoms were assessed directly and per selected item on the Eastern Cancer Oncology Group (ECOG) and European Organisation for Research and Treatment of Cancer (EORTC) questionnaires, as well as the numeric rating scale. Only 15 % of patients suffered from constipation. The incidence of stool free periods for more than 72 h was significantly higher with transdermal opioids (FEN TDS: 22 % and BUP TDS: 21 %) than with oral hydromorphone (2 %). Nausea, consumption of emetics, and laxatives did not differ significantly between the three treatment groups. However, score for emesis was significantly higher for oral hydromorphone compared to the transdermal opioids.

Furthermore, it should be noted that the previously mentioned large-scale study in cancer patients, [63] showed a reduced incidence of adverse events in the maintenance phase compared to the run-in period. Indeed, TDS formulations are expected to reduce adverse events by slowly releasing the drug into the bloodstream and maintaining a steady plasma concentration. Reduced side effects, especially for constipation, were repeatedly reported for transdermal systems and may be related to a bypass of enteral opioid receptors [81]. The constipation rate in this study was 7.4 %, which was comparable to previous results with BUP TDS and lower than FEN TDS or sustained-release morphine (producing rates between 20 and 44.5 %).

Tassinari et al. reviewed the adverse effects of transdermal opioids to long-acting morphine in the treatment of moderate to severe cancer pain [82]. They identified four trials, comparing the safety of FEN TDS and BUP TDS and slow-release oral morphine in 425 patients. A significant difference in favor of transdermal opiates was observed for constipation, and patients' preference. No significant differences were observed for overall adverse effects, overall gastrointestinal adverse effects, overall neurologic adverse effects, nausea, somnolence, hypoventilation, trial withdrawal, and changes in opioid treatments. Another prospective trial focused on the gastrointestinal symptoms occurring under opioid therapy [83]. The purpose of this trial was to evaluate the effect of long-term treatment with oral sustained-release hydromorphone, FEN TDS, and BUP TDS on nausea, emesis, and constipation. Randomly selected outpatients with cancer pain receiving one of the study medications were enrolled in a prospective, open-labeled, controlled trial ($n = 174$). Mobility, pain, and gastrointestinal symptoms were assessed directly and per selected item on the ECOG, EORTC questionnaires, NRS (Numerical Rating Scales), and analyzed statistically. Overall, only 15 % of patients suffered from constipation. Fifty-nine percent took the prescribed laxatives. The incidence of stool free periods >72 h was significantly higher with transdermal opioids (FEN

TDS: 22 %; BUP TDS: 21 %; oral hydromorphone: 2 %; $p=0.003$). Twenty-one percent of patients revealed nausea and emesis. The mean NRS for nausea (FEN TDS:1.3; BUP TDS: 1.2; oral hydromorphone: 1.5; $p=0.6$), the consumption of antiemetics (FEN TDS: 42 %; BUP TDS: 33 %; oral hydromorphone: 36 %; $p=0.6$) and laxatives (FEN TDS: 53 %; BUP TDS: 66 %; oral hydromorphone: 61 %; $p=0.2$) did not differ significantly, in contrast to the score for emesis (FEN TDS: 16 %; BUP TDS: 13 %; oral hydromorphone: 33 %; $p=0.02$). The authors conclude that gastrointestinal symptoms of cancer pain patients undergoing an opioid therapy are related to multifactorial causes. Transdermal opioids hereby showed no benefit over oral controlled-release hydromorphone with regard to gastrointestinal symptoms.

Finally, the authors of some publications on the management of chronic pain in elderly also concluded that transdermal buprenorphine can be used in clinical practice safely and efficaciously for treating chronic pain in elderly [71]. Despite the very limited available evidence form preclinical and clinical work buprenorphine treatment can nevertheless, due to its minor immunosuppressive effects, be recommended for use in elderly patients [72].

Opioids are known to greatly impact the central nervous system. These side effects, such as dizziness and confusion, have been shown to lead to an increased risk of falling with subsequent fractures and sometimes long-lasting disability. In Germany, a Markov health economic model was developed to investigate the cost-effectiveness of the most commonly used strong opioids, hereby focusing on opioid-related fractures. The most frequently prescribed strength/package-size combinations of these opioids were taken into consideration. The results of this analysis predict that BUP TDS is dominant compared to TD fentanyl and oxycodone by showing better life years gained/quality adjusted life years (QALY) [84]. As such, BUP TDS represents a cost-effective treatment option vs. morphine in patients with chronic pain. A highly interesting, study assessed the cognitive and psychomotor performance under long-term treatment with BUP TDS in 30 non-cancer patients [85]. A computerized test battery, developed to assess driving ability, was used. Attention reaction, visual orientation, motor coordination, and vigilance were hereby evaluated. According to tests that predict driving ability, patients receiving transdermal buprenorphine were shown to be noninferior to the control group. Due to the individual variability of test results, an individual assessment is always recommended.

Effective pain management depends upon balancing the effectiveness of a drug with its side effects. The specific pain management needs of patients vary and, therefore, flexible, yet careful, dose titration is the best way to achieve balanced pain management. When low dose patches are not available, cutting buprenorphine TDS patches may offer a practical solution to gradual dose titration and finding the optimal dose for the individual patient. Louis reports five case studies in which three patients had mixed pain, including neuropathic pain [86]. Two patients used one half of a 35 μg/h buprenorphine patch and one used one-quarter of a 35 μg/h buprenorphine patch, titrated to one 70 μg/h BUP TDS patch at 3 months.

One of the most particular and common adverse events with BUP TDS are site-specific adverse effects. These include erythematous regions around the patch site

(approximately 20 % incidence) and pruritus at the patch-application site. Of the latter one of the previously described studies reported an incidence of 9.3 %, vs. 5.1 % after application of placebo patches [62]. A double series of case reports described the problem of allergic contact dermatitis to BUP TDS [87, 88]. Patients developed persistent, pruritic erythematous plaques at the contact sites, with sometimes even generalized skin eruption [88]. Most of these patients also reacted to transdermal buprenorphine (without the transdermal delivery system), the placebo being negative. This skin irritancy seems to be perhaps the most negative clinical finding, and remains often difficult to manage in routine clinical setting. In another study, the skin irritation potential of a single application of transdermal fentanyl and transdermal buprenorphine patches was compared in healthy volunteers [89]. Forty-six healthy males and females (mean age [range]: 59.6 [50–69] years) with healthy skin received a single dose of both the FEN TDS 25 μg/h patch and the BUP TDS 35 μg/h patch in a randomized order. The incidence and severity of erythema was assessed at various timepoints after patch removal. The results indicate that there was a nonsignificant trend towards a higher incidence of erythema 60 min after patch removal with BUP TDS compared with transdermal fentanyl. The severity of erythema at 60 min and the incidence of erythema at 72 h after patch removal were significantly higher with BUP TDS than with FEN TDS ($p=0.01$ and 22 % vs. 4.9 %, $p=0.04$, respectively). In general, the results from the chromametric assessment of treated skin were in agreement. The incidence of topical adverse events (AEs) was lower with FEN TDS than with BUP TDS (one vs. six events) and subjects preferred the fentanyl patch and felt it was less noticeable on the skin. The FEN TDS was considered less painful to remove, and, consistent with that, the BUP TDS patch was judged to have better adhesion properties.

Finally, one should also consider other conditions when applying transdermal patches. Skin burns associated with metal containing transdermal patches have been reported with magnetic resonance imaging and external cardiac defibrillation. Transdermal drug delivery systems contain a drug reservoir in either a liquid or a matrix form (the last being the case for the buprenorphine transdermal systems). This is sandwiched between a protective and adhesive lining on the exterior and a release membrane on the interior of the patch. The protective lining may contain a metal foil usually comprising of aluminium, which is the case in patches containing buprenorphine [90]. In addition, a case was reported of a patient who suffered a dermal burn following a defibrillation due to a 7-day transdermal patch (20 μg/h) being positioned over an implantable cardioverter defibrillator (ICD). Skin lesions appeared 5 days after the ICD delivered defibrillations (15 J at 53 Ω impedance) to treat episodes of ventricular tachycardia complicated by syncope. The burn area corresponded to the drug delivery section containing aluminium foil [90].

Recently, the pharmacokinetics, analgesic efficacy, and irritancy potential of a new transdermal delivery system of buprenorphine (Buprederm®) were evaluated in rodents [91]. Interestingly, no skin irritation was demonstrated in rabbits after repeated Buprederm application. This new transdermal delivery system holds great promise to reduce the occurrence of skin irritation, but further clinical studies will need to prove its real-life value. In the mean time, several measures can be taken to

prevent the occurrence of such skin irritation or at least reduce its severity. Preemptive treatment of the skin with a transparent by permeable film or topical application of a fluticason containing aerosol before each application of a new patch can effectively reduce the occurrence and intensity of skin reactions.

Future Perspectives: New Applications of Buprenorphine

In recent years, with expanding use of the transdermal buprenorphine patches, new challenging areas of clinical application have been identified. One of the most promising applications is the use of the transdermal buprenorphine in an intensive care setting. Many of these critically ill patients suffer from prolonged severe pain conditions (e.g., posttraumatic pain, critical illness neuropathy, visceral pain syndromes), requiring sedation and intravenous administration of (high doses) of opioids for longer periods of time. This application is often complicated by (rapid) development of opioid-induced hyperalgesia (OIH) whereby opioid administration results in a lowering of pain threshold, clinically manifest as apparent opioid tolerance, worsening pain and abnormal pain sensations such as allodynia (for review see [92, 93]). Once OIH is diagnosed or provisionally considered, treatment strategies could include opioid dose reduction, use of agents with NMDA receptor antagonism, but also opioid rotation. The very specific (multimodal) pharmacological features of buprenorphine render this drug especially interesting for use in this patient population. Experience in our center has repeatedly indicated that treatment with BUP TDS is very useful in critically ill patients.

Additionally, BUP TDS should be more often considered as a first-line therapeutic option in posttraumatic patients at the beginning of their (long-term) revalidation. In these cases treatment with buprenorphine patches could be initiated immediately postoperatively, providing the transition from more invasive analgesic treatments (e.g., neuraxial or peripheral nerve blocks, PCA pumps) to prolonged continuous systemic analgesic therapy. Such treatment with BUP TDS can easily be tailored to the healing process of the patients, with decreasing doses as the patient recovers from the sustained injuries.

Conclusions

The pharmacological and clinical profiles of buprenorphine have been documented in a growing number of clinical studies, demonstrating buprenorphine's potential effectiveness in the treatment of diverse chronic pain conditions. Buprenorphine shows no relevant analgesic ceiling effect throughout the therapeutic dose range, but indeed has a ceiling effect for respiratory depression as well as other side effects. Most notably, buprenorphine seems to be potentially effective in the management of chronic nociceptive pain syndromes as well as neuropathic hyperalgesic states

and syndromes characterized by the presence of pronounced central sensitization. In addition, there seems to be no development of tolerance during long-term treatment. Finally, buprenorphine can be safely used in vulnerable patient populations, such as elderly and patients with renal impairment.

References

1. Heel RC et al. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17(2):81–110.
2. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. J Pain Symptom Manage. 2005;29(3):297–326.
3. Rance MJ, Shillingford JS. The metabolism of phenolic opiates by rat intestine. Xenobiotica. 1977;7(9):529–36.
4. Filitz J et al. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006;10(8):743–8.
5. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain. 2002;18(4 Suppl):S3–13.
6. Eisen SA et al. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med. 1990;150(9):1881–4.
7. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296–310.
8. Richter A, et al. The impact of reducing dose frequency on health outcomes. Clin Ther. 2003;25(8):2307–35; discussion 2306.
9. Bohme K. Buprenorphine in a transdermal therapeutic system–a new option. Clin Rheumatol. 2002;21 (Suppl 1):S13–6.
10. Budd K. Buprenorphine and the transdermal system: the ideal match in pain management. Int J Clin Pract Suppl. 2003;(133):9–14; discussion 23–4.
11. Vallerand AH. The use of long-acting opioids in chronic pain management. Nurs Clin North Am. 2003;38(3):435–45.
12. Kalia YN, Merino V, Guy RH. Transdermal drug delivery. Clinical aspects. Dermatol Clin. 1998;16(2):289–99.
13. Budd K. High dose buprenorphine for postoperative analgesia. Anaesthesia. 1981;36(9): 900–3.
14. Walsh SL et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569–80.
15. Lutfy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol. 2004;2(4):395–402.
16. Cowan A. Buprenorphine: new pharmacological aspects. Int J Clin Pract Suppl. 2003;(133): 3–8; discussion 23–4.
17. Hans G, Schmidt BL, Strichartz G. Nociceptive sensitization by endothelin-1. Brain Res Rev. 2009;60(1):36–42.
18. Faymonville ME, Libbrecht D. [Transdermal buprenorphine: a current overview of pharmacological and clinical data]. Rev Med Liege. 2008;63(11):671–6.
19. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain. 2009;13(3):219–30.
20. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol. 1977;60(4):537–45.
21. McCormack K, Prather P, Chapleo C. Some new insights into the effects of opioids in phasic and tonic nociceptive tests. Pain. 1998;78(2):79–98.
22. Hans G. Buprenorphine–a review of its role in neuropathic pain. J Opioid Manag. 2007; 3(4):195–206.

23. Pick CG et al. Pharmacological characterization of buprenorphine, a mixed agonist–antagonist with kappa 3 analgesia. Brain Res. 1997;744(1):41–6.
24. Schreiber S et al. The antinociceptive effect of fluvoxamine. Eur Neuropsychopharmacol. 1996;6(4):281–4.
25. McLaughlin CR, Tao Q, Abood ME. Analysis of the antinociceptive actions of the kappa-opioid agonist enadoline (CI-977) in neonatal and adult rats: comparison to kappa-opioid receptor mRNA ontogeny. Drug Alcohol Depend. 1995;38(3):261–9.
26. Sanchez JA et al. Modulation of reconstituted ATP-sensitive K(+)-channels by GTP-binding proteins in a mammalian cell line. J Physiol. 1998;507(Pt 2):315–24.
27. Wada Y et al. A region of the sulfonylurea receptor critical for a modulation of ATP-sensitive K(+) channels by G-protein betagamma-subunits. EMBO J. 2000;19(18):4915–25.
28. Mark MD, Herlitze S. G-protein mediated gating of inward-rectifier K+ channels. Eur J Biochem. 2000;267(19):5830–6.
29. Ocana M et al. Subgroups among mu-opioid receptor agonists distinguished by ATP-sensitive K+ channel-acting drugs. Br J Pharmacol. 1995;114(6):1296–302.
30. Wood JN, et al. Ion channel activities implicated in pathological pain. Novartis Found Symp. 2004;261:32–40; discussion 40–54.
31. Yang EK et al. Altered expression of potassium channel subunit mRNA and alpha-dendrotoxin sensitivity of potassium currents in rat dorsal root ganglion neurons after axotomy. Neuroscience. 2004;123(4):867–74.
32. Bloms-Funke P et al. Agonistic effects of the opioid buprenorphine on the nociceptin/OFQ receptor. Peptides. 2000;21(7):1141–6.
33. Hawkinson JE, Acosta-Burruel M, Espitia SA. Opioid activity profiles indicate similarities between the nociceptin/orphanin FQ and opioid receptors. Eur J Pharmacol. 2000;389(2–3): 107–14.
34. Huang P et al. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. J Pharmacol Exp Ther. 2001;297(2): 688–95.
35. Wnendt S et al. Agonistic effect of buprenorphine in a nociceptin/OFQ receptor-triggered reporter gene assay. Mol Pharmacol. 1999;56(2):334–8.
36. Lutfy K et al. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. J Neurosci. 2003; 23(32):10331–7.
37. Hentz JG et al. The use of intrathecal morphine in thoracic anesthesia. J Cardiothorac Anesth. 1989;3(5 Suppl 1):24.
38. Lundborg CN et al. Progressive systemic sclerosis: intrathecal pain management. Reg Anesth Pain Med. 1999;24(1):89–93.
39. Nitescu P et al. Continuous infusion of opioid and bupivacaine by externalized intrathecal catheters in long-term treatment of “refractory” nonmalignant pain. Clin J Pain. 1998; 14(1): 17–28.
40. Tejwani GA, Rattan AK. The role of spinal opioid receptors in antinociceptive effects produced by intrathecal administration of hydromorphone and buprenorphine in the rat. Anesth Analg. 2002;94(6):1542–6, table of contents.
41. Guirimand F et al. Effects of intrathecal and intracerebroventricular buprenorphine on a C-fiber reflex in the rat. J Pharmacol Exp Ther. 1995;275(2):629–37.
42. Inagaki Y, Mashimo T, Yoshiya I. Mode and site of analgesic action of epidural buprenorphine in humans. Anesth Analg. 1996;83(3):530–6.
43. Jadad AR et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
44. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2003;25(1):150–68.
45. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2004; 26(11): 1808–20.

46. Likar R, Kayser H, Sittl R. Long-term management of chronic pain with transdermal buprenorphine: a multicenter, open-label, follow-up study in patients from three short-term clinical trials. Clin Ther. 2006;28(6):943–52.
47. Przeklasa-Muszynska A, Dobrogowski J. Transdermal buprenorphine in the treatment of cancer and non-cancer pain—the results of multicenter studies in Poland. Pharmacol Rep. 2011; 63(4):935–48.
48. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice–a post-marketing surveillance study in 13,179 patients. Curr Med Res Opin. 2005;21(8):1147–56.
49. Radbruch L et al. Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. Palliat Med. 2001;15(4):309–21.
50. Tschirner M, Ritzdorf I, Brunjes R. [Post marketing surveillance study with an analgesic (transdermal buprenorphine patch) in patients with moderate to severe chronic pain]. MMW Fortschr Med. 2008;150 (Suppl 3):142–8.
51. Likar R et al. Transdermal buprenorphine patches applied in a 4-day regimen versus a 3-day regimen: a single-site, Phase III, randomized, open-label, crossover comparison. Clin Ther. 2007;29(8):1591–606.
52. Barutell C et al. High dose transdermal buprenorphine for moderate to severe pain in spanish pain centres–a retrospective multicenter safety and efficacy study. Pain Pract. 2008;8(5): 355–61.
53. Rodriguez-Lopez M. Transdermal buprenorphine in the treatment of neuropathic pain. Rev Soc Esp Dolor. 2004;11:S11–21.
54. Penza P et al. Short- and intermediate-term efficacy of buprenorphine TDS in chronic painful neuropathies. J Peripher Nerv Syst. 2008;13(4):283–8.
55. Likar R, Sittl R. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. Anesth Analg. 2005;100(3):781–5, table of contents.
56. Guetti C et al. Transdermal buprenorphine for central neuropathic pain: clinical reports. Pain Pract. 2011;11(5):446–52.
57. Aurilio C, et al. Treatment of ischemic pain in patients suffering from peripheral vasculopathy with transdermal buprenorphine plus epidural morphine with ropivacaine vs. epidural morphine with ropivacaine. Pain Pract. 2008;31(2):61–70.
58. Schutter U, Ritzdorf I, Heckes B. [Treatment of chronic osteoarthritis pain: effectivity and safety of a 7 day matrix patch with a low dose buprenorphine]. MMW Fortschr Med. 2008;150 (Suppl 2):96–103.
59. Steiner DJ et al. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage. 2011;42(6):903–17.
60. Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group noninferiority study. Clin Ther. 2009;31(3):503–13.
61. Schutter U, Ritzdorf I, Heckes B. [The transdermal 7-day buprenorphine patch—an effective and safe treatment option, if tramadol or tilidate/naloxone is insufficient. Results of a non-interventional study]. MMW Fortschr Med. 2010;152 (Suppl 2):62–9.
62. Landau CJ et al. Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. Clin Ther. 2007;29(10): 2179–93.
63. Poulain P et al. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. J Pain Symptom Manage. 2008;36(2): 117–25.
64. Attina G et al. Transdermal buprenorphine in children with cancer-related pain. Pediatr Blood Cancer. 2009;52(1):125–7.
65. Pergolizzi JV et al. The role of transdermal buprenorphine in the treatment of cancer pain: an expert panel consensus. Curr Med Res Opin. 2009;25(6):1517–28.

66. Koppert W et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain. 2005;118(1–2):15–22.
67. Mercadante S et al. Switching from transdermal drugs: an observational "N of 1" study of fentanyl and buprenorphine. J Pain Symptom Manage. 2007;34(5):532–8.
68. Freye E et al. Opioid rotation from high-dose morphine to transdermal buprenorphine (Transtec) in chronic pain patients. Pain Pract. 2007;7(2):123–9.
69. Aurilio C et al. Opioids switching with transdermal systems in chronic cancer pain. J Exp Clin Cancer Res. 2009;28:61.
70. Gianni W et al. Transdermal buprenorphine for the treatment of chronic noncancer pain in the oldest old. J Pain Symptom Manage. 2011;41(4):707–14.
71. Likar R, Vadlau EM, Breschan C, Kager I, Korak-Leiter M, Ziervogel G. Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. Clin J Pain. 2008;24(6):536-43.
72. Pergolizzi J et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8(4):287–313.
73. Vadivelu N, Hines RL. Management of chronic pain in the elderly: focus on transdermal buprenorphine. Clin Interv Aging. 2008;3(3):421–30.
74. Sittl R, Likar R, Nautrup BP. Equipotent doses of transdermal fentanyl and transdermal buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. Clin Ther. 2005;27(2):225–37.
75. Sittl R, Nuijten M, Nautrup BP. Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of noncancer and cancer pain: a retrospective data analysis in Germany. Clin Ther. 2006;28(8):1144–54.
76. Likar R. Transdermal buprenorphine in the management of persistent pain—safety aspects. Ther Clin Risk Manag. 2006;2(1):115–25.
77. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. Palliat Med. 2006;20 (Suppl 1):s3–8.
78. van Dorp E et al. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology. 2006;105(1):51–7.
79. Orwin JM. The effect of doxapram on buprenorphine induced respiratory depression. Acta Anaesthesiol Belg. 1977;28(2):93–106.
80. Greco MT et al. [Effects of transdermal buprenorphine in cancer patients. Results from the Cancer Pain Outcome Research (CPOR) Study Group]. Recenti Prog Med. 2008;99(11):538–51.
81. Radbruch L et al. Constipation and the use of laxatives: a comparison between transdermal fentanyl and oral morphine. Palliat Med. 2000;14(2):111–9.
82. Tassinari D et al. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. J Palliat Med. 2008;11(3):492–501.
83. Wirz S, et al. Gastrointestinal symptoms under opioid therapy: a prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. Eur J Pain 2009;13(7):737–43.
84. Hass B, et al. Cost-effectiveness of strong opioids focussing on the long-term effects of opioid-related fractures: a model approach. Eur J Health Econ. 2009;10(3):309–21.
85. Dagtekin O, et al. Assessing cognitive and psychomotor performance under long-term treatment with transdermal buprenorphine in chronic noncancer pain patients. Anesth Analg. 2007;105(5):1442–8, table of contents.
86. Louis F. Transdermal buprenorphine in pain management–experiences from clinical practice: five case studies. Int J Clin Pract. 2006;60(10):1330–4.
87. Perez-Perez L et al. Allergic contact dermatitis due to transdermal buprenorphine. Contact Dermatitis. 2008;58(5):310–2.

88. Vander Hulst K et al. Allergic contact dermatitis from transdermal buprenorphine. Contact Dermatitis. 2008;59(6):366–9.
89. Schmid-Grendelmeier P et al. A comparison of the skin irritation potential of transdermal fentanyl versus transdermal buprenorphine in middle-aged to elderly healthy volunteers. Curr Med Res Opin. 2006;22(3):501–9.
90. Brown MR, Denman R, Platts D. Analgesic patches and defibrillators: a cautionary tale. Europace. 2009;11(11):1552–3.
91. Park I et al. Buprederm, a new transdermal delivery system of buprenorphine: pharmacokinetic, efficacy and skin irritancy studies. Pharm Res. 2008;25(5):1052–62.
92. Mitra S. Opioid-induced hyperalgesia: pathophysiology and clinical implications. J Opioid Manag. 2008;4(3):123–30.
93. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain. 2008;24(6):479–96.
94. Muriel C, Failde I, Micó JA, Neira M, Sánchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. Clin Ther. 2005; 27(4):451–62.
95. Muriel C, Grupo de Estudio de Opioides de la Sociedad Española de Dolor. Valoración del parche transdérmico de buprenorfina en pacientes con dolor oncológico. Rev Soc Esp Dolor. 2004;11 Supl V:41–8.

Chapter 11
Buprenorphine in Maintenance Therapy

Karran A. Phillips and Kenzie L. Preston

Introduction

Although methadone maintenance is a safe and effective treatment for opioid dependence that has been available for many years, its benefits have been limited by the requirement that it be used only in licensed specialized clinics. Treatment options have been substantially expanded by the introduction of buprenorphine for office-based maintenance. Buprenorphine has been shown to be as clinically effective as methadone [1–3] and cost-effective [4, 5], and even to be preferable in some patient populations [6]. In a study of heroin-dependent incarcerated men who were voluntarily randomly assigned to methadone or buprenorphine maintenance, all of the patients in the buprenorphine group stated that they would recommend the medication to others, 93 % of them intended to enroll in buprenorphine treatment after release, and one-quarter of the methadone patients intended to enroll in buprenorphine treatment instead [7].

Buprenorphine and methadone treatment have each been shown to reduce drug-related risk behaviors in individuals with high risk of HIV transmission [8, 9]. Buprenorphine has also been shown to improve health-related quality of life [10]. In a 16-week study of buprenorphine maintenance with psychosocial counseling, responses on the Short Form 36 (a standard measure of health-related quality of life) showed improvements in bodily pain, vitality, mental health, social function, "role—emotional," "role—physical," and the mental-component summary score [11]. Studies of office-based treatment with buprenorphine are associated with retention rates and treatment outcomes comparable to those of methadone patients treated in opioid treatment programs (OTPs) [12–14].

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_11,

In this chapter we review the procedures needed to start an office-based buprenorphine maintenance practice, including how to obtain the required license and training. We also describe buprenorphine formulations and storage regulations, and review how to assess patients and begin buprenorphine treatment. Finally, we provide information on monitoring patient outcome and discuss special patient populations.

Starting a Practice

Drug Addiction Treatment Act 2000

In 2000, the US Congress passed legislation intended to destigmatize opioid-addiction treatment and address the gap between the need for and availability of such treatment. This legislation—Title XXXV, Section 3502 of the Children's Health Act of 2000 (P.L. 106-310)—enables qualified physicians to manage opioid addiction in their own practices and increases treatment options and availability [15]. Specifically, it permits qualified physicians to obtain a waiver to treat opioid addiction with Schedule III, IV, and V narcotic medications that have been specifically approved by the Food and Drug Administration (FDA) for that indication. This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Such medications may be prescribed and dispensed by waived physicians in treatment settings other than the traditional OTP (i.e., federally regulated methadone clinic) settings, including office-based settings. As of January 2012, the only medication that can be prescribed under this law is buprenorphine.

Qualifications for a Waiver

To qualify for a waiver under DATA 2000, a licensed physician (M.D. or D.O.) with a valid registration number from the Drug Enforcement Administration (DEA) must be able to provide (or refer patients for) necessary ancillary services, such as mental health services, and must agree to limit the number of concurrently buprenorphine maintained patients in his or her practice to 30 in the first year and 100 after the first year. In addition, he or she must meet at least one of the training requirements (see Table 11.1).

Training

As shown in Table 11.1, to meet the guidelines defined in the law, a training program for office-based buprenorphine maintenance must be endorsed by one of five

Table 11.1 Qualifications for a waiver

- Hold a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
- Hold an addiction certification from the American Society of Addiction Medicine (ASAM)
- Hold a subspecialty board certification in addiction medicine from the American Osteopathic Association (AOA)
- Have completed not less than 8 h of authorized training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) on the treatment and management of opioid-addicted patients. Authorized training is provided by the ASAM, the American Academy of Addiction Psychiatry (AAAP), the American Medical Association (AMA), the AOA, the American Psychiatric Association (APA)
- Have participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in Schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary by the sponsor of such approved drug
- Have such other training or experience as the state medical licensing board (of the state in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients
- Have such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients. Any criteria of the Secretary under this subclause shall be established by regulation. Any such criteria are effective only for 3 years after the date on which the criteria are promulgated, but may be extended for such additional discrete 3-year periods as the Secretary considers appropriate for purposes of this subclause. Such an extension of criteria may only be effectuated through a statement published in the Federal Register by the Secretary during the 30-day period preceding the end of the 3-year period involved

Source: http://buprenorphine.samhsa.gov/waiver_qualifications.html. Accessed January 31, 2012

Table 11.2 Buprenorphine Training

Organization	Buprenorphine training information
ASAM	http://www.asam.org/education/live-online-cme-training
APA	http://www.apaeducation.org/ihtml/application/student/interface.apa/index.htm
AAAP	http://www2.aaap.org/buprenorphine
AOAAM	http://www.aoaam.org/content.php?pg=43
AMA	At the time of this writing, the AMA had no buprenorphine training offerings

named professional organizations. Approved trainings are available in web-based, CD-ROM-based, and live formats, last about 8 h, and may earn *AMA PRA Category 1 Credit* (*TM*) for physicians who complete them. Depending on the program and the setting, there may be an associated cost to the physician. The trainings include evaluation to assess existing knowledge and attitudes, interactive modules focused on clinical skills and decision-making, post-training evaluations, and "practice change" advice on incorporation of buprenorphine treatment into the physician's practice. Training can be found at the URLs (see Table 11.2).

Obtaining a Waiver

After successful completion of an approved Buprenorphine DATA 2000 Training Program, the physician must send a Notification of Intent to the Center for Substance Abuse Treatment (CSAT), a branch of the Substance Abuse and Mental Health Services Administration (SAMHSA), in order to obtain a waiver. The Notification of Intent must be submitted to CSAT before the initial dispensing or prescribing of opioid addiction therapy. The Notification of Intent should be submitted on a Waiver Notification Form (SMA-167) (available at http://www.buprenorphine.samhsa.gov/pls/bwns/waiver) and can be sent online, via fax, or by traditional ground mail to the SAMHSA Division of Pharmacologic Therapies (DPT). For more information on how to submit a Notification of Intent, go to http://www.buprenorphine.samhsa.gov/howto.html.

SAMHSA will send an acknowledgment letter (or email) indicating that notification is under active review. SAMHSA's intent is to complete the review of notifications within 45 days of receipt. Upon completion of notification processing, SAMHSA will mail a letter confirming the waiver and containing a prescribing identification number (an "X number") assigned by the DEA.

Prescribing and Storing

The regulations covering the ordering, storing, and dispensing of controlled substances vary by state. However, DEA regulations require that the prescribing physician's "X number" be included on all buprenorphine prescriptions for opioid-addiction treatment, along with the physician's regular DEA registration number.

When buprenorphine was first approved by the FDA, few pharmacies consistently kept the medication in stock. To deal with this problem, many physicians kept a supply of buprenorphine tablets on hand and dispensed them from their office. In-office buprenorphine dispensing is still legal under DATA 2000. However, physicians who wish to dispense buprenorphine from their offices must adhere to strict federal recordkeeping guidelines and must keep the resultant records for 2 years. The records should include inventories, including amounts of buprenorphine received and amounts dispensed; reports of theft or loss; destruction of controlled drugs; and records of dispensing. Additionally, the buprenorphine tablets must be stored in a secure, locked cabinet. Physicians who have their patients get their prescriptions filled at outside pharmacies and return to the office for induction are *not* subject to the same recordkeeping guidelines as physicians who store and dispense the tablets in-office [16].

Recordkeeping

DATA 2000 requires the DEA to inspect the practices of physicians who are providing office-based treatment of opioid dependence. DEA recordkeeping requirements

go beyond the Schedule III recordkeeping requirements. Practitioners must keep records (including an inventory that accounts for amounts received and amounts dispensed) for all controlled substances dispensed, including buprenorphine products (21 PART 1304.03[b]). Practitioners must specifically record the prescription and dispensation of controlled substances for maintenance or detoxification treatment (21 CFR Section 1304.03[c]). AAAP provides guidance on preparing for a DEA inspection at http://www2.aaap.org/announcements/news-and-updates. Additional information can be found at http://www.pcssb.org/sites/default/files/How%20to%20Prepare%20for%20a%20DEA%20Inspection.pdf.

Barriers/Opportunities

Frequently cited barriers to the provision of office-based addiction treatment include inadequate clinician training, limited payment compared to what is available for other medical services, and concerns about confidentiality and stigma. In a qualitative study of 23 office-based physicians in New England, identified barriers included competing activities, lack of interest, lack of expertise in addiction treatment, patient concerns about confidentiality and cost, low patient motivation for treatment, lack of remuneration, limited ancillary support, not enough time, and a perceived low prevalence of opioid dependence in physicians' practices. Respondents in the same study also cited several potential facilitators of office-based addiction treatment, including the promotion of continuity of patient care and viewing office-based treatment as a positive alternative to methadone maintenance [17].

Despite these barriers, buprenorphine treatment presents many opportunities for physicians, such as providing access to addiction treatment to populations not previously reached [12, 18] and integrating addiction treatment with primary care, HIV care, HCV care, and mental health care. It is estimated that methadone treatment options reach only 15–20 % of those in need of treatment [19]. In a 2005 evaluation of the waiver program, 31 % of patients taking buprenorphine were new to addiction treatment and 60 % were new to medication-assisted treatment [20]. These numbers reflect a clear gap between need and access, but also show that the waiver program and buprenorphine are helping to close the gap. Integration of addiction treatment and primary care has been shown to improve both medical and substance-abuse outcomes [21–24]. Additionally, integration of buprenorphine maintenance into clinical HIV care can have a positive impact on treatment retention and opioid use, as well as stabilizing or improving the biological markers of HIV [25]. Integrated buprenorphine care also presents the opportunity and infrastructure for increased treatment of hepatitis C [26, 27].

Probably the most frequently voiced suggestion for overcoming system-, provider-, and patient-level barriers to utilization of pharmacotherapy for addiction is to educate providers, patients, and the general public about the range of treatment options and about the outcomes that pharmacotherapies can produce [28, 29].

Buprenorphine

Pharmacology

The pharmacology of buprenorphine is reviewed in detail in Chap. 10 of this text. Briefly, buprenorphine is a partial agonist at mu-opioid receptors, meaning that it binds strongly to receptors but does not activate them as strongly as endogenous opioids (or most abused opioids). At lower doses in opioid-naïve patients, its subjective and physiological effects increase with dose and are very similar to those of a full agonist. At higher doses, its effects reach a maximum beyond which increasing doses do not produce greater magnitudes of effect. This is termed the "ceiling effect." At these higher doses buprenorphine can act like an antagonist, occupying mu receptors but only partially activating them while blocking other agonists from binding to and fully activating the receptor. Due to its high affinity for the receptor, buprenorphine can displace full opioid agonists from the receptor; once bound to the receptor, it is not readily displaced by full agonists or antagonists. Buprenorphine also has a slow dissociation rate from the receptor; clinically, this contributes to its long duration of effects.

At the kappa opioid receptor, buprenorphine is an antagonist. The clinical relevance of this component of buprenorphine's actions is not fully understood.

Buprenorphine has poor gastrointestinal (GI) bioavailability and fair sublingual (under the tongue) bioavailability. The bioavailability of buprenorphine tablet administered sublingually is 29 % of that administered intravenously [15]. Buprenorphine is highly bound to plasma protein and is metabolized in the liver by the cytochrome P450 3A4 enzyme to norbuprenorphine and other products. It undergoes extensive first-pass metabolism, which accounts for its poor GI bioavailability. For these reasons, buprenorphine is administered sublingually rather than orally.

Naloxone is included in some formulations of buprenorphine to minimize the risk of misuse by intravenous injection. Naloxone is an opioid antagonist with poor sublingual and GI bioavailability [30]. When the combination product is taken sublingually as prescribed, the effect of the naloxone is negligible. If the product is misused intravenously, the naloxone effect predominates, resulting in a decreased effect of buprenorphine in opioid-naïve individuals and precipitation of withdrawal in opioid-dependent individuals [31, 32].

Formulations

Buprenorphine is available for sublingual administration as a combination tablet (buprenorphine/naloxone) whose trade name is Suboxone. A monoproduct formulation (buprenorphine), trade name Subutex, was discontinued in September 2011, but a generic version of the buprenorphine monoproduct has been approved since May 2010. Buprenorphine combination products are also available as a sublingual

film that was introduced in August 2010; the film is purported to dissolve in half the time of the tablet and have a more appealing taste. The sublingual tablet and film come in the same combination dosages: 8 mg buprenorphine with 2 mg naloxone or 2 mg buprenorphine with 0.5 mg naloxone. The buprenorphine monoproduct is available as an 8 or 2 mg sublingual tablet.

Slow-release formulations of buprenorphine are in various stages of development. These products are designed to minimize risks of patient noncompliance and diversion. A subcutaneous depot injection was shown to provide effective buprenorphine delivery for several weeks, with therapeutic effects persisting at fairly low buprenorphine plasma concentrations [33]. An implantable formulation of buprenorphine (Probuphine) that uses a polymer matrix sustained-release technology has been developed. In an initial, open-label evaluation, two doses of Probuphine were found to be safe, well-tolerated, and effective in patients with opioid dependence previously maintained on sublingual buprenorphine [34]. In a randomized trial conducted at 18 sites in the United States between April 2007 and June 2008, patients who received buprenorphine implants used fewer illicit opioids over 16 weeks (as assessed by urine testing) compared to those who received placebo implants [35].

Safety

For a complete listing of drug interactions, contraindications, warnings, and precautions, refer to the package inserts for Suboxone (http://www.suboxone.com/pdfs/SuboxonePI.pdf) and approved generics (e.g., http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c3b4fb4e-db70-407f-8481-8ae934ef73f0).

Adverse Reactions and Contraindications

As with other mu-opioid agonists, the most common adverse reactions are nausea and constipation, but these effects appear to be less severe and more self-limited with buprenorphine than with full agonists. Other adverse reactions commonly reported with buprenorphine include oral hypoesthesia, glossodynia, oral mucosal erythema, headache, vomiting, hyperhidrosis, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema.

The only contraindication to the use of buprenorphine is hypersensitivity to buprenorphine (or naloxone in the combination products). However, the prescribing information from Reckitt Benckiser lists a number of warnings and precautions that should be considered.

Drug–Drug Interactions

Buprenorphine is metabolized by the CYP3A4 isoenzyme of the P450 system. CYP3A4 inhibitors can result in higher levels of buprenorphine while CYP3A4

inducers can result in lower levels of buprenorphine. Buprenorphine patients who are starting or ending treatment with a CYP3A4 inhibitor or inducer should be closely monitored, and depending on the length of treatment with the CYP3A4 inhibitor/inducer and its effects, the dose of buprenorphine should be adjusted if needed.

Accidental Ingestion and Overdose

For full agonists at the mu-opioid receptor, the classic triad of signs of overdose is apnea (shallow respirations, <10 per minute), coma, and pinpoint pupils. Other signs include pulse rate <40 beats per minute, hypotension, cyanotic skin, flaccid muscles, and pulmonary edema [36]. Because buprenorphine is only a partial agonist, it has not been shown to cause these signs on its own. However, combination of buprenorphine with other CNS depressants, including benzodiazepines, can result in clinically significant toxicity.

Accidental ingestion of buprenorphine by swallowing results in milder effects than sublingual administration due to buprenorphine's poor GI bioavailability.

The primary management of buprenorphine overdose is the establishment of adequate ventilation.

Abuse Potential and Diversion

Buprenorphine, like all mu agonists, has some abuse liability (potential to be diverted for deliberate misuse). The abuse liability of buprenorphine is lower than that of full agonists such as methadone, morphine, and heroin. If patients are abusing or diverting buprenorphine, arrangements should be made to transfer them to more closely supervised treatment.

Buprenorphine can produce physical dependence with repeated use, but due to its partial agonist activity, the degree of physical dependence may be less than that created by a full opioid agonist [37]. Withdrawal from buprenorphine shows a delayed onset and lesser severity compared to withdrawal from full mu-opioid agonists [38].

Buprenorphine can precipitate withdrawal in individuals who are physically dependent on full opioid agonists (heroin, morphine, methadone, etc.). Because of the presence of the antagonist naloxone, this effect will likely be severe if buprenorphine/naloxone combinations are misused and injected intravenously.

Diversion of buprenorphine does not appear to be driven by recreational use. SAMHSA/CSAT commissioned an independent assessment including a literature review, analysis of all available data, interviews with key state and federal officials, and consultation with a group of outside experts to determine the extent of buprenorphine diversion and abuse. The report, which came out in 2006, concluded: "[B]uprenorphine diversion and abuse are concentrated in specific geographic areas. The phenomenon may reflect lack of access to addiction treatment, as some non-medical use appears to involve attempts to self-medicate with buprenorphine when

Table 11.3 Steps to ensure patient safety and meet Risk Evaluation and Mitigation Strategy (REMS) requirements

Physicians should
• Verify patients meet diagnostic criteria for opioid dependence
• Discuss the risks associated with buprenorphine
• Provide induction doses under appropriate supervision
• Prescribe a limited amount of medication during the initial stages of treatment
• Schedule patient appointments commensurate with patient stability (weekly or more frequent visits recommended in the first month)
• Consider pill count/dose reconciliation
• Assess whether patient is receiving counseling/psychosocial support considered necessary for treatment
• Assess whether patient is making progress toward treatment goals (including, as appropriate, urine toxicology testing)
• Continually assess appropriateness of maintenance dose
• Continually assess whether benefits of treatment outweigh the risks

Note: This REMS does not apply to buprenorphine dispensed to patients in opioid treatment program under 42 CFR Part 8 because these patients have specific requirements under those regulations
Source: www.suboxone.com. Accessed January 3, 2011

formal treatment is not available. While the largest part of the diverted drug supply likely comes from buprenorphine prescribed by physicians—either for addiction or for pain—the presence of formulations that are not approved for use in the United States suggests that some is being illegally imported as well" [39]. In another study of 100 opioid users in Providence, RI, the majority of whom were interested in receiving treatment for opioid dependence, the authors found that among the 86 % of intravenous drug users who obtained buprenorphine illegally, 74 % did so to treat opioid withdrawal symptoms, 66 % to stop using other opioids, and 64 % because they could not afford drug treatment [40]. These findings suggest that improved access to buprenorphine treatment provided by licensed treatment providers might reduce buprenorphine diversion.

As part of the initial approval of buprenorphine for office-based treatment, the FDA required that the manufacturers create a Risk Evaluation and Mitigation Strategy (REMS) to educate physicians, pharmacists, and patients. In response, the makers of Suboxone developed a list of recommendations for physicians (see Table 11.3).

Treating Patients with Buprenorphine

Patient Assessment/Patient Selection

Potential patients should be screened for the presence of an opioid-use disorder. Screening instruments include the Drug Abuse Screening Test (DAST-10, available at http://www.integration.samhsa.gov/clinical-practice/screening-tools) [41], the

Table 11.4 Elements of a substance-abuse assessment: history

Substance use history	Substances used; age at first use; routes of administration; changes in use patterns or effects; history of tolerance, physical dependence, withdrawal, and overdose; quit attempts; periods of abstinence; craving
Addiction treatment history	Previous treatment episodes, including type, length, and outcomes
Psychiatric history	Co-occurring diagnoses, psychiatric treatments recommended/attempted, treatment outcomes
Family history	Substance use disorders, medical, and psychiatric
Medical history	Review of systems, past medical and surgical history, sexual history, current and past medications, pain history
Social history	Quality of recovery environment, family/living environment, and social support; substance use in support network
Readiness to change	Understanding of patient's substance use problem, interest in treatment

Source: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Addiction, TIP 40, 2004

CAGE Questions Adapted to Include Drugs (CAGE-AID) [42], and the National Institute on Drug Abuse-Modified Alcohol, Smoking and Substance Involvement Screening Test (NMASSIST) [43] among others. Patients who screen positive on such a test should undergo a more complete assessment, including a mental-status exam and assessment of history regarding substance use, prior treatment, and medical, psychiatric, social, and family conditions. A complete physical exam is warranted in all patients with opioid-use disorders. The physical exam should include all the standard elements, with special attention given to the signs and symptoms of opioid use and its complications. Laboratory testing is also recommended.

Further details on all these elements of patient assessment are in Tables 11.4–11.6.

Patients who are appropriate for buprenorphine treatment have a diagnosis of addiction (typically operationalized in terms of the criteria for dependence from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; DSM-IV-TR), are interested in treatment, and have no contraindications to buprenorphine. In addition, they should be reasonably likely to be compliant with buprenorphine treatment, understand the risks and benefits of treatment, and be willing to follow safety precautions. Other treatment options should be reviewed with the patients so that they can make an informed decision.

Conditions that may preclude buprenorphine treatment include dependence on benzodiazepines, alcohol, or other CNS depressants; untreated severe mental health issues; active or chronic suicidal or homicidal ideation or attempts; poor response to previous high-quality attempts at buprenorphine treatment; or significant medical conditions (Table 11.7).

Table 11.5 Elements of a substance-abuse assessment: physical exam

Organ system/area examined	Signs/symptoms
General	Height, weight, calculated BMI, assessment of nutritional status
Skin and soft tissues (include between toes, groin, and genital area)	Injection-site infections
Head, eyes, ears, nose, and throat	Dental decay related to neglect and xerostomia, erosion of nasal cavity and septum from sniffing drugs, signs of opioid withdrawal (lacrimation, rhinorrhea, yawning)
Cardiovascular	Cardiac murmurs (concern for endocarditis)
Abdominal	Liver examination (possible medication- or hepatitis-induced effects)
Lymphatic	Cervical, axillary, supraclavicular, and inguinal lymphadenopathy

Source: Lowinson and Ruiz's Substance Abuse: a comprehensive textbook, Fifth Edition, editors Pedro Ruiz, Eric C. Strain. Lippincott Williams & Wilkins, 2011

Table 11.6 Elements of a substance-abuse assessment: laboratory

- Serum electrolytes
- BUN and creatinine
- CBC with differential and platelet count
- Liver function tests (GGT, AST, ALT, PT, or INR, albumin)
- Lipid profile
- Urinalysis
- Pregnancy test (for women)
- Toxicology tests for drugs of abuse
- Blood alcohol level (breath or blood test)
- Purified protein derivative (PPD) test for tuberculosis
- Hepatitis B virus (HBV) screen
- Hepatitis C virus (HCV) screen
- Hepatitis A virus (HAV) screen
- HIV antibody testing
- Serology test for syphilis

Source: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Addiction, TIP 40, 2004

Table 11.7 Cautions for buprenorphine treatment

- Seizures, because antiseizure medications and buprenorphine may alter each other's plasma levels; consider monitoring plasma levels of seizure medications
- HIV treatment, because anti-HIV medications may alter cytochrome P450 3A4 enzyme activity
- Hepatitis or impaired liver function; this may warrant periodic evaluation of liver enzymes
- Use of other drugs, including sedative-hypnotics, alcohol, and other CNS depressants

Source: Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. In: Treatment Improvement Protocol (TIP) Series 40. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004

Table 11.8 Opioid withdrawal

Stage of withdrawal	Timing after last use	Grade	Physical signs/symptoms
Early	8–24 h	1	Lacrimation and/or rhinorrhea
			Diaphoresis
			Yawning
			Restlessness
			Insomnia
		2	Dilated pupils
			Piloerection
			Muscle twitching
			Myalgia
			Arthralgia
			Abdominal pain
Full	1-3 days	3	Tachycardia
			Hypertension
			Tachypnea
			Fever
			Anorexia or nausea
			Extreme restlessness
		4	Diarrhea and/or vomiting
			Dehydration
			Hyperglycemia
			Hypotension
			Curled-up position

Source: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Addiction, TIP 40, 2004

Buprenorphine Induction

Once the patient has been assessed and found appropriate for buprenorphine treatment, plans can be made to begin the medication. Patients should be advised that on the first and perhaps second day of induction they may need to be in the clinic for several hours. Prior to initiation of buprenorphine treatment, the patient and physician should agree on a treatment contract delineating treatment goals, plan, consequences of poor adherence, and grounds for termination. Prior to the first dose of buprenorphine, the patient should not use heroin or other short-acting opioids for at least 12 h and should not use methadone or other long-acting opioids for at least 24 h. Buprenorphine induction can be undertaken with the buprenorphine–naloxone combination formulation unless the patient is pregnant or switching from long-acting opioids such as methadone (see section "Transferring from Methadone to Buprenorphine").

Buprenorphine-induced precipitated withdrawal can occur with the first dose, but is often milder and shorter than that induced by an antagonist. The possibility of precipitated withdrawal is minimized if one decreases the dose of the full agonist (i.e., the opioid that patient is abusing), increases the time elapsed since last use of the full agonist prior to medicating with buprenorphine, and starts with a low dose of buprenorphine. The first dose of buprenorphine should be given when the patient has begun to develop early signs of opioid withdrawal (Table 11.8).

Table 11.9 Clinical practice guidelines for the use of buprenorphine opioid addiction

Treatment Improvement Protocol (*TIP*) *40* "Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction" (Center for Substance Abuse Treatment, 2004)	Available at http://buprenorphine.samhsa.gov/Bup_Guidelines.pdf
Technical Assistance Publication (*TAP*) *30* "Buprenorphine: A Guide for Nurses" (Center for Substance Abuse Treatment, 2009)	Available at http://buprenorphine.samhsa.gov/TAP_30_Certified.pdf
Management of Substance Use Disorders (VA/DoD, 2009)	Available at http://www.healthquality.va.gov/Substance_Use_Disorder_SUD.asp
Vermont Buprenorphine Practice Guidelines (Vermont Department of Health, Division of Alcohol and Drug Abuse Programs (VDH/ADAP) and the Office of Vermont Health Access (OVHA), 2010)	Available at http://healthvermont.gov/adap/treatment/documents/BuprenorphinePracticeGuidelinesFINAL_01-15-2010.pdf
Best Practices in the Use of Buprenorphine, Final Expert Panel Report, Prepared for Community Care Behavioral Health Organization, October 18, 2011	Available at http://www.ccbh.com/pdfs/Providers/healthchoices/articles/Identifying_Best_Practices_in_the_Use_of_Buprenorphine_after_Stabilization_Report_and_Appendix_A.pdf

The severity of opioid withdrawal can be assessed with clinical tools such as the Clinical Opioid Withdrawal Scale (COWS) [44]. A COWS score of >12 should be obtained prior to administration of the first dose of buprenorphine. Additional tools to assess opioid withdrawal include the Clinical Institute Narcotic Assessment (CINA) Scale for Opioid Withdrawal [45]; the Narcotic Withdrawal Scale [46]; and the Subjective Opiate Withdrawal Scale (SOWS) [47–49].

There now exist several clinical guidelines for the use of buprenorphine in an office-based setting. Physicians should be familiar with these guidelines, use their clinical judgment, and individualize treatment for the patient as indicated. Below we outline one approach based on these guidelines (Table 11.9).

Day 1—Once early withdrawal signs and symptoms are present, patients can be administered buprenorphine/naloxone 4/1 mg sublingually and observed for 2 or more hours. If withdrawal symptoms persist, a second buprenorphine/naloxone dose of 4/1 mg may be administered the same day, with the patient again observed for 2 or more hours. The maximum total dose on Day 1 is buprenorphine/naloxone 8/2 mg. If withdrawal symptoms abate, the Day 1 dose is established and the patient should be asked to return to the office the next day. If withdrawal symptoms persist

despite administration of the maximum total Day 1 dose, the patient should counseled, given medications to manage withdrawal symptomatically, and asked to return the next day.

Day 2—When the patient returns to the office on Day 2, he or she should be assessed for withdrawal symptoms. If they are not present, then the patient's daily dose is established at the total Day 1 dose. If on subsequent days the patient experiences mild withdrawal, the buprenorphine/naloxone dose should be adjusted based on clinical judgment and signs and symptoms of opioid withdrawal in increments of 2/0.5 to 4/1 mg. If the patient does demonstrate symptoms of opioid withdrawal when he/she returns on Day 2, then he/she should be given the total Day 1 dose plus an additional 4/1 mg buprenorphine/naloxone and observed for 2 or more hours. If withdrawal symptoms are relieved, then the daily dose of buprenorphine/naloxone has been established. If withdrawal symptoms persist after 2 or more hours, the patient should be administered an additional buprenorphine/naloxone 4/1 mg and observed. If withdrawal symptoms are relieved, then the daily buprenorphine/naloxone dose has been established. The maximum Day 2 dose is buprenorphine/naloxone 16/4 mg. If the withdrawal symptoms have not dissipated, then the patient should be counseled, treated symptomatically, and asked to return the next day.

Day 3 onward—If the patient returns on Day 3 or on subsequent induction days with symptoms consistent with opioid withdrawal, he or she can continue with buprenorphine/naloxone 2/0.5 to 4/1 mg increases on a schedule similar to the Day 2 schedule above.

The goal of buprenorphine induction is to find the dose at which the patient has (1) discontinued or markedly decreased use of illicit opioids, (2) no cravings, (3) no opioid withdrawal, and (4) minimal or no adverse reactions. All dose adjustments during induction should be made based on clinical symptoms of opioid withdrawal and clinical judgment. In our clinical research setting, we have had success with waiting 12 h after administration of the last short-acting opioid and 24 h after the last long-acting opioid, waiting until mild opioid withdrawal is present, and then administering 8 mg buprenorphine on Day 1 *without* keeping the patient for observation or incremental dose increases. On Day 2, if opioid withdrawal is present, we administer buprenorphine 16 mg *without* keeping the patient for observation or incremental dose increases. We have had minimal precipitated withdrawal and loss to follow-up during induction. However, it should be kept in mind that in our setting, patients are seen for directly observed buprenorphine treatment daily throughout induction, stabilization, and maintenance. While there is variation among clinical guideline recommendations, the target dose is usually considered buprenorphine/naloxone 12/3 to 16/4 mg/day by the end of the first week, and the maximum recommended buprenorphine/naloxone dose is 32/8 mg/day.

Basic patient instructions for taking buprenorphine include telling the patient that the medication should be dissolved under the tongue and that drinking water to moisten the mouth before taking buprenorphine helps it dissolve. Patients should be advised not to chew or swallow tablet (or film) while it is dissolving because it will not work as well. Additionally, patients should be advised to avoid benzodiazepines, alcohol, and other CNS depressants, to keep their buprenorphine in a safe and secure place, to

take buprenorphine once per day as directed, and not to change their dose without consulting a physician. Refer to the buprenorphine prescribing information (http://www.suboxone.com/pdfs/SuboxonePI.pdf) for a complete list of recommendations.

Complicated Inductions

Buprenorphine inductions may be complicated by precipitated or protracted withdrawal symptoms. In a retrospective chart review of the first 107 patients receiving buprenorphine treatment in an urban community health center, complicated inductions occurred in 18 (16.8 %) patients. When compared to routine inductions, complicated inductions predicted poorer treatment retention. Factors independently associated with complicated inductions included recent use of prescribed methadone, recent benzodiazepine use, and no prior experience with buprenorphine [50]. Although further research is needed, physicians should be aware of these potential risk factors and try to ensure that the patient is in mild withdrawal before the first dose of buprenorphine is administered, starting with a low dose of buprenorphine, and titrating up slowly.

Home Inductions

There is observational evidence that unobserved or "home" buprenorphine inductions are effective [51–56]. In two prospective studies of home induction, approximately 60–70 % of patients were successfully inducted, defined as being retained in treatment, on buprenorphine, and free of withdrawal, 1 week after the initial clinic visit. Complications were usually mild and infrequent, with only one case of confirmed severe precipitated withdrawal. Occasions requiring phone support from clinicians or staff were brief and infrequent [53, 56]. These findings are promising, but further research is still needed before home induction can be recommended for routine use.

Buprenorphine Stabilization and Maintenance

Stabilization begins when the patient has no cravings, no withdrawal, and minimal adverse drug reactions; this phase of treatment usually lasts 1–2 months. The duration of maintenance following stabilization should be individualized based on patient needs.

Once an effective buprenorphine dose has been established during induction, the patient should be continued on this daily dose and adjustments made as needed. Dose adjustments should be based on a combination of patient preference and clinical judgment, balancing the positive effects of buprenorphine (relief of opioid withdrawal, greatly diminished opioid craving, and cessation of illicit opioid use) with its possible side effects (such as constipation and sedation). Dose adjustments can

be made in buprenorphine/naloxone 2/0.5 to 4/1 mg increments per week with a maximum daily dose of buprenorphine/naloxone of 32/8 mg. If the maximum dose is reached and maintained but illicit opioid use persists, efforts should be made to intensify the level of nonpharmacological treatment, or consideration should be given to transferring the patient to an OTP that can provide more intense care.

Regardless of buprenorphine dose, all patients should be offered access or referral to evidence-based psychosocial treatment and other nonpharmacological treatments as stipulated by DATA 2000. Follow-up frequency should be individualized, but typically, once weekly in the first month is appropriate. Buprenorphine prescriptions should reflect the length of time between visits; providing multiple refills early in treatment is discouraged. With negative urine drug toxicologies on a stable buprenorphine dose, visits and prescriptions can be monthly. Visit frequency and interval should be adjusted as needed to reflect the patient's treatment-plan compliance, demonstrated responsibility, side effects, and abstinence from illicit drugs.

Periodic, usually monthly, drug toxicology screening is an important adjunct to buprenorphine treatment. A number of screening options exist, including by urine, blood, saliva, sweat, and hair. A combination of both random and nonrandom (e.g., at monthly office visit) urine toxicology testing should be implemented. Of note, buprenorphine does not come up as positive on the standard opioid toxicology screens which test for morphine/codeine and their derivatives. If testing for buprenorphine compliance, point-of-care urine screens (i.e., dipsticks) specifically for buprenorphine are commercially available. Additionally, periodic random pill counts might be a useful adjunct for monitoring patient safety and minimizing the risk of diversion.

Medically Supervised Buprenorphine Withdrawal

Research and clinical experience have shown that opioid maintenance treatments have a higher likelihood of success than withdrawal treatment. If medically supervised withdrawal (MSW) is initiated, the evidence shows that longer withdrawal plans (>30 days) tend to have more long-term success than shorter withdrawal plans (<30 days) [57, 58]. MSW is usually undertaken in two phases: induction, during which the patient is stabilized (minimal opioid withdrawal and cessation of illicit opioid use) as quickly as possible, and dose reduction, during which the buprenorphine dose is decreased and then discontinued.

Patient Management Issues

Adherence and Retention

Treatment adherence is enhanced by a therapeutic relationship between patient and physician built on trust, mutual respect, and a two-way exchange of information.

Prolonged inductions resulting in continued opioid withdrawal signs and symptoms have been shown to increase the treatment drop-out rate [59] so every effort should be made to reach an adequate buprenorphine maintenance dose as quickly as possible, within the constraints imposed by the avoidance of precipitated withdrawal.

Ending Maintenance Treatment

Longer maintenance treatment is associated with less illicit drug use and relapse, longer retention in treatment [60], and fewer complications [61]. During maintenance, the patient's desire to taper off buprenorphine should periodically be revisited. If the patient expresses an interest in ending buprenorphine maintenance, the patient and physician should discuss the likelihood of successful taper and consider housing and income stability, adequacy of social support, and absence of legal problems. When the decision is made to discontinue buprenorphine treatment, the dose should be tapered slowly, ideally over weeks to months, at a rate agreed upon by patient and physician. If craving or withdrawal symptoms emerge, the taper should temporarily be suspended, then resumed once the symptoms have abated. The presence of both formal and informal psychosocial support can be critical during all of treatment, but especially during dose tapers.

Coordination of Care/Role of the MD

Prior to offering office-based buprenorphine treatment, physicians should familiarize themselves with federal and state regulations, training requirements, treatment guidelines, buprenorphine prescribing information, and the most recent scientific literature pertaining to buprenorphine. Additionally, clinical and administrative staff in the physician's office should be educated about addiction and about buprenorphine treatment. The physician and his or her staff should develop "standard operating procedures" for the care of buprenorphine patients. This should include compiling a list of available psychosocial services (individual and group counseling, support groups, etc.) and other community services (case management, food banks, homeless shelters, job training, needle-exchange, etc.), and all staff should become familiar with service locations, hours, and participation requirements.

The privacy and confidentiality of patients in addiction treatment are protected by federal law. Physicians and their staff should be familiar with these regulations and establish office procedures to ensure that they are maintained. A procedure through which patients can authorize release of records should be developed and implemented so that physicians may communicate with pharmacists, psychosocial treatment providers, subspecialty physicians, and other providers as needed.

Working with Pharmacies

Given the privacy regulations in the Health Insurance Portability and Accountability Act (HIPAA) and 42 CFR Part 2, it is advisable to have a patient sign an authorization for release of information between the physician and the pharmacist prior to their first buprenorphine dose. This will allow the physician to verify the buprenorphine prescription if needed, and it is important if the prescription is being phoned or faxed. Also, with authorization to communicate with the pharmacy, the physician can more easily address pre-authorization requirements from insurance companies to ensure that there is no delay in getting the prescription filled. More information regarding these regulations can be found at http://www.samhsa.gov/healthprivacy/.

FDA information for pharmacists on buprenorphine is available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatients and Providers/UCM191533.pdf.

Special Populations

Transferring from Methadone to Buprenorphine

Patients on methadone maintenance can be successfully transferred to buprenorphine maintenance [62]. This may be an option to consider for patients who have tolerable but undesirable side effects with methadone, or who want the increased flexibility that office-based buprenorphine allows once stabilization and maintenance occur. Additional reasons for transfer might include a perceived decrease in stigma, longer duration of action, and enhanced safety. When patients prepare to transfer, it is advised that their methadone dose be tapered down to 30 mg/day and maintained at that level for ideally 5–7 days prior to initiating buprenorphine treatment in order to reduce the likelihood of buprenorphine-precipitated withdrawal. Patients are also asked to wait at least 24 h after their last dose of methadone, by which time they should begin to experience symptoms of early withdrawal, prior to initiating buprenorphine. The likelihood of precipitated withdrawal may be further reduced by starting at an initially low dose (such as 2–4 mg) of buprenorphine, using the buprenorphine monotherapy formulation (no naloxone), and waiting until the patient is in mild to moderate withdrawal (e.g., COWS score >12). As with buprenorphine induction in patients who use short-acting opioids, the suggested maximum Day 1 dose for patients using long-acting opioids such as methadone is buprenorphine 8 mg. On Day 2, the patient may proceed according to the Day 2 schedule for short-acting opioids and be administered the combination of buprenorphine/naloxone.

Pregnant Women

In the United States, methadone has been the standard of care for treating opioid addiction in pregnant woman and their neonates. Pregnant women seeking buprenorphine treatment should be advised that the FDA currently classifies buprenorphine as a Category C agent. However, recent results from the MOTHER Study suggest that buprenorphine is safe and effective in pregnant women, with lower neonatal withdrawal rates and shorter neonatal withdrawal durations compared to methadone [63]. A multicenter European prospective study comparing buprenorphine to methadone also found buprenorphine as safe as methadone in the treatment for pregnant opioid-dependent women [64].

Breastfeeding while on buprenorphine is controversial, with the package insert advising against it but the Treatment Improvement Protocol (TIP) 40 consensus panel stating it is not contraindicated. In lactating women given buprenorphine at therapeutic levels, the concentration present in the breast milk was considered low [65].

Criminal Justice

Buprenorphine has proven to be a very effective tool in addressing opioid-use disorders in criminal-justice settings such as prisons [66, 67]. However, after incarceration, relapse rates are high and overdose on illicit opioids is common [68–70]. Physicians should be vigilant of their patients during this transition time and attempt to re-engage them in treatment as quickly as possible.

Adolescents/Young Adults and the Elderly

Buprenorphine has been shown to be a safe and effective treatment in adolescents and young adults. In a study by Marsch et al., comparing buprenorphine to clonidine in a 28-day detoxification, buprenorphine-treated participants were significantly more likely to be retained in treatment (72 % vs. 39 %) and had a higher percentage of opiate-negative urines (64 % vs. 32 %). Participants in both groups reported relief of withdrawal symptoms and reductions in HIV risk behaviors [71]. A 2012 study examining the outcome of buprenorphine and methadone treatment for heroin dependence among adolescents (average age 16.6 years) found that half of the participants remained in treatment for over 1 year, and among those still in treatment at 12 months, 39 % were heroin-abstinent [72].

State law varies on the circumstances under which parental consent is needed, so physicians wishing to treat adolescents and young adults should be aware of the regulations in their state.

Caution should be used when administering buprenorphine in elderly or debilitated patients or patients with liver dysfunction, as drug metabolism and absorption may be altered.

Reimbursement

Reimbursement for addiction treatment and mental health care has been limited, but advances are being made. In 2008, the Paul Wellstone Mental Health and Addiction Equity Act of 2007 (HR 1424) was signed into law. The law expands access to mental health and addiction treatment and prohibits third-party payers from placing discriminatory restrictions on reimbursement. In 2007, the Centers for Medicare and Medicaid Services (CMS) adopted new codes in the Healthcare Common Procedure Coding System (HCPCS) for assessment and intervention services for substance abuse (H0049 and H0050) and in January 2008, the American Medical Association adopted Current Procedural Terminology (CPT) codes for screening and brief intervention (99408 and 99409), and new Medicare "G" codes (G0396 and G0397) became available that parallel the CPT codes. However, there are currently no specific billing codes in addiction medicine that physicians can use for office-based treatment of opioid dependence, and reimbursement by third-party payers continues to vary. The billing codes for inpatient detoxification, outpatient detoxification, and office-based maintenance are the same as codes for other ambulatory care services.

Resources

American Academy of Addiction Psychiatry—Email: information@aaap.org. Website: www.aaap.org.

American Osteopathic Association—Email: info@osteotech.org. Website: www.osteopathic.org.

American Psychiatric Association—Email: apa@psych.org. Website: www.psych.org.

American Society of Addiction Medicine—Email: email@asam.org. Website: www.asam.org.

CSAT Buprenorphine Information Center—1.866.BUP.CSAT (1.866.287.2728). Email: info@buprenorphine.samhsa.gov. Website: http://www.buprenorphine.samhsa.gov/index.html.

Federation of State Medical Boards—Website: www.fsmb.org/pdf/2002_grpol_opioid_addiction_treatment.pdf.

National Alliance of Advocates for Buprenorphine Treatment—Website: www.naabt.org.

SAMHSA Sponsored Buprenorphine Physician Clinical Support System (*PCSS*)—The SAMHSA-funded PCSS is a national network of trained physician mentors with expertise in buprenorphine treatment and skilled in clinical education designed to assist practicing physicians in incorporating into their practices the treatment of prescription opioid- and heroin-dependent patients using buprenorphine. Website: http://www.pcssb.org/.

Acknowledgment This work was supported by the National Institute on Drug Abuse, Intramural Research Program, National Institutes of Health.

References

1. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA. 1992;267(20):2750–5. doi:10.1001/jama.267.20.2750.
2. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction. 2003;98(4):441–52. doi:10.1046/j.1360-0443.2003.00335.x.
3. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008;(2):CD002207. doi:10.1002/14651858.CD002207.pub3.
4. Barnett PG, Zaric GS, Brandeau ML. The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States. Addiction. 2001;96(9):1267–78. doi:10.1046/j.1360-0443.2001.96912676.x.
5. Barnett PG. Comparison of costs and utilization among buprenorphine and methadone patients. Addiction. 2009;104(6):982–92. doi:10.1111/j.1360-0443.2009.02539.x.
6. Maremmani I, Gerra G. Buprenorphine-based regimens and methadone for the medical management of opioid dependence: selecting the appropriate drug for treatment. Am J Addict. 2010;19(6):557–68. doi:10.1111/j.1521-0391.2010.00086.x.
7. Awgu E, Magura S, Rosenblum A. Heroin-dependent inmates' experiences with buprenorphine or methadone maintenance. J Psychoactive Drugs. 2010;42(3):339–46.
8. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2011;(8):CD004145. doi:10.1002/14651858.CD004145.pub4.
9. Sullivan LE, Moore BA, Chawarski MC, Schottenfeld RS, O'Connor PG, Fiellin DA. Buprenorphine reduces HIV risk behavior among opioid dependent patients in primary care. J Gen Intern Med. 2005;20:172.
10. Giacomuzzi SM, Ertl M, Kemmler G, Riemer Y, Vigl A. Sublingual buprenorphine and methadone maintenance treatment: a three-year follow-up of quality of life assessment. ScientificWorldJournal. 2005;5:452–68. doi:10.1100/tsw.2005.52.
11. Raisch D, Campbell H, Garnand D, Jones M, Sather M, Naik R, et al. Health-related quality of life changes associated with buprenorphine treatment for opioid dependence. Qual Life Res. 2012;21(7):1177–83.
12. Sullivan LE, Chawarski M, O'Connor PG, Schottenfeld RS, Fiellin DA. The practice of office-based buprenorphine treatment of opioid dependence: is it associated with new patients entering into treatment? Drug Alcohol Depend. 2005;79(1):113–6. doi:10.1016/j.drugalcdep.2004.12.008.
13. Marsch LA, Stephens MAC, Mudric T, Strain EC, Bigelow GE, Johnson RE. Predictors of outcome in LAAM, buprenorphine, and methadone treatment for opioid dependence. Exp Clin Psychopharmacol. 2005;13(4):293–302. doi:10.1037/1064-1297.13.4.293.
14. Stein MD, Cioe P, Friedmann PD. Brief report: buprenorphine retention in primary care. J Gen Intern Med. 2005;20(11):1038–41. doi:10.1111/j.1525-1497.2005.0228.x.
15. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction, Treatment Improvement Protocol (TIP) series 40. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
16. Clinical Tools I. BupPractice 1995–2011. http://www.buppractice.com/. Updated Wednesday, 4 Jan 2012, 10:43 am; cited 4 Jan 2012.
17. Barry DT, Irwin KS, Jones ES, Becker WC, Tetrault JM, Sullivan LE, et al. Integrating buprenorphine treatment into office-based practice: a qualitative study. J Gen Intern Med. 2009;24(2):218–25. doi:10.1007/s11606-008-0881-9.

18. Fiellin DA, Rosenheck RA, Kosten TR. Office-based treatment for opioid dependence: reaching new patient populations. Am J Psychiatry. 2001;158(8):1200–4. doi:10.1176/appi.ajp.158.8.1200.
19. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs, Treatment Improvement Protocol (TIP) series 43. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.
20. Substance Abuse and Mental Health Services Administration. Evaluation of the Buprenorphine Waiver Program: results from SAMHSA/CSAT's evaluation of the Buprenorphine Waiver Program 2005. http://www.buprenorphine.samhsa.gov/findings.pdf. Cited 31 Jan 2012.
21. Mertens JR, Flisher AJ, Satre DD, Weisner CM. The role of medical conditions and primary care services in 5-year substance use outcomes among chemical dependency treatment patients. Drug Alcohol Depend. 2008;98(1–2):45–53. doi:10.1016/j.drugalcdep.2008.04.007.
22. O'Toole TP, Pollini RA, Ford DE, Bigelow G. The effect of integrated medical-substance abuse treatment during an acute illness on subsequent health services utilization. Med Care. 2007;45(11):1110–5.
23. Samet JH, Friedmann P, Saitz R. Benefits of linking primary medical care and substance abuse services—patient, provider, and societal perspectives. Arch Intern Med. 2001;161(1):85–91. doi:10.1001/archinte.161.1.85.
24. Saitz R, Horton NJ, Larson MJ, Winter M, Samet JH. Primary medical care and reductions in addiction severity: a prospective cohort study. Addiction. 2005;100(1):70–8. doi:10.1111/j.1360-0443.2004.00916.x.
25. Sullivan LE, Barry D, Moore BA, Chawarski MC, Tetrault JM, Pantalon MV, et al. A trial of integrated buprenorphine/naloxone and HIV clinical care. Clin Infect Dis. 2006;43:S184–90. doi:10.1086/508182.
26. Kresina TF, Eldred L, Bruce RD, Francis H. Integration of pharmacotherapy for opioid addiction into HIV primary care for HIV/hepatitis C virus-co-infected patients. AIDS. 2005;19:S221–6. doi:10.1097/01.aids.0000192093.46506.e5.
27. Edlin BR, Kresina TF, Raymond DB, Carden MR, Gourevitch MN, Rich JD, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. Clin Infect Dis. 2005;40:S276–85. doi:10.1086/427441.
28. Gordon AJ, Kavanagh G, Krumm M, Ramgopal R, Paidisetty S, Aghevli M, et al. Facilitators and barriers in implementing buprenorphine in the Veterans Health Administration. Psychol Addict Behav. 2011;25(2):215–24. doi:10.1037/a0022776.
29. Oliva EM, Maisel NC, Gordon AJ, Harris AHS. Barriers to use of pharmacotherapy for addiction disorders and how to overcome them. Curr Psychiatry Rep. 2011;13(5):374–81. doi:10.1007/s11920-011-0222-2.
30. Preston KL, Bigelow GE, Liebson IA. Effects of sublingually given naloxone in opioid-dependent human volunteers. Drug Alcohol Depend. 1990;25(1):27–34. doi:10.1016/0376-8716(90)90136-3.
31. Preston KL, Bigelow GE, Liebson IA. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. Psychopharmacology. 1988;94(4):484–90. doi:10.1007/bf00212842.
32. Weinhold LL, Preston KL, Farre M, Liebson IA, Bigelow GE. Buprenorphine alone and in combination with naloxone in nondependent humans. Drug Alcohol Depend. 1992;30(3):263–74. doi:10.1016/0376-8716(92)90061-g.
33. Sigmon SC, Moody DE, Nuwayser ES, Bigelow GE. An injection depot formulation of buprenorphine: extended biodelivery and effects. Addiction. 2006;101(3):420–32. doi:10.1111/j.1360-0443.2005.01348.x.
34. White J, Bell J, Saunders JB, Williamson P, Makowska M, Farquharson A, et al. Open-label dose-finding trial of buprenorphine implants (Probuphine)(R) for treatment of heroin dependence. Drug Alcohol Depend. 2009;103(1–2):37–43. doi:10.1016/j.drugalcdep.2009.03.008.
35. Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, et al. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA. 2010;304(14):1576–83.

36. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., text revision. Washington, DC: American Psychiatric Association; 2000.
37. Eissenberg T, Greenwald MK, Johnson RE, Liebson IA, Bigelow GE, Stitzer ML. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. J Pharmacol Exp Ther. 1996;276(2):449–59.
38. Eissenberg T, Johnson RE, Bigelow GE, Walsh SL, Liebson IA, Strain EC, et al. Controlled opioid withdrawal evaluation during 72 h dose omission in buprenorphine-maintained patients. Drug Alcohol Depend. 1997;45(1–2):81–91. doi:10.1016/s0376-8716(97)01347-1.
39. Center for Health Services and Outcomes Research. Diversion and abuse of buprenorphine: a brief assessment of emerging indicators; http://buprenorphine.samhsa.gov/Vermont.Case.Study_12.5.06.pdf, 2006.
40. Bazazi AR, Yokell M, Fu JJ, Rich JD, Zaller ND. Illicit use of buprenorphine/naloxone among injecting and noninjecting opioid users. J Addict Med. 2011;5(3):175–80. doi:10.1097/ADM.0b013e3182034e31.
41. Skinner HA. The drug-abuse screening-test. Addict Behav. 1982;7(4):363–71. doi:10.1016/0306-4603(82)90005-3.
42. Brown R, Rounds L. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J. 1995;94(3):135–40.
43. National Institute on Drug Abuse. NMAssist: screening for tobacco, alcohol and other drug use. http://www.drugabuse.gov/nidamed/nmassist-screening-tobacco-alcohol-other-drug-use. Cited 31 Jan 2012.
44. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). J Psychoactive Drugs. 2003;35(2):253–9.
45. Peachey JE, Lei H. Assessment of opioid dependence with naloxone. Br J Addict. 1988;83(2):193–201.
46. Fultz JM, Senay EC. Guidelines for management of hospitalized narcotic addicts. Ann Intern Med. 1975;82(6):815–8.
47. Bradley BP, Gossop M, Phillips GT, Legarda JJ. The development of an opiate withdrawal scale (OWS). Br J Addict. 1987;82(10):1139–42.
48. Gossop M. The development of a short opiate withdrawal scale (SOWS). Addict Behav. 1990;15(5):487–90. doi:10.1016/0306-4603(90)90036-w.
49. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating-scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13(3):293–308. doi:10.3109/00952998709001515.
50. Whitley SD, Sohler NL, Kunins HV, Giovanniello A, Li XA, Sacajiu G, et al. Factors associated with complicated buprenorphine inductions. J Subst Abuse Treat. 2010;39(1):51–7. doi:10.1016/j.jsat.2010.04.001.
51. Mintzer IL, Eisenberg M, Terra M, MacVane C, Himmelstein DU, Woolhandler S. Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. Ann Fam Med. 2007;5(2):146–50. doi:10.1370/afm.665.
52. Lee JD, Grossman E, Dirocco D, Gourevitch MN. Feasibility of at-home induction in primary care-based buprenorphine treatment: is less more? J Gen Intern Med. 2008;23:303–4.
53. Lee J, DiRocco D, Grossman E, Gourevitch MN. At-home buprenorphine induction in urban primary care. Subst Abus. 2009;30(2):191.
54. Soeffing JM, Martin LD, Fingerhood MI, Jasinski DR, Rastegar DA. Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. J Subst Abuse Treat. 2009;37(4):426–30. doi:10.1016/j.jsat.2009.05.003.
55. Sohler NL, Li X, Kunins HV, Sacajiu G, Giovanniello A, Whitley S, et al. Home- versus office-based buprenorphine inductions for opioid-dependent patients. J Subst Abuse Treat. 2010;38(2):153–9. doi:10.1016/j.jsat.2009.08.001.
56. Gunderson EW, Wang XQ, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. Addict Behav. 2010;35(5):537–40. doi:10.1016/j.addbeh.2010.01.001.

57. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. Drug Alcohol Depend. 2011;119(1–2):1–9. doi:10.1016/j.drugalcdep.2011.05.033.
58. Katz EC, Schwartz RP, King S, Highfield DA, O'Grady KE, Billings T, et al. Brief vs. extended buprenorphine detoxification in a community treatment program: engagement and short-term outcomes. Am J Drug Alcohol Abuse. 2009;35(2):63–7. doi:10.1080/00952990802585380.
59. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. Int J Neuropsychopharmacol. 2008;11(5):641–53. doi:10.1017/s146114570700836x.
60. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-Year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet. 2003;361(9358):662–8. doi:10.1016/s0140-6736(03)12600-1.
61. Stein MD, Friedmann PD. Optimizing opioid detoxification: rearranging deck chairs on the titanic. J Addict Dis. 2007;26(2):1–2. doi:10.1300/J069v26n02_01.
62. Salsitz EA, Holden CC, Tross S, Nugent A. Transitioning stable methadone maintenance patients to buprenorphine maintenance. J Addict Med. 2010;4(2):88–92. doi:10.1097/ADM.0b013e3181add3f5.
63. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363(24):2320–31. doi:10.1056/NEJMoa1005359.
64. Lacroix I, Berrebi A, Garipuy D, Schmitt L, Hammou Y, Chaumerliac C, et al. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicenter study. Eur J Clin Pharmacol. 2011;67(10):1053–9. doi:10.1007/s00228-011-1049-9.
65. Grimm D, Pauly E, Poschl J, Linderkamp O, Skopp G. Buprenorphine and norbuprenorphine concentrations in human breast milk samples determined by liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2005;27(4):526–30. doi:10.1097/01.ftd.0000164612.83932.be.
66. Fiellin D, Moore B, Wang E, Sullivan L. Primary care office-based buprenorphine/naloxone treatment and the legal and criminal justice system. J Gen Intern Med. 2010;25:366.
67. Cropsey KL, Lane PS, Hale GJ, Jackson DO, Clark CB, Ingersoll KS, et al. Results of a pilot randomized controlled trial of buprenorphine for opioid dependent women in the criminal justice system. Drug Alcohol Depend. 2011;119(3):172–8. doi:10.1016/j.drugalcdep.2011.06.021.
68. Binswanger IA, Blatchford PJ, Lindsay RG, Stern MF. Risk factors for all-cause, overdose and early deaths after release from prison in Washington state. Drug Alcohol Depend. 2011;117(1):1–6. doi:10.1016/j.drugalcdep.2010.11.029.
69. Ochoa KC, Davidson PJ, Evans JL, Hahn JA, Page-Shafer K, Moss AR. Heroin overdose among young injection drug users in San Francisco. Drug Alcohol Depend. 2005;80(3):297–302. doi:10.1016/j.druglacdep.2005.04.012.
70. Krinsky CS, Lathrop SL, Brown P, Nolte KB. Drugs, detention, and death a study of the mortality of recently released prisoners. Am J Forensic Med Pathol. 2009;30(1):6–9. doi:10.1097/PAF.0b013e3181873784.
71. Marsch LA, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, Stanger C, et al. Comparison of pharmacological treatments for opioid-dependent adolescents—a randomized controlled trial. Arch Gen Psychiatry. 2005;62(10):1157–64. doi:10.1001/archpsyc.62.10.1157.
72. Smyth BP, Fagan J, Kernan K. Outcome of heroin-dependent adolescents presenting for opiate substitution treatment. J Subst Abuse Treat. 2012;42(1):35–44. doi:10.1016/j.jsat.2011.07.007.

Chapter 12
Buprenorphine Pharmacodynamics and Pharmacokinetics

Sharon L. Walsh and Lisa S. Middleton

Introduction

Buprenorphine, a derivative of the poppy alkaloid thebaine, is a semi-synthetic opioid that was initially synthesized as one of a series of compounds from oripavine [1]. Early in its development, it was recognized that buprenorphine did not behave as a typical mu opioid agonist as it could both produce mu opioid action and block mu opioid effects, hence its early characterization as an opioid agonist–antagonist [2, 3]. It is now known that buprenorphine acts as a partial opioid agonist at the mu receptor, an antagonist at the kappa opioid receptor [4], and as a partial agonist at the nociceptin/orphanin opioid-like receptor (ORL-1, FQ-NOP) [5]. As the benefits of buprenorphine in the treatment of pain and opioid dependence are attributable primarily to buprenorphine's action at mu opioid receptors, this chapter will focus on those actions. It is unclear whether the kappa antagonist and/or nociceptin/orphanin partial agonist activity of buprenorphine produce any effects of clinical relevance, although this has been the focus of some speculation. For example, as kappa agonists are known to produce significant dysphoric effects [6, 7], studies have explored the possibility that buprenorphine, with its kappa antagonist actions, may produce euphoria as a secondary effect, thereby acting as an antidepressant to enhance mood. However, controlled studies have reported no differential benefit of buprenorphine when compared to methadone (which lacks kappa receptor blockade activity) on improvement of depressive symptoms that may occur during the course of treatment for opioid dependence [8]. With regard to the ORL-1 receptor, recent preclinical data suggest that the ORL-1 partial agonist action of buprenorphine can decrease alcohol consumption in laboratory animals [9]; however, this interesting effect has not yet been carefully explored in humans.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_12,

Very soon after its synthesis, buprenorphine was tested for its analgesic activity in clinical populations in Europe and marketed in the United Kingdom in 1978 as an analgesic for moderate-to-severe pain (Temgesic®). Due to its very poor oral bioavailability (secondary to a large first-pass metabolic effect) but high sublingual bioavailability [10], buprenorphine was developed as both a sublingual tablet (Temgesic®, 0.2 mg) and as a solution for intramuscular or intravenous use (Buprenex®, 0.3 mg/mL; Temgesic®, 0.3 mg/mL). More recently, a transdermal analgesic formulation has been approved for use (Butrans®, 5, 10, and 20 μg/h 7-day patch). Buprenorphine for the treatment of opioid dependence is formulated and sold primarily as sublingual tablets but at doses much higher than those marketed for analgesia. Buprenorphine alone (Subutex®; 2 and 8 mg tablets) and buprenorphine in combination with naloxone (intended to deter parenteral misuse; Suboxone®, 8/2 and 2/0.5 mg buprenorphine/naloxone) are marketed in more than 40 countries worldwide. Sublingual tablets of buprenorphine alone are also now available in generic formulations. In 2010, a sublingual film was approved for use in the treatment of opioid dependence (2/0.5 and 8/2 mg buprenorphine/naloxone) with the aim of deterring diversion of prescribed buprenorphine [11, 12]. While the film may dissolve only a bit more quickly than the tablets, its mucoadhesive properties make it much more difficult to remove from the mouth once in place compared to the tablets. Thus, it is hoped that this will further reduce the likelihood of buprenorphine diversion from supervised dosing settings. In the United States, the parenteral analgesic preparation (Buprenex®) is restricted under the Controlled Substances Act by the Drug Enforcement Agency where it is listed as a Schedule II agent, while the sublingual preparations for opioid addiction are registered under Schedule III and, thus, allowed for use in office-based treatment of opioid dependence under the Federal Drug Abuse Treatment Act of 2000 [13]. Butrans®, the transdermal formulation, is also registered under Schedule III but cannot be used in office-based treatment of opioid dependence because it is not approved with this indication.

Pharmacodynamics in Humans: Acute and Chronic Dosing Profile

Acute administration of buprenorphine produces a profile of physiological actions consistent with its characterization as having central and peripheral mu opioid receptor agonist activity. Buprenorphine produces dose-dependent physiological effects, including miosis, slowed gastrointestinal motility, and decreased respiratory rate and related indices (e.g., decreased oxygen saturation). There is little evidence that buprenorphine reliably alters cardiopressor action (i.e., heart rate or blood pressure) under acute dosing conditions, although heart rate and blood pressure may be modestly reduced during chronic administration [14]. As with other mu opioid agonists, acute doses of buprenorphine can lead to nausea and vomiting, urinary

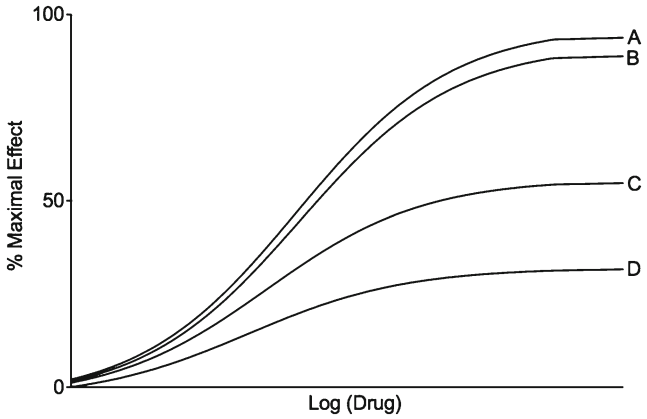

Fig. 12.1 A schematic representation of outcomes comparing a full mu agonist (function *A*) to a partial mu agonist (*B*, *C*, and *D*), whereby functions *B*, *C*, and *D* represent differential outcomes for the same agent depending on which receptor-mediated response of interest is tested (e.g., analgesia, withdrawal suppression, opioid blockade, respiratory depression). This schematic illustrates that, when tested in vivo, a partial agonist may behave similarly to a full agonist, may be comparable to a full agonist over only a portion of the curve, or may reliably produce a lower magnitude of effect over the full therapeutic dose range

retention, and constipation, and tolerance can develop to some of these effects with chronic exposure. This profile of action has been reported after buprenorphine administration by the sublingual, intranasal, subcutaneous, intramuscular, and intravenous routes of administration [14–18].

Consistent with its classification as a partial, rather than full, mu agonist [19], the dose response relationship for buprenorphine is often flattened (rather than showing increasing effects proportionate with dose; see schematic in Fig. 12.1) or even biphasic, whereby effects increase over some portion of the dose range, plateau, and then show some decrease in magnitude of response (i.e., the inverted U-shaped dose response curve). This profile of action is highly relevant from a clinical perspective because this ceiling or plateau has been reported for the respiratory depressant effects of buprenorphine [16, 20], which significantly increases the safety profile of this opioid when compared to full mu opioid agonists. Thus, there is a limit to the degree of respiratory depression that can be produced even at very high doses. In contrast to many full mu opioid agonists used clinically, buprenorphine given alone rarely leads to fatal opioid overdose in adults. However, the risk of overdose in adults is significantly increased when taken in combination with other central nervous system depressants, such as benzodiazepines or alcohol, and fatal overdoses have been reported for these drug combinations [21–23]. Moreover, there have been increasing reports of pediatric overdose [24, 25] from buprenorphine alone due to unintentional exposures, highlighting the importance of securing this medication away from children.

Although the marketed sublingual formulations of buprenorphine are solid tablets, many of the key early studies were conducted prior to the development of the

tablet with an aqueous solution (ethanol dissolved) placed and held under the tongue. While there are significant differences in regard to the relative bioavailability, with the solution having 50 % or greater bioavailability than the tablets on a mg/mg basis [26–28], their pharmacodynamic profiles (after accounting for this differential dose exposure) with regard to time action do not appreciably differ for the formulations; therefore, studies of both the liquid and solid sublingual formulations are reported here. Among individuals with histories of opioid abuse (but without physical dependence on opioids), buprenorphine produces a constellation of effects consistent with other mu opioid agonists. That is, buprenorphine increases subjective ratings of agonist-like effects (e.g., itching, nausea, nodding), increases endorsements of more global euphoric effects, such as "liking" for the drug (a standard abuse liability outcome), and produces sedation. The time to onset of these effects is related to route of administration, with the effects appearing within 30–40 min after sublingual administration and peak responses occurring around 2.5–3 h post-dosing [16, 18, 20, 29]. After parenteral administration, the effects appear within minutes after injection and generally peak within 1 h of drug administration, although peak miotic effects may appear later [14, 15, 30]. The duration of action of acute doses of buprenorphine is substantial with subjective effects persisting for out to 12 h and pupil constriction evident 24 h after a single dose or even longer up to 48 or 72 h after higher doses [14, 16].

While a ceiling on the magnitude of these subjective responses has been reported to occur typically between 8 and 16 mg (as is the case for some physiological outcomes), the overall magnitude of subjective responses predictive of abuse liability are substantial and have been shown to be comparable to acute doses of up to 60 mg methadone [16, 20]. Thus, despite its partial agonist profile, buprenorphine's pharmacodynamic profile suggested that it possessed abuse potential, and its widespread availability in some countries has been associated with reports of misuse, abuse, and dependence [31–35]. Moreover, reports of buprenorphine misuse by other routes of administration, including dissolution of the tablets followed by injection [11, 35, 36] or crushing of the tablets followed by insufflation [37–39], are not uncommon. While misuse and diversion of buprenorphine is also reported increasingly in the United States as its use in opioid dependence treatment has expanded, one study reported that buprenorphine was infrequently described as the "opioid of choice" (in less than 3 % of the cases) when alternative opioids were available for use [40]. Other studies have suggested one commonly reported reason for misuse is for treatment of withdrawal symptoms rather than to achieve euphoria [12].

Because of its highly lipophilic nature and high affinity for binding to the mu opioid receptor, it is commonly accepted that displacement of buprenorphine from the opioid receptor through treatment with an opioid antagonist will require a higher dose of antagonist than needed for reversal of effects of other opioids. One study demonstrated this principal by examining the precipitation of opioid withdrawal in buprenorphine-maintained individuals (8 mg sublingual solution/day; ~12 mg tablet) after administration of a range of opioid antagonist doses [41]. Significant opioid withdrawal occurred only after challenge with naloxone at 3 and 10 mg/70 kg i.m., but not at 0.3 and 1 mg/70 kg. In contrast, naloxone (0.1–0.3 mg/i.m.) is

generally sufficient to produce opioid withdrawal signs and symptoms in individuals dependent on other opioids, such as heroin, methadone, or morphine.

There are other clinical implications arising from the high affinity of buprenorphine for and its slow dissociation from the mu receptor. The first issue is the decreased efficacy of an opioid antagonist with lower affinity to produce full reversal of buprenorphine's action when needed. Thus, in case of buprenorphine overdose, in addition to using higher doses of opioid antagonists for reversal and mechanical assistance of respiration [42], studies have suggested that central respiratory stimulants, whose actions are not mediated through the opioid receptor system (e.g., doxapram, donepezil) [43, 44], may also be useful. Moreover, because of its long duration of action, management of buprenorphine overdose may require more sustained treatment with antagonist therapy. The second clinically important issue is how one may effectively use other opioid analgesics to treat pain in individuals who are maintained on buprenorphine, with some clinical experience suggesting that opioids with greater intrinsic activity and/or different receptor kinetics (e.g., fentanyl) can achieve analgesia in the presence of buprenorphine.

Pharmacodynamics in Analgesia

Buprenorphine can be used by the parenteral, sublingual, rectal, or transdermal routes for analgesia. It may be used as a preanesthetic analgesic, as a supplement to anesthesia and also for postsurgical analgesia. This discussion is significantly abbreviated as two preceding chapters in this volume describe the use of buprenorphine as an analgesic in great detail. Buprenorphine is generally estimated to be between 25 and 40 times more potent than morphine as an analgesic [2]. The typical intravenous dose is 0.3 mg with repeated dosing every 6–8 h, while the sublingual dose is between 0.2 and 0.8 mg every 6–8 h; in both cases, the doses are substantially lower than those used for the treatment of opioid dependence. Based on these recommended dosing regimens, it is evident that the duration of action of buprenorphine for producing analgesic effects is much shorter than would be predicted by its half-life estimates. Moreover, in contrast to the reported partial agonist effects of buprenorphine on measures such as respiratory depression, use of buprenorphine for analgesia occurs over the lower end (and linear portion) of the dose response curve where buprenorphine is reported to behave as a full opioid agonist with regard to its analgesic efficacy (see Fig. 12.1) [45].

Pharmacodynamics in Opioid Dependence

Double-blind clinical trials have demonstrated that buprenorphine is efficacious in reducing illicit opioid use in individuals with opioid dependence [46–49]. The pharmacodynamic properties of buprenorphine that underlie its efficacy include (1) the

ability to suppress withdrawal signs and symptoms, thereby stabilizing physical dependence, (2) an unusually long duration of action that allows for daily or less-than-daily dosing, (3) the ability to produce cross-tolerance (also termed "blockade") which blunts or eliminates the response to illicitly used opioids, which leads to (4) decreased illicit opioid use. Each of these key pharmacologic characteristics has been investigated and characterized in clinical studies.

The earliest work with buprenorphine in humans that characterized the drug as having morphine-like effects supported the notion that buprenorphine, like methadone (which was already in use at the time for the treatment of opioid dependence [50]), could substitute for other opioids, such as heroin, and thereby suppress opioid withdrawal upon cessation of opioid use [14]. However, as buprenorphine possessed lower intrinsic activity compared to full agonists, it was recognized early on that the transition onto buprenorphine from another opioid could itself be associated with a risk of precipitating opioid withdrawal. Receptor theory suggested that binding to the mu opioid receptor by a partial agonist with reduced intrinsic activity along with the subsequent displacement of a mu agonist possessing greater intrinsic activity could lead to a net overall decrease in agonist effect, and, under some circumstances, be expressed as precipitated withdrawal.

Numerous human laboratory studies have been conducted to characterize the critical underlying factors in determining whether buprenorphine administration will produce precipitated withdrawal in opioid-dependent subjects; this issue represented a significant clinical concern related to the comfortable initiation of buprenorphine treatment in patients with variable use of different opioids (e.g., heroin, methadone) presenting for treatment. Studies have shown that subjects maintained on methadone and then given buprenorphine may, in some cases, show no change in status while others exhibit precipitated withdrawal symptoms. For example, when buprenorphine was introduced to subjects maintained on a lower dose of methadone (i.e., 30 mg) at 20 h [51] or 24 h [52] after methadone dosing, there was no evidence of precipitated withdrawal. However, when buprenorphine challenges were given at 2 h [53] or 40 h [54] after methadone administration, significant precipitated withdrawal was observed. In the latter study, maintenance on methadone at 30 and 60 mg/day were examined, and the magnitude of the signs and symptoms was related both to maintenance dose of methadone and buprenorphine doses [54]. That is, subjects maintained on 60 mg exhibited greater withdrawal compared to those maintained on 30 mg, and higher doses of buprenorphine (8 mg, sublingual) produced worse symptoms compared to lower doses (2 and 4 mg, sublingual). Studies have examined the effect of challenging with a range of doses of buprenorphine/naloxone in subjects maintained on buprenorphine and revealed no evidence of precipitated withdrawal [55]. Finally, studies examining the effect of buprenorphine administration to subjects maintained on shorter acting opioids (e.g., morphine [56–58] or heroin [59]) have generally demonstrated that this is readily tolerated and unlikely to lead to precipitated withdrawal. The general underlying principal to avoid precipitated withdrawal, regardless of the opioid on which that individual is physically dependent, is to introduce buprenorphine under conditions when one would expect to have fewer opioid receptors occupied. Thus, the common practice

of requiring patients to be in mild withdrawal prior to induction onto buprenorphine ensures decreased receptor occupancy at the time of first buprenorphine dose. Another study capitalized on this same principal by modifying the rate at which buprenorphine was introduced to avoid precipitated withdrawal. In that study, subjects were maintained on 100 mg of methadone and challenged with ascending doses of buprenorphine [60]. This is a clinically relevant study because transferring patients from methadone to buprenorphine is more difficult than transferring patients from other mu agonists that have a much shorter half-life, and current clinical guidelines recommend that attempts to start buprenorphine should not occur until patients are on 30–40 mg of methadone daily. This is sometimes intolerable to patients either transferring from a methadone treatment program or for those whose primary opioid of abuse is illicit methadone. In order to determine if patients may be able to transfer to buprenorphine from higher methadone doses, this study first determined the specific sublingual buprenorphine dose that reliably precipitated withdrawal for each subject when given 24 h after their last 100 mg dose of methadone. Then, that same dose was administered on another occasion but was given as two *divided* doses separated by 2 h (thereby decreasing the immediate influx of buprenorphine into the central nervous system); the withdrawal syndrome was completely avoided. Thus, giving 8 mg all at once produces very different pharmacodynamic effects than giving 4 mg followed by another 4 mg. The latter is much less likely to produce uncomfortable withdrawal symptoms and supports the clinical guidances of giving 2–4 mg of buprenorphine during induction. However, there remains a lack of US guidances for transferring from high dose methadone.

The first demonstration of buprenorphine "blockade" of opioid effects was reported in the seminal work by Jasinski and colleagues conducted at the Lexington Narcotic Prison Farm Hospital [14]. Subjects in this study were maintained on buprenorphine (up to 8 mg, given as once daily subcutaneous injection) and tested with varying morphine doses given within a few hours of buprenorphine. These authors reported that blockade of morphine doses up to 120 mg (subcutaneous) was nearly complete. In a subsequent study, a range of buprenorphine maintenance doses (2, 4, 8, and 16 mg, sublingual) was explored for their ability to block the pharmacodynamic effects of hydromorphone [61]. It was demonstrated that the efficacy of buprenorphine to blunt hydromorphone effects (administered at 24 h after dosing) was systematically related to buprenorphine maintenance dose with the lowest dose producing the least protection and the highest dose producing nearly complete blockade. Another study examined the effects of hydromorphone challenge doses in a small cohort of subjects maintained on 2, 6, or 12 mg sublingual buprenorphine [62]. This study confirmed the dose-dependent nature of buprenorphine blockade but also explored its duration. Using a single-blind procedure whereby the placebo dose was substituted for the regularly scheduled dose of buprenorphine for 3 consecutive days, this study reported that buprenorphine could produce blockade of the "high" from hydromorphone for up to 72 h after the last active dose. Similarly, the dose-related opioid blockade produced by buprenorphine administration has been reported after acute dosing with buprenorphine in nondependent individuals [20] and after maintenance on the buprenorphine/naloxone combination [63].

The important clinical consequence of buprenorphine-induced opioid blockade or cross-tolerance is attributable to the finding that a reduction in the positive euphoric effects of other opioids in the presence of buprenorphine maintenance leads to reduced opioid drug taking, a critical clinical target. Pivotal early work by Mello and colleagues demonstrated that subjects maintained on buprenorphine worked to self-administer significantly less heroin compared to the placebo maintenance condition [64, 65]. Moreover, this work revealed that the magnitude of heroin self-administration suppression was systematically related to buprenorphine dose, with higher doses producing greater suppression. More recent studies have expanded these observations to demonstrate dose-dependent reductions of heroin self-administration through maintenance on sublingual buprenorphine [66] and buprenorphine/naloxone [67]. Importantly, these studies were done with buprenorphine maintenance doses that were all effective at suppressing withdrawal, reminding clinicians that the buprenorphine dose that suppresses withdrawal is not the same dose that produces opioid blockade. For patients with continued illicit opioid use, an important question to ask is whether they are getting positive effects from the illicit opioid use; a patient who continues to have positive drug effects from the illicit opioids should be strongly considered for a maintenance dose increase (assuming the patient is adhering to the current dose prescribed).

Early animal laboratory studies reported that chronic administration of buprenorphine produced limited physical dependence [2, 3]. Clinical studies indicate that buprenorphine does produce a physical dependence syndrome and that, while abrupt withdrawal from buprenorphine produces typical opioid-like withdrawal signs and symptoms (i.e., mydriasis, chills, gastrointestinal distress, urges to use opioids), the intensity of the withdrawal syndrome is mild compared to that measured after abrupt withdrawal from full mu opioids agonists [14, 68]. Observable withdrawal signs are less prominent than subjective complaints of withdrawal following abrupt discontinuation. Studies indicate that signs and symptoms typically peak between 3 and 5 days post-dosing and may persist for more than 1 week, but clinical reports suggest that the peak withdrawal may occur a bit later. Although the lower intrinsic activity of buprenorphine is likely largely responsible for the observation that withdrawal from buprenorphine is milder compared to withdrawal from full agonists, it is also likely that its long duration of action and slow dissociation from the receptor serve to moderate the intensity of the opioid withdrawal syndrome; however, these comparative data should not be interpreted to suggest that patients will discontinue buprenorphine with ease as they will experience withdrawal and should be informed of this if they intend to discontinue therapy.

As buprenorphine was recognized as having intrinsic abuse liability, the buprenorphine/naloxone combination product was developed as an abuse-deterrent formulation similarly to the pentazocine/naloxone combination product, which preceded it. As naloxone is known to have poor sublingual bioavailability [69], incorporation of lower naloxone doses in the sublingual buprenorphine formulation is essentially inert when taken by the intended route of administration. However, in the event of misuse by the parenteral route, naloxone would be functionally 100 % bioavailable, thereby likely to precipitate withdrawal and act as a

deterrent to parenteral misuse in individuals with opioid dependence. Several early studies were designed to identify the best ratio of buprenorphine:naloxone to ensure that the combination product would perform as intended [52, 55, 57, 59]. Ultimately, a 4:1 ratio of buprenorphine:naloxone was selected for development of a commercial product as 2/0.5 and 8/2 mg sublingual tablets. Indeed, studies have shown that the inclusion of naloxone does not generally alter the bioavailability or pharmacodynamic actions of buprenorphine by either the sublingual [27], intranasal [17], or parenteral routes when given to individuals who are not physically dependent on opioids, which suggests limited abuse deterrence advantage for this formulation over the buprenorphine only product in this population. In contrast, when the combination product is administered parenterally to opioid-dependent individuals, buprenorphine/naloxone produces a robust and immediate precipitated withdrawal syndrome under conditions where buprenorphine alone does not [70]. It is not known whether this also occurs when buprenorphine/naloxone is taken by the intranasal route but recent work in nondependent subjects is suggestive that it may occur as intranasal bioavailability of naloxone was relatively high [17].

Pharmacokinetics

Absorption

Parenteral solution products formulated for the treatment of pain are expected to have 100 % bioavailability. Sublingual bioavailability of buprenorphine in a buffered aqueous solution was estimated to be approximately 55 % [10]. Although several studies have compared the sublingual bioavailability of the aqueous ethanol solution of buprenorphine, few published studies have directly examined the bioavailability of the marketed tablets. Nath and colleagues [26] estimated that the bioavailability of the sublingual buprenorphine tablets may be as low as 15 % through extrapolation to previously published intravenous data. The presence of naloxone does not substantially alter absorption of buprenorphine; however, some data suggest that the combination product may actually have slightly higher bioavailability than the buprenorphine only product [71]. Data on the bioavailability of the sublingual film administration has not yet been published; however, the manufacturer's package insert suggests it may be slightly higher than that of the tablet but does not recommend dose reductions if switching from the tablet to the film (can be found at http://www.suboxone.com/). The bioavailability of the transdermal buprenorphine patch is approximately 15 % following a 7-day application of the patch [72], and absolute transdermal absorption may be dependent on patch placement (e.g., upper back > abdomen ≥ thigh > patella). Thus, patient compliance with manufacturer recommended patch placement is important to achieve optimal analgesic relief.

Distribution

Following intravenous administration of buprenorphine, the time-to-peak plasma concentration (T_{max}) occurs within minutes of infusion (see Table 12.1). Following sublingual administration (tablet or film) of doses used for opioid dependence treatment (4–24 mg), maximal plasma concentrations are dose dependent (but not necessarily dose proportional) and reached within approximately 60–90 min after dosing (see Table 12.1) [26, 27, 71, 73, 74]. The 2/0.5 mg dose of the sublingual film may result in slightly higher maximal plasma concentrations compared to the tablet; whereas, after 8/2 mg, the film reliably has higher plasma concentrations than the tablet [75]. Maximal plasma concentrations of buprenorphine for the sustained release patch were reached after 108 h following a 5 μg/h patch.

Buprenorphine is 96 % protein bound, primarily binding to alpha and beta globulin [76]. Buprenorphine (in either its base or hydrochloride form) is highly lipophilic (p*K*a = 8.5) with octanol:water and octanol:buffer partition coefficients ranging from 427 to 1,943 [77–79]. The elimination of buprenorphine from plasma follows a three-compartment model, with buprenorphine initially distributed centrally followed by distribution to the tissue, then to bone or fat [80–82]. It readily distributes throughout the blood and crosses the blood brain barrier to the central nervous system. The volume of distribution of intravenous buprenorphine is approximately 335–430 L, suggesting that buprenorphine is distributed extensively throughout the body [83]. While one study reported a lower volume of distribution (188 L) after intravenous administration; these data were collected while patients were under anesthesia, which can slow blood flow resulting in reduced distribution [80]. In vitro skin flux experiments demonstrated that skin flux of buprenorphine is 0.093–2.4 μg/cm^2/h [78, 79], and the variability may be due to differential preparation of the skin samples (i.e., cadaver vs. fresh skin samples).

Metabolism

Buprenorphine is metabolized primarily in the liver by cytochrome P450 (CYP) 3A4 with CYPs 3A5, 3A7, and 2C8 playing minor roles in its metabolism [84, 85]. Buprenorphine is metabolized through glucuronidation and dealkylation forming the major metabolites of buprenorphine-3-glucuronide and norbuprenorphine, respectively. While additional metabolites have been identified (see Fig. 12.2); norbuprenorphine is the only metabolite identified as pharmacologically active [77], and the clinical significance, if any, of the others has not been determined [84]. As described earlier, buprenorphine has low oral bioavailability due to its extensive first-pass hepatic metabolism. One recent retrospective study examined buprenorphine metabolism in opioid-dependent, buprenorphine-maintained individuals and reported higher area-under-the-curve values for females compared to males for the parent drug and its two major metabolites. However, after correction for body

Table 12.1 Summary of key pharmacokinetic outcomes for buprenorphine sublingual tablets, sublingual film, parenteral solution, and transdermal patch

Buprenorphine for opioid dependence	Dose (mg)	*C*max (ng/mL)	*T*max (h)	AUC*	*T*1/2 (h)
Sublingual tablet					
Nath et al. [26]	8	2.9	1.2	13[1]	n/a
Schuh and Johanson [28]	8	3.0	2.0	1.2[2]	n/a
Harris et al. [27]	16	5.5	1.0	33[3]	
	4/1	1.8	1.1	13	n/a
	8/2	3.0	1.0	20	n/a
	16/4	6.0	0.8	35	n/a
Strain et al. [71]	8	2.1	1.0	1.1[1,a]	n/a
	8/2	2.8	1.1	1.4	n/a
Chawarski et al. [111]	16	3.7	n/a	31[4]	n/a
	24	6.6	n/a	56	n/a
	32	6.2	n/a	54	n/a
Ciraulo et al. [74]	4	2.0	1.1	9.4[1]	n/a
	8	2.7	1.2	20	n/a
	16	4.4	0.9	35	n/a
	24	5.4	0.9	49	n/a
	4/1	2.3	1.0	13	n/a
	8/2	3.5	1.0	23	n/a
	16/4	5.8	1.1	39	n/a
	24/6	6.4	1.0	48	n/a
Compton et al. [112]	8	10	1.2	70[4]	n/a
Huang et al. [113]	16/4	4.5	0.9	32[4]	n/a
Greenwald et al. [114]	16	3.9	2.2	42[4]	22
Simojoki et al. [115]	24	9.6	1.7	108[1]	n/a
Sublingual film					
Australian Government Department of Health and Ageing [75]	2/0.5	1.0	1.5	8.7[1]	33
	4/1	1.4	1.5	14	n/a
	8/2	3.4	1.3	31	33
	12/3	4.1	1.5	41	n/a
	16/4	6.1	1.3	53	n/a
Buprenorphine for analgesia					
Intravenous solution					
Kuhlman et al. [83]	1.2	38	0.04	17[1]	3.2
Bullingham et al. [80]	0.3	18	n/a	n/a	2.2
Escher et al. [105]	0.15	n/a[b]	n/a	35[5]	2.8
Middleton et al. (unpublished data)	0.8	30	0.03	12[2]	1.9
Transdermal patch					
Purdue Pharma, Butrans Package Insert	5 μg/h	0.2	n/a	12[1]	n/a
	10 μg/h	0.2	n/a	27	n/a
	20 μg/h	0.5	n/a	54	n/a

*see superscripts for units
[1]h*ng/ml, [2]ng/ml, 3μg*h/L, [4]ng/ml*h, [5]ng*ml/h
[a]area-under-the-curve 0-6 hrs
[b]value removed due to discrepancy in manuscript
n/a-not applicable

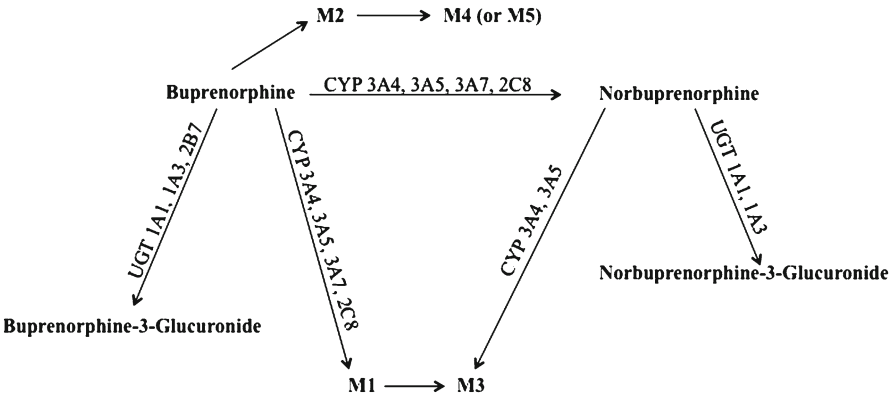

Fig. 12.2 Proposed metabolic pathways for buprenorphine enzymatic transformations

weight, only minor differences in norbuprenorphine area-under-the-curve estimates remained, suggesting that the differences may be related primarily to body composition rather than metabolic patterns [86]. In patients with severe chronic liver disease, CYP 3A expression is reduced [87, 88], but the effect of decreased CYP 3A expression on buprenorphine metabolism has not been determined. However, patients with liver disease to whom buprenorphine or buprenorphine/naloxone is prescribed should be monitored carefully as concentrations of both drugs could be higher than expected in the presence of hepatic impairment.

As buprenorphine is metabolized primarily by hepatic CYP 3A4, patients taking buprenorphine requiring additional medications that inhibit or induce activation of CYP 3A4 should be monitored. Common medications for the treatment of HIV (i.e., protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and nucleoside reverse transcriptase inhibitors) are often metabolized through the CYP 3A4 enzyme. For example, the CYP 3A4 inhibitors, delavirdine and ritonavir, can increase buprenorphine plasma concentrations but without clinically significant alterations in therapeutic response [89, 90]. Efavirenz, a CYP 3A4 inducer, was shown to decrease buprenorphine concentrations but not sufficiently so as to induce opioid withdrawal [89], while coadministration of other CYP 3A4 inducers (e.g., nevirapine) did not alter buprenorphine concentrations [91]. Other commonly used HIV medications have been tested and found to have no clinically significant interactions in patients maintained on buprenorphine [92–95]. Therefore, the need to adjust dosing when using buprenorphine in combination with antiretrovirals may be uncommon; however, patients should be monitored carefully for toxicity and/or withdrawal whenever introducing new concomitant medications. The risk of drug–drug interactions with buprenorphine is described in greater detail in a later chapter in this same volume.

Of greatest clinical concern are the risks arising from drug–drug interactions between buprenorphine and central nervous system depressants, including benzodiazepines or alcohol. It is not uncommon for opioid-dependent patients to have

problems with sleep and anxiety; while benzodiazepines can be prescribed for anxiety and sleep, the illicit combination of benzodiazepines with opioids is a commonly preferred drug combination in this population. However, whether licit or illicit, the risks of combining benzodiazepines with buprenorphine are significant and sometimes fatal [96–98]. In some instances, drug–drug interactions between these classes may be mediated at the metabolic level (i.e., because they both act as substrates at the same enzyme as with midazolam [99]); however, in others the interaction is purely pharmacodynamic (i.e., a synergistic or additive effect in absence of a common metabolic pathway). In either case, laboratory studies with nonhuman and human subjects have reported potentiation of the psychomotor impairing [100, 101] and respiratory depressant effects [102, 103]. Therefore, recommendations against co-prescribing of benzodiazepines have emerged in the literature, while others have argued that it can be safely accomplished under carefully selected and supervised conditions; recommendations for clinical management have been recently published [104].

Excretion

The initial plasma half-life of buprenorphine following intravenous buprenorphine (0.3 or 1.2 mg) ranges from 1.9 to 3.2 h [80, 83, 105], while the plasma terminal half-life of buprenorphine following sublingual (tablet and film) and transdermal buprenorphine administration is between 22 and 48 h (see Table 12.1). Buprenorphine (and/or its metabolites) is excreted in urine, feces, and breast milk. Free buprenorphine is not present in urine after sublingual administration; however, conjugated buprenorphine and norbuprenorphine are present in low amounts (1.9–14.3 %; [106]). Norbuprenorphine-3-glucuronide is the primary metabolite present in plasma and urine [113]. The effect of renal insufficiency on buprenorphine excretion has not been examined; however, the small role of the kidney in buprenorphine excretion suggests that renal insufficiency should not significantly alter buprenorphine excretion. The majority (~70 %) of free buprenorphine and norbuprenorphine along with their conjugates are found in feces following sublingual buprenorphine administration [106, 107]. The presence of free buprenorphine and norbuprenorphine in feces may be due to hepatobiliary recirculation where the conjugated metabolites of buprenorphine are excreted into the bile and hydrolyzed in the gastrointestinal tract. Buprenorphine and norbuprenorphine can also be excreted in breast milk, and while the concentrations of buprenorphine and norbuprenorphine in breast milk that would be ingested by the infant are comparatively low [108, 109], the effects on the infant have not been completely characterized. However, buprenorphine maintenance of opioid-dependent pregnant women has recently been demonstrated to lead to improved neonatal outcomes, including a shorter duration of neonatal abstinence syndrome and significantly reduced length of stay in the hospital, in comparison to neonates born to methadone-maintained mothers [110].

Summary

In summary, buprenorphine is a semi-synthetic opioid that is unique in its pharmacological profile as a partial mu opioid agonist with an unusually long duration of action. These characteristics have led to the development of buprenorphine in various marketed formulations efficacious for the treatment of acute and chronic pain and for the treatment of opioid dependence. Its partial agonist properties confers an additional safety advantage over full agonists as it produces limited respiratory depression; however, the risk for adverse outcomes is increased with concomitant use of central nervous system depressants. Its long duration of action allows its use in the treatment of opioid dependence on a once daily basis. In opioid dependence, buprenorphine effectively suppresses opioid withdrawal and at higher doses produces opioid blockade/cross-tolerance to blunt the effects of other opioids, leading to reductions in illicit opioid use. It has a favorable metabolic profile as many of the drug–drug interactions observed have not led to clinically important alterations in therapeutic response. Thus, the clinical utility of buprenorphine is characterized by high efficacy as an analgesic and opioid replacement therapy and an excellent safety profile.

Acknowledgment The authors would like to kindly acknowledge the support of the National Institute on Drug Abuse (R01 DA016718) in preparing this chapter.

References

1. Lewis JW. C-bridged derivatives of thebaine and oripavine. Adv Biochem Pharmacol. 1974;8:123–36.
2. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol. 1977;60(4):537–45.
3. Cowan A, Doxey JC, Harry EJR. The animal pharmacology of buprenorphine, an oripavine analgesic agent. Br J Pharmacol. 1977;60:547–54.
4. Lewis JW. Buprenorphine. Drug Alcohol Depend. 1985;14(3–4):363–72.
5. Bloms-Funke P, Gillen C, Schuettler AJ, Wnendt S. Agonistic effects of the opioid buprenorphine on the nociceptin/OFQ receptor. Peptides. 2000;21:1141–6.
6. Kumor KM, Haertzen CA, Johnson RE, Kocher TR, Jasinski DR. Human psychopharmacology of ketocyclazocine as compared with cyclazocine, morphine and placebo. J Pharmacol Exp Ther. 1986;238:960–8.
7. Walsh SL, Strain EC, Abreu ME, Bigelow GE. Enadoline, a selective kappa opioid agonist: comparison with butorphanol and hydromorphone in humans. Psychopharmacology (Berl). 2001;157:151–62.
8. Dean AJ, Bell J, Christie MJ, Mattick RP. Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. Eur J Psychiatry. 2004;19(8):510–3.
9. Ciccocioppo R, Economidou D, Rimondini R, Sommer W, Massi M, Heilig M. Buprenorphine reduces alcohol drinking through activation of the nociceptin-orphanin FQ-NOP receptor system. Biol Psychiatry. 2007;61:4–12.
10. Weinberg D, Inturrisi CE, Reidenberg B, et al. Sublingual absorption of selected opioid analgesics. Clin Pharmacol Ther. 1988;44:335–42.

11. Larance B, Degenhardt L, Lintzeris N, et al. Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised dosing. Drug Alcohol Depend. 2011;118(2–3):265–73.
12. Johanson CE, Arfken CL, di Menza S, Schuster CR. Diversion and abuse of buprenorphine: findings from national surveys of treatment patients and physicians. Drug Alcohol Depend. 2012;120(1–3):190–5.
13. Drug Addiction Treatment Act of 2000, 1223-1227 801, §3501 (DATA, 2000).
14. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry. 1978;35(4):501–16.
15. Pickworth WB, Johnson RE, Holicky BA, Cone EJ. Subjective and physiologic effects of intravenous buprenorphine in humans. Clin Pharmacol Ther. 1993;53(5):570–6.
16. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55:569–80.
17. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction. 2011;106(8):1460–73.
18. Duke AN, Correia CJ, Walsh SL, Bigelow GE, Strain EC. Acute effects of intramuscular and sublingual buprenorphine and buprenorphine/naloxone in non-dependent opioid abusers. Psychopharmacology (Berl). 2010;211(3):303–12.
19. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine-like drugs in the non-dependent and morphine-dependent chronic spinal dog. J Pharmacol Exp Ther. 1976;197:517–32.
20. Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: partial agonist and blockade effects. J Pharmacol Exp Ther. 1995;274:361–72.
21. Ferrant O, Papin F, Clin B, et al. Fatal poisoning due to snorting buprenorphine and alcohol consumption. Forensic Sci Int. 2011;204:e8–11.
22. Schifano F, Corkery J, Gilvarry E, Deluca P, Oyefeso A, Ghodse AH. Buprenorphine mortality, seizures and prescription data in the UK, 1980-2002. Hum Psychopharmacol. 2005;20(5):343–8.
23. Reynaud M, Tracqui A, Petit G, Potard D, Courty P. Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. Am J Psychiatry. 1998;155(3):448–9.
24. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. Am J Addict. 2009;19(1):89–95.
25. Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. Pediatrics. 2008;121(4):e782–6.
26. Nath RP, Upton RA, Everhart ET, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. J Clin Pharmacol. 1999;39:619–23.
27. Harris DS, Mendelson JE, Lin ET, Upton RA, Jones RT. Pharmacokinetics and subjective effects of sublingual buprenorphine, alone or in combination with naloxone: lack of dose proportionality. Clin Pharmacokinet. 2004;43(5):329–40.
28. Schuh K, Johanson C-E. Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet. Drug Alcohol Depend. 1999;56:55–60.
29. Strain EC, Stoller K, Walsh SL, Bigelow GE. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. Psychopharmacology (Berl). 2000;148(4):374–83.
30. Jasinski DR, Fudala PJ, Johnson RE. Sublingual versus subcutaneous buprenorphine in opiate abusers. Clin Pharmacol Ther. 1989;45(5):513–9.
31. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. Addiction. 2001;96(2):267–72.
32. O'Connor JJ, Moloney E, Travers R, Campbell A. Buprenorphine abuse among opiate addicts. Br J Addict. 1988;83(9):1085–7.
33. Chowdhury AN, Chowdhury S. Buprenorphine abuse: report from India. Br J Addict. 1990;85(10):1349–50.

34. Bruce RD, Govindasamy S, Sylla L, Kamarulzaman A, Altice FL. Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. Am J Drug Alcohol Abuse. 2009;35(2):68–72.
35. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend. 2007;88:75–8.
36. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? Addiction. 2005;100:197–205.
37. Barrau K, Thirion X, Micallef J, Chuniaud-Louche C, Bellemin B, San Marco JL. Comparison of methadone and high dosage buprenorphine users in French care centres. Addiction. 2001;96(10):1433–41.
38. Roux P, Villes V, Bry D, et al. Buprenorphine sniffing as a response to inadequate care in substituted patients: results from the Subazur survey in south-eastern France. Addict Behav. 2008;33(12):1625–9.
39. United States Department of Justice. Intelligence bulletin: buprenorphine: potential for abuse. Washington, DC: United States Department of Justice; 2004.
40. Cicero TJ, Surratt HL, Inciardi JA. Use and misuse of buprenorphine in the management of opioid addiction. J Opioid Manag. 2007;3(6):1–7.
41. Eissenberg T, Greenwald MW, Johnson RE, Liebson IA, Bigelow GE, Stitzer ML. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. J Pharmacol Exp Ther. 1996;276:449–59.
42. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. Clin Pharmacol Ther. 1989;45(1):66–71.
43. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17(2):81–110.
44. Sakuraba S, Tsujita M, Arisaka H, Takeda J, Yoshida K, Kuwana S-I. Donepezil reverses buprenorphine-induced central respiratory depression in anesthetized rabbits. Biol Res. 2009;42:469–75.
45. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627–32.
46. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med. 2000;343:1291–7.
47. Montoya ID, Gorelick DA, Preston KL, et al. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. Clin Pharmacol Ther. 2004;75(1):34–48.
48. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry. 1997;54(8):713–20.
49. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. J Nerv Ment Dis. 1993;181(6):358–64.
50. Dole VP, Nyswander ME. A medical treatment for diacetyl-morphine (heroin) addiction. J Am Med Assoc. 1965;193:646–50.
51. Strain EC, Preston KL, Liebson IA, Bigelow GE. Acute effects of buprenorphine, hydromorphone and naloxone in methadone-maintained volunteers. J Pharmacol Exp Ther. 1992;261:985–93.
52. Preston KL, Bigelow GE, Liebson IA. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. Psychopharmacology (Berl). 1988;94(4):484–90.
53. Strain EC, Preston KL, Liebson IA, Bigelow GE. Buprenorphine effects in methadone-maintained volunteers: effects at two hours after methadone. J Pharmacol Exp Ther. 1995;272(2):628–38.
54. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. Psychopharmacology (Berl). 1995;119(3):268–76.

55. Harris DS, Jones RT, Welm S, Upton RA, Lin E, Mendelson J. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. Drug Alcohol Depend. 2000;61(1):85–94.
56. Schuh KJ, Walsh SL, Bigelow GE, Preston KL, Stitzer ML. Buprenorphine, morphine and naloxone effects during ascending morphine maintenance in humans. J Pharmacol Exp Ther. 1996;278:836–46.
57. Mendelson J, Jones RT, Welm S, et al. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. Psychopharmacology (Berl). 1999;141(1):37–46.
58. Fudala PJ, Yu E, Macfadden W, Boardman C, Chiang CN. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. Drug Alcohol Depend. 1998;50(1):1–8.
59. Mendelson J, Jones RT, Fernandez I, Welm S, Melby AK, Baggott MJ. Buprenorphine and naloxone interactions in opiate-dependent volunteers. Clin Pharmacol Ther. 1996;60(1):105–14.
60. Rosado J, Walsh SL, Bigelow GE, Strain EC. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100 mg of daily methadone. Drug Alcohol Depend. 2007;90(2–3):261–9.
61. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. J Pharmacol Exp Ther. 1988;247:47–53.
62. Rosen MI, Wallace EA, McMahon TJ, et al. Buprenorphine: duration of blockade of effects of intramuscular hydromorphone. Drug Alcohol Depend. 1994;35:141–9.
63. Strain EC, Walsh SL, Bigelow GE. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. Psychopharmacology (Berl). 2002;159(2):161–6.
64. Mello NK, Mendelson JH. Buprenorphine suppresses heroin use by heroin addicts. Science. 1980;207(4431):657–9.
65. Mello NK, Mendelson JH, Kuehnle JC. Buprenorphine effects on human heroin self-administration: an operant analysis. J Pharmacol Exp Ther. 1982;223(1):30–9.
66. Comer SD, Collins ED, Fischman MW. Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. Psychopharmacology (Berl). 2001;154(28–37):28–37.
67. Comer SD, Walker EA, Collins ED. Buprenorphine/naloxone reduces the reinforcing and subjective effects of heroin in heroin-dependent volunteers. Psychopharmacology (Berl). 2005;181:664–75.
68. Fudala PJ, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. Clin Pharmacol Ther. 1990;47(4):525–34.
69. Preston KL, Bigelow GE, Liebson IA. Effects of sublingually given naloxone in opioid-dependent volunteers. Drug Alcohol Depend. 1990;25:27–34.
70. Stoller K, Bigelow GE, Walsh SL, Strain EC. Effects of buprenorphine/naloxone in opioid-dependent humans. Psychopharmacology (Berl). 2001;154:230–42.
71. Strain EC, Moody DE, Stoller KB, Walsh SL, Bigelow GE. Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. Drug Alcohol Depend. 2004;74(1):37–43.
72. Butrans®: Highlights of prescribing information (manufacturer's package insert), Purdue Pharma, 2010 (and accessible at http://app.purduepharma.com/xmlpublishing/pi.aspx?id=b)
73. Schuh KJ, Stitzer ML. Desire to smoke during spaced smoking intervals. Psychopharmacology (Berl). 1995;120(3):289–95.
74. Ciraulo DA, Hitzemann RJ, Somoza E, et al. Pharmacokinetics and pharmacodynamics of multiple sublingual buprenorphine tablets in dose-escalation trials. J Clin Pharmacol. 2006;46(2):179–92.
75. Australian Government Department of Health and Ageing, Therapeutic goods administration. 2011. http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-buprenorphine
76. Walter DS, Inturrisi CE. Absorption, distribution, metabolism, excretion of buprenorphine in animals and humans. In: Cowan A, Lewis JW, editors. Buprenorphine: combating drug abuse with a unique opioid. New York: Wiley; 1995. p. 113–35.

77. Ohtani M, Kotaki H, Sawada Y, Iga T. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. J Pharmacol Exp Ther. 1995;272(2):505–10.
78. Stinchcomb AL, Paliwal A, Dua R, Imoto H, Woodard RW, Flynn GL. Permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin. Pharm Res. 1996;13(10):1519–23.
79. Roy SD, Roos E, Sharma K. Transdermal delivery of buprenorphine through cadaver skin. J Pharmacol Sci. 1994;83(2):126–30.
80. Bullingham RE, McQuay HJ, Moore A, Bennett MR. Buprenorphine kinetics. Clin Pharmacol Ther. 1980;28(5):667–72.
81. Jensen ML, Foster DJ, Upton RN, et al. Population pharmacokinetics of buprenorphine following a two-stage intravenous infusion in healthy volunteers. Eur J Clin Pharmacol. 2007;63(12):1153–9.
82. Yassen A, Olofsen E, Romberg R, Sarton E, Danhof M, Dahan A. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine in healthy volunteers. Anesthesiology. 2006;104(6):1232–42.
83. Kuhlman Jr JJ, Lalani S, Magluilo Jr J, Levine B, Darwin WD. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. J Anal Toxicol. 1996;20(6):369–78.
84. Chang Y, Moody DE, McCance-Katz EF. Novel metabolites of buprenorphine detected in human liver microsomes and human urine. Drug Metab Dispos. 2006;34(3):440–8.
85. Picard N, Cresteil T, Djebli N, Marquet P. In vitro metabolism study of buprenorphine: evidence for new metabolic pathways. Drug Metab Dispos. 2005;33(5):689–95.
86. Moody DE, Fang WB, Morrison J, McCance-Katz E. Gender differences in pharmacokinetics of maintenance dosed buprenorphine. Drug Alcohol Depend. 2011;118(2–3):479–83.
87. George J, Murray M, Byth K, Farrell GC. Differential alterations of cytochrome P450 proteins in livers from patients with severe chronic liver disease. Hepatology. 1995;21(1):120–8.
88. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet. 1999;37(1):17–40.
89. McCance-Katz EF, Moody DE, Morse GD, et al. Interactions between buprenorphine and antiretrovirals. I. The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. Clin Infect Dis. 2006;43(Suppl 4):S224–34.
90. McCance-Katz EF, Moody DE, Smith PF, et al. Interactions between buprenorphine and antiretrovirals. II. The protease inhibitors nelfinavir, lopinavir/ritonavir, and ritonavir. Clin Infect Dis. 2006;43(Suppl 4):S235–46.
91. McCance-Katz EF, Moody DE, Morse GD, Ma Q, Rainey PM. Lack of clinically significant drug interactions between nevirapine and buprenorphine. Am J Addict. 2010;19(1):30–7.
92. McCance-Katz EF, Rainey PM, Friedland G, Kosten TR, Jatlow P. Effect of opioid dependence pharmacotherapies on zidovudine disposition. Am J Addict. 2001;10(4):296–307.
93. Baker J, Rainey PM, Moody DE, Morse GD, Ma Q, McCance-Katz EF. Interactions between buprenorphine and antiretrovirals: nucleos(t)ide reverse transcriptase inhibitors (NRTI) didanosine, lamivudine, and tenofovir. Am J Addict. 2010;19(1):17–29.
94. Gruber VA, Rainey PM, Moody DE, et al. Interactions between buprenorphine and the protease inhibitors darunavir-ritonavir and fosamprenavir-ritonavir. Clin Infect Dis. 2012;54(3):414–23.
95. Bruce RD, Altice FL, Moody DE, et al. Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone. Drug Alcohol Depend. 2009;105(3):234–9.
96. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction. 1998;93(9):1385–92.
97. Kintz P. A new series of 13 buprenorphine-related deaths. Clin Biochem. 2002;35(7):513–6.
98. Lai SH, Yao YJ, Lo DS. A survey of buprenorphine related deaths in Singapore. Forensic Sci Int. 2006;162(1–3):80–6.

99. Chang Y, Moody DE. Effect of benzodiazepines on the metabolism of buprenorphine in human liver microsomes. Eur J Clin Pharmacol. 2005;60(12):875–81.
100. Lintzeris N, Mitchell TB, Bond A, Nestor L, Strang J. Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients. J Clin Psychopharmacol. 2006;26(3):274–83.
101. Lintzeris N, Mitchell TB, Bond AJ, Nestor L, Strang J. Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. Drug Alcohol Depend. 2007;91(2–3):187–94.
102. Gueye PN, Borron SW, Risede P, et al. Buprenorphine and midazolam act in combination to depress respiration in rats. Toxicol Sci. 2002;65(1):107–14.
103. Nielsen S, Taylor DA. The effect of buprenorphine and benzodiazepines on respiration in the rat. Drug Alcohol Depend. 2005;79(1):95–101.
104. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: interactions and clinical management. Am J Addict. 2010;19(1):59–72.
105. Escher M, Daali Y, Chabert J, Hopfgartner G, Dayer P, Desmeules J. Pharmacokinetic and pharmacodynamic properties of buprenorphine after a single intravenous administration in healthy volunteers: a randomized, double-blind, placebo-controlled, crossover study. Clin Ther. 2007;29(8):1620–31.
106. Cone EJ, Gorodetzky CW, Yousefnejad D, Buchwald WF, Johnson RE. The metabolism and excretion of buprenorphine in humans. Drug Metab Dispos. 1984;12(5):577–81.
107. Brewster D, Humphrey MJ, McLeavy MA. The systemic bioavailability of buprenorphine by various routes of administration. J Pharm Pharmacol. 1981;33(8):500–6.
108. Grimm D, Pauly E, Poschl J, Linderkamp O, Skopp G. Buprenorphine and norbuprenorphine concentrations in human breast milk samples determined by liquid chromatography-tandem mass spectrometry. Ther Drug Monit. 2005;27(4):526–30.
109. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. J Hum Lact. 2009;25(2):199–205.
110. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;363:2320–31.
111. Chawarski MC, Moody DE, Pakes J, O'Connor PG, Schottenfeld RS. Buprenorphine tablet versus liquid: a clinical trial comparing plasma levels, efficacy, and symptoms. J Subst Abuse Treat. 2005;29(4):307–12.
112. Compton P, Ling W, Moody D, Chiang N. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. Drug Alcohol Depend. 2006;82(1):25–31.
113. Huang W, Moody DE, McCance-Katz EF. The in vivo glucuronidation of buprenorphine and norbuprenorphine determined by liquid chromatography-electrospray ionization-tandem mass spectrometry. Ther Drug Monit. 2006;28(2):245–51.
114. Greenwald M, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, Koeppe R, Zubieta JK. Buprenorphineduration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry. 2007;61(1):101–10.
115. Simojoki K, Lillsunde P, Lintzeris N, Alho H. Bioavailability of buprenorphine from crushed and whole buprenorphine (subutex) tablets. Eur Addict Res. 2010;16(12):85–90.

Chapter 13
Buprenorphine Metabolism and Drug–Drug Interactions

Robert Taylor Jr., Robert B. Raffa, and Joseph V. Pergolizzi Jr.

Metabolism

The metabolism of buprenorphine involves both Phase I type reactions that are catalyzed by cytochrome P450 (CYP) enzymes and Phase II type reactions that are catalyzed by UDP-glucuronosyltransferase (UGT) enzymes [1]. There is also a significant enterohepatic recirculation of glucuronidated products. This profile of biotransformation is generally similar in all mammals except cats, which lack or only poorly express UGT enzymes.

Buprenorphine undergoes a large first-pass effect. Following oral administration, a significant amount of administered buprenorphine is metabolized within the stomach, the upper intestinal tract, and the liver. This extensive first-pass metabolism is accompanied by a marked enterohepatic cycling with biliary excretion of buprenorphine glucuronide and possibly hydrolysis in the lower gastrointestinal tract [2–4]. The extensive first-pass metabolism of buprenorphine limits its widespread use as an oral medication. However, sublingual and transdermal patch formulations have been developed in order to overcome this practical impediment.

The overall metabolic pathways of buprenorphine in humans [5] are summarized in Fig. 13.1. The major Phase I type reaction involves *N*-dealkylation of parent drug

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_13,

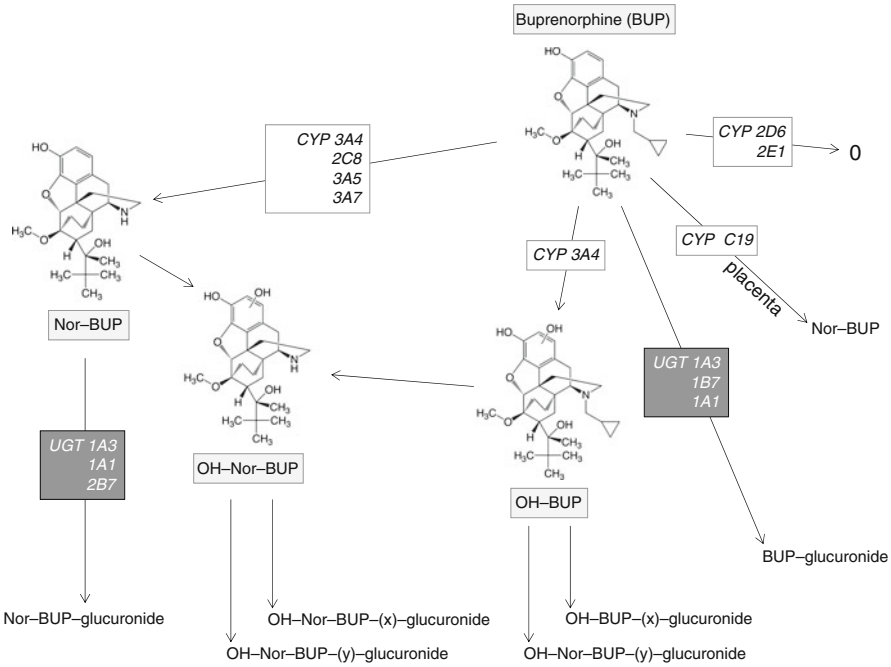

Fig. 13.1 Metabolic pathways of buprenorphine in humans

to *N*-dealkyl buprenorphine, a major metabolite that is commonly termed Nor-buprenorphine or norbuprenorphine. Nor-buprenorphine is further biotransformed in a Phase II type reaction (primarily glucuronidation) to Nor-buprenorphine glucuronide. Parent buprenorphine is also glucuronidated to buprenorphine glucuronide. These two metabolic pathways are well documented to occur in humans and the *N*-dealkylation and glucuronidation reactions lead to buprenorphine's three major metabolites in humans: buprenorphine glucuronide, Nor-buprenorphine, and Nor-buprenorphine glucuronide. These three are the predominant metabolites in humans. Following acute dosing, only small amounts (negligible amounts at low analgesic doses) of these metabolites are measurable in plasma [6]. Following more chronic administration, the plasma concentration of Nor-buprenorphine metabolite can equal or even exceed that of parent drug [7, 8]. Recently it was discovered [5] that Phase I reactions also generate hydroxy-buprenorphine and hydroxyl-Nor-buprenorphine, which undergo Phase II transformations that yield hydroxyl-buprenorphine-glucuronide and hydoxy-Nor-buprenorphine-glucuronide.

Of significant clinical importance, buprenorphine is not a substrate for the CYP 2D6 isozyme, which is a common Phase I biotransformation pathway for many currently used drugs.

In feces, the amount of buprenorphine plus buprenorphine glucuronide greatly exceeds that of Nor-buprenorphine. The opposite is the case in the urine, where the amount of Nor-buprenorphine greatly exceeds the amount of buprenorphine glucuronide.

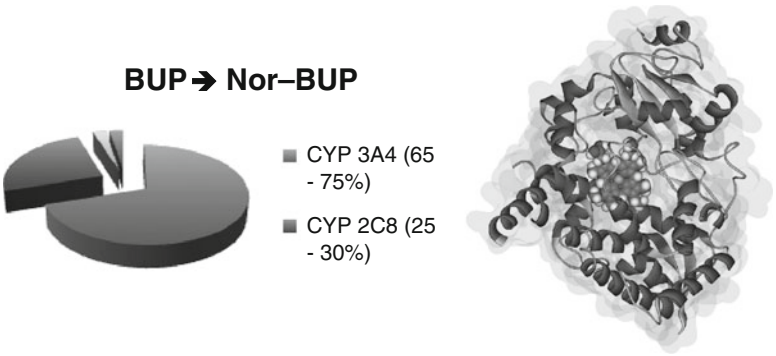

Fig. 13.2 The relative contribution of CYP 3A4 (ribbon representation shown at right with heme group in center), CYP 2C8, and minor isozymes CYP 3A5 and CYP 3A7 to the biotransformation of buprenorphine to Nor-buprenorphine

The major CYP isozymes involved in the Phase I biotransformation reactions of buprenorphine to Nor-buprenorphine are CYP 3A4, CYP 2C8, CYP 3A5, and CYP 3A7 [9] (Fig. 13.2). CYP 3A4 accounts for the majority of this biotransformation, estimated at 65–75 % [9]. CYP 2C8 accounts for most of the remainder (about 25–30 %). CYP 3A5 and 3A7 account for only a small amount.

The metabolism and excretion of buprenorphine and metabolites in human urine following subcutaneous, oral, and sublingual administration was reported by Cone et al. [9]. The participants in the study were healthy male volunteers between the ages of 21 and 45 years. The results are shown in Figs. 13.3–13.5.

The only metabolite of buprenorphine known to have pharmacological activity is Nor-buprenorphine (e.g., [10–12]). In vitro, Nor-buprenorphine exhibits high affinity for μ (mu), δ (delta), and κ (kappa) opioid receptors and lower affinity for NOP (formerly termed ORL1) receptors in CHO (Chinese hamster ovary) cells transfected with human receptors. The affinity of Nor-buprenorphine is similar to that of buprenorphine in these assays, with, in general, an apparently greater efficacy than buprenorphine [10]. Both produce an antinociceptive effect following subcutaneous administration in the mouse abdominal constriction test; the antinociceptive ED_{50} value was 0.07 mg/kg at 25 min for buprenorphine and 0.21 mg/kg for Nor-buprenorphine [10]. However, compared to buprenorphine Nor-buprenorphine is considerably less lipophilic and therefore Nor-buprenorphine does not readily cross the blood–brain barrier in measurable amounts, at least not following acute administration of buprenorphine [13, 14]. The contribution of Nor-buprenorphine to buprenorphine's clinical therapeutic or safety characteristics is still a subject of investigation.

Hepatic or Renal Insufficiency

The pharmacokinetics of buprenorphine and its metabolites does not change to a great extent in patients who have renal impairment or even renal failure [15–17]. As described by Böger [18], buprenorphine, in contrast to morphine which is

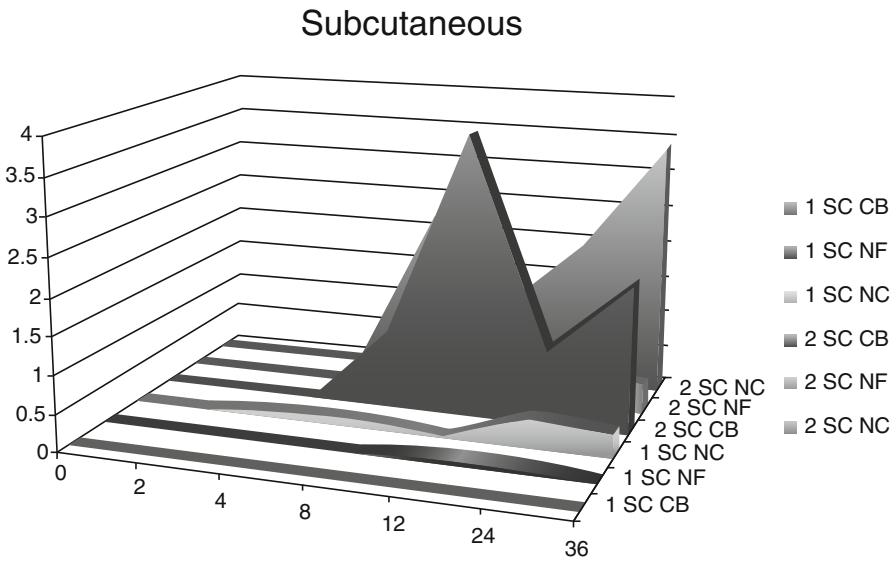

Fig. 13.3 Urinary excretion of conjugated buprenorphine (CB), Nor-buprenorphine free (NF), and Nor-buprenorphine conjugate (NC) following subcutaneous (SC), oral (PO), and sublingual (SL) administration in human volunteers

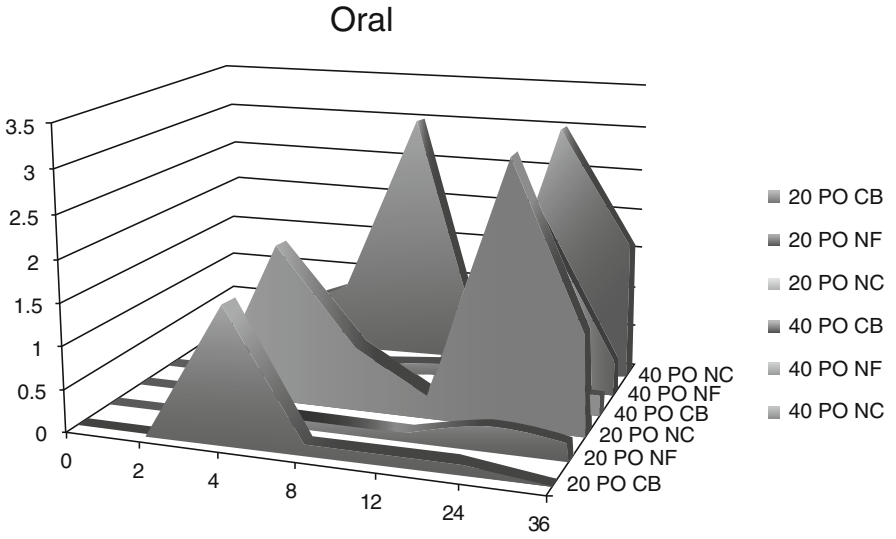

Fig. 13.4 Urinary excretion of conjugated buprenorphine (CB), Nor-buprenorphine free (NF), and Nor-buprenorphine conjugate (NC) following subcutaneous (SC), oral (PO), and sublingual (SL) administration in human volunteers

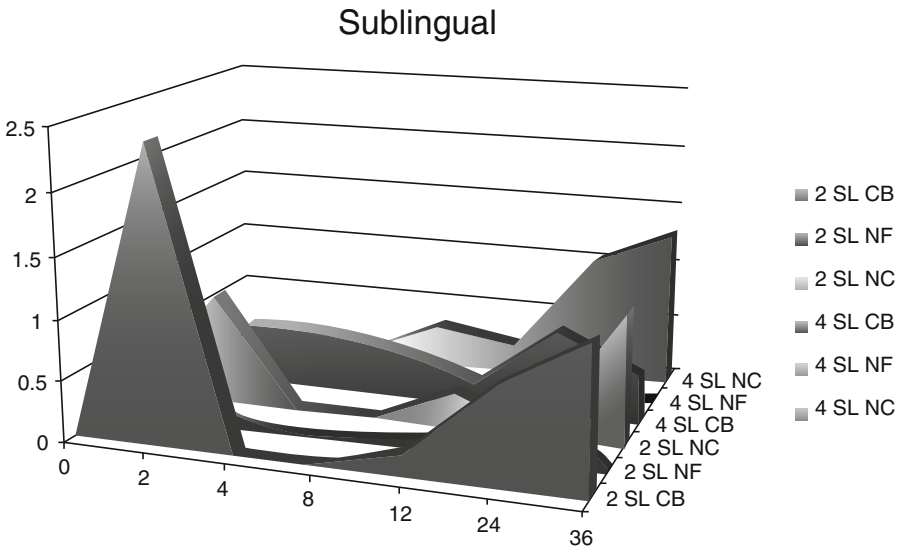

Fig. 13.5 Urinary excretion of conjugated buprenorphine (CB), Nor-buprenorphine free (NF), and Nor-buprenorphine conjugate (NC) following subcutaneous (SC), oral (PO), and sublingual (SL) administration in human volunteers

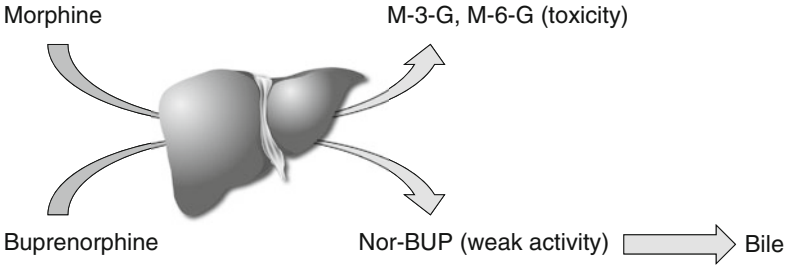

Fig. 13.6 The major difference between buprenorphine and morphine metabolism in renal impairment

metabolized to a toxic metabolite (morphine-6-glucuronide; M-6-G) that accumulates in renal failure with the potential to cause severe adverse effects [19–21], buprenorphine undergoes enterohepatic recirculation and is excreted unchanged to a significant extent in the feces. Nor-buprenorphine, which accounts for about 30 % of total buprenorphine metabolism, is only weakly active and it is not thought to contribute to toxicity. Thus, excretion in bile and an only weakly active major metabolite prevents accumulation or toxicity by buprenorphine in patients with renal dysfunction (Fig. 13.6). In a multiple-dosing study [22], plasma concentrations of buprenorphine glucuronide and Nor-buprenorphine were higher by 4- and 15-fold, respectively, but did not lead to clinically relevant effects.

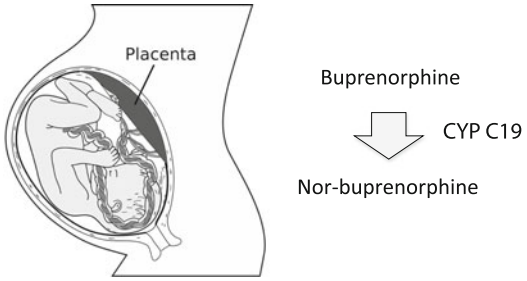

Fig. 13.7 The major buprenorphine metabolite in human placenta is Nor-buprenorphine

Pregnancy and Breastfeeding

Due to the fact that buprenorphine is being used to help manage opioid addiction, the metabolism of buprenorphine in pregnant women is of special concern.

The urinary excretion of buprenorphine and its metabolites in 9 women 22–32 years of age receiving buprenorphine for maintenance treatment was studied [23]. The mean dose of buprenorphine was 15–18 mg/day during each trimester and postpartum period. The primary metabolite identified in the urine of these women was Nor-buprenorphine-glucuronide and it exceeded the concentration of buprenorphine glucuronide in 99 % of the collected specimens. Buprenorphine and buprenorphine glucuronide are found in only low concentrations [24].

By far the primary buprenorphine metabolite formed by the human placenta is Nor-buprenorphine and CYP 19 (aromatase) is the major isozyme that catalyzes this biotransformation in human placentas [25] from about 17 weeks of gestation until term [26] (Fig. 13.7).

In a study of nursing mothers who were on buprenorphine maintenance therapy [27], buprenorphine and Nor-buprenorphine were detected in the breast milk 2 h after the administered dose and they were present in higher amounts than in the maternal plasma over 24 h. The extent of transfer of ingested drug in any individual fetus depends on multiple physiological parameters of the mother and fetus. In this study, four of six infants demonstrated mild signs of opioid abstinence on the second day. Morphine replacement therapy was required in one, but no other problems arose in the first week of life and development was uneventful and within normal range at follow-up visit 1 month later. The authors conclude that nursing infants' exposure to buprenorphine in breast milk is low compared to the maintenance dose in the mother and that there is no pharmacokinetic or clinical reason to discourage mothers receiving buprenorphine from breastfeeding their infants.

Drug–Drug Interactions

Buprenorphine drug–drug interactions can occur through several mechanisms. The following sections summarize some of the more commonly encountered interactions.

Table 13.1 Some inducers and inhibitors of CYP3A4 that might affect the metabolism of buprenorphine

Common CYP3A4 inducers	Common CYP3A4 inhibitors
HIV protease inhibitors	Azole antifungals (e.g., ketoconazole)
Non-nucleoside reverse transcriptase inhibitors	Macrolide antibiotics (e.g., erythromycin)
Phenobarbital	HIV protease inhibitors
Phenytoin	Benzodiazapines
Rifampin	
Carbamazepine	
Cocaine	
St. John's Wort	

Cytochrome P450 Inhibitors and Inducers

As previously described, buprenorphine is metabolized primarily by cytochrome oxidase isoform CYP3A4. Thus, compounds that can affect the activity of CYP3A4, whether they are inducers or inhibitors of CYP3A4, have the potential to alter the pharmacokinetics of buprenorphine (Table 13.1). During such combination drug therapy, monitoring and possibly changes in dosage of either compound might be required.

Antiretrovirals

In the United States, approximately 38 % of opioid-dependent Americans are infected with HIV [28]. Therefore, physicians can be confronted with the challenge of treating both conditions in the same individual. Coadministration of therapies is important and failure to administer one or the other can have severe clinical consequences [29–31]. For example individuals not being treated for their substance dependence can have behavioral fluctuations that can decrease adherence to the complex therapies required for HIV treatment and result in poor treatment outcomes [32–35]. Unwarranted excess concern is also not helpful, leading to under-dosing, poor compliance, reduced effectiveness [30, 36–38], and even relapse [39, 40].

Several antiretroviral medications are substrates of CYP450 3A4 and have been shown to inhibit the activity of CYP3A4 in vitro (Table 13.2).

Antiretroviral Protease Inhibitors

Protease inhibitors (PIs) are known to affect the CYP450 system (Table 13.2). Not all act on CYP3A4 in the same manner, so they must be considered individually. For example, the CYP3A4 inhibitors darunavir, nelfinavir, lopinavir/ritonavir, ritonavir

Table 13.2 Antiretroviral agents and their effects on CYP450 enzymes (Adapted from [41])

Drug	Drug family	Enzyme inhibited	Enzyme induced
Atazanir	PI[a]	CYP3A4, UGT1A1	
Darunavir	PI	CYP3A4	
Fosamprenavir	PI	CYP3A4	
Lopinavir	PI	CYP3A4	
Ritonavir	PI	CYP3A4, CYP2D6	CYP1A2, CYP2C8, CYP2C9/19, UGT1A1
Tipranavir	PI	CYP1A2, CYP2C9/19, CYP2E1	CYP3A4
Efavirenz	NNRTI[b]	CYP1A2, CYP2C9/19, CYP2D6	CYP3A4
Etravirine	NNRTI	CYP2C9/19	CYP3A4
Nevirapine	NNRTI		CYP3A4, CYP2B6

[a]Protease inhibitor
[b]Non-nucleoside reverse transcriptase inhibitor

[42, 43], and inducer tipranavir [44] have minimal clinical effects on buprenorphine's pharmacokinetics or pharmacodynamics. Other PIs, such as the CYP3A4-inhibiting atazanavir or atazanavir/ritonavir, displayed no interaction in one study [45], but post-marketing reports suggest that dose reduction of buprenorphine might be warranted when atazanavir is co-prescribed with buprenorphine [46].

Non-Nucleoside Reverse Transcriptase Inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4 and thus interactions with buprenorphine might be expected. The fact that many of these agents have been shown to affect the metabolism of methadone [47–50] initially suggested that they would affect buprenorphine in a similar fashion. Although clinical studies examining NNRTI interactions with buprenorphine are limited, it appears that neither efavirenz nor nevirapine has a significant clinical effect on buprenorphine [51]. In patients who were coadministered the NNRTI nevirapine [52], a more rapid clearance of buprenorphine and buprenorphine-3-glucuronide was observed. However, no dose adjustments of either drug appear to be necessary when these drugs are coadministered at the doses used for the treatment of opiate dependence and HIV disease.

Nucleoside Reverse Transcriptase Inhibitors

Unlike NNRTIs and PIs, nucleoside reverse transcriptase inhibitors (NRTIs) (e.g., didanosine, lamivudine, tenofovir, zidovudine, zalcitabine, stavudine, abacavir, emtricitabine, entecavir, and apricitabine) generally do not induce or inhibit the P450 enzyme pathway significantly [41] and thus interactions with buprenorphine are not generally expected. Coadministration of didanosine or tenofovir with

buprenorphine has no significant effects on the pharmacokinetics of buprenorphine or its metabolites (norbuprenorphine, buprenorphine glucuronides); although coadministration of lamivudine significantly increased norbuprenorphine-3-glucuronide, there were no clinically significant drug interactions [53].

Antiretroviral Conclusion

Current research indicates that the metabolism of buprenorphine may be altered when combined with specific NNRTI and PI antivirals (Table 13.3), but generally without clinically significant effect. Nevertheless, proper precaution should be exercised with coadministration of buprenorphine and antiretroviral agents (especially atazanavir).

Antiretroviral Combination Therapy

Benzodiazepines

Estimates of benzodiazepine use among opioid-dependent therapy range from about 10–45 % [54–63]. In addition, benzodiazepine may be used to relieve problems associated with opioid withdrawal [64]. There have been a number of post-marketing reports reporting toxicity, coma, or death associated with the concomitant use of buprenorphine with benzodiazepines [65–73].

A potential mechanism for interactions between benzodiazepines and buprenorphine is through shared CYP enzyme metabolic pathways. Many benzodiazepines are metabolized by the CYP450 (typically 3A4). For example, diazepam is metabolized by CYP3A4 and CYP2C19 and flunitrazepam, alprazolam, clonazepam, and midazolam are largely metabolized by CYP3A4. Most benzodiazepines are weak competitive inhibitors of CYP3A4 enzymes in human liver microsomes [74]. Midazolam and zolpidem have been shown to inhibit formation of buprenorphine's metabolite norbuprenorphine [74, 75], but many benzodiazapines, including alprazolam, α-hydroxyalprazolam, chlordiazepoxide, norchlordiazepoxide, clonazepam, 3-hydroxy-7-acetamidoclonazepam, demoxepam, diazepam, flunitrazepam [76], nordiazepam, oxazepam, estazolam, flurazepam, lorazepam, nitrazepam, temazepam, and triazolam [74] have been shown do not produce clinically relevant inhibition of buprenorphine metabolism. A summary of some of the studies analyzing buprenorphine's pharmacokinetics in the presence of benzodiazapines is shown in Table 13.4.

Benzodiazepines Conclusion

Many of the benzodiazapines have been shown to be weak inhibitors of the cytochrome oxidase P450 3A4 enzyme. Pharmacokinetic studies and observations in vitro have not correlated well with in vivo studies and thus non-pharmacokinetic interactions between benzodiazepine and buprenorphine have been suggested [77].

Table 13.3 Summary of studies analyzing clinical effects of buprenorphine/naloxone and antiretroviral combination therapy

Study	Antiretroviral	Effects on buprenorphine	Clinical outcome
Baker et al. [53]	Didanosine Lamivudine Tenofovir	No significant change in pharmacokinetics when combined with didanosine or tenofovir	No opioid withdrawal symptoms felt by subjects
		↑ Norbuprenorphine AUC when combined with lamivudine	Buprenorphine dosage adjustment unnecessary
Bruce et al. [44]	Tiprianivr/ritonavir	No significant pharmacokinetic changes in buprenophine	No opioid withdrawal symptoms felt by subjects
		Norbuprenophine $AUC_{0\text{–}24\ h}$ and C_{max} ↓	Buprenorphine dosage adjustment unnecessary
Bruce et al. [42]	Lopinavir/ritonavir	No significant pharmacokinetic changes in buprenophine	No opioid withdrawal symptoms felt by subjects
		C_{max} of Norbuprenophine ↓	Buprenorphine dosage adjustment unnecessary
Sekar et al. [43]	Darunavir/ritonavir	Mean $C_{0\,h}$, C_{min}, C_{max}, and AUC 24 h values for norbuprenorphine were ↑	Mild opioid withdrawal symptoms felt by some subject
			Buprenorphine dosage adjustment unnecessary
Vergara-Rodriquez et al. [45]	Atazanavir	Pharmacokinetics not studied	No hepatoxicity occurred
			No clinical significant effects observed
McCance-Katz et al. [54]	Efavirenz Delavirdine	Efavirenz ↓ buprenorphine AUC ($P<0.001$)	Clinically significant consequences pharmacokinetic changes were not observed
		Delavirdine ↑buprenorphine concentrations ($P<0.001$)	Buprenorphine dosage adjustment unnecessary
McCance-Katz et al. [55]	Nelfinavir Ritonavir	No significant pharmacokinetic changes observed with Nelfinavir or Lopinavir/ritonavir	Symptoms of buprenorphine overdose were not observed
	Lopinavir/ritonavir	Ritonavir ↑ buprenorphine AUC	Buprenorphine dosage adjustment
McCance-Katz et al. [56]	Atazanavir Atazanavir/ritonavir	↑ Concentrations of buprenorphine, norbuprenorphine, buprenorphine glucuronide, and norbuprenorphine glucuronide	Cognitive dysfunction in some patients
			Dosage adjustment of buprenorphine may be necessary

Table 13.4 Summary of studies analyzing buprenorphine pharmacokinetics/pharmacodynamics in the presence of benzodiazepines

Study	Model	Benzodiazapine	Buprenorphine Pharmacokinetics	Pharmacodynamic effects
Kilicarslan et al. [79]	Human liver microsomes	Flunitrazepam	↓ BPN metabolism by 0.08 %	Not studied
Chang et al. [77]	Human liver microsomes	Diazepam/Clonazepam/3-hydroxy-7-acetamidoclonazepam/ alpha-hydroxy-triazolam	No effect	Not studied
Bomsien et al. [78]	Human in vitro study	Midazolam	IC_{50} for *N*-BPN formation = 20.25 μM	Not studied
Megarbane et al. [80]	Rat model	Flunitrazepam	No difference in distribution	↑ Respiratory depression
Pirnay et al. [81]	Rat model	Flunitrazepam	Not studied	↑ Respiratory toxicity
Pirnay et al. [82]	Rat model	Oxazepam or Nordiazepam	Not studied	↑ Sedation
Lintzeris et al. [83]	Opioid-dependent patients	Diazepam	Not studied	↑ Sedation and impaired performance on psychological tests
Lintzeris et al. [84]	Opioid-dependent patients	Diazepam	Not studied	↑ Sedation and impaired performance on psychological tests
Bomsien et al. [78]	Human liver microsomes	Midazolam/zolpidem	Inhibition of norbuprenorphine formation	Not studied
Gueye et al. [85]	Rat models	Midazolam	Not studied	↑ Respiratory depression

Selective Serotonin Reuptake Inhibitors

Some selective serotonin reuptake inhibitors have been shown to inhibit cytochrome P450 3A4 in vitro and thus potential interactions with buprenorphine might occur. For example, fluoxetine does not inhibit dealkylation of buprenorphine, but norfluoxentine inhibits buprenorphine metabolism [78]. The clinical significance of such interactions is unknown.

Lithium and Anticonvulsants

Lithium is not metabolized in the liver and poses no major drug interaction threat with buprenorphine [79]. Carbamazepine metabolism occurs primarily in the liver [79] via CYP3A4, with a minor contribution by CYP2C8 [80]. No clinically significant interaction effects have been reported [81–83].

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are prescribed for the treatment of depression, a symptom many opioid-dependent patients have [84, 85]. The administration of opioid agonist medications and MAOIs has been reviewed [86–88]. In the case of buprenorphine, no studies indicate clinically significant interactions such as the development of serotonin syndrome [89]. A study found no significant changes in the body temperature, arterial pressure, or heart rate in rabbits when phenelzine was coadministered with buprenorphine [90].

Other Drugs

Rifampin

Tuberculosis (TB) is among the most common infectious diseases worldwide and occurs in considerably increased incidence in individuals with opioid addictions [91–94]. Nearly 30 % of incident TB cases occur within the drug-using population in the United States. Rifampin, a first-line agent for treatment of tuberculosis, is a potent inducer of CYP 450 [95] and its use is associated with induction of methadone metabolism, significant reduction in methadone exposure, and onset of opiate withdrawal [96, 97].

In a study of 21 patients maintained on buprenorphine [98], rifampin significantly reduced plasma buprenorphine concentration (70 % reduction in mean area

under the curve (AUC)) and onset of opiate withdrawal symptoms in 50 % of participants. The authors concluded that patients requiring rifampin are likely to require an increase in buprenorphine dose to prevent withdrawal symptoms.

Cocaine

Patients enrolled in opioid maintenance programs may revert back to illicit drug use while on dependence medication. In a retrospective study, patients in a total of 90 studies were analyzed for changes in buprenorphine metabolism while taking cocaine [99]. Patients who were taking cocaine had lower AUC and C_{max} values for buprenorphine, reducing the effectiveness of the therapy.

Conclusion

Buprenorphine is metabolized through Phase I and Phase II type reactions and, therefore, metabolic interaction with other drugs is a mechanistic possibility. The major CYP isozymes involved in the biotransformation of buprenorphine are CYP 3A4, CYP 2C8, CYP 3A5, and CYP 3A7. CYP 3A4 accounts for the majority of this biotransformation, thus compounds that affect the activity of CYP3A4 have the potential for interaction with buprenorphine. CYP 2C8 accounts for most of the remainder of buprenorphine Phase I metabolism. CYP 3A5 and CYP 3A7 account for only a small amount. Notably, buprenorphine is not a substrate for CYP 2D6, which is a common Phase I biotransformation pathway for many currently used drugs.

Rifampin can significantly reduce plasma buprenorphine concentration (70 % reduction in mean AUC) such that patients requiring rifampin are likely to require an adjustment in the dose of buprenorphine.

There have been several reports of toxicity, coma, or death associated with concomitant use of buprenorphine with benzodiazepines. Interaction at the level of metabolism could be involved, but as yet unidentified other factors could also be contributory, and thus far appear to be more important than metabolism.

Many of the drugs used for the management of HIV infection are metabolized through CYP-catalyzed pathways, so buprenorphine levels may be altered when combined with specific antiviral therapy, but generally this does not lead to clinically significant effect. Nevertheless, the proper precaution needs to be exercised when buprenorphine is coadministered with antiretroviral agents, particularly atazanavir.

Some selective serotonin reuptake inhibitors inhibit cytochrome P450 3A4 in vitro and thus potential interactions with buprenorphine might occur, but evidence to-date suggests that the clinical significance of such interactions might not be very great. There also appears to be little evidence for metabolic interaction between buprenorphine and MAOIs.

Patients enrolled in opioid maintenance programs may revert back to illicit drug use, including cocaine. Cocaine can lower the AUC and C_{max} of buprenorphine, thus reducing the effectiveness of buprenorphine therapy.

In summary, the metabolic profile of buprenorphine suggests that metabolic drug–drug interactions are a potential occurrence with other drugs that are metabolized by CYP isozymes, with the important exception of CYP 2D6 (since buprenorphine is not a good substrate for this isozyme). However, there is little evidence of clinically significant metabolic interactions between buprenorphine and the majority of other drugs, although there are some important exceptions as noted above. As for all drugs, awareness of the potential metabolic interaction with coadministered drugs is an important part of pharmacotherapeutic vigilance.

References

1. Cowan A, Friderichs E, Straburger W, Raffa RB. Basic pharmacology of buprenorphine. In: Budd K, Raffa RB, editors. Buprenorphine—the unique opioid analgesic. Stuttgart: Thieme; 2005. p. 3–21.
2. Brewster D, Humphrey MJ, McLeavy MA. Biliary excretion, metabolism and enterohepatic circulation of buprenorphine. Xenobiotica. 1981;11(3):189–96.
3. Castle SJ, Tucker GT, Woods HF, et al. Assessment of an in situ rat intestine preparation with perfused vascular bed for studying the absorption and first-pass metabolism of drugs. J Pharmacol Methods. 1985;14(4):255–74.
4. Rance MJ, Shillingford JS. The metabolism of phenolic opiates by rat intestine. Xenobiotica. 1977;7(9):529–36.
5. Picard N, Cresteil T, Djebli N, Marquet P. In vitro metabolism study of buprenorphine: evidence for new metabolic pathways. Drug Metab Dispos. 2005;33(5):689–95.
6. Ohtani M, Shibuya F, Kotaki H, Uchino K, Saitoh Y, Nakagawa F. Quantitative determination of buprenorphine and its active metabolite, norbuprenorphine, in human plasma by gas chromatography–chemical ionization mass spectrometry. J Chromatogr. 1989;487(2):469–75.
7. Hand CW, Ryan KE, Dutt SK, et al. Radioimmunoassay of buprenorphine in urine: studies in patients and in a drug clinic. J Anal Toxicol. 1989;13(2):100–4.
8. Kuhlman Jr JJ, Levine B, Johnson RE, Fudala PJ, Cone EJ. Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induction, maintenance and withdrawal from sublingual buprenorphine. Addiction. 1998;93(4):549–59.
9. Cone EJ, Gorodetzky CW, Yousefnejad D, Buchwald WF, Johnson RE. The metabolism and excretion of buprenorphine in humans. Drug Metab Dispos. 1984;12(5):577–81.
10. Huang P, Kehner GB, Cowan A, Liu-Chen L-Y. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. J Pharmacol Exp Ther. 2001;297(2):688–95.
11. Ohtani M, Kotaki H, Nishitateno K, Sawada Y, Iga T. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. J Pharmacol Exp Ther. 1997;281(1):428–33.
12. Ohtani M, Kotaki H, Sawada Y, Iga T. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. J Pharmacol Exp Ther. 1995;272(2):505–10.
13. Pontani RB, Vadlamani NL, Misra AL. Disposition in the rat of buprenorphine administered parenterally and as a subcutaneous implant. Xenobiotica. 1985;15(4):287–97.

14. Yue H, Borenstein MR, Jansen SA, Raffa RB. Liquid chromatography-mass spectrometric analysis of buprenorphine and its N-dealkylated metabolite norbuprenorphine in rat brain tissue and plasma. J Pharmacol Toxicol Methods. 2005;52(3):314–22.
15. Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet. 1996;31(6):410–22.
16. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care. 2005;33(3):311–22.
17. Summerfield RJ, Allen MC, Moore RA, Sear JW, McQuay HJ. Buprenorphine in end stage renal failure. Anaesthesia. 1985;40(9):914.
18. Boger RH. Renal impairment: a challenge for opioid treatment? The role of buprenorphine. Palliat Med. 2006;20(Suppl 1):s17–23.
19. Chan G, Matzke G. Effects of renal insufficiency on the pharmacokinetics and pharmacodynamics of opioid analgesics. Ann Pharmacother. 1987;21(10):773–83.
20. Mercadante S. The role of morphine glucuronides in cancer pain. Palliat Med. 1999;13(2):95–104.
21. Peterson GM, Randall CT, Paterson J. Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. Eur J Clin Pharmacol. 1990;38(2):121–4.
22. Hand CW, Sear JW, Uppington J, Ball MJ, McQuay HJ, Moore RA. Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. Br J Anaesth. 1990;64(3):276–82.
23. Kacinko SL, Jones HE, Johnson RE, Choo RE, Concheiro-Guisan M, Huestis MA. Urinary excretion of buprenorphine, norbuprenorphine, buprenorphine-glucuronide, and norbuprenorphine-glucuronide in pregnant women receiving buprenorphine maintenance treatment. Clin Chem. 2009;55(6):1177–87.
24. Concheiro M, Jones HE, Johnson RE, Choo R, Shakleya DM, Huestis MA. Maternal buprenorphine dose, placenta buprenorphine, and metabolite concentrations and neonatal outcomes. Ther Drug Monit. 2010;32(2):206–15.
25. Deshmukh SV, Nanovskaya TN, Ahmed MS. Aromatase is the major enzyme metabolizing buprenorphine in human placenta. J Pharmacol Exp Ther. 2003;306(3):1099–105.
26. Fokina VM, Patrikeeva SL, Zharikova OL, Nanovskaya TN, Hankins GV, Ahmed MS. Transplacental transfer and metabolism of buprenorphine in preterm human placenta. Am J Perinatol. 2011;28(1):25–32.
27. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. J Hum Lact. 2009;25(2):199–205.
28. Altice FL, Bruce RD, Lucas GM, et al. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. J Acquir Immune Defic Syndr. 2011;56:S22–32. doi:10.1097/QAI.1090b1013e318209751e.
29. Bruce RD, Altice FL. Three case reports of a clinical pharmacokinetic interaction with buprenorphine and atazanavir plus ritonavir. AIDS. 2006;20(5):783–4.
30. Bruce RD, McCance-Katz E, Kharasch ED, Moody DE, Morse GD. Pharmacokinetic interactions between buprenorphine and antiretroviral medications. Clin Infect Dis. 2006;43(Suppl 4):S216–23.
31. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). Int J Drug Policy. 2007;18(4):262–70.
32. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med. 2002;17(5):377–81.
33. Howard AA, Arnsten JH, Lo Y, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. AIDS. 2002;16(16):2175–82.
34. Mehta S, Moore RD, Graham NMH. Potential factors affecting adherence with HIV therapy. AIDS. 1997;11(14):1665–70.

35. Williams A, Friedland G. Adherence, compliance, and HAART. AIDS Clin Care. 1997;9(7):51–54, 58.
36. Lucas GM, Gebo KA, Chaisson RE, Moore RD. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. AIDS. 2002;16(5):767–74.
37. Basu S, Smith-Rohrberg D, Bruce RD, Altice FL. Models for integrating buprenorphine therapy into the primary HIV care setting. Clin Infect Dis. 2006;42(5):716–21.
38. Lucas GM, Mullen BA, McCaul ME, Weidle PJ, Hader S, Moore RD. Adherence, drug use, and treatment failure in a methadone-clinic-based program of directly administered antiretroviral therapy. AIDS Patient Care STDS. 2007;21(8):564–74.
39. Altice FL, Friedland GH, Cooney EL. Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadone. AIDS. 1999;13(8):957–62.
40. Bruce RD, Altice FL. Clinical care of the HIV-infected drug user. Infect Dis Clin North Am. 2007;21(1):149–179, ix.
41. Jimenez-Nacher I, Alvarez E, Morello J, Rodriguez-Novoa S, de Andres S, Soriano V. Approaches for understanding and predicting drug interactions in human immunodeficiency virus-infected patients. Expert Opin Drug Metab Toxicol. 2011;7(4):457–77.
42. Bruce RD, Altice FL, Moody DE, et al. Pharmacokinetic interactions between buprenorphine/naloxone and once-daily lopinavir/ritonavir. J Acquir Immune Defic Syndr. 2010;54(5):511–4.
43. Sekar V, Tomaka F, Lefebvre E, et al. Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenance therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol. 2011;51(2):271–8.
44. Bruce RD, Altice FL, Moody DE, et al. Pharmacokinetic interactions between buprenorphine/naloxone and tipranavir/ritonavir in HIV-negative subjects chronically receiving buprenorphine/naloxone. Drug Alcohol Depend. 2009;105(3):234–9.
45. Vergara-Rodriguez P, Tozzi MJ, Botsko M, et al. Hepatic safety and lack of antiretroviral interactions with buprenorphine/naloxone in HIV-infected opioid-dependent patients. J Acquir Immune Defic Syndr. 2011;56(Suppl 1):S62–7.
46. Reckitt Benckiser Pharmaceuticals Inc. Suboxone Package Insert; 2010.
47. Barry M, Mulcahy F, Merry C, Gibbons S, Back D. Pharmacokinetics and potential interactions amongst antiretroviral agents used to treat patients with HIV infection. Clin Pharmacokinet. 1999;36(4):289–304.
48. Back D, Gibbons S, Khoo S. Pharmacokinetic drug interactions with nevirapine. J Acquir Immune Defic Syndr. 2003;34(Suppl 1):S8–14.
49. Clarke SM, Mulcahy FM, Tjia J, et al. Pharmacokinetic interactions of nevirapine and methadone and guidelines for use of nevirapine to treat injection drug users. Clin Infect Dis. 2001;33(9):1595–7.
50. McCance-Katz EF, Gourevitch MN, Arnsten J, Sarlo J, Rainey P, Jatlow P. Modified directly observed therapy (MDOT) for injection drug users with HIV disease. Am J Addict. Fall 2002;11(4):271–8.
51. McCance-Katz EF. Treatment of opioid dependence and coinfection with HIV and hepatitis C virus in opioid-dependent patients: the importance of drug interactions between opioids and antiretroviral agents. Clin Infect Dis. 2005;41(Suppl 1):S89–95.
52. McCance-Katz EF, Moody DE, Morse GD, Ma Q, Rainey PM. Lack of clinically significant drug interactions between nevirapine and buprenorphine. Am J Addict. 2010;19(1):30–7.
53. Baker J, Rainey PM, Moody DE, Morse GD, Ma Q, McCance-Katz EF. Interactions between buprenorphine and antiretrovirals: nucleos(t)ide reverse transcriptase inhibitors (NRTI) didanosine, lamivudine, and tenofovir. Am J Addict Jan-Feb. 2010;19(1):17–29.
54. Stitzer ML, Griffiths RR, McLellan AT, Grabowski J, Hawthorne JW. Diazepam use among methadone maintenance patients: patterns and dosages. Drug Alcohol Depend. 1981;8(3):189–99.

55. Gossop M, Marsden J, Stewart D, Kidd T. The National Treatment Outcome Research Study (NTORS): 4–5 year follow-up results. Addiction. 2003;98(3):291–303.
56. Darke S. The use of benzodiazepines among injecting drug users. Drug Alcohol Rev. 1994;13(1):63–9.
57. Nielsen S, Dietze P, Lee N, Dunlop A, Taylor D. Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. Addiction. 2007;102(4):616–22.
58. Thirion X, Lapierre V, Micallef J, et al. Buprenorphine prescription by general practitioners in a French region. Drug Alcohol Depend. 2002;65(2):197–204.
59. Lavie E, Fatseas M, Denis C, Auriacombe M. Benzodiazepine use among opiate-dependent subjects in buprenorphine maintenance treatment: correlates of use, abuse and dependence. Drug Alcohol Depend. 2009;99(1–3):338–44.
60. Kandel DB, Huang FY, Davies M. Comorbidity between patterns of substance use dependence and psychiatric syndromes. Drug Alcohol Depend. 2001;64(2):233–41.
61. Farrell M, Howes S, Taylor C, et al. Substance misuse and psychiatric comorbidity: an overview of the OPCS National Psychiatric Morbidity Survey. Addict Behav. 1998;23(6):909–18.
62. Marsden J, Gossop M, Stewart D, Rolfe A, Farrell M. Psychiatric symptoms among clients seeking treatment for drug dependence. Br J Psychiatry. 2000;176(3):285–9.
63. Ross J, Teesson M, Darke S, et al. The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS). Drug Alcohol Rev. 2005;24(5):411–8.
64. Fry CL, Bruno RB. Recent trends in benzodiazepine use by injecting drug users in Victoria and Tasmania. Drug Alcohol Rev. 2002;21(4):363–7.
65. Pirnay S, Borron SW, Giudicelli CP, Tourneau J, Baud FJ, Ricordel I. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. Addiction. 2004;99(8):978–88.
66. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int. 2001;121(1–2):65–9.
67. Kintz P. A new series of 13 buprenorphine-related deaths. Clin Biochem. 2002;35(7):513–6.
68. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction. 1998;93(9):1385–92.
69. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. J Anal Toxicol. 1998;22(6):430–4.
70. Tracqui A, Tournoud C, Flesch F, et al. Acute poisoning during substitution therapy based on high-dosage buprenorphine. 29 clinical cases–20 fatal cases. Presse Med. 1998;27(12):557–61.
71. Gueye PN, Megarbane B, Borron SW, et al. Trends in opiate and opioid poisonings in addicts in north-east Paris and suburbs, 1995–99. Addiction. 2002;97(10):1295–304.
72. Druid H, Holmgren P, Ahlner J. Flunitrazepam: an evaluation of use, abuse and toxicity. Forensic Sci Int. 2001;122(2):136–41.
73. Boyd J, Randell T, Luurila H, Kuisma M. Serious overdoses involving buprenorphine in Helsinki. Acta Anaesthesiol Scand. 2003;47(8):1031–3.
74. Chang Y, Moody DE. Effect of benzodiazepines on the metabolism of buprenorphine in human liver microsomes. Eur J Clin Pharmacol. 2005;60(12):875–81.
75. Bomsien S, Aderjan R, Mattern R, Skopp G. Effect of psychotropic medication on the in vitro metabolism of buprenorphine in human cDNA-expressed cytochrome P450 enzymes. Eur J Clin Pharmacol. 2006;62(8):639–43.
76. Kilicarslan T, Sellers EM. Lack of interaction of buprenorphine with flunitrazepam metabolism. Am J Psychiatry. 2000;157(7):1164–6.
77. Saber-Tehrani AS, Bruce RD, Altice FL. Pharmacokinetic drug interactions and adverse consequences between psychotropic medications and pharmacotherapy for the treatment of opioid dependence. Am J Drug Alcohol Abuse. 2011;37(1):1–11.

78. Iribarne C, Picart D, Dréano Y, Berthou F. In vitro interactions between fluoxetine or fluvoxamine and methadone or buprenorphine. Fundam Clin Pharmacol. 1998;12(2):194–9.
79. Ketter TA, Frye MA, Cora-Locatelli G, Kimbrell TA, Post RM. Metabolism and excretion of mood stabilizers and new anticonvulsants. Cell Mol Neurobiol. 1999;19(4):511–32.
80. Kerr BM, Thummel KE, Wurden CJ, et al. Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. Biochem Pharmacol. 1994;47(11):1969–79.
81. Kristensen O, Lolandsmo T, Isaksen A, Vederhus JK, Clausen T. Treatment of polydrug-using opiate dependents during withdrawal: towards a standardisation of treatment. BMC Psychiatry. 2006;6:54.
82. Schneider U, Paetzold W, Eronat V, et al. Buprenorphine and carbamazepine as a treatment for detoxification of opiate addicts with multiple drug misuse: a pilot study. Addict Biol. 2000;5(1):65–9.
83. Seifert J, Metzner C, Paetzold W W, et al. Detoxification of opiate addicts with multiple drug abuse: a comparison of buprenorphine vs. methadone. Pharmacopsychiatry. 2002;35(5):159–64.
84. Maddux JF, Desmond DP, Costello R. Depression in opioid users varies with substance use status. Am J Drug Alcohol Abuse. 1987;13(4):375–85.
85. Darke S, Wodak A, Hall W, Heather N, Ward J. Prevalence and predictors of psychopathology among opioid users. Br J Addict. 1992;87(5):771–6.
86. El-Ganzouri AR, Ivankovich AD, Braverman B, McCarthy R. Monoamine oxidase inhibitors. Anesth Analg. 1985;64(6):592–6.
87. Insler SR, Kraenzler EJ, Licina MG, Savage RM, Starr NJ. Cardiac surgery in a patient taking monoamine oxidase inhibitors: an adverse fentanyl reaction. Anesth Analg. 1994;78(3):593–7.
88. Michaels I, Serrins M, Shier NQ, Barash PG. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. Anesth Analg. 1984;63(11):1041–4.
89. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth. 2005;95(4):434–41.
90. MacKenzie JE, Frank LW. Influence of pretreatment with a monoamine oxidase inhibitor (phenelzine) on the effects of buprenorphine and pethidine in the conscious rabbit. Br J Anaesth. 1988;60(2):216–21.
91. Wang W, Xiao H, Lu L. Case–control retrospective study of pulmonary tuberculosis in heroin-abusing patients in China. J Psychoactive Drugs. 2006;38(2):203–5.
92. Conover C, Ridzon R, Valway S, et al. Outbreak of multidrug-resistant tuberculosis at a methadone treatment program. Int J Tuberc Lung Dis. 2001;5(1):59–64.
93. Friedland G. Infectious disease comorbidities adversely affecting substance users with HIV: hepatitis C and tuberculosis. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2010;55:S37–42. doi:10.1097/QAI.1090b1013e3181f1099c1090b1096.
94. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. Int J Drug Policy. 2007;18(4):306–12.
95. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR Recomm Rep. 1998;47(RR20):1–58.
96. Holmes VF. Rifampin-induced methadone withdrawal in AIDS. J Clin Psychopharmacol. 1990;10(6):443–4.
97. Kreek MJ, Garfield JW, Gutjahr CL, Giusti LM. Rifampin-induced methadone withdrawal. N Engl J Med. 1976;294(20):1104–6.
98. McCance-Katz EF, Moody DE, Prathikanti S, Friedland G, Rainey PM. Rifampin, but not rifabutin, may produce opiate withdrawal in buprenorphine-maintained patients. Drug Alcohol Depend. 2011;118(2–3):326–34.
99. McCance-Katz EF, Rainey PM, Moody DE. Effect of cocaine use on buprenorphine pharmacokinetics in humans. Am J Addict. 2010;19(1):38–46.

Chapter 14
Buprenorphine: Side Effects and Tolerability

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Introduction

Buprenorphine is a potent partial opioid agonist and is available in parenteral, sublingual, and transdermal applications. Concern regarding its side effect and tolerability profile, as well as incomplete understanding surrounding its pharmacokinetic and pharmacodynamic profile has limited its use. Its association with addiction treatment has reduced the acceptance of prescribing for its analgesic properties by both patients and practitioners. Patients negatively associate the drug with its use in addiction and may feel stigmatized when the drug is recommended by their provider for treatment of pain [1, 2].

As discussed in previous chapters, buprenorphine is a partial mu opioid agonist with a high affinity for the mu opioid receptor; in addition, it is a nociceptin receptor (ORL1) agonist and a kappa receptor antagonist. Its binding at different receptors is responsible for its analgesic activity as well as its side effect profile. An understanding of these receptors and their actions can help practitioners understand and treat side effects from buprenorphine.

Buprenorphine has partial mu agonistic activity, as compared to the full agonistic activity of other opioids such as morphine, oxycodone, and methadone. This means that its maximal analgesic effects are less than that of full agonists, and reach a ceiling where higher doses do not result in increasing effect. Because it is a partial agonist, higher doses of buprenorphine can be given with fewer adverse effects such as respiratory depression, than are seen with higher doses of full agonist opioids. At lower doses, buprenorphine is much more potent than morphine. Individuals who are not dependent on opioids have a strong analgesic and positive opioid effect when they receive an acute dose of buprenorphine.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_14,

Buprenorphine has a higher affinity for the mu receptor than other opioids; therefore, if a patient is already taking other opioids, buprenorphine introduction may displace the existing drug and may precipitate acute opioid withdrawal. However, if a patient is already on buprenorphine, it is bound tightly to the mu receptor, and therefore does not readily dissociate upon injection of other mu agonists. Therefore, adding another opioid can help control pain and does not produce opioid withdrawal symptoms.

Buprenorphine's equivalent analgesic potency as compared to morphine is about 30 times greater. There is a ceiling for the analgesic effects secondary to the low intrinsic activity of buprenorphine at the mu receptor. In the United States, parenteral and transdermal forms are FDA approved for analgesia with usual doses of 0.3–0.6 mg every 6–8 h. For analgesia, dosing is usually 3–4 times a day as the duration of analgesia is 4–8 vs. 24–48 h for opioid withdrawal.

If a practitioner understands buprenorphines properties, and unique pharmacokinetic and pharmacodynamic aspects, and is comfortable with its use, it will be an extremely useful agent for the treatment of patients with chronic pain. This understanding will allow for proper patient selection, outcome measurement, and monitoring in the treatment of pain.

Side Effects

Buprenorphine has a side effect profile similar to full opioid agonist and can include nausea, vomiting, dizziness, constipation, headache, and others [3], but the intensity or severity of side effects may be less than produced by full agonists.

Risk of Abuse, Addiction, Misuse, Overdose, and Tolerance

Abuse has been reported in epidemiological and human clinical studies with patients taking buprenorphine [4, 5]. Psychological dependence or addiction to buprenorphine can occur in patients following chronic administration. Psychological dependence is a syndrome characterized by maladaptive behaviors employed to obtain the opioid and the continued need for and use of the drug despite its harmful effects. Physical dependence is a state in which withdrawal symptoms may occur with decreased opioid levels caused by a multitude of scenarios; cessation, dose reduction, antagonists, or others. This may also occur with buprenorphine; however, since buprenorphine dissociates slowly from the mu opioid receptor, withdrawal symptoms are usually mild [6]. Withdrawal symptoms are similar in characteristic to other opioid discontinuation and can persist for up to 2 weeks. As compared with full opioid agonists, patients to whom buprenorphine is administered who are already dependent on full mu receptor agonists (such as fentanyl, morphine, oxycodone, etc.) may develop withdrawal symptoms. This is the result of buprenorphines

high affinity for the mu receptor displacing the full agonist; however, having less intrinsic activity at this receptor, it precipitates withdrawal.

Although there is reported abuse with patients on buprenorphine [4, 5], there may be a lower incidence of physical dependence and limited development of tolerance secondary to its partial agonist activity. Buprenorphine activates the opioid receptor at lower levels, is relatively less reinforcing, and is a less abused opioid. It is an option for patients with chronic pain and can be closely monitored by providers, as with other opioids. Buprenorphine can be identified in urine toxicology by gas chromatography mass spectroscopy (GCMS), however it is costly.

Although buprenorphine has a better safety profile than methadone, buprenorphine-related overdose deaths have been reported [7–9]. Most of these deaths, similarly to full opioid agonists, have occurred with a combination of benzodiazepines or alcohol. In addition, most involved intravenous use of buprenorphine.

Buprenorphine is a partial agonist; however, its analgesic dose response curve is linear over the therapeutic dose range, suggesting it acts as a full agonist in respect to analgesia through this range. In patients with chronic opioid use, tolerance can develop to the analgesic effects of the opioid requiring higher doses to be administered to produce similar effects. The development of tolerance may be secondary to desensitization or down regulation of the mu opioid receptors [10]. In a study looking at opioids and their receptors, both fentanyl and morphine were shown to down regulate their opioid receptors, while buprenorphine had an increase [11]. In a study of patients maintained on buprenorphine as compared with fentanyl for the treatment of cancer and noncancer pain, there was a more substantial increase in daily dose of fentanyl as compared with buprenorphine [12].

Respiratory Depression

Buprenorphine is a partial mu opioid agonist and therefore does not activate the mu receptor fully, resulting in a ceiling effect that prevents larger doses of the opioid from producing greater effects [13]. This can result in a greater margin of safety from death by respiratory depression with increased doses as compared to full agonist [14, 15].

Buprenorphine has been reported to cause less respiratory depression as compared with full agonists [16, 17]. There are, however, reports of carbon dioxide retention in critically ill patients [18] and is a relative contraindication in severe respiratory compromise (hypoxia, hypercapnia, elderly, obstructive disease, central nervous system [CNS] depression), as with all opioids. The metabolite of buprenorphine, norbuprenorphine is a potent respiratory suppressant. Dahan et al. [19] showed a nonlinear effect on $PaCO_2$, with a ceiling effect at doses greater than 1.4 μg/kg. In a comparative study of intramuscular buprenorphine 0.3 mg and IM morphine 10 mg, there was no difference seen in peak analgesic effect, while buprenorphine resulted in little significant change in respiration rate, pulse, or blood pressure [20]. A study showed increasing dose of buprenorphine for analgesia

increased pain relief with limited respiratory depression, in contrast to fentanyl, which caused a dose-related increase in respiratory depression [14].

In general, buprenorphine alone is the cause of death in a minority of patients on maintenance therapy for addiction. Most deaths were attributed to polysubstance abuse with benzodiazepines present. The respiratory depressant effects of buprenorphine may be increased when used in combination with other depressants (alcohol, benzodiazepines, and opioids); therefore careful monitoring of patient's is recommended. In addition, due to buprenorphine's tight binding at the opioid receptor, buprenorphine-induced respiratory depression may not be fully reversed by the administration of a single dose of naloxone and therefore higher and repeated doses may be necessary, but can be effective [21].

Gastrointestinal

The most common side effects of buprenorphine are its gastrointestinal side effects. Nausea and vomiting can occur in up to 25 % of patients [22–24]. In a few studies, buprenorphine was reported to cause more nausea and vomiting as compared to morphine [20, 25]. As with other opioids, these symptoms seem to be secondary to the direct stimulation of chemoreceptor trigger zones and/or the vestibular system, and gastric stasis. If patients develop these symptoms, they may respond to medications, including promethazine and serotonin antagonist such as ondasetron. Campora et al. surveyed 260 cancer patients for opioid-induced vomiting. The incidence was similar to other opioids, 8 % had moderate to severe nausea, and 23 % had nausea and vomiting [22].

Constipation is a commonly encountered side effect of opioid use that can significantly affect a patient's quality of life. Constipation is due to direct action on opioid receptors in the gut wall, decreased intestinal motility, and dehydration of stool. The incidence of constipation with buprenorphine has been shown to be lower than with morphine use [26–28]. Previous studies have shown that long-term use of buprenorphine is associated with a low incidence of constipation [29]. This may be in part due to its preparation; as parenteral or transdermal preparations bypass the mu opioid receptors in the intestines. Treatment is similar with all opioids, with a focus on prevention by means of stool softeners and a motility agent, and in severe cases using a peripheral opiate antagonist (e.g., Alvimopan or methylnaltrexone).

Hepatitis has been reported in patients taking high doses. Increased liver enzymes have been found in patients who are receiving buprenorphine and who have hepatitis C [30]. In addition, 53 cases of buprenorphine-associated hepatitis were reported in France since 1996 [27, 31, 32]. One report suggested an association between buprenorphine injection and liver toxicity, possibly from buprenorphines increased bioavailability when administered parenterally [33]. In summary, patients with a history of hepatitis C are at increased risk for elevations of liver function tests while on buprenorphine; however, these increases appear to be mild and clinically insignificant. Acute intravenous use of buprenorphine can result in high elevations of

liver function tests in patient with a history of hepatitis. Baseline periodic liver function tests are recommended in patients receiving buprenorphine and are at increased risk of hepatotoxicity (e.g., history of alcoholism, intravenous drug use, or preexisting liver disease).

Patients may also experience abdominal pain, anorexia, diarrhea, or dyspepsia with use [34].

Central Nervous System

As with other opioids, CNS depression can result in impaired cognition, somnolence, and alterations in consciousness. When given in combination with other CNS depressants, these attacks can worsen. However, the slightly lower incidence of CNS effects with buprenorphine may be a result of its kappa antagonist properties [29]. While buprenorphine can cause headaches, studies have shown a decreased incidence of dizziness and headaches in patients on buprenorphine [26, 27].

In general, opioids including buprenorphine can result in increased intracranial pressure. Therefore, use these medications cautiously in patients with head injuries, intracranial lesions or other circumstances when CSF pressure may be increased.

Cardiac

QT interval prolongation has been associated with buprenorphine use. In clinical trials in patients receiving buprenorphine or methadone for treatment of opioid dependence, buprenorphine use was associated with less effect on QT interval than methadone [34]. A study of buprenorphine transdermal patch demonstrated QT prolongation at a dose of 40 μg/h. In contrast 10 μg/h did not demonstrate meaningful effect on the QT interval [34].

Buprenorphine can precipitate hypotension in some patients, similar to other opioids [20].

Skin

Allergic reactions from buprenorphine have occurred, although uncommon, anaphylactic shock is possible. Patients using the transdermal system have reported skin reactions including pruritus, rash, erythema, and skin irritation around the patch site [24, 35–37]. For patients with pruritus, 1/3 will have resolution of symptoms without patch discontinuation [38], although patients also usually respond to diphenhydramine or hydroxyzine.

Immune and Endocrine

Most opioids have been found to suppress the immune system to some extent. These immunosuppressive effects have been due to their mu receptor agonistic activity and are independent of their analgesic effects. Studies in rats have shown that buprenorphine shows no immunosuppressive activity [39]. Although clinical relevance is yet to be established, buprenorphine may provide a greater margin of safety in patients who are immune compromised or at risk for infection.

Chronic opioid use has been shown to affect the hypothalamo-pituitary axis [40, 41]. Opioid-induced hypogonadism mainly occurs in men [42] but has been found in women as well [42, 43]. The symptoms can cause an impact on a patient's quality of life as they may have fatigue, anemia, decreased libido, and depression. Buprenorphine has been reported not to affect testosterone levels in the brains of male rats [44]. Moreover, a prospective study looking at women on buprenorphine for 6 months, showed no side effects suggestive of hypogonadism [45]. In a different study of 17 men on maintenance buprenorphine, 37 on methadone, and 51 healthy blood donors, testosterone levels were higher in the buprenorphine as compared with the methadone group [46]. The lack of opioid-induced effects on the endocrine system is important to improve tolerability and reduce side effects of patients on chronic opioid therapy.

Psychiatric

As with other opioid agonists, buprenorphine is associated with various psychiatric effects. In clinical trials the following side effects have been noted; anxiety, fatigue, confusion, CNS depression, dizziness, headaches and insomnia, nervousness, and vertigo [34]. Available evidence in patients treated with buprenorphine, indicate no clinically significant disruption in cognitive and psychomotor effects [13].

Special Populations

Practitioners are faced with a wide array of comorbidities in patients with pain. There are several populations of patients who although have significant medical issues can benefit from pain control utilizing buprenorphine.

In patients with hepatic failure, buprenorphine is relatively safe. Lasseter et al. found kinetics unaltered by mild or moderate hepatic impairment [47]. Buprenorphine, as with other opioids, is predominately metabolized by the liver. If metabolism is decreased secondary to liver disease, its analgesic efficacy may be compromised and side effects increased. However, the major metabolic pathway for most opioids is oxidation, the exception being morphine and buprenorphine, which

undergo glucuronidation. In patients with hepatic cirrhosis, this pathway is less affected by liver disease [48].

Patients with renal failure may benefit from buprenorphine, as the pharmacokinetics of buprenorphine is unaltered in patients with renal failure [49, 50]. Buprenorphine is excreted as an inactive glucuronide of its parent drug, norbuprenorphine, which is unlikely to cause clinically significant side effect [51]. In contrast to buprenorphine, accumulation of morphine's active metabolite morphine-6-glucuronide cautions its use in patients with renal failure. In summary, there is a lack of drug accumulation in patients with renal dysfunction [52, 53], and doses may not need to be altered.

In elderly patients, buprenorphine may prove to be an easy, safe, and effective analgesic.

Buprenorphine is relatively safe in the elderly as both CYP3A4 and UGT are well preserved. In addition, clinical doses of up to 10 mg have shown analgesic efficacy with no respiratory depression [14]. The low incidence of constipation is important in this population as well [54].

Buprenorphine is of particular usefulness in patients with preexisting gastroenteritis and intestinal problems as it may improve their quality of life. The transdermal formulation is designed to overcome the pharmacokinetic problems of oral and parenteral opioids which include poor GI absorption, first pass metabolism, and low bioavailability. The only other transdermal delivery system is fentanyl.

Opioids have been shown to be effective in some patients with neuropathic pain; however, the abnormal pain sensitivity caused by neuropathic pain can oftentimes be resistant to opioid therapy, and combination therapy is often established. There is a unique analgesic mechanism, as compared with full agonists, such that buprenorphine has shown a pronounced antihyperalgesic effect and may play a role in treating severe refractory neuropathic pain [55–57].

Tolerability

In a study comparing buprenorphine vs. morphine for analgesic qualities and side effect profile, buprenorphine was better tolerated with similar analgesic efficacy [58]. In a subset of patients with chronic pain, the efficacy of sublingual buprenorphine and sustained-release morphine were similar in analgesia; however, the patients treated with buprenorphine had significantly fewer side effects [58]. A post-marketing surveillance study with 13,179 patients showed the side effect of transdermal buprenorphine to be similar to other opioids. Long-term use was characterized by a low rate of constipation (0.97 %), nausea (3.95 %), and dizziness (1.5 %) [6].

As discussed previously, buprenorphine can be better tolerated by patients with moderate to severe pain. The gastrointestinal adverse events associated with buprenorphine have a lower incidence in practice. Constipation, another commonly encountered side effect of opioids, incidence with buprenorphine has been shown to be lower than with morphine [58, 59]. Lastly, CNS-related adverse events that may

occur in opioid treatment in general has increased incidence in patients with declining kidney function. As opposed to other opioids, less than 20 % of buprenorphine is excreted by the kidneys and therefore accumulation is low as comparison with morphine or fentanyl where greater than 70 % is excreted by the kidney. Thus, buprenorphine has a lower risk of CNS adverse events.

Conclusion

In conclusion, buprenorphine has been a widely used opioid and has been shown to be effective for analgesia. Its pharmacokinetics and partial agonistic activity, potency, and safety profile make it a valuable option for patients with chronic pain. Buprenorphine is a partial mu agonist with a profile of effects similar to other mu agonists, but has less respiratory depression, constipation, sexual dysfunction, and a lower level of physical dependence. In addition, the ability to use a transdermal application is invaluable in certain patient populations and a lack of accumulation in patients with renal impairment.

References

1. Fishman SM, Wilsey B, Yang J, Reisfield GM, Bandman TB, Borsook D. Adherence monitoring and drug surveillance in chronic opioid therapy. J Pain Symptom Manage. 2000;20(4):293–307.
2. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage. 1996;11(4):203–17.
3. Radbruch L, Vielvoye-Kerkmeer A. Buprenorphine TDS: the clinical development rationale and results. Int J Clin Pract Suppl. 2003;133:15–8; discussion 23–4.
4. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int. 2001;121(1–2):65–9.
5. Kintz P. A new series of 13 buprenorphine-related deaths. Clin Biochem. 2002;35(7):513–6.
6. Tzschentke TM. Behavioral pharmacology of buprenorphine, with a focus on preclinical models of reward and addiction. Psychopharmacology (Berl). 2002;161(1):1–16.
7. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction. 1998;93(9):1385–92.
8. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. J Anal Toxicol. 1998;22(6):430–4.
9. Gaulier JM, Marquet P, Lacassie E, Dupuy JL, Lachatre G. Fatal intoxication following self-administration of a massive dose of buprenorphine. J Forensic Sci. 2000;45(1):226–8.
10. Whistler JL. Examining the role of mu opioid receptor endocytosis in the beneficial and side-effects of prolonged opioid use: from a symposium on new concepts in mu-opioid pharmacology. Drug Alcohol Depend. 2012;121(3):189–204.
11. Zaki PA, Keith Jr DE, Brine GA, Carroll FI, Evans CJ. Ligand-induced changes in surface mu-opioid receptor number: relationship to G protein activation? J Pharmacol Exp Ther. 2000;292(3):1127–34.
12. Sittl R, Nuijten M, Nautrup BP. Changes in the prescribed daily doses of transdermal fentanyl and transdermal buprenorphine during treatment of patients with cancer and noncancer pain in Germany: results of a retrospective cohort study. Clin Ther. 2005;27(7):1022–31.

13. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569–80.
14. Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br J Anaesth. 2005;94(6):825–34.
15. Yassen A, Olofsen E, Dahan A, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine and fentanyl in rats: role of receptor equilibration kinetics. J Pharmacol Exp Ther. 2005;313(3):1136–49.
16. Zenz M, Piepenbrock S, Tryba M, Klauke W, Everlien M. [Sublingual buprenorphine tablets: initial clinical experiences in long-term therapy of cancer pain]. Fortschr Med. 1983;101(5):191–4.
17. Radbruch L, Sabatowski R, Petzke F, Brunsch-Radbruch A, Grond S, Lehmann KA. Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. Palliat Med. 2001;15(4):309–21.
18. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol. 1977;60(4):537–45.
19. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627–32.
20. Kjaer M, Henriksen H, Knudsen J. A comparative study of intramuscular buprenorphine and morphine in the treatment of chronic pain of malignant origin. Br J Clin Pharmacol. 1982;13(4):487–92.
21. Pergolizzi J, Aloisi AM, Dahan A, et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract. 2010;10(5):428–50.
22. Campora E, Merlini L, Pace M, et al. The incidence of narcotic-induced emesis. J Pain Symptom Manage. 1991;6(7):428–30.
23. Noda J, Umeda S, Arai T, Harima A, Mori K. Continuous subcutaneous infusion of buprenorphine for cancer pain control. Clin J Pain. 1989;5(2):147–52.
24. Likar R, Kayser H, Sittl R. Long-term management of chronic pain with transdermal buprenorphine: a multicenter, open-label, follow-up study in patients from three short-term clinical trials. Clin Ther. 2006;28(6):943–52.
25. Tantucci C, Paoletti F, Bruni B, et al. Acute respiratory effects of sublingual buprenorphine: comparison with intramuscular morphine. Int J Clin Pharmacol Ther Toxicol. 1992;30(6):202–7.
26. Fudala PJ, Bridge TP. Foreword to: buprenorphine and buprenorphine/naloxone: a guide for clinicians. Drug Alcohol Depend. 2003;70(2 Suppl):S1–2.
27. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. Addiction. 1998;93(4):475–86.
28. Robbie DS. A trial of sublingual buprenorphine in cancer pain. Br J Clin Pharmacol. 1979;7 (Suppl 3):315S–7.
29. Przeklasa-Muszynska A, Dobrogowski J. Transdermal buprenorphine in the treatment of cancer and non-cancer pain—the results of multicenter studies in Poland. Pharmacol Rep. 2011;63(4):935–48.
30. Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. Am J Addict. Summer 2000;9(3):265–9.
31. Fudala PJ, Bridge TP, Herbert S, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949–58.
32. Auriacombe M, Fatseas M, Franques-Reneric P, Daulouede JP, Tignol J. [Substitution therapy in drug addictions]. Rev Prat. 2003;53(12):1327–34.
33. Berson A, Gervais A, Cazals D, et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. J Hepatol. 2001;34(2):346–50.
34. Purdue Pharmaceuticals. Butrans® (buprenorphine) transdermal system package insert. Richmond, VA; 2010.

35. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2003;25(1): 150–68.
36. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2004;26(11):1808–20.
37. Radbruch L. Buprenorphine TDS: use in daily practice, benefits for patients. Int J Clin Pract Suppl. 2003;133:19–22; discussion 23–4.
38. Likar R, Griessinger N, Sadjak A, Sittl R. [Transdermal buprenorphine for treatment of chronic tumor and non-tumor pain]. Wien Med Wochenschr. 2003;153(13–14):317–22.
39. Sacerdote P. Opioids and the immune system. Palliat Med. 2006;20(Suppl 1):s9–15.
40. Meczekalski B, Podfigurna-Stopa A, Warenik-Szymankiewicz A, Genazzani AR. Functional hypothalamic amenorrhea: current view on neuroendocrine aberrations. Gynecol Endocrinol. 2008;24(1):4–11.
41. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002;3(5):377–84.
42. Aloisi AM, Pari G, Ceccarelli I, et al. Gender-related effects of chronic non-malignant pain and opioid therapy on plasma levels of macrophage migration inhibitory factor (MIF). Pain. 2005;115(1–2):142–51.
43. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J Pain. 2008;9(1):28–36.
44. Ceccarelli I, De Padova AM, Fiorenzani P, Massafra C, Aloisi AM. Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. Neuroscience. 2006;140(3):929–37.
45. Aurilio C, Ceccarelli I, Pota V, et al. Endocrine and behavioural effects of transdermal buprenorphine in pain-suffering women of different reproductive ages. Endocr J. 2011;58(12):1071–8.
46. Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmuller D. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. J Clin Endocrinol Metab. 2005;90(1):203–6.
47. Lasseter KC, Venitz J, Eltahtawy A, et al. Systemic pharmacokinetic (PK) study of buprenorphine (B) in mild to moderate chronic hepatic impairment (CHI). Clin Pharmacol Ther. 2001;69:P2.
48. Tegeder I, Geisslinger G, Lotsch J. [Therapy with opioids in liver or renal failure]. Schmerz. 1999;13(3):183–95.
49. Deng J, St Clair M, Everett C, Reitman M, Star RA. Buprenorphine given after surgery does not alter renal ischemia/reperfusion injury. Comp Med. 2000;50(6):628–32.
50. Summerfield RJ, Allen MC, Moore RA, Sear JW, McQuay HJ. Buprenorphine in end stage renal failure. Anaesthesia. 1985;40(9):914.
51. Bennett WM, Aronoff GR, Morrison G, et al. Drug prescribing in renal failure: dosing guidelines for adults. Am J Kidney Dis. 1983;3(3):155–93.
52. Filitz J, Griessinger N, Sittl R, Likar R, Schuttler J, Koppert W. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006;10(8):743–8.
53. Mercadante S, Arcuri E. Opioids and renal function. J Pain. 2004;5(1):2–19.
54. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13,179 patients. Curr Med Res Opin. 2005;21(8):1147–56.
55. Likar R, Sittl R. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. Anesth Analg. 2005;100(3):781–5, table of contents.
56. Hans G. Buprenorphine—a review of its role in neuropathic pain. J Opioid Manag. 2007;3(4):195–206.

57. Induru RR, Davis MP. Buprenorphine for neuropathic pain--targeting hyperalgesia. Am J Hosp Palliat Care. 2009–2010;26(6):470–3.
58. Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Curr Med Res Opin. 2012;28(5):833–45.
59. Tassinari D, Sartori S, Tamburini E, et al. Adverse effects of transdermal opiates treating moderate-severe cancer pain in comparison to long-acting morphine: a meta-analysis and systematic review of the literature. J Palliat Med. 2008;11(3):492–501.

Chapter 15
Buprenorphine and Opioid Rotation

Douglas L. Gourlay and Howard A. Heit

Introduction

Buprenorphine, as a therapeutic agent was brought to market as a parenteral analgesic in 1972 [1]. Initially recognized as a partial μ agonist with k antagonist activity, this novel opioid has enjoyed a renewed interest both in terms of its analgesic properties as well as its ability to stabilize and maintain opioid-dependent patients suffering from the disease of opioid addiction [2].

This truly versatile molecule has enjoyed an enviable safety record, as compared to traditional full μ opioid agonists, showing great potential for the treatment of higher risk patients.

The purpose of this chapter is to provide information to those who might consider using this agent in the context of an opioid rotation. The role of this drug will be examined from three unique perspectives:

1. As an analgesic agent onto which μ-dependent pain patients may rotate to or from
2. As an opioid stabilizing agent in the context of withdrawal-mediated pain due to "opioid debt" [3]
3. As part of an exit strategy in which the ultimate goal is to terminate opioid therapy [3]

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_15,

Clinical Pharmacology

Depending on the delivery system chosen, and the expected role the molecule may play, buprenorphine may assist in patient care in a variety of ways. Unfortunately, the simple role of μ analgesic is only one of the potential roles that this versatile drug may take. Failure to appreciate the mode of action in any given patient may lead to unnecessary confusion and less than optimal clinical outcomes.

When introduced in the United States as a parenteral analgesic agent in 1981, buprenorphine was limited to the management of acute pain [1]. More recently, the on-label use of the sublingual form has taken on the unique role of maintenance agonist treatment (opioid addiction) in the office-based setting [4], something that has not been possible in the United States since the Harrison Narcotic Treatment Act of 1914 [5].

Under DATA 2000 (Drug Addiction Treatment Act 2000) [6], the sublingual versions of buprenorphine, with or without naloxone, has been offered as a safer agent for the treatment of opioid addiction, adding a new pharmacologic tool with significantly less restrictive regulatory scrutiny on both patient and prescriber.

Of course, partial μ agonist medications can have peculiar properties which have proven to be clinically challenging both in terms of use for their primary indication but also in their ability to impact on future management of acute pain. In fact, the high receptor affinity and the reported blocking effect of buprenorphine has led some clinicians to erroneously believe that acute pain cannot be safely managed in the patient who is a chronic buprenorphine user. Fortunately, this is not the case [7].

Clinically, it is tempting to assume that any improvement in pain scores associated with the addition of an opioid medication is, by definition, "opioid responsive pain." Sadly, this is often untrue. In the context of the physically dependent pain patient, who has come to require a minimum level of μ agonism to achieve pharmacologic stability, unstable opioid levels may present themselves as worsening or "withdrawal-mediated" pain [3, 8].

For example, in patients who have become overly reliant on short acting, immediate release opioids, such as hydrocodone or oxycodone compound analgesics, there may be a significant worsening of morning pain, directly related to inadequate levels of the primary opioid analgesic. In some cases, conversion to a controlled release version of the same drug may help, at least temporarily to stabilize opioid levels and so improve pain scores. For some however, this is a transient response [9, 10].

This can also occur in patients who suffer acutely painful injuries superimposed upon a chronic pain complaint that has been treated with daily opioids. The following example will illustrate this point.

A chronic pain patient presents to the Emergency Room, with an acute fractured ankle. They routinely take morphine sulfate extended release (ER) 15 mg q8 h for a total daily dose of 45 mg morphine. On day 1, in the inpatient setting, they are given 5 mg morphine sulfate, 3 times per day for acute pain management. The total dose on day one is 15 mg morphine, compared to 45 mg expected for an "opioid debt" [3] of 30 mg. On day 2, the dose is doubled to 10 mg q8 h for a total dose of 30 mg

compared to an expected chronic daily dose of 45 mg morphine per day, resulting in an "opioid debt" of 15 mg. If on day 3, if the dose is tripled to 15 mg q8 h, it is only at this point that the patient's expected chronic opioid needs are met and acute opioid analgesia can begin. Prior to this point, all the morphine that was being given was servicing the "opioid debt" incurred by chronic daily opioid therapy, rather than treating pain associated with this acute injury. Not only is acute pain not well served by previously given doses of chronic opioids, the patient is likely to require considerably greater doses and so, greater care in managing their acute pain needs. Failure to address a potential "opioid debt" can exacerbate both acute and chronic pain.

Opioid Rotations

Opioid rotations are considered for one of several reasons [11]. The first is often associated with diminished analgesic efficacy. In this case, the patient is no longer receiving adequate pain relief with acceptable doses of the current opioid medication. Problems with tolerance are expected to be addressed by the new molecule, once again reinstating analgesic relief, hopefully with a decreased total daily dose in morphine equivalents. The second case involves rotations that are aimed at addressing unacceptable side effect profiles. In both these cases, the assumption made is that the pain generator is, in the prescriber's estimation, likely to be opioid responsive. Unfortunately, this is not always the case, even in pain treatment which appears, at least initially to respond to the addition of a new member of the opioid class of medications. Equally, opioid responsiveness is sometimes incorrectly defined by worsen pain associated with discontinuation of opioid therapy. In fact, some patients are almost certainly consigned to chronic opioid therapy, based not on how well they do on therapy but rather how poorly their pain responds to discontinuation of the opioid class of drug [12].

In some cases, the novelty of a new drug or a new drug dose is associated with a transient but unsustainable improvement in the symptom of pain [12]. It is in these cases, that the third role for opioid rotation becomes relevant: exiting from the opioid class of drug. Of course, in some situations, simply tapering the drug may lead to a successful discontinuation of the current medication however, contrary to once popular belief; people who no longer need opioids do not always come off them easily [12]. For these patients, an apparent increase in pain, associated with a lowering of the opioid medication is considered evidence of the positive role that opioids are playing in the patient's life. This is especially true if the patient unilaterally increases the dose and finds once again that their pain scores improve. This really only confirms that withdrawal-mediated pain can worsen most types of pain, be it opioid responsive or not, consigning the patient to a lifetime of chronic opioid therapy. In fact, some practitioners will see these cases as "the best of a bad situation," feeling that if their pain is poorly controlled on the opioid class of drug, it will only be worse off opioids. Of course, too rapid a taper or even abrupt discontinuation ("Drug Holiday") of the opioid class of medication will often reinforce these beliefs.

Clinical Implications of Opioid Rotations Involving Buprenorphine

Buprenorphine can find itself in the opioid rotation setting in one of several ways. In the first case, buprenorphine is the drug onto which the patient rotates. In the second case, buprenorphine is the incumbent molecule from which the rotation occurs. In the third case, we will examine the implications of the route of administration of buprenorphine as it relates to the process of opioid rotation.

Rotations onto Buprenorphine

In the current market, buprenorphine is available in one of two forms. The first is as an injectable form, in sub-milligram doses/mL, under the trade name Buprenex or Temgesic [13]. In the chronic pain setting, these products have largely been replaced by the off-label use of sublingual buprenorphine, with or without naloxone (Subutex®/Suboxone®). In this capacity, a cross-over period is often used whereby the first opioid is gradually decreased while the new opioid is introduced and titrated upward, to effect. However, when buprenorphine is given to a patient who is in opioid withdrawal, it is much more likely to reduce or eliminate rather than precipitate this constellation of symptoms [14].

In some cases, it may be useful to consider switching the patient to an intermediate μ agonist, typically short acting, which can be tapered to as low a dose as the patient is able to tolerate prior to initiating the 12–24 h opioid free period that is commonly recommended in most buprenorphine induction protocols prior to introduction of sublingual buprenorphine. Although the induction protocols in the DATA 2000 (Drug Addiction Treatment Act 2000) training recommend a minimum of 12–24 h "Opioid Free," and even longer if induction is from methadone [15], precipitated withdrawal is anything but certain. Many patients simply find that the process of discontinuation in preparation for buprenorphine induction, is too distressing. In these cases, careful discussion of the risks of precipitated withdrawal should be documented in the medical record prior to attempting conversion to buprenorphine. Ultimately, an informed patient is often in the best position to determine when induction should begin.

While the risk of precipitated withdrawal is often discussed, it is also important to remember that in patients with relatively low μ tolerance, a potent opioid like buprenorphine can result in nausea and diaphoresis, not through precipitated withdrawal but rather through excess μ agonist activity [16]. This is more commonly seen with patients who have been using relatively small quantities of opioids, such as combination products containing codeine or hydrocodone. Only by careful clinical assessment can this distinction be made.

In some cases, clinicians with more experience and resources may elect to try and mitigate these symptoms of withdrawal through the limited use of centrally acting

α-2-agonists (e.g., clonidine), NSAIDs (e.g., ibuprofen), and other over-the-counter agents such as loperimide (Imodium®).

More recently, a 7 day transdermal buprenorphine preparation for the treatment of chronic pain has come on the market. (Butrans® Purdue Pharma). It is interesting to note, that when rotating onto this product, an opioid free period is not recommended prior to the initiation of the patch. Clinical experience has shown that rotation onto transdermal buprenorphine can be accomplished without risk of precipitated withdrawal, presumably due to the relatively slow absorption of buprenorphine through this delivery system (as compared to rapid absorption through the sublingual routes of administration). [http://app.purduepharma.com/xmlpublishing/pi.aspx?id=b].

Rotations from Buprenorphine

In some cases, it may be necessary to rotate from buprenorphine onto a full μ agonist, as commonly seen during an acute anticipated or unanticipated pain event such as a planned surgical procedure or acute trauma [7]. Unlike the case where buprenorphine is being added to a patient who is fully μ dependent, full μ agonists can always be added to a patient who is buprenorphine dependent without fear of precipitating withdrawal. Practically speaking, this may result in the gradual reduction in buprenorphine while the new opioid is being titrated up. Since buprenorphine is a partial agonist, it is important to consider the possibility that there may be μ receptor upregulation that could increase μ sensitivity. Although it is technically possible to use any full agonist with buprenorphine, the chronic concurrent use of full and partial agonists may be difficult to defend in the context of any adverse outcome.

Buprenorphine as Part of an Exit Strategy

One of the reported advantages of buprenorphine is the apparently milder withdrawal syndrome associated with discontinuation of this agent [14, 17, 18]. While there is literature to support this statement when comparing buprenorphine to methadone withdrawal, the fact is that the withdrawal experience is highly personal. There are patients who successfully discontinue relatively high doses of oxycodone with ease, while those who might be expected to taper easily from lower doses may complain of disabling withdrawal symptoms. Unfortunately, the relationship between dose and degree of withdrawal is not a simple one: Those on higher doses of potent opioids will generally have more difficulty tapering than those who are on smaller doses. That said, it may be extremely dangerous to assume that the reason a patient was able to taper off a high dose, potent opioid with apparent ease was related to drug diversion or noncompliance. On the other hand, a patient who has difficulty tapering or discontinuing the opioid class of drug only proves that there is physical dependency or psychological reliance on this medication. Whether there is addiction or drug misuse requires a much more thorough evaluation.

Potential Opportunities and Threats with Opioid Rotations

When rotating onto a new molecule, there is a temptation to assume that any success (or potential failure) is solely a function of that molecule. In fact, with any new therapeutic intervention, there is a significant risk of missing the behavioral opportunities associated with this change. As an example, patients who rotate onto a more pharmacologically stabile opioid such as methadone or buprenorphine and who do well, often do well because of the opportunities that a new molecule offers in terms of new structure and support rather than simply the introduction of a novel agent. Rarely is success a sole function of a new molecule or the "optimum" dose of drug but rather sustainable success is often a function of the structure and support which can quite legitimately be imposed upon the patient in the name of safety. "New molecules" should mean "New Rules" [19] and with these new rules, success which previously eluded the patient and clinician may now be possible.

This is not to suggest that improvements in pain score or function are somehow placebo driven, but rather sustainable improvements encompass a biopsychosocial dynamic that is more complex than one could expect from the addition of or change to a new molecule. In fact, one of the hallmarks of over reliance on a pharmacologic intervention is a transient improvement. This is often followed by a progressive pattern of diminishing returns with dose escalation leading ultimately to the patients' recognition that "the medication doesn't make their pain better; it just takes the edge off". Alternatively, a patient may state that they "Don't feel the drug working anymore." There are many derivatives of this concept but it has likely played at least some role in the sometimes gram-quantities of morphine equivalent doses per day being prescribed, often to patients with less than satisfying diagnoses to justify the many risks associated with this practice.

Unfortunately, "No Ceiling" as a pharmacologic principle associated with full agonist class of drugs has come to mean "No Limit" which is clearly contrary to even the most limited application of common sense [3]. The limit to any pharmacologic intervention is and always has been the therapeutic versus adverse effect profile. That said, the potential role of buprenorphine as a drug to rotate onto from a previous pattern of problematic opioid use is even more important in these often challenging cases.

Unfortunately novel medications, especially those with apparent μ receptor blocking capabilities and limited μ activity can leave practitioners with the impression that it is difficult or impossible to manage acute pain in patients who are using buprenorphine. Fortunately, this does not appear to be the case [7].

While it is true that buprenorphine's high receptor affinity can reduce the effectiveness of other opioid molecules, even patients who are on maximal daily therapy (*as per* DATA 2000 training) do not have 100 % μ receptor occupancy [20]. It has been suggested that in cases of mild to moderate "anticipated acute pain" [7] (e.g., painful procedures which are planned for in the future), the patient might benefit from temporary discontinuation of buprenorphine with addition of another potent high receptor affinity μ agonist (e.g., fentanyl or hydromorphone) to alleviate any withdrawal symptomatology prior to the acutely painful event. A typical

example of this would be a patient who is on buprenorphine who is preparing to undergo a planned orthopedic reconstruction of their knee. Given the degree of pain anticipated postoperatively, it may well be wise to at least temporarily stop the buprenorphine a few days prior to surgery. Of course buprenorphine, in multiple daily dosing regimens is an excellent analgesic, allowing for a modest, temporary dose increase during the acute event and recovery period, should the expected postop pain be within the analgesic range of buprenorphine. This offers several advantages including an easier return to basal buprenorphine treatment after the acute injury has subsided as well as simplifying the interpretation of Urine Drug Test results, should testing be considered necessary.

Even in the context of "unanticipated acute pain" [7], such as seen in the case of trauma or the acute abdomen, the expected level of pain post operatively may be such that the drug can simply be continued, with a modest dose increase to assist in managing the new pain demands for analgesia with the addition of a short acting opioid with high μ affinity such as fentanyl or hydromorphone for additional pain relief [7]. Of course, any increase in sublingual buprenorphine for pain management must be in at least a twice if not 3 times daily dosing schedule for effective analgesia, given that the drug has an analgesic duration of action considerably shorter than the "once daily" dosing schedule seen with maintenance therapy [21]. Transdermal dosing increases will typically be delayed in onset due to the nature of the concentration-driven characteristics of that route of administration making it unsuitable for acute management of pain. Time to steady state of transdermal buprenorphine is typically reported to be 72 h [22]. Therefore it would be appropriate in this situation to temporarily add a short acting opioid as stated above during the acute period.

Buprenorphine has been reported to have limited μ activity. This has led some clinicians to consider buprenorphine in only those cases where the incumbent opioid level is less than 60–80 mg equivalents of methadone per day. However, patients who are struggling on considerably higher daily doses of methadone have done very well on buprenorphine despite this apparent limitation. One possible explanation for this may well rest in the observed clinical instability of the patient on higher doses of methadone (or other μ agonists that are in dose equivalences beyond buprenorphine's apparent reach). The daily dose may not actually represent what the patient "needs" in terms of μ equivalence but rather the amount of μ activity that the patient can tolerate. In the authors' experience, many of these patients do extremely well with rotation onto this (buprenorphine) medication.

Mechanics of Opioid Rotation

When rotating from a full μ agonist such as morphine onto buprenorphine, the patient should be apprised of the rationale behind the impending change. In some cases it may be apparent; such as a patient who has continuously run out of medication, requiring frequent early medication releases or dose escalation. However, it

should not be assumed that the patient fully appreciates the potential benefit of buprenorphine or it's expected role, in their particular situation. Discuss this with the patient, noting expectations and any potential concerns that they might have prior to addressing any dose reduction that might be helpful in facilitating the transition from the current full μ agonist onto buprenorphine. If the patient is rotating onto sublingual buprenorphine, the risk of precipitous withdrawal necessitates an opioid free period that is ideally over 24 h for immediate release opioids and 48–72 h for intrinsically long acting agents such as methadone [15]. Unfortunately, some patients will not be able to comply with these instructions. In these cases, encouraging the patient to discontinue opioid use for as long as possible to create a sense of maximally tolerable withdrawal symptoms may well be sufficient to effect a safe and effective transition onto this drug. In the authors' opinion, it is reasonable to ask this of the patient, recognizing that some may actually not have been fully compliant with the recommended abstenance period. To deny the patient induction onto buprenorphine due to the potential risk of precipitated withdrawal may not be reasonable. As long as the patient is clearly aware of the risk of precipitated withdrawal, and it has been appropriately documented in the clinical record, the responsibility should rest solely with the patient. For the most part, the risk of precipitated withdrawal may be more of a theoretical risk as compared to the very real risk of worsening pain and withdrawal side effects associated with an inadequate CNS level of μ agonist. Assuming that the rotation remains within the primary role of pain management, a twice to three times daily dosing schedule is recommended [7]. Again, this is "off-label" use of the sublingual preparation, which was launched in the United States under DATA 2000, for the treatment of opioid dependency [23]. Dose increases can safely occur on a 3–5 day basis, or sooner if withdrawal remains a problem. Fortunately, the amount of drug required to offset opioid withdrawal is significantly lower than any theoretical equivalence table that might be found. The following example illustrates the above points.

A patient currently using 15 mg of Morphine Sulfate, three times daily is to rotate onto buprenorphine sublingual. The patient is advised of the potential risk of precipitated withdrawal as well as the probability that at least during the time where the morphine will be discontinued, their pain may well worsen due to withdrawal-mediated pain. A prescription for buprenorphine 2 mg (or, where there is a reasonable expectation that the patient may require a more substantial per diem dose to alleviate opioid withdrawal, an 8 mg tablets may be more practical) is given, sufficient for 2 mg, q8 h for 1 week with the patient to report in on the second and third days of therapy in order to assess efficacy and any untoward effects of the new medication. On the first day of rotation, usually earlier in the week, the patient has filled and brings in their medication for in-office induction onto buprenorphine. At that time, any discrepancy in tablet number can be noted and if necessary, discussed with the patient. The patient takes a 2 mg tablet SL (or 4mg i.e. ½ tablet if 8 mg tablets are being used) and is observed for the next ½–1 h for any signs of worsening of withdrawal symptoms, after which they remain in the waiting room for a minimum of 2–4 h to determine if an additional dose is required. The patient is then observed for an additional hour after the last

dose is given, in case there is either precipitated withdrawal or, in cases where μ tolerance is actually quite low, signs of excess μ agonism. If after 4 h or more, the patient begins to suffer withdrawal symptoms again, they are encouraged to take another dose of buprenorphine or the remainder of a split dose (eg., ½ 8 mg dose = 4 mg) for a total of 4–8 mg on day one. While it is possible to safely go beyond 8 mg, the failure to stabilize the patient on a conservative dose of buprenorphine should alert the prescriber to the potential that this may be more of a maintenance model of care rather than a simple opioid rotation for pain relief. As a general rule, patients are dramatically improved on as little as 4–8 mg of buprenorphine, especially if opioid withdrawal has been a significant problem.

Unfortunately, as a potent opioid, individual variability may actually result in diaphoresis and nausea due to the patients inability to tolerate the buprenorphine dose given. The vast majority of patients ultimately tolerate buprenorphine quite well, even after an initial stormy induction. Further titration of dose can be done either in person, in those more complex boundary-challenged patients or by telephone in the otherwise stable primary care pain patient.

One group of patients who seem to appear to tolerate the mono product (Subutex®) over the combination product (Suboxone®) are those with established sensitivities to the artificial sweetener, acesulfame potassium [24]. In such cases, the argument can be made to switch to Subutex® or to remain on this product if induction was begun on the mono product.

Assuming the patient tolerates buprenorphine reasonable well, it is important to remember that until there is μ receptor balance between buprenorphine and the CNS active sites; all the *per diem* buprenorphine is essentially going to go to "pay the opioid agonist debt" [3]. Failure to appreciate the potential debt that the rotation may create will often leave both patient and practitioner alike, with the impression that buprenorphine is an inadequate agent for pain relief. Fortunately, this is usually not the case. It is also important to consider a thorough reassessment of the underlying pain generator, once there is no further evidence of any agonist debt that might be helping to relegate the patient to a life of chronic opioids, despite compelling evidence that their pain may not be particularly well served by the opioid class of drug. Rushing into a 3 or 4 times daily dosing structure may actually be no more effective than a once-daily dosing regimen of an equivalent dose. Where there is good evidence that the pain is likely to be μ responsive, early introduction of a multiple daily dosing scheme is warranted, otherwise sticking with a once-daily dosing schedule may help to confirm a significant withdrawal-mediated component to the pain problem.

Once the patient has achieved a reasonable degree of opioid stability, it may be worthwhile considering a therapeutic trial of previously ineffective adjunctive agents whose success or failure previously may have been defined in terms of reduction in opioid dose.

In cases where buprenorphine is offered to the patient in the form of a transdermal delivery system, the delayed onset in CNS effect that is intrinsic to the concentration-driven route of administration actually allows a more traditional "cross-over" rotation where the incumbent μ agonist is actually gradually reduced

over the 3–5 days necessary for transdermal buprenorphine to reach steady state. Again, starting with a lower rather than higher dose can help restore adequate opioid levels while minimizing any risk of side effects associated with excessively high doses.

In cases where the patient is being rotated *from* buprenorphine to a full μ agonist, the process is relatively trivial: You can always add a full μ agonist to a buprenorphine-dependent patient with impunity. The one caveat to this is a theoretical risk of opioid receptor upregulation (Personal Communication Walter Ling) (due to the partial agonist character of buprenorphine); however, this potential risk of opioid hypersensitivity may be offset by the reduction in available opioid receptors due to buprenorphine binding. Regardless, these issues can be easily addressed by the sage words of the conservative clinician: "Start low-go slow. You can always add more but once given, it is difficult to take back!"

To repeat a most important point in any opioid rotation, always eliminate the "opioid debt" prior to any attempts to assess analgesic efficacy. Similarly, reintroduction of previously failed adjunctive agents, such as tricyclic's or gabapentinoids may be worth considering, especially if the proposed pain generator is likely to respond. Failure to do so may deny your patient a potentially beneficial therapeutic effect.

Exit Strategies

While opioid rotations are often considered when attempting to improve analgesia or side effect profile, the rotation can also be useful as part of a well-considered exit strategy following a failed opioid trial or where the opioid class of medication is no longer appropriate [3].

In fact, there are three general reasons why an exit strategy from opioids may be necessary [11, 25]. The first is when the original pain generator has resolved. In this case, the patient may have come to the realization that they no longer need the medication for pain relief but rather to address the physical consequences of opioid withdrawal.

In the second case, it has become apparent that the opioid class of drug is no longer part of the solution but rather has become part of a problem. This is frequently seen in the context of a failed opioid trial. For some prescribers, the perception that once on the opioid class of medications, their patient will never come off, needs to be tempered by a realistic option for addressing the need to terminate full agonist therapy.

The third reason why one might attempt to rotate off of the opioid class of drug is where there is clear evidence that the drug is "doing more to the patient than for the patient" [12, 26]. As an example, many pain generators will respond initially to the opioid class of medication but fail, in the long run, to achieve any sustainable relief with reasonable doses of drug. Worsening of the underlying pain due to inadequate analgesic relief may transiently improve with further dose escalation; however long-term success may paradoxically be achieved by discontinuing the opioid

medication altogether. Some of the very high doses of opioid medications recently reported [27, 28] have almost certainly resulted from the belief that "if the dose is high enough, all types of pain will ultimately respond." This logical construct has been tested clinically and as a result, most current guidelines for the treatment of chronic pain include some upper limit, above which the risks are likely to exceed the benefit for ongoing dose escalation [29, 30].

In practical terms, the rotation onto buprenorphine has been described previously, in this chapter. What distinguishes the role of buprenorphine rotation in the context of an exit strategy is the apparent milder opioid withdrawal syndrome that has been reported in the literature [14, 31] with buprenorphine tapers. Buprenorphine has been described as having less physical dependence (as compared to full μ agonists) and so less intense withdrawal symptoms [31]. Unfortunately, withdrawal from any agonist drug with potential for a discontinuation syndrome is a highly personal experience. Many patients have commented on the ease with which they had discontinued buprenorphine; however some patients perceive their withdrawal experience as anything but mild, especially if they have no reference point against which to compare.

When considering buprenorphine rotation as part of an opioid exit strategy, two important points are worth considering. The first is that any medication taper is a balance between time and neuroadaptation as compared to overall clinical response on a patient-by-patient basis. So, if the degree of withdrawal associated with a 10 % drop every month is the same as a 10 % drop every week, it makes good sense to drop the dose on a weekly basis since a monthly taper schedule only prolonged the patients' misery [9]. On the other hand, the ease with which a patient accomplishes the initial taper may not reflect the degree of difficulty experienced as the drug is ultimately discontinued. If problems are to occur, they are most often seen at the end rather than the beginning of any taper [9].

For most patients, discontinuation of an opioid trial has little or no long-term sequelae. For those patients who find it difficult or impossible to taper off this class of drug, it may be that buprenorphine is playing a mood stabilizing role [32–34] which may positively affect hedonic tone (Personal Communication E Salitz). Whether this continued need for opioids represents an undiagnosed substance use disorder (necessitating a maintenance agonist treatment role) or an undiagnosed or inadequately treated mood disorder may never be known. This topic falls well outside the scope of this chapter. Interested readers might seek advice from clinicians with more experience or resources to address these challenging cases.

Treatment Caveats

Buprenorphine, as a molecule has certain common characteristics that it shares with other μ agonist agents. The route of administration, however, can significantly alter some of these characteristics and so must be considered when using this medication. With this in mind, we will first consider the sublingual (SL) route of administration.

With the current forms of SL buprenorphine available, including the branded forms of Subutex® (buprenorphine mono) and Suboxone® (combination buprenorphine/naloxone 4:1 ratio) (Reckitt Benckizer) and the generic buprenorphine mono product (Buprenorphine by Roxane™), the patient must remember to allow the tablet to dissolve thoroughly beneath the tongue, allowing sufficient time for adequate sublingual absorption. Interestingly, despite clinician's best efforts at reminding patients to properly dissolve these tablets, some patients remain less vigilant in this regard, often complaining of decreased effect with worsening nausea associated with greater enteral absorption of the parent molecule (Unpublished Gourlay/Heit). Extensive first-pass effect seen with oral administration is thought to account for some of the nausea seen via the oral route likely through its extensive conversion to the primary metabolite, nor-buprenorphine (Personal Communication Walter Ling).

There is some confusion in the literature as to bioavailability of buprenorphine when delivered via the SL route. Early data published related to sublingual buprenorphine mono product has most often referred to the tincture of buprenorphine (alcoholic solution) [35] whereas virtually all data related to the combination product (Suboxone®) specifically documents absorption from dry, sublingual tablets. Buprenorphine is better absorbed from an alcoholic solution as compared to a dry sublingual tablet. Dosing "to effect" tends to make this something of a moot point.

In the second case, where the patient is being rotated onto transdermal buprenorphine, there is no need to ask the patient to endure a prolonged period of opioid withdrawal, as recommended with induction onto the sublingual delivery systems. Unlike the sublingual route, where serum levels of buprenorphine (and so CNS levels) rise relatively quickly, the transdermal concentration-driven delivery system has a much slower onset of action. For this reason, patients rotating onto transdermal buprenorphine will typically decrease the first opioid dose with the addition of the buprenorphine patch, thereby creating an effective "opioid debt" [12] which the buprenorphine molecule can gradually correct. The rotation then proceeds in the usual fashion, eventually resulting in the first opioid being discontinued in 3–5 days. It is important to remember that while it may be possible to continue on with both agents, it is generally unwise to use full and partial μ agonists at the same time, even if the patient indicates that this combination "appears to be" effective. The risk of a potentially avoidable bad outcome in the context of a "difficult to defend" treatment course, is simply too great. An obvious exception to this, as previously stated, would be the short term use of a full agonist in the management of acute pain.

Buprenorphine Abuse

Buprenorphine, as a drug of abuse has been well documented in the addiction medicine literature [36]. To what extent the addition of the μ antagonist naloxone may have on drug likability and perhaps, abuse and diversion remains to be seen [37].

Drug abuse and diversion are complex issues that are guided by societal, medical and economic as well as regulatory factors. It would be unwise to estimate risk based largely on the pharmacologic properties of any one or combination of drugs. It has, however, been this apparent improved safety profile that has led to buprenorphine's use in higher risk patients.

While opioids in general have long been associated with disordered sleep architecture, including both central and obstructive components, formal studies have largely focused on the full μ agonists such as methadone [38].

Patients who are at risk for or who have documented cases of sleep apnea may theoretically benefit from the use of a partial agonist such as buprenorphine; however recent data by Farney et al. suggest that the risks of sleep disordered breathing with the buprenorphine-naloxone containing product may be under-recognized [39]. An obvious exception to this, as previously stated, would be the short term use of a full agonist in the management of acute pain.

Similarly, patients who have documented histories of prescription opioid misuse may benefit from the use of buprenorphine in the treatment of chronic pain despite the lack of randomized controlled studies to support this practice. Regardless, more carefully set limits and boundaries with rotations onto this 'new' medication may well play as great or even greater a role in the successful treatment of their chronic pain [3, 40].

Addressing Pain and Concurrent Addiction (the High Risk Patient)

While a detailed examination of this subject is beyond the scope of this chapter, it is important to have an approach to identify the primary problem, where pain and addiction co-occurs so that adequate steps may be taken to manage risks associated with treatment of this often challenging patient population [9].

When a high risk patient complains of pain, it is sometimes tempting to believe that risk is simply a function of inadequate symptom resolution (decreased pain/improved function). In these cases, it is often better to assess risk independently of the pain, especially when determining which might be the dominant issue [3]. So, where pain and addiction coexist, it is critically important to determine which is the dominant process, particularly where aberrant behavior is significant. Failure to do so is unlikely to result in treatment gains in either domain. This is vitally important when considering the use of multiple daily doses of buprenorphine, as is needed for a primary analgesic effect, since there is an increased level of patient responsibility for their medication when given in this fashion. In the special case of the patient who is reluctant to focus on anything but their chronic pain, the use of controlled substances in a traditional pain management setting may be relatively contraindicated unless there are sufficient resources and experience "in house" to manage primary substances use disordered patients while concurrently assessing and managing their chronic pain.

When very tight limits are being considered, the fact that the higher risk pain patient will need multiple daily doses of medication does not eliminate the value of frequent follow up, either at the prescribers clinic, or more practically, at the dispensing pharmacy using smaller pill-loads, repeated multiply over short intervals e.g., weekly prescriptions, refilled on a monthly or longer basis, as individual clinical circumstances dictate [3]. It should be pointed out that buprenorphine (as the sublingual preparation) is regulated in America somewhat differently from other opioid molecules. Specific mention has been made of the DATA2000 regulatory framework for the use of this drug in the office-based treatment of opioid addiction. Prescribers under DATA2000 are required to fulfill certain educational requirements in order to prescribe this drug. Specifically, prescribers are required to preface their DEA number with an "X" to indicate compliance with the DATA2000 regulations. This implies that the medication is being used *primarily* for the treatment of opioid addiction. When buprenorphine SL is being prescribed "off-label" *primarily* for the treatment of pain, the drug no longer falls under DATA2000 and so does NOT require a special "X" to precede the DEA number. In fact, the specific educational requirements for DATA2000, while useful are not required to prescribe for this indication. *It is important to ensure that the medical record accurately reflects the primary diagnosis for which the drug is being prescribed* [23].

Conclusion

Buprenorphine remains a versatile drug, available in a variety of forms and formulations, in use for both on-label as well as off-label treatment of pain and opioid dependency. Success or failure associated with these products will likely depend as much on patient selection as the novelty of the drug itself.

References

1. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol. 1977;60(4):537–45.
2. Lewis JW, Walter D. Buprenorphine–background to its development as a treatment for opiate dependence. NIDA Res Monogr. 1992;121:5–11.
3. Gourlay DL, Heit HA. Universal precautions revisited: managing the inherited pain patient. Pain Med. 2009;10(Suppl 2):S115–23.
4. Manlandro Jr JJ. Buprenorphine for office-based treatment of patients with opioid addiction. J Am Osteopath Assoc. 2005;105(6 Suppl 3):S8–13.
5. Terry CE. Six months of the Harrison Act. Am J Public Health. 1916;6(10):1087–92.
6. Authority for practitioners to dispense or prescribe approved narcotic controlled substances for maintenance or detoxification treatment. Final rule. Federal Register. 2005;70(120): 36338–44.
7. Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. Clin J Pain. 2008;24(2):93–7.

8. Li X, Clark JD. Hyperalgesia during opioid abstinence: mediation by glutamate and substance P. Anesth Analg. 2002;95(4):979–84; table of contents.
9. Heit HA, Gourlay D. Bonica's Management of Pain. In: Balantyne JC, Fishman SM, Rathmell JP (eds). Treatment of chronic pain in patients with a history of substance abuse. Philadelphia: Lippicott, Williams & Wilkins; 2010.
10. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. Clin J Pain. 2008;24(6):469–78.
11. Gammaitoni AR, Fine P, Alvarez N, McPherson ML, Bergmark S. Clinical application of opioid equianalgesic data. Clin J Pain. 2003;19(5):286–97.
12. Gourlay DL, Heit HA. Pain and addiction: managing risk through comprehensive care. J Addict Dis. 2008;27(3):23–30.
13. Buprenorphine injection (Temgesic). Drug and therapeutics bulletin. 1979;17(5):17–9.
14. Stock C, Shum JH. Bupreorphine: a new pharmacotherapy for opioid addictions treatment. J Pain Palliat Care Pharmacother. 2004;18(3):35–54.
15. Laura McNicholas CPC. TIP 40: Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
16. Gordon AJ, Liberto J, Granda S, Salmon-Cox S, Andree T, McNicholas L. Outcomes of DATA 2000 certification trainings for the provision of buprenorphine treatment in the Veterans Health Administration. Am J Addict. 2008;17(6):459–62.
17. Nutt D, Lingford-Hughes A. Addiction: the clinical interface. Br J Pharmacol. 2008;154(2):397–405.
18. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. Br J Anaesth. 1985;57(2):192–6.
19. Maher W. HBO: Real Time with Bill Maher. 2011.
20. Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology. 2003;28(11):2000–9.
21. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127–34.
22. Purdue Pharma Canada. BuTrans product monograph. Pickering, ON: Purdue Pharma Canada; 2010.
23. Heit HA, Covington E, Good PM. Dear DEA. Pain Med. 2004;5(3):303–8.
24. Benckiser R. Suboxone product insert. Richmond, VA: Reckitt Benckiser; 2010, p. 6.
25. McPherson ML. Demystifying opioid conversion calculations: guide for effective dosing. Bethesda, MD: American Society of Health System Pharmacists; 2010.
26. Heit HA, Gourlay DL. Chronic pain and addiction. In: Pasricha P, Willis WD, Gebhart GF, editors. Chronic abdominal pain and visceral pain. 1st ed. New York, NY: Informa Healthcare US; 2007.
27. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152(2):85–92.
28. McLellan AT, Turner BJ. Chronic noncancer pain management and opioid overdose: time to change prescribing practices. Ann Intern Med. 2010;152(2):123–4.
29. Ballantyne JC, Mao J. Opioid therapy for chronic pain. N Engl J Med. 2003;349(20):1943–53.
30. Washington State Agency Medical Directors' Group. Interagency guideline for opioid dosing for chronic non-cancer pain: an educational aid to improve care and safety with opioid safety. Olympia, WA: The Group; 2010.
31. Sporer KA. Buprenorphine: a primer for emergency physicians. Ann Emerg Med. 2004;43(5):580–4.
32. Emrich HM, Vogt P, Herz A. Possible antidepressive effects of opioids: action of buprenorphine. Ann N Y Acad Sci. 1982;398:108–12.

33. Emrich HM, Vogt P, Herz A, Kissling W. Antidepressant effects of buprenorphine. Lancet. 1982;2(8300):709.
34. Seifert J, Metzner C, Paetzold W, Borsutzky M, Ohlmeier M, Passie T, et al. Mood and affect during detoxification of opiate addicts: a comparison of buprenorphine versus methadone. Addict Biol. 2005;10(2):157–64.
35. Nath RP, Upton RA, Everhart ET, Cheung P, Shwonek P, Jones RT, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. J Clin Pharmacol. 1999;39(6):619–23.
36. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev. 2011;4(1): 28–41.
37. Bazazi AR, Yokell M, Fu JJ, Rich JD, Zaller ND. Illicit use of buprenorphine/naloxone among injecting and noninjecting opioid users. J Addict Med. 2011;5(3):175–80.
38. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. Pain Med. 2008;9(4):425–32.
39. Farney RJ, Jain V, McDonald A, Wander T, Coudreaut M, Walker JM. Sleep disordered breathing (SDB) in patients undergoing detoxification from opioids with buprenorphine-naloxone. Chest. 2011;140(794A).
40. Gourlay D, Heit H, Almarhezi A. Universal precautions in pain medicine: a rational approach to the management of chronic pain. Pain Medicine. 2005;6(2).

Chapter 16
Methadone and Buprenorphine Use During the Perinatal Period

Alice Ordean

Prevalence

Opioid dependence is a growing concern during the perinatal period. While heroin use remains relatively steady, prescription opioids have become responsible for a larger proportion of opioid misuse. Due to the surge of prescription opioid addiction in the 1990s, its use by women of childbearing age is also becoming increasingly more common. According to the results from the 2010 National Survey on Drug Use and Health, 5.1 million Americans were nonmedical users of pain relievers and 0.2 million used heroin [1]. Among pregnant women, 4.4 % reported current illicit drug use in 2009–2010 [1]. Opioid misuse is also frequently implicated in emergency department visits. In 2009, 600,000 visits involved nonmedical use of opioid analgesics [2]. The most frequently reported formulations involved oxycodone (175,949), hydromorphone (104,490), and methadone (70,637).

Screening and Assessment

There are several factors associated with at-risk substance use during pregnancy. Women with a history of opioid dependence tend to be younger, less than 25 years of age [3]. They have a current or past personal and/or family history of substance use [4]. Concurrent psychiatric disorders such as mood and anxiety disorders, as well as childhood history of sexual abuse are also commonly diagnosed in this population [3, 5]. Polysubstance use is also common among pregnant women with opioid dependence. Comorbid abuse of cocaine, alcohol, tobacco, marijuana, and benzodiazepines has been reported among opioid-dependent pregnant women [5–7].

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_16,

All pregnant women should be screened for alcohol, tobacco, and other drug use including prescription medication misuse during pregnancy. Many women who are opioid-dependent are more likely to have a delayed diagnosis of pregnancy and therefore, present for care only in the second or third trimester. Some women may only be diagnosed with opioid dependence while they are in labor or in the postpartum period when the neonate starts to show signs of neonatal withdrawal.

Pregnant women requesting treatment for opioid addiction require an assessment to make a diagnosis of substance use disorder and to make an appropriate management plan. A thorough assessment includes a detailed inquiry into the following areas: opioid use history (amount, duration, route of use, source); concomitant alcohol, tobacco, and other drug use history; medical health (e.g., sexually transmitted infections, hepatitis C), mental health, and obstetrical history; psychosocial history; and previous treatment attendance and outcomes [8]. Treatment planning should focus on opioid dependence as well as concomitant disorders and psychosocial needs.

Management of Opioid Dependence During Pregnancy

The management of opioid dependence during pregnancy may include the following options: symptomatic treatment, methadone detoxification, or opioid agonist treatment (OAT) (methadone or buprenorphine). Currently, OAT with methadone remains the recommended standard of care. Promising research evidence is also giving support to the use of buprenorphine as an alternative to methadone during the perinatal period. Buprenorphine may be prescribed if the benefits outweigh risks and the patient refused methadone or if methadone services are not available in their community.

Pregnant women presenting with a history of opioid dependence typically continue their substance use due to the severity of opioid withdrawal. Physical symptoms of opioid withdrawal consist of flu-like symptoms such as nausea, vomiting, diarrhea, sweating, rhinorrhea, and myalgias. Psychological symptoms are manifested by anxiety, insomnia, dysphoria, and strong drug cravings which lead to a high risk of relapse to opioid use. During pregnancy, opioid withdrawal may also present as uterine irritability leading to an increased risk of spontaneous abortion, premature labor, fetal distress, or fetal death [9].

Therefore, symptomatic relief of opioid withdrawal symptoms may be offered until other treatments become effective [10]. Treatment regimen should focus on relieving specific symptoms. For example, nausea can be treated with dimenhydramine (Gravol), diarrhea with loperamide (Imodium), and myalgias with acetaminophen. Short acting morphine can also be offered in small amounts (e.g., morphine 5–10 mg po q4–6h prn) until an alternative opioid agonist becomes available. The use of clonidine during pregnancy is not indicated due to the lack of human safety data [11].

Obstetrical complications associated with heroin or prescription opioid dependence are secondary to fluctuating serum levels during repeated cycles of opioid intoxication and withdrawal (mentioned above). The are many benefits to OAT during pregnancy including decreased withdrawal symptoms, decreased illicit opiate use, decreased cravings, reduced fetal and neonatal complications, improved maternal health status, and enhanced compliance with prenatal care [12]. Therefore, since the benefits of OAT outweigh risks associated with untreated opioid dependence, pregnant women who meet criteria for opioid dependence should be offered OAT.

Methadone Maintenance Treatment

MMT is a substitute for both heroin and prescription opioid addiction. Methadone is a mu agonist with similar properties to morphine [12, 13]. Methadone is dispensed as a orange drink to prevent injection use and is well absorbed from the gastrointestinal tract into the bloodstream. Its effect occurs within 30 minutes of ingestion with a peak at 2–4 hours and long duration of action of up to 24–36 hours. Methadone accumulates in tissues with repeated daily administration and avoids fluctuating opioid levels associated with repeated use of short-acting opioids (e.g., heroin or prescription opioids). Once stabilized on a dose of methadone, subsequent doses should not cause sedation or euphoria. MMT allows individuals to function and to perform normal physical and mental tasks.

Fetal and neonatal effects: Methadone crosses the placenta but has not been found to be teratogenic [13]. A couple of studies have demonstrated an association between antenatal opioid exposure, especially methadone, and an increased incidence of strabismus [14]. However, more studies are needed to determine a casual relationship. There have also been inconsistent results related to the association between MMT and intrauterine growth restriction. Some studies found that infants exposed to methadone in utero tend to be smaller (smaller head circumference and length and lower birth weight) with growth differences resolving 1–2 years after birth [15–18].

Breastfeeding: Methadone has been detected in breast milk in small quantities, but levels are not sufficient to have any clinical effects. Breastfeeding does not prevent neonatal withdrawal and additional observation and treatment is still required. Therefore, based on the current literature, breastfeeding is safe regardless of maternal methadone dose [19–21]. The American Academy of Pediatrics has also found methadone to be compatible with breastfeeding [22]. Neonatal withdrawal makes breastfeeding more difficult. Additional support should be offered to make the breastfeeding process a success. No long-term outcome data is currently available to determine the risk of exposure to negligible amounts of methadone in breast milk.

Long-term effects: There are inconsistent results regarding long-term neurological and developmental effects of methadone exposure in utero based on limited

follow-up data [15, 22, 23]. Studies have only documented outcomes up to age 3. Findings indicate that opiate-exposed newborns are at risk for poorer neurodevelopmental outcomes related to physical and cognitive development. Studies failed to control for confounding factors such as other substance use and environment (e.g., parenting skills, low socioeconomic status). Therefore, developmental delays can be attributed mainly to environmental deprivation and parental drug addiction instead of the drug itself. Social, environmental, and biological factors moderate developmental outcomes and more research is needed to clarify the actual effect of opioid exposure on development.

Dosing: Patients stabilized on methadone before conception should continue on MMT for duration of pregnancy. Follow MMT guidelines for women undergoing MMT stabilization during pregnancy. This protocol is only valid for the first day of inpatient initiation so it is not a useful guide for physicians who want to initiate pregnant women to MMT [9, 12]. The goal of MMT is to achieve an appropriate maintenance dose which alleviates withdrawal and cravings for 24 h but permits normal daily function. No studies demonstrated efficacy and safety of inpatient versus outpatient stabilization during pregnancy. Inpatient initiation may not be feasible due to personal or systemic variables. Consider admission if a pregnant woman complains about uterine irritability (e.g., abdominal cramping or contractions) and monitoring for premature labor and fetal distress is recommended.

Dose adjustments during pregnancy: Methadone clearance has been documented to increase from the first to third trimester of pregnancy resulting in lower mean trough plasma methadone concentrations as the pregnancy progresses [24–28]. Factors contributing to increased methadone clearance include: increased volume of distribution and tissue binding, slower methadone absorption, and additional metabolism by the placenta and the fetus. Therefore, if a pregnant woman complains about withdrawal symptoms, small increments in maternal methadone dose will be required (e.g., 5–10 mg). Increased methadone dosing will be required to maintain steady methadone blood levels and to remain asymptomatic throughout pregnancy.

Dose splitting during pregnancy: Split dosing (i.e., twice-daily) of methadone is an alternative to increasing maternal methadone dose during pregnancy. Split-dosing is associated with sustained methadone levels and fewer withdrawal symptoms, thus leading to improved adherence to treatment and decreased use of other substances [28, 29]. Fetal behavior is also altered by change in dosing schedule. Women on single dosing regimens had significant reductions in body movements, respiratory activity and inactivity. In comparison, split-dosing treatment was associated with less suppression in fetal movements or fetal breathing [30, 31]. Therefore, during pregnancy, if a woman continues to experience withdrawal symptoms despite dose increases, especially at the end of the dosage interval, split dosing to decrease the dosing interval should be considered. Based on the limited description in the literature, the methadone dose can be split into equal doses and given 12 hours apart. Women who are more stable on MMT may be the most suitable candidates for split-dosing since the second dose should consist of a take home dose.

Buprenorphine Maintenance Treatment

Buprenorphine is an alternative treatment for pregnant opioid-dependent women. In nonpregnant individuals, buprenorphine maintenance has been shown to be as effective as methadone in reducing illicit opioid use. Buprenorphine has actually been shown to have lower retention rates so this is not accurate [32]. Therefore, with the introduction of buprenorphine in the management of opioid dependence, women are becoming pregnant while on buprenorphine maintenance treatment. To date, there is limited research evidence about the use of buprenorphine in pregnancy. A systematic review of over 30 studies demonstrated that buprenorphine was as efficacious and safe as methadone during pregnancy [33].

Buprenorphine is a sublingual tablet with partial mu agonist properties. It produces opioid-like effects equivalent to methadone in terms of relieving withdrawal symptoms and cravings for opioid use. In contrast, buprenorphine has a ceiling effect with no additional benefit found after a maximum dose leading to increased safety profile in case of overdose. Based on these pharmacological properties, buprenorphine was associated with less physical dependence and milder withdrawal upon abrupt discontinuation of this medication in nonpregnant populations [33].

Fetal and neonatal effects: Based on limited clinical studies, buprenorphine has not been associated with any adverse obstetrical or neonatal outcomes [33]. Birth outcomes including birth weight and Apgar scores were within normal range and similar to methadone-exposed infants. Buprenorphine has not been associated with any congenital birth defects.

NAS secondary to buprenorphine exposure occurs in ~60 % of neonates exposed to buprenorphine with approximately half requiring treatment [34, 35]. Earlier studies suggested that buprenorphine may be associated with milder neonatal withdrawal symptoms [36–38]. A recent randomized controlled trial (the MOTHER study) demonstrated no difference in treatment rates for NAS, but neonates exposed to buprenorphine required less morphine, had shorter duration of morphine treatment and shorter length of hospital stay [39].

Breastfeeding: The safety of buprenorphine during lactation is uncertain due to the lack of controlled clinical studies. Based on case reports, buprenorphine has been measured in breast milk at low concentrations [35, 40]. The plasma to breast milk ratio was found to be ~1; however, based on the poor oral bioavailability, the neonate will be exposed to a smaller amount of the buprenorphine while breastfeeding (e.g., 1/5–1/10) [35]. NAS is not changed by the presence of buprenorphine in breast milk nor has withdrawal resulted from breastfeeding cessation.

Long-term effects: Long-term neurodevelopmental outcomes studies are limited in this area. Three small studies have been published in the literature [41–43]. Four children were monitored until ages 3–5 years and reported to be "well" [41]. Another study assessed developmental milestones at 6–9 months and found 11/13 infants demonstrated normal development by 9 months of age [43]. More research is needed to determine the effect of buprenorphine on short- and long-term development outcomes.

Clinical considerations: The buprenorphine-naloxone combination product (Suboxone) is commonly prescribed for opioid dependence in nonpregnant individuals. The safety of naloxone during pregnancy is unknown and women on Suboxone should be switched to the buprenorphine monoproduct (Subutex) once pregnancy is diagnosed [44]. Women on MMT should not be switched to buprenorphine since initiation of buprenorphine requires abstinence from methadone for several days and the presence of withdrawal symptoms. During pregnancy, the risks of opioid withdrawal can be significant and it is not recommended to destabilize someone who has reached clinical stability on MMT [44]. Therefore, methadone-maintained pregnant women are not appropriate candidates for buprenorphine since there is no transitioning protocol available that will avoid withdrawal risks.

Dosing: The available evidence supports buprenorphine as an alternative treatment option for the management of opioid dependence in pregnant women in the following circumstances: refusal of methadone maintenance treatment or unavailability of specialized services in the community. After a completing an assessment for opioid dependence, pregnant women may be initiated to buprenorphine maintenance treatment. Dosing protocols outlined in clinical guidelines should also be followed during pregnancy [44].

Methadone Detoxification

Methadone detoxification is defined as methadone-assisted withdrawal. Many women may consider this treatment option as a way to prevent neonatal abstinence syndrome after delivery. Early reports of fetal distress associated with methadone withdrawal caused concern, but more recent reports using larger samples have different findings [45, 46]. Recent studies have failed to document any significant obstetrical complications or adverse neonatal outcomes with the use of this approach during second or third trimesters of pregnancy [47–51]. However, methadone detoxification was associated with poorer maternal outcomes due to clinical instability and a high risk of relapse to opioid use leading to resumption of MMT in some cases. Due to the above mentioned negative consequences, methadone detoxification should only be considered for highly motivated pregnant women with a short addiction history, medical and social stability with good supports and no concurrent active psychiatric disorders.

There is limited guidance in the literature in terms of the rate for methadone dose reduction. Based on the protocols published, a slow taper that reduces the dose by 5–10 % per week is an appropriate approach. Consider halting any further dose decreases if the woman complains about any adverse outcomes such as increased drug cravings, severe withdrawal symptoms, and relapse to drug use or obstetrical complications.

Neonatal Abstinence Syndrome

All neonates exposed to opioids in utero are at risk for neonatal withdrawal syndrome also known as neonatal adaptation syndrome (NAS). The incidence of NAS ranges from 45 to 97 % [52]. NAS is characterized by symptoms and signs of central nervous system hyperirritability (e.g., tremors, increased muscle tone), gastrointestinal dysfunction (e.g., poor feeding, regurgitation, loose stools) and metabolic, vasomotor, and respiratory disturbances (e.g., recurrent sneezing and yawning) [53]. Based on a meta-analysis, maternal methadone dose is not associated with the incidence and severity of NAS [52]. There are other determinants of NAS besides maternal dose. Thus, pregnant women should be maintained on an adequate dose which allows for clinical and social stability.

Symptoms and signs usually begin within hours of birth depending on the half-life of the opioid used and may last up to several weeks or months. The onset of NAS following methadone or buprenorphine exposure appears within the first 2 days of life, peaks within 3–4 days and lasts for 5–7 days [12, 44]. Therefore, infants require monitoring for NAS for a minimum of 4–5 days using a neonatal abstinence scoring system. The Neonatal Abstinence Score (developed by Dr. L. Finnegan) is commonly used to determine the severity of NAS symptoms and signs and to assess response to pharmacological treatment.

Non-pharmacological care contributes significantly to the management of NAS. There is some evidence for interventions such as swaddling to decrease arousals and prolong sleep, gentle handling, pacifier use, as well as provision of a quiet environment (minimizing overhead lighting, decreasing noise) to support neonatal neurobehavioral maturation and self-organization [54, 55]. Involvement of the mother in neonatal care is also encouraged since cuddling and skin-to-skin contact can promote mother–infant bonding and behavioral adaptation of infants with NAS.

Pharmacological care consists primarily of opioids (morphine) and sedatives (phenobarbital or diazepam). Based on several studies, opiates have been found to be the most effective treatment for NAS in newborns [33, 56]. Sedatives may be helpful as an adjunct to opioids to reduce withdrawal severity and specifically, phenobarbitone is preferred to diazepam as a second line treatment [57].

Comprehensive Care

Pregnant opioid-dependent women face numerous barriers to accessing substance abuse treatment services. Personal barriers to attending a drug treatment program include lack of child care and transportation, fear of losing custody of children, and lack of personal support especially from partners [58, 59]. Systemic barriers include fragmented care provided by multiple providers in multiple settings, and lack of appropriate services for pregnant women [59]. The delivery of comprehensive

services to pregnant opioid-dependent women can reduce barriers and can have a significant impact on improving maternal and neonatal outcomes. Integrated treatment programs that combine drug treatment, psychosocial counselling, and prenatal care provide the most effective approach to increase patient retention and participation in prenatal care, as well as improve pregnancy outcomes such as higher birth weight and lower prematurity rate [60–62]. Pregnant women also reported less stigma and reduced barriers with this model of care [63]. The "One-stop shopping" model of care addresses the needs of pregnant opioid-dependent women by providing multiple on-site services at one location and helping to enhance attendance for prenatal visits [64]. Concomitant psychosocial needs ranging from housing and financial assistance to child protection (antenatal self-referral) and parenting support (public health home visit nurse, parenting classes, drop-in centers) also need to be considered as part of comprehensive case management.

Intrapartum and Postpartum Care

During labor and delivery, women should continue on the same dose of methadone or buprenorphine. In addition, pregnant opioid-dependent women require additional medications for management of intrapartum pain. Patients on opioid agonist therapy (methadone or buprenorphine) have less tolerance to pain and report higher pain scores (hyperalgesia); therefore, they often require higher and more frequent doses of opioids for pain management due to cross-tolerance [64, 65]. Opioids have been found to be safe and effective in opioid-dependent individuals. There is no evidence that opioid use increases relapse in these patients.

For pregnant women on MMT, additional opioids can be used in addition to their daily methadone dose [65, 66]. Postoperative delivery, methadone-maintained women may also require more opioid analgesia [67].

For women on buprenorphine maintenance treatment, pain can be controlled with the use of short-acting opioids and nonsteroidal anti-inflammatory medications. Short-acting opioids need to be titrated to effect due to the high affinity of buprenorphine for the mu receptor [65, 68]. Alternatively, dividing the buprenorphine dose q6–8h and using additional opioids may be another option. Similarly, buprenorphine maintained women may also require more opioids following caesarean delivery [68].

Postpartum, women should continue on the same dose of methadone or buprenorphine. A dose reduction in maintenance opiate dosing may be indicated if women complain about feeling sedated after methadone or buprenorphine ingestion [9].

Conclusion

Methadone remains the standard of care for management of opioid dependence during pregnancy. Methadone maintenance has additional benefits over methadone-assisted withdrawal including reduced risk of relapse, reduced fetal exposure to

illicit drugs, improved attendance for obstetrical care and enhanced neonatal outcomes. Due to limited experience with the use of buprenorphine during pregnancy, its use can be considered in certain situations after a discussion about risks and benefits of treatment.

References

1. Substance Abuse and Mental Health Services Administration. Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-41, HHS Publication No. (SMA) 11–4658. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011.
2. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The DAWN Report: Highlights of the 2009 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Rockville, MD, Dec 28, 2010. http://www.oas.samhsa.gov/2k10/DAWN034/EDHighlights.htm.
3. Kahan M, Srivastava A, Wilson L, Gourlay D, Midmer D. Misuse of and dependence of opioids: study of chronic pain patients. Can Fam Physician. 2006;52:1081–7.
4. Chasnoff IJ, Neuman K, Thornton C, Callaghan MA. Screening for substance use in pregnancy: a practical approach for the primary care physician. Am J Obstet Gynecol. 2001;184(4):752–8.
5. Sander SCE, Hays LR. Prescription opioid dependence and treatment with methadone in pregnancy. J Opioid Manag. 2005;1(2):91–7.
6. Almario CV, Seligman NS, Dysart KC, Berghella V, Baxter JK. Risk factors for preterm birth among opiate-addicted gravid women in a methadone treatment program. Am J Obstet Gynecol. 2009;201(326):e1–6.
7. Brown HL, Britton KA, Mahaffey D, Brizendine E, Hiett AK, Turnquest MA. Methadone maintenance in pregnancy: a reappraisal. Am J Obstet Gynecol. 1998;179:459–63.
8. Center for Substance Abuse Treatment. Pregnant, Substance-using women. Treatment Improvement Protocol (TIP) Series 2. Rockville, MD: Substance Abuse and Mental Health Services Administration; 1993.
9. Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Obstet Gynecol Clin North Am. 1998;25(1):139–51.
10. Jones HE, Martin PR, Heil SH, et al. Treatment of opioid-dependent pregnant women: clinical and research issues. J Subst Abuse Treat. 2008;35:245–59.
11. Briggs GG, Rk F, Yaffe SJ. Drugs in pregnancy and lactation. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.
12. Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs. Treatment Improvement Protocol (TIP) Series 43. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.
13. Selby P, Kahan M. Methadone maintenance: a physician's guide to treatment. 2nd ed. Toronto, ON: Centre for Addiction and Mental Health; 2011.
14. Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, Lui K. Strabsimus in infants of opioid-dependent mothers. Acta Paediatr. 2003;92:379–85.
15. Kaltenbach K, Finnegan LP. Perinatal and developmental outcome of infants exposed to methadone in-utero. Neurotoxicol Teratol. 1987;9:311–3.
16. Vance JC, Chant DC, Tudehope DI, Gray PH, Hayes AJ. Infants born to narcotic dependent mothers: physical growth patterns in the first 12 months of life. J Paediatr Child Health. 1997;33(6):504–8.
17. Wilson GS, Desmond MM, Wait RB. Follow-up of methadone-treated and untreated narcotic-dependent women and their infants: health, developmental and social implications. J Pediatr. 1981;98(5):716–22.

18. Chasnoff IJ, Hatcher R, Burns WJ. Polydrug- and methadone-addicted newborns: a continuum of impairment? Pediatrics. 1982;70:210–3.
19. Glatstein MM, Garcia-Bournissen F, Finkelstein Y, Koren G. Methadone exposure during lactation. Can Fam Physician. 2008;54:1689–90.
20. Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. J Hum Lact. 2004;20:62–71.
21. American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics. 2001;108(3):776–89.
22. Hunt et al. Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. Early Hum Dev. 2008;84:29–35.
23. Hans SL. Developmental consequences of prenatal exposure to methadone. Ann N Y Acad Sci. 1989;562:195–207.
24. Wolff K, Boys A, Rostami-Hodjegan A, Hay A, Raisrick D. Changes to methadone clearance during pregnancy. Eur J Clin Pharmacol. 2005;61:763–8.
25. Drozdick J, Berghella V, Hill MK, Kaltenbach K. Methadone trough levels in pregnancy. Am J Obstet Gynecol. 2002;187:1184–8.
26. Pond S, Kreek MJ, Tong TG, Raghunath J, Benowitz N. Altered methadone pharmacokinetics in methadone-maintained pregnant women. J Pharmacol Exp Ther. 1985;233(1):1–6.
27. Jarvis MAE, Wu-Pong S, Kniseley JS, Schnoll SH. Alterations in methadone metabolism during late pregnancy. J Addict Dis. 1999;18(4):51–61.
28. Swift RM, Dudley M, DePetrillo P, Camara P, Griffiths W. Altered methadone pharmacokinetics in pregnancy: implications for dosing. J Subst Abuse. 1989;1:453–60.
29. DePetrillo PB, Rice JM. Methadone dosing and pregnancy: impact on program compliance. Int J Addict. 1995;30(2):207–17.
30. Wittmann BK, Segal S. A comparison of the effects of single- and split-dose methadone administration on the fetus: ultrasound evaluation. Int J Addict. 1991;26(2):213–8.
31. Jansson LM, Dipietro JA, Velez M, Elko A, Knauer H, Kivlighan KT. Maternal methadone dosing schedule and fetal neurobehaviour. J Matern Fetal Neonatal Med. 2009;22(1):29–35.
32. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone for opioid dependence. Cochrane Database Syst Rev;2003;(2):CD002207.
33. Johnson R, Jones HE, et al. Use of buprenorphine in pregnancy: patient management and effects on neonate. Drug Alcohol Depend. 2003;70(2 Suppl):S87–101.
34. Fischer G, Johnson RE, Eder H, et al. Treatment of opioid-dependent pregnant women with buprenorphine. Addiction. 2000;95(2):239–44.
35. Johnson RE, Jones HE, Jasinki DR, et al. Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. Drug Alcohol Depend. 2001;63: 97–103.
36. Fischer G, Ortner R, Rohrmeister K, et al. Methadone versus buprenorphine in pregnant addicts: a double blind, double dummy comparison study. Addiction. 2006;101(2):275–81.
37. Jones H, Johnson R, et al. Buprenorphine versus methadone in the treatment of pregnant opioid dependent patients: effects on the neonatal abstinence syndrome. Drug Alcohol Depend. 2005;79(1):1–10.
38. Lejeune C, Simmat Durand L, Gourarier L, Aubisson S; the Groupe d'Etudes Grossesse et Addictions (GEGA). Prospective multicenter observation study of 260 infants born to 259 opiate dependent mothers on methadone or high dose buprenorphine substitution. Drug and Alcohol Dependence. 2006;82(3): 250–7.
39. Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med. 2010;263:2320–31.
40. Marquet P, Chevrel J, Lavignasse P, Merle L, Lachatre G. Buprenorphine withdrawal syndrome in a newborn. Clin Pharmacol Ther. 1997;62(5):569–71.
41. Reisinger M. Use of buprenorphine during pregnancy. Res Clin Forums. 1997;19(2):43–5.

42. Schindler SD, Eder H, Ortner R, Rohrmeister K, Langer M, Fischer G. Neonatal outcome following buprenorphine maintenance during conception and throughout pregnancy. Addiction. 2003;98:103–10.
43. Kayemba-Kay's S, Laclyde JP. Buprenorphine withdrawal syndrome in newborns: a report of 13 cases. Addiction. 2003;98:1599–604.
44. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
45. Rementeria JL, Nunag NN. Narcotic withdrawal in pregnancy: stillbirth incidence with a case report. Am J Obstet Gynecol. 1973;116(8):1152–6.
46. Zuspan FP, Gumpel JA, Mejia-Zelaya A, et al. Fetal stress from methadone withdrawal. Am J Obstet Gynecol. 1975;1221(1):43–6.
47. Blinick G, Wallach RC, Jerez E. Pregnancy in narcotic addicts treated by medical withdrawal. Am J Obstet Gynecol. 1969;105(7):997–1003.
48. Maas U, Kattner E, Weingart-Jesse B, Schaefer A, Obladen M. Infrequent neonatal opiate withdrawal following maternal methadone detoxification during pregnancy. J Perinat Med. 1990;18:111–8.
49. Dashe JS, Jackson GL, Olscher DA, Zane EH, Wendel GD. Opioid detoxification in pregnancy. Obstet Gynecol. 1998;92(5):854–8.
50. Luty J, Nikolau V, Bearn J. Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat. 2003;24:363–7.
51. Jones HE, O'Grady KE, Malfi D, Tuten M. Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. Am J Addict. 2008;17:372–86.
52. Cleary BJ, Donnelly J, Strawbridge J, et al. Methadone dose and neonatal abstinence syndrome—systematic review and meta-analysis. Addiction. 2010;105:2071–84.
53. Finnegan LP, Kaltenbach K. Neonatal abstinence syndrome. In: Hoekelman N, editor. Primary pediatric care. 2nd ed. St. Louis, MO: Mosby Yearbook; 1992. p. 1367–78.
54. Provincial Council for Maternal and Child Health. Report of the Maternal-Newborn Advisory Committee Neonatal Abstinence Syndrome Work Group. Toronto, ON: PCMCH; 2011.
55. Velez M, Jansson LM. The opioid dependent mother and newborn dyad: nonpharmacologic care. J Addict Med. 2008;2(3):113–20.
56. Osborn DA, Jeffery HE, Cole M. Opiate treatment for opiate withdrawal in newborn infants. Cochrane Database Syst Rev. 2010;(10):CD002059.
57. Osborn DA, Jeffery HE, Cole MJ. Sedatives for opiate withdrawal in newborn infants. Cochrane Database Syst Rev. 2005;(3):CD002053.
58. Whiteside-Mansell L, Crone CC, Conners NA. The development and evaluation of an alcohol and drug prevention and treatment program for women and children: the AR-CARES program. J Subst Abuse Treat. 1999;16(3):265–75.
59. Roberts G, Nanson J. Best practices: fetal alcohol syndrome/fetal alcohol effects and the effects of other substance use during pregnancy. Ottawa: Health Canada; 2001.
60. Armstrong MA, Gonzales Osejo V, Lieberman L, Carpenter DM, Pantoja PM, Escobar GJ. Perinatal substance abuse intervention in obstetric clinics decreases adverse neonatal outcomes. J Perinatol. 2003;23(1):3–9.
61. Jansson LM, Svikis D, Lee J, Paluzzi P, Rutigliano P, Hackerman F. Pregnancy and addiction: a comprehensive care model. J Subst Abuse Treat. 1996;13(4):321–9.
62. Milligan K, Niccols A, Sword W, Thabane L, Henderson J, Smith A. Birth outcomes for infants born to women participating in integrated substance abuse treatment programs: a meta-analytic review. Addict Res Theory. 2011;19(6):542–55.
63. Lefebvre L, Midmer D, Boyd JA, et al. Participant perception of an integrated program for substance abuse in pregnancy. J Obstet Gynecol Neonatal Nurs. 2010;39:46–52.
64. Mehta V, Langford RM. Acute pain management for opioid dependent patients. Anaesthesia. 2006;61:269–76.

65. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127–34.
66. Jones HE, O'Grady K, Dahne J, et al. Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. Am J Drug Alcohol Abuse. 2009;35(3):151–6.
67. Meyer M, Wagner K, Benvenuto A, Plane D, Howard D. Intrapartum and postpartum analgesia for women maintained on methadone during pregnancy. Obstet Gynecol. 2007;110(2 Pt 1):261–6.
68. Meyer M, Paranya G, Norris AK, Howard D. Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. Eur J Pain. 2010;14:939–43.

Chapter 17
Methadone and Buprenorphine Prescribing in the Palliative Care Population

Shalini Dalal and Eduardo Bruera

Introduction

Mu-opioid receptor agonists have been the mainstay for the relief of pain in the palliative care population. An increasing number of new opioids or newer formulations of existing opioids have become available, and chosen based on availability, costs, patient/clinician experience, and available routes for administration. The concept of individualizing analgesic therapy to the patient's pain syndrome with close monitoring of treatment outcomes (pain relief, adverse effects) and changing clinical circumstances is fundamental to achieving success with pain management in the terminally ill. Individual responsiveness to opioids during the course of illness is affected by a constellation of factors, be it the progression of disease, genetics, development of opioid tolerance, CNS side effects or opioid-induced hyperalgesia, drug pharmacokinetics, and patient-specific factors such as poor adherence to the analgesic regimen [1–4]. Frequently, switching from one opioid to another becomes necessary due to inadequate analgesia and/or the presence of side effects. Further, some opioids may be better suited than others among vulnerable patients, such as the elderly or terminal cancer patients, who may already have, or be at increased risk for impaired renal and hepatic functions. Assessment of hydration status and renal functions plays an important role when using opioids in palliative care patients. Some opioids such as morphine have active metabolites that can accumulate and lead to neurotoxic effects when renal functions are impaired and appropriate dose adjustments are not considered.

In this chapter we will focus our discussion on methadone and buprenorphine, two opioids that have been well recognized for their potent analgesic effects for

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_17,

more than half a decade, but predominantly used for the medical treatment of opioid addiction. It is only recently in the last decade or so that these old drugs have been "re-discovered" for their potentially advantageous role in managing pain in cancer and noncancer patients, especially in the palliative setting when organ failure is either present or expected. Both these opioids have distinct receptor binding and pharmacological characteristics (such as a prolonged half-life, metabolism via cytochrome P450 (CYP) 34A enzymes, and usefulness in refractory pain syndromes), which must be understood to allow for appropriate patient selection and safe administration of these agents. Some of these characteristics and the potential usefulness of these agents in the palliative care setting will be discussed in this chapter.

Methadone

Methadone is a synthetic mu-opioid receptor agonist developed over 50 years ago [5] and offers several advantages for pain management in the palliative care setting such as its analgesic efficacy, low cost, long half-life, and availability in several formulations allowing for administration via almost every route. However, methadone's unique and complex pharmacology, with interindividual variability in absorption, metabolism, and relative analgesic potency [6–8], necessitates a cautious and highly individualized approach to prescribing. Some of the benefits and problems associated with methadone are illustrated in Table 17.1.

Pharmacological profile: Methadone is a potent mu-opioid receptor agonist, and has potent antagonist activity at *N*-methyl-D-aspartate (NMDA) receptors [9, 10].

Table 17.1 Potential benefits and problems of methadone as compared to other opioids in palliative care

Benefits	Problems
• Considered to be safe in renal failure: mainly eliminated by fecal route, does not accumulate significantly with renal impairment	• Due to methadone's long and variable elimination half-life, there is potential for drug accumulation, and delayed adverse effects
• No known active metabolites	• Methadone inadequately studied as a first-line agent
• NMDA receptor antagonism: may have role in opioid-resistant and neuropathic pain	• Rotating to methadone is complex; conversion dose ratios for methadone to other opioids not well researched
• Oral, rectal, and intravenous routes available for administration with very good oral bioavailability	• Drug interactions at the CYP450 3A4 and 2D6 levels
• Inexpensive (15–20 times cheaper than other opioids)	• QTc prolongation reported with high methadone dose; requires caution in patients with preexisting cardiac disease or use of other QT prolonging medications
• Extended dosing interval, 2–3 times a day and/or even once daily may be possible in selected individuals	• Stigmatization because of its traditional use in the management of opioid addiction

NMDA N-methyl-D-aspartate

Methadone's NMDA receptor blockage effects may play a role in refractory neuropathic pain, and reversal of previously developed opioid tolerance [11]. Methadone has also been reported to inhibit uptake of neurotransmitters norepinephrine and serotonin [12]. Methadone is available in most countries as a racemic mixture of two stereoisomers. *R*-methadone (levorotatory) is the major isomer involved in pain relief and activates mu-opioid receptors. *S*-methadone (dextrorotatory) exhibits negligible mu-opioid receptor activity, has equal NMDA effects, and less potent norepinephrine and serotonin uptake inhibition, as compared to *R*-methadone [7, 12]. *R*-methadone is available in Germany, where it is the preferred agent for pain management.

Methadone is highly lipophilic, with excellent oral bioavailability (~67–95 %). Following oral administration, it is rapidly absorbed and subject to extensive tissue distribution, from where it is slowly released [13]. The volume of distribution gradually increases, until a steady state is achieved (usually 3–5 days). This tissue reservoir sustains plasma concentrations during chronic therapy with methadone [14]. The initial distribution phase half-life is short (~1–4 h), and followed by a longer elimination phase (β-half-life; ~15–60 h) which is highly variable. Elimination phase half-lives ranging from 4.2 to 130 h have been reported [15–20]. Methadone is also highly bound (60–90 %) to the plasma protein, α1-acid-glycoprotein. This extensive protein and tissue binding is predominantly responsible for the long plasma half-life of the drug, particularly with continuous use [21]. Methadone is primarily metabolized by the liver isoenzyme CYP34A, with some contribution from CYP2C9 and CYP2D6 enzymes. Following hepatic metabolism, methadone is excreted as an inactive metabolite [22]. Methadone has no active metabolites and hepatic metabolism has no significant effect on methadone concentrations, clearance, or clinical disposition. It is predominantly excreted in the feces; however, acidification of the urine will increase renal excretion [14].

The interindividual variations in methadone's half-life have been attributable to the differences in adipose reserves and protein binding, metabolism between the two methadone isomers, single vs. multiple dosing schedule, and pharmacogenetic differences in metabolizing enzymes [22]. Disease states and drugs influence may also affect plasma protein concentrations, which in turn affects free methadone levels [22, 23]. Cancer, for instance, is associated with increased protein levels, thereby decreasing free methadone levels. Conversely drugs such as propranolol, phenothiazines, tricyclic antidepressants, and progesterone compete for protein binding and may result in increased levels.

Clinical implications of methadone pharmacokinetics in pain management: In contrast to other commonly used opioids, methadone's plasma elimination half-life does not match its duration of analgesic effects [17, 20, 24, 25]. No correlation between plasma methadone levels and analgesic effects has been shown [21]. The discrepancy between methadone extended half-life and duration of analgesic effects is of clinical importance as it may result in drug accumulation and toxicity [20, 26]. Further, wide interindividual variations in its half-life contributes to difficulties in appropriately prescribing this drug and the potential toxic accumulation in some individuals.

Table 17.2 Example of drugs that affect CYP450 system and potential for interaction with methadone

Drug	Proposed mechanism
May ↑ serum methadone levels/↑ methadone effects	
Antibiotics/antifungals/antiretrovirals	
• Erythromycin and other macrolides	Strong CYP3A4 enzyme inhibitor
• Ciprofloxacin and other quinolones	CYP3A4 inhibition
• Fluconazole, ketoconazole, and other azole antifungals	CYP3A4 inhibition
• Delavirdine	CYP450 enzyme inhibition
Antidepressants/anxiolytics	
• Selective serotonin reuptake inhibitors (in particular fluvoxamine)	CYP450 enzyme inhibition
• Atypic antidepressants (e.g., nefazodone)	CYP450 enzyme inhibition
• Diazepam	Mechanism undetermined
GI medications	
• Cimetidine	CYP450 enzyme inhibition
Grape fruit	Intestinal CYP3A4 inhibition
Cardiac/hypertension medications	
• Verapamil	CYP450 enzyme inhibition
• Amiodarone	CYP450 enzyme inhibition
• Quinidine	CYP450 enzyme inhibition
May ↓ serum methadone levels/↓ methadone effects	
Anticonvulsants	
• Barbiturates	CYP450 enzyme induction
• Phenytoin, carbamazepine	CYP3A4 and CYP2B6 enzyme induction
Antituberculosis drug: rifampacin	Induces CYP450 enzymes
Dexamethasone	CYP3A4 and CYP2B6 enzyme inducer
Antiretrovirals	
• Amprenavir	CYP3A4 enzyme induction
• Efavirenz	CYP3A4 and/or CYP2B6 induction
• Nelfinavir	CYP3A4 induction
• Nevirapine	CYP3A4 and/or 2B6 enzyme induction

Methadone has a rapid onset of action, with analgesic effects occurring within 30–60 min, and an analgesic peak between 2.5 and 4 h. Methadone's typical duration of analgesic effects is approximately 4–8 h with single dose, and 6–12 h after steady state is achieved [17, 24]. Steady-state plasma concentrations and full analgesic effects are usually not attained until 3–5 days of dosing. The shorter observed duration of methadone's analgesic effects relative to its longer elimination half-life (~15–60 h) require frequent methadone dosing (2–4 times per day) for pain management, but can lead to tissue accumulation, and delayed opioid toxicity.

Due to methadone's extensive metabolism by CYP450 isoenzymes, potentially all agents metabolized by this system could interact with this drug. Induction or inhibition of CYP34A enzyme is the primary mechanism behind methadone's drug interactions. Examples of common drugs used in the palliative care setting that may interact with methadone via the CYP450 system is shown in Table 17.2. Pharmacogenetic

differences in these enzymes also play an important role in the wide interindividual variation in the plasma half-lives reported [22]. For example, due to a polymorph of CYP2D6, a subset of the white population (<10 %) are considered to be poor metabolizers of methadone [27] and may result in increased toxicity from methadone. More clinical research is needed to better understand methadone drug interactions, and in the meantime it is advisable to limit the use of agents metabolized by CYP3A4 and possibly the 2D6 isoenzymes in patients using methadone. If this is not possible, increased clinical monitoring of side effects is indicated.

Formulations: Methadone hydrochloride is available in multiple formulations, including 5-, 10-, and 40-mg scored tablets; solution in concentrations of 1 mg/mL, 10 mg/5 mL, and 10 mg/mL for oral administration, and a 10 mg/mL solution for parenteral administration. In the USA, the DEA advisory stresses that the 40-mg formulation of methadone hydrochloride is indicated only for the detoxification and maintenance treatment of opioid-addicted patients and is not FDA-approved for use in pain management.

Clinical Uses of Methadone in Palliative Care for Pain Management

Methadone is most commonly used as a second-line agent, when patients are switched to methadone from their existing opioids. In recent years, however, methadone is increasingly being used as a first-line opioid in the management of pain, particularly in the setting of renal failure or neuropathic pain.

Methadone is an excellent alternative opioid when opioid rotation becomes necessary due to opioid-induced neurotoxicity (OIN) or the development of opioid tolerance. OIN includes a constellation of neuropsychiatric symptoms such as excessive sedation, cognitive impairment, delirium, hallucinations, myoclonus, and opioid-induced hyperalgesia [28, 29]. Mechanism includes increase in excitatory non-analgesic opioid metabolites and NMDA activation [30, 31]. Palliative care patients are at an increased risk of OIN due to dehydration and renal impairment. Methadone rotation offers several advantages over other opioids in this setting as it has no active metabolites, has NMDA receptor antagonist effects, and can be safely used in renal failure. Successful rotation to methadone has been demonstrated in several prospective and retrospective studies [32–35].

Methadone is increasingly being used as a first-line agent for the treatment of cancer pain. Four randomized controlled trials (RCTs) compared the use of oral methadone to other opioids (morphine or transdermal fentanyl), as a first-line agent for treating cancer pain [18, 36–38]. In all of these studies, methadone was comparable to other opioids with regard to analgesic efficacy. Adverse events were also similar except in one study (which used 2:1 morphine to methadone dose conversion ratio), which had higher incidence of sedation and drop outs [37]. The other three trials using conversion ration of ≥4:1 had similar adverse events between methadone and other groups.

Starting Patients on Methadone

When methadone is initiated, as with all opioids, it is necessary to adjust the dosing regimen for each patient individually, taking into account patient's prior analgesic treatment experience and methadone's unique pharmacological properties. Clinicians should follow appropriate pain management principles of careful assessment and ongoing monitoring of treatment outcomes (such as pain relief and opioid side effects). The recommendations in the following section should only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of pain of each individual patient.

Opioid rotation to methadone from other opioids: Switching to methadone from another opioid should only be attempted by experienced clinicians in pain management. Optimal methadone initiation and dose titration strategies for the treatment of pain have not been determined. As mentioned previously, methadone's analgesic effects do not match its long and variable half-life, and there is potential for toxic accumulation of the drug. Additionally, inherent uncertainties of dose conversion ratios and incomplete cross-tolerance between mu-opioid agonists makes determination of dosing during opioid conversion complex.

Published equianalgesic conversion ratio tables between common opioids, and between methadone and morphine, provide average analgesic potencies of single opioid doses in non-tolerant patients. This may greatly underestimate methadone's analgesic potency, and its potential for adverse effects in repeated-dose settings. Regardless of the dose determination strategy employed, methadone is most safely initiated and titrated using small initial doses and gradual dose adjustments.

Recommended steps for obtaining methadone dose during opioid rotation are shown in Tables 17.3 and 17.4. As morphine is used as the standard for opioids, the initial step involves converting the current daily opioid dose to oral morphine equivalent daily dose (MEDD) from equianalgesic tables. The second step involves calculating the approximate methadone dose from morphine to methadone conversion tables. The equianalgesic conversion ratio to obtain methadone dose is based on the

Table 17.3 Recommended initial morphine to methadone conversion ratios

Oral morphine equivalent daily dose (MEDD) in milligrams	Conversion ratio[a]
<100	3:1
>100–300	5:1
>300–600	10:1
>600–800	12:1
>800–1,000	15:1
>1,000	20:1

[a]Dose of methadone is calculated by dividing the MEDD by the conversion ration. This dose should be decreased by 25–50 % to accommodate for lack of incomplete tolerance

Table 17.4 Recommended methadone rotation schedule

Recommended steps for a 3-day phased conversion from morphine to methadone (with example)
Calculate methadone dose from Table 17.3 and decrease by 25–50 % for lack of incomplete tolerance. If pre-switch oral morphine dose is 600, the calculated methadone dose will be ~30 mg/day (after 50 % reduction)
Day 1: Administer 2/3 of the pre-switch morphine (400 mg) and 1/3 of the planned methadone dose (5 mg twice/day)
Day 2: Administer 1/3 of the pre-switch morphine dose (200 mg) and 2/3 of the planned methadone dose (10 mg every 12 h)
Day 3: Stop morphine. Administer all of the planned methadone dose (10 mg every 8 h)

pre-switch morphine equivalent dose range [32], with higher MEDD requiring *higher morphine to methadone conversion ratios*, as shown in Table 17.3. The third step involves reducing the methadone dose by 25–50 % for incomplete cross-tolerance between opioids. It is important to note that the methadone dose obtained from these steps is approximate [39], and methadone should be further titrated to patient's response.

The best schedule for dosing methadone once the approximate equianalgesic dose is calculated has not been determined. Both a phased rotation (done over days) and a "stop and go" approach (rapid switch) have been proposed. When pre-switch MEDD is higher than 100 mg, the switch to methadone should ideally be done over several days [40]. In the slower approach described by Bruera et al. [35] and Ripamonti et al. [41], the opioid to be discontinued is gradually decreased over 3 successive days and is replaced by gradually increasing methadone by one third increments, as shown in Table 17.4. Longer schedules may also be used. Some studies suggest that when pre-switch MEDD is more than 600, switching to methadone should be done more slowly (3–6 days) and in the inpatient setting [42].

In the rapid switching approach described by Morley and Makin [43], Mercadante et al. [44], and the German model [42], the current opioid is abruptly discontinued and replaced by methadone. For those patients receiving opioids with MEDD approximately 100 mg or less per day, a rapid switch to methadone seems to be most appropriate. In the study by Mercadante et al., the mean morphine dose for all patients was 125 mg/day, with more than half the patients receiving 90 mg/day of morphine or less daily. A fixed morphine to methadone conversion ratio of 5:1 was initially used and subsequently adjusted as appropriate. This approach was successful in approximately 80 % of patients. However, in the setting of higher pre-switch opioid dose, a phased 3-day switch is recommended to avoid opioid toxicity. In a recent prospective study of 42 cancer patients on morphine or oxycodone, patients were randomized to a rapid methadone switch vs. a 3-day phased rotation to methadone [45]. The mean pre-switch morphine doses in the two groups were 900 and 1,330 mg/day, respectively. The rapid switch group had higher number of drop outs and serious adverse events (two deaths and one severe sedation).

When rotating from 12 h sustained release preparations, it is recommended to delay initiation of methadone by up to 12 h [46]. Similarly, a wash-out period when switching from fentanyl to methadone is recommended. A small study ($n = 17$)

Table 17.5 Recommendations for dosing methadone on opioid naïve patients

Days 1–3	Start with 2.5–5 mg PO q 12 for first 3 days. Use short-acting opioids (example morphine or hydromorphone) for breakthrough pain
Days 4–5	Increase dose of methadone by 50–100 % if patient has uncontrolled pain, and no evidence of opioid toxicity

demonstrated a safe switch to methadone by instituting a wash-out period after removal of the fentanyl patch (8–12, 12–16, 16–18, or 18–24 h depending on whether previous transdermal fentanyl doses were ≤100, 100–200, 200–300, or >300 μg/h, respectively). This study used a morphine to methadone conversion ratio of 5:1 and made methadone dose adjustments no earlier than every 72 h.

Rotation from methadone to other opioids: With the wider use of methadone for pain management, it is no longer uncommon for palliative care patients to be on methadone, and require a switch to alternative opioids. Methadone to morphine rotation has received limited study, but is not bidirectional. One prospective study and two retrospective studies have reported on methadone to morphine rotation. In the prospective study by Moryl et al. [47], 12 of a total of 13 patients were unable to complete a rotation from methadone to another opioid due to uncontrolled pain and adverse side effects. The pre-switch methadone dose in this study ranged from 2 to 80 mg/h. However, two retrospective studies have reported successful switch from methadone to morphine or another opioid [33, 48]. Lawlor et al. [49] reported on six patients rotated from oral methadone to morphine. The median pre-switch methadone dose was 60 mg/day (range 3–240), and the median methadone to morphine dose ratio was 8.3 (range 4.4–11.0). In the study by Walker et al. [48], the conversion ratios were reported separately for patients on IV methadone ($n=13$, median methadone dose 20 mg/day) and oral methadone ($n=16$, 26 mg/day), and were found to be approximately 14 and 5, respectively. For both groups, stable dose was achieved in approximately 3 days. This study suggests higher analgesic potency for IV methadone vs. oral methadone, than previously thought (1:3 vs. 1:1 to 1:2).

Initiation of methadone in opioid naïve patients: When oral methadone is used as the first opioid for management of chronic pain, the recommended starting dose should be 2.5–5 mg orally every 12 h, and slowly titrated to effect. Dose escalations should ideally be made not earlier than every 72 h (Table 17.5). More frequent administration may be required during methadone initiation in patients who have uncontrolled pain, but extreme caution is necessary to avoid toxicities, taking into account methadone's long elimination half-life.

Treating breakthrough pain (*BTP*) *when on scheduled methadone*: Short-acting opioids such as morphine, hydromorphone, and oxycodone are generally preferred agents for BTP. While methadone has also been used in doses 10–30 % of the calculated daily methadone dose for managing BTP [32, 43], caution is advised as repeated dosing could lead to drug accumulation. In selected patients who have previously experienced adverse effects from several opioids, and those at risk

of opioid-induced toxicity (dehydration, renal failure), we recommended use of methadone for BTP as 10 % of the total methadone dose every 2–3 h, once steady state (usually 3–5 days) has been achieved.

Conversion from parenteral methadone to oral methadone: As methadone has excellent bioavailability ranging from 60 to 90 %, a parenteral to oral methadone conversion ratio ranging from 1:2 to 1:1 has been suggested. We recommend a more conservative approach ratio of 1:2. A recent retrospective review of methadone to alternate opioid rotation [48] has suggested higher (1:3) analgesic potency for IV vs. oral methadone, and requires further studies for clarification.

Methadone Dosing in Special Populations

Renal failure: Methadone and its metabolites (inactive) are excreted in the urine (20–50 %) and feces (10–45 % as the pyrrolidine metabolite). For patients with impaired renal function, methadone clearance via feces increases and no dose adjustment is necessary [50]. Because methadone is highly protein bound and has a large volume of distribution, removal by dialysis is not expected to be significant [51].

Liver failure: Methadone is not hepatotoxic; however, the liver has a central role in methadone metabolism, clearance, and drug storage. Studies of patients with severe uncompensated chronic liver disease or acute fulminant liver failure have not been conducted. In preclinical studies, methadone metabolism was shown to be significantly altered in the presence of severe liver disease or abrupt changes in liver functions [52]. However, methadone is well tolerated and successfully used in patients with mild liver disease. Therefore, we recommend that for patients with chronic, stable liver functions, the usual methadone doses may be implemented, and in patients with progressive failure methadone is best avoided.

Age considerations: As age does not appear have a major influence on methadone clearance, no change in dose is usually required in elderly patients. Methadone has been used and shown to be safe and effective in pediatric patients with neuropathic pain or nociceptive pain unresponsive to other opioids [53].

Buprenorphine

Buprenorphine is a semisynthetic derivative of the opium alkaloid thebaine. Although well recognized for its potent analgesic effects [54], buprenorphine's classification as a partial agonist or as a mixed agonist–antagonist discouraged further development of this drug for the management of chronic pain. Concerns about limited and ceiling analgesic effects, precipitation of opioid withdrawal when given to opioid-tolerant patients, and non-reversal of effects with naloxone have been some of the widespread misconceptions of this drug. However, over the past decade and

half, improved understanding of buprenorphine's pharmacological profile, analgesic effectiveness, tolerability, and recent availability of the transdermal system (TDS) formulation has led to a resurgence of interest in its use for chronic pain management. Much of the research and experience of using buprenorphine has emerged from European countries, where the TDS formulation has been available since 2001 as a 3–4 day formulation. Buprenorphine TDS has been successfully initiated in both opioid naïve and tolerant patients with chronic cancer and noncancer pain, and there are no published data indicating an analgesic ceiling dose with clinical use. While published research is promising, there is still need for more evidence from well-designed studies before there can be definite conclusions regarding use of buprenorphine in the palliative care setting.

Buprenorphine formulations: Buprenorphine is currently available in sublingual, parenteral, and TDS formulations. Although a solution form has been tested and found to have higher bioavailability than sublingual tablets [55], this is not currently approved for clinical use. Lower dose sublingual tablets of 0.2 mg buprenorphine are available for analgesia in some European and Asian countries. Higher dose sublingual tablets are approved for opioid addiction and are available as combination tablets with naloxone (2 mg/0.5 mg and 8 mg/2 mg tablets) and as buprenorphine alone (2 and 8 mg tablets).

Buprenorphine TDS formulation incorporates buprenorphine into a polymer adhesive matrix. In Europe, buprenorphine TDS is available in three strengths with release rates of 35-, 52.5-, and 70-μg/h over a 3-day period, corresponding to daily doses of 0.84, 1.26, and 1.68 mg, respectively. Although it is recommended that the patch be replaced every 3 days, a recent open-label, randomized, crossover phase III study of patients with stable pain control with buprenorphine TDS doses ranging from 17.5 to 105 mg/h, demonstrated that prolongation of the patch for an additional day, to a 4-day regimen, had no impact on analgesic efficacy or tolerability [56]. In Canada and the USA, buprenorphine TDS became available in 2010 and 2011, respectively, at lower doses and as a 7-day formulation. These patches deliver buprenorphine doses of 5-, 10-, and 20-μg/h over a 7-day period, corresponding to daily doses of 0.12, 0.24, and 0.48 mg, respectively.

Pharmacological profile: Buprenorphine's analgesic properties are attributed to its unique agonist or antagonist effects at various opioid receptors—mu, kappa, delta, and nociceptin [57–60]. Buprenorphine has high binding affinity for both mu- and kappa-receptors. At the mu-receptor, buprenorphine is a partial agonist, and is an antagonist at the kappa-receptor. Once bound to the mu-receptor, buprenorphine dissociates much slower than other full opioid receptors, which partly accounts for its longer duration of effects, and fewer signs and symptoms of opioid withdrawal upon termination of therapy [57–60]. Buprenorphine also has delta-receptor antagonist, and opioid-like-1 (ORL-1) receptor (nociceptin/orphanin FQ receptor) agonist effects [57–60]. The clinical implications of delta-receptor effects are not well understood, while the ORL-1 receptor has been attributed to pay a role in opioid tolerance.

One of the major concerns of using buprenorphine for analgesia in chronic pain is the potential for ceiling effects due to its partial mu-opioid agonistic activity.

While earlier studies of rodent models of acute pain did demonstrate a typical bell-shaped dose–response curve with high doses of buprenorphine [61], more recent experiments conducted in acute and chronic pain models did not confirm the same [62]. Further, in humans, at therapeutic dose levels, buprenorphine showed a linear analgesic dose–response curve, with no evidence of ceiling effects [63, 64], suggesting that over the relevant dose range buprenorphine acts as a full agonist for analgesia [65, 66]. However, as a partial mu-opioid receptor there is potential existence of an analgesic ceiling effect, and based on preclinical studies this has been estimated to be above doses of 15–25 mg daily, which is much higher than currently recommended doses [67]. Among subjects using sublingual buprenorphine for opioid addiction, maximal effects of buprenorphine have been reported to occur in the 16–32 mg dose range [68]. In contrast, a ceiling effect for respiratory depression has been observed in human and animal studies [64, 66].

Buprenorphine has low oral bioavailability because of extensive first pass metabolism [66].

Buprenorphine's low molecular weight and high lipophilicity makes it very suitable for sublingual and transdermal delivery. Sublingually, buprenorphine's bioavailability is approximately 60 %, with peak effects within 0.5–3 h, as compared to 20 min following intravenous dose. It is highly bound (96 %) to plasma proteins, primarily to α- and β-globulin fractions [69]. Buprenorphine is metabolized via CYP3A4, to the active metabolite norbuprenorphine, which has weak analgesic properties [70]. Both the parent compound and norbuprenorphine are subject to glucuronidation, and are eliminated mainly via excretion into the bile (70 %), and to a lesser extent by the kidneys (30 %) [66, 71]. Due to rapid glucuronidation of buprenorphine and its metabolites, the risk of pharmacokinetic interactions with other drugs is considered to be low, and buprenorphine is also considered to be safe in patients with renal impairment.

The elimination half-life of buprenorphine in humans is approximately 20–73 h. The half-life of sublingual buprenorphine is higher than intravenous due to sublingual tissue reservoirs [72]. With the buprenorphine TDS formulation, bioavailability is approximately 60 %. Effective plasma concentrations are reached within 12–24 h of patch application, while T_{max} occurs at approximately 60 h for the 35- and 70-μg/h patch.

Clinical implications of buprenorphine's pharmacological profile in pain management: As a partial mu-opioid agonist, theoretical concerns of ceiling analgesic effects with buprenorphine dose increase exists. However, as discussed previously, linear analgesic dose–response curves have been demonstrated at therapeutic levels. Up to two buprenorphine 70 μg/h TDS have been used in clinical trials and published reports without evidence of ceiling effects, suggesting that at relevant doses, buprenorphine acts as a full mu-opioid agonist [65, 66]. Buprenorphine has high affinity for mu-opioid receptors and is not easily displaced by opioid antagonists. Consequently, the effects of buprenorphine in overdose may only be partially reversed by naloxone. As naloxone has a relatively short half-life, multiple doses, or naloxone infusions may be required in settings of overdosage and respiratory

compromise. Buprenorphine is predominantly excreted via the fecal route (70 %) and therefore can be safely used in patients with renal failure. Further, despite buprenorphine undergoing initial metabolism via CYP3A4 enzymes, the risk of pharmacokinetic interactions with other drugs is considered to be low, as both the parent compound and its metabolites undergo rapid glucuronidation.

Clinical Uses of Buprenorphine for Managing Pain in Palliative Care Populations

Analgesic efficacy: The analgesic effect and tolerability of buprenorphine TDS have been investigated in four RCTs. Three of these were 15 day, double-blinded, placebo-controlled phase-III trials [73–75] involved in the clinical development of buprenorphine were conducted in patients with cancer or noncancer pain, who were on weak (Step-II on the WHO analgesic ladder) or low doses of strong (Step-III) opioids. In the first two trials [73, 74], patients were randomized to placebo vs. three dose strengths of buprenorphine TDS (35-, 52.5-, and 70-μg/h) every 72 h, and sublingual buprenorphine at 0.2 mg was allowed for BTP. In the first trial by Sittl et al. [73] ($n = 157$) buprenorphine TDS at 35- and 52.5-μg/h were both associated with significantly higher proportion of analgesic responders, improved sleep, and lower number of rescue medications. Surprisingly, buprenorphine TDS 70 μg/h as compared to placebo did not reach significance. In the study by Bohme and Likar [74] ($n = 151$), analgesic response was shown to be dose-dependent (34 %, 37 %, and 50 % for 35-, 52.5-, and 70-μg/h, respectively) but did not reach statistical significance.

In the third study by Sorge et al. 174 patients were treated in an open, run-in phase with buprenorphine sublingual tablets for 6 days. Patients who obtained at least satisfactory pain relief ($n = 137$) were then randomized to either buprenorphine TDS 35 μg/h or placebo for 9 days. The number of rescue sublingual buprenorphine used (main endpoint of study) was significantly lower in the active treatment group. When the daily dose delivered by the patch was added to the additional sublingual buprenorphine required, the total dose in the double-blind phase was comparable to the sublingual dose during the run-in phase. Patients' assessment of pain intensity and relief suggested better analgesia with buprenorphine TDS, although these results never gained statistical significance during the study protocol ($P > 0.05$).

The fourth trial by Poulain et al. [76] was conducted to evaluate the maintenance of efficacy of buprenorphine TDS in 289 opioid-tolerant cancer patients with severe pain. Prior to study entry, these patients were consuming opioids (single opioids or combination therapy, including oral tramadol, morphine, hydromorphone, oxycodone, and transdermal fentanyl) in the dose range of 90–150 mg/day oral morphine equivalents. The study included a 2-week run-in phase, during which all patients were switched to buprenorphine TDS 70 μg/h, following which patients who were successfully switched entered into the placebo-controlled maintenance phase of the trial. A significant number ($n = 100$, 53 %) of patients discontinued treatment due to lack of analgesic efficacy or adverse events. Of the 189 patients who continued treatment in

the maintenance phase (94 buprenorphine TDS, 95 placebo), a significantly higher number of patients responded well in the active treatment group (74.5 % vs. 50 %, $P=0.0003$) with lower daily pain intensities, lower intake of rescue medication (buprenorphine sublingual tablets). Further, there were lower dropout rates in the buprenorphine TDS group vs. placebo group (7 vs. 24). The mean daily pain intensity and the mean daily intake of rescue medication both decreased in 70 % of patients during the first 12 h following active patch application, indicating a rapidly developing distinct analgesic response from buprenorphine TDS. Further, this study demonstrated that opioid-tolerant patients can be switched to buprenorphine, and the latter did not precipitate a withdrawal syndrome.

Maintenance of efficacy was also demonstrated in an open-label follow-up trial by Likar et al. [77], that enrolled 239 patients from the first three above mentioned RCTs. Buprenorphine TDS were found to be effective for managing chronic pain in 134 cancer patients (maximum study participation was 3.4 years) and 105 noncancer patients (5.7 years), with 90 % reporting at least satisfactory analgesia.

An 8-week randomized, open label prospective study of 52 cancer patients pain [78], compared buprenorphine TDS (35 μg/h) vs. morphine (60 mg sustained release) for the treatment of chronic pain. Patients treated with buprenorphine experienced significantly greater improvement in pain intensity, sleep, and quality of life.

A number of post-marketing surveillance studies [79–81] and retrospective studies [82] continue to demonstrate the efficacy of buprenorphine TDS in the management of cancer and noncancer pain. Although these results are promising, more evidence from well-designed studies are warranted before there can be definite conclusions regarding this drug. A recent systematic review published in 2009 [83] identified six randomized trials and two observational studies for analysis of clinical endpoints, but was unable to conduct a meta-analysis due to heterogeneity between studies and variances in outcome measures.

Switching between buprenorphine and other opioids: Several trials involving patients with cancer or noncancer chronic pain suggest that patients can be safely and efficaciously switched bidirectionally between buprenorphine TDS and another opioid [76, 84–87]. In a small prospective "N of 1" study by Mercadante et al. [84], 22 cancer patients with adequately controlled pain using buprenorphine TDS (35 or 70 μg/h; $n=6$) or fentanyl TDS (25 or 50 μg/h; $n=16$) were switched from one transdermal opioid to the other for 3 days, and then switched back again. This study used a fentanyl:buprenorphine conversion ratio of 0.6:0.8, and found no significant differences in pain or use of rescue opioids between the two groups, thereby suggesting that patients on stable doses of either transdermal opioid could be safely switched to another, and that concomitant presence of both opioids was feasible without important consequences.

In another study by Mercadante et al. [85], ten cancer patients with adequate pain control and on stable doses morphine (120–240 mg) or fentanyl TDS (50–100 μg/h) for more than 6 days were switched to buprenorphine TDS, using equipotency ratios of 70:1 with morphine and 0.6:0.8 with fentanyl. The study found no significant differences in pain intensity or use of rescue medications before the opioid switch,

or days 3 and 6 after switch. Significant improvements in constipation and global satisfaction with analgesia were also observed after the switch.

In clinical practice, switching from one opioid to another is usually undertaken in the presence of inadequate analgesia or in the presence of intolerable opioid side effects. Several trials have evaluated buprenorphine's efficacy in these circumstances. In a prospective open-label study by Freye et al. [86], 42 patients (nine with cancer) were switched (due to inadequate analgesia, side effects, or other) from morphine (dose range 120–800 mg/day) to buprenorphine TDS. Buprenorphine dose (at least 52.5 μg/h) was titrated individually by the treating physician. Outcome assessments (pain relief, sleep, and adverse events) were conducted over a minimum period of 10 weeks and up to 1 year. Following rotation, patients experiencing good/very good pain relief increased from 5 to 76 % ($P<0.001$), and only 5 % reported insufficient relief. In the majority of patients, relief was achieved with buprenorphine alone (77.4 %), while a minority (17 %) needed additional opioids for BTP. Adverse effects were reported in 11.9 %, mostly because of local irritation, and did not result in buprenorphine discontinuation. In another study, Aurilio et al. assessed the efficacy and tolerability of switching between transdermal opioids in 32 cancer patients with chronic pain receiving insufficient analgesia using either fentanyl TDS ($n=16$) or buprenorphine TDS ($n=16$) [87]. The dosages used to switch opioids were 50 % of that obtained from commonly used fentanyl:buprenorphine equianalgesic ratio of 0.6:0.8 (75-fentanyl TDS converted to 52.5-buprenorphine TDS; 70-buprenrophine TDS converted to 25-fentanyl TDS). Patients were assessed at weekly intervals for 3 weeks. The study demonstrated significant reductions in pain levels, use of rescue medications, and side effects in both groups, suggesting that opioid switching between the two at 50 % of the calculated equianalgesic dose was successful in reducing pain and side effects.

Buprenorphine TDS combined with other opioids for BTP: Buprenorphine TDS has been shown to be successfully combined with other opioids for managing BTP. In an open label study by Mercadante et al. [88], 29 consecutive advanced cancer patients who reported acceptable basal analgesia with buprenorphine TDS (mean dose 44.5 μg/h), but who experienced BTP, were treated with an intravenous morphine bolus, the dose being 1/5 of the MEDD of buprenorphine. Of 106 episodes, 92 % were successfully treated and the mean pain intensity decreased from 7.3 to 2.9 on an 11-point NRS after 15 min. Adverse events occurred in 18 % of episodes after administration of the morphine bolus. This study suggests that morphine is effective and safe for use in BTP in patients receiving buprenorphine TDS.

No Demonstration of Ceiling Effect of Buprenorphine in Clinical Studies to Date

In human trials to date there is no evidence of a ceiling effect of buprenorphine with respect to analgesia. A study of the use of i.v. buprenorphine for postoperative pain following cesarean section in 50 patients showed that doses up to 7 mg were

effective and provided long-lasting analgesia [63]. In a preliminary open label trial by Mercadante et al. [89], ten cancer patients who were already receiving 70 μg/h buprenorphine TDS and had uncontrolled pain, were administered higher doses up to a maximum of 140 μg/h within 6 days, when the study was completed. Intravenous morphine was given as needed (a 7-mg bolus for each 70 μg/h patch). Dose increase to 105–140 μg/h was shown to successfully relieve pain in six patients, with no increase in adverse events. The remaining four patients had inadequate pain relief with 140 μg/h buprenorphine TDS and required switch to an alternative opioid at equianalgesic doses that were higher than 140 μg/h buprenorphine TDS. This study suggests that there was no evidence of a ceiling effect with doses used a higher than 140 dose may have been effective in controlling pain and that concomitant use of rescue morphine was effective in managing pain. A case report of a palliative patient with metastatic cancer using buprenorphine TDS at escalating doses up to 280 μg/h (6.4 mg/day) was described to provide effective pain relief. It is now considered that within the analgesic dose range of 0.2 mg to approximately 7 mg buprenorphine per day, there is no ceiling effect with buprenorphine [90].

Potential benefit of using buprenorphine in neuropathic pain syndromes: There are various reports of buprenorphine successfully treating cases of neuropathic pain, such as for management of trigeminal neuralgia, post-herpetic neuralgia, radicular pain, phantom limb pain, and post-thoracotomy pain [91–96]. Additional benefits of buprenorphine in neuropathic pain have been proposed due to demonstration of potent anti-hyperalgesic and anti-allodynic effects in preclinical [62] and human [97] studies. Further research is warranted to identify the role of buprenorphine for neuropathic pain.

Use of Buprenorphine in Special Populations

Renal failure: Buprenorphine and its metabolites are predominantly excreted via the fecal route, and it is generally considered to be safe in renal failure. However, there are only few small studies that have been conducted. In a small study [98], ten selected patients who were able to tolerate buprenorphine TDS and receiving dialysis, buprenorphine, and norbuprenorphine blood levels before and after dialysis did not change significantly. There were no reports of severe toxicities predialysis; however, three patients reported either nausea or sweating predialysis. Among surgical patients, two studies suggest that buprenorphine disposition is not significantly altered in renally impaired patients. In one study [93], buprenorphine levels over a 3-h sampling period did not significantly differ between patients with renal failure and healthy controls, and there was no clinical evidence of sedation or respiratory depression. This study did not measure buprenorphine metabolites and was of a very short duration. Another study examined buprenorphine disposition utilizing both single- and multiple-dosing [92]. In the single-dose study intravenous 0.3 mg buprenorphine was given to 15 anesthetized patients undergoing surgery. There were no differences in buprenorphine kinetics between healthy ($n=6$) and renally impairment patients ($n=9$) over a 24 h period, and buprenorphine metabolites were undetectable.

In the multiple-dose study of 20 patients, a variable-rate of buprenorphine infusion (median infusion rate of 161 μg/h) was utilized with controlled ventilation to provide analgesia in the intensive care unit for a median duration of 30 h. Buprenorphine clearance in patients with normal ($n=12$) and impaired renal function ($n=8$) was similar, as were dose-corrected plasma concentrations of buprenorphine. However, in patients with renal failure, plasma concentrations of metabolites were significantly increased (by a median of 4 and 15 times for norbuprenorphine and buprenorphine-3-glucoronide), but were not associated with symptoms.

Hepatic failure: There is sparse date with regard to the safety of using buprenorphine in patients with hepatic failure. The liver plays a prominent role in metabolism of buprenorphine, and as CYP3A4 protein expression is reduced in severe chronic liver disease, dose reduction/monitoring may be required when on buprenorphine. In patients with mild to moderate hepatic impairments, a study by Lasseter et al. [99], found that the pharmacokinetic profile of buprenorphine (0.3 mg intravenous) did not differ from matched healthy controls, for most parameters. However, maximum plasma concentrations of buprenorphine and norbuprenorphine were lower (by 50 % and 30 %, respectively) in patients with hepatic impairments, and these patients had less nausea/vomiting. These results suggest that buprenorphine dosage does not need to be adjustment in mild to moderate chronic hepatic impairment.

Age considerations: Buprenorphine has not been studied in pediatric patients for pain management, although case reports of use in chronic or cancer pain suggest that it is well tolerated and efficacious [100].

Acknowledgment Eduardo Bruera is supported in part by National Institutes of Health grant numbers: RO1NR010162-01A1, RO1CA122292-01, RO1CA124481-01.

References

1. Du Pen SL, Du Pen AR, Polissar N, et al. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. J Clin Oncol. 1999;17(1):361–70.
2. Ferrell BR, Juarez G, Borneman T. Use of routine and breakthrough analgesia in home care. Oncol Nurs Forum. 1999;26(10):1655–61.
3. Miaskowski C, Dodd MJ, West C, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. J Clin Oncol. 2001;19(23):4275–9.
4. Mercadante S. Predictive factors and opioid responsiveness in cancer pain. Eur J Cancer. 1998;34(5):627–31.
5. Fainsinger R, Schoeller T, Bruera E. Methadone in the management of cancer pain: a review. Pain. 1993;52(2):137–47.
6. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. Pain. 1997;70(2–3):109–15.
7. Garrido MJ, Troconiz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. J Pharmacol Toxicol Methods. 1999;42(2):61–6.
8. Wolff K, Rostami-Hodjegan A, Shires S, et al. The pharmacokinetics of methadone in healthy subjects and opiate users. Br J Clin Pharmacol. 1997;44(4):325–34.

9. Gorman AL, Elliott KJ, Inturrisi CE. The d- and l-isomers of methadone bind to the non-competitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett. 1997;223(1):5–8.
10. Ebert B, Andersen S, Krogsgaard-Larsen P. Ketobemidone, methadone and pethidine are non-competitive N-methyl-D-aspartate (NMDA) antagonists in the rat cortex and spinal cord. Neurosci Lett. 1995;187(3):165–8.
11. Elliott K, Minami N, Kolesnikov YA, Pasternak GW, Inturrisi CE. The NMDA receptor antagonists, LY274614 and MK-801, and the nitric oxide synthase inhibitor, NG-nitro-L-arginine, attenuate analgesic tolerance to the mu-opioid morphine but not to kappa opioids. Pain. 1994;56(1):69–75.
12. Codd EE, Shank RP, Schupsky JJ, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. J Pharmacol Exp Ther. 1995;274(3):1263–70.
13. Sawe J. High-dose morphine and methadone in cancer patients. Clinical pharmacokinetic considerations of oral treatment. Clin Pharmacokinet. 1986;11(2):87–106.
14. Bruera E, Sweeney C. Methadone use in cancer patients with pain: a review. J Palliat Med. 2002;5(1):127–38.
15. Wolff K, Hay AW, Raistrick D, Calvert R. Steady-state pharmacokinetics of methadone in opioid addicts. Eur J Clin Pharmacol. 1993;44(2):189–94.
16. de Vos JW, Geerlings PJ, van den Brink W, Ufkes JG, van Wilgenburg H. Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. Eur J Clin Pharmacol. 1995;48(5):361–6.
17. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther. 1987;41(4):392–401.
18. Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain. 1986;25(3):297–312.
19. Plummer JL, Gourlay GK, Cherry DA, Cousins MJ. Estimation of methadone clearance: application in the management of cancer pain. Pain. 1988;33(3):313–22.
20. Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacologic considerations in the use of methadone in cancer patients. Cancer Treat Rep. 1979;63(3):457–9.
21. Ripamonti C, Bianchi M. The use of methadone for cancer pain. Hematol Oncol Clin North Am. 2002;16(3):543–55.
22. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002;41(14):1153–93.
23. Israili ZH, Dayton PG. Human alpha-1-glycoprotein and its interactions with drugs. Drug Metab Rev. 2001;33(2):161–235.
24. Grochow L, Sheidler V, Grossman S, Green L, Enterline J. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. Pain. 1989;38(2):151–7.
25. Johnson VM, Teno JM, Bourbonniere M, Mor V. Palliative care needs of cancer patients in U.S. nursing homes. J Palliat Med. 2005;8(2):273–9.
26. Oneschuk D, Bruera E. Respiratory depression during methadone rotation in a patient with advanced cancer. J Palliat Care. Summer 2000;16(2):50–4.
27. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999;94(7):961–72.
28. Bruera E, Neumann CM. Management of specific symptom complexes in patients receiving palliative care. CMAJ. 1998;158(13):1717–26.
29. Mercadante S. Opioid rotation for cancer pain: rationale and clinical aspects. Cancer. 1999;86(9):1856–66.
30. Bowsher D. Paradoxical pain. BMJ. 1993;306(6876):473–4.
31. Mercadante S, Ferrera P, Villari P, Arcuri E. Hyperalgesia: an emerging iatrogenic syndrome. J Pain Symptom Manage. 2003;26(2):769–75.

32. Mercadante S, Casuccio A, Fulfaro F, et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. J Clin Oncol. 2001;19(11):2898–904.
33. Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. Pain. 1997;72(1–2):79–85.
34. Bruera E, Rico M, Bertolino M, et al. A prospective, open study of oral methadone in the treatment of cancer pain. Paper presented at proceedings of the 9th world congress on pain 2000, Seattle; 2000.
35. Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. Cancer. 1996;78(4):852–7.
36. Mercadante S, Porzio G, Ferrera P, et al. Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain. 2008;12(8):1040–6.
37. Bruera E, Palmer JL, Bosnjak S, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol. 2004;22(1):185–92.
38. Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. J Pain Symptom Manage. Fall 1986;1(4):203–7.
39. Mercadante S, Porzio G, Ferrera P, et al. Low morphine doses in opioid-naive cancer patients with pain. J Pain Symptom Manage. 2006;31(3):242–7.
40. Feldt KS. The checklist of nonverbal pain indicators (CNPI). Pain Manag Nurs. 2000;1(1):13–21.
41. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol. 1998;16(10):3216–21.
42. Nauck F, Ostgathe C, Dickerson ED. A German model for methadone conversion. Am J Hosp Palliat Care. 2001;18(3):200–2.
43. Morley JS, Makin MK. The use of methadone in cancer pain poorly responsive to other opioids. Pain Rev. 1998;5:51–8.
44. Mercadante S, Casuccio A, Calderone L. Rapid switching from morphine to methadone in cancer patients with poor response to morphine. J Clin Oncol. 1999;17(10):3307–12.
45. Moksnes K, Dale O, Rosland JH, Paulsen O, Klepstad P, Kaasa S. How to switch from morphine or oxycodone to methadone in cancer patients? A randomised clinical phase II trial. Eur J Cancer. 2011;47(16):2463–70.
46. Twycross R, Wilcock A, Charlesworth S, Dickman A. Guidelines for the use of methadone for cancer pain. Palliative Drugs 2004; newsletter. http://www.palliativedrugs.com/view-legacy-newsletter.html?&nlid=337. Accessed 20 Jan 2012.
47. Moryl N, Santiago-Palma J, Kornick C, et al. Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. Pain. 2002;96(3):325–8.
48. Walker PW, Palla S, Pei BL, et al. Switching from methadone to a different opioid: what is the equianalgesic dose ratio? J Palliat Med. 2008;11(8):1103–8.
49. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. Cancer. 1998;82(6):1167–73.
50. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage. 2004;28(5):497–504.
51. Furlan V, Hafi A, Dessalles MC, Bouchez J, Charpentier B, Taburet AM. Methadone is poorly removed by haemodialysis. Nephrol Dial Transplant. 1999;14(1):254–5.
52. Kreek MJ, Oratz M, Rothschild MA. Hepatic extraction of long- and short-acting narcotics in the isolated perfused rabbit liver. Gastroenterology. 1978;75(1):88–94.
53. Anghelescu DL, Faughnan LG, Hankins GM, Ward DA, Oakes LL. Methadone use in children and young adults at a cancer center: a retrospective study. J Opioid Manag. 2011;7(5):353–61.
54. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17(2):81–110.

55. Nath RP, Upton RA, Everhart ET, et al. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. J Clin Pharmacol. 1999;39(6):619–23.
56. Likar R, Lorenz V, Korak-Leiter M, Kager I, Sittl R. Transdermal buprenorphine patches applied in a 4-day regimen versus a 3-day regimen: a single-site, phase III, randomized, open-label, crossover comparison. Clin Ther. 2007;29(8):1591–606.
57. Cowan A, Lewis JW, Macfarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol. 1977;60(4):537–45.
58. Leander JD. Buprenorphine has potent kappa opioid receptor antagonist activity. Neuropharmacology. 1987;26(9):1445–7.
59. Romero DV, Partilla JS, Zheng QX, et al. Opioid peptide receptor studies. 12. Buprenorphine is a potent and selective mu/kappa antagonist in the [35S]-GTP-gamma-S functional binding assay. Synapse. 1999;34(2):83–94.
60. Cowan A, Friderichs E, Straßburger W, Raffa RB. Basic pharmacology of buprenorphine. In: Budd K, Raffa R, editors. Buprenorphine—the unique opioid analgesic. Stuttgart: Georg Thieme Verlag; 2005. p. 3–21.
61. Wheeler-Aceto H, Cowan A. Buprenorphine and morphine cause antinociception by different transduction mechanisms. Eur J Pharmacol. 1991;195(3):411–3.
62. Christoph T, Kogel B, Schiene K, Meen M, De Vry J, Friderichs E. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. Eur J Pharmacol. 2005;507(1–3):87–98.
63. Budd K. High dose buprenorphine for postoperative analgesia. Anaesthesia. 1981;36(9): 900–3.
64. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627–32.
65. Walsh SL, Preston KL, Bigelow GE, Stitzer ML. Acute administration of buprenorphine in humans: partial agonist and blockade effects. J Pharmacol Exp Ther. 1995;274(1):361–72.
66. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain. 2009;13(3):219–30.
67. Villiger JW, Taylor KM. Buprenorphine: characteristics of binding sites in the rat central nervous system. Life Sci. 1981;29(26):2699–708.
68. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569–80.
69. Walter DS, Inturrisi C. Absorption, distribution, metabolism, and excretion of buprenorphine in animals and humans. In: Cowan A, Lewis J, editors. Buprenorphine: combatting drug abuse with a unique opioid. New York: Wiley-Liss; 1995. p. 113–35.
70. Ohtani M, Kotaki H, Sawada Y, Iga T. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. J Pharmacol Exp Ther. 1995;272(2):505–10.
71. Agarwal N, Pacher P, Tegeder I, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. Nat Neurosci. 2007;10(7):870–9.
72. McAleer SD, Mills RJ, Polack T, et al. Pharmacokinetics of high-dose buprenorphine following single administration of sublingual tablet formulations in opioid naive healthy male volunteers under a naltrexone block. Drug Alcohol Depend. 2003;72(1):75–83.
73. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2003;25(1):150–68.
74. Bohme K, Likar R. Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain. A randomised, double-blind, placebo-controlled study. Pain Clinic. 2003;15:19.
75. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2004;26(11):1808–20.

76. Poulain P, Denier W, Douma J, et al. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. J Pain Symptom Manage. 2008;36:117–25.
77. Likar R, Kayser H, Sittl R. Long-term management of chronic pain with transdermal buprenorphine: a multicenter, open-label, follow-up study in patients from three short-term clinical trials. Clin Ther. 2006;28(6):943–52.
78. Pace MC, Passavanti MB, Grella E, et al. Buprenorphine in long-term control of chronic pain in cancer patients. Front Biosci. 2007;12:1291–9.
79. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13,179 patients. Curr Med Res Opin. 2005;21(8):1147–56.
80. Muriel C, Failde I, Mico JA, Neira M, Sanchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. Clin Ther. 2005;27(4):451–62.
81. Tschirner M, Ritzdorf I, Brunjes R. [Post marketing surveillance study with an analgesic (transdermal buprenorphine patch) in patients with moderate to severe chronic pain]. MMW Fortschr Med. 2008;150(Suppl 3):142–8.
82. Camba M, Rodriguez-Lopez M, Muriel C, Grupo de Estudio de Opioides de la Sociedad Espanola del dolor. Buprenorphine TDS in the treatment of chronic nociceptive, neuropathic and cancer-related pain. J Appl Ther Res. 2007;6(2):3–13.
83. Deandrea S, Corli O, Moschetti I, Apolone G. Managing severe cancer pain: the role of transdermal buprenorphine: a systematic review. Ther Clin Risk Manag. 2009;5(5):707–18.
84. Mercadante S, Porzio G, Fulfaro F, et al. Switching from transdermal drugs: an observational "N of 1" study of fentanyl and buprenorphine. J Pain Symptom Manage. 2007;34(5):532–8.
85. Mercadante S, Casuccio A, Tirelli W, Giarratano A. Equipotent doses to switch from high doses of opioids to transdermal buprenorphine. Support Care Cancer. 2009;17(6):715–8.
86. Freye E, Anderson-Hillemacher A, Ritzdorf I, Levy JV. Opioid rotation from high-dose morphine to transdermal buprenorphine (Transtec) in chronic pain patients. Pain Pract. 2007;7(2):123–9.
87. Aurilio C, Pace MC, Pota V, et al. Opioids switching with transdermal systems in chronic cancer pain. J Exp Clin Cancer Res. 2009;28:61.
88. Mercadante S, Villari P, Ferrera P, et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. J Pain Symptom Manage. 2006;32(2):175–9.
89. Mercadante S, Ferrera P, Villari P. Is there a ceiling effect of transdermal buprenorphine? Preliminary data in cancer patients. Support Care Cancer. 2007;15(4):441–4.
90. Pergolizzi Jr JV, Mercadante S, Echaburu AV, et al. The role of transdermal buprenorphine in the treatment of cancer pain: an expert panel consensus. Curr Med Res Opin. 2009;25(6):1517–28.
91. Likar R, Sittl R. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. Anesth Analg. 2005;100(3):781–5, table of contents.
92. Fogliardi A. Transdermal buprenorphine (buprenorphine TDS) in post-herpetic neuropathy. Paper presented at international forum on pain medicine, Sofia, Bulgaria, 5–8 May 2005.
93. Induru RR, Davis MP. Buprenorphine for neuropathic pain—targeting hyperalgesia. Am J Hosp Palliat Care. 2009–2010;26(6):470–3.
94. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. J Pain Symptom Manage. 1992;7(2):69–77.
95. Benedetti F, Vighetti S, Amanzio M, et al. Dose-response relationship of opioids in nociceptive and neuropathic postoperative pain. Pain. 1998;74(2–3):205–11.
96. Guetti C, Angeletti C, Marinangeli F, et al. Transdermal buprenorphine for central neuropathic pain: clinical reports. Pain Pract. 2011;11(5):446–52.
97. Koppert W, Ihmsen H, Korber N, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain. 2005;118(1–2):15–22.

98. Filitz J, Griessinger N, Sittl R, Likar R, Schuttler J, Koppert W. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006;10(8):743–8.
99. Lasseter KC, Venitz J, Eltahtawy A, Miotto J, Munera C, Reder R, et al. Systemic pharmacokinetic (PK) study of buprenorphine (B) in mild to moderate chronic hepatic impairment (CHI). Clin Pharmacol Ther. 2001;69(2):P2.
100. Michel E, Anderson BJ, Zernikow B. Buprenorphine TTS for children—a review of the drug's clinical pharmacology. Paediatr Anaesth. 2011;21(3):280–90.

Chapter 18
Methadone Prescribing in the Sickle Cell Patient

Wally R. Smith and Abdulkhaliq J. Alsalman

Pain in Sickle Cell Disease

Pain is the most common symptom reported by the 89,000 [1] to 100,000 [2] Americans with sickle cell disease (SCD) [3]. Vaso-occlusive pain, often occurring as an extremely painful vaso-occlusive crisis (VOC), is the hallmark of SCD [4]. VOC is the most common cause of hospitalization for SCD [5]. Typical VOC pain is acute, disabling, and intense enough to require opioids. It usually affects the extremities, the back, the abdomen, or rarely the head and jaw [6].

However, rather than leading to hospitalization, most vaso-occlusive pain in SCD, even pain characterized as a VOC and requiring opioids, is managed at home [7, 8]. The "iceberg" of pain in SCD is mostly "submerged," out of the sight of health care professionals, and only the tip of the iceberg, 3.5 % of days in adults, is seen in hospitals and Emergency Departments [9].

Despite significant strides in our understanding of the underlying pathophysiology of vaso-occlusive pain and VOC [10, 11], and the potential of novel pharmacological interventions to modify this pathophysiology [12–15], the evidence base for pain management of SCD is lacking [16], and resources utilized for pain management in SCD have remained stagnant for decades, consisting mainly of fluids and opioids. Most of the practices in use to treat pain in SCD seem to have derived from care of pain in cancer patients [17–21]. But unlike usual cancer pain, vaso-occlusive

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_18,

Table 18.1 Characteristics of usual sickle cell pain vs. usual cancer pain

Sickle cell pain	Cancer pain
Ischemic initially	Non-ischemic usually
Episodic to continuous	Continuous
Widely variable intensity	Steady intensity
Unpredictable	Predictable
Throughout life	Terminal event
Validity questioned	Validity not questioned
Few objective correlates	Many objective correlates
Prominent feature of disease	May be absent
Frequent emergency visits	Few to no emergency visits
Children, adults	Mostly adults
Episodic care	Longitudinal specialty care

pain in SCD is often unpredictable, temporally irregular, of widely variable intensity, and acute-on-chronic (Table 18.1).

Further, pain research in SCD is scant compared to other diseases, even though pain is the predominant presentation of the disease. The American Pain Society (APS) published consensus SCD pain guidelines in 1999 [22] which were based on few clinical studies in SCD. Similar consensus guidelines were developed in the UK in 2003 [23]. A 2010 review by APS staff to determine if an update was needed concluded that there was insufficient new information to warrant an update (C. Miaskowski, personal communication). A 2011 search of Clinical Trials.gov yielded 257 registered trials related to SCD [24]. Of these, only 25 either mentioned "pain" or "crisis" or various analgesics in their titles or keyword descriptors.

Besides the hallmark VOC, various other pain syndromes may also affect patients with SCD. Some syndromes derive from regional or local nociceptive complications, including ischemic (venous stasis) leg ulcers, avascular necrosis of the hip, shoulder, or knee, cholecystitis or gall bladder colic, priapism, headache, and gout. Consensus definitions of these syndromes in SCD have recently been agreed to [25], to clearly distinguish them from vaso-occlusive pain for research and practice purposes. Because of their pathophysiology, these complications are treated differently than vaso-occlusive pain.

Early in life, vaso-occlusive pain in SCD appears purely *nociceptive*, i.e., potentially or actually damaging. The nociceptive nervous system involves the periphery, spinal cord, brain stem, thalamus and cerebral cortex, and links recognition of a damaging stimulus (via the afferent arm) to an adaptive behavioral response (via the efferent arm), such as avoidance if possible, through an intense and unpleasant sensation (pain) [26]. This innate physiological response is repeated countless times during every painful episode, but may be distorted after decades of recurrences.

As a result, later in life, the ravages of vaso-occlusion may result in vaso-occlusive nociceptive SCD pain transforming from acute to chronic pain [27]. Patients may also develop *neuropathic pain*, pain occurring as a result of malfunction or injury in the peripheral or central nervous system [28], like that seen in diseases such as diabetes mellitus, immune deficiencies, trauma, ischemic disorders, malignant diseases, and fibromyalgia [29]. This permanent nerve injury from

multiple prior nociceptive painful episodes may be expressed phenotypically as lowering of the pain threshold, hyperalgesia, and allodynia. There may actually be anatomical brain manifestations of this phenomenon, i.e., *neuroplasticity or remodeling*—that contribute to the maintenance of an altered, neuronal phenotype. Adjectives associated with neuropathic pain, e.g., burning, tingling, shooting, numbness, and lancinating, have recently been endorsed by adults with SCD pain who completed the McGill Pain Questionnaire [30].

SCD may share this mechanism of transformation from acute to chronic pain with other originally nociceptive pain syndromes, including neck and back pain [31] and postoperative pain [32]. This chronic pain, via neurological changes in the prefrontal cortex as part of neuroplasticity and remodeling, may also affect emotion. This has been seen with chronic back pain and fibromyalgia, both associated with decreased grey matter in the prefrontal cortex, which may be associated with a decreased ability to inhibit the experience of pain, and the above lowering of the pain threshold [33]. Indeed, SCD may share a common, "centrally driven" pathophysiologic pain mechanism with several other diseases, all previously thought to be unrelated. These include fibromyalgia, irritable bowel syndrome, interstitial cystitis, and somatization. These central nervous system pathologic processes are manifested clinically as a diffuse hyperalgesia, identifiable using experimental sensory testing, and corroborated by functional neuroimaging [34].

The focus of most literature on opioid management for pain in SCD is vaso-occlusive nociceptive pain, managed in hospitalized patients [35–39]. Texts imply or state that chronic pain is far less prevalent. However, the studies of SCD pain epidemiology showing highly prevalent chronic pain suggest a mixed nociceptive/neuropathic pathophysiology, and the need for a more comprehensive treatment regimen for pain in SCD that can address neuropathic pain as well as acute and chronic nociceptive pain. Only a few articles have acknowledged the need to focus on chronic pain management in SCD [40, 41].

As is true for all pain, there are not only biological underpinnings and correlates of SCD pain, but also psychological, social, and health care seeking correlates. Unlike the former, the latter have been well studied by many over the past 30 years [42–47].

Anecdotally, many individuals with SCD, even those not expected to be tolerant to opioids, fail to achieve adequate analgesia with standard doses of opioids. For example, SCD patients who underwent cholecystectomy had an increased requirement of postoperative opioids [48]. Unfortunately, when there is a clinical finding of an increased opioid requirement in SCD, it is often labeled as addiction or psychological drug-seeking behavior by many health care providers [49–51]. Mistrust between SCD patients and their physicians is now well-documented in the literature [52–55]. SCD patients may manifest *pseudoaddiction*, defined as appropriate drug-seeking behavior in a patient who is in pain and is undermedicated, that is misinterpreted as addiction by clinicians [56]. This misclassification of patient behavior and bilateral mistrust likely leads to delays in presentation for treatment, and to further undermedication of pain in SCD.

Besides misplaced fear of addiction or opioid abuse, some also suspect that underlying racism partially explains undermedication of SCD patients. This is supported by disparities in prescribing opioids in general to blacks vs. whites [57]. Paradoxically, in 2003 the prevalence of prescription abuse in whites was significantly higher than blacks (6.9 % vs. 3.7 %) [58].

Pharmacokinetics and Pharmacodynamics of Opioids in Sickle Cell Disease

Instead of addiction, a variety of biological factors likely explain the sometimes increased opioid requirements in SCD. Factors generally hypothesized to be responsible for altered opioid responsiveness in SCD include altered pharmacokinetics and tolerance [59].

In general, there are known racial and genetic differences in drug metabolism and drug response [60]. In the USA, most SCD patients are African American. It is unclear whether the pharmacokinetics and pharmacodynamics seen in SCD patients result from those attributable to racial differences, or those attributable to SCD itself.

However, the pharmacokinetics of opioids is clearly altered in SCD [61]. First, early on in SCD, both hepatic and renal blood flow are increased as a consequence of the high cardiac output state associated with the chronic anemia of SCD especially in children [62–65]. All of these may accelerate glucuronidation and elimination and thereby explain the reported increases in clearance of opioid during a VOC of SCD [66]. This increased clearance may mean that SCD patients require higher doses and frequency of opioids to achieve comparable plasma levels to controls. Second, acute vaso-occlusive pathology could itself alter the disposition of opioids, due to acute hemodynamic and inflammatory changes associated with vaso-occlusion and pain [67].

Third, opioid clearance in SCD may vary based on genetic differences in metabolism. This has been studied in morphine [68, 69], codeine [61], and mepridine [70]. Methadone pharmacokinetics is discussed later in this chapter, but we found no studies of its clearance in SCD.

Later in life, hepatic and renal dysfunction frequently occur in patients with SCD [71, 72], leading to likely diminished metabolism and excretion of drugs through hepatic and renal pathways. Repetitive episodes of vaso-occlusive ischemia and sickle vasculopathy damage these organs, along with all others. Regarding the liver, hepatomegaly and hepatic dysfunction may be related to impaired sinusoidal blood flow from vaso-occlusion, sinusoidal obstruction caused by Kupffer cell engorgement as a result of erythrophagocytosis, chronic hepatitis C and B infections, and iron overload from multiple transfusions, until recently poorly treatable and leading to cirrhosis. On occasion, patients develop serum hyperbilirubinemia not explained by severe acute hemolysis, viral hepatitis, extrahepatic obstruction, or hepatic sequestration, called sickle hepatopathy [73]. Recently, a new classification system for hepatic dysfunction in SCD has been proposed [74].

Regarding the kidney, aside from older-age-related losses in renal plasma flow along with GFR, proteinuria and glomerulopathy, specifically focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, glomerulopathy specific to SCD [75], and thrombotic microangiopathy, have all been reported in SCD [76].

But it is unclear whether and when in any individual SCD patient these effects dominate the enhanced metabolism due to increased cardiac output. Thus, opioid pharmacokinetics and pharmacodynamics are not easily predictable between SCD patients. Unusual opioid-related side effects may also occur. For example, in children morphine administration showed a dose–response association with acute chest syndrome of SCD [77].

Next, many SCD patients develop cardiovascular and pulmonary complications which could disturb drug metabolism. Pulmonary hypertension is the most common and most fatal finding [78], but may be confounded by left ventricular or right ventricular dilatation and/or hypertrophy, after years of high-output heart failure [79]. Diastolic dysfunction is an independent predictor of death, separate from pulmonary hypertension [80]. Chronic oxygen desaturation may underlie the cardiac abnormalities [81]. Fluid and electrolyte imbalances including hypokalemia and hypomagnesemia have been reported [82]. The effects of these on drug metabolism in SCD have not been measured.

Methadone is primarily metabolized by CYP3A4 and CYP2B6; CYP2C8, CYP2C19, CYP2D6, and CYP2C9 also contribute in varying degrees to its metabolism [83–87]. Methadone is also a very weak serotonin reuptake inhibitor. Thus, methadone has interaction potential with selective serotonin reuptake inhibitors, tricyclic antidepressants, β-blockers, and antiarrhythmics. An array of other drugs are substrates, inducers, or inhibitors of the CYP2D6 enzyme [88]. Occurrence of the serotonin syndrome after co-administration with an amine uptake inhibitor, such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors, is sometimes cited as a danger.

It is tempting to blame racial differences in opioid metabolism for the differences in responses to opioids in SCD, including methadone. But we found only one paper with evidence of CYP2D6-based opioid metabolism differences in African-Americans vs. whites [89], and only a few papers studying African populations [90, 91]. All patients studied showed variably altered CYP2D6 gene metabolism.

Advantages and Disadvantages of Methadone Use in SCD

For SCD patients with chronic pain, methadone offers some features that suit it well to the management of pain in SCD. Compared to other opioids, its pharmacokinetics are not significantly affected by the hepatic impairment that may occur in SCD [92]. Similarly, reviews summarize that methadone may be less affected by renal impairment than other opioids. It does not seem to be removed by dialysis [93]. Thus, in stage 3 to stage 5 chronic kidney disease, it may be preferred [94, 95].

Table 18.2 Advantages and disadvantages of methadone as a maintenance opioid for sickle cell disease (SCD)

Advantages of methadone
• Relatively cheap
• Intrinsically long acting; stable inter-dose opioid levels
• High oral bioavailability (80 %), high lipid solubility
• No active or toxic metabolites
• Does not accumulate with renal insufficiency. Effective in hemodialysis
• Blocks non-opioid receptors—NMDA receptors and monoaminergic reuptake transporters; useful for neuropathic pain
• Available as an oral liquid or pill
• Tolerance and physical dependence develop more slowly than with morphine
• Relatively low street value
Disadvantages of methadone
• Highly variable pharmacokinetics and highly variable metabolism leading to a long and unpredictable half-life
• Potential for accumulation and overdose during titration
• Unpredictable equianalgesic potency compared to other opioids
• Variable protein binding
• Social stigma because of its association with drug addiction treatment
• Low familiarity by SCD practitioners
• Potential risk of prolonged QT-based cardiac arrhythmias

In anuric patients, methadone excretion in the feces may be enhanced with limited accumulation in plasma [96]. Further, methadone does not produce active metabolites, exerting its activity—both analgesic and toxic—through the parent compound.

A special advantage of methadone is that it may be better suited than other opioids for treating chronic severe SCD pain. In rats, methadone is not only a potent μ-opioid receptor agonist, but also a noncompetitive antagonist for *N*-methyl-D-aspartate (NMDA) receptors [97].

The activation of NMDA receptors is an important mechanism for the development of hyperalgesia/allodynia and opioid resistance occurring during neuropathic pain [98]. Thus, along with a host of drugs including tricyclics, ketamine, gabapentin, and the opioids codeine, oxycodone, tramadol, morphine, and buprenorphrine [99], methadone has been used in the treatment of neuropathic pain [100–102], including noncancer neuropathic pain [103], with at least one trial showing dramatic therapeutic success [104]. Thus, if SCD patients with chronic pain syndrome have a mixed nociceptive and neuropathic picture, methadone may be ideal among opioids. It is a potent analgesic, may minimize the likelihood of opioid tolerance, and may treat the neuropathic component of pain.

On the other hand, like all opioids, methadone may produce CNS-depressant effects, reduced ventilatory drive, sedation, hypotension, coma, and even death. Vigilance is critical during methadone treatment initiation and during dose titration. Similar vigilance is necessary during conversion from methadone to another opioid, or vice versa. This is because methadone has a 12–190-h half-life [105], and its

pharmacodynamics reflect this—analgesic and other effects lag and intensify well after their onset, and wane slowly, long after drug withdrawal [106]. Misunderstanding methadone's pharmacokinetics and pharmacodynamics could lead to drastic underdosing or overdosing. This pharmacokinetic and pharmacodynamic profile and need for vigilance have led some to question its safety in the outpatient setting. Its daily use for chronic pain in SCD has not been widely studied. But at least in cancer pain, it appears to be safe [107].

In particular, methadone may increase cardiovascular arrhythmia risk, namely QT interval prolongation, and torsades de pointes. In SCD, methadone was associated with these phenomena in doses at or in excess of 200 mg daily [108]. Some authorities now suggest not only obtaining baseline EKGs prior to chronic administration of methadone, but also obtaining EKGs if methadone doses exceed 100 mg daily [109].

Managing Sickle Cell Disease Pain with Methadone

Table 18.3 lists some common-sense principles for the use of methadone in SCD. Several adult sickle cell practitioners are now using methadone for pain in SCD. Usually methadone is not the first opioid used. Following principles used in treatment of cancer pain [110], analgesia is first established with a short-acting opioid. Patients may then have methadone or another long-acting opioid added to their analgesic regimen if a short-acting only regimen fails and/or there is significant breakthrough pain. However, unlike in cancer where long-term survival is not expected, in SCD, long-term maintenance for chronic pain is usually necessary. Once a long-acting opioid regimen is added, it may be necessary to continue it for years to maintain long-term analgesia. Thus, methadone is used in SCD as the long-term opioid component of a multi-opioid treatment strategy consisting of a short-acting opioid for breakthrough pain (usually VOC) and a long-acting opioid for chronic pain (Table 18.3).

Anecdotally, patients may often stay on the same maintenance dose of methadone for years, without requirement of dose escalation. One advantage of using methadone and other long-acting opioids is its flexibility during various settings of care. We recently recommended continuing the oral maintenance dose of methadone or other long-acting analgesics, begun as an outpatient, during hospitalization for acute VOC, as a substitute for the maintenance or basal opioid infusion sometimes used during patient-controlled analgesia [111]. Its advantage in the inpatient setting is that there is no expected toxicity from continuing a "basal" dose of methadone with a known lack of prior toxicity. In contrast, toxicity sometimes occurs from starting a previously untried parenteral dose of short-acting opioid as a basal infusion during patient-controlled analgesia [37].

Among adult hematologists in the USA, methadone is not the most often-used long-acting opioid, trailing behind long-acting morphine and oxycodone in frequency of prescription. However, it is one of the best tolerated, with fewer side effects than either long-acting morphine or oxycodone. Doses much lower than the

Table 18.3 Principles of management of the pain of SCD with methadone

Ambulatory patients
• SCD pain may be managed at home with methadone in combination with other opioids
• Methadone should be used as maintenance opioid therapy, along with an immediate-release analgesic as rescue medication for breakthrough pain
• It is acceptable to prescribe methadone as a first-line maintenance opioid
• Methadone prescribing for analgesia must be individualized. Typical doses are 20–40 mg daily
• The initial methadone dose should usually be low and be based on previous pain pattern, history of response to other opioids, current status, and other medical conditions
• In contrast to its use in suppressing symptoms of opioid withdrawal, use of methadone as an analgesic typically requires administration at intervals of no more than 8 h
• Methadone should be prescribed as scheduled, never as-needed. The time to reach steady-state concentration following a change in dosage may be up to 12 days
• Titration of methadone to analgesia requires patience, frequent reassessment over days to weeks, and vigilance for toxicity and effect
• Patients on methadone should be carefully observed for cumulative toxicity, heralded by sedation or confusion
• Treating adverse effects of opioids is part of pain management
• Tolerance to methadone may be slower to develop than to other opioids after continuous long-term use
• Patients with SCD may have disease-specific, renal, or hepatic complications which alter methadone metabolism
• Published tables of equianalgesic doses of opioids indicate that methadone is 1–2 times as potent as morphine
• In morphine-tolerant individuals, methadone is closer to ten times as potent as morphine
• When analgesic tolerance or intolerable side effects have developed with the use of increasing doses of morphine or hydromorphone, "opioid rotation" to methadone has provided superior analgesia at 10–20 % of the morphine-equivalent daily dose
• Avoid abrupt discontinuation of methadone. If for any reason methadone has to be abruptly stopped, an alternative opioid should be considered to fill the "opioid debt"
Hospitalized patients
• Hospitalized SCD patients should not be started on methadone without assurance of close outpatient follow-up
• Hospitalized SCD patients with *moderate to severe breakthrough pain* may continue any previously started methadone dose as maintenance throughout hospitalization

200 mg daily associated with prolonged QTc interval and torsades de pointes are usually required, even when switching from another long-acting agent. Typical doses in our practice are 20–40 mg daily, sometimes in divided doses.

Clinicians need to be especially cautious when prescribing methadone for SCD patients with diminished metabolic capacities due to organ dysfunction. Dose adjustments of methadone and of other opioid analgesics may be required to achieve adequate pain relief without unwanted side effects. Both dose reduction and/or prolongation of dose intervals may be necessary depending on the severity of organ impairment. Moreover, especially when hepatic or renal impairment is a factor, clinicians should adopt a "start low and go slow" approach to methadone titration—begin with very low doses, monitor carefully, and titrate upward slowly [112].

Behavioral Factors Related to Methadone Use for Sickle Cell Pain

In practice, clinicians may be reluctant to use methadone for SCD pain. Knowing that methadone is often the drug of choice for prevention of opioid withdrawal among heroin addicts [113], clinicians may fear that their prescribing methadone will be misinterpreted as prescribing to treat drug abuse. This is especially true given the reputation for misuse SCD patients sometimes carry in the minds of clinicians. Reluctance to prescribe methadone could also stem from clinicians' unfamiliarity with methadone's pharmacokinetics and pharmacodynamics. Or, clinicians might be unfamiliar with possible advantages for prescribing methadone over other long-acting opioids.

Much of this hesitation can be overcome with education. Physicians caring for SCD patients may not know that methadone maintenance for substance abuse requires special training, designation, and legal requirements, all of which are unnecessary for the use of methadone to treat pain. For this legal reason, when prescribing methadone for pain, prescribers should spell out the indication, "for pain," on the prescription, to avoid the implication they are treating substance abuse. In practice, use of the term "for pain" on the prescription may not only meet legal requirements but also avoid calls from questioning pharmacists. Even family members and non-prescribing clinicians must sometimes be educated that patients are being prescribed methadone to treat pain, not to prevent opioid abuse.

Similar to clinicians, patients with SCD are also sometimes reluctant to use methadone. They may know that methadone maintenance is commonly prescribed for opioid abusers, and may suspect that clinicians believe they are opioid abusers. They may therefore refuse methadone to avoid stigmatization. Or, patients may not trust that clinicians intend to prescribe methadone to achieve adequate analgesia for their pain. They may suspect that, instead, methadone is being prescribed as a substitute for other opioids with superior analgesia. In order to convince patients to use methadone, this mistrust must be overcome.

An additional hesitancy may result when methadone, prescribed at usual low starting doses and titrated slowly, does not give immediate analgesia. Patients may lose faith in its efficacy. Some patients cannot be convinced to finish an adequate therapeutic trial, and bail out of therapy in only a few days.

Patients must be educated and reeducated about the need for dose titration and patience while doses are slowly escalated to analgesia. Typical patient failings are overuse of methadone acutely, in a panic to obtain immediate analgesia, and/or substitution of short-acting opioids for methadone when expected analgesia is not obtained in one or a few days.

References

1. Brousseau DC, Panepinto JA, Nimmer M, Hoffmann RG. The number of people with sickle-cell disease in the United States: national and state estimates. Am J Hematol. 2010;85(1):77–8.

2. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38 (Suppl 4):S512–21.
3. Smith WR, Scherer M. Sickle-cell pain: advances in epidemiology and etiology. Hematology Am Soc Hematol Educ Program. 2010;2010:409–15.
4. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. N Engl J Med. 1991;325:11–6.
5. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. JAMA. 2010;303(13):1288–94.
6. McClish DK, Smith WR, Dahman BA, Levenson JL, Roberts JD, Penberthy LT, et al. Pain site frequency and location in sickle cell disease: the PiSCES project. Pain. 2009;145(1–2):246–51.
7. Dampier C, Ely E, Brodecki D, O'Neal P. Home management of pain in sickle cell disease: a daily diary study in children and adolescents. J Pediatr Hematol Oncol. 2002;24(8):643–7.
8. Dampier C, Ely B, Brodecki D, O'Neal P. Characteristics of pain managed at home in children and adolescents with sickle cell disease by using diary self-reports. J Pain. 2002;3(6):461–70.
9. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008;148:94–101.
10. Hebbel RP, Vercellotti G, Nath KA. A systems biology consideration of the vasculopathy of sickle cell anemia: the need for multi-modality chemo-prophylaxis. Cardiovasc Hematol Disord Drug Targets. 2009;9(4):271–92.
11. Conran N, Franco-Penteado CF, Costa FF. Newer aspects of the pathophysiology of sickle cell disease vaso-occlusion. Hemoglobin. 2009;33(1):1–16. Review.
12. Chang J, Patton JT, Sarkar A, Ernst B, Magnani JL, Frenette PS. GMI-1070, a novel pan-selectin antagonist, reverses acute vascular occlusions in sickle cell mice. Blood. 2010;116(10):1779–86.
13. L-Glutamine therapy for sickle cell anemia and sickle ß0 thalassemia. Emmaus Medical, Inc. ClinicalTrials.gov Identifier: NCT00125788.
14. Gibbs WJ, Hagemann TM. Purified poloxamer 188 for sickle cell vaso-occlusive crisis. Ann Pharmacother. 2004;38(2):320–4. Review.
15. Vandy Black L, Smith WR. Evidence-based mini-review: are systemic corticosteroids an effective treatment for acute pain in sickle cell disease? Hematology Am Soc Hematol Educ Program. 2010;2010:416–7.
16. Field JJ, Knight-Perry JE, DeBaun MR. Acute pain in children and adults with sickle cell disease: management in the absence of evidence-based guidelines. Curr Opin Hematol. 2009;16(3):173–8.
17. Caraceni A, De Conno F, Kaasa S, Radbruch L, Hanks G. Update on cancer pain guidelines. J Pain Symptom Manage. 2009;38(3):e1–3.
18. Green E, Zwaal C, Beals C, Fitzgerald B, Harle I, Jones J, et al. Cancer-related pain management: a report of evidence-based recommendations to guide practice. Clin J Pain. 2010;26(6):449–62.
19. Forbes K. Pain in patients with cancer: the World Health Organization analgesic ladder and beyond. Clin Oncol (R Coll Radiol). 2011;23(6):379–80. Review.
20. Ripamonti CI, Bandieri E, Roila F, ESMO Guidelines Working Group. Management of cancer pain: ESMO clinical practice guidelines. Ann Oncol. 2011;22(Suppl 6):vi69–77.
21. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al.; European Palliative Care Research Collaborative (EPCRC); European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012;13(2):e58–68. Review.
22. Benjamin L, Dampier C, Jacox A, The Guideline Committee. Guidelines for the management of acute and chronic pain in sickle cell disease. APS Clinical Practice Guideline Series, No. 1. Glenview, IL: American Pain Society; 1999.
23. Rees D. Guidelines for the management of the acute painful crisis of sickle cell disease. Br J Haematol. 2003;120:744–52.

24. http://clinicaltrials.gov. Accessed 10 April 2011.
25. Ballas SK. Defining the phenotypes of sickle cell disease. Hemoglobin. 2011;35(5–6):511–9. Review.
26. Woolf CJ; American College of Physicians; American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004;140(6):441–51. Review.
27. Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth. 2010;105 Suppl 1:i69-85. Review.
28. Mersky H, Bogduk N, editors. Classification of chronic pain. Seattle, WA: IASP Press; 1994.
29. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002;46:1333–43.
30. Wilkie DJ, Molokie R, Boyd-Seal D, Suarez ML, Kim YO, Zong S, et al. Patient-reported outcomes: descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. J Natl Med Assoc. 2010;102(1):18–27.
31. Young Casey C, Greenberg MA, Nicassio PM, Harpin RE, Hubbard D. Transition from acute to chronic pain and disability: a model including cognitive, affective, and trauma factors. Pain. 2008;134(1–2):69–79.
32. De Kock M. Expanding our horizons: transition of acute postoperative pain to persistent pain and establishment of chronic postsurgical pain services. Anesthesiology. 2009;111(3):461–3.
33. Jensen MP. A neuropsychological model of pain: research and clinical implications. J Pain. 2010;11(1):2–12.
34. Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states—maybe it is all in their head. Best Pract Res Clin Rheumatol. 2011;25(2):141–54. Review.
35. Gonzales ER, Bahal N, Hansen LA, et al. Intermittent injection vs. patients controlled analgesia for sickle cell crisis pain. Arch Intern Med. 1991;151:1373–8.
36. Dampier CD, Smith WR, Kim HY, Wager CG, Bell MC, Minniti CP, et al. Opioid patient controlled analgesia use during the initial experience with the IMPROVE PCA trial: a phase III analgesic trial for hospitalized sickle cell patients with painful episodes. Am J Hematol. 2011;86:E70–3. doi: 10.1002/ajh.22176.
37. Trentadue NO, Kachoyeanos MK, Lea G. A comparison of two regimens of patient-controlled analgesia for children with sickle cell disease. J Pediatr Nurs. 1998;13(1):15–9.
38. van Beers EJ, van Tuijn CF, Nieuwkerk PT, et al. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. Am J Hematol. 2007;82(11):955–60.
39. Jacob E, Hockenberry M, Mueller BU, Coates TD, Zeltzer L. Analgesic response to morphine in children with sickle cell disease: a pilot study. J Pain Manag. 2008;2(1):179–90.
40. Ballas SK, Bauserman RL, McCarthy WF, Castro OL, Smith WR, Waclawiw MA, et al. Utilization of analgesics in the multicenter study of hydroxyurea in sickle cell anemia: effect of sex, age, and geographical location. Am J Hematol. 2010;85(8):613–6.
41. Smith WR, Ballas SK, McCarthy WF, Bauserman RL, Swerdlow PS, Steinberg MH, et al. The association between hydroxyurea treatment and pain intensity, analgesic use, and utilization in ambulatory sickle cell anemia patients. Pain Med. 2011;12(5):697–705. doi: 10.1111/j.1526-4637.2011.01096.x.
42. Gil KM, Abrams MR, Phillips G, Keefe FJ. Sickle cell disease pain: relation of coping strategies to adjustment. J Consult Clin Psychol. 1989;57(6):725–31.
43. Laurence B, George D, Woods D. Association between elevated depressive symptoms and clinical disease severity in African-American adults with sickle cell disease. J Natl Med Assoc. 2006;98:365–9.
44. Reese FL, Smith WR. Psychosocial determinants of health care utilization in sickle cell disease patients. Ann Behav Med. 1997;19(2):171–8.
45. McClish DK, Penberthy LT, Bovbjerg VE, Roberts JD, Aisiku IP, Levenson JL, et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes. 2005;3:50.

46. Citero VA, Levenson JL, McClish DK, Bovbjerg VE, Cole PL, Dahman BA, et al. The role of catastrophizing in sickle cell disease—the PiSCES project. Pain. 2007;133(1–3):39–46.
47. Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, de A Citero V, Penberthy LT, et al. Depression and anxiety in adults with sickle cell disease: the PiSCES project. Psychosom Med. 2008;70(2):192–6.
48. Crawford MW, Galton S, Naser B. Postoperative morphine consumption in children with sickle-cell disease. Paediatr Anaesth. 2006;16(2):152–7.
49. Elander J, Marczewska M, Amos R, Thomas A, Tangayi S. Factors affecting hospital staff judgments about sickle cell disease pain. J Behav Med. 2006;29:203–14.
50. Solomon LR. Treatment and prevention of pain due to vaso-occlusive crises in adults with sickle cell disease: an educational void. Blood. 1987;111:997–1003.
51. Yaster M, Kost-Byerly S, Maxwell LG. The management of pain in sickle cell disease. Pediatr Clin North Am. 2000;47:699–710.
52. Shapiro BS, Benjamin LJ, Payne R, Heidrich G. Sickle cell-related pain: perceptions of medical practitioners. J Pain Symptom Manage. 1997;14(3):168–74.
53. Shapiro BS. The management of pain in sickle cell disease. Pediatr Clin North Am. 1989;36(4):1029–45.
54. Murray N, May A. Painful crises in sickle cell disease–patients' perspectives. BMJ. 1988;297(6646):452–4.
55. Bobo L, Miller ST, Smith WR, Elam JT, Rosmarin PC, Lancaster DJ. Health perceptions and medical care opinions of inner-city adults with sickle cell disease or asthma compared with those of their siblings. South Med J. 1989;82(1):9–12.
56. Elander J, Lusher J, Bevan D, Telfer P, Burton B. Understanding the causes of problematic pain management in sickle cell disease: evidence that pseudoaddiction plays a more important role than genuine analgesic dependence. J Pain Symptom Manage. 2004;27(2):156–69.
57. Chen I, Kurz J, Pasanen M, Faselis C, Panda M, Staton LJ, et al. Racial differences in opioid use for chronic nonmalignant pain. J Gen Intern Med. 2005;20(7):593–8.
58. SAMHSA. Overview of findings from the 2003 National survey on drug use and health. Office of Applied Studies, NSDUH Series H-24, DHHS Publication No. SMA 04-3963. Rockville, MD: SAMHSA; 2004.
59. Beyer JE. Judging the effectiveness of analgesia for children and adolescents during vaso-occlusive events of sickle cell disease. J Pain Symptom Manage. 2000;19:63–72.
60. Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352(21):2211–21. Review.
61. Shord SS, Cavallari LH, Gao W, Jeong HY, Deyo K, Patel SR, et al. The pharmacokinetics of codeine and its metabolites in Blacks with sickle cell disease. Eur J Clin Pharmacol. 2009;65(7):651–8.
62. Nath KA, Katusic ZS, Gladwin MT. The perfusion paradox and vascular instability in sickle cell disease. Microcirculation. 2004;11:179–93.
63. Gremse DA, Fillingim E, Hoff CJ, Wells DJ, Boerth RC. Hepatic function as assessed by lidocaine metabolism in sickle cell disease. J Pediatr. 1998;132:989–93.
64. Covitz W, Espeland M, Gallagher D, Hellenbrand W, Leff S, Talner N. The heart in sickle cell anemia. The Cooperative Study of Sickle Cell Disease (CSSCD). Chest. 1995;108:1214–9.
65. de Santis Feltran L, de Abreu Carvalhaes JT, Sesso R. Renal complications of sickle cell disease: managing for optimal outcomes. Paediatr Drugs. 2002;4:29–36.
66. Darbari DS, Neely M, van den Anker J, Rana S. Increased clearance of morphine in sickle cell disease: implications for pain management. J Pain. 2011;12(5):531–8. doi: 10.1016/j.jpain.2010.10.012.
67. Dampier CD, Setty BN, Logan J, Ioli JG, Dean R. Intravenous morphine pharmacokinetics in pediatric patients with sickle cell disease. J Pediatr. 1995;126:461–7.
68. Darbari DS, Minniti CP, Rana S, van den Anker J. Pharmacogenetics of morphine: potential implications in sickle cell disease. Am J Hematol. 2008;83(3):233–6.
69. Darbari DS, van Schaik RH, Capparelli EV, Rana S, McCarter R, van den Anker J. UGT2B7 promoter variant -840G>A contributes to the variability in hepatic clearance of morphine in patients with sickle cell disease. Am J Hematol. 2008;83(3):200–2.

70. Yang YM, Hoff C, Hamm C, Mankad V, Boerth RC, Friedrich L. Pharmacokinetics of meperidine in sickle cell patients. Am J Hematol. 1995;49(4):357–8.
71. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639–44.
72. Guasch A, Navarrete J, Nass K, Zavas CF. Glomerular involvement in adults with sickle cell hemoglobinopathies: prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol. 2006;17(8):2228–35.
73. Ahn H, Li CS, Wang W. Sickle cell hepatopathy: clinical presentation, treatment, and outcome in pediatric and adult patients. Pediatr Blood Cancer. 2005;45(2):184–90. Review.
74. Berry PA, Cross TJ, Thein SL, Portmann BC, Wendon JA, Karani JB, et al. Hepatic dysfunction in sickle cell disease: a new system of classification based on global assessment. Clin Gastroenterol Hepatol. 2007;5(12):1469–76; quiz 1369.
75. Guasch A, Cua M, You W, Mitch WE. Sickle cell anemia causes a distinct pattern of glomerular dysfunction. Kidney Int. 1997;51(30):826–33.
76. Maigne G, Ferlicot S, Galacteros F, Belnfant X, Ulinski T, Niaudet P, et al. Glomerular lesions in patients with sickle cell disease. Medicine. 2010;89:18–27.
77. Finkelstein Y, Schechter T, Garcia-Bournissen F, Kirby M, Nurmohamed L, Juurlink DN, et al. Is morphine exposure associated with acute chest syndrome in children with vaso-occlusive crisis of sickle cell disease? A 6-year case-crossover study. Clin Ther. 2007;29(12):2738–43.
78. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. JAMA. 2012;307(12):1254–6.
79. Ahmed S, Siddiqui AK, Sadiq A, Shahid RK, Patel DV, Russo LA. Echocardiographic abnormalities in sickle cell disease. Am J Hematol. 2004;76(3):195–8.
80. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol. 2007;49(4):472–9.
81. Johnson MC, Kirkham FJ, Redline S, Rosen CL, Yan Y, Roberts I, et al. Left ventricular hypertrophy and diastolic dysfunction in children with sickle cell disease are related to asleep and waking oxygen desaturation. Blood. 2010;116:16–21.
82. Zehtabchi S, Sinert R, Rinnert S, Chang B, Heinis C, Altura RA, et al. Serum ionized magnesium levels and ionized calcium-to-magnesium ratios in adult patients with sickle cell anemia. Am J Hematol. 2004;77(3):215–22.
83. Foster DJ, Somogyi AA, Bochner F. Methadone N-demethylation in human liver microsomes: lack of stereoselectivity and involvement of CYP3A4. Br J Clin Pharmacol. 1999;47(4):403–12.
84. Totah RA, Allen KE, Sheffels P, Whittington D, Kharasch ED. Enantiomeric metabolic interactions and stereoselective human methadone metabolism. J Pharmacol Exp Ther. 2007;321(1):389–99.
85. Wang JS, DeVane CL. Involvement of CYP3A4, CYP2C8, and CYP2D6 in the metabolism of (R)- and (S)-methadone in vitro. Drug Metab Dispos. 2003;31(6):742–7.
86. Li Y, Kantelip JP, Gerritsen-van Schieveen P, Davani S. Interindividual variability of methadone response: impact of genetic polymorphism. Mol Diagn Ther. 2008;12(2):109–24.
87. Crettol S, Déglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. Clin Pharmacol Ther. 2006;80(6):668–81.
88. Smith HS. Opioid metabolism. Mayo Clin Proc. 2009;84(7):613–24. Review.
89. Relling MV, Cherrie J, Schell MJ, Petros WP, Meyer WH, Evans WE. Lower prevalence of the debrisoquin oxidative poor metabolizer phenotype in American black versus white subjects. Clin Pharmacol Ther. 1991;50(3):308–13.
90. Bathum L, Skjelbo E, Mutabingwa TK, Madsen H, Hørder M, Brøsen K. Phenotypes and genotypes for CYP2D6 and CYP2C19 in a black Tanzanian population. Br J Clin Pharmacol. 1999;48(3):395–401.
91. Masimirembwa C, Persson I, Bertilsson L, Hasler J, Ingelman-Sundberg M. A novel mutant variant of the CYP2D6 gene (CYP2D6*17) common in a black African population: association with diminished debrisoquine hydroxylase activity. Br J Clin Pharmacol. 1996;42(6):713–9.

92. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. Clin Pharmacol Ther. 1981;30(3):353–62.
93. Furlan V, Hafi A, Dessalles MC, Bouchez J, Charpentier B, Taburet AM. Methadone is poorly removed by haemodialysis. Nephrol Dial Transplant. 1999;14(1):254–5.
94. Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage. 2004;28(5):497–504. Review.
95. Murtagh FE, Chai MO, Donohoe P, Edmonds PM, Higginson IJ. The use of opioid analgesia in end-stage renal disease patients managed without dialysis: recommendations for practice. J Pain Palliat Care Pharmacother. 2007;21(2):5–16. Review.
96. Kreek MJ, Schecter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. Drug Alcohol Depend. 1980;5(3):197–205.
97. Gorman AL, Elliott KJ, Inturrisi CE. The d- and l-isomers of methadone bind to the noncompetitive site on the N-methyl-D-aspartate (NMDA) receptor in rat forebrain and spinal cord. Neurosci Lett. 1997;223(1):5–8. PubMed PMID: 9058409.
98. Mizoguchi H, Watanabe C, Yonezawa A, Sakurada S. New therapy for neuropathic pain. Int Rev Neurobiol. 2009;85:249–60. Review. PubMed PMID: 19607975.
99. Davis MP. What is new in neuropathic pain? Support Care Cancer. 2007;15(4):363–72. Epub 2006 Nov 28. Review. PubMed PMID: 17131133.
100. Gagnon B, Bruera E. Differences in the ratios of morphine to methadone in patients with neuropathic pain versus non-neuropathic pain. J Pain Symptom Manage. 1999;18(2):120–5. PubMed PMID: 10484859.
101. Namaka M, Gramlich CR, Ruhlen D, Melanson M, Sutton I, Major J. A treatment algorithm for neuropathic pain. Clin Ther. 2004;26(7):951–79. Review. Erratum in: Clin Ther. 2004;26(12):2163. PubMed PMID: 15336464.
102. MacPherson RD. The pharmacological basis of contemporary pain management. Pharmacol Ther. 2000;88:163–85.
103. Moulin DE, Palma D, Watling C, Schulz V. Methadone in the management of intractable neuropathic noncancer pain. Can J Neurol Sci. 2005;32(3):340–3. PubMed PMID: 16225176.
104. Gagnon B, Almahrezi A, Schreier G. Methadone in the treatment of neuropathic pain. Pain Res Manag. 2003;8(3):149–54. PubMed PMID: 14657982.
105. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. Pain. 1997;70:109–15.
106. Peng PW, Tumber PS, Gourlay D. Review article: perioperative pain management of patients on methadone therapy. Can J Anaesth. 2005;52(5):513–23. Review.
107. Parsons HA, de la Cruz M, El Osta B, Li Z, Calderon B, Palmer JL, et al. Methadone initiation and rotation in the outpatient setting for patients with cancer pain. Cancer. 2010;116(2):520–8.
108. Porter BP, Coyne PJ, Smith WR. Methadone-related torsades de pointes in a sickle cell patient treated for chronic pain. Am J Hematol. 2005;78(4):316–7.
109. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. Ann Intern Med. 2009;150(6):387–95.
110. Nicholson AB. Methadone for cancer pain. Cochrane Database Syst Rev. 2004;(2):CD003971.
111. Smith WR, Jordan LB, Hassell KL. Frequently asked questions by hospitalists managing pain in adults with sickle cell disease. J Hosp Med. 2011;6(5):297–303. doi:10.1002/jhm.933.
112. Moskowitz MH. Pharmacotherapy of neuropathic low back pain. Curr Pain Headache Rep. 2003;7(3):178–87. Review.
113. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127–34.

Chapter 19
Methadone and Buprenorphine Analgesia in Older Patients

David Lussier

Persistent pain is a common problem in older adults, with prevalence reported in epidemiological studies varying between 20 and 80 %, both in community-dwelling and institutionalized older adults [1]. Persistent pain diminishes the quality of life of older adults in many ways, due to its impact on functional autonomy, mood, sleep, and social interactions.

Unfortunately, both persistent and acute pain remain largely undertreated in older patients. Older patients receive opioid analgesics less frequently than younger ones, with resulting lower pain relief [2, 3]. Although opioids are clearly not without risk and toxicity in older patients, opiophobia partly explains the underutilization of opioids in this population [3]. After reviewing the scientific evidence of their effectiveness and safety, several organizations and authors support their use in appropriate conditions and dosing [4–8].

Age-Related Pharmacological Changes

Before reviewing the pharmacological properties of buprenorphine and methadone in older patients, it is useful to briefly review the age-related pharmacological changes. Table 19.1 provides a summary of these changes, with clinical significance for methadone and buprenorphine.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2_19,

Table 19.1 Age-related pharmacokinetic changes and possible or reported impact on pharmacokinetics of methadone and transdermal buprenorphine

Age-related pharmacokinetics changes	Methadone	Transdermal buprenorphine
Decreased gastrointestinal motility		Possible delayed absorption and onset of action
Skin modifications		Possible increased interindividual variability of absorption
Increased body fat	• Increased volume distribution • Decreased plasma concentrations • Increased half-life?	• Increased volume distribution • Decreased plasma concentrations • Increased half-life?
Decreased serum albumin		Possible increased free fraction
Decreased renal function	None	None

Pharmacokinetic Changes

Absorption

Although aging is associated with decreased gastric secretion and higher gastric pH, decreased splanchnic flow, decreased number of active transporters and decreased absorption surface, these changes do not seem to have any significant impact on absorption of oral medications [9]. Slower gastric emptying and gastrointestinal transit, combined with frequent occurrence of chronic constipation and decreased gastrointestinal motility, can however delay the absorption of oral medications, thereby delaying the achievement of therapeutic plasmatic levels and analgesic efficacy [10–13].

Several age-related modifications of the skin have been reported, including decreased hydration of the corneal layer, reduced skin thickness and elasticity, and decreased subcutaneous fat tissue. While these changes might modify the absorption of hydrophilic drugs, the impact on absorption of lipophilic drugs such as buprenorphine is minimal [9]. Transdermal absorption nevertheless presents important interindividual variability and less predictable absorption in older patients [9].

Distribution

Plasma concentrations and half-lives of medications are significantly modified by age-related changes in body composition. The lean mass and total body water volume are decreased, while the fat mass is increased [9, 14]. As a result, the

volume of distribution of lipophilic drugs such as methadone and buprenorphine is increased, which decreases the plasma concentrations and prolongs the half-life, favoring drug accumulation.

Decreased plasma albumin is often encountered in older patients, especially when they are medically sick, suffer from cancer or are malnourished [15]. This results in increased free fraction of the medication, which is however clinically significant only in medications that are more than 90 % protein-bound, have a small volume of distribution and a narrow therapeutic index [16]. An increased level of α_1-glycoprotein is also frequent but this does not seem to have clinical consequences [9].

Metabolism

Due to decreased hepatic mass and blood flow, drug clearance of flow-limited (high-clearance) drugs is reduced, while the data on capacity-limited (low-clearance) drugs are conflicting [17]. The activity of phase 1 enzymatic reactions (oxidation, reduction, hydrolysis) is reduced, whereas phase II reactions (glucuronidation, acetylation, sulfation) seems to be preserved [14, 18]. The age-related changes of cytochrome activity remain largely unknown, but it probably does not undergo any significant deterioration [11].

Renal Excretion

The age-related modification with the most clinical significance is decreased renal function that results from decreased kidney mass and tubular secretion, with a 30–50 % decreased glomerular filtration at 80 years old [19]. This favors accumulation of renally excreted drugs, which should therefore be avoided or prescribed in lower doses or longer dosing intervals in older patients.

Pharmacodynamic Changes

Increased risk of ventilatory depression and lower postoperative opioid requirements in older patients suggest that they are more sensitive to opioids [20–23], which has been confirmed by pharmacokinetic–pharmacodynamic studies of fentanyl and congeners in perioperative analgesia [24, 25]. Using pharmacokinetic–pharmacodynamic models, some have suggested that initial doses should be lowered in older patients, while keeping the same dosing interval [26]. This is also recommended by treatment guidelines, based on clinical experience confirming that older patients often respond or experience adverse effects with lower doses of opioids than younger patients [4].

Analgesic Efficacy and Adverse Effects of Opioids in Older Patients

There are very few studies addressing specifically the analgesic efficacy of opioids in older patients. Furthermore, older subjects are often underrepresented in clinical trials and, because of strict exclusion criteria, the ones who are included are not representative of the frail older patients with several comorbidities often seen in clinical practice. According to clinical trials studying the efficacy of transdermal fentanyl [27] and sublingual [28] or transdermal buprenorphine [29] in persistent pain, and of morphine in postoperative pain [20], older patients obtain as good pain relief as younger ones. Because of pharmacokinetics and pharmacodynamics alterations, they often respond to lower doses of opioids or respond better to a similar dose [20, 29].

Even though opioids can be used safely in older patients if initiated at low doses and titrated up progressively, they are clearly not without toxicity and risks. While the most common adverse effects are similar to those occurring in younger patients, clinical experience suggests that they are more frequent. Because of their frailty, older patients are also at higher risk of serious adverse effects. Risk of ventilatory depression is significantly higher in older patients when prescribed opioids in postoperative setting [21–23]. Opioids have also been linked to a higher risk of injury and fracture [30–35], which has been reported to be as much as five times higher compared to nonsteroidal anti-inflammatory users [34]. The risk of fracture might be higher with codeine preparations [36] and lower with tramadol [36]. While a propensity-cohort retrospective study has reported increased hospitalization and mortality compared to NSAIDs [34], especially for codeine and oxycodone [36], these results have been questioned [37]. To our knowledge, no such study has included buprenorphine or methadone in the analyses.

Guidelines on Utilization of Opioids in Older Patients

Following an extensive review of available evidence, the American Geriatrics Society has issued guidelines on the use of opioids in older patients, stating that “All patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy” [4]. More specifically, “Patients with frequent or continuous pain on a daily basis may be treated with around-the-clock time-contingent dosing aimed at achieving steady-state opioid therapy” [4]. The need for frequent monitoring of analgesic efficacy and adverse effects of prescribed opioids is emphasized.

In order to reduce risk of overdose when prescribing opioids to older patients, recently published Canadian guidelines emphasize the importance of monitoring adverse effects (mostly sedation) and renal function, to favor hydromorphone and oxycodone over morphine, to use initial doses at least 50 % lower than in younger adults, and not to concomitantly prescribe benzodiazepines [8].

Methadone

There are unfortunately no data on the pharmacokinetics and pharmacodynamics properties of methadone in older patients, and only a few case series of successful prescription have been published. For this reason, we have to base our analysis on known pharmacological properties of methadone and age-related pharmacological changes.

Methadone is a highly lipophilic drug with a resulting large volume of distribution [38]. Since the fat volume is increased in older patients, the volume of distribution of lipophilic drugs such as methadone is even larger than in younger patients, which prolongs its half-life. While its long half-life might sometimes represent an advantage because it provides a stable plasmatic level for a longer duration, it also increases the risk of adverse effects due to drug accumulation. The wide interindividual variability of its half-life, as well as the induction of its own metabolism with chronic use, is a significant problem in older patients because it makes the dose adjustment difficult. A linear equianalgesic dose ratio also complicates opioid rotation [7]. αμ

Because of its lipophilicity, methadone crosses the blood–brain barrier more rapidly and easily than less lipophilic opioids. Although it has not been demonstrated, this could increase the frequency of cognitive adverse effects and sedation in older patients.

Methadone is 90 % protein bound, mostly to α_1-acid glycoprotein, which is increased in inflammatory states and might then reduce free methadone. Although increased α_1-acid glycoprotein levels are also associated with aging, it is not thought to have any significant pharmacological impact. The high protein binding of methadone should therefore not have any clinical implications for older patients.

Methadone is mainly metabolized by the liver. Its pharmacokinetics appears to be impaired only in the presence of severe liver impairment, resulting in increased volume of distribution, decreased protein binding and increased plasma concentrations [39, 40]. The mildly decreased hepatic function observed in some older adults, due to decreased hepatic blood flow and number of hepatocytes, should therefore not modify the pharmacokinetics of methadone. Although there are no data on older patients with liver disease, dose adjustment seems to be necessary only in those with significant liver disease [5, 41].

Older patients often present with chronic renal failure, at least of mild to moderate severity. The predominant liver metabolism of methadone therefore represents an advantage for use in older patients, since pharmacokinetics is not significantly modified in renal failure, without accumulation of the parent drug or metabolites [38]. Because the half-life and pharmacokinetics are highly variable, some authors however nevertheless recommend decreasing doses in older patients with renal impairment [5, 42].

Older patients often receive several concomitant medications, which increases the risk of drug–drug interactions. For this reason, it is preferable to use medications not metabolized by the cytochrome P450 system, such as hydromorphone, buprenorphine, or tapentadol, which are mainly metabolized by hepatic glucuronidation.

Methadone is mostly metabolized by N-demethylation to an inactive metabolite, via the CYP3A4 isozyme. Consequently, other medications metabolized by this isozyme can interact with the metabolism of methadone.

Concerns have been raised on possible cardiac toxicity of methadone due to QTc interval prolongation and resulting torsades de pointe [43]. Although older age has not been identified as a risk factor for methadone-induced QTc interval prolongation, most studies were done in patients treated in methadone maintenance programs for opioid addiction, and few older patients were included in the analyses. A history of structural heart or arrhythmia is however recognized as a risk factor [43], as well as concomitant treatment with other medications prolonging the QTc interval [43]. Since these two conditions are frequent in older patients, caution should be exerted when prescribing methadone to an older patient, with an electrocardiogram performed at baseline, after a 30-day treatment period and, thereafter, annually or when doses are increased [43].

There are no clinical trials of methadone for the management of chronic pain in older patients. In a case series of six older patients successfully treated with methadone, the prescribing of low dose methadone is recommended as first-line therapy for older patients because of its long duration [44]. This suggestion has however been questioned and criticized [45].

Mainly because of its long and highly variable half-life, most authors and organizations recommend exerting caution when prescribing methadone to older patients, and only using it when other better studied and safer long-acting opioids have been tried unsuccessfully [4, 6, 7, 13]. According to the American Geriatrics Society guidelines on the pharmacological management of persistent pain in older persons, “only clinicians well versed in its use should initiate it and titrate it cautiously” [4]. A brief review of available evidence also concludes that, although there are some advantages to the use of methadone, the lack of pharmacological data and the availability of several better studied long-acting analgesics (e.g., morphine, oxycodone, fentanyl) support the use of methadone as a second- or third-line opioid in older patients [45]. Specific indications however justify its use as first-line, such as true allergy to phenanthrene derivatives and concomitant treatment with CYP2D6 hepatic enzyme inhibitors that could diminish the clearance of several other opioids (e.g., codeine, tramadol, oxycodone) [45]. Table 19.2 summarizes the most important advantages and disadvantages of the use of methadone in older patients.

Buprenorphine

The pharmacokinetics and pharmacodynamics of buprenorphine are better known than those of methadone, and studies provide some specific data on pharmacological profile and efficacy/adverse effects in older subjects. Since the parenteral and sublingual formulations are not widely available and rarely used, we limit this review to the transdermal formulation.

Table 19.2 Advantages and disadvantages of methadone in older patients

Advantages	Disadvantages
No accumulation in renal failure	Highly lipophilic, with large volume of distribution and increased half-life
Long duration of action	Long, variable, and unpredictable half-life
Cheap	Linear equianalgesic dose ratio makes opioid rotation difficult
N-methyl-D-aspartate antagonist activity can block central sensitization and decrease opioid tolerance	Risk of QT interval prolongation and torsades de pointe
No cross-allergy with morphine, codeine, oxycodone, tramadol	Drug–drug interactions with other medications metabolized by CYP3A4
	Very limited data on pharmacological profile and tolerability in older patients

As previously noted, aging is have associated with several modifications of the skin, which however do not seem to have any clinical impact in older patients with normal weight. The transdermal absorption of buprenorphine however appears to be decreased in older patients with low body fat, in whom it has been reported to be 20 % lower compared to those with normal or high body fat [46]. Transdermal buprenorphine is therefore likely not the opioid of choice in older cachectic patients.

In order to be absorbed properly, the transdermal patch should be applied to a site with appropriate subcutaneous fat, as confirmed by a small study in older subjects, in which exposure to the drug after application to the patella was only 29 % compared to application on the upper back [46]. Other sites not providing adequate absorption were the abdomen and the thigh [46].

As methadone, buprenorphine is highly lipophilic and has a large volume of distribution, which is increased in older patients due to age-related increases in fat volume [47]. Its lipophilicity also favors blood–brain barrier crossing, with concentrations in the cerebral spinal fluid reported as 15–25 % of the plasma drug concentrations [48]. Buprenorphine is highly (96 %) protein bound [48]. Its free portion could therefore be increased in older patients with decreased plasma proteins due to acute or severe medical disease, undernutrition, or cancer.

The metabolism of buprenorphine is almost entirely hepatic, with metabolites eliminated via biliary and renal excretion. Hepatic metabolism is mediated via cytochrome P450 3A4 isoenzymes, with its active metabolite norbuprenorphine metabolized by glucuronidation [48]. Interactions with other medications metabolized by CYP450 3A4 is therefore possible but do not occur with all inhibitors of CYP450 3A4 [47]. Elimination of the active metabolite should not be modified, since glucuronidation is nonsaturable.

Elimination of buprenorphine and its metabolites is not modified in the presence of chronic renal failure, even in patients undergoing hemodialysis [49], without relationship between estimated creatinine clearance and steady-state plasma concentrations [48]. Given the age-related changes deterioration of renal function and the frequent occurrence of chronic renal failure, this lack of accumulation in the presence of impaired renal function is a significant advantage for use in older patients.

A few pharmacokinetics studies provide specific data on the buprenorphine properties in older patients. In a single dose study of buprenorphine 10 μg/h, pharmacokinetics in older (70 years and older) and younger subjects were similar, with similar rate of elimination after patch removal, but a trend toward higher plasma concentrations immediately after removal [48]. These observations were confirmed by a fixed dose-escalation study of transdermal buprenorphine 5, 10, and 20 μg/h, in which mean and maximum plasma concentrations, as well as drug exposure, were similar in healthy younger and older, as well as hypertensive older subjects [48]. Frequency of adverse effects in older subjects was similar or less than in younger ones, except for a more frequent occurrence of constipation and urinary retention [48].

Another advantage of buprenorphine in older patients is its ceiling effect for respiratory depression but not for analgesia [50], which reduces the risk of respiratory arrest from overdose in frail older patients, especially those living alone.

While some opioids such as morphine and fentanyl possess immunosuppressive properties that can favor infections and cancer progression or metastasis, buprenorphine does not seem to exert any effect on the immune system [51]. This is another advantage in frail older patients who are more prone to infections due to age-related impairment of the immune system [52].

Sedation and cognitive impairment are among the most common and feared adverse effects of opioids in older patients. While there are no specific data in older subjects, a clinical trial did not show any significant difference between subjects treated with a stable dose of transdermal buprenorphine and matched controls, on a series of cognitive tests (reaction time, attention, visual orientation) done to assess driving ability [53]. Data on more complex cognitive functions and older patients are however lacking.

Scientific evidence is accumulating rapidly on the important role of descending inhibitory pain pathways, also called conditioning pain modulation (CPM), in the prevention and control of chronic pain. Impaired CPM has been shown in several diseases, including osteoarthritis [54], and has also been observed in healthy older adults [55]. Buprenorphine and fentanyl are currently the only two drugs for which there is human evidence of potentiation of the descending pain inhibition [56], which might offer an advantage for the management of chronic pain in older adults.

The availability of low-dose transdermal patches of buprenorphine, which are equianalgesic to very low doses of morphine, is a significant advantage in older patients who often do not tolerate higher doses of opioids. Such low doses (e.g., 5 μg/h) can even be used in opioid naïve older patients [52].

Since several clinical trials have been performed in patients suffering from osteoarthritis and that this disease is mostly common in older patients, a significant number of older subjects have been included in clinical trials. This allows assessment of the analgesic efficacy and tolerability of buprenorphine in older patients. According to the US monograph of the low-dose buprenorphine transdermal formulation (BuTrans), it was administered to 1,377 and 457 patients aged 65 and 75 years and older, respectively [48]. Adverse effects, including those at the application site, were slightly higher in older subjects.

Table 19.3 Advantages and disadvantages of buprenorphine in older patients

Advantages	Disadvantages
No accumulation in renal failure	Lipophilic, with large volume of distribution and increased half-life
Low-dose transdermal formulation can be prescribed safely to opioid naïve older patients	Highly protein bound, free portion could be increased in undernourished patients
Ceiling effect for respiratory depression	
No immunosuppressive effects	
Possible potentiation of descending pain inhibition	
Metabolism via hepatic glucuronidation decreases drug–drug interactions	
Data on efficacy and tolerability from clinical trials	

In a post-marketing surveillance study of 13,179 patients treated with transdermal buprenorphine 35–70 μg/h, patients older than 70 years responded as well as younger ones with effective, dose-dependent, and sustained pain relief over the 9-month observation period [57]. The occurrence of adverse effects was not related to age either, with an approximate 10 % frequency [57].

It is very uncommon that a clinical trial is designed to specifically assess age-related differences in efficacy and tolerability of a medication. Fortunately, such a study has been done for buprenorphine, in a prospective, three-age group (50, 51–64, ≥65 years old), open clinical trial [29]. Interestingly, and consistent with experimental studies suggesting increased opioid sensitivity, pain relief was mildly but significantly better in older compared to younger- and middle-aged patients. Both older groups used less rescue doses of sublingual buprenorphine than younger patients. Improvement of sleep duration was also better in older patients. Surprisingly, adverse effects did not occur more frequently in older patients. Although differences were not statistically significant, older patients even experienced less dizziness, nausea, pruritus, malaise, and fatigue than the younger age groups, but more frequent constipation and hyperhidrosis. The middle-age group tended to experience less adverse effects than the younger and older patients. Although the results of this study are encouraging and such studies should be encouraged, it is unclear to what extent it can be generalized to clinical practice, because the exclusion criteria and the age range of the oldest group are not specified, and older patients with comorbidities, most frequently encountered in clinical practice, are often excluded from clinical trials. The surprising better tolerability in older patients supports the possibility of such a selection bias.

In summary, transdermal buprenorphine offers several advantages in older patients, including lower risk of respiratory depression, no immunosuppressive effects, no dose adjustment necessary in renal impairment, low opioid equianalgesic doses available, and data on similar efficacy and tolerability in older compared to younger patients (Table 19.3). Because of these various advantages over other opioid analgesics, buprenorphine has been recommended as the opioid of choice for older patients by an expert panel [52].

References

1. Gibson SJ, Lussier D. Prevalence and relevance of pain in older persons. Pain Med. 2012;13 (Suppl 2):S23–6.
2. Hwang U, Richardson LD, Sonuyi TO, Morrison RS. The effect of emergency department crowding on the management of pain in older adults with hip fracture. J Am Geriatr Soc. 2006;54:270–5.
3. Auret K, Schug SA. Underutilisation of opioids in elderly patients with chronic pain: approaches to correcting the problem. Drugs Aging. 2005;22:641–54.
4. AGS Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57:1331–46.
5. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8:287–313.
6. Gloth FM. Pain management in older adults: prevention and treatment. J Am Geriatr Soc. 2001;49:188–99.
7. Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. Drugs Aging. 2003;20:23–57.
8. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 2: special populations. Can Fam Physician. 2011;57:1269–76.
9. Hammerlein A, Derendorf H, Lowenthal DT. Pharmacokinetic and pharmacodynamic changes in the elderly: clinical implications. Clin Pharmacokinet. 1998;35:49–64.
10. Shi S, Mörike K, Klotz U. The clinical implications of ageing for rational drug therapy. Eur J Clin Pharmacol. 2008;64:183–99.
11. Tumer N, Scarpace PJ, Lowenthal DT. Geriatric pharmacology: basic and clinical considerations. Annu Rev Pharmacol Toxicol. 1992;32:271–302.
12. Montamat SC, Cusack BJ, Vestal RE. Management of drug therapy in the elderly. N Engl J Med. 1989;321:303–9.
13. Lussier D, Pickering G. Pharmacological considerations in older patients. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH, editors. Pharmacology of pain. Seattle: IASP Press; 2010. p. 547–65.
14. Kinirons MT, Crome P. Clinical pharmacokinetics considerations in the elderly: an update. Clin Pharmacokinet. 1997;33:302–12.
15. Paolisso G, Gambardella A, Balbi V, Ammendola S, D'Amore A, Varrichio M. Body composition, body fat distribution, and resting metabolic rate in healthy centenarians. Am J Clin Nutr. 1995;62:746–50.
16. Grandison MK, Boudinot FD. Age-related changes in protein binding of drugs: implications for therapy. Clin Pharmacokinet. 2000;38:271–90.
17. Butler JM, Begg EJ. Free drug metabolic clearance in elderly people. Clin Pharmacokinet. 2008;47:297–321.
18. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging. 2001;18:837–51.
19. Mallet L. Age-related changes in renal function and clinical implications for drug therapy. J Geriatr Drug Ther. 1991;5:5–29.
20. Kaiko RF. Age and morphine analgesia in cancer patients with postoperative pain. Clin Pharmacol Ther. 1980;28:823–6.
21. Cepeda MS, Farrar JT, Baumgaten M, Boston R, Carr DB, Strom BL. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther. 2003;74:102–12.

22. Aubrun F, Salvi N, Coriat P, Riou B. Sex- and age-related differences in morphine requirements for postoperative pain relief. Anesthesiology. 2005;103:156–60.
23. Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. Pain. 1996;64:357–64.
24. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentail. I. Model development. Anesthesiology. 1997; 86:10–23.
25. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamics evaluation. J Pharmacol Exp Ther. 1987;240:159–66.
26. Gupta DK, Avram MJ. Rational opioid dosing in the elderly: dose and dosing interval when initiating opioid therapy. Clin Pharmacol Ther. 2012;91:339–43.
27. Menten J, Desmedt M, Lossignol D, Mullie A. Longitudinal follow-up of TTS-fentanyl use in patients with cancer-related pain: results of a compassionate-use study with special focus on elderly patients. Curr Med Res Opin. 2002;18:488–98.
28. Nasar MA, McLeavy MA, Knox J. An open study of sub-lingual buprenorphine in the treatment of chronic pain in the elderly. Curr Med Res Opin. 1986;10:251–5.
29. Likar R, Vadlau EM, Breschan C, Kager I, Korak-Keiter M, Ziervogel G. Comparable analgesic efficacy of transdermal buprenorphine in patients over and under 65 years of age. Clin J Pain. 2008;24:536–43.
30. Buckeridge D, Huang A, Hanley J, et al. Risk of injury associated with opioid use in older adults. J Am Geriatr Soc. 2010;58:1664–70.
31. Ensrud KE, Blackwell T, Mangione CM, et al. Central nervous system active medications and risk for fractures in older women. Arch Intern Med. 2003;163:949–57.
32. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc. 1999;47:30–9.
33. Schorr RI, Griffin MR, Daugherty JR, et al. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. J Gerontol. 1992;47:M111–5.
34. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010;170:1968–78.
35. Takkouche B, Montes-Martinez A, Gill SS, et al. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf. 2007;30:171–84.
36. Solomon DH, Rassen JA, Glynn RJ, Garneau G, Levin R, Lee J, et al. The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med. 2010;170:1979–86.
37. Becker WC, O'Connor PG. The safety of opioid analgesics in the elderly: new data raise new concerns. Arch Intern Med. 2010;170:1986–8.
38. 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.
39. Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc. 2010;85:451–8.
40. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet. 1999;37:17–40.
41. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. Clin Pharmacol Ther. 1981;30:353–62.
42. Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet. 1996;31:410–22.
43. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. Ann Intern Med. 2009;150:387–95.
44. Gallagher R. Methadone: an effective, safe drug of first choice for pain management in frail older adults. Pain Med. 2009;10:319–26.
45. Hanlon JT, Weiner DK. Methadone for chronic pain in older adults: blast from the past but are we ready for it to return to prime time? Pain Med. 2009;10:287–8.

46. Schofield J, Smith KJ, Mundin G, et al. Pharmacokinetics of buprenorphine 5 micrograms/hour transdermal analgesic patch when applied at four application sites in healthy elderly subjects of varying body fat composition [abstract no. PH307]. Twelfth world congress on pain, Glasgow, 17–22 Aug 2008.
47. Plosker GL. Bupenorphine 5, 10 and 20 mcg/h transdermal patch: a review of its use in the management of chronic non-malignant pain. Drugs. 2011;71:2491–509.
48. Butrans (buprenorphine) transdermal system for transdermal administration: US prescribing information [online]. http://www.purduepharma.com/pi/prescription/butranspi.pdf. Accessed 20 Feb 2012.
49. Filitz J, Griessinger N, Sittl R, Likar R, Schüttler J, Koppert W. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006;10:743–8.
50. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. Palliat Med. 2006;20:S3–8.
51. Martucci C, Panerai AE, Sacerdote P. Chronic fentanyl or buprenorphine infusion in the mouse: similar analgesic profile but different effects on immune responses. Pain. 2004; 110:385–92.
52. Pergolizzi J, Aloisi AM, Dahan A, et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract. 2010;10:428–50.
53. Dagtekin P, Gerbershagen HJ, Wagner W, Petzke F, Radbruch L, Sabatowski R. Assessing cognitive and psychomotor performance under long-term treatment with transdermal buprenorphine in chronic non-cancer patients. Anesth Analg. 2007;105:1442–8.
54. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. Pain. 2010;149:573–81.
55. Washington LL, Gibson SJ, Helme RD. Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. Pain. 2000;89:89–96.
56. Arendt-Nielsen L, Andresen T, Malver LP, Oksche A, Mansikka H, Drewes A. A double-blind, placebo-controlled study on the effect of buprenorphine and fentanyl on descending pan modulation: a human experimental study. Clin J Pain. 2012;28:623–7.
57. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13 179 patients. Curr Med Res Opin. 2005;21:1147–56.

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R.A. Cruciani and H. Knotkova (eds.), *Handbook of Methadone Prescribing and Buprenorphine Therapy*, DOI 10.1007/978-1-4614-6974-2,