Opioid Pharmacology

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Background: Mu agonists have been an important component of pain treatment for thousands of years. The usual pharmacokinetic parameters (half-life, clearance, volume of distribution) of opioids have been known for some time. However, the metabolism has, until recently, been poorly understood, and there has been recent interest in the role of metabolites in modifying the pharmacodynamic response in patients, in both analgesia and adverse effects. A number of opioids are available for clinical use, including morphine, hydromorphone, levorphanol, oxycodone, and fentanyl. Advantages and disadvantages of various opioids in the management of chronic pain are discussed.

Objective: This review looks at the structure, chemistry, and metabolism of opioids in an effort to better understand the side effects, drug interactions, and the individual responses of patients receiving opioids for the treatment of intractable pain.

Conclusion: Mu receptor agonists and agonist-antagonists have been used throughout recent medical history for the control of pain and for the treatment of opiate induced side effects and even opiate withdrawal syndromes.

Key words: Opioid metabolism, opioid interactions, morphine, codeine, hydrocodone, oxycodone, hydromorphone, methadone, intractable pain, endorphins, enkephalins, dynorphins, narcotics, pharmacology, propoxyphene, fentanyl, oxymorphone, tramadol

Pain Physician 2008; 11:S133-S153

Opioids have been used for thousands of years for the treatment of pain. Ancient Egyptian papyrus records reported the use of opium for pain relief (1). In 1973, a graduate student, Candace Pert, used radioactive morphine to evaluate the location of the site of action of morphine, and found, surprisingly, that the drug attached to very specific areas of the brain, dubbed "morphine receptors"(2). Since mice would not have a "need" for a receptor for an alien alkaloid of the poppy plant, this finding triggered a search for the molecule that would endogenously stimulate that receptor, culminating in the discovery of "endogenous morphines" or "endorphins" by John Hughes and Hans Kosterlitz in 1975 (3). Since that time, a wide variety of these receptors and subtypes have been identified, to be discussed below. The majority of the clinically relevant opioids have their primary activity

at the initial "morphine receptor" or "mu receptors" and are therefore considered "mu agonists."

The usual pharmacokinetic parameters (half-life, clearance, volume of distribution) of opioids have been known for some time. However, the metabolism has, until recent, been poorly understood, and there has been a recently interest in the role of metabolites in modifying the pharmacodynamic response in patients, in both analgesia and adverse effects, which has begun to explain some previously puzzling clinical findings. This review looks at the structure, chemistry, and metabolism of opioids in an effort to better understand the side effects, drug interactions, and the individual responses of patients receiving opioids for the treatment of intractable pain.

Opioid Structure

Morphine (the archetypal opioid) consists of a benzene ring with a phenolic hydroxyl group at position 3 and an alcohol hydroxyl group at position 6 and at the nitrogen atom (Fig. 1). Both hydroxyl groups can be converted to ethers or esters. For example, codeine is morphine that is O-methylated at position 3, while heroin is morphine O-acetylated at position 3 and 6 (diacetyl morphine). The tertiary form of the nitrogen

appears to be crucial to the analgesia of morphine; making the nitrogen quaternary greatly decrease the analgesia, since it cannot pass into the central nervous system. Changes to the methyl group on the nitrogen will decrease analgesia as well, creating antagonists such as nalorphine. Morphine is optically active, and only the levorotatory isomer is an analgesic.

Opioid History

The opium poppy was cultivated as early as 3400 BC in Mesopotamia. The term opium refers to a mixture of alkaloids from the poppy seed. **Opiates** are naturally occurring alkaloids such as morphine or codeine. **Opioid** is the term used broadly to describe all compounds that work at the opioid receptors. The term *narcotic* (from the Greek word for stupor) originally was used to describe medications for sleep, then was used to describe opioids, but now is a legal term for drugs that are abused.

Opioid Receptors

There are opioid receptors within the CNS as well as throughout the peripheral tissues. These receptors are normally stimulated by endogenous peptides (endorphins, enkephalins, and dynorphins) produced in response to noxious stimulation. Greek letters name the opioid receptors based on their prototype agonists (Table 1).

Mu (µ) (agonist morphine) Mu receptors are found primarily in the brainstem and medial thalamus. Mu receptors are responsible for supraspinal analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility, and physical dependence. Subtypes include Mu1 and Mu2, with Mu1 related to analgesia, euphoria, and serenity, while Mu2 is related to respiratory depression, pruritus, prolactin release, dependence, anorexia, and sedation. These are also called OP3 or MOR (morphine opioid receptors).

Kappa (κ) (agonist ketocyclazocine) Kappa receptors are found in the limbic and other diencephalic areas, brain stem, and spinal cord, and are responsible for spinal analgesia, sedation, dyspnea, dependence, dysphoria, and respiratory depression. These are also known as OP2 or KOR (kappa opioid receptors).

Delta (δ) (agonist delta-alanine-delta-leucine-enkephalin) Delta receptors are located largely in the brain and their effects are not well studied. They may be responsible for psychomimetic and dys-
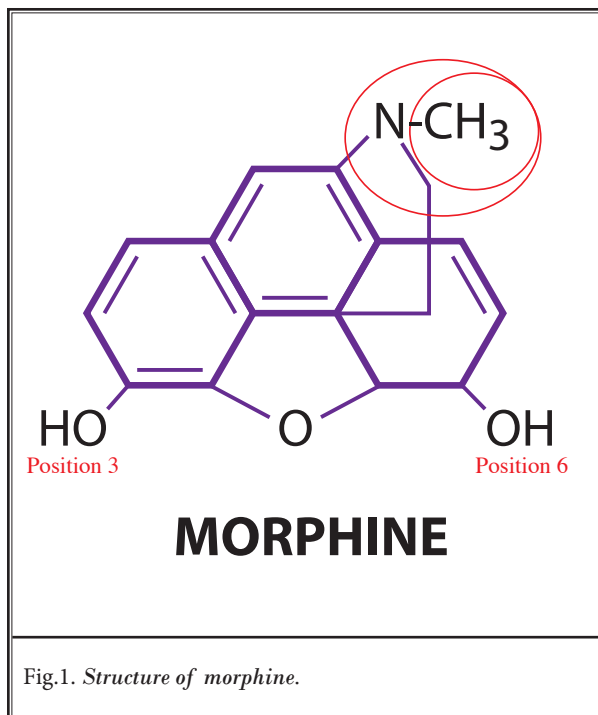

Fig.1. *Structure of morphine.*

Table 1. *Analgesic effects at opioid receptors*.

	Mu (μ)	Delta (δ)	Kappa (κ)
	• Mu 1 – Analgesia • Mu 2 – Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	• Analgesia, spinal analgesia	• Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea
Endogenous Peptides			
Enkephalins	Agonist	Agonist	
β-Endorphin	Agonist	Agonist	
Dynorphin A	Agonist		Agonist
Agonists			
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl	Agonist		
Meperidine	Agonist	Agonist	
Methadone	Agonist		
Antagonists			
Naloxone	Antagonist	Weak Antagonist	Antagonist
Naltrexone	Antagonist	Weak Antagonist	Antagonist

Modified from Miller's Anesthesia (4)

phoric effects. They are also called OP1 and DOR (delta opioid receptors).

Sigma (σ) (agonist N-allylnormetazocine) Sigma receptors are responsible for psychomimetic effects, dysphoria, and stress-induced depression. They are no longer considered opioid receptors, but rather the target sites for phencyclidine (PCP) and its analogs.

Different genes control each of the 3 major opioid receptors. Each receptor consists of an extracellular N-terminus, 7 transmembrane helical twists, 3 extracellular and intracellular loops, and an intracellular C-terminus (Fig. 2). Once the receptor is activated, it releases a portion of the G protein, which diffuses within the membrane until it reaches its target (either an enzyme or an ion channel). These targets alter protein phosphorylation via inhibition of cyclic AMP (cAMP) which acts as a second messenger within the cell resulting in the activation of protein kinases (short term effects) and gene transcription proteins and/or
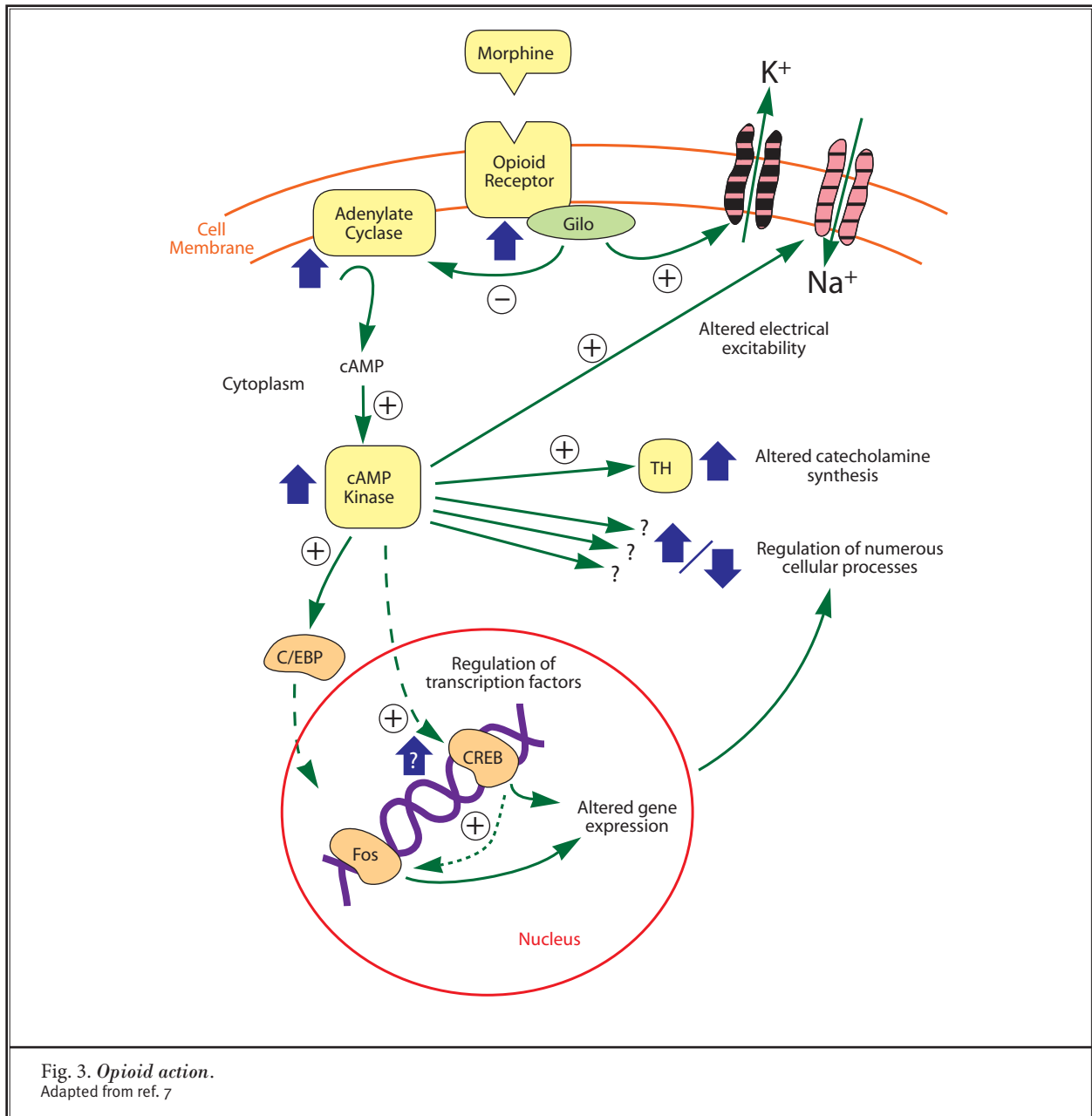

EL-Extracellular loop

TM - Transmembrane helix

IL - Intracellular loop

Fig. 2. *Opioid receptor structure*.
Adapted from ref. 6
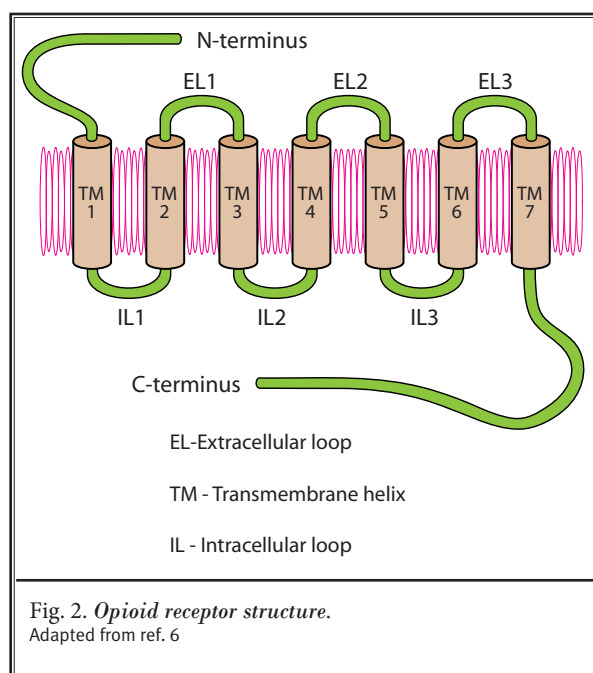
Fig. 3. *Opioid action*.
Adapted from ref. 7

gene transcription (long term effects) (Fig. 3). Opioid receptors located on the presynaptic terminals of the nociceptive C-fibers and A delta fibers, when activated by an opioid agonist, will indirectly inhibit these voltage-dependent calcium channels, decreasing cAMP levels and blocking the release of pain neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide from the nociceptive fibers, resulting in analgesia (5) (Fig. 4).

Opioids and endogenous opioids activate presynaptic receptors on GABA neurons, which inhibit the release of GABA in the ventral tegmental area (Fig. 5). The inhibition of GABA allows dopaminergic neurons to fire more vigorously, and the extra dopamine in the nucleus accumbens is intensely pleasurable. The varying effects of opioids may therefore be related to

varying degrees of affinity for the various receptors.

Opioids, to varying degrees, may antagonize N-methyl-D-aspartate (NMDA) receptors, activating the descending serotonin and noradrenaline pain pathways from the brain stem. Stimulation of these same NMDA receptors may result in neuropathic pain and the development of tolerance (9).
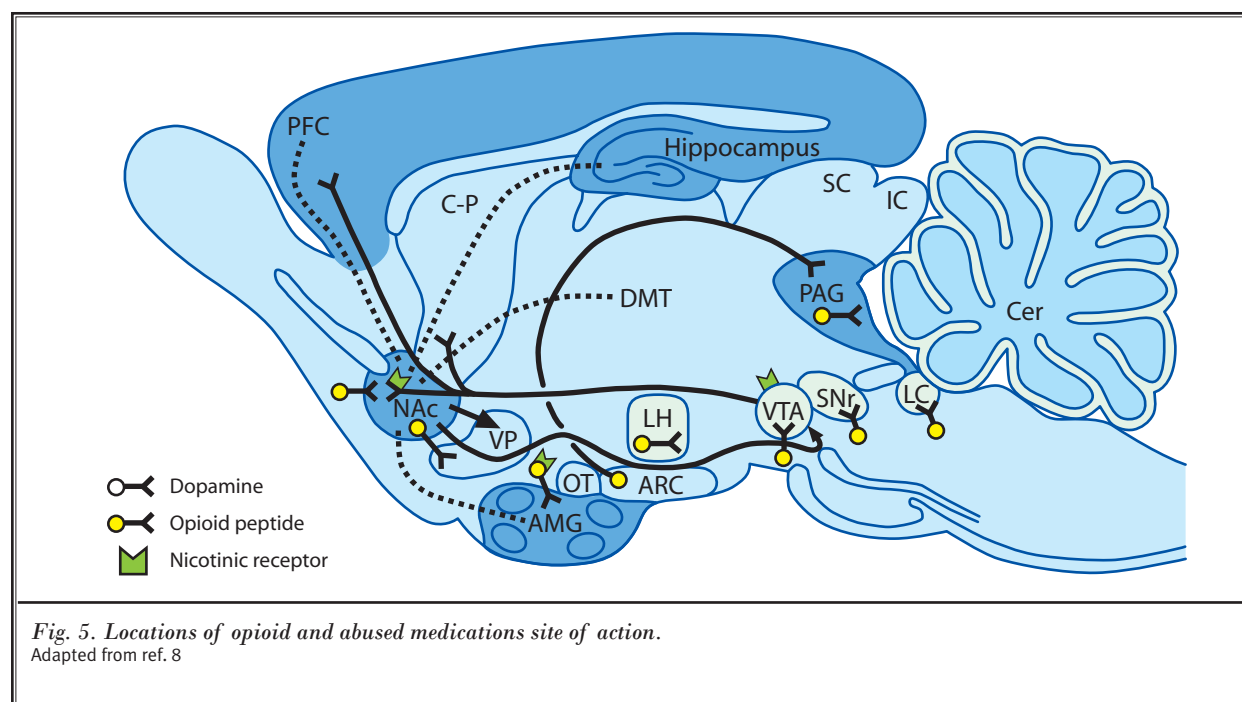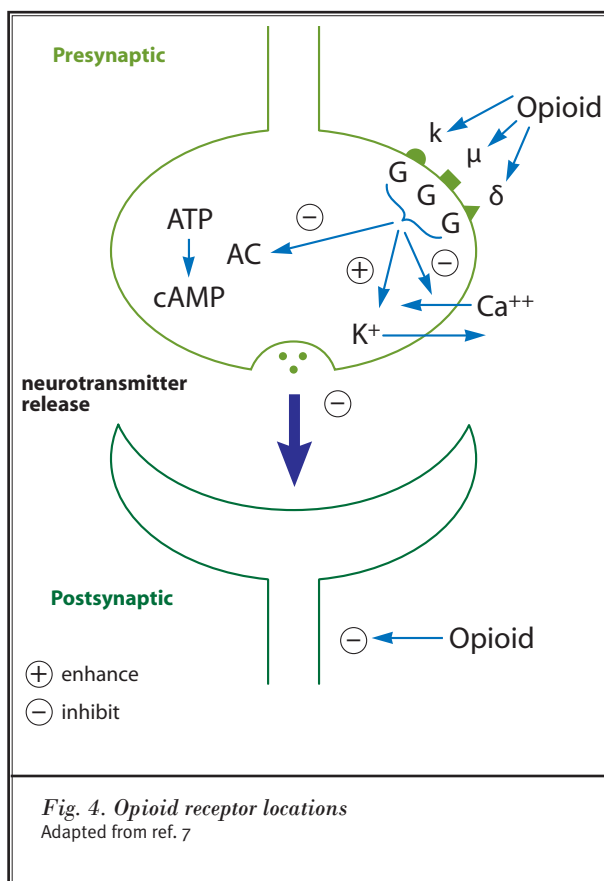
The location of endogenous opioids or endorphins in the CNS opioid receptors were discovered in 1973, and the first endogenous opioid (enkephalin) was discovered in 1975. Their location in the CNS allows them to function as neurotransmitters, and they may play a role in hormone secretion, thermoregulation, and cardiovascular control.

Enkephalins are derived from pro-enkephalin and are relatively selective δ ligands.

Endorphins are derived from pro-opiomelanocortin (also the precursor for ACTH and MSH) and bind to the μ receptor.

Dynorphins are derived from pro-dynorphins and are highly selective at the μ receptor.

Nociceptins (nociceptin/orphaninFQ [N/OFQ]) (orphanin), identified in 1995, may have potent hyperalgesic effects. They have little affinity for the μ, δ, or κ receptors, and their receptors are now being called ORL-1 ("opioid-receptor-like"). Nociceptin antagonists may be antidepressants and analgesics.

Fig. 4. Opioid receptor locations
Adapted from ref. 7

Fig. 5. Locations of opioid and abused medications site of action.
Adapted from ref. 8

Pure opioid agonists (e.g., morphine, hydromorphone, fentanyl) stimulate μ receptors and are the most potent analgesics. As the dose is increased, analgesia theoretically occurs in a log linear fashion; the degree of analgesia induced is limited only by intolerable dose-related adverse effects. In contrast, opioid agonists/antagonists and opioid partial agonists (buprenorphine, pentazocine, nalbuphine, butorphanol, nalorphine) exhibit a ceiling effect on the degree of analgesia that they can produce. Opiate agonist/antagonists and partial agonists can precipitate opioid withdrawal reactions. The respiratory depressant effects of partial agonists are not completely reversed with naloxone.

OPIOID CATEGORIES

The Drug Enforcement Agency (DEA) classifies opioids into schedules as illustrated in Table 2 and Table 3.

There are 4 chemical classes of opioids (Fig. 6):

Phenanthrenes are the prototypical opioids. The presence of a 6-hydroxyl may be associated with a higher incidence of nausea and hallucinations. For example, morphine and codeine (both with 6-hydroxyl groups) are associated with more nausea than hydromorphone and oxycodone (which do not have 6-hydroxyl groups). Opioids in this group include morphine, codeine, hydromorphone, levorphanol, oxycodone, hydrocodone, oxymorphone, buprenorphine, nalbuphine, and butorphanol.

Benzomorphans have only pentazocine as a member of this class. It is an agonist/antagonist with a high incidence of dysphoria.

Phenylpiperidines include fentanyl, alfentanil, sufentanil, and meperidine. Fentanyl has the highest affinity for the mu receptor.

Diphenylheptanes include propoxyphene and methadone.

Tramadol does not fit in the standard opioid classes. A unique analgesic, tramadol is an atypical opioid, a 4-phenyl-piperidine analogue of codeine, with partial mu agonist activity in addition to central GABA, catecholamine and serotonergic activities.

Opioids can further be classified by their actions: agonist, agonist/antagonist or partial agonist, or antagonist. Compounds can have intrinsic affinity and efficacy at receptors, with **affinity** being a measure of the "strength of interaction" between a compound binding to its receptor and **efficacy** being a measure of the strength of activity or effect from this binding at the receptor. An **agonist** has both affinity and efficacy; an **antagonist** has affinity but no efficacy; a **partial agonist** has affinity, but only partial efficacy. Regarding the opioids, the relevant receptors are the mu, kappa, and delta receptors. Compounds can have differing degrees of affinity and efficacy at these various receptors.

Opioid Agonists

Most of the most common opioids are agonists, and create their effect by stimulating the opioid receptors. Differences in activity and efficacy appear to be related to the relative stimulation of the various opioid receptors (mu, kappa, etc.) as well as genetic differences in opioid receptor sensitivity.

Opioid Partial Agonists

Buprenorphine is classified as a partial agonist. It has a high affinity, but low efficacy at the mu receptor where it yields a partial effect upon binding, yet possesses kappa receptor antagonist activity making it useful not only as an analgesic, but also in opioid abuse deterrence, detoxification, and maintenance therapies. Buprenorphine has a poor bioavailability with extensive first pass effect by the liver.

These agents can be used as analgesics, but have a ceiling to their analgesic effect, such that escalating

Table 2: *DEA schedules of controlled drugs*.

| Schedule	Criteria	Examples
I	No medical use; high addiction potential	Heroin, marijuana, PCP
II	Medical use; high addiction potential	Morphine, oxycodone, methadone, fentanyl, amphetamines
III	Medical use; moderate addiction potential	Hydrocodone, codeine, anabolic steroids
IV	Medical use; low abuse potential	Benzodiazepines, meprobamate, butorphanol, pentazocine, propoxyphene
V	Medical use; low abuse potential	Buprenex, Phenergan with codeine

Modified from ref. 10

Table 3 *DEA schedules of common medications (may vary by State).*

	Schedule I	Schedule II	Schedule III	Schedule IV	Schedule V

Opioid Agonists	Benzylmorphine
	Dihydromorphinone
	Heroin
	Ketobemidone
	Levomoramide
	Morphine-methylsulfonate
	Nicocodeine
	Nicomorphine
	Racemoramide
		Codeine
		various
		Fentanyl
		  Sublimaze®
		Hydrocodone
		Hydromorphone
		  Dilaudid®
		Meperidine
		  Demerol®
		Methadone
		Morphine
		Oxycodone
		  Endocet®
		  OxyContin®
		  Percocet®
		Oxymorphone
		  Numorphan®
			Buprenorphine
			  Buprenex®
			  Subutex®
			Codeine compounds
			  Tylenol #3®
			Hydrocodone compounds
			  Lorcet®
			  Lortab®
			  Tussionex®
			  Vicodin®
				Propoxyphene
				  Darvon®
				  Darvocet®
					Opium preparations
					  Donnagel PG®
					  Kapectolin®

Mixed Agonist-Antagonists			Buprenorphine + naloxone
			  Suboxone®
				Pentazocine
				naloxone
				  Talwin-Nx®	

Stimulants	N-methyl-amphetamine
	3,4-methylenedioxy amphetamine
	  MDMA, Ecstasy
		Amphetamine
		  Adderall®
		Cocaine
		Dextro amphetamine
		  Dexedrine®
		Methamphetamine
		  Desoxyn®
		Methylphenidate
		  Concerta®
		  Metadate®
		  Ritalin®
		Phenmetrazine
		  Fastin®
		  Preludin®
			Benzphetamine
			  Didrex®
			Pemoline
			  Cylert®
			Phendimetrazine
			  Plegine®
				Diethylpropion
				  Tenuate®
				Fenfluramine
				Phentermine
				  Fastin®
					1-deoxy-ephedrine
					  Vicks Inhaler®

Hallucinogens, Other	Lysergic acid diamine
	  LSD
	Marijuana
	Mescaline
	Peyote
	Phencyclidine
	  PCP
	Psilocybin
	Tetrahydro-cannabinols
			Dronabinol
			  Marinol®		

Sedative-Hypnotics	Methaqualone
	  Quaalude®
	Gamma-hydroxy butyrate
	  GHB
		Amobarbital
		  Amytal®
		Glutethimide
		  Doriden®
		Pentobarbital
		  Nembutal®
		Secobarbital
		  Seconal®
			Butabarbital
			  Butisol®
			Butalbital
			  Fiorecet®
			  Fiorinal®
			Methyprylon
			  Noludar®
				Alprazolam
				  Xanax®
				Chlordiazepoxide
				  Librium®
				Chloral betaine
				Chloral hydrate
				  Noctec®
				Clonazepam
				  Klonopin®
				Clorazepate
				  Tranxene®
				Diazepam
				  Valium®
				Estazolam
				  Prosom®
				Ethchlorvynol
				  Placidyl®
				Ethinamate
				Flurazepam
				  Dalmane®
				Halazepam
				  Paxipam®
				Lorazepam
				  Ativan®
				Mazindol
				  Sanorex®
				Mephobarbital
				  Mebaral®
				Meprobamate
				  Equanil®
				Methohexital
				  Brevital Sodium®
				Methyl-phenobarbital
				Midazolam
				  Versed®
				Oxazepam
				  Serax®
				Paraldehyde
				  Paral®
				Phenobarbital
				  Luminal®
				Prazepam
				  Centrax®
				Temazepam
				  Restoril®
				Triazolam
				  Halcion®
				Zaleplon
				  Sonata®
				Zolpidem
				  Ambien®
					Diphenoxylate preparations
					Lomotil®

the dosage beyond a certain level will only yield greater opioid side effects. The stimulation of kappa receptors can provide undesired dysesthesias, as with pentazocine (Talwin®). Both categories of opioid partial agonist/antagonists, because of their high mu affinity, can diminish opioid mu activity and potentially precipitate withdrawal in opioid-dependent individuals.

Fig. 6. *Opioid chemical classification.*

Buprenorphine (Suboxone®, Subutex®) has a poor bioavailability with extensive first 00 pass effect by the liver. Conversely, because of high lipid solubility, it has an excellent sublingual bioavailability. It is used on a once-a-day dose for maintenance therapy. Buprenorphine's usual adverse effects may include sedation, nausea and/or vomiting, dizziness, headache, and respiratory depression
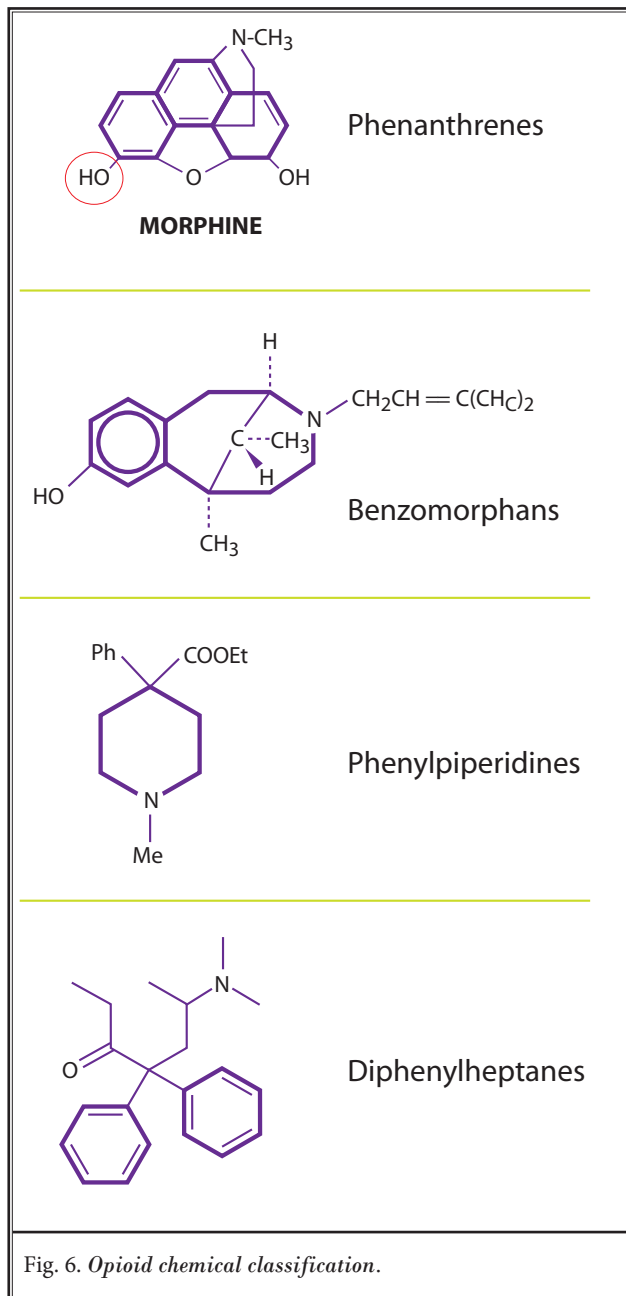
Opioid Agonists-Antagonists

Opioids classified as agonist-antagonists are those with poor mu opioid receptor efficacy and thus, may act functionally as mu opioid receptor antagonists as well as having kappa agonistic properties. Partial agonist-antagonists, such as pentazocine, nalbuphine, and butorphanol, share high mu affinity but have little mu efficacy (they are partial mu agonists which may also function as mu-opioid receptor antagonists) and also have partial kappa agonist activity. These agents can be used as analgesics, but have partial or a ceiling to their analgesic effect, such that escalating the dosage beyond a certain level will only yield greater opioid side effects and therefore potentially have decreased abuse potential. The stimulation of kappa receptors can provide undesired dysesthesias. It must be remembered that their antagonist properties may precipitate withdrawal.

Opioid Antagonists

The opioid receptor antagonists naloxone and naltrexone are competitive antagonists at the mu, kappa, and delta receptors, with a high affinity for the mu receptor but lacking any mu receptor efficacy. Naloxone and naltrexone act centrally and peripherally, but have differing pharmacokinetic profiles favoring different therapeutic uses. Naloxone has low oral bioavailability, but a fast onset of action following parenteral administration, for rapid reversal of acute adverse opioid effects. Its short duration of action risks the potential for "re-narcotization," thus not providing adequate duration of effect coverage for long-acting opioid maintenance or deterrent therapy. Naltrexone is orally effective with a long duration of action, making it useful in abuse deterrent, detoxification, and maintenance treatment modalities. Nalmefene, a mu-opioid receptor antagonist, is a water-soluble naltrexone derivative with a longer duration of action than naloxone, and is available for use in the United States for the reversal of opioid drug effects. Naloxone and naltrexone can be combined with mu agonists or partial agonists. Naloxone is used with sublingual bu-

prenorphine (Suboxone®) to prevent the intravenous abuse of buprenorphine. The same product (sublingual buprenorphine) when used alone (i.e., without naloxone) is marketed as Subutex®. Ultra-low dose naltrexone combined with oxycodone (Oxytrex®) is currently under study to see if the naltrexone will suppress opioid tolerance. Methylnaltrexone and alvimopan are peripherally acting mu receptor antagonists currently under investigation for use in treating postoperative ileus and opioid-induced bowel dysfunction.

Tramadol

A unique analgesic, tramadol is an atypical opioid, a 4-phenyl-piperidine analogue of codeine, with partial mu agonist activity in addition to central GABA, catecholamine and serotonergic activities. Tramadol is used primarily as an analgesic, but has demonstrated usefulness in treating opioid withdrawal (12).

Opioid Metabolism

Many of the side effects of opioids, as well as their effects, may be related to the opioid metabolites. It is generally assumed that most of the metabolism occurs in the liver. The basal rate of metabolism is determined by genetic makeup, gender, age, as well as environment including diet, disease state, and concurrent use of medications. There is no clear evidence of renal metabolism, though the kidney is an important site of excretion. Most opioids are metabolized by glucuronidation or by the P450 (CYP) system. There is also evidence that polymorphism in the human OPRM1 gene, which encodes the mu opioid peptide (MOP) receptor, might also contribute to the wide variation in opioid sensitivity (13). Ikeda et al (14) reviewed the current state of knowledge regarding opioid receptor genes, and concluded that differences in the OPRM1 genes are likely to affect opioid analgesia, tolerance, and dependence; other mouse studies indicate that this gene might also play a role in the abuse of alcohol and other non-opioid abused drugs.

Drug interactions in medicine can be overwhelming. On average, over the last 10 years, there were 60 papers per year cited in PubMed with "drug interaction" in the title (15). The CYP450 enzymes are a super-family of heme-containing, microsomal drug-metabolizing enzymes that are important in the biosynthesis and degradation of endogenous compounds, chemicals, toxins, and medications. More than 2,700 individual members of the CYP450 super-family have been identified, and 57 cytochrome P450 enzymes are recognized in humans

(16). CYP3A4 is the isoenzyme most frequently involved in drug metabolism, and accounts for approximately 50% of marketed drug metabolism; levels of CYP3A4 may vary as much as 30-fold between individuals (17), leading to large variability in blood levels. The metabolism of more than 90% of the most clinically important medications can be accounted for by 7 CYP isozymes (3A4, 3A5, 1A2, 2C9, 2C19, 2D6, and 2E1) (18). CYP1A2, CYP2C8, and CYP2C9 make up about 10% of the enzymes, CYP2D6 and CYP2E1 each around 5%, and CYP2C19 around 1%. CYP2D6 is entirely absent in some populations; for example, 6-10% of Caucasians are 2D6 deficient (19) while other persons have high levels of this enzyme, leading to rapid metabolism of the medicines. The high potential for drug interactions was illustrated by a recent study in Denmark (20). A total of 200 medical and surgical patients who were discharged from a hospital were surveyed and visited to ascertain the medications that they had in their homes and how frequently they used them. This information was cross-referenced with a drug-interaction database and with hospital records to clarify the impact of the possible interactions. The average age of patients was 75 years; the median number of drugs used was 8 (range, 1–24 drugs). Drug usage consisted of prescription medications (93% of patients), over-the-counter medications (91%), and herbal medications or dietary supplements (63%). A total of 476 potential drug interactions were identified in 63% of the patients. However, none of these interactions represented absolute contraindications to the use of the interacting drugs together, and only 21 (4.4%) were classified as relative contraindications.

Pharmacology of Specific Opioids

Morphine

Morphine is a Schedule II substance used to control moderately severe to severe pain. This drug was isolated in 1804 by the German pharmacist Freidrich Wilhelm Adam Serturner, and named "morphium" for the god of sleep. The development of the hypodermic needle escalated the use of this drug for the control of pain. After the American Civil War, 100,000 soldiers suffered from "soldier's disease" or morphine addiction. Morphine is the prototypical mu receptor opiate and is a phenanthrene derivative.

After oral administration, only approximately 40 to 50 percent of the administered dose reaches the central nervous system, within 30 minutes for the immediate release morphine and within 90 minutes

of any extended released form (21). The reason for this poor penetration is poor lipid solubility, protein binding, rapid conjugation with glucuronic acid, and ionization of the drug at a physiologic pH. The non-alkalized form of morphine crosses the blood brain barrier easier and alkalination of the blood increases the fraction of non-ionized morphine. It is interesting to note that respiratory acidosis increases brain concentrations of morphine because of increased cerebral blood flow secondary to higher carbon dioxide tension and facilitated delivery of the non-ionized form to the blood brain barrier. The elimination half-life of morphine is approximately 120 minutes.

Morphine is metabolized by demethylation and glucuronidation; glucuronidation is the predominant mode of metabolism, producing morphine-6 glucuronide (M6G) and morphine-3 glucuronide (M3G) in a ratio of 6:1, while approximately 5% of the drug is demethylated into normorphine. Glucuronidation occurs almost immediately after morphine enters the serum in both hepatic and extra hepatic sites, with evidence that a limited amount of intrahepatic recycling occurs (22). M3G in high enough concentrations is believed to potentially lead to hyperalgesia (23); M6G is believed to be responsible for some additional analgesic effects of morphine (24). Phase one of this metabolism is carried out by CYP450 and phase two by the enzyme UGT2B7 (25). Demethylation via CYP3A4 and CYP2C8 produces normorphine (26). Ferrari et al (27) found that only 8 of 12 patients on morphine produced normorphine. Morphine is also metabolized in small amounts to the drug codeine and hydromorphone. Hydromorphone is present in 66% of morphine consumers without aberrant drug behavior (28); this usually occurs with doses higher than 100 mg/day.

Drug – drug interactions with morphine are believed to be rare; however studies have shown that drugs that inhibit the UGT2B7 pathway may alter the amount of M3G and M6G available (29). The drugs that are the most potent inhibitors of this pathway include tamoxifen, diclofenac, naloxone, carbamazepine, tricyclic and heterocyclic antidepressants, and benzodiazepines. However, if these alterations occur they may not be clinically relevant. Other studies have shown rifampin and ranitidine may alter morphine metabolism (30).

Morphine is characterized as a relatively long acting opioid. Its side effect profile is associated with histamine release (which can cause bronchospasm and hypotension) and direct respiratory depression medi-ated by the nucleus accumbens in the brain stem, resulting in a decreased response to the arterial carbon dioxide tension, and shifting the response curve to the right. Recall that respiratory acidosis will increase the delivery of morphine to the brain compartment, leading to increased respiratory compromise.

Morphine may also decrease sympathetic nervous system tone, resulting in decreased tone in peripheral veins, and causing venous pooling and orthostatic hypotension. Morphine will have effects on the digestive tract including spasm of biliary smooth muscle, sphincter of Oddi spasm, and decreased intestinal motility resulting in constipation. Similar effects occur in the genitourinary system, resulting in spasm of the bladder trigone, causing urinary retention. Morphine may induce nausea and vomiting by direct stimulation of the chemoreceptor trigger zone in the floor of the 4th ventricle. Cutaneous changes may occur as manifested by peripheral vasodilatation and flushing of the skin with urticaria, a response to the histamine releasing properties of morphine. The parenteral forms of morphine contain sulfites that may cause anaphylactic or life threatening, allergic-type reactions in individuals with sulfa allergies.

Codeine

Codeine, first isolated in 1832, is the prototype of the weak opioid analgesics with weak affinity to μ opioid receptors. Codeine in its pure form is a Schedule II substance, whereas in combination with other analgesics, it is Schedule III. Its analgesic potency is approximately 50% of morphine with half-life of 2.5 to 3 hours. It is believed that the analgesic activity from codeine occurs from metabolism of codeine to morphine. There is some evidence that the metabolite codeine-6 glucuronide is active (31). Codeine is metabolized by CYP2D6, and therefore is susceptible to drug–drug interactions. This includes the inhibitors bupropion, celecoxib, cimetidine, and cocaine, as well as the inducers dexamethasone and rifampin. There is also great heterogeneity in the CYP450 enzymes and therefore codeine may not be an effective drug in all populations, since it is a pro-drug. Codeine has a half-life of 3 hours, and more than 80% of the dose is excreted within hours. The side effect profile of codeine is similar to other opiate agonists. A low dose of codeine is paradoxically more emetic than higher doses of codeine because of presumed competing effects the chemoreceptor trigger zone. Doses of codeine greater than 65 mg are not well tolerated.

Recently, the FDA has issued a Public Health Advisory (32) regarding a very rare but serious side effect in nursing infants whose mothers are taking codeine, and are apparent ultra-rapid metabolizers of codeine, resulting in rapid and higher levels of morphine in the breast milk, and the subsequent potentially fatal neonate respiratory depression. When prescribing codeine-containing medications to nursing mothers, the physician should use the lowest effective dose for the shortest period of time.

Dihydrocodeine

As the name implies, dihydrocodeine is very similar in structure to codeine. Its only difference is that it has a single bond between carbons 7 and 8 instead of a double bond. Its analgesic properties are generally considered equipotent to codeine (33). Similar to codeine, demethylation at the 3-carbon site occurs via 2D6 to create dihydromorphine (a minor metabolite, <5%), and nordihydrocodeine is created by 3A4 activity (34). It is unclear what primarily causes dihydrocodeine's analgesic properties—parent drug, metabolites, or some combination.

Hydrocodone

Hydrocodone is indicated for moderate-to-moderately severe pain as well as symptomatic relief of nonproductive cough, and it is the most commonly used opioid. Hydrocodone in its pure form would be a Schedule II substance; however it is only available for pain control as a Schedule III combination product with non-opioid analgesics, such as ibuprofen and acetaminophen. Hydrocodone bioavailability after oral administration is high, and the half-life of hydrocodone is 2.5 to 4 hours. Hydrocodone is similar in structure to codeine, with a single bond at carbons 7 and 8 and a keto (=O) group at 6-carbon instead of a hydroxyl (–OH) group. Hydrocodone displays weak binding capacity for the μ receptor, but the 2D6 enzyme demethylates it at the 3-carbon position into hydromorphone, which has much stronger μ binding than hydrocodone (35). Like codeine and dihydrocodeine, it has been proposed that hydrocodone is a prodrug. In other words, patients who are CYP2D6 deficient, or patients who are on CYP2D6 inhibitors, may not produce these analgesic metabolites, and may have less than expected analgesia. Unfortunately, studies that would help demonstrate that hydrocodone is a prodrug are scant, and no human studies have been done with pain models or with pain patients.

Oxycodone

Oxycodone is a phenanthrene class opioid available as a Schedule II substance whether in its pure form or in combination with Tylenol or aspirin. Oxycodone has activity at multiple opiate receptors including the kappa receptor. Oxycodone shares similarities with hydrocodone except for the addition of a hydroxyl group at the #14 carbon. Bioavailability of oxycodone is high in oral dosage, with a half-life of 2.5 to 3 hours. It undergoes extensive hepatic conjugation and oxidative degradation to a variety of metabolites excreted mainly in urine. Oxycodone is metabolized by glucuronidation to noroxycodone (which has less than 1% of the analgesia potency of oxycodone), and by 2D6 to oxymorphone (36). Oxycodone is an analgesic, not a pro-drug; however, oxymorphone is an active metabolite of oxycodone, and may have some impact on analgesia; however, the parent compound itself, oxycodone, produces the lion's share of the analgesia. Because oxycodone is dependent on the 2D6 pathway for clearance, it is possible that drug–drug interactions can occur with 2D6 inhibitors.

Oxymorphone

Oxycodone has activity at multiple receptors, but oxymorphone has high affinity for the μ receptor with negligible interaction with κ and δ receptors. Oxymorphone is about 10 times more potent than morphine, and is not affected by CY2D6 or CY3A4. Considerable individual variability occurred in the excretion of free and conjugated oxymorphone by 6 human subjects following oral dosing (37). It has recently become available in an immediate release and sustained release formulation.

Hydromorphone

Hydromorphone is a Schedule II semi-synthetic opioid agonist and a hydrogenated ketone of morphine (38). Like morphine, it acts primarily on μ opioid receptors and to a lesser degree on delta receptors. Hydromorphone is significantly more potent than morphine (with estimates of a relative potency of 7:1 up to 11:1 compared to morphine), and is highly water-soluble which allows for very concentrated formulations (39). In patients with renal failure it may be preferred over morphine (with morphine's risk of toxic metabolite accumulation). Hydromorphone is extensively metabolized in the liver with approximately 62% of the oral dose being eliminated by the liver on the first pass. For orally administered immediate release preparations, the onset of action is approximately 30 minutes

with a duration of action of 4 hours. Hydromorphone can also be administered parenterally by intravenous, intramuscular, and subcutaneous routes.

Hydromorphone is metabolized primarily to hydromorphone-3-glucuronide (H3G), which, similar to the corresponding M3G, is not only devoid of analgesic activity but also evokes a range of dose-dependent excited behaviors including allodynia, myoclonus, and seizures in animal models.

Methadone

Methadone is a synthetic μ opioid receptor agonist Schedule II medication; in addition to its opioid receptor activity, it is also an antagonist of the N-methyl-D-aspartate (NMDA) receptor. Methadone is a racemic mixture of 2 enantiomers; the R form is more potent, with a 10-fold higher affinity for opioid receptors (which accounts for virtually all of its analgesic effect), while S-methadone is the NMDA antagonist. The inherent NMDA antagonistic effects make it potentially useful in severe neuropathic and "opioid-resistant" pain states. The S isomer also inhibits reuptake of serotonin and norepinephrine, which should be recognized when using SSRIs and TCAs. Although it has traditionally been used to treat heroin addicts, its flexibility in dosing, use in neuropathic pain, and cheap price has lead to a recent increase in its use. Unfortunately, a lack of awareness of its metabolism and potential drug interactions, as well as its long half-life, has lead to a dramatic increase in the deaths associated with this medication.

Methadone is a unique synthetic opioid, unrelated to standard opioids (leading to its usefulness in patients with "true" morphine allergies). It is a basic and lipophilic drug with an excellent (though highly variable) oral bioavailability (from 40% to 100%). It can be crushed or dissolved to deliver down an NG tube and is also available in a liquid. Methadone is metabolized in the liver and intestines and excreted almost exclusively in feces, an advantage in patients with renal insufficiency or failure. Because of its high lipid solubility, it is redistributed to the fat tissues, and has a very long elimination phase, with a half-life of 12 to 150 hours. It may also cause less constipation than morphine, and it is very inexpensive (40).

The metabolism of methadone is always variable. Methadone is metabolized by CYP3A4 primarily and CYP2D6 secondarily; CYP2D6 preferentially metabolizes the R-methadone, while CYP3A4 and CYP1A2 metabolize both enantiomers. CYP1B2 is possibly in-

volved, and a newly proposed enzyme CYP2B6 may be emerging as an important intermediary metabolic transformation (41). CYP3A4 expression can vary up to 30-fold, and there can be genetic polymorphism of CYP2D6, ranging from poor to rapid metabolism. The initiation of methadone therapy can induce the CYP3A4 enzyme for 5 to 7 days, leading to low blood levels initially, but unexpectedly high levels about a week later if the medication has been rapidly titrated upward, and an intestinal CYP3A4 transport enzyme may also be involved. A wide variety of substances can also induce or inhibit these enzymes (Tables 4 and 5) (42). The potential differences in enzymatic metabolic conversion of methadone may explain the inconsistency of observed half-life. Methadone has no active metabolites, and therefore may result in less hyperalgia, myoclonus, and neurotoxicity than morphine. It may be unique in its lack of profound euphoria, but its analgesic action (4-8 hours) is significantly shorter than its elimination half-life (up to 150 hours), and patient self-directed redosing and a long half-life may lead to the potential of respiratory depression and death.

Methadone also has the potential to initiate Torsades de Pointes, a potentially fatal arrhythmia caused by a lengthening of the QT interval. Congenital QT prolongation, high methadone levels (usually over 60 mg per day), and conditions that increase QT prolongation (such as hypokalemia and hypomagnesemia) may increase that risk (43).

There is an incomplete cross-tolerance between methadone and other opioids. Even when prescribed in low doses, and used appropriately by individuals experienced with opioids, the long half-life of methadone may be underestimated while dosing is titrated to analgesic effect. In general, better relief is observed with methadone doses that are 10% of the calculated equianalgesic doses of conventional opioids.

Additional interactions may be seen with venlafaxine (a known CYP3A4 inhibitor) (44).

Fentanyl

Fentanyl is a strong opioid agonist, a Schedule II substance, available in parenteral, transdermal, and transbuccal preparations (45). Fentanyl is the oldest synthetic piperidine opioid agonist, interacting primarily with mu receptors. It is approximately 80 times more potent than morphine and is highly lipophilic and binds strongly to plasma proteins.

Fentanyl undergoes extensive metabolism in the liver. When administered as a lozenge for oral trans-

Table 4. *Medications that may decrease methadone levels.*

Key: ♥ denotes drugs that have been associated in the literature with cardiac rhythm disturbances and should be used cautiously with methadone.

♦ Interaction demonstrated via published clinical studies and/or by the specific pharmacology of methadone.

♦ Based on published case series reports and/or laboratory investigations in animals or tissues (invitro).

♦ *Proposed in the literature, but predicted from general pharmacologic principles and/orsporadic anecdotal cases.*

Abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase; PI = protease inhibitor; SML = serum methadone level; SSRI = selective serotonin reuptake inhibitor; TCA = tryclic antidepressant.

Generic Name(s)	Brands/Examples	Actions/Uses	Notes/References
abacavir (ABC)	**Ziagen**	**NRTI antiretroviral.**	**Methadone level mildly decreased; also reduces ABC peak concentration (Bart et al. 2001; Gourevitch 2001; Sellers et al. 1999; Ziagen PI 2002).**
amprenavir	**Agenerase**	**PI antiretroviral.**	**CYP3A4 enzyme induction may decrease methadone levels (Agenerase PI 1999; Bart et al. 2001; Chrisman 2003; Eap et al. 2002), but no adjustment in methadone dose required (Henrix et al. 2000, 2004). Amprenavir levels also may be reduced but the clinical significance is unclear.**
barbiturates amobarbital, amylo-barbitone butabarbital, mephobarbital, **pheno-barbital**, *pentobarbital, secobarbital, others*	*Amytal, Butisol, Fioricet, Fiorinal, Lotusate, Luminal, Mebaral, Nembutal,* **Pheno-barbital***, Seconal, Tal-butal, Tuinal, and others*	*Barbiturate sedatives and/or hypnotics.*	*CYP450 enzyme induction (Kreek 1986).* **Phenobarbital, the most studied, can cause sharp decrease in methadone (Alvares and Kappas 1972; Faucette et al. 2004; Gourevitch 2001; Liu and Wang 1984; Plummer et al. 1988) A methadone dose increase may be required.**
carbamazepine	**Atretol, Tegretol**	**Anticonvulsant for epilepsy and trigeminal neuralgia.**	**Strong CYP3A4 and** *CYP2B6* **enzyme induction may cause withdrawal (Bochner 2000;** *Faucette et al. 2004;* **Kuhn et al. 1989).** *Effect not seen with valproate (Depakote; Saxon et al. 1989).*
cocaine♥	*Crack, coke, others*	*Illicit stimulant.*	*Accelerates methadone elimination (Moolchan et al. 2001).*
dexamethasone	*Decadron, Hexadrol*	*Corticosteroid.*	*CYP3A4 and CYP2B6 enzyme inducer (Eap et al. 2002; Faucette et al. 2004); cases reported in pain patients (Plummer et al. 1988).*
efavirenz	**Sustiva**	**NNRTI antiretroviral.**	**Due to CYP3A4 and/or CYP2B6 induction (Barry et al. 1999; Boffito et al. 2002; Clarke et al. 2000, 2001a; Eap et al. 2002, Gerber et al. 2004; Marzolini et al. 2000; McCance-Katz et al. 2002; Pinzanni et al. 2000; Rotger et al. 2005; Tashima et al. 1999). Methadone withdrawal is common and a significant methadone dose increase is usually required.**
ethanol (chronic use)	*Wine, beer, whiskey, etc.*	*Euphoric, sedative.*	*CYP450 enzyme induction (Borowsky and Lieber 1978; Kreek 1976, 1984; Quinn et al. 1997).*
fusidic acid	*Fucidin*	*Steroidal antibacterial.*	*CYP450 enzyme induction (Eap et al. 2002; Van Beusekom and Iguchi 2001); reports of opioid withdrawal symptoms after 4-weeks of therapy (Reimann et al. 1999).*
heroin	*Smack, scat, others*	*Illicit opioid.*	*Decreases free fraction of methadone (Moolchan et al. 2001).*
lopinavir + ritonavir	**Kaletra**	**PI antiretroviral.**	**Combination lowers SML (Clarke et al. 2002), although there is some evidence to the contrary (Stevens et al. 2003). Withdrawal symptoms might occur requiring methadone dose increase; however, side effects of Kaletra may mimic GI side effects of opioid withdrawal.** *Most* **but not all research suggests this effect is not seen with ritonavir alone or ritonavir/saquinavir combination (Beauverie et al. 1998; Chrisman 2003; Geletko and Erickson 2000; Gerber et al. 2001; Hsu et al. 1998; Kharasch and Hoffer 2004; McCance-Katz et al. 2003; Munsiff et al. 2001; Shelton et al. 2001, 2004)** *although ritonavir induces CYP 2B6 (Faucette et al. 2004).*

Table 4. *continued.*

nelfinavir	Viracept	PI antiretroviral.	CYP3A4 and P-gp induction (Beauverie et al. 1998; Eap et al. 2002), but clinical methadone withdrawal is rare (Brown et al. 2001; Hsyu et al. 2000; Maroldo et al. 2000; McCance-Katz et al. 2004); however, manufacturer suggests methadone may need to be increased (Viracept PI 2000). Interaction may (Chrisman 2003) or may not (McCance-Katz et al. 2004) occur to decrease nelfinavir, which also is a potent inhibitor of CYP2B6 (Antoniou and Tseng 2002).
nevirapine	Viramune	NNRTI antiretroviral.	CYP3A4 and/or 2B6 enzyme induction reduces methadone level and precipitates opioid withdrawal. Methadone dose increase necessary in some patients (Altice et al. 1999; Clarke et al. 2001; Eap et al. 2002; Gerber et al.; Heelon et al. 1999; Otero et al. 1999; Pinzanni et al. 2000; Rotger et al. 2005; Staszewski et al. 1998).
phenytoin	Dilantin	Control of seizures.	Sharp decrease in methadone due to CYP3A4 and *CYP2B6* enzyme induction (Eap et al. 2002; *Faucette et al. 2004*; Finelli 1976; Kreek 1986; Tong et al. 1981).
primidone	*Myidone, Mysoline*	*Anticonvulsant.*	*Proposed in the literature (Vlessides 2005) due to CYP450 enzyme induction (Michalets 1998) including CYP2B6 (Brown & Griffiths 2000) but not clinically verified.*
rifampin (rifampicin) and rifampin/isoniazid	Rifadin, Rimactane Rifamate	Treatment of pulmonary tuberculosis.	Induces CYP450 enzymes; cases of severe withdrawal reported (Bending and Skacel 1977; Borg and Kreek 1995; Eap et al. 2002; Faucette et al. 2004; Holmes 1990; Kreek 1986; Kreek et al. 1976). Effect not seen with rifabutin (Mycobutin: Brown et al. 1996; Gourevitch 2001; Levy et al. 2000).
spironolactone	*Aldactone*	*K^+-sparing diuretic.*	*Possible CYP450 induction (Eap et al. 2002). Effect observed in patients receiving methadone for cancer pain (Plummer et al.).*
St. John's wort (Hypericum perforatum)	*Ingredient in various OTC products*	*Herb used as antidepressant.*	*Induces CYP3A4 and P-gp; 47% decrease in methadone noted in one study (Eich-Höchli et al. 2003; Scot and Elmer 2002).*
tobacco	*Various brands*	*Habitual smoking.*	*Some mixed reports, but most indicate reduced effectiveness of methadone, possibly due to CYP1A2 induction (Eap et al. 2002; Moolchan et al. 2001; Tacke et al. 2001).*
urinary acidifiers (e.g., ascorbic acid)	*Vitamin C (extremely large doses); K-Phos*	*Dietary supplement; keeps calcium soluble.*	*Proposed, methadone excreted by kidneys more rapidly at lower pH (Nillson et al. 1982; Strang 1999).*

Source: Leavitt SB, ed. Addiction Treatment Forum (44).

mucosal absorption, a portion is swallowed and is subject to first-pass metabolism in the liver and possibly small intestine. It is metabolized to hydroxyfentanyl and norfentanyl.

Fentanyl is metabolized by CYP3A4, but to inactive and nontoxic metabolites (46). However, CYP3A4 inhibitors may lead to increased fentanyl blood levels. The transdermal formulation has a lag time of 6-12 hours to onset of action after application, and typically reaches steady state in 3-6 days. When a patch is removed, a subcutaneous reservoir remains, and drug clearance may take up to 24 hours.

Meperidine

Meperidine, a Schedule II substance, is a relatively weak opioid µ agonist with only approximately 10% effectiveness of morphine with significant anticholinergic and local anesthetic properties, with an oral-to-parental ratio of 4:1. The half-life of meperidine is approximately 3 hours. It is metabolized in the liver to normeperidine, which has a half-life of 15-30 hours, and significant neurotoxic properties. Meperidine must not be given to patients being treated with monoamine oxidase inhibitors (MAOI); combination with MAOIs may produce severe respiratory depres-

Table 5. *Medications that may increase methadone levels.*

Generic Name	Brands/Examples	Actions/Uses	Notes/References
Asthma Medications *zafirlukast, zileuton*	*Accolate, Zyflo*	*Prevention and control of asthma symptoms.*	*Proposed in the literature (Vlessides 2005) due to CYP450 inhibition (Flockhart 2005), but not clinically verified.*
Cardiac Medications *amiodarone♥, diltiazem* *quinidine♥*	*Cordarone, Cardizem, Diltia, Tiazac, Cardioquin, Quinaglute, Dura-Tabs, others*	*Heart rhythm stabilizers, antihypertensives.*	*Recently proposed in the literature (Vlessides 2005) possibly due to CYP450 inhibition (Flockhart 2005), but not otherwise verified.*
cimetidine	*Tagamet*	*H_2-receptor antagonist for GI disorders.*	*CYP450 enzyme inhibitor (Bochner 2000; Dawson and Vestal 1984; Sorkin and Ogawa 1983; Strang 1999).*
ciprofloxacin	*Cipro*	*Quinolone antibiotic.*	*Inhibition of select CYP450 enzymes (Eap et al. 2002; Herrlin et al. 2000).*
delavirdine	*Rescriptor*	*NNRTI antiretroviral.*	*Predicted effect due to CYP450 enzyme inhibition (Gourevitch 2001; McCance-Katz et al. 2004, 2005); manufacturer suggests methadone dose may need to be decreased (Rescriptor PI 2001).*
diazepam	*Dizac, Valium, Valrelease*	*Control of anxiety and stress.*	*Mechanism undetermined (Eap et al. 2002; Iribarne et al. 1996; Preston et al. 1984, 1986) but unlikely due to metabolic interaction (Foster et al. 1999; Pond et al. 1982) and effect sporadic (Levy et al. 2000).*
dihydroergotamine	*D.H.E., Migranal*	*Migraine treatment.*	*Predicted due to CYP3A4 enzyme inhibition (Van Beusekom and Iguchi 2001).*
disulfiram	*Antabuse*	*Alcoholism treatment.*	*Sedation in MMT patients noted with higher doses of disulfiram (Bochner 2000), but some reports inconclusive (Tong et al. 1980).*
ethanol (acute use)	*Wine, beer, whiskey, etc.*	*Euphoric, sedative.*	*Competition for CYP450 enzymes or CYP450 inhibition (Borowsky and Lieber 1978; Kreek 1976, 1984; Quinn et al. 1997).*
fluconazole	**Diflucan**	**Anti-fungal antibiotic.**	**CYP450 enzyme inhibition (Eap et al. 2002); increased methadone levels (Cobb et al. 1998; Gourevitch 2001); clinical significance uncertain (Levy et al. 2000, Tamuri et al. 2002).** *Other azole antifungals may potentially influence opioid toxicity: e.g., itraconazole, ketoconazole♥, voriconazole.*
grapefruit	**juice or whole fruit**	**Food.**	**Inhibits intestinal CYP3A4 (Bailey et al. 1998; Dresser et al. 2000; Hall et al. 1999) and P-gp (Benmebarek et al. 2004; Dresser et al. 2000; Eagling et al. 1999; Eap et al. 2002); although, there is some conflicting evidence (Kharasch et al. 2004). This effect is not expected with other fruits/juices (Karlix 1990).**

Key: ♥ denotes drugs that have been associated in the literature with cardiac rhythm disturbances and should be used cautiously with methadone.
♦ Interaction demonstrated via published clinical studies and/or by the specific pharmacology of methadone.
♦ Based on published case series reports and/or laboratory investigations in animals or tissues (invitro).
♦ *Proposed in the literature, but predicted from general pharmacologic principles and/orsporadic anecdotal cases.*
Abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
Source: Leavitt SB, ed. Addiction Treatment Forum (44).

sion, hyperpyrexia, central nervous system excitation, delirium, and seizures.

Meperidine is metabolized by glucuronidation to normeperidine (47). Normeperidine has T1/2 of 8-12 hours so significant amounts can accumulate in only 2 days. Adverse effects of normeperidine are not reversible by naloxone. Initially this is characterized by subtle mood effects (e.g., anxiety), followed by tremors, multifocal myoclonus, and occasionally by seizures. This CNS hyperexcitability occurs commonly in patients with renal disease but it can occur following repeated administration in patients with normal renal function.

Levorphanol

Levorphanol is a synthetic morphine analogue, the optical isomer of dextromethorphan. It is as potent as hydromorphone but longer lasting. It is a mu, kappa, and delta agonist, as well as being a NMDA antagonist. It is metabolized to a 3-glucuronide of unknown activity.

There has been recent interest in using levorphanol for refractory pain, much like methadone. Like methadone, there is a variable dosing equivalent; for morphine doses less than 100 mg, the conversion factor has been described as 12:1, while doses over 600 mg may need a conversion factor of 25:1. Unfortunately, levorphanol demonstrates the potential for interaction at the glucuronidation enzyme sites, with theoretic (but not proven) interactions with NSAIDs, valproic acid, lorazepam, and rifampin. It was noted to be "pharmaceutically incompatible" with aminophylline, amobarbital, heparin, methicillin, pentobarbital, phenobarbital, phenytoin, secobarbital, and thiopental (48).

Buprenorphine

Buprenorphine (Buprenex®) has been approved for use in the U.S. since December 1981. A 72-hour transdermal product designed to continuously release buprenorphine at 35, 52.5, or 70 mcg/hr is available in Europe (but not in the U.S.) for the treatment of persistent pain. An oral or sublingual form (Subutex®) was approved in 2002. It is also available with naloxone as Suboxone®. The naloxone component exhibits almost no sublingual absorption and very little oral absorption. The intent of its addition is to reverse the effects of an IV or IM administered buprenorphine that might be attempted. Because of high lipid solubility, it has an excellent sublingual bioavailability. After sublingual administration, there is a rapid onset of effect (30-60 minutes) with a peak effect at about 90-100 minutes. It is used on a once-a-day dose for maintenance therapy. Buprenorphine is primarily metabolized by P450 3A4 (49). There are extensive drug-drug interactions which can exist based on the induction or inhibition of the 3A4 system. The typical daily dose for opioid addiction ranges from 4 to 32 mg daily buprenorphine. Buprenorphine's usual adverse effects may include sedation, nausea and/or vomiting, dizziness, headache, and respiratory depression. It may precipitate withdrawal in patients who have received repeated doses of a morphine-like agonist and developed physical dependence. Buprenorphine's respiratory depressant effects are reversed only by relatively large doses of naloxone (50).

Propoxyphene

Propoxyphene is a mild, opioid agonist used in mild to moderate pain and is a Schedule IV substance. Propoxyphene has central nervous system effects such as dizziness, sedation, weakness and falls, mild visual disturbances, agitation, paradoxical excitement, and insomnia, that can result in drug-related deaths when propoxyphene is used in combination with other drugs that can cause drowsiness (51). The Government Accountability Office (GAO), after 2 studies conducted in 1991 and 1995, recommended that propoxyphene not be used in the elderly patient because of the existence of other analgesic medications that are more effective and safer (52). Propoxyphene is a synthetic analgesic that is structurally related to methadone and has an opioid dose equipotency similar to codeine. The analgesic activity is confined to its d-stereoisomer (dextropropoxyphene) with a half-life of 6 to 12 hours, with duration of effective analgesia of 3 to 5 hours. It is metabolized in the liver to norpropoxyphene (not via CYP2D6), which has a long half-life of 30 to 60 hours and is considered to have cardiac toxicity. Further, propoxyphene itself can produce seizures (naloxone-reversible) after overdose. In addition to being μ receptor agonist, propoxyphene is a weak and noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. It is also a CYP3A4 inhibitor, and therefore may increase methadone, carbamazepine, and ritonavir blood levels.

Clinically, there are groups of people who describe better relief with propoxyphene than hydrocodone, which may reflect a CYP2D6 deficiency, so that propoxyphene (which is not a prodrug) would have more effect than hydrocodone (which has to be metabolized by CYP2D6 to its more active form), as well as its NMDA antagonist activity.

Tramadol

A unique analgesic, tramadol is an atypical opioid, a 4-phenyl-piperidine analogue of codeine (53). The M1 derivative (O-demethyl tramadol) produced by CYP2D6 has a higher affinity for the μ receptor than the parent compound (as much as 6 times). Tramadol is a racemic mixture of 2 enantiomers — one form is a selective μ agonist and inhibits serotonin reuptake, while the other mainly inhibits norepinephrine reuptake. Maximum dose is 400 mg/day. Toxic doses cause CNS excitation and seizures.

Tramadol is a federal non-scheduled drug. State regulations may vary. Tramadol is absorbed rapidly and extensively after oral doses, and is equal to anal-

Table 6. *Drug interactions of opioids.*

Tricyclic antidepressants	Inhibit morphine glucuronidation leading to ⇑ blood levels --- Nortriptyline inhibits non-competitively --- Amitriptyline and clomipramine inhibit competitively
Methadone and morphine	⇓ metabolism of TCAs, leading to toxicity
Quinine	⇓ conversion of codeine to morphine leading to ⇓ analgesia
Metoclopramide	Earlier peak plasma levels with controlled-released opioids
Meperidine	MAO inhibitors trigger hyperpyrexia
Propoxyphene	⇑ carbamazepine, doxepin, metoprolol, propranolol levels ⇓ excretion of benzodiazepines, leading to accumulation and overdose
Erythromycin	⇑ opioid effects
Venlafaxine	⇑ methadone levels
Rifampin Phenytoin Carbamazine	⇓ methadone levels
Phenytoin Phenobarbital	⇓ meperidine levels
CY2D6 inhibitors	⇑ tramadol levels ⇓ analgesia from hydrocodone/codeine
CY2D6 substrates	⇑ tramadol levels because of competition for metabolism
CYP3A4 inhibitors	⇑ methadone levels
CYP3A4 inducers	⇓ methadone levels

gesic potency of codeine. Tramadol is used primarily as an analgesic, but has demonstrated usefulness in treating opioid withdrawal (54).

DRUG INTERACTIONS

A drug interaction occurs when the amount or the action of a drug is altered by the administration of another drug or multiple drugs (55). Multiple hepatic drug interactions may influence opioid drug levels (56) as illustrated in Table 6.

- There have been isolated reports of interactions between opioid and H2 blockers (cimetidine and ranitidine) causing breathing difficulties, confusion, and muscle twitching.
- A patient taking Tamoxifen (a CY2D6 substrate) was noted to get poor relief with oxycodone (which is metabolized by CY2D6) but excellent relief with morphine (57).

Methadone has multiple drug interactions. Phenytoin, carbamazepine, rifampin, erythromycin, barbiturates, and several anti-retrovirals induce methadone metabolism, resulting in decreased blood levels and the potential for withdrawal. The azole antifungals, the SSRIs, and tricyclic antidepressants may increase methadone levels (58). Methadone may also increase TCA levels. Overmedication occurring within a few days is usually due to P450 (CYP) inhibition, while withdrawal reactions taking a week or more are usually due to CYP induction (59). Methadone also has the potential to cause cardiac arrhythmias, specifically prolonged QTc intervals and/or Torsade de Pointes under certain circumstances. Combining methadone with a CYP3A4 inhibitor such as ciprofloxin (60) and even grapefruit can increase that risk (61). (Although, for grapefruit juice, this appears to be mostly theoretic and not clinically significant). It is recommended that a switch to methadone from another opioid be accompanied by a large (50% to 90%) decrease in the calculated equipotent dose (62).

Drug Conversions

While there have been multiple opioid conversion charts developed, none are reliable and none take into consideration the vast individual differences in

effect and metabolism between patients and within medications. Brand name and generic medications may have significant differences in bioavailability, and metabolism of medications may be influenced by genetic polymorphism and dug interactions. It is therefore important to recognize that "equipotent" doses of medications may have very different degrees of analgesia and side effects. In general, to switch between medications, the clinician must calculate a rough equivalent 24-hour dose, divide by the dosing

Table 7. *Oral Morphine to oral methadone conversion.*

Oral morphine dose	Morphine: methadone ratio
<100 mg	3:1
101 -300 mg	5:1
301-600 mg	10:1
601-800 mg	12:1
801-1000 mg	15:1
> 1000 mg	20:1

Adapted from EPERC (ref. 63)

Table 8. *Plasma half life values for opioids and their active metabolites.*

Drug	Plasma half-life (hours)
Short Half-Life Opioids	
Morphine	2 -3.5
Morphine 6 glucoronide	2
Hydromorphone	2-3
Oxycodone	2-3
Fentanyl	3-4
Codeine	3
Meperidine	3-4
Nalbuphine	5
Butorphanol	2.5 -3.5
Buprenorphine	3-5
Long Half-Life Opioids	
Methadone	24
Levorphanol	12-16
Propoxyphene	12
Norpropoxyphene	30-40
Normeperidine	14-21

Adapted from ref 65.

schedule, and then "under-dose," with subsequent titration to effect.

An important property of methadone is that its apparent potency, compared to other opioids, varies with the patient's current exposure to other opioids. The conversion factor depends on the current dose of the opioid to be converted (63) (Table 7).

With chronic administration the ratio of oral morphine: intravenous (IV) morphine is 3:1. Hydromorphone is approximately 5-12 times more potent than morphine. Ten to 20 mg of IV morphine (and perhaps up to 90mg of oral morphine) is roughly equivalent to 25 mcg of transdermal fentanyl (TDF). Similarly, 25mcg TDF is roughly equivalent to 45mg of oral oxycodone or 12mg of oral hydromorphone per day. Although methadone has been described as equipotent to morphine, it is now clearer that dosing methadone on a milligram-for-milligram basis will lead to a life threatening overdose. For doses of morphine under 100 mg, a ratio of 3:1 may be appropriate, while for higher doses of morphine a ratio of 20 mg morphine for each mg of methadone may be appropriate (64). Methadone appears to be significantly more potent via the IV route, perhaps because of intestinal CYP3A4 metabolism. It cannot be too strongly emphasized that the dosing of methadone can be potentially lethal and must be done with knowledge and caution.

Pharmacokinetics

Opioids differ significantly in the plasma half-life value (Table 8). Thus, while morphine and hydromorphone are short half-life opioids that on repeated dosing reach steady state in 10-12 hours, levorphanol and methadone are long half-life opioids that on an average may need 70 to 120 hours respectively to achieve steady state. During dose titration, the maximal (peak) effects produced by a change dose of a short half-life opioid will appear relatively quickly, while the peak effects resulting from a change in the dose of a long half-life opioid will be achieved after a longer accumulation period. For example, a patient who reports adequate pain relief following the initial dose of methadone may experience excessive sedation if this dosage is fixed and not modified as required during the accumulation period of 5-10 days. Active metabolites, such as normeperidine and norpropoxyphene, may have longer plasma half-life values than their corresponding parent drugs (meperidine and propoxyphene).

Conclusion

Mu receptor agonists and agonist-antagonists have been used throughout recent medical history for the control of pain and for the treatment of opiate induced side effects and even opiate withdrawal syndromes. The fundamental concept that underlies the appropriate and successful management of pain by the use of opioid and nonopioid analgesics is individualization of analgesic therapy. This concept entails an understanding of the clinical pharmacology of opioids to provide the information necessary for the selection of the right analgesic, administered at the right dose and with a dosing schedule to maximize pain relief and minimize side effects. This comprehensive approach begins with non-opioids or "mild" analgesics for mild pain. In patients with moderate pain that is not controlled by non-opioids alone, the so-called "weak" opioids or in combination should be prescribed. In patients with severe pain, a "strong" opioid is the drug of choice alone or in combination. The analgesic efficacy of opioids does not have a conventional dose-related ceiling, but rather dose escalation is usually limited by the incidence and severity of adverse effects. Therefore, individual titration of the dose combined with measures to reduce adverse effects is key to optimizing the management of pain with these drugs.

With advances in research, the complex interplay between opioid receptor active substances and other substances in both Phase I and Phase II metabolism has become apparent. We are truly at the forefront of the understanding of opiate pharmacology, although these substances and their use seem conveniently familiar to us. This misperception is no more apparent to us than the now obvious misapplication of oral methadone dosing in the setting of the chronic pain management practice, which has been cautioned against here. The reclassification of opiate receptors and the removal of receptor subtypes from the opiate class to entirely different classes should remind us as practitioners that caution should be the guiding principle over the use of these medications in the treatment of patients. Pharmacodynamics, pharmacokinetics, and pharmacogenetics are of paramount importance, and as our knowledge base develops, complete mastery of these sub-disciplines will be dictated by society in the care of our patients.

Acknowledgements

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