Selecting an Opioid: Pharmacologic Principles

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After earning a bachelors degree at Florida State University in Tallahassee, Dr. Finch earned his medical degree at the University of South Florida, Tampa. He completed a residency in family medicine at Lancaster General Hospital, an affiliated hospital of Temple University, Philadelphia, and went on to complete a clinical teaching fellowship in family medicine at Duke University. He has been an Assistant Professor in the Duke Family Practice Residency Program and Medical Director of the Duke Alcoholism and Addictions Program. He also has directed upload treatment programs in Raleigh and Durham, North Carolina.

In addition to the North Carolina Governor’s Institute on Alcohol and Substance Abuse, Dr. Finch has been active in many physician education projects at the national level. He served as national chair of the Substance Abuse Work Group of the Society of Teachers of Family Medicine and as a member of the executive committee of Project SAEFP (Substance Abuse Education for Family Physicians). He also was a member of the Physician Consortium on Substance Abuse Education of the U.S. Public Health Service, and a consultant to the National Institute on Alcohol Abuse and Alcoholism on development of Nicaea’s Physician’s Guide to Helping Patients with Alcohol Problems.

Dr. Finch has taught primary care physicians about the identification and management of alcohol and other drug use disorders at workshops across the U.S. and in Mexico, Poland and Russia. He is the author of many journal articles, with a special emphasis on the identification and management of patients with alcohol and drug problems in primary care settings.
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Opiates
• Present in opium from seedpod of Papaver somniferum
• Morphine, codeine

Opioids
• Are manufactured
• Semisynthetics are derived from an opiate
• Synthetics are synthesized to have function similar to natural opiates

Mu Receptor
• G protein-coupled receptor family, signal via second messenger (cAMP)
• Found in many sites: pre- and post-synapse in periphery, spinal cord dorsal horn, brain stem, midbrain, thalamus, cortex…
• Mu receptor subtypes
  – Not all patients respond to same opioid in same way
  – Not all pain responds to same opioid in the same way
  – Incomplete cross-tolerance between opioids

Activation of Mu Receptors
• Inhibit activation of nociceptors
• Inhibit cells that release inflammatory mediators
• Inhibit terminals of C-fibers in the spinal cord
• Prevent ascending transmission of pain signal
• Turn on descending inhibitory systems

Responses Mediated by Opioid Receptors

<table>
<thead>
<tr>
<th>G-protein coupled receptor</th>
<th>Response on activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>mu</td>
<td>Analgesia, respiratory depression, sedation, miosis, euphoria, reduced GI motility</td>
</tr>
<tr>
<td>delta</td>
<td>Analgesia, euphoria</td>
</tr>
<tr>
<td>kappa</td>
<td>Analgesia, dysphoria, psychotomimetic effects, miosis, respiratory depression</td>
</tr>
</tbody>
</table>

Opioid Intrinsic Activity

Full Agonist
Morphine, Oxycodone, Hydromorphone

Partial Agonist
Buprenorphine

Antagonist
Naloxone, Nalbuphine

Opioid Responsiveness/Resistance

• Degree of pain relief with
  – Maximum opioid dose
  – In the absence of side effects i.e. sedation
• Not all pain is opioid responsive
  – Varies among different types of pain
    • Acute > Chronic
    • Nociceptive > Neuropathic
  – Varies among individuals

Pseudo-Opioid-Resistance

• Some patients with adequate pain relief believe it is not in their best interest to report pain relief
  – Fear that care would be reduced
  – Fear that physician may decrease efforts to diagnose problem

Evers GC. Support Care Cancer. 1997

Opioid Efficacy in Chronic Pain

• Most literature surveys & uncontrolled case series
• RCTs are short duration <4 months with small sample sizes <300 pts
• Mostly pharmaceutical company sponsored
• Pain relief modest
  – Some statistically significant, others trend towards benefit
  – One meta-analysis decrease of 14 points on 100 point scale
• Limited or no functional improvement

Balshyke JC. Moe J. NEJM 2003

Number Needed to Treat *(NNT)*

* to obtain one patient with 50% pain relief

| Tricyclic Antidepressants | 2.3 |
| Oxycodone                 | 2.5 |
| Gabapentin                | 3.2 |
| Capsaicin                 | 5.3 |

Sindrup SH, Jensen TS. Pain. 1999

Multimodal Analgesia

Morphine, Gabapentin, or Their Combination for Neuropathic Pain

Jain K et al. Pain. 2000

NEJM 2005; 352:1324-34
Opiophobia

• Overestimate potency and duration of action
• Fear of being scammed
• Often prescribed with too small a dose and too long a dosing interval
• Exaggerated fear of addiction risk

Morgan, J. Adv Alcohol Subst Abuse, 1985

Opioid Safety

• Side effects are common
  – Nausea and vomiting
  – Sedation, respiratory depression
  – Constipation and urinary retention
  – Sweating, insomnia, decreased sexual function
  – Cognitive impairment and psychomotor dysfunction
    • Opioid-induced delirium

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    • Opioid-induced delirium

• Overdose esp when combined w/ other sedatives
• Worsening pain? withdrawal or hyperalgesia
• Risk of addiction (opioid dependence)?
• Societal toxicity - diversion and trafficking

Ballantyne & Mao: NEJM 2003

Opioid Allergies

• Opioids release histamine from mast cells
  – Pruritis, urticaria may not mean allergy
• Allergies, when they occur, tend to be to entire chemical families:
  – Diphenylheptanes: methadone, propoxyphene
  – Phenylpiperidines: meperidine, fentanyl
  – Phenanthrenes: codeine, hydromorphone, morphine, oxycodone, hydrocodone
• Rashes more likely from inactive additives

Opioids and the Brain

The Reward Pathway
(VTA→NAc→PFC)

Ballantyne & Mao: NEJM 2003
Pain Alters Opioid Responses

- Significantly less opioid reward or euphoria
- Less morphine analgesic tolerance in pain assays
- Less morphine physical withdrawal symptoms
- Patients on morphine with successful nerve block will develop respiratory and CNS depression

Brown et al., 2002, Vaccarino et al., 1993, Zacny et al., 1996

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Opioid Withdrawal

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms / Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Anxiety, Drug Craving</td>
</tr>
<tr>
<td>1</td>
<td>Yawning, Sweating, Runny nose, Tearing eyes, Restlessness Insomnia</td>
</tr>
<tr>
<td>2</td>
<td>Dilated pupils, Gooseflesh, Muscle twitching &amp; shaking, Muscle &amp; Joint aches, Loss of appetite</td>
</tr>
<tr>
<td>3</td>
<td>Nausea, extreme restlessness, elevated blood pressure, Heart rate &gt; 100, Fever</td>
</tr>
<tr>
<td>4</td>
<td>Vomiting / dehydration, Chemosis, Dilated pupils, Frightful body position</td>
</tr>
</tbody>
</table>

Can Opioids Worsen Pain?

- Animal studies¹ chronic opioid administration results in increased pain sensitivity versus placebo
- Methadone maintenance patients² with enhanced pain sensitivity versus controls
- ? Release of peptides "anti-opioids", increase levels of dynorphin
- ? Neuroadaptation to chronic opioids

Li X et al. Brain Res Mol Brain Res 2001
Doverly M et al. Pain 2001
Angst MB, Clark JD. Anesthesiology 2006

Opioid-Induced Hyperalgesia

Adapted from Compton P. AMERSA 2002

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Opioid Withdrawal-Mediated Pain

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Opioid-Induced Hyperalgesia

Adapted from Compton P. AMERSA 2002
Opioid Options

• Strong vs weak (ceiling effect)
• Duration and onset of action
  – “Rate hypothesis” - fast on, fast off – most addicting
• Patient’s prior experience
  – Mu polymorphisms – differences in opioid responsiveness
• Route of administration
• Side effects and Cost
• There are NO abuse resistant opioids or opioid formulations!!

Opioid Options

Short-acting
• Hydrocodone
• Hydromorphone
• Morphine
• Oxycodone

Long-acting
• Slow-release delivery system
  – Transdermal fentanyl
  – Extended release morphine
  – Extended release oxycodone
• Intrinsic pharmokinetic property
  – Methadone

Opioid Rotation

• Switch to another opioid as means of restoring analgesic efficacy or limiting adverse effects
• Based on large intra-individual variation in response to different opioids
• Different variants of mu-opioid receptors
• Based on surveys and anecdotal evidence
• Use equianalgesic table to calculate dose of new opioid
  – Determine clinically relevant starting point
  – Decrease equianalgesic dose by 25-50%

Opioid Conversion Chart

<table>
<thead>
<tr>
<th>ANALGESIC</th>
<th>ORAL</th>
<th>PARENTERAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Codeine</td>
<td>200</td>
<td>120</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Methadone</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100-200 mcg (1T)</td>
<td>100 mcg (1D)</td>
</tr>
<tr>
<td>Meperidine</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>Tramadol</td>
<td>100-150</td>
<td>-</td>
</tr>
</tbody>
</table>

adapted from © Copyright 2008 American College of Physicians

Equianalgesic Tables

• Derived from relative potency ratios using single-dose analgesic studies
• Subjects with limited opioid exposure
• Do not reflect clinical realities of chronic opioid administration
• Therefore dose ratios are guidelines to be used cautiously

Morphine

• e.g. MSIR, MSContin, Oramorph SR
• OA: 15-60 min, PE: 30-60 min, DOA: 4-6 hrs (SR preparation: 8-12 hrs)
• Moderate to severe pain
• Morphine-6-glucuronide: active metabolite: renal excretion
• Morphine-3-glucuronide: metabolite with excitatory effects
• Crosses placenta and in breast milk
### Codeine
- e.g. Tylenol #2, 3, 4
- OA: 15-30 min, PE: 30-60 min, DOA: 3-6 hrs
- Mild to moderate pain
- Hepatic and renal elimination
- Prodrug: 10% transformed to morphine
- Crosses placenta and in breast milk

### Oxycodone
- e.g. Percocet, Roxicet, OxyContin
- OA 10-15 min, PE: 30-60 min, DOA: 3-6 hrs (SR preparation 8-12 hrs)
- Moderate to severe pain
- Hepatic and renal elimination
- Crosses placenta and in breast milk

### Hydromorphone
- e.g. Dilaudid
- 7 time more potent than morphine
- OA 15-30 min, PE 30-60 min, DOA 4-6 hrs
- Moderate to severe pain
- Hepatic elimination
- No active metabolites
- Crosses placenta and in breast milk

### Hydrocodone
- e.g. Lortab, Vicodin, Vicoprofen
- OA: 15-30 min, PE: 30-60 min, DOA: 4-8 hrs
- Mild to moderate pain
- Hepatic and renal elimination
- Crosses placenta and in breast milk

### Transdermal Fentanyl
- Requires predictable blood flow to dermal application site
- 25µg = morphine 30-60 mg po = 6-9 percocet
- Takes ~8-14 hours to achieve peak serum levels
- Removal of patch still leaves SQ reservoir t½ ~18 hrs
- Absorption altered with fever, broken skin, edema and decrease subcutaneous fat
- Crosses placenta and in breast milk

### Propoxyphene
- e.g. Darvon, Darvocet
- OA: 15-60 min, PE: 2-3 hrs, DOA: 4-6 hrs
- Mild to moderate pain
- Hepatic and renal elimination
- Synthetic, structurally similar to methadone
- No antitussive effects
- Active metabolite-Norpropoxyphene may cause cardiac conduction delays
- Crosses placenta and in breast milk
Methadone

- e.g. Dolophine
- OA: 30-60 min, PE: 2-3 hrs, DOA: 6-8 hrs but t½ VARIABLE and UNPREDICTABLE
- NMDA receptor antagonist
- 5HT, NE uptake inhibition
- QTc prolongation, risk of torsade de points

Tramadol

- e.g. Ultram
- OA: <1 hr, PE: 2-3 hrs, DOA: 3-6 hrs
- Hepatic and renal elimination
- Mild to moderate pain
- Provides analgesia via at least 2 mechanisms
  - 30% effect – low binding to opioid receptors
  - 70% of effect – inhibition of NE and serotonin reuptake
- Adverse effects – N/V, constipation, sedation
- May lower seizure threshold
- Clinical physical dependence, ?Abuse potential
- Crosses placenta and in breast milk

New Abuse-Deterrent and Abuse-Resistant Systems

- Pharmacokinetic
  - Modified-release delivery systems
  - Alternative routes of administration
- Pharmacodynamic
  - Drug combination products
  - Receptor-specific agents
- Pharmacogenomics
  - Genetically mediated drug-host interactions

Emerging Opioid Formulations

- Abuse-resistant formulations
  - Physical barriers
  - If barriers defeated, drug becomes available
- Abuse-deterrent formulations
  - Pharmacologic barriers
  - If altered, antagonist or irritant released
  - If not digested as intended, drug is inactive

Abuse-Resistant Formulation

- Oxycodone
- Controlled Release
- Crush
- Resists physical and mechanical manipulation aimed at disrupting the controlled-release feature
- Cannot be chewed or crushed
- Cannot be snorted
- Cannot be injected

Abuse-Resistant Long-Acting Oxycodone

- AR-LAO:
  - AR-LAO crushed in water
  - AR-LAO crushed in alcohol
- Commercial IR
- AR-LAO crushed in water
- AR-LAO crushed in alcohol

**Agonist–Antagonist Formulations**

Simultaneous release of agonist and antagonist


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**Agonist-Antagonist**

- Pentazocine (Talwin), Butorphanol (Stadol)
- OA: 15-30 min, PE: 1-3 hrs, DOA: 3-6 hrs
- Mild to moderate pain
- Hepatic and renal elimination
- Analgesia in opioid naïve patients
- Precipitated withdrawal in physically dependent patients
- Psychotomimetic (psychosis) effects

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**Abuse-Deterrent Morphine Sulfate ER With Sequestered Naltrexone**

- New Drug Application (NDA) submitted to FDA.

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**Abuse-Resistant/Deterrent Oxycodeone IR/Niacin**

- Niacin to deter excessive oral dosing
  - Warmth or flushing
  - Itching
  - Sweating and/or chills
  - Headache
  - General feeling of discomfort
  - Viscous gel in aqueous solution
  - Prevents injecting and snorting
  - Surfactant
  - Irritation in nasal passages

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**Abuse-Resistant/Deterrent Technology**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Deterrent/Resistant Properties</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR hydromorphone</td>
<td>Difficult to crush and extract</td>
<td>Phase III</td>
</tr>
<tr>
<td>CR oxycodone + naltrexone</td>
<td>Sequestered antagonist</td>
<td>Phase III</td>
</tr>
<tr>
<td>IR hydrocodone</td>
<td>Produg</td>
<td>Phase II</td>
</tr>
<tr>
<td>CR opioid</td>
<td>Difficult to crush, chew, extract</td>
<td>Phase I</td>
</tr>
<tr>
<td>CR broad-spectrum opioid</td>
<td>Difficult to crush, melt, extract</td>
<td>Phase I</td>
</tr>
<tr>
<td>CR morphine + naltrexone</td>
<td>Sequestered antagonist</td>
<td>NDA soon to be filed</td>
</tr>
<tr>
<td>IR oxycodone + niacin</td>
<td>Niacin (+ physical properties)</td>
<td>NDA soon to be filed</td>
</tr>
<tr>
<td>CR oxycodone</td>
<td>Abuse resistant physical properties</td>
<td>NDA filed</td>
</tr>
</tbody>
</table>

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**Summary**

- Opioids are good but not perfect analgesics
- There are differences between opioids
- Risks include side effects, overdose, addiction; but organ toxicity is low
- Slow onset and slow offset is less rewarding
- Some chronic pain may worsen with chronic opioids
- Equianalgesic charts are just estimates and can vary
- Optimal dose determined by careful titration and monitoring
- Exploit synergism with other treatments
Opioid Pharmacology

Examples of widely used opioids include:

- **Buprenorphine** (*trade names*: Buprenex®, Subutex®)
- **Buprenorphine with naloxone** (*trade name*: Suboxone®)
- **Butorphanol** (*trade name*: Stadol®)
- **Codeine** (*trade names*: with acetaminophen – Tylenol® with codeine No. 2, No. 3, No. 4)
- **Fentanyl** (*trade names*: Actiq® lozenge, Fentora® buccal tablet, Duragesic® patch)
- **Hydromorphone** (*trade name*: Dilaudid®)
- **Meperidine** (*trade name*: Demerol®)
- **Methadone** (*trade names*: Dolophine®, Methadose®, Westadone®)
- **Morphine** (*trade names*: Avinza TM®, Duramorph®, Kadian®, MS Contin®, MSIR®, Oramorph SR®, Roxanol TM®)
- **Oxycodone** (*trade names*: OxyContin®, OxyIR®, RoxicodoneTM; with acetaminophen – Endocet®, Percocet®, Perloxx®, Roxicet®, Tylox®; with aspirin – Endodan®, Percodan®, with ibuprofen – Combunox®)
- **Oxymorphone** (*trade names*: Numorphan®, Opana®)
- **Pentazocine** (*trade names*: Talwin®, with acetaminophen – Talacen®; with aspirin – Talwin® compound)

**OPIOID RECEPTORS.** The opioid class includes the natural opiates (drugs derived from opium) and their manmade congeners, which are the agonist and antagonist drugs with mostly morphine-like activity (primarily at the mu opioid receptor), as well as other naturally occurring endogenous opioid peptides, which also are active at the opioid receptors (Borg & Kreek, 2003; ACPA, 2007).

Opioids are formulated as both short- and long-acting. Some are used around-the-clock, while others are used as needed for breakthrough pain. All opioids bind to three principal receptors in the central nervous system – the mu, kappa, and delta receptors – producing analgesia as well as typical opioid side effects (Toombs & Kral, 2005). For example:
Opioid action at the *mu* receptor leads to clinical effects such as analgesia, euphoria, respiratory depression, physical dependence, miosis, and decreased gastric motility.

Opioid action at the *kappa* receptor leads to clinical effects such as analgesia, sedation, and respiratory depression.

Opioid action at the *delta* receptor leads to clinical effects such as analgesia, dysphoria, and hallucinations.

The mu opioid receptor is part of the family of seven transmembrane-spanning G protein-coupled receptors. The effects of opioids on their function is partially mediated by changes in adenyl cyclase activity, with resultant effects on cyclic adenosine 3'5' monophosphate, or cAMP (Dhawan, Cesselin et al., 1996).

- **Opioid Pharmacokinetics and Metabolism**

  The pharmacokinetics of morphine and its metabolites vary, depending on the route of administration. Plasma concentration of morphine given orally every four hours to cancer patients with chronic pain demonstrate a significant, linear correlation between dose and mean plasma level by radioimmunoassay (RIA) with low cross-reactivity. However, considerable variation was found in individual plasma measures of morphine during the same dose intervals, possibly related to rapid absorption and short elimination half-life (Neumann, Henriksen et al., 1982).

  *Aging* also affects morphine pharmacokinetics. For example, the higher sensitivity of older adults to the analgesic properties of morphine may be related in part to altered pharmacokinetics. For example, there is a 50% reduction in total apparent volume of distribution because of lowered central and peripheral kinetic compartment volumes, along with higher calculated peripheral morphine measures after 10 mg/70 kg given intravenously (Borg & Kreek, 2003; Owen, Sitar et al., 1983).

- **Opioid Pharmacodynamics**

  The pharmacodynamics of the clinically important mu opioid receptor agonists are wide-ranging, with the most pronounced effects produced in the CNS and the GI tract. The mechanism of action for all of the clinically relevant opioids is at the mu opioid receptor, in which they act preferentially as agonists (except for buprenorphine, which is a partial mu opioid agonist with high affinity at the opioid receptor, resulting in antagonist-like properties under some conditions).

  *CNS effects* of opioids include analgesia, sleepiness, mood changes, and impaired mentation. Prudent dosing is important, as diminished respiration occurs with opioids until tolerance develops. This is partially because of a direct effect on the brainstem and also because of reduced response of centers in the brainstem, pons, and medulla to carbon dioxide, which can lead to CO₂ retention. Initially there is depressed cough (which is mediated by the medulla), as well as nausea and vomiting, which is mediated by the area postrema of the medulla and which disappear with the development of tolerance. Constriction of the pupil is the result of parasympathetic nerve excitation. In opioid overdose, convulsions can occur, probably
because of inhibition of the release of gamma-aminobutyric acid in the CNS (Borg & Kreek, 2003).

In the cardiovascular system, opioids cause peripheral vasodilatation, decreased peripheral resistance, reduced baroreceptor reflexes, histamine release, and decreased reflex vasoconstriction caused by raised PCO₂.

In the stomach, hydrochloric acid secretion is inhibited and somatostatin release from the pancreas is elevated. Acetylcholine release from the GI tract is inhibited and motility is slowed, as is absorption of drugs. The presence of increased feeding also has been noted. Biliary, pancreatic, and intestinal secretions may be reduced and digestion in the small intestine slowed. In the large intestine, there is reduced propulsion and higher tone.

Immunologic effects also occur. The short-acting opioids such as morphine reduce rosettes formed by human T lymphocytes. Morphine reduces cytotoxic activity of natural killer cells and increases growth of implanted tumors. Beta-endorphin increases cytotoxic action of human monocytes in vitro, and enhances recruitment of precursor cells to the killer cell population. With the use of methadone, absolute numbers of T cells, T-cell subsets, B cells, and quantitative immunoglobulins are restored to normal, with normal natural killer cell activity (Novick, Ochshorn et al., 1989). These indices are abnormal with the use of heroin, possibly because of mediation through the neuroendocrine system, as cortisol suppresses many parameters of immune function.

- Complications and Side Effects of Opioids

Opioid side effects can be classified in three groups: respiratory depression, other physical side effects, and central nervous system side effects that may affect function. Common opioid side effects, particularly at higher doses, include nausea, vomiting, constipation, thought and memory impairment, and drowsiness. Most of these side effects are easily treated with dose adjustments, resolve over time, or can be offset by other medications, such as naloxone.

 Constipation should be anticipated and treated proactively with a bowel regimen that includes dietary changes, stimulant laxatives, and stool softeners.

Mild sedation and impaired judgment or coordination also should be anticipated. Until tolerance or a baseline is reached, the patient and his or her family need to be warned against driving and the potential for falls. Like many other side effects, sedation and cognitive dysfunction may be managed or avoided by changing medications, by continuous administration of the minimum dose necessary to achieve analgesia, or by administration of a treatment medication. When significant persistent opioid-induced sedation occurs in cancer pain patients or patients with other severe intractable pain, stimulants such as methylphenidate and dextroamphetamine may be helpful. The use of stimulant medications, which may be abused by some individuals, requires the same caution in patients with addictive disorder as that required in the use of opioids.

Mild nausea can be treated with medications, but if it does not resolve within a few days, a trial of an alternate opioid may be warranted.

More serious side effects can include respiratory depression (slowed rate of breathing or loss of
urge to breathe) and other physical effects. In July 2005, the FDA issued a public health advisory about reports of death and other serious side effects from overdoses in individuals using fentanyl transdermal patches. FDA issued a similar warning in 2006 about overdoses and deaths related to the use of methadone. However, some patients and health care providers may not be fully aware of the dangers of these medications.

*Respiratory Depression.* Opioid-induced respiratory depression results from depression of brain stem respiratory responses to carbon dioxide. Although CO₂ response decreases in a dose-dependent manner with the administration of mu opioids, clinically significant respiratory depression does not usually occur in the course of treatment of healthy patients with standard analgesic doses of opioids. Respiratory depression may be significant, however, when high-dose opioids are used for acute pain in opioid-naive patients, particularly those who are elderly or debilitated. In such patients, respiratory monitoring is important. Pain is an antidote to respiratory depression so care should be taken when a patient using high dose opioids undergoes a definitive procedure that relieves pain, such as a nerve block or spinal cord ablation. Significant sedation is most often a precursor to respiratory depression and may signal a need to hold medication and adjust the dose.

Respiratory depression rarely is a clinical problem in chronic opioid administration because tolerance to the respiratory depressant effects of opioids tends to occur more rapidly than tolerance to their analgesic effects. Patients should be closely observed, however, when doses are abruptly increased or when patients are rotated to from one opioid to another. Special care should also be used in titration of opioids with long half-lives, such as methadone or levodromoran, because delayed respiratory depression may occur.

*Other Physical Effects.* Common physical side effects of opioid use include constipation, nausea, urinary retention, and pruritus. Side effects are minimized when opioids are prescribed in a manner that reduces the peak blood levels required to sustain analgesia, because the higher blood levels may be associated with increased side effects. To achieve stable analgesic blood levels, scheduled doses of long-acting or controlled release opioids may be used when oral preparations are used. Continuous infusions or patient-controlled analgesia achieve the same goal when parenteral administration is required.

Most often, with the exception of constipation, side effects are transient and may improve or resolve with continued use of opioids at a stable dose. Side effects sometimes are specific to a particular drug with a particular individual and can sometimes be eliminated by use of an alternative opioid. Persistent physical side effects may be managed through pharmacological treatments, such as anti-emetics for nausea or anti-histamines for pruritus.

Constipation is often a persistent side effect of opioid use that may not resolve without treatment. The constipating effects of opioids are thought to occur through direct action on opioid receptors in the gut wall. This causes a decrease in intestinal motility and results in dehydration of stool. It generally is advisable, therefore, to give both a stool softener and a bowel stimulant to effectively manage constipation. When long-term and/or high dose use of opioids is anticipated, introduction of such treatment on a preemptive basis is recommended. Hepatic, renal and other organ toxicity are not reported with opioids as often as they are with many non-opioid analgesics, such as acetaminophen and non-steroidal anti-inflammatories. However, close observation and dose adjustments may be appropriate in persons with impairment in hepatic or renal function that may result in reduced drug clearance.
**Dependence and Addiction.** Among the major factors contributing to the development of addiction to opioids are genetic factors that probably involve specific alleles of multiple genes, which collectively act to increase or reduce vulnerability to addiction. Because the mu opioid receptor is the primary site of action for heroin, it is notable that five single nucleotide polymorphisms have been identified in the coding region of the human mu opioid receptor gene (Bond, LaForge et al., 1998). Three of these five single nucleotide polymorphisms lead to amino acid changes, and two (the A118G and the C17T variants) have very high allelic frequencies: 2% to more than 40% in various populations. On the basis of association studies, the A118G variant can confer some protection against opiate dependency in certain population subsets but increases vulnerability in others. The C17T variant, on the other hand, may have some association with opiate dependence, although significant associations have not been confirmed (Borg & Kreek, 2003).

*Note that addiction should be distinguished from physical dependence.* Any individual who takes sufficient doses of certain types of drugs for a significant length of time can have withdrawal symptoms if the drug is suddenly stopped or reversed by another medicine. This demonstrates the presence of physical dependence but does not constitute addiction.