Pharmacologic Pain Management

- Mild to moderate pain: Acetaminophen (APAP), Aspirin (ASA), and NSAIDs may be sufficient
- Moderate to severe pain, especially acute pain: short course of opioids may be necessary
- Cancer pain: opioids are generally required

Acetaminophen (APAP)

- APAP may be as effective as NSAIDs for analgesic and antipyretic effects, without risk of GI bleeding
- dose: 500-1000 mg PO Q6H, not to exceed 4000 mg/day for short-term use
    - 3000 mg/day max for long-term use
    - 2000 mg/day max for older patients, for patients with liver disease, and for patients with heavy alcohol use
- APAP are combined with opioid meds to reduce the amount of opioid needed
- APAP is the most common cause of hepatotoxicity in the US
    - hepatotoxicity is common due to APAP content in OTC products and combination APAP-opioid products
    - FDA has reduced APAP doses in combination opioid analgesics (Norco and Percocet: 650 mg APAP/tab → 325 mg APAP/tab)

Aspirin (ASA)

- ASA is an effective analgesic, antipyretic, and anti-inflammatory (900-1000mg/dose)
- GI upset and GI bleeding are lessened with enteric-coated products and concomitant use of proton-pump inhibitors (PPI, e.g., omeprazole)
- GI bleeding, allergy, and association with Reye syndrome in children limit ASA use

NSAIDs (e.g., Naproxen / Ibuprofen)

- NSAIDs are effective analgesics, antipyretics, and anti-inflammatory agents

- NSAIDs increase the risk of GI bleeding (PGE inhibition) and nephrotoxicity (PGI inhibition), especially in the elderly
    - GI bleeding and ulceration may be prevented with concurrent use of PPI / Cytotec (misoprostil) / Celebrex (celecoxib) → COX-2 inhibitor
    - NSAIDs, including Celebrex, can cause fluid retention → exacerbate HTN / CHF
    - NSAIDs interfere with antiplatelet effect of ASA

- Voltaren (diclofenac) is also available as a topical patch and gel for use in musculoskeletal pain / osteoarthritis as an alternative to systemic NSAIDs, especially in patients at risk of GI bleeding

- Indocin (indomethacin): very potent PG inhibitor (i.e., high incidence of GI bleeding and nephrotoxicity) used for short-term treatment (tx) of acute gout

- Toradol (ketorolac) IM/IV → common alternative to opioids in ER setting
    - PO/IM/IV → short-term (< 5 days) due to increased risk of GI bleeding and nephrotoxicity, especially in the elderly

Summary Statements: ASA, Acetaminophen, NSAIDs, Glucocorticoids, and Opioids

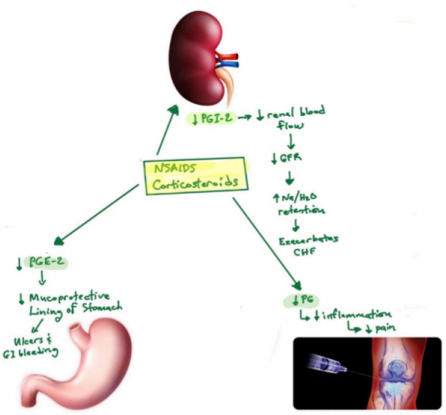
Acetaminophen (Tylenol)

- Properties: antipyretic and analgesic
- Disadvantage: no anti-inflammatory properties
- Advantage: does not cause GI upset, gastritis, GI bleeding/ulcers
- Acetaminophen (APAP) does not exert antiplatelet effect
- APAP overdose --> hepatoxicity

Aspirin (ASA)

- Pharmacologic effects are dose-dependent
  - ASA 81 mg/day --> antiplatelet effect --> reduces risk of recurrent thromboembolic events in post-stroke / post-MI patients.
  - ASA 325-500 mg/dose --> analgesic effect (e.g., headache)
  - ASA 1000 mg/dose --> anti-inflammatory effect
- Disadvantages
  - PGE_2 inhibition (stomach) --> decreases muco-protective lining --> GI upset, gastritis, GI bleeding / ulcers
  - PGI_2 (prostacyclin) inhibition --> decreases renal blood flow --> decreases GFR --> increases sodium/water retention --> exacerbates HTN / CHF

NSAIDs: Ibuprofen (Motrin, Advil) and Naproxen (Naprosyn)



- Properties: antipyretic, analgesic, and anti-inflammatory.
- Disadvanages
  - PGE_2 inhibition (stomach) --> decreases muco-protective lining --> GI upset, gastritis, GI bleeding / ulcers
  - PGI_2 (prostacyclin) inhibition (kidneys) --> decrease renal blood flow --> decrease GFR --> increases sodium/water retention --> exacerbates HTN/CHF
- Naproxen (Aleve is OTC, Naprosyn is Rx) is a more potent NSAID than ibuprofen (Advil, Motrin)
- Naproxen (BID dosing) has a longer duration of action than ibuprofen (TID-QID dosing).

Glucocorticoids = Corticosteroids = Anti-Inflammatory Steroids (Example: Prednisone)

- Properties: potent anti-inflammatory agents; no antipyretic effects.
- Disadvantages
  - PGE_2 inhibition --> decreases muco-protective lining (stomach) --> GI upset, gastritis, GI bleeding / ulcers
  - PGI_2 (prostacyclin) inhibition (kidneys) --> decreases renal blood flow --> decreases GFR --> increases sodium/water retention --> exacerbates HTN / CHF
  - Systemic adverse effects with short-term and long-term use: HPA-axis suppression, immunosuppression, cataract formation, osteoporosis, myopathy, weight gain, hypertension, hyperglycemia, etc …

Opioids: Morphine, Codeine, Hydrocodone, etc…

- Properties: potent analgesic effects; no antipyretic effects and no anti-inflammatory properties.
- Disadvantages: drug tolerance, drug dependence, and potential for opioid addiction.

Narcotic Analgesics

- Short-acting (oral): (1) morphine 4-8 mg PO Q3-4H, (2) hydromorphone (Dilaudid) 1-2 mg Q3-4H, (3) oxycodone (Percocet) 5 mg Q3-4H → for severe acute pain
- Long-acting (oral): MS Contin (morphine) 15-60 mg PO BID, (2) Exalgo (hydromorphone) tablets 12 mg PO daily, and (3) OxyContin (oxycodone) 10-80 mg PO BID.

- Clinicians prescribing opioids must understand the concept of equi-analgesic dosing and calculating morphine milligram equivalence (MME) → converting doses from one opioid to another
    - Equi-analgesic tables are used for estimating the appropriate dose of a long-acting opioid based on the amount of short-acting opioid
    - Equi-analgesic determinations are required for initiating fentanyl patches (FDA requirement)

- Methadone → longest acting opioid
    - Methadone is used for opioid detox and for neuropathic / chronic pain due to it's duration of action and low cost
    - High doses (100-150 mg/day) → risk of QT prolongation on EKG
        - baseline EKG is recommended prior to tx and monthly thereafter

- Fentanyl transdermal patches (Duragesic) → 12.5 – 100 mcg/hour for 72 hours
    - not for use in opioid naïve patients → FDA regulation
    - indicated for patients who have been taking stable dose of opioids for at least 1 week of oral morphine milligram equivalents (MME) of 60 mg/day
    - fentanyl patch may require 12-24 hours to achieve steady state levels; therefore, short acting opioids should be given while waiting the full analgesic effect of the 1st fentanyl patch application

- Meperidine (Demerol) is not a preferred opioid since its metabolite causes irritability and seizures, especially in elderly patients and patients with renal insufficiency

- Tramadol (Ultram) → Schedule IV (SIV) opioid which binds to opioid receptor and blocks reuptake of serotonin-norepinephrine
    - tramadol 50 mg is an approx equivalent analgesic effect to codeine 30 mg
    - risk of serotonin syndrome in patients taking SSRIs and tramadol
    - side effects include risk of seizures

- Buprenorphine / Naloxone (Suboxone) and Buprenorphine (Buprenex)
    - buprenorphine is a SIII long-acting opioid (Q8H) with partial agonist effects
    - concomitant use with other opioids for acute pain may result in competitive inhibition → blunting of analgesic effect of the stronger opioid

Common Side Effects of Opioids

1. Opioid-induced constipation (OIC) should be anticipated and prevented in all patients
    - unlike other side effects, tolerance to constipation does not develop over time

1. Opioid-Induced Constipation (cont.)

    - prescribing a bowel regimen in patients taking opioids long term is recommended for quality of care measures
        - Stool Surfactant: docusate sodium (Colace)
        - Fiber Laxatives: methylcellulose (Citrucel) / Psyllium (Metamucil)
        - Osmotic Laxative: milk of magnesia (Phillips MOM) or polyethylene glycol (Miralax)
        - Stimulant Laxative: bisacodyl tabs (Dulcolax) – onset: 6-8 hours or bisacodyl suppository (Dulcolax) – onset 1 hour

    - methylnaltrexone (Relistor) 8 mcg SC daily for opioid-induced constipation (OIC)
        - methylnaltrexone is a peripheral acting mu-opioid receptor antagonist (GI tract) without affecting central analgesia

    - naloxegol (Movantik) 25 mg PO daily for OIC as a peripheral acting mu-opioid receptor antagonist (PAMORA)

2. Sedation can be expected with opioids, although tolerance to this side effect develops within 24-72 hours at a stable dose
    - caffeinated beverages may reverse minor opioid sedation

3. Neurotoxicity: hyperalgesia, delirium with hallucinations, and seizures may develop with high doses of opioids used for prolonged periods
    - opioid-induced hyperalgesia → increased sensitivity to pain with chronic use of high dose opioids
    - hyperalgesia occurs when typically benign stimuli (e.g., light massage) may be perceived as painful (allodynia)
    - opioid-induced hyperalgesia usually resolves with lowering the opioid dose or switching opioids (“opioid rotation”)

4. Nausea
    - nausea usually resolves after a few days of opioid use
    - unrelieved constipation may be the likely cause of nausea with opioids
    - treatment: ondansetron (Zofran) 4 mg PO/IV Q6H / prochlorperazine (Compazine) 10 mg PO/IV Q6H (25 mg suppository Q12H)

5. Respiratory Depression
    - respiratory depression is uncommon when low opioid doses are given initially and titrated upward slowly
    - COPD patients are particularly at risk for respiratory depression with opioids
        - COPD patients who require high doses of opioids should be monitored closely
    - Naloxone (Narcan), an opioid antagonist, is given as 0.4 mg IV to reverse opioid-induced respiratory depression
    - Narcan nasal spray (4 mg) is sold in California pharmacies without a prescription
        - repeated doses every 2-3 minutes in alternating nostrils
    - Evzio (naloxone) Auto-Injector 2 mg IM injection – may repeat every 2-3 min
        - Cost: $4000 by Kaleo Pharm, Inc.

6. Drug Tolerance
    - opioid tolerance requires increasing dosage to achieve the same analgesic effect

7. Drug Dependence
    - opioid dependence requires continued dosing to prevent a opioid withdrawal syndrome
    - drug dependence is characterized by a withdrawal syndrome following administration of an narcotic antagonist (naloxone) or by abruptly discontinuing a narcotic after chronic use

8. Psychological Addiction
    - addiction is characterized by cravings, resulting in an inability to abstain from continued drug use, despite harm and impairment in behavioral control

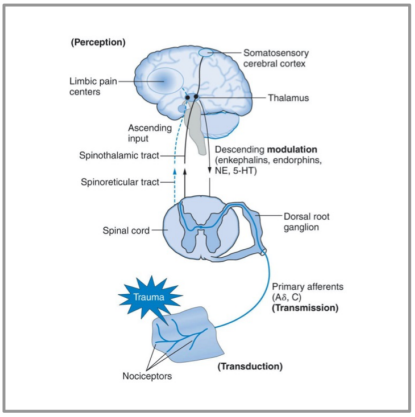
    - clinicians must understand that physical dependence and tolerance are not equivalent to addiction; physical dependence is expected with chronic opioid treatment

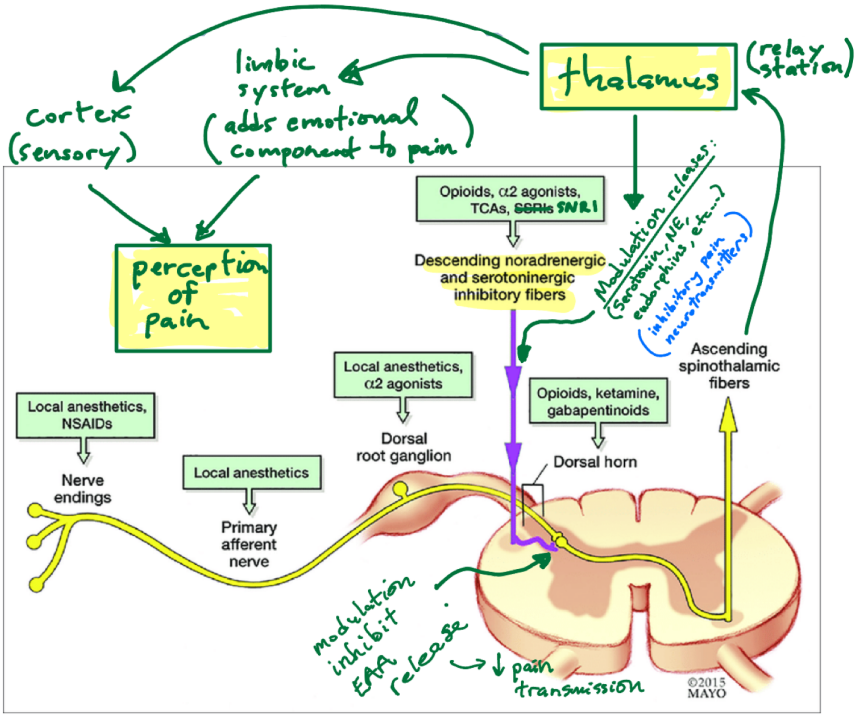
<u>Coanalgesics</u>

- Chronic pain which has a neuoropathic component (e.g., diabetic neuropathy, postherpetic neuralgia) requires coanalgesic therapy

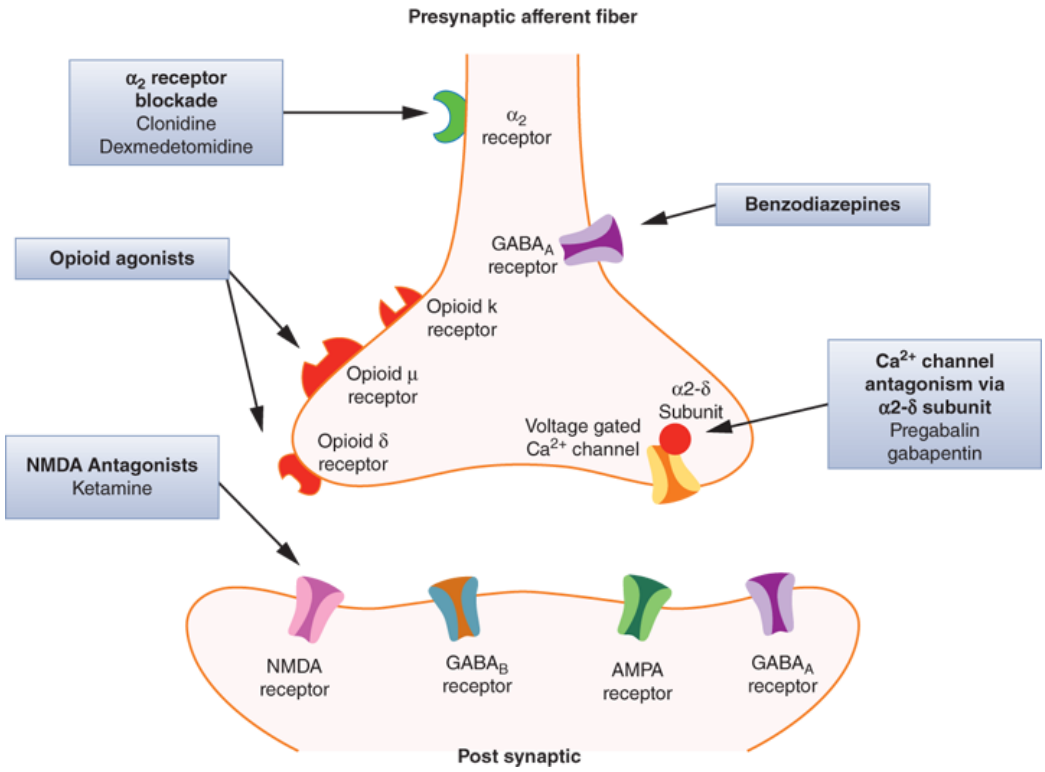
1. Gabapentin (Neurontin) and Pregabalin (Lyrica)
    - bind to voltage-gated calcium channels at the alpha 2-delta subunit and inhibit neurotransmitter release

<u>Pain Transmission</u>: Transduction, Transmission, Perception, & Modulation





1. Gabapentin (Neurontin) and Pregabalin (Lyrica)…. continued
   - side effects (dose-dependent): dizziness and sedation
     - Start with lower doses and titrate upward to lowest effective dose
   - pregabalin (Lyrica) may cause euphoria → classified as Schedule V



2. Antidepressants

   - Tricyclic antidepressants (TCAs) and SE/NE reuptake inhibitors (SNRIs) possess analgesic qualities; SSRIs possess weak analgesic effects;

   - Analgesic antidepressants may provide pain relief separate from their antidepressant effects, since analgesic effects appear to occur earlier (approx. 1 week) and at lower doses than for antidepressant effects

   - Analgesic effects of antidepressants in neuropathic pain has been established in non-depressed

   - In patients with underlying depression, SSRIs may also contribute to relief of pain symptomology

2. Antidepressants (continued)

    A. Tricyclic Antidepressants (TCAs): amitriptyline (Elavil) and nortriptyline (Pamelor)
        - analgesic MOA with TCAs is uncertain, but analgesic properties are associated with their actions as NE reuptake inhibitors
            - evidence suggests that they potentiate endogenous opioid system
        - TCAs also relieve depressive symptoms associated with chronic pain
        - Side Effects: anticholinergic effects (e.g., dry mouth, orthostatic hypotension, constipation, urinary retention, blurred vision) and sedation

    B. Serotonin / Norepinephrine Reuptake Inhibitors (SNRIs)
        - venlafaxine (Effexor) and Duloxetine (Cymbalta) are better tolerated than TCAs
        - duloxetine (Cymbalta) has recently shown to be effective for chronic low back pain and osteoarthritis
        - duloxetine (Cymbalta) may cause nausea, insomnia, drowsiness, fatigue, and dizziness
        - venlafaxine (Effexor) can cause hypertension and induce EKG changes in patients with cardiovascular risk factors

    C. SSRIs → Analgesia with SSRIs are mainly associated with relief of depression in patients with chronic pain

3. Topical Agents

    A. Lidocaine 5% Patch (Lidoderm)
        - Lidoderm is useful in patients with localized neuropathic pain
        - often used as an adjunct to systemic medication
        - apply patch on skin for 12 hours, then remove for 12 hours to reverse tachyphylaxis

    B. Capsaicin (Zostrix) Cream → depletes substance P from primary afferent neurons → reducing pain afferent impulses
        - burning, stinging, and erythema at the site of application leads to intolerance in up to 1/3 of patients

4. Benzodiazepines (BZDs): alprazolam (Xanax), lorazepam (Ativan), diazepam (Valium)

    - BZDs may be utilized in patients with chronic pain complicated by anxiety disorder
    - Disadvantages: addictive potential and respiratory depression in patients who use opioids concurrently

GRAPHICS

Schedules of controlled substances in the United States*

Schedule	Examples	Medical use?	Potential for abuse/dependence	Prescription
I	Heroin, marijuana, LSD ¶	No	High	Not applicable
II	Narcotics: ▪ Codeine ▪ Fentanyl ▪ Hydrocodone and hydrocodone combinations (eg, with acetaminophen) ▪ Hydromorphone ▪ Morphine ▪ Methadone ▪ Oxycodone and oxycodone combinations (eg, with acetaminophen) Stimulants: ▪ Amphetamine ▪ Methamphetamine ▪ Methylphenidate Other: ▪ Cocaine ▪ Pentobarbital, secobarbital	Yes	High	Require a written prescription by a licensed practitioner. Refilling of individual prescriptions is prohibited.
III	Narcotics: ▪ Buprenorphine ▪ Combination products with <90 mg codeine/unit (eg, acetaminophen with codeine) Non-narcotics: ▪ Dronabinol ▪ Ketamine	Yes	Less than with Schedule I and II drugs	A prescription for a drug in Schedules III through V must be issued by a practitioner and may be communicated orally, in writing, or by facsimile to the pharmacist; may be refilled up to five times
IV	Narcotics: ▪ Tramadol and combinations (eg, with acetaminophen) Others: ▪ Alprazolam ▪ Diazepam ▪ Clonazepam ▪ Lorazepam ▪ Midazolam	Yes	Less than with Schedule III drugs	
V	Preparations containing limited quantities of certain narcotic and stimulant drugs used for antitussive, antidiarrheal, and analgesic purposes (eg, cough preparation with <200 mg codeine/100 mL [eg, Robitussin AC])	Yes	Lower than with Schedule IV drugs	

Commonly used, oral and transdermal, long-acting pure mu-opioid agonists for chronic pain in adults (refer to notes)

Drug	Brand name (United States)	Sample initial dose in opioid-tolerant adults	Serum half-life (hours)	Duration of analgesic effect (hours)	Comments
Oral, long-acting preparations					
Hydrocodone	Hysingla ER	20 mg orally every 24 hours	7 to 9	24	▪ May interact with drugs that alter CYP3A4 and 2D6 metabolism ▪ Converted to active metabolite by CYP2D6, which is subject to polymorphisms; individual effects vary ▪ Hysingla ER and Zohydro ER have abuse-deterrent* properties
	Zohydro ER	10 mg orally every 12 hours	13	≤12 in patients with non-cancer back pain	
Hydromorphone	Exalgo	8 mg orally every 24 hours	11	24	▪ Use reduced dose in renal and/or hepatic impairment ▪ Exalgo has abuse-deterrent* properties
	Hydromorph Contin (available in Canada)	3 mg orally every 12 hours	Not specified	≥12	
Morphine	MS Contin, Oramorph SR	15 mg orally every 12 hours	Not specified	8 to 12	▪ Active metabolites are dependent on kidney function for clearance; avoid or use reduced dose-frequency in organ dysfunction ▪ Accumulation of metabolite may contribute to hyperalgesia or other neurotoxicity ▪ Arymo ER has abuse-deterrent* properties
	Kadian	30 mg orally daily in 1 or 2 divided doses	11 to 13	12 to 24	
	Arymo ER	15 mg orally every 8 or 12 hours	Not specified	8 to 12	
Oxycodone	OxyContin, Oxaydo	10 mg orally every 12 hours	4.5	8 to 12	▪ OxyContin and Oxaydo have abuse-deterrent* properties
	Xtampza ER	9 mg orally every 12 hours	5.6	≤12	▪ Xtampza ER has abuse-deterrent* properties
Oxymorphone	Generic only	5 mg orally every 12	9 to 11	12	▪ Take on empty stomach

		hours			▪ Opana ER brand, an abuse-deterrent formulation, was withdrawn from the United States market in mid-2017 due to concerns related to IV injection abuse, including reports of thrombotic microangiopathy; generic extended-release preparations of oxymorphone remain available
Transdermal					
Fentanyl	Duragesic	12 or 25 mcg per hour, patch applied every 72 hours	17 following patch removal	48 to 72 Some analgesic effect may persist for up to 12 hours following patch removal	▪ Onset of analgesic effect is delayed 12 to 24 hours after initial application ▪ Approximate dose conversions for fentanyl transdermal and commonly used oral opioids are provided as a separate table in UpToDate

NOTES:

- The total daily dose requirement for a long-acting opioid formulation should be established first with the use of an appropriate immediate-release opioid analgesic. Details for initiating and adjustment of dose vary by each agent. Refer to UpToDate reviews on cancer pain management with opioids and individual drug monographs (ie, Lexicomp) for detailed information on individual agents.
- Opioids have similar equianalgesic potency whether administered as an immediate-release form (ie, smaller, more frequently divided doses) or an extended-release preparation. To convert from oral immediate-release to an extended-release preparation of the same opioid, use the sum of doses of immediate-release administered during the usual interval of the extended-release form. As an example, morphine sulfate immediate-release 30 mg orally every four hours (total of 180 mg per day) may be converted to morphine sulfate extended-release 60 mg orally every eight hours (total of 180 mg per day).
- Approximate equianalgesic dose equivalents and information on oral immediate-release and parenteral pure mu-opioid agonists that are commonly used in management of cancer pain are provided as separate tables within UpToDate.

mcg: microgram; IV: intravenous.

* Abuse-deterrent formulations have one or more properties that make intentional manipulation of the dose form more difficult (eg, resistant to crushing and dissolution) or less likely to produce an opioid effect (eg, altered to minimize absorption through nasal mucosa). No oral opioid formulation prevents ingestion of an excessive dose.

Courtesy of Kathleen Broglio, DNP, MN, ANP-BC, ACHPN and Russell K Portenoy, MD.

Additional data from:

1. *National Comprehensive Cancer Network. Adult Cancer Pain, Version 2.2016.*
2. *Lexicomp Online. Copyright © 1978-2018 Lexicomp, Inc. All Rights Reserved.*

Graphic 111207 Version 6.0

Approximate oral equianalgesic doses for commonly used opioids

Drug	Approximate equivalent doses (oral immediate-release preparations)	Approximate equianalgesic dose ratio (morphine:alternate opioid)
Codeine*	200 mg	1:7
Fentanyl	No oral equivalent	
Hydrocodone	30 mg	1:1
Hydromorphone	7.5 mg	4:1
Morphine	30 mg	1:1 (reference standard)
Oxycodone	20 mg	1.5:1
Oxymorphone	10 mg	3:1

Equianalgesic conversions serve only as a general guide to estimate opioid dose equivalents. For a review of multiple factors that must be considered for safely individualizing conversion of opioid analgesia, refer to UpToDate topic on cancer pain management with opioids: optimizing analgesia.

* Generally not recommended due to high variability in response.

Graphic 108955 Version 4.0

MORPHINE MILLIGRAM EQUIVALENTS:
CENTERS FOR DISEASE CONTROL AND PREVENTION

This information sheet provides summary information from the Centers for Disease Control and Prevention (CDC) on opioids and their oral morphine milligram equivalent (MME) conversion factors.[1]

The CDC's Injury Center has compiled a listing of medications to help with analyzing prescription data for the purpose of preventing prescription drug misuse, abuse, and overdose.

Oral Morphine Milligram Equivalent Conversion Factors[1]

Opioid (strength in mg except where noted)	MME Conversion Factor*
Buprenorphine, transdermal patch† (µg/hr)	12.6
Buprenorphine, tablet or film‡	30
Buprenorphine, buccal film (µg)§	0.03
Butorphanol	7
Codeine	0.15
Dihydrocodeine	0.25
Fentanyl, buccal/SL tablet or lozenge/troche (µg)	0.13
Fentanyl, film or oral spray (µg)	0.18
Fentanyl, nasal spray (µg)	0.16
Fentanyl, transdermal patch† (µg/hr)	7.2
Hydrocodone	1
Hydromorphone	4

Opioid (strength in mg except where noted)	MME Conversion Factor*
Levomethadyl acetate	8
Levorphanol tartrate	11
Meperidine	0.1
Methadone	3
Morphine	1
Opium	1
Oxycodone	1.5
Oxymorphone	3
Pentazocine	0.37
Tapentadol	0.4
Tramadol	0.1

Please visit the CDC website for additional information, including the full data file containing the MME conversion factors "Oral MMEs - Excel Data File": https://www.cdc.gov/drugoverdose/media/

*To be used in the formula: (Strength per Unit) X (Number of Units/Days Supply) X (MME conversion factor) = MME/Day
†Please see Documentation for additional information on using the formula with transdermal patches.
‡Note: With the August 2016 revision the CDC has increased the conversion factor for sublingual buprenorphine from 10 to 30 for formulations with strength in milligrams.
§Note: The conversion factor for sublingual buprenorphine is 0.03 for formulations with strength in micrograms.

MME: Oral morphine milligram equivalent

The MME conversion factors are intended only for analytic purposes where prescription data are used to retrospectively calculate daily MME to inform analyses of risks associated with opioid prescribing. **This value does not constitute clinical guidance or recommendations for converting patients from one form of opioid analgesic to another.** Please consult the manufacturer's full prescribing information for such guidance.

Use of the above table for the purposes of any clinical decision-making warrants caution. This is particularly true with regard to methadone. Calculating MME for methadone in clinical practice often involves a sliding-scale approach whereby the conversion factor increases with increasing dose. The conversion factor of 3 for methadone presented in the above table would underestimate MME for a given patient. Please see clinical guidance provided here: https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf.

The content used in this document was created by the CDC National Center for Injury Prevention and Control, August 2016.

CALCULATION OF MORPHINE MILLIGRAM EQUIVALENTS PER DAY

(Strength per Unit) X (Number of Units/Days Supply) X (MME conversion factor) = MME/Day

The "Number of Units" and "Days Supply" comes from the prescription. Strength per Unit and MME conversion factor is sourced from the CDC Excel file noted under the table on the front of this document.

Example: 900 µg buprenorphine buccal film X (60 films/30 days) X .03 = 54 MME/day

Example: 25 µg/hr fentanyl patch X (10 patches/30 days) X 7.2 = 60 MME/day

Example: 60 mg hydrocodone ER tablets X (30 tablets/30 days) X 1 = 60 MME/day

Example: 20 mg oxycodone ER tablets X (60 tablets/30 days) X 1.5 = 60 MME/day

Example: 100 mg tapentadol ER tablets X (60 tablets/30 days) X 0.4 = 80 MME/day

NOTES ON SELECTED MME CONVERSION FACTORS

1. A special adjustment was made to permit use of the above formula with fentanyl and buprenorphine patches to account for the fact that such patches are described in units of micrograms per hour rather than milligrams and are used for more than one day.

a. The MME conversion factor for fentanyl patches is based on the assumption that 1 milligram of parenteral fentanyl is equivalent to 100 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour dose over a 24-hour day.

Example:

25 µg/hr fentanyl patch X 24 hrs = 600 µg/day fentanyl = 60 mg/day oral morphine milligram equivalent.

In other words, the conversion factor not accounting for days of use would be 60/25 or 2.4.

However, since the fentanyl patch remains in place for 3 days, we have multiplied the conversion factor by 3 (2.4 X 3 = 7.2). In this example, MME/day for ten 25 µg/hr fentanyl patches dispensed for use over 30 days would work out as follows:

Example:

25 µg/hr fentanyl patch X (10 patches/30 days) X 7.2 = 60 MME/day

Please note that because this allowance has been made based on the typical dosage of one fentanyl patch per 3 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for fentanyl patches = # of patches X 3.

b. The MME conversion factor for buprenorphine patches is based on the assumption that one milligram of parenteral buprenorphine is equivalent to 75 milligrams of oral morphine and that one patch delivers the dispensed micrograms per hour over a 24-hour day.

Example:

5 µg/hr buprenorphine patch X 24 hrs = 120 µg/day buprenorphine = 0.12 mg/day = 9 mg/day oral morphine milligram equivalent.

In other words, the conversion factor not accounting for days of use would be 9/5 or 1.8.

However, since the buprenorphine patch remains in place for 7 days, we have multiplied the conversion factor by 7 (1.8 X 7 = 12.6). In this example, MME/day for four 5 µg/hr buprenorphine patches dispensed for use over 28 days would work out as follows:

Example:

5 µg/hr buprenorphine patch X (4 patches/28 days) X 12.6 = 9 MME/day

Please note that because this allowance has been made based on the typical dosage of one buprenorphine patch per 7 days, you should first change all Days Supply in your prescription data to follow this standard, i.e., Days Supply for buprenorphine patches = # of patches x 7.

2. The MME conversion factor for fentanyl buccal tablets, sublingual tablets, and lozenges/troche is 0.13. This conversion factor should be multiplied by the number of micrograms in a given tablet or lozenge/troche.

3. The MME conversion factor for fentanyl films and oral sprays is 0.18. This reflects a 40% greater bioavailability for films compared to lozenges/tablets and 38% greater bioavailability for oral sprays compared to lozenges/tablets.

4. The MME conversion factor for fentanyl nasal spray is 0.16, which reflects a 20% greater bioavailability for sprays compared to lozenges/tablets.

5. Tapentadol is a µ-receptor agonist and norepinephrine reuptake inhibitor. Oral MMEs are based on degree of µ-receptor agonist activity, but it is unknown if this drug is associated with overdose in the same dose-dependent manner as observed with medications that are solely µ-receptor agonists

CDC Suggested Citation/Reference:

1. National Center for Injury Prevention and Control. CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2016 version. Atlanta, GA: Centers for Disease Control and Prevention; 2016. https://www.cdc.gov/drugoverdose/media/index.html.

MAIN SOURCES CONSULTED FOR MME CONVERSION FACTORS (as listed by the CDC)

1. Von Korff M, Saunders K, Ray GT, et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain*. 2008;24:521-527.

2. Technical Assistance Guide No. 01-13: Calculating Daily Morphine Milligram Equivalents. Waltham (MA): Prescription Drug Monitoring Program Technical Assistance Center; 2013. http://www.pdmpassist.org/pdf/BJA_performance_measure_aid_MME_conversion.pdf. Accessed April 23, 2014.

3. Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OMS) for opioid utilization studies. *Pharmacoepidemiol Drug Safety*. 2016;25:733-737.

4. McPherson ML. Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. American Society of Health-System Pharmacists, 2010.

5. A variety of additional sources were consulted for drugs not included in these publications.

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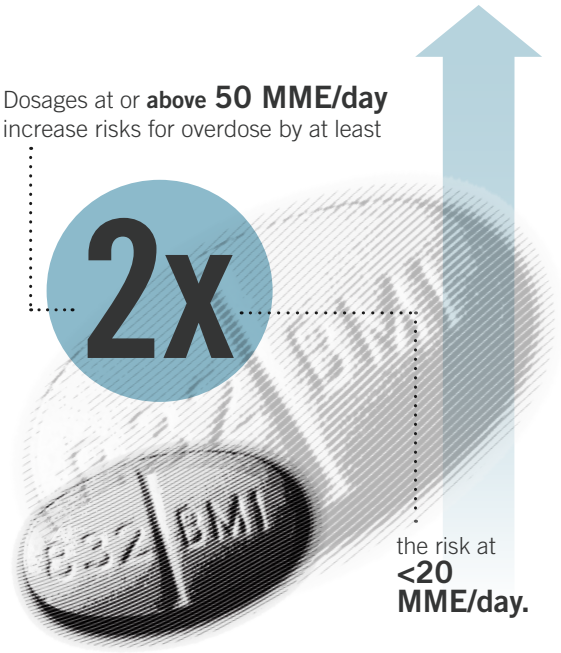
CALCULATING TOTAL DAILY DOSE OF OPIOIDS FOR SAFER DOSAGE

Higher Dosage, Higher Risk.

Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven't been shown to reduce pain over the long term. One randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy (with average final dosage 52 MME) and maintenance of current dosage (average final dosage 40 MME).



WHY IS IT IMPORTANT TO CALCULATE THE TOTAL DAILY DOSAGE OF OPIOIDS?

Patients prescribed higher opioid dosages are at higher risk of overdose death.

In a national sample of Veterans Health Administration (VHA) patients with chronic pain receiving opioids from 2004–2009, **patients who died** of opioid overdose were prescribed an average of **98 MME/day**, while **other patients** were prescribed an average of **48 MME/day**.

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce risk of overdose.

HOW MUCH IS 50 OR 90 MME/DAY FOR COMMONLY PRESCRIBED OPIOIDS?

50 MME/day:

- 50 mg of hydrocodone (10 tablets of hydrocodone/acetaminophen 5/300)
- 33 mg of oxycodone (~2 tablets of oxycodone sustained-release 15 mg)
- 12 mg of methadone (<3 tablets of methadone 5 mg)

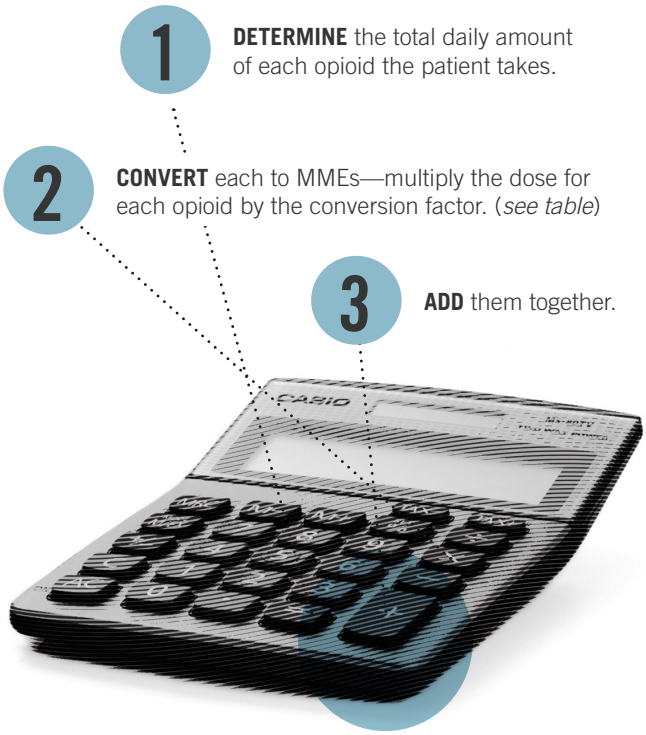
90 MME/day:

- 90 mg of hydrocodone (9 tablets of hydrocodone/acetaminophen 10/325)
- 60 mg of oxycodone (~2 tablets of oxycodone sustained-release 30 mg)
- ~20 mg of methadone (4 tablets of methadone 5 mg)

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

HOW SHOULD THE TOTAL DAILY DOSE OF OPIOIDS BE CALCULATED?



Calculating morphine milligram equivalents (MME)

OPIOID (doses in mg/day except where noted)	**CONVERSION FACTOR**
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3

These dose conversions are estimated and cannot account for all individual differences in genetics and pharmacokinetics.

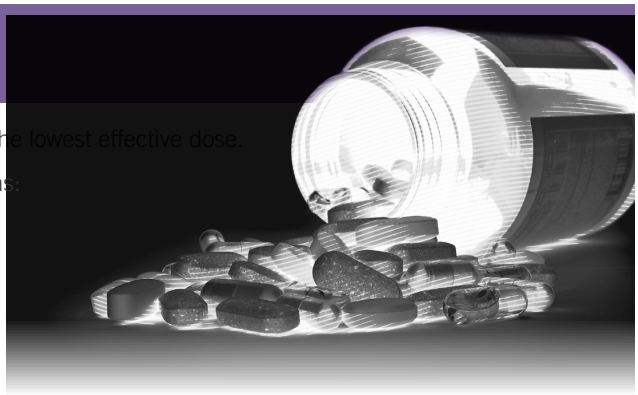
CAUTION:

- Do not use the calculated dose in MMEs to determine dosage for converting one opioid to another—the new opioid should be lower to avoid unintentional overdose caused by incomplete cross-tolerance and individual differences in opioid pharmacokinetics. Consult the medication label.

USE EXTRA CAUTION:

- **Methadone:** the conversion factor increases at higher doses
- **Fentanyl:** dosed in mcg/hr instead of mg/day, and absorption is affected by heat and other factors

HOW SHOULD PROVIDERS USE THE TOTAL DAILY OPIOID DOSE IN CLINICAL PRACTICE?



- Use caution when prescribing opioids at any dosage and prescribe the lowest effective dose.
- Use extra precautions when increasing to ≥50 MME per day* such as:
  - Monitor and assess pain and function more frequently.
  - Discuss reducing dose or tapering and discontinuing opioids if benefits do not outweigh harms.
  - Consider offering naloxone.
- Avoid or carefully justify increasing dosage to ≥90 MME/day.*

* These dosage thresholds are based on overdose risk when opioids are prescribed for pain and should not guide dosing of medication-assisted treatment for opioid use disorder.

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

Opioid Conversion Table

Chronic Pain Management Toolkit

Calculating total daily doses of opioids is important to appropriately and effectively prescribe, manage, and taper opioid medications. There are a number of conversion charts available, so caution is needed when performing calculations. As with all medications, consulting the package insert for dose titration instructions and safety information is recommended. Treatment should be individualized and begin with lower doses and gradual increases to manage pain.

Once the dose is calculated, the new opioid should not be prescribed at the equivalent dose. The starting dose should be reduced by 25-50% to avoid unintentional overdose due to incomplete cross-tolerance and individual variations in opioid pharmacokinetics. This dose can then be gradually increased as needed.

To calculate the total daily dose:

1. Determine the total daily doses of current opioid medications (consult patient history, electronic health record, and PDMP as necessary).
2. Convert each dose into MMEs by multiplying the dose by the conversion factor.
3. If more than one opioid medication, add together.
4. Determine equivalent daily dose of new opioid by dividing the calculated MMEs of current opioid by new opioid's conversion factor. Reduce this amount by 25-50% and then divide into appropriate intervals.

Calculating Morphine Milligram Equivalents (MME)*			
Opioid	**Conversion Factor** (convert to MMEs)	**Duration (hours)**	**Dose Equivalent Morphine Sulfate (30mg)**
Codeine	0.15	4-6	200 mg
Fentanyl (MCG/hr)	2.4		12.5 mcg/hr**
Hydrocodone	1	3-6	30 mg
Hydromorphone	4	4-5	7.5 mg
Morphine	1	3-6	30 mg
Oxycodone	1.5	4-6	20 mg
Oxymorphone	3	3-6	10 mg
Methadone†			
1-20 mg/d	4		7.5 mg
21-40 mg/d	8		3.75 mg
41-60 mg/d	10		3 mg
≥61 mg/d	12		2.5 mg

**The dose conversions listed above are an estimate and cannot account for an individual patient's genetics and pharmacokinetics.*

***Fentanyl is dosed in mcg/hr instead of mg/day, and absorption is affected by heat and other factors.*

†Methadone conversion factors increase with increasing dose.

Sample Case

Your patient is a 45-year-old man who is taking oxymorphone 10 mg 4 times a day for chronic pain. You have determined he is an appropriate candidate for a long-acting regimen and decide to convert him to extended release oxycodone.

1. Total daily dose of oxymorphone → 10 mg X 4 times /d = 40 mg/d
2. Convert to MMEs (oxymorphone conversion factor = 3) →40 X 3 = 120 MME
3. Determine MMEs of oxycodone (oxycodone conversion factor = 1.5) → 120/1.5 = 80 mg/d
4. Decrease dose by 25% → 25% of 80 = 20 → 80 – 20 = 60
5. Divide by interval (q 12 hours) → 60/2 = 30

The starting dose of extended release oxycodone is 30 mg q 12h.

Additional Resources

CDC Opioid Conversion Guide

https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf