USE OF OPIOIDS IN OLDER ADULTS
A Physician’s Perspective

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I, Robert F. Allen, have no actual or potential conflict of interest in relation to this program.
1. Explain the various types, forms and doses of opiates, opioids and synthetic narcotic agonists

2. Discuss clinical conditions in the elderly population in which scheduled analgesics may be appropriate

3. Explain the conversion of scheduled analgesics into morphine milligram equivalents (MME) and potential side-effects, contraindications and drug interactions related to these drugs
PAIN
TRUE OR FALSE

Older adults are less sensitive to pain than younger adults.
TRUE OR FALSE

Older adults may attach lesser importance to their pain in the face of other problems such as loss of a spouse, loss of a job, income, benefits, house, etc.
American Geriatric Society (AGS)

Guidelines for the Management of Persistent Pain in Older Adults

1) **Medical history** to include pain location, severity, frequency, past use of medications, exacerbating activities, use of alcohol, health risks.

2) **Non-pharmacologic interventions:** exercise, physical therapy, ice/heat, education about pain, cognitive behavioral therapy, massage, etc.

3) **Treat with medication**, but simplify any pain medicine regimen.

4) Use acetaminophen or celecoxib on a scheduled basis.

5) Use opiates for persistent pain if the potential benefits outweigh risks.

6) Begin drugs at lower dose, and titrate upward if needed.
7) Be aware of unacceptable risks of non-selective NSAID's in older adults:
   a) substantial risk of gastrointestinal bleeding;
   b) 40% increase in major vascular events (MI, CVD, PVD).

8) Appropriate use of opioids in cases of moderate-to-severe persistent non-malignant pain. Know a few drugs well, adverse effects, etc.

9) Monitor the response to therapy, including more frequent office visits, be aware that chronic pain is associated with anxiety and depression.

10) Multi-disciplinary approach, with appropriate referrals.
What do these terms mean?

- Opium
- Opiates
- Opioids
- Narcotics
**AGONIST:** A molecule, such as a NEUROTRANSMITTER, HORMONE or DRUG, that attaches (binds) to a cell receptor site to produce a physiological effect on / in the cell.

- Many drugs are agonists, having an effect similar or identical to the biological effects of naturally occurring agonists.

**PARTIAL AGONIST:** A drug that binds to and activates a given receptor, but with less efficacy relative to a full agonist.

**ANTAGONIST:** A molecule or drug that blocks, interferes with, or prevents the action of an agonist. In the case of opioids, naloxone is an antagonist that “blocks” the opiate effect.
**ADJUVANT:** Something (drug or otherwise) that supplements or enhances the effectiveness of a medical treatment. In the case of pain management, adjuvant therapies may include:

- **NSAID’s, acetaminophen** (often mixed with opioids), *Celebrex®.*
- Anti-convulsant drugs (*gabapentin, pregabalin, carbamazepine*).
- Anti-depressants (*tricyclics, duloxetine, venlafaxine*), not SSRI’s.
- Antipsychotics (older typicals, newer atypical s).
- Benzodiazepines, *buspirone, hydroxyzine,* and other sedatives.
- **Others:** topical and regional anesthetics, botulinum toxins, ketamine, *capsaicin,* TENS, biofeedback, hypnosis, yoga, etc.
POPPIES (scientific names: *Papaver* species) are popular and attractive garden plants, whose flowers vary greatly in color, size and form. This photo shows a flowering opium poppy and seed pods at a Buddhist lodge in Nepal.

The earliest known seed pods date back to 5000 BCE. Many ancient cultures utilized opium for pain relief, allowing surgeons to perform long procedures.
POPPY SEEDS

POPPY SEEDS are a common flavorful topping for rolls, breads and cakes.

The seed pods contain a mixture of latex alkaloids (morphine, codeine, thebaine, papaverine, noscapine).

Private garden opium poppy cultivation is not usually subject to legal controls.

The 3 narcotic latex alkaloids (morphine, codeine, thebaine) make up less than 14% of opium latex in seed cultivars.
Because they contain opiates, the seed pods can be boiled in water to produce a bitter poppy tea that induces a long-lasting intoxication.

Eating poppy seeds may produce a positive urine drug test, which is interpreted as a false positive indicator of drug use.

Gas-Liquid Chromatography can distinguish poppy seeds from morphine and heroin. Thus, GLC can be used as legal defense.
OPIUM, aka poppy tears (scientific name: Lachryma papaveris) is dried latex obtained from the opium poppy Papaver somniferum.

A traditional, labor-intensive method of obtaining the latex is to scratch or score the immature seed pods (fruits) by hand. The latex leaks out and dries to a sticky yellow-brown residue that is later scraped off and dehydrated.

This traditional production method has not changed since ancient times.
18th Century Spread of Opium

- In the 18th century, Europeans (Brits in particular) had a high demand for Chinese goods like tea and silk.
- However, the Chinese did not have a high demand for European goods, creating a trade deficit.
- The British were forced to pay the Chinese in silver.
- In order to obtain enough silver, the British had to buy it from other European countries, which in turn created even further debt.
18th Century Spread of Opium

- In 1773, Britain conquered the Bengal Province in India, at the time the world's largest producer of opium.

- Once the Indian poppy fields were under British control, Britain elected to start trading opium as a way of addressing the trade imbalance with China.

- Soon, opium addiction had spread throughout China.

- In 1839, the Chinese emperor seized and burned opium brought in by British ships. This marked the beginning of the “Opium Wars,” won by the British, who then resumed the opium trade.
Some historical figures were known users of opium, often for cultural purposes such as writing, artistic and musical inspiration:

- **Thomas DeQuincey** – “Confessions of an English Opium-Eater” - in 1804 - the first published documentation of an opium addict.
- **Samuel T. Coleridge** – “Kubla Khan” – ‘the stately pleasure dome’.
- **John Keats** – “Ode to a Nightingale” – ‘a drowsy numbness’.
- **Charles Dickens** – “The Mystery of Edwin Drood” – opening was set in an opium den - Dickens died before completing the work.
- **Edgar Allen Poe** – “The Raven” and many other works were either inspired by, or written under the influence of opium and alcohol.
OPIUM & MUSICALITY

- **Frederic Chopin** – among the very top composers of piano music, Chopin regularly used opium on a sugar cube to aid his TB cough.

- **Hector Berlioz** –

  “**Symphonie Fantastique**”

  Often referred to as the ‘druggiest’ piece of music in the classical canon.

- 90+ musicians, 55 minutes of highly inventive, dream-state, love-gone-wrong genius.
OPIATES

- **OPIATE**: A narcotic analgesic from the opium plant.

- Opium latex (resin) contains over 20 alkaloids. Approximately 12% of non-modified opium latex is made up of the analgesic alkaloid morphine. The latex also contains closely-related opiates codeine and thebaine, and non-analgesic alkaloids papaverine and noscapine.

- **Morphine** is processed chemically to produce semi-synthetic opioids for medicinal use. Morphine is also processed to heroin for illegal drug trade. By selective breeding or genetic modification of the Papaver somniferum plant, the content of the morphine, codeine and thebaine can be greatly increased, even to 90% of the resin (latex).
ORIGINS OF ILICIT OPIUM FOR HEROIN
Opiates

- The USA has a policy of sourcing **80%** of its narcotic raw materials from the traditional producers, India and Turkey; while some comes from Australia (mostly from Tasmania).
- Multiple pharmaceutical companies process the opium products into scheduled opioids.
- For the illegal drug trade, extracting morphine from the opium latex reduces the bulk by 88%, making it easier to smuggle and easier to convert into heroin. Heroin is 2-4 times more potent and equally more expensive than morphine.
TRUE OR FALSE

All opiates are opioids, and all opioids are opiates.
OPIOIDS

- **OPIOID**: A narcotic analgesic that is either:
  - derived directly from the opium plant (natural opiate);
  - synthesized from an opiate (semi-synthetic opioid); or
  - manufactured to resemble an opiate, making it capable of binding to an opiate receptor (synthetic opioid).

- **Morphine, codeine and thebaine** are opiates (from opium latex).

- **Thebaine** is the usual raw material for synthesis of hydrocodone, oxycodone, hydromorphone, oxymorphone, buprenorphine, and other semi-synthetic opioids.

- Currently, most thebaine originates not from Papaver somniferum, but rather from extracting P. bracteatum or P. orientale.
SYNTHETIC OPIOIDS

- **SYNTHETIC OPIOID**: A narcotic substance that is **not** derived from the opium poppy plant, but instead is fully human-made in a laboratory. Synthetic opioids include:
  - **Methadone** (Dolophine®, Methadose®, Diskets®, Intensol®).
  - **Fentanyl** (Duragesic®) transdermal patches, (Actiq®) lollipops.
  - **Meperidine** (Demerol®) oral, IM, IV.
  - **Tramadol** (Ultram®, Ultram ER®, Ultracet® with APAP 325, oral).
  - **Tapentadol** (Nucynta®, Nucynta ER®) oral.
  - Others are for IV dosing, only in general anesthesia induction.
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TRUE OR FALSE

Pain is an experience that is a natural part of the aging process.
**PHYSIOLOGY OF PAIN**

- **PAIN:** “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” *

- **NOCICEPTIVE PAIN:** Physiological process that occurs in the body during activation and sensitization of tissue nociceptors.

- **NEUROPATHIC PAIN:** Pain arising from a lesion or disorder in the nervous system or abnormal pain circuits in the CNS.

* International Association for the Study of Pain (1979),

* Amended (1994), noting that pain could occur in the absence of tissue damage and it is impacted by psychological factors.
MEDICAL CONDITIONS IN WHICH THE USE OF OPIOIDS MAY BE NEEDED

With Special Emphasis on Conditions that Affect Older Adults
POSSIBLE NEED FOR OPIOIDS
LOW BACK CONDITIONS

- Degenerative joint disease (DJD), facet joint osteoarthritis
- Degenerative disc disease (DDD), 75% at L5-S1 level
- Bulging disc or herniated nucleus pulposus (HNP)
- Lumbar / lumbosacral spinal stenosis (LSS)
- Vertebral compression fracture (traumatic vs. osteoporotic)
- Scoliosis (usually thoracic, but also other levels)
- Ankylosing spondylitis (M:F = 3:1, autoimmune: HLA-B27)
POSSIBLE NEED FOR OPIOIDS
HIP, KNEE, & FOOT CONDITIONS

- Osteoarthritis of hip(s) in 1/2 men, 1/3 women ≥ 65 yrs
- Osteoarthritis of knee(s), often post-traumatic in origin
- Tendinitis (inflamed tendons) due to age-related reduced elasticity of tendons, often strained during activity or tasks such as gardening, squatting, crouching, etc.
- Trochanteric bursitis (inflamed subtrochanteric bursa)
- Traumatic (falls) or pathological (osteoporotic) fractures
POSSIBLE NEED FOR OPIOIDS

MYOPATHIC PAIN SYNDROMES

- Fibromyalgia (an archaic term) of neck and shoulder girdle muscles. Treatment modalities may include:
  - 1° - Thermal, physical therapy, chiropractic, massage, meditation, exercise, yoga, hypnosis, cognitive behavioral therapy
  - 1° - Tricyclics and muscle relaxers (tizanidine, baclofen, carisoprodol)
  - 1° - SNRI’s - Cymbalta® (duloxetine), Savella® (milnacipran)
  - 2° - Anticonvulsants - Lyrica® (pregabalin), Neurontin® (gabapentin)
  - 3° - Opioids are considered tertiary and PRN, keep doses low
- Since tissue inflammation is not a factor, avoid NSAID’s and steroids
- Polymyalgia rheumatica (PMR) - ? autoimmune HLA-DR4
- Limb myalgias of various causes: statin-induced, hypothyroidism
POSSIBLE NEED FOR OPIOIDS
CRANIO-FACIAL CONDITIONS

- Chronic daily headache subtypes:
  - Chronic daily migraine
  - Chronic tension-type headache (CTTH)
  - Cluster headache, M:F = 9:1 (often worsened by opioids)
  - Medication overuse (NSAID’s, benzo’s, butalbital)
- Temporomandibular joint (TMJ), nearby jaw muscle pain
  (botulinum toxin injections have become 1st line therapy)
- Trigeminal neuralgia (tic doloreaux) V3 > V2 > V1
- Post-herpetic neuralgia (rare in facial dermatomes)
POSSIBLE NEED FOR OPIOIDS
NERVOUS SYSTEM CONDITIONS

- Peripheral neuropathies, often in diabetics
  - 1° - Lyrica® (pregabalin)
  - 1° - Tricyclics (amitriptyline, nortriptyline)
  - 2° - Vimpat® (lacosamide)
  - 3° - Opioids at lowest effective dose
- Multiple sclerosis (MS)
- Post-stroke pain (use tricyclics, tizanidine or baclofen first)
- Post-herpetic neuralgia – commonly thoracic dermatomes
Possible Need for Opioids
Neoplastic Conditions

- Cancer-related pain may be caused by:
  - Solid tumor pressing on bones, nerves, or other nearby organs;
  - Lowering the pH (from 7.4 to ~6.8) in surrounding tissues;
  - Production of inflammatory cytokines that cause irritation;
  - Remote (paraneoplastic) effects.

- Many solid tumors metastasize (spread) to spine, brain, or internal organs; bone mets are particularly painful.

- Hematopoietic: bone pain in leukemias, lymphomas, myeloma

- Treatment-related pain: neuropathy, stomatitis, radiation
Morphine Milligram Equivalents

- **Morphine**, in 1805, was the first opiate to be isolated from the opium poppy plant, *Papaver somniferum*.

- The potency of each of the other opiates and opioids is compared with the potency of morphine.

- The comparative potency for each drug is calculated in **MME’s** (Morphine Milligram Equivalents).

- **PLEASE NOTE:** This is **NOT** an exact science !!! The MME is NOT to be used for converting a patient’s therapy from one opioid to another, due to cross-tolerance and individual differences in opioid pharmacokinetics.
For initial dosing regimens, this table may help with perspective:

- Morphine 30 mg
- Hydrocodone 30 mg
- Oxydocone 15 mg
- Hydromorphone 7.5 mg
- Oxymorphone 7.5 mg
- Codeine 180 mg

- Fentanyl: Too variable to use a conversion chart, and more commonly dosed in a transdermal patch at mcg/hr.
- Methadone: Reserve for prescribers with advanced training.
FATAL PAINKILLER OVERDOSES SOAR IN US, CDC SAYS:

- (CBS News) Methadone accounts for only 2 percent of painkiller prescriptions in the United States - but the drug is behind more than 30 percent of prescription painkiller overdose deaths, the Centers for Disease Control and Prevention has announced.

- Methadone is commonly known for treating withdrawal symptoms from heroin addiction, but the drug is also prescribed for pain (increasing since 1999). Health officials say most of the overdose deaths are people who take it for pain - not heroin or drug addicts.

- **Study:** Heroin may be cheaper and more effective than methadone at treating addicts
Equianalgesic Dosing of Opioids

- Equianalgesic (equal pain-relieving) tables are approximate, not exact. Err on the side of a lower dose (‘haircut’ analogy).

- When necessary to change from one opioid to another in a patient (efficacy, adverse effects, cost, method of delivery), start the new drug at about 50% MME of the former drug.

- Titrate dose to an effective, yet safe, pain control response.

- **Opioid Conversion Algorithm**
  
True or False

Compared with younger adults, older patients usually have an increased rate of comorbid medical conditions.
OPIOID DOSE ADJUSTMENTS

Older adults (we will use ≥ 65 years for most of the current discussion) may present to us for pain management with clinical situations such as:

- **Impairment** of memory, judgment, reasoning and self-care;
- **Tendency to falls** due to unsteady gait, vertigo, or other risks;
- **Physical debilitation** due to any of numerous origins;
- **Renal insufficiency** (based on creatinine clearance or GFR);
- **Hepatic insufficiency** (based on serum hepatic enzymes);
- Taking other drugs having **Cytochrome P450 metabolism**.
Opioid use in older adults should be implemented only when alleviation of pain, increase in function, and improvement in activities of daily living outweigh the risks to the patient.

Use cautious dosing of opioids for older adults.

“Start low and go slow” is a rule, not a recommendation.

It is imperative to understand “Who is in the house?”

Who is the primary caregiver?

Who will be responsible for actual dosing (drug, dose, time)?

Who is in the home, or comes in and goes out, that can steal a controlled scheduled medication (drug diversion)?
TRUE OR FALSE

For treating persistent pain in older adults, it may be best to use long-acting or extended release formulations from the beginning.
In many conditions, non-steroidal anti-inflammatory drugs (NSAID’s) have been a mainstay for mild to moderate pain.

Increasing concerns center on serious adverse effects of both the selective and non-selective NSAID’s, because all NSAID’s (except naproxen) are associated with a **40% increased risk of serious vascular events** compared with placebo.

Acetaminophen (APAP) is an obvious alternative to NSAID’s, but dose is limited by hepatotoxicity. Also, APAP cannot provide sufficient pain relief in the management of disabling inflammatory conditions such as osteoarthritis and rheumatoid arthritis.
The careful use of opioid analgesics should be considered in the treatment of moderate to severe pain when non-pharmacologic options and non-opioid analgesics (APAP and low-dose NSAID’s) have proven inadequate for pain control.

Opioids are still considered to be the most potent and most effective ‘broad-spectrum’ analgesics in the treatment of chronic pain.

Opioids can be prescribed to patients suffering from moderate to severe disabling pain of both cancer and non-cancer origin.

The analgesic action of morphine and other opioid agonists is well known and utilized clinically in pain management.
**OPIATES & OPIOIDS**

- **MORPHINE, IMMEDIATE-RELEASE (IR) (CII)**

- **THERE IS NO STANDARD DOSE.** One example of a treatment plan is to start 10 mg oral every 4 hours, as scheduled, not on demand.

- Offer “rescue” doses if the q 4 hr. dose is insufficient.

- Adjust dose daily by adding together the total doses for the past 24 hr.

- Add a laxative (Lactulose) after 48 hr. (on day 3).

- Parenteral (10 mg/1mL) and Suppository 5 mg, 10 mg, 20 mg, 30 mg

- Once pain is controlled, convert to an extended-release oral formula if the drug is to be continued.

- **REDUCE DOSE BY 50% IN OLDER ADULTS, AGE ≥ 65 YEARS,** due to hepatic metabolism to the active metabolite M6G.
**Opiates & Opioids**

- **Morphine, Controlled-Release (CII)**
  - MS Contin® oral tablets: 15 mg, 30 mg, 60 mg, 100 mg* and 200 mg*  
    * 100 mg and 200 mg are for use in opioid-tolerant patients only.
  - To convert from Morphine IR to MS Contin® → 30 mg q 12 hr → titrate.
  - MS Contin® tablets are to be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed MS Contin® tablets leads to rapid release and absorption of a potentially fatal dose of morphine.
  - Kadian® Extended-release capsules: 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg.
  - Life-threatening respiratory depression and other complications are more likely to occur in older adults and in debilitated patients.
OPIATES & OPIOIDS

MORPHINE, EXTENDED-RELEASE CAPSULE (CII)

Avinza® and MorphaBond ER® are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. REMS required by the manufacturers.

Common starting dose is 30 mg q 24 hrs in an opioid-naïve patient, or 60 mg daily in opioid-tolerant patients.

Doses of 90 mg to 120 mg daily are only for opioid-dependent patients in whom doses of other opioids (in MME) have been established and in whom the tolerance is mostly known.

Capsules must be taken whole, without chewing, crushing, opening or dissolving in liquid; aberrance may cause overdose or death.
OPIATES & OPIOIDS

- OXYDOCONE (CII)
- Roxicodone® and generic, oral tablet containing 5 mg, 10 mg or 15 mg as oxycodone hydrochloride.
- Also in combination form with APAP 325 mg: Percocet®, Roxicet®.
- Dose for acute moderate to severe pain: 5-15 mg q 4-6 hr.
- For use in chronic severe non-malignant pain control in opioid-tolerant patients, dose range is 5 mg q 4-12 hr or 10 mg q 8-12 hr.
- Reduce the dose to 1/3 to 1/2 of a more usual starting dose in older adults, in debilitated patients, and in patients with hepatic insufficiency.
- When feasible, after stabilization, convert to OxyContin® (controlled-release oxycodone film-coated tablets), dosed q 12 hr. Rescue medication may be needed for breakthrough pain (not over twice per 24 hr).
CONTROLLED-RELEASE OXYCODONE (CII)

OxyContin® is available as a film-coated tablet in doses of 10 mg, 20 mg, 40 mg, 60 mg and 80 mg.

Dose schedule is typically one tablet q 12 hr.

Though frowned upon by some insurers, I have from time to time been able to get approval for other dose schedules: for example, 40 mg morning, 40 mg afternoon, 60 mg bedtime (total 140 mg/24 hr).

Be aware that, although both oxycodone and hydrocodone are now classified in Schedule II, oxycodone was there first and may be generally considered more potent and/or more addictive.
OPIOATES & OPIOIDS

- HYDROCODONE (CII) as of 2014
  - Dose range: 2.5 mg, 5 mg, 7.5 mg, 10 mg plus a congener.
  - Hydrocodone is mixed with APAP 325 mg (Norco, Lortab, Vicodin) or with ibuprofen 200 mg (Vicoprofen) in tablet form.
  - It is also available as a syrup (Lortab Elixir) 7.5 mg hydrocodone and 500 mg APAP per 15cc.
  - Doses are 5-10 mg q 4 hr for acute moderate to severe pain, or 5-10 mg q 4-12 hr for chronic non-malignant pain.
  - 95% → neuroexcitatory hydromorphone-3-glucuronide (H3G). There is no long-acting formulation of hydrocodone.
**OPiates & Opioids**

- **Hydromorphone (CII)**
  - Oral tablet, as hydrochloride: Dilaudid®, generic: 2 mg, 4 mg, 8 mg
  - Oral liquid, as hydrochloride: Dilaudid®, generic: 1 mg/mL (sweet)
  - Solution for Injection, as hydrochloride: Dilaudid®: 1 mg/mL (0.5 mL, 1 mL); 2 mg/mL; 4 mg/mL
  - High-potency liquid: Dilaudid-HP®: 10 mg/mL (1 mL, 5 mL, 50 mL)
  - Suppository, Rectal, as hydrochloride: only in generic: 3 mg (6 ea)
  - Extended-release hydromorphone:
    - Exalgo® and generic ER 24-Hour abuse-deterrent, as hydrochloride: 8 mg, 12 mg, 16 mg, 32 mg. **NOTE:** For opioid-tolerant patients only, with no recommendations for initial opioid-naïve patients.
OPIATES & OPIOIDS

- **OXYMORPHONE (CII)**
- **Opana®** is an immediate-release oxymorphone.
- For acute pain, the dose range is 10-20 mg q 4-6 hr.
- For use in moderate to severe non-malignant chronic pain, the dose range is 5-10 mg q 4-12 hr.
- **Opana ER®** was the extended-release branded form, which was removed from the U.S. market in 2017. The FDA had requested Endo to make a “voluntary recall” because Opana ER® was never approved by the FDA in abuse-deterrent formulation (ADF).
EXTENDED-RELEASE OXYMORPHONE (C II)

When Opana ER® was recalled in 2017, prescribers had to make an educated and safe rotation to an alternative opioid based on the best therapeutic decisions and clinical evidence available.

Patients could still be treated with a generic oxymorphone ER; although it had no abuse-deterrent properties and was more easily abused, it was not affected by the FDA recall request.

Opana ER® was then reformulated and came back to the U.S. market, only to again be removed by the FDA. The second recall was because of a shift in the route of abuse of Opana ER® from intra-nasal to injection, with a concomitant increase in the spread of HIV and hepatitis C among abusers. (YGDAW).
MEPERIDINE (CII)

Demerol® (meperidine hydrochloride) should be used IV or IM for acute dosing only, due to a short duration of action (2.5 to 3.5 hrs) and its neurotoxic metabolite, normeperidine.

Avoid in older adults, and use caution in renal insufficiency and in hepatic impairment, due to high potential for toxicity secondary to accumulation of normeperidine.

Seizures, myoclonus, tremor, confusion, and delirium may occur.

Although an oral product is marketed, the biopharmacokinetics are highly aberrant and frankly, other products with better benefits and less risks are available and preferred.
FENTANYL (C II)

Non-injectable fentanyl products are for opioid-tolerant patients only. Do NOT convert mcg for mcg among fentanyl products, including Duragesic® or generic patch, Actiq® transmucosal lozenge, Fentora® buccal tablet, Abstral® sublingual tablet, Onsolix® buccal film, Lazanda® nasal spray.

See specific product labeling (U.S.: Drugs@FDA) for dosing. Or, for U.S. products only, see the Pharmacist’s Letter (PL) Chart, “Fentanyl Products for Breakthrough Pain.”

Some experts use this conversion in cancer patients only: oral morphine 60 mg total daily dose = 25 mcg/hr fentanyl patch.

Round up or down based on patient factors and available patch sizes.
TAPENTADOL (CII)

- A very strong synthetic opioid with a high affinity for the mu-opioid receptor.
- Initial dosing of the immediate-release form:
  - Nucynta® 50 to 100 mg orally q 4-6 hr as needed for pain control.
    - Day 1: A second dose may be administered as soon as 1 hour after the first dose if needed.
    - Subsequent dosing: 50, 75, or 100 mg orally q 4-6 hr; adjust dosing to maintain adequate analgesia with acceptable tolerability.
  - Maximum dose: 700 mg on day 1; 600 mg/day on subsequent days
  - Nucynta ER® in 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, dosed q 12 hr.

- REMS from the manufacturer is strongly recommended prior to prescribing.
- Potential for respiratory depression is a major concern in older adults.
OPIATES & OPIOIDS

- **CODEINE with APAP (C III)**
  - The most commonly taken opiate, codeine is a Class II in its pure form, but is a Class III when mixed with APAP or Ibuprofen. It is also available as a Class V in two cough syrups at low dosage of 10 mg per dose. Seven (7) active metabolites!
  - Tylenol #2® (codeine 15 mg) and Tylenol #3® (codeine 30 mg), Tylenol #4® (codeine 60 mg) each of which are mixed with APAP 325 mg.
  - Dose ranges are 15-60 mg q 4 hr for mild to moderate pain, or 15-30 mg q 4-12 hr for moderate chronic non-malignant pain.
  - **Ibuprofen with Codeine** (200 mg/12.8mg), film-coated tablet.
  - **REDUCE DOSE 50%, AVOID CHRONIC USE IN OLDER ADULTS.**
**OPIATES & OPIOIDS**

- **TRAMADOL (CIV)**
  - Ultram® (tramadol) potency is about one-tenth that of morphine, and similar to codeine.
  - Ultram® and its generic are dosed as single 25 mg or 50 mg tablets, one q 4-6 hr, with maximum dose of around 400 mg/24 hr.
  - Ultracet® contains tramadol 37.5 mg with APAP 325 mg, dose limited by the APAP component to 2 tabs QID (300 mg tramadol/day).
  - Ultram ER® once-daily dose, available in 100 mg, 200 mg and 300 mg.
  - **Dose reduction by 50% is generally recommended in older adults.** See product labeling for doses in renal or hepatic dysfunction.
  - Contraindicated in patient on serotonergic meds (SSRI, SNRI, tricyclic).
OPIATES & OPIOIDS

**PENTAZOCINE (CIV)**

- *Talwin®* (pentazocine hydrochloride 50 mg) and *Talwin NX®* (pentazocine hydrochloride 50 mg plus naloxone 0.5 mg) are synthetic opioids used for management of acute moderate to severe pain. Dosing intervals are q 4-6 hr for both products.

- *Talwin NX®* contains the narcotic antagonist naloxone to aid in preventing improper use (melting and injecting) among abusers.

- As with other opioids (natural and synthetic) the frequency of dosing of *Talwin®* or *Talwin NX®* should be reduced in older adults, in the cognitively impaired, and in the presence of hepatic insufficiency.
METHADONE (CII) for use in opioid-tolerant patients only.

From discussions with members of the Alabama Board of Medical Examiners, it is my best understanding that Alabama physicians should only prescribe Methadone as a part of a sanctioned Methadone clinic.

The conversion ratio of methadone is highly variable depending on factors such as patient tolerance, MME dose, and length of dosing (short-term vs more chronic dosing). Because the analgesic duration of action is shorter than the half-life, toxicity due to drug accumulation can occur within a few doses.

Some experts recommend that only those with substantial experience with its use should prescribe methadone. Methadone is not registered with PDMP.

For some conversion methods, see http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/page3.
DISEASES & CONDITIONS IN WHICH TO AVOID OPIOIDS

- **Impaired GI motility** - can lead to toxic megacolon
- **Gastrointestinal obstruction** - drug remains in GI tract and can be suddenly released in mass (fatal dose) with restored GI motility
- **Infectious diarrhea** - delays excretion of viruses, bacteria or their toxins, and can prolong pseudomembranous enterocolitis
- **Liver disease** - increased serum concentrations and prolonged ½ life
- **Renal dysfunction** - altered elimination of active metabolites
- **Acute alcohol intoxication** - CNS depressant effects are additive
- **Drug dependence** - tolerance, abuse, addiction, withdrawal
- **Hypotension** - vasodilation, worsening of hypotension and shock
DISEASES & CONDITIONS IN WHICH TO AVOID OPIOIDS

- **Increased intracranial pressure** - can cause cerebral hypoxia, and may interfere with neuro checks (consciousness, respiratory status, pupils)
- **Respiratory depression** - avoid use in asthma, hypoxia, sleep apnea, COPD (due to decreased ciliary dysfunction and cough reflex)
- **Adrenal insufficiency** - potentiation of adrenal function in Addison’s disease
- **Biliary spasm** - increases biliary tract pressure (esp at sphincter of Oddi)
- **Hypothyroidism** - potentiates lethargy, depression, mental slowness
- **Seizure disorders** - proconvulsant activity, potentiation of seizures
- **Urinary retention** - inhibits voiding reflex, may need catheterization
- **Arrhythmias** - cholinergic activity leading to bradycardia
TRUE OR FALSE

Compared with younger adults, older patients usually stick with one doctor and thus avoid multiple prescribers.
Goals of healthcare providers should be to control patients’ pain while limiting bothersome side effects and adverse outcomes.

Pain management is subjective and fraught with potential adversity, even more so in older adults.

The side effect profile of opioids is, in many ways, similar for all age groups.

However, the older adult population is at a greater risk for opioid side effects and adverse complications of therapy given the high incidence of medical comorbidities and higher rate of polypharmacy in the over-65 age group.
Pain management in the older adult population is especially challenging when one considers all of the numerous pharma-co-dynamic changes that occur with normal aging.

**Opioid** use at the most efficacious dosage matched to the type and severity of pain becomes crucial in older adults.

Knowing how to increase and decrease opioid doses and to move among the different classes is imperative for the safe, successful management of acute and chronic pain.

**Adjuvant therapy** is encouraged as standard practice.
The liver is responsible for the metabolism of opioids to their (often many) metabolites.

The kidneys are responsible for the elimination of some opioid metabolites (some active, some inactive).

Since older adult patients may have an increased risk of drug accumulation because of decreased renal or hepatic function, there is a narrow therapeutic window between dosages that are safe and dosages that could lead to impaired judgment, driving errors, unsteadiness, falls, overdose, respiratory depression, sedation, coma or death.
OPIATES IN RENAL INSUFFICIENCY

- **BUPRENORPHINE** – In patients with reduced renal function, chronic renal insufficiency and hemodialysis, buprenorphine appears to be a **safe choice** when opioid treatment is initiated. The pharmacokinetics of buprenorphine are unchanged in hemodialysis patients, which means that there is no need for dose-reduction with this drug.

- **FENTANYL** – Safe for use. The metabolites are inactive.

- **MORPHINE** – Use with caution. Dose must be adjusted because the metabolite (morphine-6-glucuronide or M6G) is a more potent analgesic than morphine, can cause CNS toxicity.
**Opiates in Renal Insufficiency**

- **Hydromorphone** – Avoid. Metabolite has CNS toxicity.

- **Oxycodone** – Avoid. Metabolized to oxymorphone which can accumulate and cause CNS impairment.

- **Demerol, Codeine** – Do not use. Toxicity from metabolites.

- **Methadone** – Safe for use if GFR ≥ 30 mL/min. No active metabolites, negligible amount of plasma accumulation in renal insufficiency. **BUT**!!! Remember that Methadone accounts for under 3% of opioid prescriptions, but accounts for over 30% of opioid-related deaths. The most deadly opioid **without** renal failure is also the most deadly **with**...
Opiates in Renal Insufficiency

- **Fentanyl** – Safe. Pharmacokinetics not affected by cirrhosis.
- **Hydromorphone** and **Oxycodone** – Reduce dose to 1/3 - 1/2 of the ‘usual’ dose, due to decreased metabolism of parent compounds and decreased elimination.
- **Buprenorphine** – Avoid due to accumulation.
- **Morphine** – Use with caution due to increased half-life and oral bioavailability, and decreased clearance. Reduce both the total daily dose and the frequency of dosing.
- **Meperidine** – No, due to accumulation of toxic normeperidine.
- **Methadone, Codeine** – Not recommended (accumulation).
True or False

Older adults have the same responses (good & bad) to pain medicines as young adults.
ADVERSE EFFECTS OF OPIOIDS

BY ORGAN SYSTEM

- GASTROINTESTINAL SYSTEM
  - URINARY SYSTEM
- CENTRAL NERVOUS SYSTEM
  - RESPIRATORY SYSTEM
- CARDIOVASCULAR SYSTEM
  - ENDOCRINE SYSTEM
- OSTEOPOROSIS and FRACTURES
ADVERSE EFFECTS OF OPIOIDS

GASTROINTESTINAL SYSTEM

OPIOID-INDUCED NAUSEA: Opioids stimulate the CTZ

- Chemoreceptor Trigger Zone (CTZ) is located in the 4th ventricle of the medulla oblongata.
- The CTZ detects noxious chemicals in the blood, then sends signals to the vomiting center, located in the lateral medulla.
- The vomiting center sends signals to multiple locations, thus coordinating closing the glottis, contracting the diaphragm and chest wall muscles, to result in expelling gastric contents.
Triggers for Vomiting

- Pain, repulsive sights, smells and emotional factors
- Motion sickness and vestibular disorders
- Endogenous toxins, numerous drugs, radiation
- Stimuli from pharynx, G.I. tract and other viscera
- Pregnancy
- Intracranial pathology

VC = Vomiting centre

CTZ = Chemoreceptor trigger zone (located in the area postrema, detects circulating emetic agents e.g. toxins, opiates, apomorphine)
ADVERSE EFFECTS OF OPIOIDS

GASTROINTESTINAL SYSTEM

OPIOID INDUCED CONSTIPATION (OIC): Both opioid peptides and receptors are distributed along the GI tract. The presence of peripherally released endogenous opioids may modulate GI motor and secretory functions.

- Most opioids having predominant \[\mu\] (mu) agonist activity in brain inhibit gastric (stomach) motility and delay gastric emptying.
- Circular colonic motility (waves) is increased, but colon transit is reduced, propulsive motion is greatly reduced → OIC.
ADVERSE EFFECTS OF OPIOIDS

GASTROINTESTINAL SYSTEM

Opioid Induced Constipation (OIC)

- Most common dose dependent side effect of opiates, despite mode of administration IV, IM, PO, Intrathecal, or Epidural
- **Tolerance does not develop to this side effect**
- **15-90% of patient receiving opiates for non cancer pain develop constipation**
- Opiates bind to receptors in the myenteric plexus
- Within the longitudinal smooth muscle of the gut, opiates inhibit release of acetylcholine, thereby decreasing propulsive effects. Circular > longitudinal muscle contraction occurs
- As a result of increased transit time, more water is absorbed from the stool
- Decreased intestinal, biliary, gastric and pancreatic secretions are observed in patients on opiates
- Increased rectal sphincter tone results from opiate administration
In addition to the endocrine effects as noted later, opioids may interfere with **micturition**, the physical act of urination.

The opioid interference with micturition occurs at higher nervous system levels (the pons and cerebral cortex.)
ADVERSE EFFECTS OF OPIOIDS

CENTRAL NERVOUS SYSTEM

- **Sedation** may occur even at therapeutic (pain-reducing) doses.
- **Cognitive impairment** (ability to follow instructions, memory, judgment, reasoning) may also occur at therapeutic doses.
- CNS effects are amplified when opioids are taken in combination with other CNS-active drugs (ethyl alcohol, benzodiazepines, barbiturates, antidepressants, antipsychotics, antihistamines).
- CNS effects of opioids are more pronounced in older adults.
- **Myoclonus** (muscle jerking) is a dose-related effect of morphine.
ADVERSE EFFECTS OF OPIOIDS

Respiratory System

- The agonist activity of opioids at the μ-opiate receptors is very important clinically in the alleviation of pain.

- However, it is also the cause of an unwanted side effect which is the marked depression of breathing that can complicate their clinical administration, and can be potentially life-threatening when opiates are abused.

- The degree of respiratory depression is dependent upon the serum level of opioids, somewhat on method of delivery.
ADVERSE EFFECTS OF OPIOIDS

RESPIRATORY SYSTEM

- First, patients become *drowsy or somnolent*.
- Then, they become *less responsive* to stimulation.
- The pattern of respiration becomes slower and more shallow.
- Finally, they become obtunded, comatose, or they die.

*Naloxone* is the *opioid receptor antagonist*, but is not recommended for use until:
- Patient’s respiratory rate is less than 8 breaths per minute
- Patient’s oxygen saturation is less than 90%

This is done to avoid pain crisis and acute withdrawal symptoms.
ADVERSE EFFECTS OF OPIOIDS
CARDIOVASCULAR SYSTEM

- Chronic opioid use can lead to bradycardia, vasodilation, edema, hypotension, orthostatic hypotension, syncope and coma.
- Torsades de pointes [tôr,säd deˈpwänt]: atypical ventricular tachycardia with periodic waxing and waning of QRS amplitude on ECG.
- It is usually drug-related (quinidine, procainamide, disopyramide) or may be the result of hypokalemia, hypomagnesemia, or profound bradycardia.
- Torsades may be self-limiting or progressing to ventricular fibrillation.
- Methadone causes a dose-related QT prolongation and may lead to torsades.
ADVERSE EFFECTS OF OPIOIDS

ENDOCRINE SYSTEM

- Opioids have an effect on the **hypothalamic-pituitary-gonadal** axis
- Reduced levels of luteinizing hormone (LH) and testosterone
- Diminished libido is reported with chronic opioid use
- Impaired sexual performance (short-term and long-term opioid use)
- Inhibited hypothalamic dopamine secretion leads to increased prolactin levels, and may lead to male gynecomastia and galactorrhea
- Opioids have an effect on the **hypothalamic-pituitary-adrenal** axis
- One result is decreased cortisol levels
- Diminished bone mass is reported with chronic opioid use
ADVERSE EFFECTS OF OPIOIDS

OSTEOPOROSIS & FRACTURES

Current literature shows an increased risk for bone fracture in chronic opioid analgesics users. There are three main hypotheses for this:

1) an increased risk of falls caused by central nervous system effects;
2) reduced bone density caused by a direct opioid effect on osteoblasts;
3) chronic opioid-induced hypogonadism (testosterone deficiency).

The impact of opioids varies by sex and among the type of opioid used (less with tapentadol and buprenorphine). Opioid-associated androgen deficiency correlates with increased risk of osteoporosis. Although standards have not been set for monitoring and treating opioid-induced hypogonadism or hypoadrenalism, I believe all patients chronically taking opioids (esp. at doses ≥90 mg morphine daily) should be monitored for early detection of hormonal impairment and low bone density.
**Adverse Effects of Opioids**

**Others**

- **Pruritus** (itching, with or without mild rash) develops in 2-10% of patients with opioid use. This often resolves within one week.

- **Hyper-excitability** effects (Delirium, Seizures, Myoclonus)

- **Opioid-induced hyperalgesia** is a phenomenon of increasing sensitivity to both painful stimuli (hyperalgesia) and ordinarily non-painful stimuli (allodynia). Hyperalgesia may be due to:
  - **M3G** – a toxic opioid metabolite morphine-3-glucuronide
  - **H3G** – a toxic opioid metabolite hydromorphone-3-glucuronide
  - Activation of **NDMA** (N-methyl-D-aspartame) receptors in CNS
MANAGING OPIOID ADVERSE EFFECTS

Methods of managing opioid side-effects may include:

- **Dose reduction** – If pain is well-controlled on an opioid but there are bothersome adverse effects, a reduction in opioid dose gradually will help in resolving the adverse effects while maintaining pain relief. The recommended dose reduction is about 25%. If dose reduction interferes with efficacy of pain control, one or more forms of adjuvant therapy (steroid, gabapentin, pregabalin, duloxetine, low-dose tricyclic antidepressant, etc.) can be added, preferably one at a time. Be aware of higher rate of adverse effects with age.

- Switching the **route of administration**.

- **Rotation** of opioids, using MME as an approximate guide.

- **Symptomatic management** of the adverse effects using medications and/or other measures that target the symptoms.
MANAGING OPIOID ADVERSE EFFECTS

- To prevent and manage **constipation**, increase fiber and water intake, increase physical activity, use daily stool softeners, use laxatives as needed. Drugs are available for OIC.

- To manage **dry mouth**, practice regular gentle dental hygiene, use saliva substitutes (Xerostom®) and enzymes (Biotene®), and have regular dental visits for cleaning and monitoring.

- For **nausea** control, use antiemetics (Zofran®, etc) or switch to another opioid.

- If **drowsiness** is present, avoid alcohol, driving and machinery.

- **Confusion** is usually transient after initiation or dose increases.
TRUE OR FALSE

Persistent pain is described as typically lasting over 3-6 months, or extending beyond the time of normal tissue healing.
Opioids can be **safely** used in a number of **clinical situations**: moderate to severe **musculoskeletal** and **spinal pain**, **peripheral neuropathies**, **rheumatoid** and **osteoarthritis**.

The safe chronic use of opioids in older adults includes:

- **Accurate diagnosis**, including objective documentation when available (X-rays, CT, MRI, bone scan, bone density, cancer),
- Careful notation as to the lack of, or poor **response to non-narcotic analgesia**, physical therapy, non-pharmacological modalities;
- Careful notation of the **opioid selected** and the reason(s) why one drug is selected over another, and **response to the drug used**.
What do these terms mean?

- Opioid Chronic Use
- Opioid Abuse
- Opioid Addiction
- Opioid Overdose
- Opioid Withdrawal
OPIOID ABUSE

- Abuse of an *opioid* occurs anytime that the patient is **NOT** following the *prescription* as stated by the *prescriber*.
- Taking the drug *more often* than prescribed.
- Taking *higher doses* without the prescriber’s approval.
- Using the medication to *gain pleasure* instead of pain relief.
- Mixing the drug with *other drugs* or *alcohol*.
- Taking an opioid that *was not prescribed* for the patient.
- Giving a drug to *anyone* for whom it was not prescribed.
Opioid compliance can be monitored with:

a) Family and caregiver interviews
b) Urine drug screens
c) In-office pill counts
d) The PDMP in your state and other states
e) All of the above
f) Legally, none of the above (federal HIPAA laws)
Avoiding Opioid Abuse

- Carefully read the prescription label as to dose and time interval.
- Do not take more drug (pills or teaspoons or whatever) or dose more often (one every 4 hours, two every 6 hours, etc.).
- Read the “side labels” as to driving, operating heavy machinery, avoidance of alcohol, and other (usually yellow) instructions.
- If prescribed for a patient with dementia, other impaired memory, altered awareness, insufficient judgment or reasoning, have a responsible designee do the dosing.
- Be observant for changes in behavior that may be drug-induced.
- Do not share drugs with others. Period.
**Multiple Choice**

Some factors predicting greater risk of opioid addiction are:

a) Depression and/or anxiety  
b) Daily or frequent alcohol use  
c) Being a victim or previous victim of sexual abuse  
d) History of prior drug abuse  
e) Positive family history for substance abuse  
f) All of the above
Abusing opioids can rapidly lead to addiction, and opioid addiction is an all-consuming condition that requires help to overcome. “You might have an opioid use disorder if you…”:

- Spend a lot of the day getting, using, or recovering from use.
- Crave more of the drug when you do not have any remaining.
- See multiple doctor visits to get more painkiller medications.
- Constantly seem sedated, confused, forgetful, irresponsible.
- Defensively argue with family and friends about your drug use.
- Show signs of tolerance and physical dependence.
CHANGE
THAT
THOUGHT!
PERSISTENT PAIN PATIENT

- Medication use is under safe control.
- Medication use improves the quality of life.
- Wants to decrease medication if adverse effects develop.
- Is concerned about the physical problem that is being treated, asks questions about diagnosis/prognosis.
- Follows the doctor-patient agreement for use of the opioid.
- Frequently has leftover medication.
Addicted Patient

- Medication use is **out of control**.
- Medication use causes a **diminished** quality of life.
- Medication use continues or increases despite **adverse effects**.
- Is **unaware** of, **unconcerned** about, or **in denial** of any problems that develop as a result of drug treatment.
- Does **not adhere** to the doctor-patient agreement for opioid use.
- **Never has leftover medication**, “loses” or “misplaces” drugs or prescriptions, comes in near the end of the day and always has a “story” as to why **more drug treatment** is necessary.
OPIOID ADDICTION

- Abusing opioids can rapidly lead to addiction, and opioid addiction is an all-consuming condition that requires help to overcome. “You might have an opioid use disorder if you...”:
  - Spend a lot of the day getting, using, or recovering from use.
  - Crave more of the drug when you do not have any remaining.
  - See multiple doctor visits to get more painkiller medications.
  - Constantly seem sedated, confused, forgetful, irresponsible.
  - Defensively argue with family and friends about your drug use.
  - Show signs of tolerance and physical dependence.
OPIOID OVERDOSE

- It is extremely important that a person using opioids or a person living with someone taking opioids know **signs of overdose**:
  - Appearing pale or feeling clammy to the touch;
  - Bluish or purplish coloration to the fingernails, toes or lips;
  - Body going limp, falling, sliding out of a chair or bed;
  - Vomiting and gurgling noises from the throat;
  - Loss of consciousness, unable to be aroused, unable to speak;
  - Slowed or stopped breathing;
  - Slowed or stopped heartbeat.

**GIVE NARCAN® (naloxone) and CALL 911 for help!**
RULES FOR PRESCRIBING SCHEDULE II DRUGS

1) A written original prescription from practitioner licensed by DEA to prescribe in Schedule II, or
2) An electronic prescription generated and sent in accordance with E-prescribe laws.
3) Prescriptions for Schedule II may not be phoned to a pharmacy or sent via facsimile (FAX).
4) Prescriptions in Schedule II are for a maximum of 30 days, with NO REFILLS.
5) An individual practitioner may issue multiple prescriptions authorizing a patient to receive a total of up to a 90-day supply of a Schedule II controlled substance, if these conditions are met:

(a) Each separate prescription is dated on the date written, and issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice;

(b) The individual practitioner provides written instructions on each prescription indicating the earliest date on which a pharmacy may fill each prescription (at intervals of 30 days);

(c) The individual practitioner concludes that providing the patient with multiple prescriptions in this manner does not create an undue risk of diversion or abuse;

(d) The issuance of multiple dated prescriptions is permissible under applicable state laws.
**RULES FOR PRESCRIBING SCHEDULE II DRUGS**

**EXAMPLE:** An older, jolly, obese patient Nicholas St. Claus comes to clinic with persistent, non-malignant right hip pain 2° severe degenerative X-ray-confirmed osteoarthritis; surgery contraindicated due to ....

You elect to continue hydrocodone/APAP 7.5/325 TID for pain control.

Write the **1st prescription** for hydrocodone/APAP 7.5/325 mg, #90 (ninety). Sig: One tab TID for chronic right hip pain ICD-10 Code M16.11. Date the prescription today 07/20/19 and write ‘May be filled today.’

Write the **2nd prescription** for same drug, same instructions, date 07/20/19, an write ‘Do not fill before 08/19/19.’

Write the **3rd prescription** for same drug, same instructions, date 07/20/19, and write ‘Do not fill before 09/18/19.’
QUESTIONS OR COMMENTS?

Please feel free to contact me at either of these email addresses:

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