CANCER PAIN MANAGEMENT 101

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- I have no disclosures

OBJECTIVES

- Identify the types of cancer pain
- Apply pharmacokinetic principles to develop a pain regimen with opioid naïve patients
- Create a safe pain plan for opioid tolerant patients
- Utilize the principles of opioid conversion calculations to manage pain crisis.

MRS. J

- Ms J is a 55yo with stage IV pancreatic cancer. She is opioid naïve and does not have a history of substance use disorder.
- She is having persistent epigastric pain that is worse with lying flat and eating.
- She has started pancreatic enzymes which helped with pain, bloating and early satiety.
- But she is ready to start an opioid.
    - **What opioid do you start first?**


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WHAT IS PAIN?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

- International Association for the Study of Pain

PAIN ASSESSMENT – THE INTERVIEW

- PQRSTT
  - Precipitating/alleviating
  - Quality
  - Radiation
  - Severity
  - Timing
  - Temporal
    - Constant
    - Breakthrough
    - Intermittent
- OLDCARTS
  - Onset
  - Location
  - Duration
  - Character
  - Aggravating/Alleviating
  - Radiation
  - Timing
  - Severity

PAIN ASSESSMENT - NOCIOCEPTIVE

- Direct stimulation of intact nocioceptors
  - Mechanical
  - Temperature
  - Chemical

- Tissue injury apparent
  - Example- stubbing toe or dental procedure

- Language: **sharp, aching, throbbing**

PAIN ASSESSMENT - VISCERAL

- Ill-defined, difficult to localize
  - Visceral nerves are not associated with proprioception

- Language: **colicky, squeezing, pressure, ache, cramping**

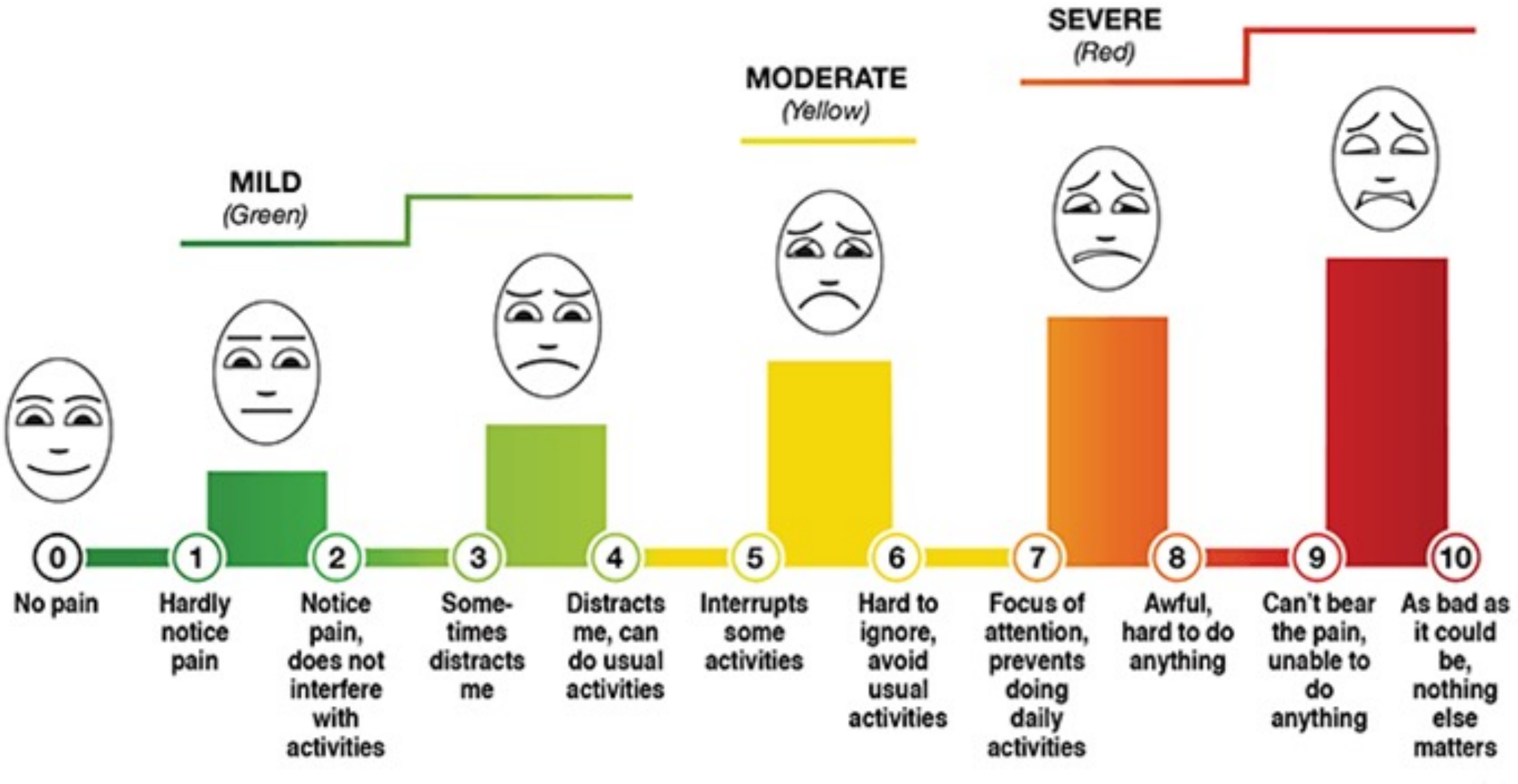
PAIN ASSESSMENT - NEUROPATHIC

- Disordered peripheral or central nerves
- Causes
  - compression, transection, infiltration, ischemia, metabolic injury
- Language: **burning, tingling, shooting, electrical**

BONE METASTASES

- Language: **deep, constant throbbing pain, often pinpoint**
- NSAIDs
- Steroids
  - Dexamethasone 4mg BID
  - Or Prednisone 20mg daily
  - if no benefit in 5-7 days then **STOP**
- Palliative Radiation
- IV Bisphosphonates
- Cord compression or compression fracture?
- Pregabalin adjuvant

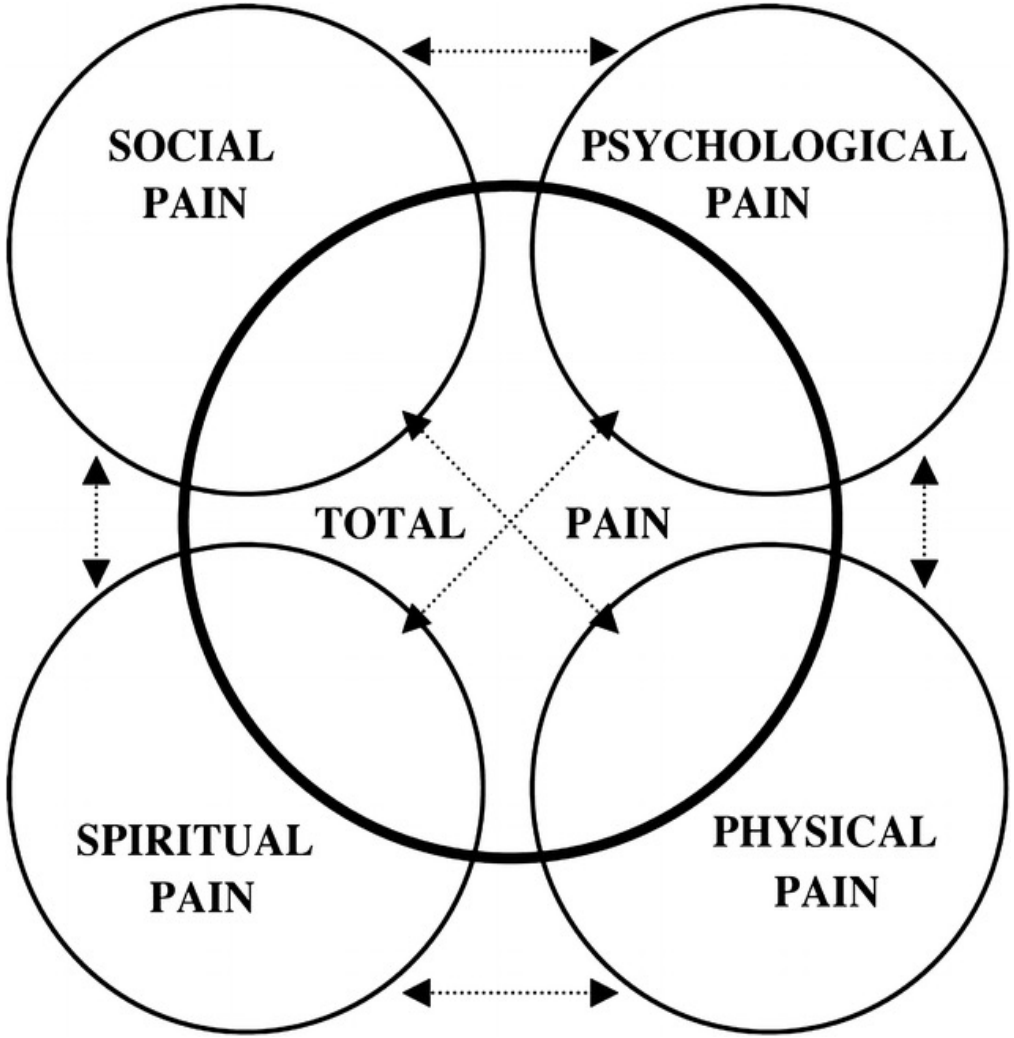
Defense and Veterans Pain Rating Scale



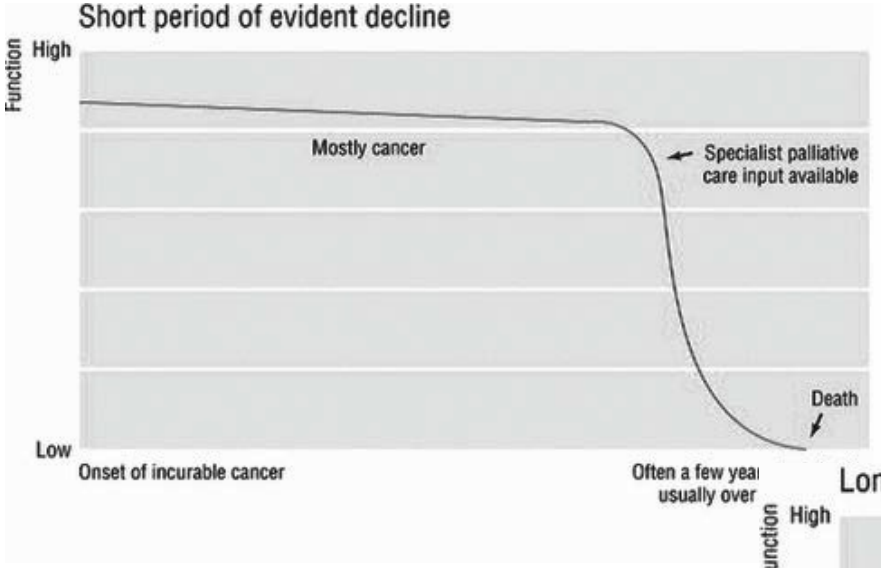
ACUTE VS CHRONIC PAIN

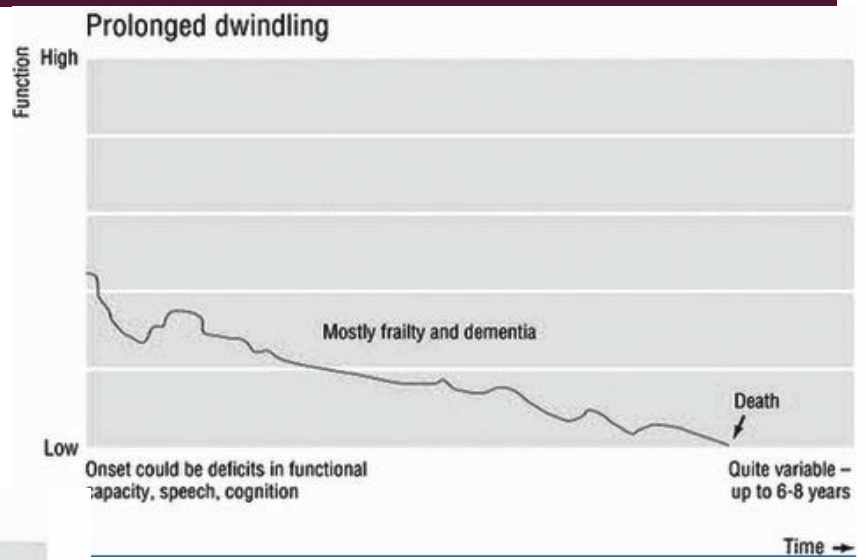
- Know what type of pain you are treating
- Have a duration of treatment plan in mind
- Set expectations with patient
- Do not start long acting opioid pain meds for **acute pain** that is expected to get better

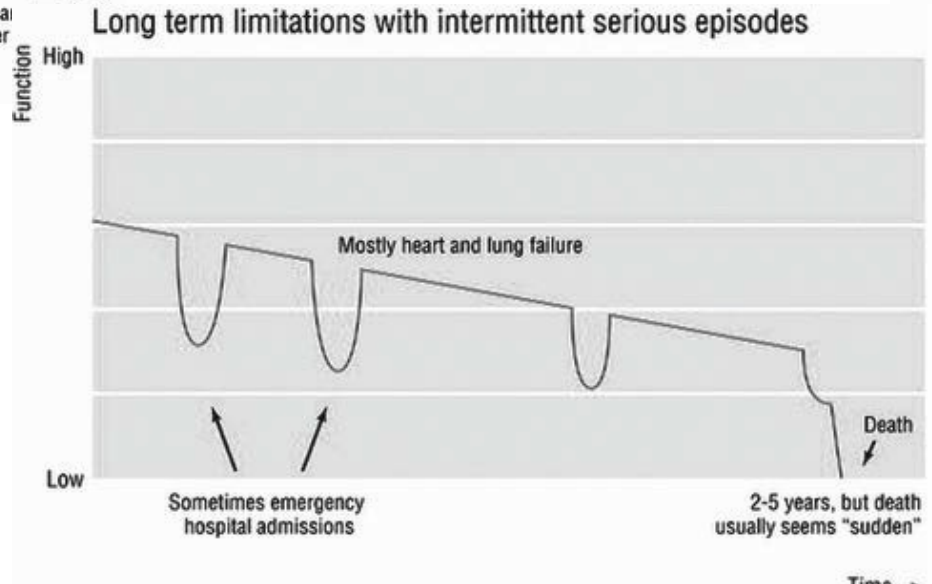
CONSIDER TOTAL PAIN



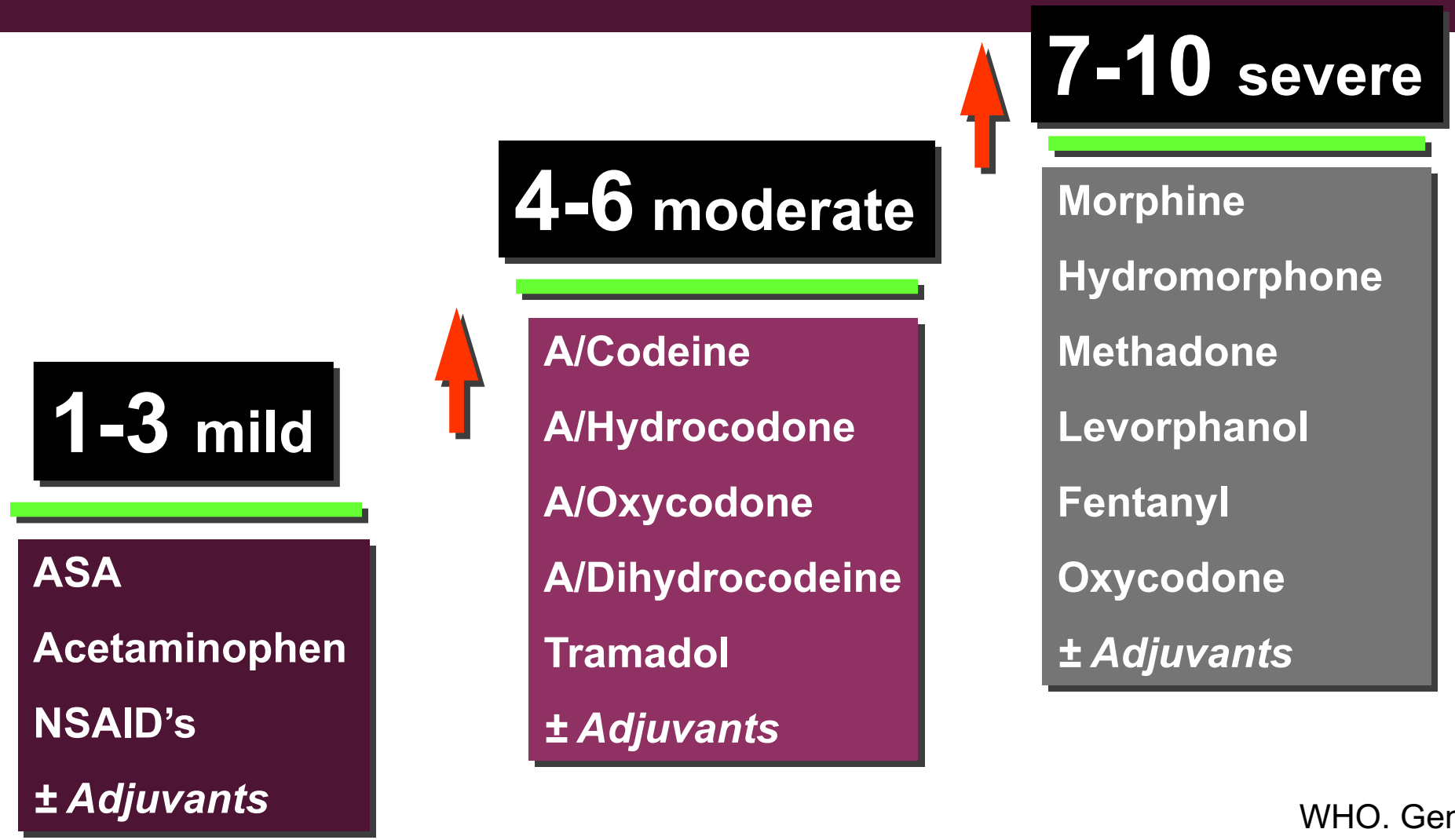
LIFE TRAJECTORIES





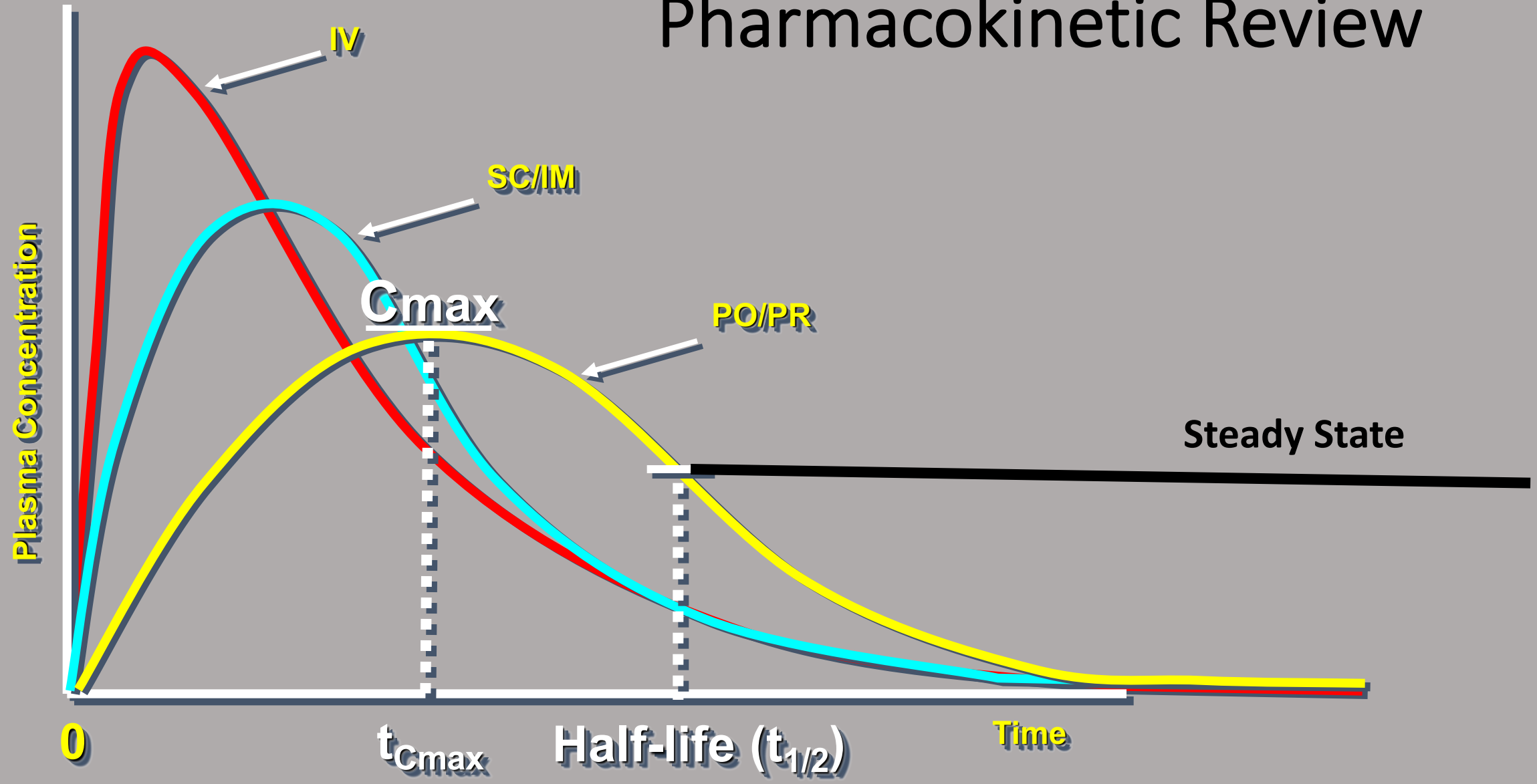


WHO 3-STEP LADDER



WHO. Geneva, 1986.

Pharmacokinetic Review



PHARMACOKINETICS REVIEW

- Time to Cmax (t_{Cmax})
  - Time it takes to reach maximum concentration of drug
- t½ life = elimination

- Determinants of T_{Cmax}
  - ABSORPTION
  - Route of administration
  - Variability of absorption

- **Why does time to Cmax matter?**
  - Safety when re-dosing breakthrough symptom medications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SORE KNEE, HUH? HAVE YOU TRIED ICING IT?

ACETAMINOPHEN (APAP)

- Exact mechanisms of action unknown
  - CNS – blocks prostaglandin synthesis & inhibits hypothalamic heat-regulation
  - Peripherally – blocks pain impulse generation

- **Caution: Hepatic toxicity**
  - Ceiling effect, dose: >3-4 grams/24 hours
  - Increase susceptibility if hepatic disease, heavy alcohol use

- Metabolized: Liver
  - Excretion: Urine

- t_{Cmax}: 1h

- $t_{1/2}$: 4h

Mitchell JR, Potter WZ. *Med Clin North Am*. 1975.
Lexicomp. "Acetaminophen" 2017

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

- Mechanism of Action: Inhibit cyclooxygenase (COX)
- Effective for bone, inflammatory pain

- **Cautions/Adverse Effects**
  - Gastropathy/GI Bleed
  - Renal Injury
  - Bleeding

- Metabolized: Liver
  - Excretion: Urine

- $_{t}C_{max}$: 1-2h

- $_{t}1/2$: 4-12h

Carson LJ, Willett LR. *Drugs*.1993.
Peura DA. *Cleve Clin J Med*. 2002.

TRAMADOL

- Mechanism unclear
  - Weak mu agonist
  - Weak NE/5HT3 reuptake inhibitor
- Metabolized: Liver (active metabolite)
  - Excretion: Urine
  - Renal & hepatic dosing
    - **Avoid in CrCl < 30**
    - **Avoid in Child –Pugh Class C**
- t_{Cmax}: 2h
- $t_{1/2}$: 6h (8h for metabolite)

NEUROPATHIC AGENTS

- Gabapentin
  - Start LOW, go SLOW
    - Dizziness, drowsiness, GI upset
  - Caution with renal insufficiency/ Chronic kidney disease
- Duloxetine
  - Start 20mg or 30mg daily- Max dose 60mg
  - Caution with sudden discontinuation
- Pregabalin
  - Start 75mg twice daily and increase every couple of weeks- Max dose 600mg/day
  - Caution it's expensive!

INITIATING OPIOIDS

- Determine goal of pain control and chose the right agent
- Use lowest most effective dose for shortest duration
- Screen for high risk behavior
  - ORT scores
  - Set boundaries
  - **Narcan**
- Set expectation with patient
  - Use pain agreement
  - Use Interdisciplinary team if available
- **GIVE A BOWEL REGIMEN**

OPIOID PHARMACOKINETICS = DOSING

Opioid Pharmacokinetics

- Time to Cmax (t_{Cmax})
  - IV ~ 6 min
  - SC (IM) ~ 30 min
  - PO (PR) ~ 60 min
- Half-life ($t_{1/2}$)
  - 3-4 hours

Opioid Dosing

- Breakthrough/PRN dosing
  - IV Q6-15min PRN
  - SC (IM) Q30min PRN
  - PO (PR) Q1h PRN
- Scheduled dosing (for steady state)
  - Q4h

OPIOID PHARMACOLOGY EXCEPTIONS

- Opioids are cleared renally
  - EXCEPT: Methadone, Fentanyl
- Opioids have an oral Time to Cmax of 1 hour
  - EXCEPT: Methadone
- Opioids have a half life of 4 hours
  - EXCEPT: Methadone, Fentanyl

COMBINED OPIOID AGENTS

- Codeine/APAP (Tylenol #3 or #4)
- Hydrocodone/APAP (Vicodin or Norco)
- oxycodone/APAP (Percocet)

- Challenge?
  - **Ceiling effect 2/2 hepatotoxicity**

SHORT ACTING CONSIDERATIONS

- **Hydrocodone/**APAP and **Oxycodone/**APAP- cheap and have ceiling effect
- **Morphine IR-** cheap but starts at 15mg
  - Can half a tablet = 7.5mg
  - Comes in oral solution
  - Avoid with renal disease
- **Oxycodone-** cheap in lower doses
  - Comes in oral solution
- **Hydromorphone-** Reserve for higher pain needs

IR = INTERMEDIATE RELEASE

TITRATING PRNS…TALK TO THE PATIENT

Dose

- How did your pain respond to the dose of medication?
  - Treated it completely:
    : Maintain dose
  - Helped a little
    : Increase 20-30%
  - No change at all
    : Increase 50%-100%

Frequency

- When did you pain start to come back or get worse?
  - Before the next dose was due
    : consider modifying the frequency
  - Hours later, but was unbearable
    : educate patient on early signs of pain and encourage to dose appropriately

TRANSITIONING TO LONG ACTING

- Goal of long acting is to control pain as basal dose
  - Caution if patient routinely taking SA around the clock
  - Learn goals
- Calculate total short acting OMEs in 24 hour period
- If needed divide by opioid conversion and/or dose reduction for cross tolerance
- Divide by dosing frequency
  - Every 12 hours divide by 2
  - Every 8 hours divide by 3

SA = SHORT ACTING
OME = ORAL MORPHINE EQUIVALENTS

BREAK THROUGH DOSING

- 10-20% of total long acting requirements
- Dose appropriately based on tmax
- Goal is 50%or less of short acting use while using long acting pain meds

LONG ACTING OPIOIDS

- **Hydrocodone LA** (Hysingla ER) expensive and starts at 20mg
- **Morphine ER** (MS Contin)
- **Oxycodone ER** (OxyContin)
- **Fentanyl patch** (Duragesic patch)- not for opioid naiive pts
- **Hydromorphone ER**
- **Methadone**-as LA vs adjuvant, Cheep

- ER = EXTENDED RELEASE
- LA = LONG ACTING

Do not alter long acting pain meds!!!

NALTREXONE CONTAINING OPIOIDS

- Embeda = Morphine ER + Naltrexone

- Xtampza = Oxycodone ER + Naltrexone
  - Benefits can be opened and used via PEG
  - Needs high fat meal for absorption
  - Great for chronic pain

LONG ACTING OPIOIDS

- Morphine ER
  - 1st line
  - Cheapest
  - Careful, comes in 24 hour dose
- Oxycodone ER
  - 2nd line
  - Generally needs prior auth
  - Expensive

- OME = ORAL MORPHINE EQUIVALENT
- PO = BY MOUTH

- Fentanyl patch
  - 3rd line
  - Needs prior authorization
  - Expensive
  - No metabolites = CLEAN
  - Do not start on opioid naïve pt or <50 OME
  - Good for pt who cannot tolerate PO
  - Caution with pt that sweats or radiation
  - Avoid hot showers, heating pad, fevers or sun exposure
  - There are also Fentanyl buccal, lollipops and SL formulations but they are expensive and not LA.

DOSING AND TITRATION

Medication	Route	Onset of Action	Duration of Action	Usual Dosing Interval	Appropriate for PCA	Concentration for PCA	†Equi-analgesic Dosing	Notes
Fentanyl (Sublimaze®, Duragesic®, Actiq®, Fentora®)	IV	immediate	30 to 60 min	1 to 2 hr	Yes	50 micrograms/mL	100 micrograms IV (0.1 mg IV)	**See page 4 for details**
	SC**	15 min	30 min to 2 hr	3 to 6 hr	N/A	N/A	100 micrograms SC (0.1 mg SC)	**See page 4 for details**
	TM	5 to 15 min	highly variable	**See page 4**	N/A	N/A	**See page 4**	**See page 4 for details**
	TD	12 to 24 hr	72 hr per patch	72 hr	N/A	N/A	**See page 4**	**See page 4 for details**
HYDROmorphONE (Dilaudid®)	PO	15 to 30 min	4 to 6 hr	3 to 6 hr	N/A	N/A	7.5 mg PO	**HYDROmorphONE is not equivalent to morphINE**
	IV/SC	15 min	4 to 6 hr	3 to 6 hr	Yes	1 mg/mL	1.5 mg IV	
Methadone (Dolophine®, various)	PO	30 to 60 min	> 8 hr (chronic use)	8 to 12 hr (chronic use)	N/A	N/A	**See page 5**	****See page 5 for details**** Equianalgesic dosing is variable with chronic dosing
MorphINE immediate release (MSIR®, Roxanol®, various)	PO	30 to 60 min	3 to 6 hr	3 to 6 hr	N/A	N/A	30 mg PO	**morphINE is not equivalent to HYDROmorphONE**
	IV	5 to 10 min	3 to 6 hr	3 to 6 hr	Yes	1 mg/mL 5 mg/mL	10 mg IV	
	SC	15 to 30 min	3 to 6 hr	3 to 6 hr	Yes	N/A	10 mg IM/SC	
MorphINE extended release (MS Contin®, various)	PO	30 to 90 min	8 to 12 hr	8 to 12 hr	N/A	N/A	30 mg PO	**morphINE is not equivalent to HYDROmorphONE** Do not crush, chew, or break.
MorphINE extended release (Kadian®, Avniza®)^	PO	30 to 90 min	12 to 24 hr	12 to 24 hr (Kadian®) 24 hr (Avniza®)	N/A	N/A	30 mg PO	**morphINE is not equivalent to HYDROmorphONE** Do not crush, chew, or break.
OxyCODdone immediate release (Roxicodone™, OxyIR®, various)	PO	10 to 15 min	4 to 6 hr	4 to 6 hr	N/A	N/A	20 mg PO	**oxyCODone is not equivalent to OxyMORphone**
OxyCODone controlled release (OxyContin®, various)	PO	1 hr	12 hr	12 hr	N/A	N/A	20 mg PO	**oxyCODone is not equivalent to OxyMORphone** Do not crush, chew, or break.
OxyMORphone immediate release (Opana®, various)^	PO				N/A	N/A	10 mg	**OxyMORphone is not equivalent to oxyCODone**
OxyMORphone extended release (Opana ER®, various)^	PO				N/A	N/A	10 mg	**OxyMORphone is not equivalent to oxyCODone** Do not crush, chew, or break.

Medication	Route	Onset of Action	Duration of Action	Usual Dosing Interval	†Equi-analgesic Dosing	Notes
HydroCODONE combinations (see below)	PO	30 to 60 min	4 to 6 hr	4 to 6 hr	30 mg PO	Maximum dose of hydrocodone is 40 mg/day
Oxycodone combinations (see below)	PO	10 to 15 min	4 to 6 hr	4 to 6 hr	20 mg PO	
Codeine combinations (see below)	PO	30 to 60 min	4 to 6 hr	4 to 6 hr	200 mg PO	Doses should not exceed 120 mg/day in opiate naïve patients

- **Mary Lynn McPherson, PharmD, MA, BCPS, CPE**

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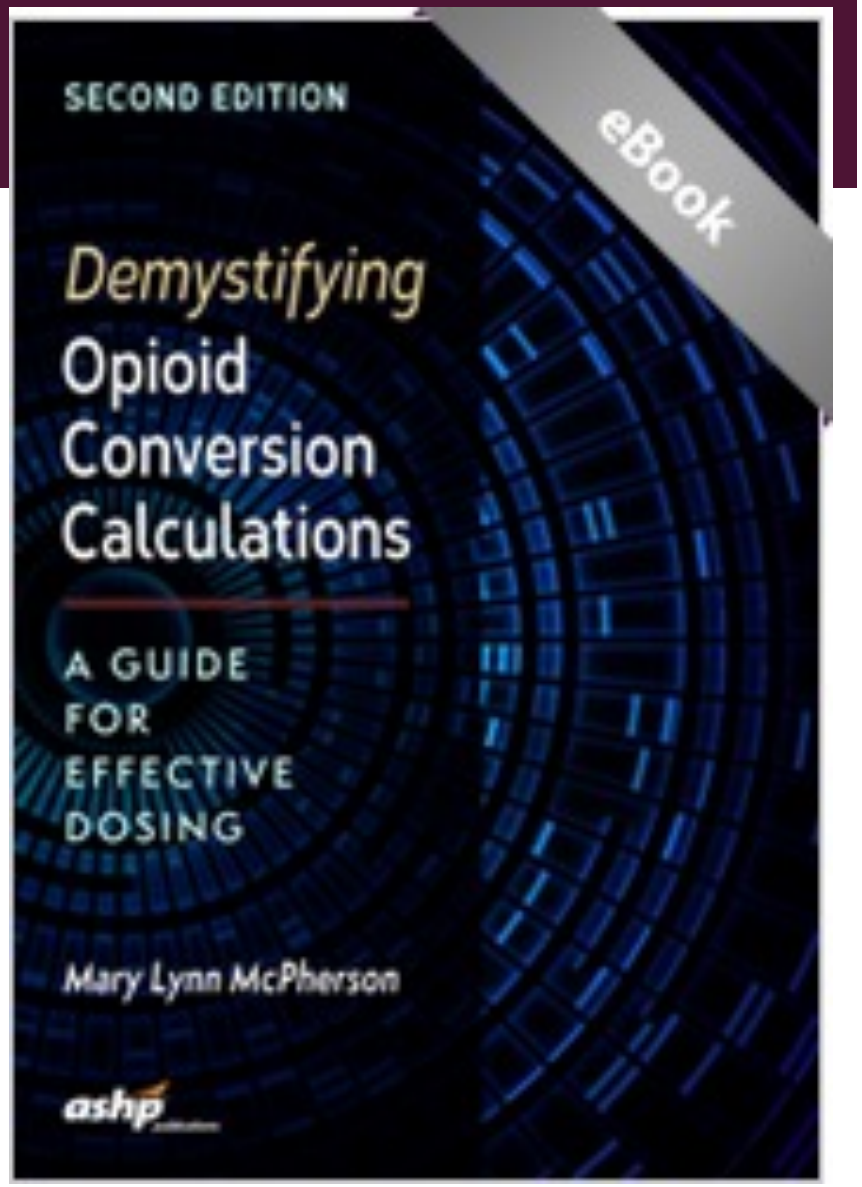
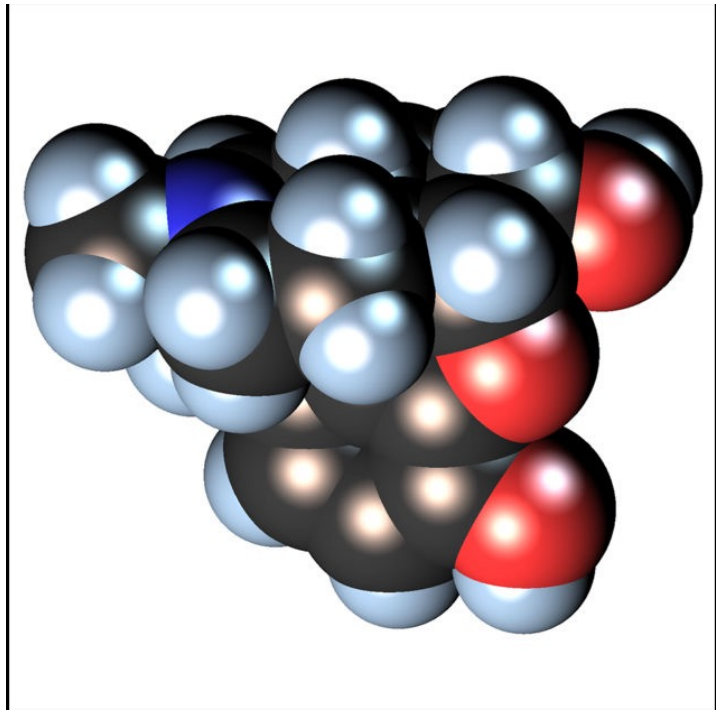


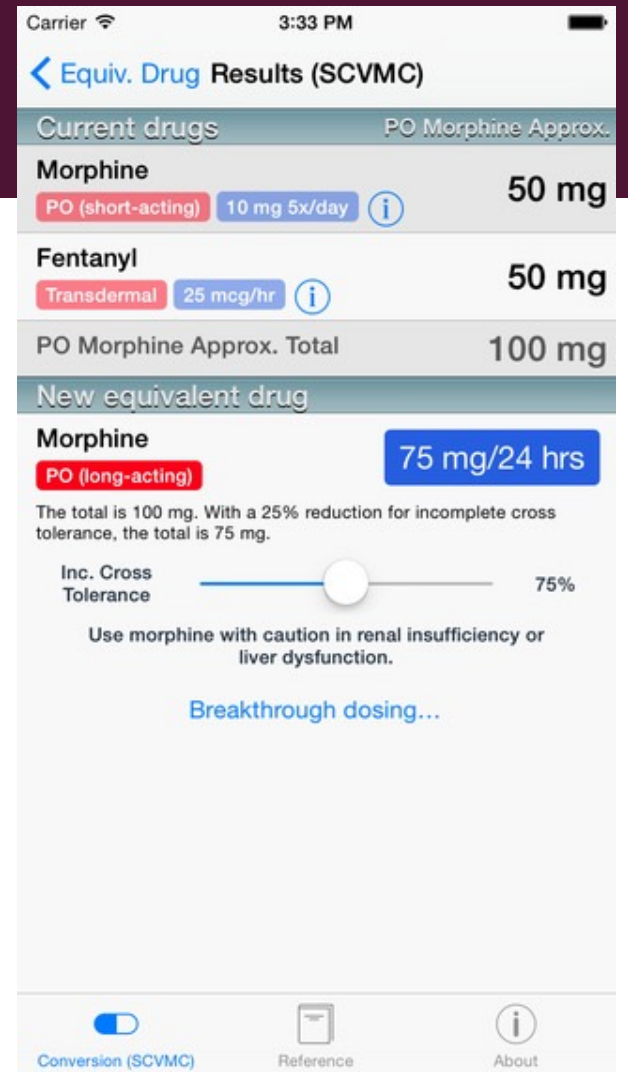
EQUIANALGESIC TABLES- OLD AND NEW

2010	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	30
Fentanyl	0.1	N/a
Hydrocodone	N/A	30
Hydromorphone	1.5	7.5
Oxycodone	10*	20

2018	Equianalgesic Doses (mg)	
Drug	Parenteral	Oral
Morphine	10	25
Fentanyl	0.15	N/a
Hydrocodone	N/A	25
Hydromorphone	2	5
Oxycodone	10*	20

THERE'S AN APP FOR THAT…





MRS. J

- Which short acting opioid would you start?
  - Hydrocodone/APAP 5mg or 7.5mg
  - Morphine IR 7.5mg
  - Oxycodone +/- APAP 5mg

MRS. J IS HOSPITALIZED

- Patient newly diagnosed in hospital with Pancreatic cancer with metastases to bone
- Initially treated with 4mg IV morphine
- Eleven doses in 24h
- Now needing to transition to PO Morphine regimen

- Conversion from IV Morphine to PO Morphine
  - 4mg x 2.5 = 10mg PO Morphine
  - Calculate opioid need for 24 hours
    - 10mg x 11 doses = 110mg
  - Divide 24 hours dose by 4-6h
- Morphine 18mg PO q4h prn
  - What's the problem?
  - Morphine IR comes in 15mg or 30mg
  - Chose lower and dose more frequent
    - MS IR 15mg q4 prn ~90mg
    - MS IR 30mg q6 prn ~120mg

MRS. J IS OPIOID TOLERANT

- Total OMEs = 50mg
- New acute on chronic cancer pain
- Increase OME by 50%
  - 50mg x 0.5 = 25
  - 25 + 50 = 75mg / 6 dose = 12.5mg
    - Start Hydrocodone/APAP 10-15mg
    - Start Morphine IR 15mg
    - Start Oxycodone 10mg
    - Start Hydromorphone 2mg

MRS. J IS IN A PAIN CRISIS

- Calculate total OMEs
- Increase OME by 75%-100%
- Total OME = 60mg x 2 = 120mg
- Consider increasing dose of opioid vs frequency of opioid
  - For instance Mrs. J is taking Morphine 15mg every 6 hours = 60mg
  - But if increase dose to 1.5 tablets = Morphine IR 22.5mg every 5 hours = 112.5mg or every 4 hours = 135mg
  - Or increase frequency of Morphine 15mg every 3 hours = 120mg

- Re-evaluate pain after 2-3 cycles, then goals of care conversation

METHADONE TIPS

- Great, cheap option for opioid tolerant patients with nerve pain
- Evaluate risk(prolonged QTc, respiratory depression, high risk for abuse, electrolyte, Lives alone, pain history, prognosis)
- Start LOW and go SLOW
  - Opioid naïve Methadone 2.5mg BID
  - Opioid tolerant >60-199 OMEs = 10mg OME : 1mg oral Methadone
  - Opioid Tolerant >200 an/or > 65yo CALL PALLIATIVE CARE or PHARMACIST
  - **Do not exceed starting dose >30-40mg/day**
- **Do not increase dose before 5-7 days**
- Assess patient 5-14 days after initiation and then make adjustments
- Avoid in Acute liver failure, paralytic ileus, illicit drug use

Reference: palliative@umaryland.edu

DON'T FORGET THE NARCAN

- Rx: One Box- Use as directed for opioid overdose
- Doesn't take punch from Sooner care/Medicaid patients.
- Most insurances cover it or can get free sample

OTC ADJUVANTS

- Lidocaine creams or patches for nerve pain
- Capsaicin cream for nerve pain
- Biofreeze, emu oil, CBD oil, menthol cream for joint of muscle pain
- Diclofenac gel for joint pain

OTC = OVER THE COUNTER

COMPLEMENTARY PAIN TREATMENTS

- Cognitive behavioral therapy
  - Psychologist or LCSW
- Spiritual assessment/prayer
- Acupuncture or Acupressure
- Reiki or Healing touch
- Meditation

CONCLUSION

- I hope you feel comfortable developing a pain plan for your cancer patient
- Know how to safely prescribe and transition between opioids for naïve and tolerant cancer patients

REFERENCES AND ACKNOWLEDGEMENTS

- **The EPIC Project**
- **McPherson, Mary Lynn Pharm.D. BCPS CPE *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing,* 2nd Edition, 2018**

- **Jennifer Hardcopf, Pharm. D. at Stephenson Cancer Center, Supportive and Palliative care clinic**
- **All my patients that have taught me lessons over the years on how to better manage pain**

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THANK YOU

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