Treatment of Complex Cancer-Related Pain: When Primary Palliative Pain Management Provides Insufficient Relief

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Pain:
Increases Suffering in Patients with Cancer

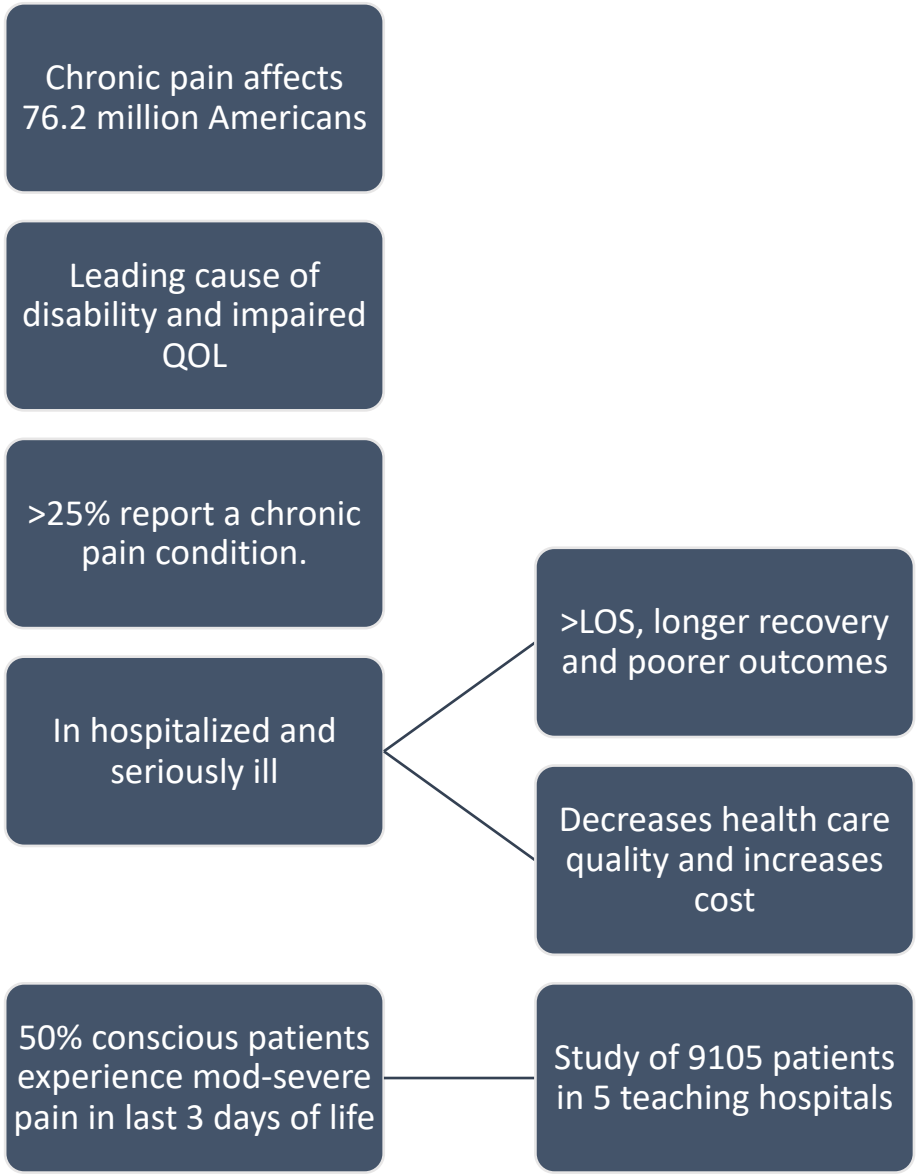
Pain impacts more than 5 million cancer patients

57% of patients perceive that death from cancer will be painful

69% of patients with untreated cancer pain consider suicide

Akhtar, S.S., Cancer Pain Management Brief Guidelines,

Prevalence of Pain



Prevalence of Cancer-Related Pain:

- 25% Patients at time of diagnosis
- 59% Patients during anticancer treatment
- 33% Patients after curative treatment
- 64% Patients with metastatic, advanced, or terminal disease
- 5% - 10% Cancer survivors have chronic severe pain

Fallon, M. et all. 2018. Annals of Oncology 29: iv 166-191

Prevalence of Cancer-Related Pain

- Undertreatment of pain is common in all stages of cancer
- 56-82.3% Patients report pain not adequately treated
- 33% Patients do not receive appropriate analgesia proportional to their pain intensity (study 2014)
- Hematology patients have highest prevalence at diagnosis, during treatments, and in last month of life
- Estimated that > 15 million new cases of cancer worldwide in 2020
- Data supports recommendation that patients with advance or metastatic cancer require management with integrated system

Fallon, M. et all. 2018. Annals of Oncology 29: 166-191

Barriers to Treatment of Pain

Patients and family reluctant to report pain

- Fear pain is sign of disease progression or not responding to treatment

Patient and family reluctant to take/give opioids

- fear of addiction/overdose, fatigue, constipation
- misconception – precipitate death, loss of effectiveness with consistent use

Physician unwilling to prescribe opioids

- Lack of knowledge, fear of addiction/overdose/misuse/abuse

Nursing staff hesitant to give prescribed opioids

- Lack of knowledge, fear of sedation/overdose/abuse

Regulatory constraints

- Federal/State/Hospitals

Pain Management Considerations

Thorough Assessment of Pain

Define Goals of Care

List and prioritize each pain complaint

Individualize the Treatment Plan

Medications
Psychosocial
Cultural/Spiritual
Diagnostic test as appropriate

Simplest approach

Improves compliance
Minimizes side effects
Education patient and family

Reassess often

Improved/worse
Compliance
Psychologic state

Consult Pain Experts for complex, intractable or refractory pain

Palliative Medicine
Pain management

Neurophysiology

- Nociceptive Receptors
  - Myelinated nerve fibers
    - Rapid conduction
    - Stimuli – noxious mechanical
    - “A” delta fibers
    - Sharp, stinging pain
  - Unmyelinated fibers
    - Slow conduction
    - Stimuli: chemical, mechanical, thermal
    - “C” fibers
    - Dull, burning, aching pain

Categories of Pain

Nociceptive pain

(Caused by ongoing tissue damage)

- **Somatic pain**
  - ➢Direct stimulation of nociceptors in skin, muscles, connective tissue, bone
  - ➢Tissue inflammation, mechanical deformation, ongoing injury or destruction
  - ➢Sharp, aching, throbbing, dull, changing with movement, well localized
- **Visceral pain**
  - ➢Bowel obstruction, dyspepsia, dysmenorrhea, angina
  - ➢Deep, aching, cramping, poorly localized, commonly referred to cutaneous sites

Neuropathic pain

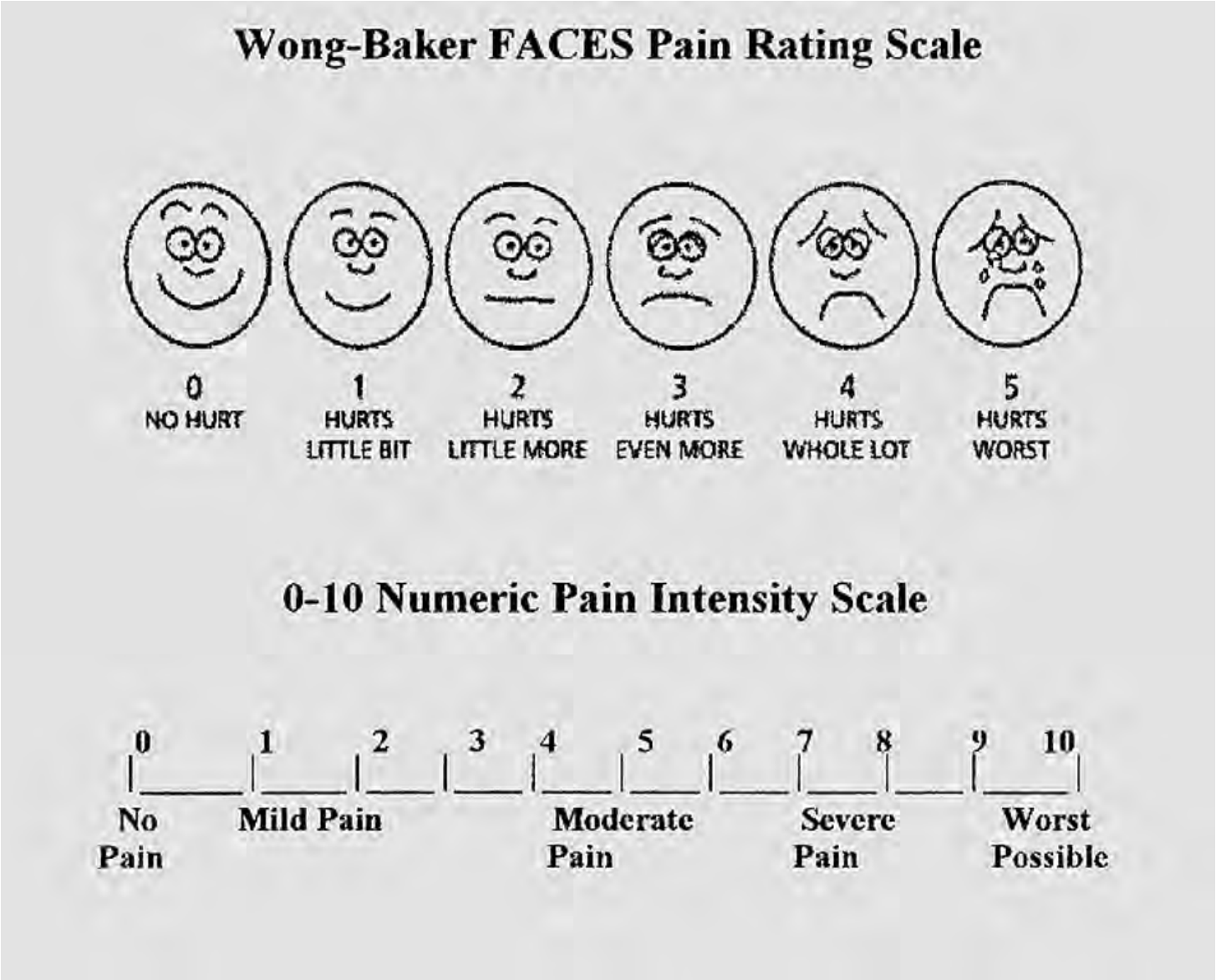
(Caused by damage or dysfunction in the nervous system)

- Results from pathophysiological process that involves injury to peripheral or central nervous system
- Characterized by burning, tingling, shooting, stabbing
- Examples: diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, post stroke pain, post amputation phantom pain, spinal cord compression, and brachial plexopathy
- Respond to tricyclic antidepressants or anticonvulsants

Faces and Numeric Pain Scales

- Use a validated standardized scale
  - Visual analogue scale (VAS)
    - FACES
  - Verbal rating scale (VRS)
    - Mild, moderate, severe
  - Numerical rating scale (NRS)
    - 0 - 10

- Ask, “Worst pain in last 24 hours?”
- If pain score <3, monitor, reassess daily
- If pain score > 3 or if patient distressed by pain
  - Complete a comprehensive pain assessment
  - Treat with appropriate analgesia
  - Reassess both pain and side effects



Comprehensive Pain Assessment

Medical History

- Oncologic diagnosis
  - Primary and metastasis
  - Prior and current treatment
- Other significant comorbidities
- Current advance directives
- Medications
  - Current prescribed
  - Over the counter including supplements
- Complimentary/Alternative therapies

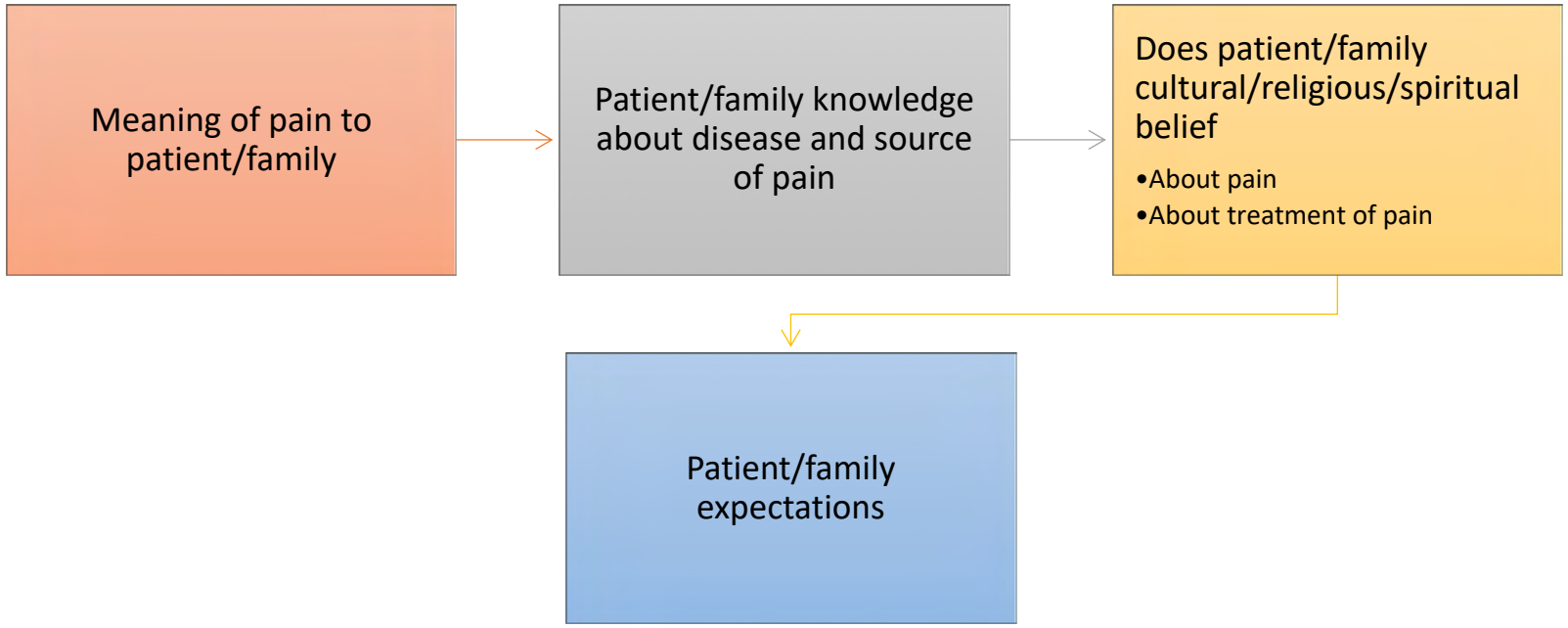
Presumptive Etiology

- Tumor infiltration
- Related to cancer treatment (adverse effect/side effect)
- Unrelated to cancer or cancer treatment
  - Injury, chronic illness

Comprehensive Pain Assessment

- **Pain History**
  - Location
  - Duration
    - Onset, Last how long, frequency
  - Intensity
    - At rest, with activity, limitations
  - Quality/Character
    - Somatic (aching, throbbing); Visceral (cramping, gnawing); Neuropathic (tingling, burning, shooting, radiating)
  - Temporal patterns
  - Aggravating/alleviating factors
  - Previous treatment
    - Response to prior and current rx, why discontinued
  - Alcohol or drug dependence

Comprehensive Pain Assessment



Assessment of Pain in the Cognitively Impaired

Consider physical and verbal responses (e.g., facial grimacing, crying out when moved, decreased function or avoidance of contact.)

Consider change in behavior such as becoming withdrawn, increasing agitation or aggression.

Consider existing disorders that might be painful (e.g., arthritis, gout, neuropathy).

Assessment of Pain in the Cognitively Impaired

- Pain rating scales for the cognitively impaired
  - Doloplus-2 scale (1997)
  - Assessment of Discomfort in Dementia Protocol (1999)
  - Pain Assessment in Advanced Dementia (PAINAD) (2003)
  - Checklist of Nonverbal Pain Indicators (2000)
  - Pain Assessment for the Demented Elderly (2003)
  - Pain Assessment for Seniors with Limited Ability to Communicate (2004)
  - Abbey Pain Scale (2004)
- No trials showing clear superiority of one of these scales.
- Choose one tool and use it consistently to ensure uniformity among health care providers and across shifts.

Wilner. LS and Arnold, R. PCNOW Fast Facts and Concept #126: Pain Assessment in the Cognitively Impaired. July 2015

Principles of Pain Management

Inform patients about possible onset of pain at any stage of disease related to the disease, testing, and treatment

- Empowers patient
- Encourages communication about suffering, efficacy, and side effects

Educate patients on appropriate use of pharmacologic and non-pharmacologic therapies

- Improves compliance
- Improves pain relief
- Minimizes overuse and underuse

WHO Ladder

- Sequential three step analgesic ladder
- From non-opioid to weak opioid to strong opioid

Sequential approach to opioid use

- Dose find with short acting
- Maintenance with long-acting opioid combined with short-acting opioid for breakthrough pain

Integrated approach

- Primary antitumor treatments
- Interventional analgesic therapy and
- Non-invasive, non pharmacologic therapies (psychological, spiritual, and rehabilitative interventions)

Nonpharmacologic Therapy

Cognitive/behavior modification

Mind/body therapies

- Meditation and breathing exercises
- Progressive muscle relaxation
- Guided imagery
- Hypnotherapy

Cognitive reframing

Support groups

Pastoral counseling/prayer

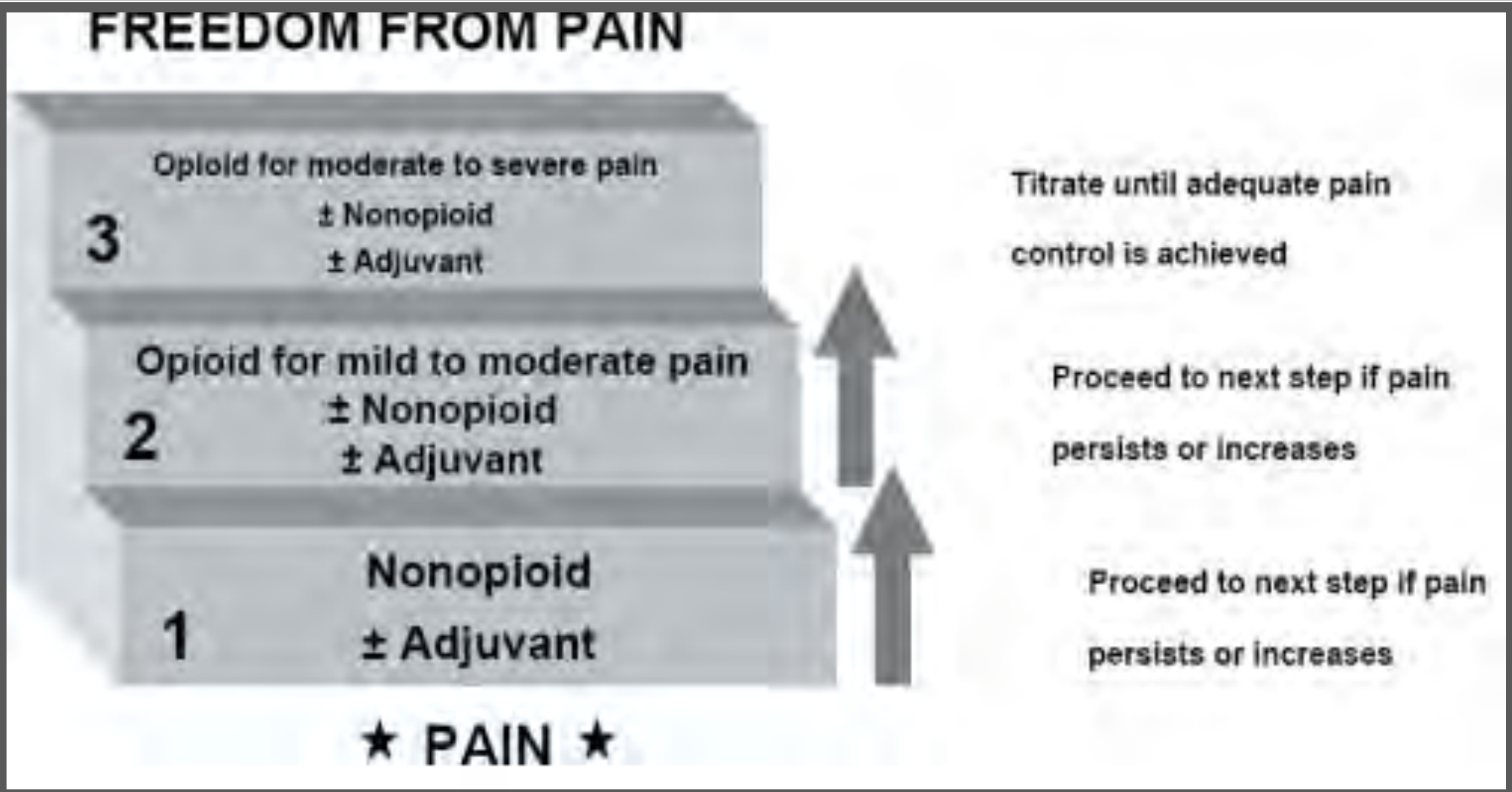
Physical measures

Heat/cold, Repositioning/bracing

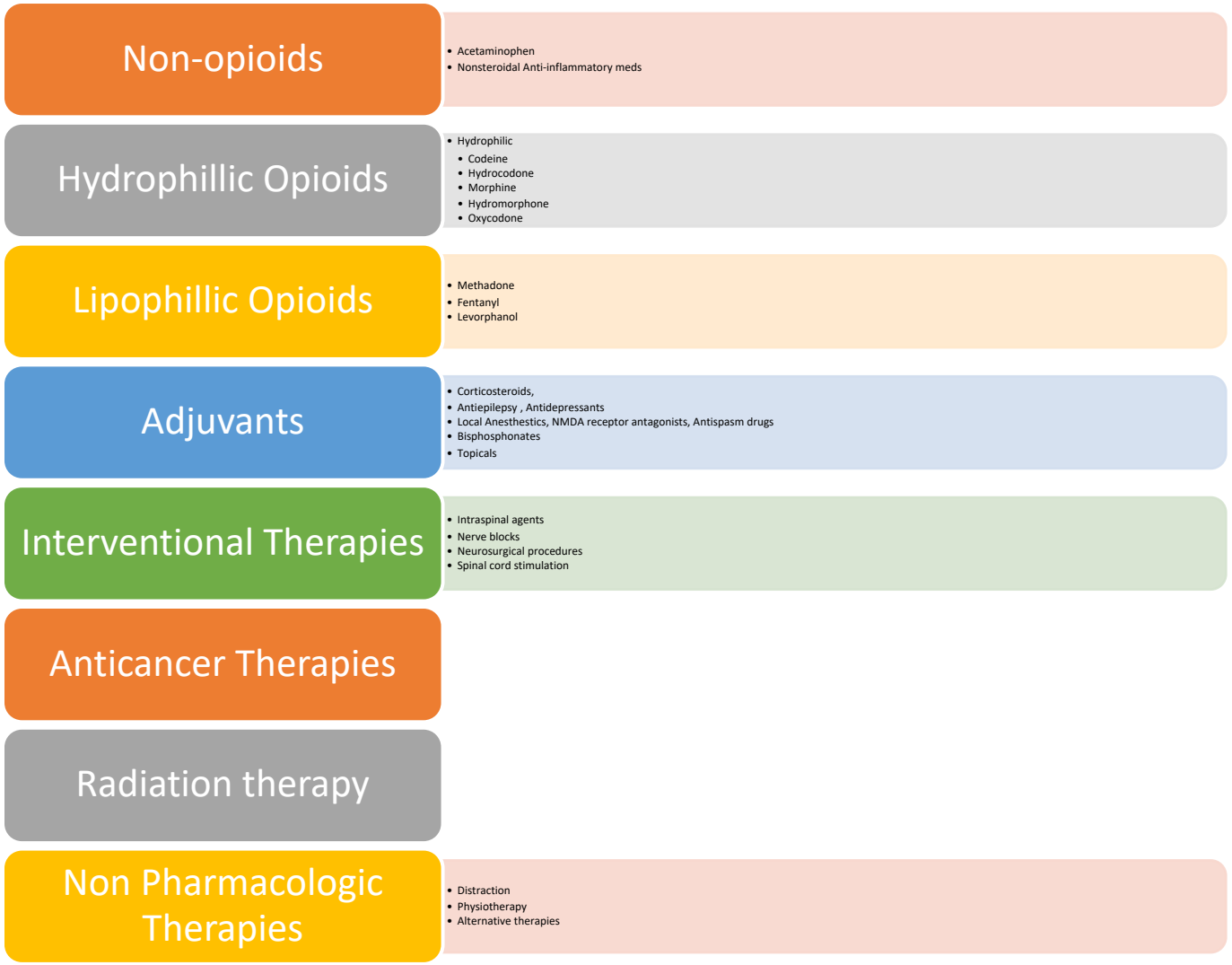
Massage

Acupuncture

The World Health Organization cancer pain treatment step ladder.



Therapeutic Approaches in Pain



Treatment of Mild Pain

Non-opioids analgesia (alone or in combination)

- Paracetamol/Acetaminophen
  - Avoid in liver failure and significant liver metastasis
- NSAIDs/Cyclo-oxygenase-2 (COX-2) selective inhibitors
  - Long term use monitor for toxicity
    - gastrointestinal bleeding, platelet dysfunction, and renal failure (NSAIDs and COX-2)
    - Increase risk of thrombotic cardiovascular adverse reaction (COX-2)
- Dipyrone

Treatment of Mild to Moderate Pain

Weak Opioids

- Tramadol
  - Weak centrally acting opioid
  - Side effects: drowsiness, dizziness, nausea, vomiting, and constipation
  - Contraindicated in patients with seizures (reduces sz threshold)
  - Activity at the opioid, norepinephrine, and serotonin receptors
    - potential for serotonin toxicity, caution in patients receiving antidepressants
  - Adjust dose in renal failure
- Dihydrocodone
  - Used to treat mild to moderate pain, as well as cough and shortness of breath
- Codeine
  - Analgesic effect occurs after metabolism to morphine
  - Side effect: nausea, vomiting, and constipation

Treatment of Moderate to Severe Pain

Strong Opioids

- Hydrophilic
  - Hydrocodone
  - Morphine
  - Hydromorphone
  - Oxycodone
- Lipophillic
  - Fentanyl
  - Methadone
  - Buprenorphine

Hydrophilic Opioid Pharmacokinetics

- Affinity for mu receptor primarily
- Metabolized by the liver
  - First pass effect, 2/3 metabolized
  - Bioavailability of PO Morphine 30%
  - Bioavailability of PO Hydromorphone 50%
  - Bioavailability of PO Oxycodone 80%
- Predominantly excreted renally
- Metabolites (renally excreted only)
  - Morphine-6-glucoronate (active); Morphine-3-glucoronate (neurotoxic)
  - Hydromorphone-3-glucoronate (neurotoxic)

Tmax Dependent on Route

Tmax (maximal effect) after

- Po/pr ≈ 1 h
- SC,IM ≈ 30 min
- IV ≈ 6 min

Half-life at steady state

- PO / PR / SC / IM / IV ~ 4 hours

Acute Titration

- Can redose at Tmax if pain persists. Safe rule is redose short-acting q2 hr and long-acting q24.
- Mild to moderate pain, increase 25-50%
- Moderate to severe, increase 50-100%
- Monitor closely
- 3-5 doses to reach steady state (12 to 20 hr)
- Once 24 hr requirements known, dose short acting opioids on t ½ or convert to long acting opioid to minimize bolus effect.

Treating Breakthrough Pain

- BTcP is transient pain exacerbation in patient with stable controlled background pain treated with opioid
- Treatment must be individualized
- Guidelines:
  - Use immediate releases opioid
  - Give 10%-15% of 24 hours dose prn based on Tmax
  - For unpredictable, rapid-onset cancer pain may use Transmucosal Fentanyl (oral, buccal, sublinqual, and intranasal)
- If using frequent breakthrough doses, consider adding to baseline long acting opioid
- Consider adding prn to baseline for incident/anticipatory pain

Converting from One Opioid to Another

- Use equianalgesic table
- Based on total daily dose
- Take in account “Incomplete Cross tolerance”(multiple mu receptors and heterodimers)
- Use 50-75% of calculated equianalgesic dose to have similar analgesic effect
- Ensure adequate breakthrough doses available

Equianalgesic Doses (mg)

Drug	Parenteral	Oral
Morphine	10	30
Hydrocodone	N/A	30
Hydromorphone	2	10
Oxycodone	10	20
Oxymorphone	1.0	10
Codeine	N/A	300
Tramadol	N/A	300

Lipophilic Opioid Pharmacokinetics

- Methadone and Fentanyl metabolized by the liver
- Neither has active or known toxic metabolites
- Methadone and metabolites 50% fecal excretion and 50% renal excretion. This makes it easier to titrate whether there is renal or liver failure.
- Fentanyl and metabolites primarily renally cleared.

Methadone (Dolophine)

Bioavailability of 80%

Broad spectrum affinity to opioid receptors (mu, delta, kappa) including NMDA-blocking effects

Tmax at 2.5-4hrs though effects starts within 30 min

Lipophilic and absorbed well orally, buccally or rectally

No active metabolites so preferred in renal failure

Steady analgesic effect and only long-acting opioid available as solution

Effective for somatic and neuropathic pain

Low cost

Methadone

- Long, variable half-life (6-190 hours)
- Small changes have larger effect >30mg/day
- Hold for sedation
- Prolonged QTc interval >400mg/day, check EKG if structural heart disease
- Increased levels with SSRIs, tricyclics, antifungals, flouroquinolones, amiodarone.
- Decrease levels with rifampin, phenytoin, corticosteroids, carbamazipine, phenobarbital, antiretrovirals

Methadone

In opioid-naïve patients, or converting from low doses of other opioids(<60mg morphine equiv)-not to exceed 2.5mg tid.

- Dose increases 5mg/d every 5-7days

Converting from higher doses of other opioids, use 1:10 ratio for morphine equivalent doses <300mg, 1:20 ratio at doses >600mg

- Do not exceed methadone 30-40mg daily
- Dose increases no more than 10mg/d q5-7d

Fentanyl transdermal

- Creates equilibrium with SC space, stored in fat cells. Not indicated for opioid naïve or acute pain. Fever can increase absorption.
- Onset of action about 12-24 hrs, dissipates in 12-24 hrs
- Peak plasma levels ~36-48 hrs
- Change q2-3 days
- Serum t ½ ~ 17 hrs
- Avoid if cachectic or poor perfusion
- Breakthrough is usually with po morphine

Fentanyl and Methadone Conversion

- Morphine to Methadone conversion ratios
  - 10:1 for morphine <1000mg, age <65 generally not below 15mg daily if chronic pain and long term opioid use
  - 20:1 for morphine >1000mg, age >65
  - Not below dosing for opioid naive
  - Ensure adequate breakthrough dosing available. 10-15%of morphine equivalent
- Fentanyl conversion is 1:2 (caveat: patient cachectic or suspect poor perfusion reduce 25-50%)

Buprenorphine

Mixed opioid agonist-antagonist

Indications

- Treatment of moderate to severe pain
- Treatment of opioid dependence/addiction (prevent opioid withdrawal symptoms)

Active ingredient in Suboxone and Subutex

Excreted in stool therefore role in renal failure and hemodialysis

Addiction and Tolerance

TOLERANCE - REDUCED EFFECTIVENESS TO SET DOSE OVER TIME. THIS IS NOT A PRACTICAL PROBLEM, IT MEANS THE DISEASE IS WORSENING

DO DEVELOP TOLERANCE TO COGNITIVE CLOUDING, NAUSEA AND RESPIRATORY DEPRESSION OVER 4DAYS

ADDICTION – PSYCHOLOGICAL DEPENDENCE AND COMPULSIVE USE DESPITE HARM

PSEUDO ADDICTION – UNDERTREATMENT

PHYSICAL DEPENDENCE IS COMMON BUT NOT TO BE CONFUSED WITH ADDICTION

Opioid Adverse Effect

Common	Uncommon
Cognitive Clouding	Pruritus/Urticaria
Nausea/Vomiting	Urinary Retention
Constipation	Respiratory Depression
? Delirium	Neurotoxicity -Myoclonic jerks -Opioid induced hyperalgesia

- Consider dose reduction or opioid rotation with intractable symptoms.
- Treat the side effect.

Side Effect Management

Sedation or cognitive clouding

- Lower dose
- Rotate opioids
- Methylphenidate (Ritalin) for chronic sedation

Nausea/Vomiting

- Antiemetic such as Haloperidol, Metoclopramide, Promethazine, Prochlorperazine
- If associated chemo-induced nausea: Olanzapine, Ondansetron

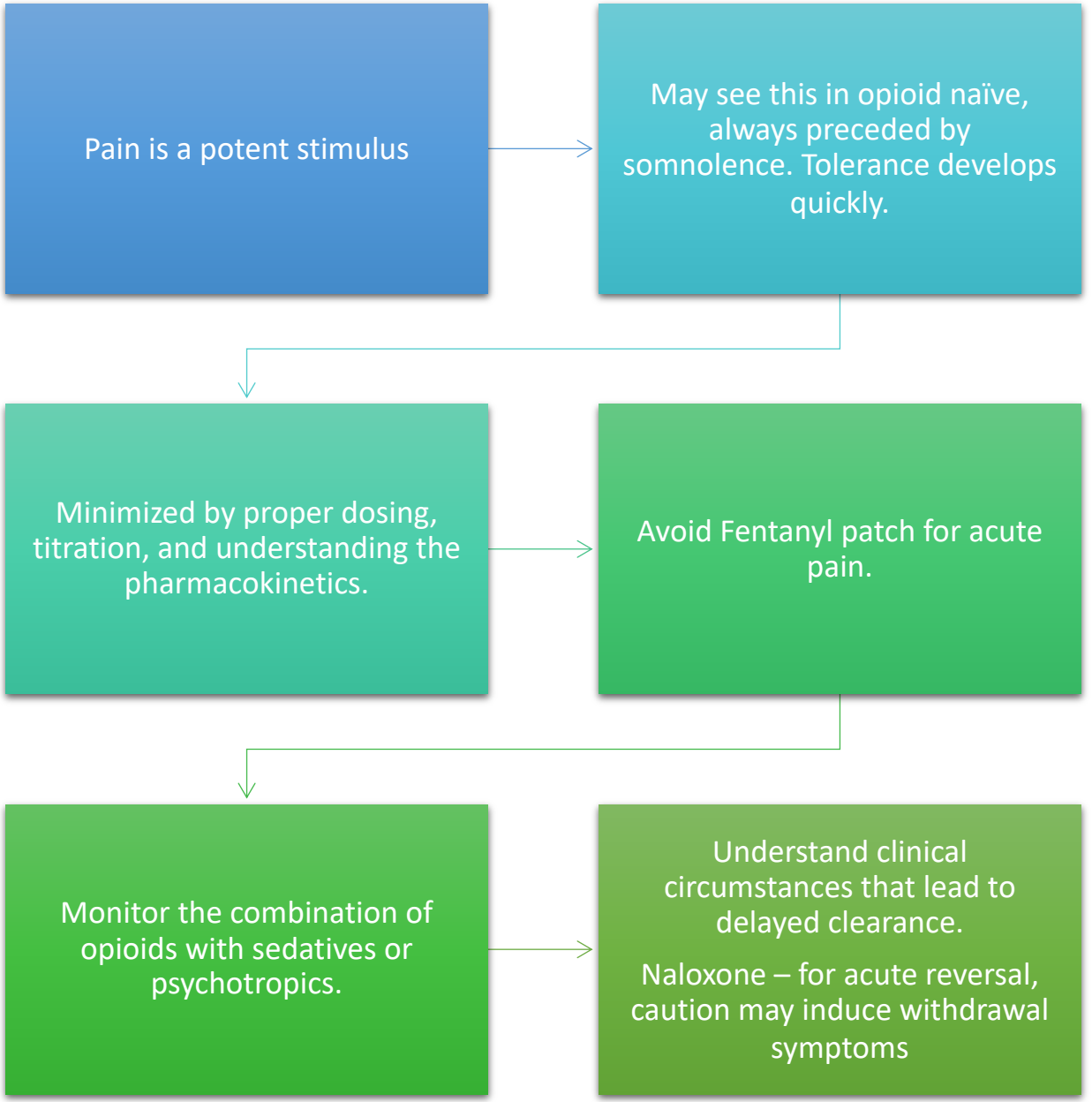
Constipation

- Stool softener and stimulant with opioid order
- Prokinetic and osmotic agents if refractory
- Peripherally acting mu opioid receptor antagonist (PAMORAs) – Methylnaltrexone,
- Opioid antagonist: Lubiprostone, Naloxone/Opioid combination

Pruritis

- Benadryl or vistaril
- Consider opioid rotation

Respiratory Depression



Neurotoxicity

Morphine and Hydromorphone metabolites

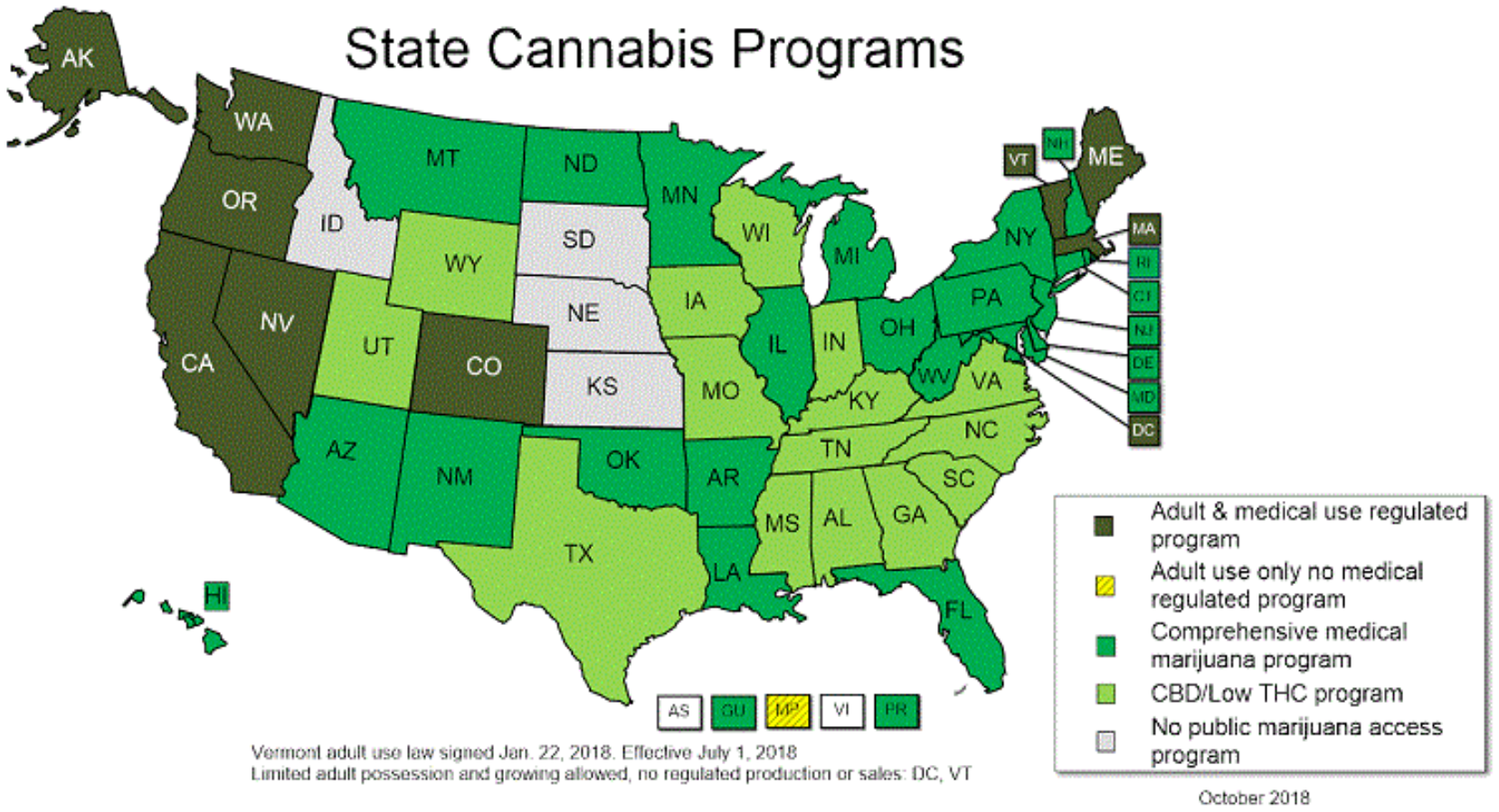
- Delirium
- Myoclonus
- Seizure
- Allodynia

Treatment

- Hydration (help excrete renally cleared metabolites)
- Opioid rotation to methadone, fentanyl
- NMDA receptor antagonists (methadone, ketamine)
- GABA agonists (lorazepam, midazolam)

Medical Cannabis in U.S.

- 1996 California first legalized marijuana for medical purposes
- 2013 Illinois legalized medical use
- 2018 (Sept) Thirty one states and DC approved medical use of cannabis



http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Medical Cannabis in Illinois

- Certifying physicians are required to have a relationship with the patient established at a physician's office, hospital, or other healthcare facility and the physician must have an ongoing responsibility for the patient's assessment, care, and treatment.
- Qualifying patients must be diagnosed with a debilitating condition, as defined in the Compassionate Use of Medical Cannabis Pilot Program Act, to be eligible for a medical cannabis registry identification card in Illinois.
- 55 Dispensaries

Medical Cannabis Approved Conditions

- Agitation of Alzheimer's disease
- HIV/AIDS
- Amyotrophic lateral sclerosis (ALS)
- Arnold-Chiari malformation
- Cancer
- Causalgia
- Chronic inflammatory demyelinating polyneuropathy
- Crohn's disease
- CRPS (complex regional pain syndrome Type II)
- Dystonia
- Fibrous Dysplasia
- Glaucoma
- Hepatitis C
- Hydrocephalus
- Hydromyelia
- Interstitial cystitis
- Lupus
- Multiple Sclerosis
- Muscular Dystrophy
- Myasthenia Gravis
- Myoclonus
- Nail-patella syndrome
- Neurofibromatosis
- Parkinson's disease
- Post-Concussion Syndrome
- Post-Traumatic Stress Disorder (PTSD)
- Reflex sympathetic dystrophy
- Residual limb pain
- Rheumatoid arthritis
- Seizures (including those characteristic of Epilepsy)
- Severe fibromyalgia
- Sjogren's syndrome
- Spinal cord disease (including but not limited to arachnoiditis)
- Spinal cord injury is damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity
- Spinocerebellar ataxia
- Syringomyelia
- Tarlov cysts
- Tourette syndrome
- Traumatic brain injury
- Cachexia/wasting syndrome
- *Last updated November 1, 2016*
- Terminal diagnosis (6 months or less)

Medical Marijuana

- Using the whole, unprocessed marijuana plant or its basic extracts
- To treat symptoms of illness and other condition
- FDA has not approved the marijuana plant as medicine
- FDA approved two cannabinoids, chemical in marijuana
  - The plant contain more than 100 cannabinoids
  - Delta-9-tetrahydrocannabinol (THC) is the mind-altering ingredient, also increases appetite, reduce nausea, decrease pain, inflammation, and muscle control problems
  - CBD, does not contain mind altering ingredient, used to decrease pain and inflammation, control epileptic seizures, and possible treat mental illness and addiction
- In Illinois:
  - Marijuana-derived CBD is purchased from a dispensary
  - Hemp-based CBD products are brought over-the-counter
- Recent research on marijuana extracts
  - Marijuana extracts may kill certain cancer cells and reduce cell size in others in animal studies
  - Slows growth of cancer cells in brain tumors
  - Treatment with purified THC and CBC, increased cancer killing effects of radaiton
- Adverse effects:
  - Cannabis hyperemesis syndrome – can occur with chronic use but also can bee seen with acute or acute on chronic
    - Abdominal pain, vomiting or nausea typically relieved by hot showers
    - RX: IV hydration, antiemetics (ondansetron) and benzodiazepines, ceasing marijuana use,
    - Other rx: capsaicin cream applied over the abdomen, haloperidol,
  - C-I Psychotic d/o, mood d/o, anxiety d/o,

Anticancer Therapies

Radiation therapy very effective

Chemotherapy, risks generally outweigh the benefits.

Bisphosphonates, prevent fractures in breast and prostate cancer but do not effect analgesia except in multiple myeloma

Surgery/anesthesia

Treatment of Bone Pain

Analgesic drug

Opioids

Steroids

Bisphosphonates

*Treat hypercalcemia and pain related to bone metastasis

* Preventative dental care before starting BP to avoid osteonecrosis of the jaw

* May experience pain flare after initial BP IV infusion, may require additional analgesia

Denosumab

Targeted receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor

Alternative to Bisphosphonates for bone mets from solid tumors and myeloma

Preventive dental measures before starting

External beam radiation therapy (EBRT)

Effective in metastatic bone pain and metastatic spinal cord compression

Relief in 60-80% patients

Dose range varies based on clinical status and goals of care (3 Gy in 10 fractions vs 8 Gy single dosevs 4 Gy in 6 fractions

Retreatment of recurrent bone pain with single dose 8 Gy is affective

Radioisotopes

Radium -223, strontium, samarium, and rhenium

Effective when multiple osteoblastic bone metastasis

Pain relief in multiple sites

Shown improved pain, QoL in patients with prostate cancer resistant pain

Targeted therapy

Stereotactic body RT (SBRT) high ablation dose

- 10-16 Gy or 27 GY in 3 fractions
- Consider in patient with oligometastases with good performance status, well controlled primary site

Oncologic Emergencies Presenting with Pain

Spinal Cord Compression

- Pain can precede the diagnosis by days to months in 95% of patients
- Pain may be localized to neck or back, radicular
- Early diagnosis is critical
  - Neurologic deficits may progress rapidly, once present chances of recovery lessens (poor prognosis)
  - MRI can used to confirm the diagnosis

Brain Metastasis

- Pain may be present with change in mental status and/or debility
- MRI used to confirm diagnosis

Treatment

- Immediate treatment with high dose steroids
  - Dexamethasone is drug of choice
  - 10 – 100 mg IV bolus followed by 8 - 16mg/day
  - Taper over 2 weeks
- Radiation therapy RT – first line treatment (consider)
  - Symptom relief in 50-58% patients
  - Spine - If prognosis is > 6 months lower dose radiation o/w 20 Gy in 5 fractions, or 8 Gy single dose
  - Brain - Gamma knife or whole brain radiations
- Surgery in patient with good performance status who have spinal instability or operable brain metastasis

Adjuvants: Corticosteroids

- All have potent antiinflammatory effect.
- Effective for bone (somatic) and visceral pain.
- Dexamethasone has least mineralcorticoid effect, all produce glucocorticoid effects.
- Can be given PO, IV, SQ. Can be given daily because of long half life.
- May produce psychosis (usually resolves.)
- Long-term use can cause proximal muscle wasting.

Cancer-Related Neuropathic Pain

Due to direct cancer–induced injury to somatosensory system

Differs from other NP: Nerve fibrosis s/p RT. Chemo-induced, post surgical

Treat using opioid combination therapies with scheduled adjuvant (TCA or anticonvulsant) monitor for side effect

Gabapentine, pregabalin, duloxetine, and TCA can be use first line as single agent

Studies show addition of adjuvants to opioid, resulted in improvement within 4-8 days

Recommend against Levetiracetam and mexiletine

Ketamine, a NMDA antagonist, lacks evidence of reliable pain relief

Neuropathic Pain - Antiepileptics

Older agents have significant adverse effects

- Carbamazepine – aplastic anemia
- Phenytoin – hepatotoxicity

Gabapentin

- Side effects: dizziness, sedation
- Start100-300mg qHS and titrate (q3-5d) up to 3600mg/day. Effect often decreases after 1800 mg.

Pregabalin, 50mg TID, max 600mg daily

Both need renal dosing

Neuropathic Pain: Tricyclic Antidepressants

- Most studied agent, amitriptyline, has most anticholinergic effects
- Alternate agents: nortriptyline, desipramine
- Usually sedating, administer at night
- Start low, titrate gradually every 2 or 3 days
- Prevent constipation

Neuropathic Pain: Other Antidepressants

- Duloxetine (Cymbalta)
- Mechanism: inhibits NE, 5HT, Dopamine reuptake
- Cymbalta – 60mg daily
  - Reduce dose with renal disorder, avoid with hepatic impairment
- There is no evidence that Venlafaxine (Effexor) is effective for pain

Other Adjuvants

No effect with SSRIs (use if presence of depression/anxiety)

Topical Anesthetics

- EMLA cream (pediatrics)
- Doxepin cream (itching)
- Diclofenac cream
- Capsaicin cream
- Arnica cream
- Lidoderm gel, patch (post-herpetic neuralgia), spray
  - Intact skin
  - 12 on/12off

Antispasm Drugs

Baclofen

- 5-20 mg po TID
- Drowsiness, dizziness, hallucinations (60-80mg/d)

Tizanidine

- 2 mg po TID
- Drowsiness

Clonazepam

- 0.5 mg po BID-QID, antiseizure as well as antispasm
- Sedating

Treatment of Refractory Pain

- 10% of cancer patients have difficult to manage pain with oral and parenteral analgesics
- Invasive interventional methods in combination with oral analgesic
    - Intraspinal agents
        - Indications:
            - Inadequate pain control despite escalating opioids and adjuvant analgesia
            - Inadequate response to opioid rotation, changing route
            - Experiencing side effects when titrating
            - Life expectancy > 6 months
        - Spinal Analgesia
            - Via epidural or intrathecal
            - Lower dose results in fewer side effects
            - Effect for pain in head, neck, upper and lower extremities and the trunk
            - Most effective for pain below the diaphragm
            - Contraindicated in patients with infections, coagulopathy, or very short life expectancy
            - Process: Insert temporary catheter or injection for initial trial of intraspinal analgesia; if successful trial, implant pump
            - Medications: Morphine, Ziconotide, Baclofen, and Bupivacaine (0.125%-0.25%)

Treatment of Refractory Pain

- Nerve blocks or Plexus blocks
  - Indication
    - Pain in field of one or more peripheral nerve (localized to a few dermatomes)
    - Pain caused by complication e.g. Vascular occlusion or pathologic fracture
  - Typically not primary mode of treatment, combine with systemic analgesia and multimodal approach
  - Typically allow decrease in total dose of systemic drugs and related side effects
  - Caution: Neuritis can occur by use of neurolytic agents on peripheral nerves resulting in pain that is more difficult to control
  - Neurolytic blocks last 3-6 months, therefore, reserved for patient with limited prognosis
  - For sympathetic (visceral) and somatic pain
    - Celiac plexus block (for cancer-related visceral pain in upper abdomen or pancreas)
    - Superior hypogastric plexus block (for pelvic pain)
    - Ganglion impar block (for perineal pain of visceral origin)
    - Intercostal nerve block (for chest wall pain due to rib metastasis)
    - Peripheral nerve block

Treatment of Refractory Pain

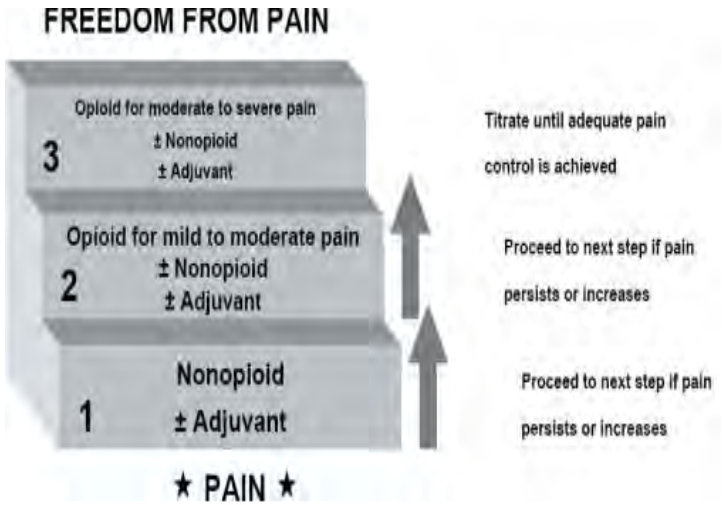
Neurosurgical procedures

- Neurolysis
- Thoracic splanchnicectomy (for intractable pain due to chronic pancreatitis/pancreatic cancer)
- Midline myelotomy (intractable abdominal and pelvic cancer pain)
- Cordotomy
  - Percutaneous or surgical
  - High cervical c. for unilateral pain below the shoulder (C4)
  - For movement related pain (incidental pain) e.g. inoperable pathologic fracture pelvis or long bone

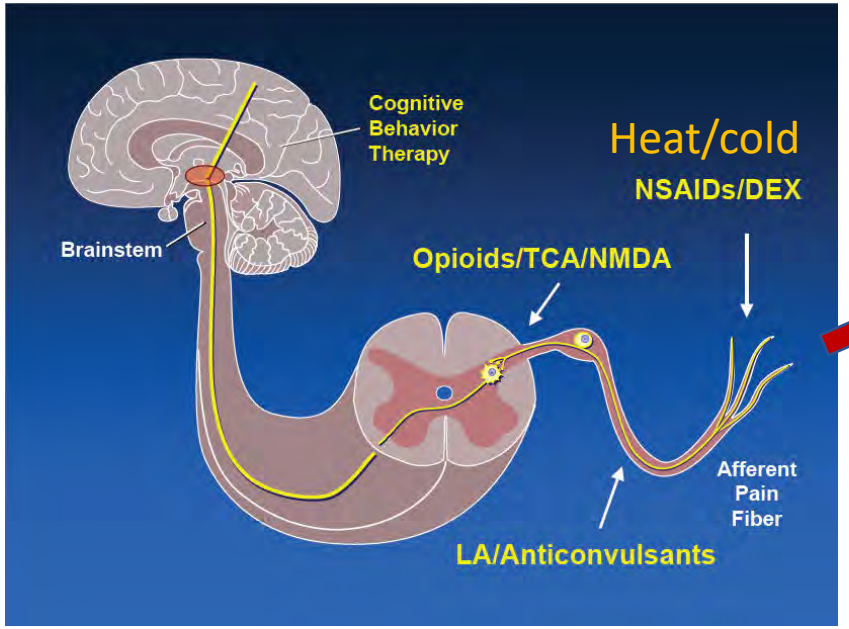
Spinal cord stimulation

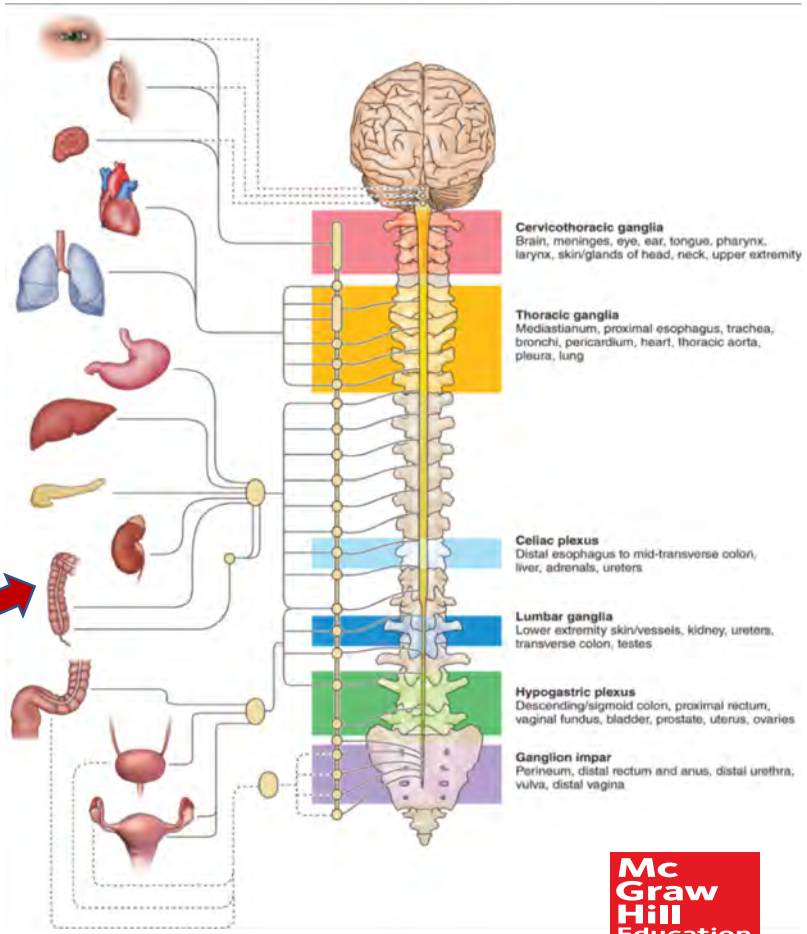
- For chronic neuropathic pain
- For malignant and non-malignant sources of pain
- Effective in slow growing cancer
  - Possible extension of pain to areas not covered by the stimulator
  - Possible neurologic deficit

SUMMARY
Multimodal Therapy: Management of Intractable or Refractory Pain



World Health Organization cancer pain treatment step ladder





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Questions