Basic Science of *Cannabis* and *Cannabinoids*

- Analgesic effect mediated via cannabinoid-1 (CBI) receptor in nociceptive area of CNS and peripheral Nervous System, modulates serotonergic, dopaminergic, glutamatergic .
- Produces complimentary effects on endogenous opioids.
- Non-receptor effects – anti-inflammatory; immunomodulatory (non-psychoactive cannabinoid – CBD) for RA and other autoimmune diseases via inhibition of TNF-Alfa2A
  - McCarberg BH. Cannabinoids: Their Role in Pain and Palliation. *Jour Pain & Palliative Care Pharmacotherapy,* The Haworth Press, Inc. 2007;21(3):19-28.

Types of *Cannabinoids*

1. Endocannabinoids (analgesic effect mediated via cannabinoid-1 (CBI) receptor in nociceptive area of CNS and peripheral Nervous System, modulates serotonergic, dopaminergic, glutamatergic .Produces complimentary effects on endogenous opioids.

2. Synthetic Cannabinoids – replicated naturally occurring cannabinoids.

- Synthetic THC – Marinol for chemo-induced nausea (1985), Pain and appetite stimulation IN HIV/AIDS (1992)

3. Phytocannabinoids – plant/herbal or smoked cannabis, two Phytocannabinoids products available

Neuropathic Pain

- Treatment modalities
  - Central and peripheral nervous system cannabinoid receptors (endogenous ligands are unknown)
  - Cannabis or cannabinoids, tetrahydrocannabinol (THC) poor analgesics and have adverse effects due to psychoactive and physical adverse effects, i.e.,
    - Psychomotor and cognitive impairment
    - Anxiety and panic attacks
    - Acute psychosis and paranoia
    - Physical – xerostomia, blurred vision, palpitations, tachycardia and postural hypotension
  - CT-3 a synthetic analog of THC-11-oic acid effective in neuropathic pain (antiallodynic) free of psychoactive effects
    - Karst M, et al. Analgesic Effect of the Synthetic Cannabinoid CT-3 on Chronic Neuropathic Pain. *JAMA, Oct 1, 2003;290(13):1757-1762*

Non-opioid Modalities: Local Anesthetics

- Bupivacaine 1%
- Lidocaine 5%
- Combination: Lidocaine 2% + Ketoprofen 10% + cyclobenzaprine 2%
- Local anesthetics bind to the intracellular portion of the sodium channels and blocks sodium influx into the nerve cells which prevent depolarization.

Non-opioid Modalities: Anti-inflammatory

- Diclofenac 5%
- Flurbiprofen 10%
- Ketoprofen 10%
- Combination: Ketoprofen 10% + Cyclobenzaprine 2%

Non-opioid Modalities: Muscle Spasm

- Cyclobenzaprine 2%
- Baclofen 2% - Baclofen produces its effects by activating the GABA receptor; however, it does not have significant affinity for the Gamma-hydroxybutyrate receptor (GHB), and has no known abuse potential. It has been used for alcoholism and Autism.

Non-opioid Modalities
Alfa-2A Adrenoreceptor Agonist

- Clonidine 0.2%
- The alfa-2a Adrenoreceptor is responsible for the anesthetic and sympatholytic action. Transdermal preparation appear to enhance the release of enkephalin-like substances. As an adjuvant it attenuates tolerance to opioids and side effects, e.g., sedation, anxiolysis and respiratory depression.
  - McClain BC. New Modalities for Pain Management. SPA Annual Meeting, 2006.

Non-opioid Modalities: Tricyclic Antidepressant

- Amitriptyline 5%
- Doxepin 3%
- Imipramine 3%
- The mechanism of action is its serotonin-norepinephrine reuptake inhibitor, with strong actions on the serotonin transporter and moderate effect on the norepinephrine transporter

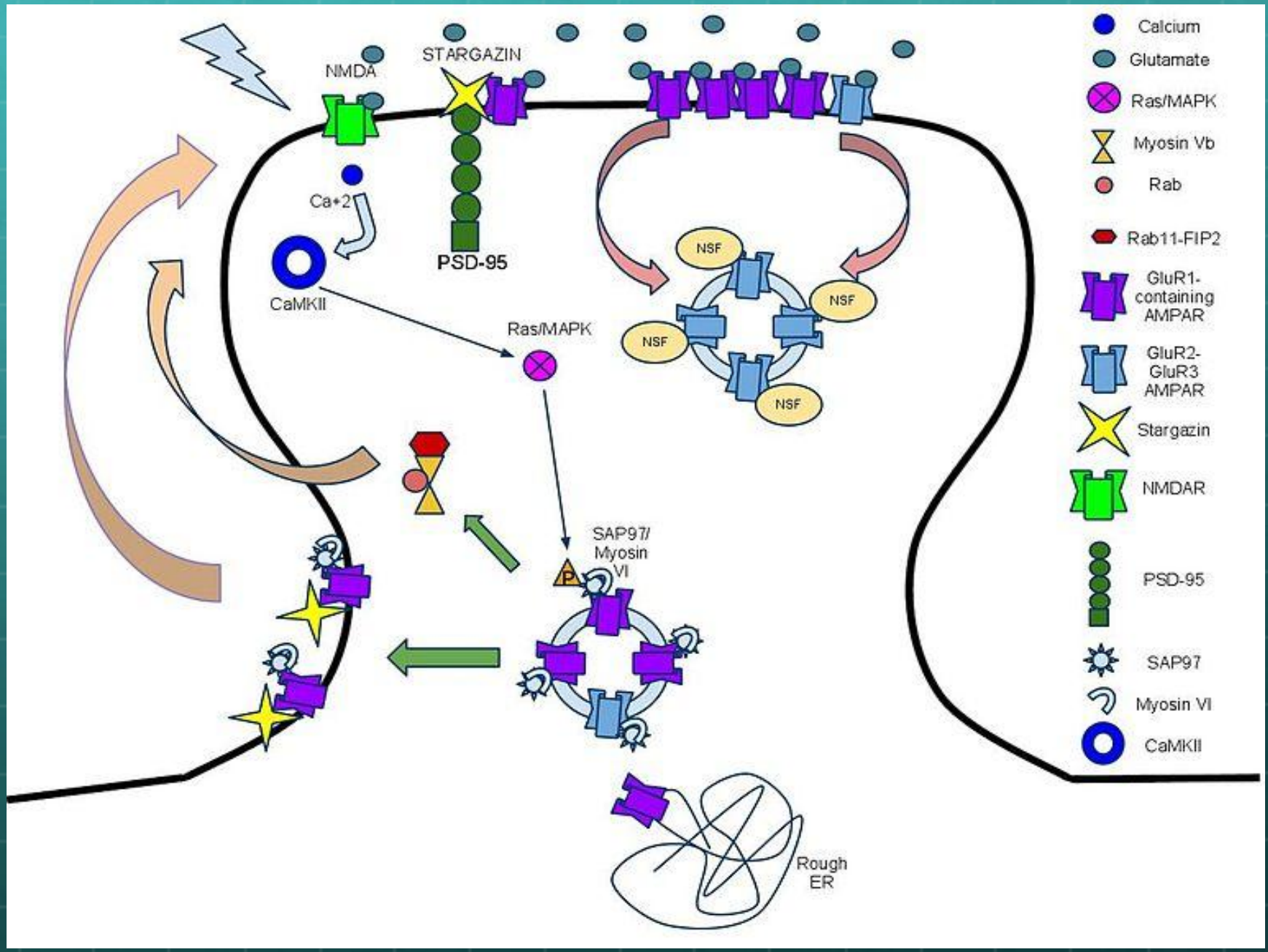
Non-opioid Modalities: Anticonvulsants

- Gabapentin 6%
- Carbamazepine 3%
- Topiramate 1%
- Most anticonvulsants produce a blockage of voltage-dependent/gated sodium & calcium channels, an augmentation of gamma-aminobutyrate acid activity at some subtypes of the GABA- A receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV .

AMPA RECEPTORS

- **The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor** (also known as **AMPA receptor, AMPAR,** or **quisqualate receptor**) is a non-NMDA-type ionotropic transmembrane receptor of glutamate that mediates fast synaptic transmission in the CNS. Its name is derived from its ability to be activated by the artificial glutamate analog – AMPA.

- AMPARs are found in many parts of the brain and are the most commonly found receptor in the nervous system. The AMPA receptor GluA2 (GluR2) tetramer was the first and currently only glutamate receptor ion channel to be crystallized.
  - Tage Honore and colleagues at the School of Pharmacy in Copenhagen,1982 *Journal of Neurochemistry*


NMDA
STARGAZIN
Ca+2
PSD-95
CaMKII
Ras/MAPK
NSF
NSF
NSF
NSF
SAP97/
Myosin
VI
P
Rough
ER
Calcium
Glutamate
Ras/MAPK
Myosin Vb
Rab
Rab11-FIP2
GluR1-
containing
AMPAR
GluR2-
GluR3
AMPAR
Stargazin
NMDAR
PSD-95
SAP97
Myosin VI
CaMKII

Non-opioid Modalities: N-methyl-D-Aspartate Antagonist

- Ketamine 10% - is used in acute and chronic pain. It is a noncompetitive antagonist analgesic.
- Amantadine 8% - It is a dopaminergic, noradrenergic and serotonergic substance, blocks monoamine oxidase A and NMDA receptors and seems to raise beta-endorphin/beta-lipotropin levels. monoamine oxidase A and NMDA receptors.

Non-opioid Modalities: Calcium Channel Blockers

- Diltiazem 2% for proctalgia fugax
- Verapamil 6% for scarring and fibrosis
- Nifedipine 2% for proctalgia and claudication
- Calcium channel blockers are a Class IV antiarrhythmic agents because they block voltage-dependent calcium channels in smooth muscles that line the blood vessels. By relaxing the tone of these smooth muscles, calcium channel blockers dilate blood vessels.
  - Jonas M, Neal KR, Abercrombie JF, Scholefield JH. A randomized trial of oral vs. topical diltiazem for chronic anal fissures. Dis Colon Rectum. 2001 Aug;44(8):1074-8.

Opioid Agonist and Antagonist

- The use of an agonist-antagonist is sometimes a practical way to address pain and reduce side effects. Unfortunately, most agonist-antagonists like butorphanol (Stadol), nalbuphine (Nubain) and pentazocine (Talwin) have agonist activity in the kappa receptor and partial antagonist activity in the mu receptor. This causes attenuated pain relief and may precipitate a pain crisis if the patient is on a mu-receptor drug like morphine and receives butorphanol or nalbuphine in the emergency room or hospital.

Opioid Agonist and Antagonist

- There is an emerging body of studies in the use of mu-receptor agonist like morphine with low-dose opioid antagonists like naloxone (Narcan) parenterally. Two studies revealed the patients with this combination experienced less nausea, vomiting and pruritus (due to histamine release from certain opiates, e.g., morphine).
- Suboxone (Buprenorphine 2mg/naloxone 0.5mg or 8mg/2mg)
  - Cepeda MS, Alvarez H, Morales O, Carr DB. Addition of ultralow dose naloxone to postoperative morphine PCA: unchanged analgesia and opioid requirement but decreased incidence of opioid side effects. *Pain*. 2004;107(1-2):41-6.
  - Maxwell LG, Kaufmann SC, Bitzer S, et al. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: a double-blind, prospective, randomized, controlled study. *Anesth Analg*. 2005;100(4):953-8.

Pain Assessment Tools

- Visual Analogue Scales:
- 1. Descriptive Scale: 0-10, describing no pain as zero and worst pain as ten
- 2. Wong-Baker Faces: 0-5, faces of no pain to severe pain
- 3. Numeric scale: 0-10, Zero no pain; rating of mild pain from 1-3; moderate pain from 4-7 and severe pain from 8-10
- 4. Pain Thermometer in the elderly: 0-10, zero is no pain; 1-2 is little pain; 3-4 is moderate pain; 5-6 is quite bad pain; 7-8 is very bad pain; 9-10 pain that is almost unbearable

WILDA ASSESSMENT TOOL

A Word to describe pain:

- Intensity
- Location
- Duration
- Aggravating and /or alleviating factors
  - Brian Ginsberg, MB, BCH, Duke University Medical Center

Nonspecific Behavior Observations Suggesting Pain

- Non-Verbal Behaviors:
  - Restlessness, guarding, bracing, rubbing, fidgety, striking out, recurrent agitation
- Vocalizations:
  - Crying, moaning, groaning, calling out, sighing, labored breathing
- Facial Expressions:
  - Frowning, grimacing, wincing, fearful faces, grinding of teeth
- Others:
  - Decrease in: ADL, function, appetite, sleep
  - Resisting ROM during care, abnormal gait
  - Hand grip
    - *Chronic Pain Management in the Long-Term Care Setting,* AMDA, Clinical Practice Guidelines, 1999. Modified by A. Peralta

Types of Analgesics

- 1. Non-opioid or non-steroidal anti-inflammatory drugs (NSAID's)- work primarily at the peripheral nervous system level:
  - a. Over the counter (OTC) - mainly ASA, acetaminophen, ibuprofen.
  - b. Prescription, e.g., ibuprofen, naproxen, and indomethacin
- 2. Opioids work primarily at the CNS level:
  - a . Opioid agonist, e.g., morphine, meperidine, hydromorphone, fentanyl (Duragesic), levorphanol (Levo-Dromoran), oxymorphone (Numorphan), oxycodone, tramadol & codeine.
  - b. Opioid agonist-antagonist, e.g., pentazocine (Talwin), nalbuphine (Nubain), butorphanol (Stadol), and buprenorphine (Buprenex).

Types of Analgesics (cont'd)

- 3. Adjuvant analgesics - various actions:
  - a. Anticonvulsant, e.g., phenytoin (Dilantin) and carbamazepine (Tegretol), Valproate, Gabapentin.
  - b. Antidepressants, e.g., Tricyclic's - amitriptyline (Elavil) and desipramine (Norpramin), SNRI's – venlafaxine (Effexor), duloxetine.
  - c. Others: e.g., steroid, Baclofen, Eutectic mixture of local anesthetics (EMLA, e.g., lidocaine or Lidoderm), Lidocaine IV,

    dextromethorphan, bisphosphonates (Ardia, Fosamax).

Peralta A: Pain Management in the Elderly. *International Jour of Pharmaceutical Compounding*, May/June 2004; 8(3):187-192.

Medications for Fibromyalgia

1. Pregabalin (Lyrica) – 75mg bid may increase to 150mg bid to maximum of 450mg/day
2. Duloxetine (Cymbalta) - 30mg daily x 1 week then increase to 60mg daily
3. Milnacipran (Savella) – titrated dose for 12.5mg on day 1 to 12.5mg on day 2-3, Days 4-7 25mg bid with maintenance dose at 50mg bid

WHO ANALGESIC LADDER

SEVERE(8-10)	Opioid NSAID & Adjuvants	Morphine, methadone, meperidine, fentanyl, oxycodone
MODERATE(4-7)	Opioid NSAID & ± Adjuvants	Oxycodone, codeine, tramadol, COX 1 & 2
MILD(1-3)	NSAID & mild analgesics	COX 1 & 2, APAP, ASA

- NON-PHARMACOLOGICAL MEASURES MAY BE USED IN ALL STEPS

- World Health Organization. Cancer Pain Relief (2nd ed.), 1996

Common Types of Episodic Pain

1. End of Dose Failure
   - Dose of medication does not last the desired or prescribed time parameters
2. Incident Pain
   - Pain on movement or with activity
3. Breakthrough Pain
   - Crescendo (escalating) pain superimposed over stable or managed chronic pain
     - Coluzzi, PH, Cancer Pain Management: Newer Perspectives on Opioids and Episodic Pain. *Am J Hospice and Palliative Care.* 1998:13-22.

Use of opiates in pain management

- Opioids like Morphine have a short half-life (t1/2) of 60 to 90 minutes. Therefore, they reach steady state within 4-5 half-lives. Once steady state is achieved, you can titrate the dose up by 50-100% within 24-48 hours. Once the patient's pain is controlled, i.e., pain rating of 0-2, you can convert the immediate release opioid to long acting opioid for pain.
- Note: It is paramount to initiate a bowel regiment when starting opioid therapy.

- Peralta A. Symptom management in hospice and palliative care. *Texas Medicine*. 2001; 97(8):42-51.

Equianalgesic Conversion for opioid analgesics

- Morphine IV/IM/SQ to oral is a 1:3 ratio
- Morphine IV/IM/SQ to meperidine (Demerol) is a 1:10 ratio
- Morphine IV/IM/SQ to hydromorphone (Dilaudid) is a 1:7 ratio
- Hydromorphone IV/IM/SQ to oral is a 1:5 ratio
- Breakthrough dose for opioids:
  - 10% of the 24 hour dose every 1-2 hours
    - Education for Physicians in End-of-Life Care Project, Institute of Ethics. American Medical Association; 1999. Module 4.

Dosage Conversion-Oral Morphine to Transdermal Fentanyl

Oral Morphine (mg/24hr)	Transdermal Fentanyl (mcg/hr)
45-134	25
135-224	50
225-314	75
315-404	100
**	**
1035-1124	300

Source: Janssen Pharmaceutical

Equianalgesic Conversion for opioid analgesics

- Duragesic (transdermal fentanyl system):
- mcg/h dose of Duragesic = 1/2 x mg/day dose of oral morphine
- Example:
- Duragesic 100mcg/hr dose every 72 hrs = Oral Morphine SA 100mg q 12 hrs. or
- Duragesic 2400mcg or 2.4mg/day = MS 200mg/day (approx. 1:100)
    - Levy, MH. Pain Management Center, Fox Chase Cancer Center at NHO Annual Meeting, Oct., 1992

The use of opioids in dyspnea

- Mechanism of Action:
  - Cerebral sedation
  - Vagal stimulation
  - Vasodilatation
  - Analgesia
  - Action on airway opioid receptors - J receptors
  - Carbon dioxide-sensitive medullary respiratory center
    - Peralta A. Symptom management in hospice and palliative care. *Texas Medicine*. 2001;97(8):42-51.

Opioid-induced Neurotoxicity

- Side effects of opioid therapy in pain management may include nausea, vomiting, pruritus, euphoria, constipation, cerebral sedation, and psychotomimetic phenomenon. The psychotomimetic effects are the auditory and visual hallucinations and distortion of perception. Most of these side effects can be anticipated and treated prophylactically, e.g., antihistamine for pruritus, bowel regimen for constipation, methylphenidate for sedation, antiemetic for nausea and vomiting, anxiolytic and psychotropic medications for psychotomimetic symptoms. Patients may also exhibit tactile hallucinations, which is the action of patients picking insects or bugs of their skin, bedding, walls and from the air. Tactile hallucinations sometimes respond to reduction of the opioid medications by 25% or 50% or opioid rotation (changing to another opioid).

Opioid-induced Neurotoxicity

- Additional neurotoxic symptoms such as opioid-induced myoclonus, agitation, delirium and hyperalgesia not only respond to anxiolytic and psychotropic medications but also to opioid rotation. Neurostimulants such as methylphenidate (Ritalin®) and modafinil (Provigil®) may also be useful in the hospice and palliative care setting to treat opioid-induced sedation.
  - Peralta A. Pain Report #13 End-of-Life Care: The Management of Pain in Palliative Medicine. Internet Monograph. Dannemiller Education Center, July 2011; www.Dannemiller.com

Ethical Issues in End of life Care

- As medical professionals we must be cognizant that our clinical clarity in treating diseases sometimes becomes absent when caring for the terminally ill; therefore, we must be willing to accept the uncertainty in the dynamic care of patients near death and consistently focus on providing comfort both physically and psycho-spiritually.

Barriers to Pain Management

- PATIENT
  - "Wimp"
  - Fear of adverse drug effects/events
  - Fear of addiction
  - Other illness or disease/pathology
  - Knowledge deficit
- CAREGIVER
  - Knowledge deficit
  - Fear of opioids
  - Legal pressure
  - Pain as a "symptom"
  - Fear of addiction
  - PRN

Barriers to Pain Management

- Normal/natural reluctance to discuss end of life issues, especially those related to pain
- Paucity of clinical education and training in pain and symptom management
- Limited exposure and knowledge of health care professionals on the signs and symptoms of impending death
- Paradigm shift from cure to comfort care

Chronic Pain Misconceptions in the Elderly

- Personal weakness to acknowledge pain and conversely, strength in character to bear pain.
- Chronic pain is part of aging.
- Chronic pain is a punishment for past actions.
- Chronic pain heralds a serious disease.
- Acknowledging pain will cause painful and invasive testing and loss of autonomy.
- Cognitively impaired elders have higher thresholds and cannot be assessed for pain.
- Elders in LTCF seek attention with pain symptoms and are likely to become addicted to pain medications.
  - *Chronic Pain Management in the Long-Term Care Setting*, AMDA, Clinical Practice Guidelines, 1999.

Treatment Alternatives

- Continued Aggressive Treatment
- - the "biotechnical" primary worldview of cure and prolongation of life the "technologic imperative"
- Alternative Approaches - bringing the "ethical imperative" and "spiritual imperative" into the decision process
  - Passive Euthanasia (PE) - Terminating or withholding life sustaining treatments, allowing the patient to die
  - Indirect Euthanasia (IE) - Administering narcotics or other pharmaceuticals to relieve pain, dyspnea, nausea, or other symptoms of dying with the unintended or incidental consequence of causing death

Treatment Alternatives

- **Physician Assisted Suicide (PAS) -** PAS occurs when a physician facilitates a patient's death by providing the necessary means and/or information to enable the patient to perform the life-ending act.

- **Active Euthanasia (AE) -** The administration of a lethal agent by another person to a patient for the purpose of relieving the patient's intolerable and incurable suffering"

Ethical Imperatives

- ETHICAL RESPONSIBILITY:
- The Principal of Double Effect recognizes that one's actions may have multiple effects, and that the primary intent of an act is determinative. For example, it is considered medically appropriate to administer morphine to relieve pain and respiratory distress to a terminally ill patient. The accompanying secondary side-effect may be a slight decrease in respiration and provides a state of comfort that allows the patient to die peacefully. The primary intent should always be symptom control.
  - Modified from Hospice Code of Ethics, NHO Ethics Committee 1993-1994.
  - Peralta A. Pain Report #13 End-of-Life Care: The Management of Pain in Palliative Medicine. Internet Monograph. Dannemiller Education Center, July 2011; www.Dannemiller.com

Ethical Imperatives to adequate pain management

- MORAL ISSUES:
  - Patients have a strong prima facie right to freedom from unnecessary pain.
  - Pain is dehumanizing.
  - Pain destroys autonomy. The Ethical Principal of Autonomy allows self-determination by patients.
  - Pain is humiliating.
  - In its extreme, pain destroys the "soul" itself and all will to live.
    - E. Cassell, MD. The Nature of Suffering. Oxford Press, 1991 and Lisson, Nurs Clin North Am. 1987; 22:654.

Precepts to Pain Management

- Moderate to severe pain is experienced by 30 to 60% of patients with cancer
- 70% of patients with advanced cancer have moderate to severe pain
- The success of the Agency for Health Care Policy and Research Guidelines in the treatment of cancer pain and chronic non-malignant pain
- Basic sciences, research pharmacology and applied clinical experience have provided a template for the use of opioid and non-opioid drugs in a clinically diverse population with pain
- JCAHO: New Standards for the Assessment and Management of Pain; January 2002.

General Principles for Pain Control

- Administer medications routinely, not PRN.
- Use the least invasive route of administration first, e.g., oral, rectal, transdermal.
- Begin with a low dose and titrate carefully until pain is alleviated or comfort achieved.
- Reassess and adjust dose frequently to optimize pain relief while monitoring and managing side effects.
  - *Chronic Pain Management in the Long-Term Care Setting*. AMDA, Clinical Practice Guidelines; 1999.

Questions ???