Evolution of Palliative Care

-Dame Cicely Saunders (1918-2005)
  -British nurse, social worker, and physician
  -Holistic approach to end-of-life, including concept of total pain/suffering
  -Founder of first modern hospice (St Christopher's Hospice in London in 1967)
  -First hospice in the US in 1970s and Medicare Hospice Benefit in 1980s
  -Palliative care increasingly considered more than end-of-life care by the 1980s
  -Nursing certification in hospice and palliative care in US in 1994
  -Palliative care recognized as a medical sub-specialty in US in 2006

Modern palliative care

-Palliative Care TODAY (per CMS, WHO, CAPC, etc.):
  -Can be provided at any point in the treatment of a serious illness
  -Patient AND loved ones/family
  -Improve quality of life
  -Anticipates, prevents, and treats suffering
  -Physical, emotional/psychological, social, and spiritual suffering
  -Facilitates patient autonomy, access to information, and choice
  -Generally involves a multi-disciplinary team

Hospice & Comfort Care

-In the US, hospice generally defined by Medicare Hospice Benefit
  -A program that delivers palliative care to patients at end-of-life
  -Prognosis of six months or less
  -No treatment of the certifying illness (focus on comfort)
  -Provided wherever the patient calls home
  -Patient on comfort care usually means:
    -Actively dying patient
    -Comfort more important than prolonging life
    -Patient may or may not be enrolled with a hospice agency
    -Term usually used when patient hospitalized or at nursing home

Pharmacology in palliative care

-This presentation will focus on comfort-focused medical management of common symptoms of patients with advanced/end-stage disease
-Remember that depending on prognosis and goals of care:
  -Identifying and treating the cause of symptoms may or may not be indicated/possible
  -Non-pharmacological treatments and less aggressive medication regimens may or may not be indicated/possible
  -Examples: fan/repositioning for dyspnea, hydroxyzine/SSRI for anxiety

Challenges of complex medication regimens

-Polypharmacy/complex medication regimens often mean:
  -Multiple interactions and side effects
  -Medications to treat side effects of other medications
  -Difficult-to-follow dosing schedules leading to poor compliance
  -Multiple prescribers
  -OTC medications/supplements
  -Comprehensive medication reconciliation is key
Pharmacokinetics in advanced disease

**How the body affects the drug**

- **Absorption**
  - Often see decreased GI motility and gastric secretions
- **Metabolism**
  - May see reduced first-pass metabolism (leading to increased bioavailability of some drugs)
- **Distribution**
  - Affected by changes in body composition (muscle mass, body fat, total body water) and albumin levels
- **Clearance**
  - Reduced renal function impairs elimination of drugs (check creatinine clearance)
  - Hepatic impairment and/or reduced hepatic blood flow reduces drug clearance by the liver

Pharmacodynamics in advanced disease

**The body's response to the drug**

- May see exaggerated, paradoxical, and poor response to drugs due to:
  - Changes in drug-receptor interaction
  - Changes in number of receptor sites
  - Renal/hepatic impairment
  - Changes in adaptive homeostatic responses
  - Increased susceptibility to side effects due to exacerbation of existing impairment/pathology
  - Start low and go slow may or may not be indicated/possible

Common symptoms when nearing end-of-life

**Symptoms**

- Tumor invasion, pressure ulcers, infection, contracture, venous injury
- Dyspnea
  - Lung/pleural malignancy, infection, immobility/packaging, anemia, pulmonary edema
- Constipation
- Neurologic and vomiting
- Medications/treatments, immobility, low PO intake
- Neuropathy
  - Polyneuropathy, bowel obstructive, gastroparesis, increased IOP
- Anemia and cachexia
  - Medications/treatments, most malignancy, fatigue, altered taste or smell, constipation, infection

Common symptoms when nearing end-of-life cont.

**Symptoms**

- Fatigue
  - Electrolyte imbalance, organ failure, medication adverse effects, dyspnea/hypoxia
- Nausea and vomiting
  - Medications/treatments, GI malignancy, bowel obstruction, gastroparesis, increased IOP
- Emesis
  - Medications/treatments, most malignancy, fatigue, altered taste or smell
- Anorexia and cachexia
  - Medications/treatments, most malignancy, confusion, anorexia, fatigue, altered taste or smell
- Pain
  - Neuropathic and nociceptive pain
  - Neuropathic pain results from abnormal neural activity caused by disease, injury, or dysfunction of the nervous system
- Nociceptive pain
  - Visceral and somatic pain
  - Visceral results from injury to internal organs and is poorly localized
  - Somatic is from injury to tissues and is well localized
- Treatment varies by severity
  - Acetaminophen and NSAIDs for mild nociceptive pain
  - Opioids for moderate to severe nociceptive pain

Special considerations in the dying process

- Common symptoms in last days to weeks of life
  - Increased sleep/unresponsiveness, confusion, decreased PO intake, hypotension, respiratory changes, changes in temperature regulation, mottling of extremities, decreased urinary output
  - Simplify medication regimen and focus on immediate comfort
  - Prefer use few drugs that treat multiple symptoms
  - Use alternate routes of administration as lose ability to swallow
  - Common routes include sublingual/transmucosal, IV (if have access), subQ, rectal (consider dignity), transdermal and topical

Pain

- Neuropathic versus nociceptive pain
- Neuropathic pain results from abnormal neural activity caused by disease, injury, or dysfunction of the nervous system
- Nociceptive pain
  - Visceral versus somatic pain
  - Visceral results from injury to internal organs and is poorly localized
  - Somatic is from injury to tissues and is well localized
  - Treatment varies by severity
  - Acetaminophen and NSAIDs for mild nociceptive pain
  - Opioids for moderate to severe nociceptive pain
Neuropathic pain

- Choice of treatment depends on:
  - Etiology, comorbidities, medication interactions, organ function, and potential adverse effects
- Commonly used first-line medications include:
  - Gabapentin and pregabalin (anticonvulsants)
  - Duloxetine and venlafaxine (SNRIs)
  - Amitriptyline and nortriptyline (TCAs)
  - Lidocaine (topical anesthetic)
- Opioids are second-line

Mild nociceptive pain

- Acetaminophen
  - Centrally-acting with no anti-inflammatory action
  - Risk hepatotoxicity
    - Max 3000 mg/day or less with advanced disease
    - Max 2000 mg/day in liver impairment or heavy alcohol users
  - Notes
    - Risk hepatotoxicity, GIB, and adverse cardiovascular effects
    - Recommend short-term and in lowest effective dose
    - Can be very effective for arthritic pain
    - Buy with lowest cardiovascular risk (consider 250-500 mg, bid, PRN, take with food or add PPI if history GIB)

Opioids

- Opioid mechanism of action
  - Endogenous opioids & exogenous opioids act on opioid receptors (mu, delta, kappa) primarily in the central and peripheral nervous systems (also in GI tract and lung)
  - Morphine and related opioids are believed to preferentially bind and activate mu receptors in the CNS, causing:
    - Analgesia, respiratory depression, cough suppression, constipation, euphoria, and physical dependence
  - No analgesic ceiling for most opioids unlike for acetaminophen and NSAIDs
- Opioids for moderate to severe pain

  - Morphine 10 mg PO =
    - Methadone variable (strong)
    - Fentanyl 0.03-0.04 mg (parenteral) (strong)
    - Hydromorphone 2-2.5 mg (PO) (strong)
    - Oxycodone 5-6.5 mg (PO) (strong)
    - Hydrocodone 10 mg (PO) (strong)
    - Tramadol 100 mg PO (weak)
  - STRONG opioids are preferred in palliative care

The Principle of Double Effect

- It is ethically defensible to perform an action with the side effect of serious harm, even death, if the intention of the action is a beneficial effect.
- Example: aggressive use of opioids for pain despite expected respiratory depression that may hasten death
- Note that this does NOT apply to the use of medication in assisted death.

Equianalgesic dosing of opioids

- Strength of an opioid is its potency relative to morphine
  - Morphine 10 mg PO =
    - Methadone variable (strong)
    - Fentanyl 0.03-0.04 mg (parenteral) (strong)
    - Hydromorphone 2-2.5 mg (PO) (strong)
    - Oxycodone 5-6.5 mg (PO) (strong)
    - Hydrocodone 10 mg (PO) (strong)
    - Tramadol 100 mg PO (weak)
  - STRONG opioids are preferred in palliative care

Strong opioids

- Morphine
  - Natural opioid (opiate) made from opium poppy
  - Has been used for hundreds of years (isolated in early 1800s)
  - Opiate likely has been used for thousands of years
  - Inexpensive and many routes of administration
  - More histamine reactions than other opioids (nausea, itching, bronchospasm)
  - Treat with antihistamine or switch to another opioid
- Methadone
  - Generally considered equianalgesic to morphine
  - Semi-synthetic opioid mainly used in US with FDA approval in 1940s
  - Only available PO
    - All forms is combined with acetaminophen or NSAID, which limits dosing
    - ER forms without apparent benefit over morphine ER
**Strong opioids cont.**

**Oxycodone**
- Semi-synthetic opioid in use since 1910s
- Many formulations more expensive than morphine
- Often used for cancer pain
- Only available PO in the US (IR and ER tablets and oral concentrate)

**Hydromorphone**
- Semi-synthetic opioid created in 1920s
- Generally inexpensive
- Many routes of administration (ER tablet approved 2010)

**Fentanyl**
- Fully synthetic opioid made in 1960
- Quick on, quick off
- Available sublingual, transmucosal (buccal), intranasal, parenteral, and transdermal
- Transferable because of high potency and lipophilicity
- Nondiffusible through skin and deposited in adipose
- Very effective in patients due to inadequate adhesion
- Suitable patients may receive too much drug, hypoventilation patients too little
- Takes 12-24 hours to reach full effectiveness, change every 48-72 hours

**Methadone**
- Fully synthetic opioid developed in 1930s
- Inexpensive and effective
- Dosed daily for heroin/narcotic addiction and TID for pain
- Analgesic action shorter than half-life
- Generally used as long-acting (not short-acting)
- Does not block effect of other opioids
- Effective for nausea and vomiting multiple and antagonizes NMDAR
- Only long-acting analgesic available in liquid concentrate
- High lipophilic so better SL bioavailability than morphine
- Generally used as long-acting (not short-acting)
- Does not block effect of other opioids
- Effective for neuropathic pain (inhibits NE and serotonin reuptake and antagonizes NMDAR)
- Only long-acting analgesic available in liquid concentrate
- High lipophilic so better SL bioavailability than morphine
- Generally used as long-acting (not short-acting)
- Does not block effect of other opioids
- Effective for neuropathic pain (inhibits NE and serotonin reuptake and antagonizes NMDAR)

**Opioid initiation, conversion, and titration**
- Stanford School of Medicine Palliative Care: [https://palliative.stanford.edu/opioid-conversion/](https://palliative.stanford.edu/opioid-conversion/)
- Long-acting opioids indicated in treatment of severe, constant pain
- Only for opioid-tolerant patients
- Convert total daily PNC to morphine equivalents and convert to long-acting
- Generally start with morphine ER 80
- Titratin and conversion tend to be more aggressive in palliative care
- Note that risk of respiratory depression highest in opioid naïve patients

**Weak opioids**

**Codeine**
- Natural opioid (opiate) made from opium poppy (like morphine)
- Does not provide analgesic benefit in poor CYP2D6 metabolizers (up to 10% of patients) or if another medication inhibits CYP2D6
- Does NOT work better for cough than morphine
- Maximum daily dose is 360 mg IR: switch to strong opioid if need higher doses

**Tramadol**
- Unrelated to morphine (less than half analgesic effect is from mu agonism; remainder from inhibition of reuptake of norepinephrine and serotonin)
- Less respiratory depression, constipation, addiction potential BUT multiple drug interactions and adverse effects
- Especially: risk serotonin toxicity and reduces seizure threshold
- Maximum daily dose 400 mg

**Opioid special considerations**

- Renal impairment
  - Gentamicin and heparin are considered safe even in renal failure
- Hepatic impairment
  - Reduce doses, increase time between doses, generally avoid long-acting
  - Adverse effects (including itching, N/V, drowsiness, confusion) usually improve relatively quickly with tolerance
  - Note that constipation does not improve, so always start bowel regimen
- True allergy is rare and most common with morphine and codeine
  - Symptoms include urticaria or other rash, severe hypotension, bronchospasm, angioedema

---

**Pharmacology for APRN’s – Day 3**

©TCHP Education Consortium, September 2017
**Pharmacology for APRN’s – Day 3**

©TCHP Education Consortium, September 2017

---

**dyspnea**

- **Mechanisms of dyspnea**
  - Physical: respiratory stimuli, including blood gas abnormalities, hypercapnia, or hyperoxia, activate sensory receptors which transmit information to the brain where dyspnea is perceived.
  - Psychological: anxiety/panic and depression may worsen the experience.
- Treat underlying cause, if possible.
  - Antibiotics for PNA, diuretics for fluid overload, steroids for COPD, albuterol and ipratropium bromide inhalers/nebulizers for bronchoconstriction, thoracentesis for pleural effusion.
  - Supplemental oxygen, fan, repositioning may also be effective.
  - If not responsive to other treatment, try opioids.

**Opioids for dyspnea**

- **Opioid effect on dyspnea**
  - Decrease respiratory drive, alter central perception of dyspnea, alter activity of related receptors in the brain and hypothalamus.
  - In opioid-naïve patient, low doses of opioids generally effective for dyspnea.
  - Higher/additional doses necessary in opioid-tolerant patients.
  - Note that morphine does NOT necessarily work better for dyspnea than other opioids.
  - Any route is effective, and some anecdotal evidence supports nebulized opioids.
  - Benzodiazepines may be considered if anxiety believed to be contributing to dyspnea.

**Constipation**

- Start with peristaltic stimulant.
  - Cramping may limit use.
  - Commonly use senna (1-4 8.6mg tablets BID PRN).
  - No additional benefit shown with adding docusate (surfactant).
  - Bisacodyl 5-10mg daily also an option.
  - If not effective, ADD osmotic laxative.
    - Commonly use polyethylene glycol (17-34g daily PRN).
    - Less well-tolerated: lactulose, sorbitol, magnesium citrate, magnesium hydroxide.

**Constipation cont.**

- For persistent constipation, add:
  - Suppository (bisacodyl, glycerin).
  - Enema (mineral oil).
  - Avoid sodium phosphate (Fleets).
  - If constipation persists and is believed to be primarily opioid-induced, consider methylnaltrexone (subQ).
  - Always order bowel regimen if patient regularly taking opioids.
  - Generally avoid bulk-forming laxatives (psyllium) as may inadvertently cause obstruction (due to slow GI motility and low PO fluid intake).

**Nausea & vomiting**

- Vomiting center (in medulla oblongata) is activated by stimuli from:
  - Chemoreceptor Trigger Zone (drugs, metabolic changes).
  - GI tract and pharynx (obstruction, stasis, inflammation).
  - Vestibular apparatus (motion, lesions).
  - Higher cortical centers (increased ICP, anxiety, memory, sensory input).
- Receptors involved in above process include:
  - Dopamine, serotonin, histamine, neurokinin-1, muscarinic, cannabinoid.
- Treat contributing factors, for example:
  - Dyspepsia, constipation, gastroparesis, increased ICP.

**Commonly used anti-emetics**

- **Ondansetron**
  - Selective serotonin (5-HT3) receptor antagonist peripherally and in the CRZ.
  - Well-tolerated, very effective, but can be expensive and cause constipation.

- **Metoclopramide**
  - N/V: blocks dopamine receptors (and serotonin receptors in CRZ at higher doses).
  - Prokinetic: increases response to acetylcholine in upper GI tract.
  - Risk QT prolongation, elderly/frail have higher risk tardive dyskinesia.
  - Recommend do not use >12 weeks.
Commonly used anti-emetics cont.
- Prochlorperazine
  - First-generation (typical) antipsychotic
  - Blocks dopamine receptors in CTZ
  - Risk EPS (dystonia) and tardive dyskinesia
- Haloperidol
  - First generation (typical) antipsychotic
  - Blocks dopamine receptors in the CTZ
  - Risk EPS (dystonia) and QT prolongation
  - Commonly used in hospice

Commonly used anti-emetics CONT.
- Dexamethasone
  - Long-acting corticosteroid
  - Decreases inflammation and suppresses normal immune response
  - Mechanism of antiemetic activity is unknown
  - Side effects of increased appetite, increased energy, mood changes, insomnia

Other anti-emetics
- Synthetic cannabinoids (THC)
  - Dronabinol has modest antiemetic activity and is FDA-approved for chemotherapy-induced N/V
  - Limited by vertigo, xerostomia, hypotension, sedation, euphoria/dysphoria
- Benzodiazepines
  - Weak anti-emetics
  - Lorazepam may be given for anxiety associated with N/V
- Antihistamines
  - Meclizine for motion sickness
- Anticholinergics
  - Scopolamine for motion sickness

Anorexia & cachexia
- Anorexia
  - Loss of appetite
  - Differential diagnoses/potentially contributing factors include: constipation, mood disorders, dehydration, gastroparesis, nausea, depression, pain, fatigue, medications, low testosterone, thyroid abnormalities
- Cachexia
  - Complex metabolic syndrome
  - Associated with underlying illness and systemic inflammation
  - Cancer, AIDS, HF, ESRD, RA, COPD, chronic infection
  - Characterized by loss of muscle with or without loss of fat mass
  - Cannot be entirely attributed to poor caloric intake or reversed by supplementation or calories

Anorexia/cachexia syndrome
- Pharmacological treatment
  - May stimulate appetite but generally will not reverse cachexia
  - Weight gain usually modest and temporary
  - Generally not shown to improve lean body mass, survival, or QOL
  - First-line generally megestrol acetate (progesterone analog)
    - Synthetic progestin with unclear mechanism of appetite stimulation
    - Significant risk DVT and weight gained is primarily adipose
    - 160 mg to 800 mg daily
    - If no improvement in several weeks, discontinue

Other Medications for anorexia/cachexia syndrome
- Dexamethasone (corticosteroid) 4 mg daily
- Dronabinol (synthetic THC)
  - FDA approved as appetite stimulant in AIDS patients
  - No proven benefit in cancer patients
- Mirtazapine (atypical/tetracyclic antidepressant) may be helpful if patient also with insomnia and/or depression
- Olanzapine (atypical/second-generation antipsychotic) may also help with sleep and agitation
Delirium

- Hyperactive (agitated, hypertensive) vs. hypoactive (lethargic, somnolent, unresponsive)
- Characterized by altered orientation, incoherent thinking/speech, delusions, hallucinations, emotional lability, memory impairment

**Haloperidol**
- Drug of choice for delirium in palliative care
- Generally low doses required: 0.5-1mg PO/SL/subQ/IV q1-4hr (max 5mg/day)
- Less sedating and less hypotension than other antipsychotics
- Inexpensive and can be administered by multiple routes
- Common side effects are somnolence and urinary retention
- Does have risk EPS, although rare (avoid in Parkinson’s)
- Short-term administration is optimal

**Atypical antipsychotics**
- Less risk for EPS and other side effects than haloperidol
- Chlorpromazine may also stimulate appetite, dosed daily, oral and IM
- Quetiapine can be used in Parkinson’s

**Benzodiazepines**
- lorazepam 0.5-2mg PO/SL q6-8hr PRN
- Consider adding if haloperidol alone not effective
- Use for delirium from alcohol withdrawal
- If delirium severe and refractory at end-of-life (terminal agitation/delirium), consider palliative sedation

Other medications for delirium

**Anxiety**

- Anxiety often described as feeling of helplessness or fear, often associated with sense of loss of control
- True anxiety disorders are relatively rare
- Differential diagnoses: depression, delirium, dementia, dyspnea, pain
- Common anxiety-related diagnoses in palliative care: adjustment disorder with anxious features, generalized anxiety disorder, panic disorder, PTSD
- Before/with pharmacotherapy: try psychotherapy, complementary therapies, exercise, caffeine and alcohol reduction, treat sleep issues/pain/dyspnea

**Benzodiazepines**

- Lorazepam is most commonly used in palliative care
- Intermediate-acting (half life 12 hours)
- 0.25 to 2mg PO/SL q6-8hr PRN
- Avoid short-acting (alprazolam, oxazepam) due to rebound anxiety and withdrawal
- Avoid long-acting (clonazepam, diazepam) as may accumulate and cause toxicity
- Significant side effects, including: memory loss, delirium, increased fall risk, impaired respiratory function in COPD
- Paradoxical effect more likely in elderly and dementia
- Interact with other sedating medications (opioids)
- Tolerance and withdrawal

**Antidepressants & other medications for anxiety**

- Consider antidepressants for chronic anxiety or mixed anxiety/depression
- Only for patients with prognosis of months to years (not weeks to months)
- Consider start benzodiazepine while wait for antidepressant to take effect
- Avoid fluoxetine (SSRI) and bupropion (aminoketone antidepressant)
- Trazodone (SARI) 25 mg PO can be used q1hr PRN breakthrough anxiety
- Buspirone (azapirone): “If you’ve had the benz, you can’t take the bus.”
- See further discussion of antidepressants in Depression section

**Depression**

- Most common mental health problem in palliative care
- Expected sadness/grief versus persistently feeling hopeless, worthless, excessively guilty
- Best screening method is often to ask if you’re depressed!
- Before/with pharmacotherapy: treat pain, try to change meds that may contribute, psychotherapy if possible, dignity therapy, Chaplin intervention, reduce isolation
- Choice of pharmacotherapy depends on prognosis and severity of symptoms
- Weeks to months of life and severe symptoms: consider antidepressants
- Months to years of life: consider antipsychotic (usually SSRI)
Antidepressants

- Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Generally effective in depression and anxiety, good side-effect profile and low risk overdose, but need time to see benefit
  - Paroxetine is sedating, good for anxious depression and insomnia, may see severe discontinuation symptoms
  - Sertraline: generally well-tolerated except for GI side effects
  - Citalopram and escitalopram: generally well-tolerated, relatively few drug interactions, potential serotonin reuptake interaction with citalopram
  - Fluoxetine is activating (so may exacerbate anxiety), less well-tolerated, long half-life means no withdrawal but takes longer to titrate to effect

- Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
  - Duloxetine and venlafaxine effective for depression, anxiety, and neuropathic pain
  - Consider duloxetine if neuropathy-depression and venlafaxine if depression-amenorrhoea
  - Less well-tolerated than SSRIs (nausea, dizziness, excessive sweating)

- Tricyclic Antidepressants (TCAs)
  - Amitriptyline, doxepin, nortriptyline effective for depression, anxiety, pain
  - Broad spectrum: interact with many neurotransmitter systems
  - Amitriptyline and doxepin strongly antihistaminic (for insomnia, anorexia)
  - Significant adverse effects: anticholinergic (less nortriptyline), drug interactions, potentially cardiotoxic, overdose may be fatal

- Atypical Antidepressants
  - Mirtazapine (tetracyclic)
    - Potentially beneficial side effects of sedation and appetite stimulation
  - Bupropion (aminoketone)
    - Can cause significant anxiety and insomnia
  - Serotonin Agonist and Reuptake Inhibitors (SARIs)
    - Trazodone effective for depression at higher doses (antihistaminic)
    - Anxiolytic and hypnotic at lower doses

Psychostimulants for depression

- Methylphenidate (also consider dextroamphetamine and modafinil)
  - Poor prognosis or if require rapid relief of symptoms (onset 24-48 hours)
  - Effective for apathy, cognitive impairment, low energy, hypersomnia (including opioid-related), and may reduce anorexia (by reducing apathy)
  - Adverse effects: insomnia, agitation, palpitations, hypertension, tremor, dry mouth, anorexia
  - Risk cardiac decompensation in patients with heart disease
  - Start 2.5 mg PO morning and noon
  - Titrate to effect, maximum recommend 10 mg morning and noon

Fatigue

- Most common physical symptom in palliative care
- Usually multifactorial: anemia, hypoxia, infection, dehydration, medication side effects, dehydration/malnutrition, deconditioning, depression
- Pharmacological treatment
  - Dexamethasone (corticosteroid) 4-8 mg every morning
  - Methylphenidate (psychostimulant) follow dosing for depression
  - Consider activating antidepressants in fatigue with depression
  - Fluoxetine (SSRI)
  - Bupropion (atypical antidepressant)

Insomnia

- Benzodiazepines
  - May be effective but with significant risk (see Anxiety)
  - Commonly use lorazepam and temazepam (intermediate-acting)
  - Rapid tolerance and return of insomnia
- Zolpidem (benzodiazepine receptor agonist)
  - May be safer for COPD patients than benzodiazepines
  - Increased risk falls
Insomnia cont.

- **Antidepressants**
  - **Doxepin** (TCA): 3 mg to 6 mg
    - Only antidepressant approved by FDA for insomnia
  - **Amitriptyline** (TCA) also commonly used for insomnia
  - **Trazodone** (SARI): 25-50 mg
    - Recommended for patients who also have depression
    - Can be used in addition to other antidepressants, generally well-tolerated, even with dementia
  - **Mirtazapine** (atypical antidepressant): 7.5 to 15 mg
    - Helps with anxiety/depression as well as sleep and appetite

- **Ramelteon** (selective melatonin receptor agonist)
  - Non-habit forming and does not appear to have the side effects associated with other hypnotics
  - Significant drug interactions
  - **Melatonin** (neurohormone secreted by the pineal gland)
    - Widely available OTC
    - Can assist with maintaining sleep-wake cycle, but not effective for most patients with insomnia
    - Little data to support use, but well-tolerated without significant adverse effects
  - **Diphenhydramine** (antihistamine)
    - In many OTC sleep aids
    - NOT recommended due to anticholinergic effects and little evidence it improves insomnia

references

American Academy of Hospice and Palliative Medicine UNIPAC series
Lexicomp Online
Medscape Online
Up To Date Online