DETERMINING MEDICATION RISK VS. BENEFIT

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OBJECTIVES

- Examine medication appropriateness
- Review rational prescribing
- Analyze common nonessential medications in the hospice setting
- Evaluate medication risk and benefit at end of life
- Discuss interdisciplinary team (IDT) determinations
- Complete several case examples

MEDICATION APPROPRIATENESS

- Few guidelines exist for determining how and when to discontinue medications
- Medication appropriateness provides a means to evaluate medication need
- But what is medication appropriateness?

Medication appropriateness refers to whether a medication is useful in an individual clinical situation based on both the attributes of the medication and those of its recipient.
MEDICATION APPROPRIATENESS

- Important factors for determining medication appropriateness:
  - Remaining life expectancy of patient
  - Time until therapeutic benefit of medication
  - Goals of care
  - Treatment target

MEDICATION APPROPRIATENESS INDEX

1. Is there an indication for the drug?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug-drug interactions?
7. Are there clinically significant drug-disease/condition interactions?
8. Is there unnecessary duplication with other drugs?
9. Is the duration of therapy acceptable?
10. Is this drug the least expensive alternative compared with others of equal utility?

PRESCRIBING MODEL
INDICATIONS FOR DISCONTINUATION

- Diminished benefit
  - Clinical improvement
  - Stabilization
- Increased risk
  - Medication-related adverse effects
  - Drug interactions
  - Unsafe use
    - High-risk drugs in older adults

STEPS FOR DISCONTINUING

- Recognizing an indication for discontinuing a medication
- Identifying and prioritizing the medication to be targeted for discontinuation
- Documentation and approval of discontinuation recommendation
- Discontinuing the medication along with proper coordination with the patient, caregivers and other healthcare providers
- Monitoring the patient for beneficial or harmful effects
ADVERSE DRUG WITHDRAWAL EVENTS
- Significant set of signs or symptoms caused by the removal of a drug
- Often abbreviated ADWE to distinguish from adverse drug events (ADE)
- Common medications
  - β-blockers
  - Centrally acting sympatholytics
  - Sedative hypnotics
  - Opiates
  - Tricyclic antidepressants
  - Antipsychotics
  - Stimulants
  - Corticosteroids

ADVERSE DRUG WITHDRAWAL EVENTS
- True physiological withdrawal reactions
  - Reappearance or increase in the condition for which the drug was prescribed
  - Ex. hypertension after stopping clonidine
  - New set of symptoms
  - Ex. weakness and nausea after stopping corticosteroids for COPD
  - Exacerbation of the underlying disease
  - Ex. worsening angina after discontinuation of nitrates

TYPES OF DISCONTINUATION
- **Abrupt**
  - Most agents may be discontinued without ADE or ADWE
  - Low likelihood of dependence or withdrawal
  - Ex. Antihistamines, corticosteroids (< 2 weeks)
- **Taper**
  - High likelihood of dependence or withdrawal
  - Ex. Cardiovascular agents, benzodiazepines, corticosteroids (> 2 weeks)
- **Stop and Monitor**
  - Other agents can be stopped with monitoring
  - Ex. Gastro, respiratory tract, musculoskeletal agents
ADVERSE DRUG WITHDRAWAL EVENTS

- Patient
  - Frequency and severity of disease state exacerbations
  - Comorbidities
  - Drug interactions
- Type of medication
  - Most problematic are cardiovascular and CNS agents
  - Carefully monitor patients after medication discontinuation

COMMON NONESSENTIAL MEDICATIONS

- HMG-CoA reductase inhibitor
- Inhibits HMG-CoA reductase (rate limiting step in cholesterol synthesis)
- Increase in LDL receptors and LDL catabolism
- Lescol® (fluvastatin)
- Pravachol® (pravastatin)
- Mevacor® (lovastatin)
- Zocor® (simvastatin)
- Lipitor® (atorvastatin)
- Livalo® (pitavastatin)
- Crestor® (rosuvastatin)

STATINS
MECHANISM OF ACTION

- HMG-CoA reductase inhibited (rate-limiting step in cholesterol synthesis)
- Reduction in the production of mevalonic acid (early precursor of cholesterol)
- Upregulation of LDL receptor expression on hepatocytes
- Catabolism
  - Accelerated LDL uptake
  - Decreased TC, LDL, VLDL, TG levels

Indications
- Primary prevention
- Secondary prevention
- Primary hyperlipidemia
- Mixed hyperlipidemia
- Other lipidemias as appropriate

Adverse Effects
- GI upset (N/V, pain)
- Muscle injury (myalgias, myopathy and rhabdomyolysis)
- Hepatic and renal dysfunction
- Incident risk of impaired glucose metabolism and diabetes
- Drug interactions
- Cognitive impairment

STATINS

CLINICAL EVIDENCE

- A recent 2014 multisite study randomized 381 patients with life-limiting illness to discontinue or continue their statins (1:1).
  - Rate of death within 60 days was not statistically significant between the continue and discontinue groups.
  - The discontinue group had longer median time to death.
  - Total QOL was better among the discontinue group.
- The investigators concluded that it is unlikely that harm will accrue when statins being used for primary prevention are discontinued in the setting of end of life.
**CLOPIDOGREL**

- Antiplatelet agent (P2Y<sub>12</sub> antagonist)
- Inhibits ADP-mediated platelet aggregation
- Platelets blocked by clopidogrel are affected for the remainder of their lifespan (~7 to 10 days)
- Plavix® (clopidogrel)
- Similar drugs in this class include:
  - Brilinta® (ticagrelor)
  - Effient® (prasugrel)
- Aspirin (antiplatelet with differing MOA)

**Indications**
- Recent MI, stroke or established peripheral arterial disease (PAD)
- Acute coronary syndrome (ACS)
- PCI (stent placement) for ACS and non-ACS indications

**Adverse Effects**
- Increases risk of bleeding
  - Epistaxis
  - Hemorrhage
  - Purpura
  - Skin rash, pruritus
- Drug interactions

**MECHANISM OF ACTION**

- Irreversible inhibition of the P2Y<sub>12</sub> receptors on platelets
- Inhibition of activation of the platelet glycoprotein complex
- Inhibition of platelet aggregation for the life of the platelet (typically 7 to 10 days)
The CAPRIE trial found clopidogrel to only be modestly more effective than aspirin in reducing CV events in patients with atherosclerosis, but treatment periods ranged from 1 to 3 years, exceeding life expectancy for most hospice patients.

- Clopidogrel seems beneficial when added to ASA before and after PCI and acute coronary events.
- There is no evidence to suggest that any patient should use clopidogrel for more than one year after an MI or PCI.

**FUROSEMIDE**

- Loop Diuretic
- Inhibits reabsorption of sodium and chloride
- Increases excretion of water, sodium, and other electrolytes

**Lasix® (furosemide)**

- Similar drugs in this class include:
  - Bumex® (bumetanide)
  - Demadex® (torsemide)

**FUROSEMIDE**

**Indications**

- Edema, heart failure
- Acute pulmonary edema
- Hypertension

**Adverse Effects**

- Dizziness, lightheadedness, blurred vision, hyperglycemia
- Dehydration
- Muscle cramps, tiredness, fainting
- Polyuria, nocturia
- Hypotension

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MECHANISM OF ACTION

Inhibition of sodium and chloride reabsorption in the ascending loop of Henle and distal renal tubule
Increased excretion of water, sodium, chloride, magnesium and calcium
Decreased fluid equates to decreased blood volume and blood pressure

CLINICAL EVIDENCE

- At least one study has suggested that only certain subpopulations of congestive heart failure patients actually benefit from diuretics.
- JNC-8 guidelines do not recommend loop diuretics (i.e. furosemide) for the initial treatment of hypertension.
- A study of ADEs that required an ER visit found that 86.1% of ADEs were associated with a single drug. Diuretics and anti-diabetic agents comprised 29% of these hospital visits related to electrolyte imbalances and AMS in the elderly.

BISPHOSPHONATES

- Bisphosphonates
- Inhibit bone resorption, leading to an indirect increase in bone mineral density
- Fosamax® (alendronate)
- Actonel® (risedronate)
- Boniva® (ibandronate)
MECHANISM OF ACTION

- Binds to hydroxyapatite sites in bone
- Inhibits osteoclast mediated bone resorption
- Reduced bone turnover, increased bone mass, indirect increase in bone mineral density

BISPHOSPHONATES

**Indications**
- Osteoporosis in postmenopausal females
- Osteoporosis in males
- Osteoporosis secondary to glucocorticoid use
- Paget’s disease

**Adverse Effects**
- GI effects (reflux, esophagitis, ulcers)
- Flu-like symptoms
- Hypocalcemia
- Musculoskeletal pain
- Osteonecrosis of the jaw
- Atypical femur fractures

CLINICAL EVIDENCE

- Bisphosphonates have not been shown to appreciably reduce fractures among postmenopausal women who have not had a previous fracture, as well as those with relatively normal bone density.
- Long-term studies of bisphosphonates suggest that their benefit does not extend beyond three years of initial treatment.
- Bisphosphonate elimination half-life exceeds 10 years.
Donepezil

**Acetylcholinesterase inhibitor**
- Inhibits centrally-active acetylcholinesterase
- Increasing acetylcholine available for synaptic transmission in the CNS

**Aricept® (donepezil)**

**Mechanism of Action**

**Inhibition**
- Reversibly and noncompetitively inhibits acetylcholinesterase (enzyme responsible for the breakdown of acetylcholine)

**Increase**
- Increased concentrations of acetylcholine available for synaptic transmission in the CNS

**Improvement**
- Modest improvements in cognitive deficits

**Indications**
- Alzheimer's disease
  - Mild to moderate
  - Moderate to severe

**Adverse Effects**
- N/V/D
- More common in low weight patients (<55kg)
- Insomnia
- Headache, pain
- Anorexia and weight loss
- Hypertension
- Syncope
Courtney et al., investigated whether donepezil actually produced clinical benefit in 565 Alzheimer’s patients.

- MMSE cognition scores improved by 0.8 points
- Functionality BADLS scores improved by 1.0 point
- No significant benefits were seen between donepezil and placebo in behavioral or psychological symptoms, psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths.

**SULFONYLUREAS**

- Stimulates insulin release from the pancreatic beta cells, reduces glucose output from the liver, increases insulin sensitivity at peripheral sites
- Glucotrol® (glipizide)
- Diabeta® (glyburide)
- Micronase® (glyburide)
- Glynase® (glyburide)
- Amaryl® (glimepiride)

**MECHANISM OF ACTION**

- Stimulation of insulin from the pancreatic beta cells
- Decreased glucagon production in the liver
- Release of insulin moves glucose from the blood into cells
- Reduction in blood glucose levels
**SULFONYLUREAS**

**Indications**
- Diabetes (Type 2)

**Adverse Effects**
- Hypoglycemia
- Nausea
- Skin reactions
- Abnormal LFTs

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**CLINICAL EVIDENCE**

- Gerstein et al., studied 10,251 diabetic patients to determine whether intensive glucose control would reduce CV events in these patients (who had CVD or additional CV risk factors).
  - Intensive therapy actually increased mortality and did not significantly reduce major CV events.
  - Hypoglycemia is a significant risk factor for dizziness, weakness and altered mental status which can lead to devastating falls.
  - Long-acting sulfonylureas (ex. glyburide) meet the Beers Criteria and are not recommended in the elderly.

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**VITAMINS AND SUPPLEMENTS**

**Vitamin supplementation**

**Examples**
- Multivitamins
- Calcium
- Vitamins A, D, E, K (fat soluble)
- Vitamins B, C (water soluble)
- Saw palmetto
- Ginger
- Glucosamine
**VITAMINS AND SUPPLEMENTS**

**Indications**
- Indicated as a supplement to diet in:
  - Alcoholism
  - Malabsorption or gastric bypass
  - Prenatal women
  - Hemodialysis or parenteral nutrition patients

**Adverse Effects**
- GI upset (N/V/D)
- Fat soluble vitamins (A, D, E, and K) can accumulate and cause toxicity
- Vitamin A (osteopenia and birth defects)
- Iron (constipation)
- Vitamin D (hypercalcemia)
- Beta-carotene (increased risk of lung cancer in high risk adults)
- Vitamin C (nephrolithiasis)

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**CLINICAL EVIDENCE**

- Randomized trials that have examined the role of antioxidant supplements in reducing CV disease have not found positive effects.
- MVI supplementation is not recommended for primary prevention of chronic diseases due to lack of efficacy.
- Vitamin E and beta-carotene have been associated with adverse outcomes in lung cancer and all-cause mortality.
- It is suggested that supplementing the diet of well nourished adults has no clear benefit in the prevention, nor the treatment of chronic disease.

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**ANTIHYPERTENSIVES**

- Evaluate patient specific antihypertensive goals, as well as diuretic use when they elect hospice
- Contrast patients with symptoms (ex. angina) versus patients with no symptoms (ex. primary prevention)
- Don’t treat “numbers”
  - Overtreatment can lead to orthostatic hypotension
    - Increases fall risk
    - Decreases quality of life
- Recognize agents that commonly cause orthostasis
MECHANISM OF ACTION

ANTIHYPERTENSIVES

Selected Indications
- Treatment of hypertension
- Management of angina and heart failure
- Acute MI treatment
- Diabetic nephropathy
- Secondary prevention in post-MI

Adverse Effects
- Hypotension
- Dizziness
- Fatigue
- Cough
- Hypersensitivity reactions
  - Angioedema

CLINICAL EVIDENCE

- JNC-8 recommends a blood pressure goal of <150/90mmHg in patients 60 years of age or older without diabetes or chronic kidney disease.
- The ACCORD trial of 4,733 diabetic patients at high risk for CV events found that intensive blood pressure control (i.e. targeting SBP<120mmHg versus SBP<140mmHg) did not reduce rate of fatal and nonfatal major CV events.
- In the JATOS trial of 4,418 elderly (65-85 years) hypertensive patients, no differences were found between the strict-treatment group (SBP<140 mm Hg) and the mild-treatment group (SBP<140 mm Hg and <160 mm Hg) in the incidence of CVD and renal failure for two years of treatment.
Medications that affect the central nervous system are commonly used in hospice patients. However, most meet Beers Criteria as potentially inappropriate in the elderly. Adverse effects range from mild sedation to cardiac arrhythmias and death.

**So how do we evaluate the use of CNS agents in the hospice population?**

Central Nervous System Agents

- CNS agents have a place in hospice care when used appropriately.
- Always consider all sources for changes in cognition, mood and behavior before initiating CNS agents.
- Screen for underlying etiology:
  - Triggers
  - Environmental changes
  - Iatrogenic
- Redirect the patient if no source found.

**Triggers**
- Infection
- Constipation
- Urinary retention
- Pain (untreated or uncontrolled)
- Hunger

**Environment**
- Strong lights
- Noise
- Unfamiliar (i.e. moving from home to long term care)

**Iatrogenic**
- Use of precipitating medications
- Anticholinergics
- Benzodiazepines
MECHANISM OF ACTION

Antidepressants
- SSRI, SNRI, Atypical, Tricyclics
- Serotonin Modulators

Antipsychotics
- Typical, Atypical

Antianxiety Agents
- Benzodiazepines
- Miscellaneous

Mood Stabilizers
- Anticonvulsants
- Antimanics

CENTRAL NERVOUS SYSTEM AGENTS

Indications
- Depression
- Anxiety
- Insomnia
- Seizure control
- Behavioral issues
- Psychoses

Adverse Effects
- Sedation
- Cognitive impairment
- Dizziness
- Hypotension
- QT prolongation
- Anticholinergic effects
- Extrapyramidal symptoms (EPS)

CENTRAL NERVOUS SYSTEM AGENT RECOMMENDATIONS

- For appropriate use of CNS agents, consider the following:
  1. Start with PRN dosing.
  2. Choose agents with lowest adverse effects.
  3. When titrating, use lowest dose and largest dosing interval.
  4. Monitor for clinical improvement, adverse effects and need for additional or alternate therapy.
  5. Use frequent medication reviews (or stop dates) to reduce risk of unnecessary use.
Information about discontinuing nonessential medications should be used as recommendations only.

Each patient and their medications must be evaluated individually by the IDT team, medical director, attending physician, and care managers.

Medications should not be discontinued without IDT approval.

Continued medications should be deemed included or excluded from the hospice benefit by the IDT team.
**PATIENT CASE**

AG is a 68 year old male with end stage COPD on hospice service. His medications include oxygen 2L per nasal cannula, Duoneb®, simvastatin, vitamin C, Advair® 500/50, and temazepam.

Which medications might be considered for discontinuation in this patient?
A. Simvastatin  
B. Temazepam  
C. Vitamin C  
D. Advair  
E. A and C

**PATIENT CASE**

BE is a 92 year old female with end stage dementia (FAST 7c) on hospice service. Her medications include donepezil, morphine concentrate, lorazepam, APAP, calcium carbonate, MVI and Senna-S.

Which medications might be considered for discontinuation in this patient?
A. APAP  
B. Calcium carbonate  
C. Donepezil  
D. MVI  
E. B, C, and D

**PATIENT CASE**

ES is a 72 year old male admitted to hospice service for metastatic pancreatic cancer. His medications include furosemide, Oxycontin®, MVI, atorvastatin, and Senna-S.

Which medications might be considered for discontinuation in this patient?
A. Furosemide  
B. MVI  
C. Atorvastatin  
D. Senna-S  
E. B and C
QUESTIONS?

Call your AvaCare pharmacist with questions or concerns about discontinuing nonessential medications.

Phone: 866-794-1044
Fax: 866-794-5661

REFERENCES


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