Potpourri of Potions Pertaining to Pertinent Pharmacology

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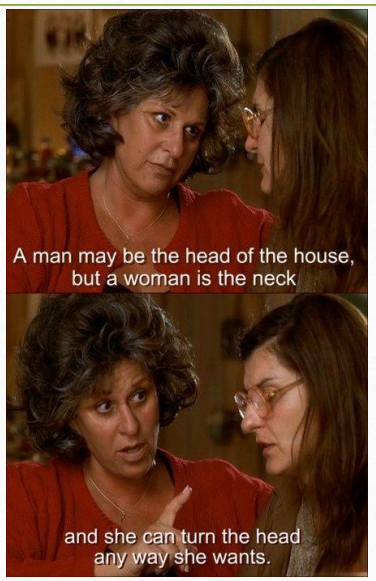
A Big Fat Greek Wedding



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The Good, The Bad, the Ugly

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My Different View

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Overview

- Pain Management Issues
- Methadone
- Drug Dosing in Kidney Dysfunction
- Delirium Not Just In The ICU
- Iatrogenesis

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Opium

The NEW ENGLAND JOURNAL of MEDICINE

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Hematology Oncology Clinics 2018

Methadone

Maximizing Safety and Efficacy for Pain Control in Patients with Cancer

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Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper

- **McPhearson ML, et al. Journal of Pain and Symptom Management 2019:57;635-45**
- **Consensus guidelines for the use of Methadone**
- **Appropriate candidates for methadone**
- **Dosing,**
- **Titration**
- **Monitoring of patients' response to methadone therapy.**

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Table 1
Patient Selection for Methadone Therapy

Potentially Appropriate Candidates for Methadone in HPC	Potentially Inappropriate Candidates for Methadone in HPC
• Moderate to severe pain (especially as a second-line opioid choice)	• Patient lives alone, or poor cognitive functioning, without a responsible caregiver
• Pain refractory to other opioids	• Lack of knowledgeable practitioner on transfer
• True phenanthrene (e.g., morphine) allergy	• History of opioid/medication nonadherence
• Significant renal impairment	• History of substance misuse or SUD (patient or family)
• Need for a long-acting opioid (particularly as an oral concentrate solution)	• Multiple risk factors for methadone toxicity (e.g., clinical instability, multiple transitions in care, history of transplant)
• High opioid tolerance	• History of QTc prolongation or at high risk for such
• Poorly controlled opioid-induced adverse effects with other opioids	• Prognosis less than projected time to methadone steady state (i.e., five to seven days)
• History of dysphagia, inability to swallow, or feeding tube placement	• Obstructive or central sleep apnea
	• Determined to be medically inappropriate after risk assessment (see next section)

HPC = hospice and palliative care.

J Pain and Symptom Management 2019;57:635-45

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Table 2
Precautions and Contraindications to Methadone Therapy

Risk Factor	Precaution	Contraindication	Applies to all Opioid Including Methadone	Applies Specifically to Methadone
Impaired liver function or liver failure	x		x	
Acute or unstable liver injury/damage	x (avoid use)		x (precaution)	x (contraindicated)
Active illicit drug use or misuse (cocaine, amphetamines, ephedrine, heroin, opioids)		x	x (overall risk)	x (additional risk of QTc prolongation)
Congenital QTc syndrome (patient or family)		x	(buprenorphine and methadone only)	x
Structural heart disease (congenital heart defects, history of endocarditis, or heart failure)[a]	x			x
Electrolyte abnormalities, or at risk for same (e.g., hypokalemia, hypomagnesemia)	x			x
Disordered breathing syndromes	x		x	
Paralytic ileus		x	x	

[a]See ECG monitoring section.

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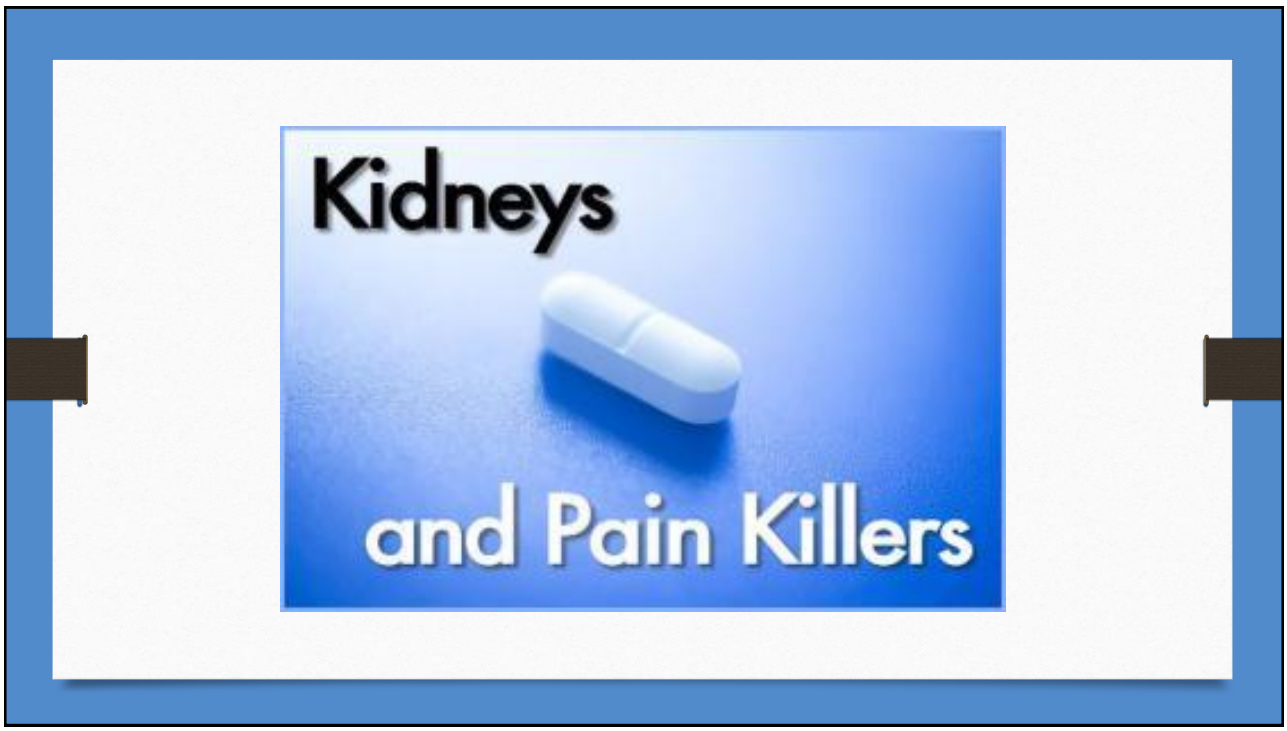

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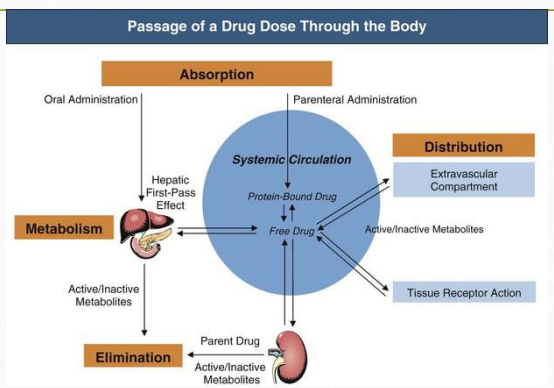
Pharmacokinetics (from Ancient Greek pharmakon "drug" and kinetikos "moving, putting in motion";



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Opioid Management in CKD

Emily Lu, Jane O. Schell, and Holly M. Koncicki

Patients with chronic kidney disease (CKD) experience a high pain and symptom burden. Concurrently, opioid prescription and use in patients with CKD continues to increase, leading to concern for opioid-related risks. Nephrologists increasingly face challenging clinical situations requiring further evaluation and treatment of pain, for which opioid use may be indicated. However, nephrologists are not commonly trained in pain management and may find it difficult to compile the necessary information and tools to effectively assess and treat potentially multidimensional pain. In these situations, they may benefit from using an evidence-based stepwise approach proposed in this article. We address current approaches to opioid use for pain management in CKD and offer a stepwise approach to individualized opioid assessment, focusing on kidney-specific concerns. This includes thorough evaluation of the pain experience, opioid use history, and treatment goals. We subsequently discuss considerations when initiating opioid therapy, strategies to reduce opioid-related risks, and recommended best practices for opioid stewardship in CKD. Using this sequential approach to opioid management, nephrologists can thereby gain a broad overview of key patient considerations, the foundation for understanding implications of opioid use, and a patient-tailored plan for opioid therapy.

Complete author and article information provided before references.

Am J Kidney Dis. 77(5):786-795. Published online October 22, 2020.

doi: 10.1053/j.ajkd.2020.08.018

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Box 1. Stepwise Approach to Individualized Opioid Use Assessment for Pain Management in CKD When Considering Opioid Initiation

1. Establish general knowledge of pain and pain syndromes in CKD to allow for the formulation of a broad differential diagnosis.
2. Assess and identify the patient's pain experience.
3. Clarify the impact of pain on the patient's functional status.
4. Clarify the patient's prognosis and anticipated illness trajectory.
5. Evaluate previously attempted approaches to pain management.
6. Discuss and screen for risks versus benefits of opioid use for the individual patient.
7. Discuss precautions and strategies to reduce opioid-related risks.
8. Establish the goal(s) of opioid therapy.
9. Counsel and educate regarding anticipated pain management treatment goals and expectations.
10. Make a shared decision regarding initiation of opioid therapy.

Abbreviation: CKD, chronic kidney disease. Based on information from Dowell et al[18] and Portenoy.[30]

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Table 2. Suggested Starting Doses of Preferred Opioids for Use in Advanced CKD

Opioid	Normal Kidney Function (eGFR > 100)	CKD Stage 4 (eGFR 15-30)	CKD Stage 5 (eGFR <15)
Hydromorphone (short-acting)	2- to 4-mg oral tab every 4-6 h	1-mg oral tab every 6 h	0.5-mg oral tab every 6 h
Fentanyl (long-acting)	Not recommended in opioid-naive patients; dose may be variable based on oral opioid equivalent dose	12.5- or 25-μg patch transdermally every 72 h (decrease to 50%-75% of normal dose)	12.5-μg patch transdermally every 72 h (decrease to 50% of normal dose)
Methadone	Recommend referral to specialist; requires pretreatment and follow-up ECG monitoring for QT interval prolongation		
Buprenorphine	5-μg patch transdermally every 7 d; may precipitate withdrawal in patients already receiving opioids; should discontinue other long-acting opioids; may need to continue short-acting analgesics until adequate analgesia from buprenorphine is achieved	5-μg patch transdermally every 7 d (no clear evidence for dosage adjustments; use with caution)	5-μg patch transdermally every 7 d (no clear evidence for dosage adjustments; use with caution)
Oxycodone	10-30 mg every 4-6 h; use with caution	5 mg every 6-8 h; use with caution	2.5-5 mg every 8-12 h; use with caution

Abbreviation: CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2).
Based on information from Davison et al,[9] Koncicki et al,[10] and Davison.[23]

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The Correct dose should not be a bitter elixir!

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Gabapentin or pregabalin induced myoclonus: A case series and literature review

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Gabapentin or pregabalin induced myoclonus: A Case series and literature review

- **Both drugs approved for adjunctive treatment of partial seizures and post-herpetic neuralgia.**
- **Medical records reviewed between January and May 2017**
- **Six (6) patients who were on either gabapentin or pregabalin were identified who developed likely myoclonus.**
- **All but 1 patient had renal dysfunction**
- **Resolved with drug discontinuation or hemodialysis**

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Gabapentin Toxicity in Patients with Chronic Kidney Disease: A preventable Cause of Morbidity

American Journal of Medicine 2010;123,367-73

- Popular analgesic for neuropathic pain
- Wide therapeutic dosing range with the exception of kidney disease
- 729 patient records were studies at the Mayo Clinic from 1998-2007
  - Group I eGFR > 90 (n =126_; Group II <90 (n=594); Group III Dialysis (n=9)
- Patients in Group II and III has higher serum gabapentin levels
- Greater incidence of toxicity in those patients with renal dysfunction and elderly
- Gabapentin toxicity was initially expected in 41.5% of symptomatic cases
- Group II patients experienced: dizziness, drowsiness, confusion, mental sluggishness, unsteady gait, myoclonus, episodic leg spasm, ataxia, asterixis and tremulousness
- Group III patients experienced obtundation, unresponsiveness. One patient had progressive weakness and ataxia , resulting in a fall and complex humerus fracture

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Gabapentin and Pregabalin Dosing Recommendations Based on varying Degrees of renal Dysfunction

Creatinine cl	Gabapentin	Pregabalin
30-59 mls/min	700 mg BID	150 mg BID /100 mg TID
15-29 mls/min	700 mg once daily	75 mg BID/50 mg TID
< 15 mls/min	300 mg once a day	75 mg once a day
Supplemental	100-300 mg Post dialysis	75-150 mg post dialysis
Doses in hemodialysis		

J Pain Res. 2017;10:275-278

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Management of Neuropathic Pain in the Geriatric Population

Elizabeth J. Pedowitz, MD[a,*], Rory M.C. Abrams, MD[b], David M. Simpson, MD[c]

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Table 1
Pharmacologic therapies for neuropathic pain in the elderly

Drug Class	Agent	Route	Initial Dose	Dose Increment	Typical Dose	Adverse Effects
Calcium Channel α2-δ Ligands	Gabapentin	PO	100–300 mg daily three times/d	100-300mg daily in 1-3 divided doses	300-2700mg daily in 1-3 divided doses	• Sedation, altered mental status • Dizziness, ataxia • Visual disturbances • Peripheral edema; recommend caution with heart failure • Administer at lower doses in renal failure to avoid excess sedation, dizziness
	Pregabalin	PO	25–75 mg daily three times/d	25-75mg daily in 1-3 divided doses	50-300mg daily in 2-3 divided doses	
Serotonin-Norepinephrine Reuptake Inhibitors	Duloxetine	PO	20–30 mg daily	Increase 20–30 mg every 1 wk	60 mg daily	• Sedation • Nausea, constipation • Dry mouth • Hypertension, palpitations • Caution with cardiac conduction derangements • Taper on cessation to avoid withdrawal syndrome
	Venlafaxine	PO	37.5 mg daily	37.5–75 mg every 1-2 wk	150–225 mg daily (extended release)	

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Tricyclic Antidepressants	Amitriptyline Desipramine Nortriptyline	PO	10–20 mg daily	Increase 10–25 mg every 1 wk	25–75 mg daily	• Fewer anticholinergic effects with nortriptyline: sedation, dizziness, falls, dry mouth, constipation, urinary retention • Caution with cardiovascular disease and cardiac conduction derangements • Avoid in glaucoma, prostate hypertrophy, angina, heart failure, cardiac conduction abnormalities
Alpha Lipoic Acid		IV/PO	600 mg		600–1800 mg daily	• Nausea and vomiting
Cannabinoids		INH/PO				• Sedation • Dizziness • Confusion/psychosis • Abuse potential
Sodium Channel Antagonists	Carbamazepine	PO	100–200 mg daily	100-200mg/day every 1 wk	600-800mg/day in 3-4 divided doses	• Sedation • Dizziness • Skin rash • Rarely, can cause hyponatremia, leukopenia, thrombocytopenia, and liver damage

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DELIRIUM

A nonspecific, potentially preventable, and often reversible disorder of impaired cognition, which results from several causes in ICU patients.

Prompt recognition is important to reduce modifiable risk factors and start treatment.

CHEST

WHAT IS DELIRIUM?

- Acute state of confusion with:
  - Fluctuating levels of consciousness
  - Inattention
  - Disorganized thinking

Hyperactive
- Agitated, irritable, "ICU psychosis"
- <2% of cases

Mixed
- 54% of cases

Hypoactive
- Lethargy, flat affect
- Often unrecognized
- 44% of cases

WHY DOES DELIRIUM MATTER?

- Increased risk of prolonged ICU and hospital stay
- Increased risk of mortality
- Increased risk of long-term cognitive impairment
- Reduced functional status at 3 & 6 months after ICU discharge
- Early sign of sepsis

SCREENING TOOLS

- Assess level of consciousness before delirium screening
  - Richmond Agitation-Sedation Scale (RASS)
- Screening tools for delirium in adults will assess judgement and attentiveness, with deficits in either suggesting delirium
  - Confusion Assessment Method for the ICU (CAM-ICU)
    - 80% sensitivity, 96% specificity
  - Intensive Care Delirium Screening Checklist (ICDSC)
    - 74% sensitivity, 82% specificity

RISK FACTORS FOR DELIRIUM

Patient-related
- Age ≥65 years
- Pre-existing cognitive impairment or neurologic disorder
- Comorbid conditions
- Malnutrition
- Alcoholism
- Prior history of delirium

Illness-related
- Illness severity
- Stroke
- Dehydration
- Infection
- Hypothermia/fever
- Hypoxia
- Electrolyte disturbances

Environment-related
- Social isolation
- Visual or hearing deficit
- Immobility
- Use of restraints
- Unfamiliar environment
- Stress
- Pain

Medication-related
- Polypharmacy (addition of ≥3 medications)
- Benzodiazepine use
- Nicotine or alcohol withdrawal
- Psychoactive medications, anesthetics, or anticholinergics

TREATING DELIRIUM

- Assess and treat modifiable risk factors
  - Avoid benzodiazepines and other sedative-hypnotics
  - Avoid physical restraints to manage behavioral symptoms
  - Treat dehydration, infection, and other underlying causes
- **ABCDEF bundle**
  - Evidence-based guide of organizational changes needed for optimizing ICU patient recovery
  - **Early mobilization, promotion of sleep hygiene**, and **preventing sleep disruption** may reduce incidence and duration of delirium
- **Medications:** For symptomatic relief (may not affect delirium duration)
  - Haloperidol (Haldol)
    - Most titratable, used in acutely agitated
  - Quetiapine (Seroquel)
    - Slow onset, short half-life, used for insomnia or agitation
  - Olanzapine (Zyprexa)
    - Used acutely, long half-life
  - Dexmedetomidine (Precedex)
    - Useful in refractory hyperactive delirium

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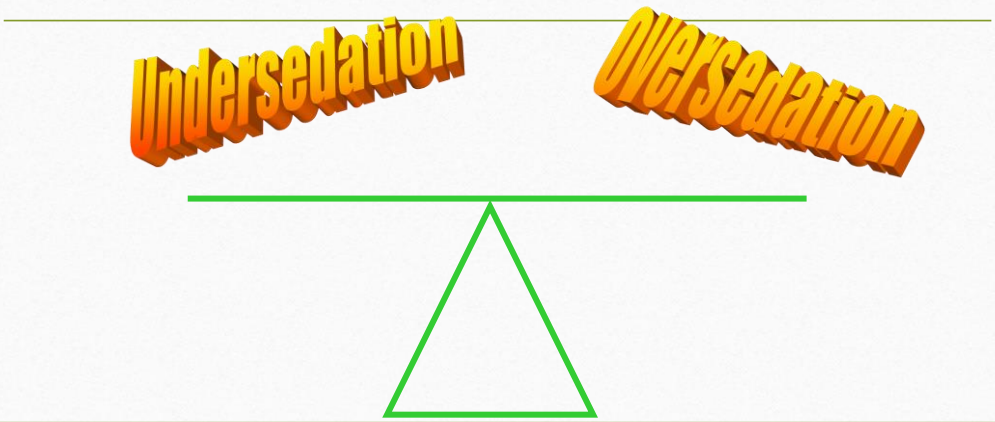
The Fine Balance in Patient Comfort



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The doctor said I can give her a shot of anything that would keep her quiet

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Current Limitations

	Midazolam	Propofol	Fentanyl	Dex
Hypotension	+	++		++
Bradycardia			+	++
Respiratory depression	+	+	+++	
Disorientation	++	+	+	
Prolonged weaning	++		++	
Hyperlipidemia		++		
Increased infection		+		
Constipation			++	
Tolerance	+	±	++	?

Dex=dexmedetomidine.

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α_2 Agonists: Chemical Structures

Clonidine

Dexmedetomidine

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Clinical Effects of a_2 Agonists

- Sedation/hypnosis[1]
- Anxiolysis[1]
- Analgesia[1]
- Decreased sympathetic activity[1]
- Decreased BP and HR[2]
- Vasoconstriction at high doses[1]

Kamibayashi, Maze. *Anesthesiology*. 2000;93:1345-1349. 2. Wagner, O'Hara. *Clin Pharmacokinet*. 1997;33:426-453.

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Dexmedetomidine

- **The major advantage of dexmedetomidine is that it doesn't suppress respiration**
- **Safe to use in a non-intubated patient. Therefore, dexmedetomidine may be continued *throughout* the weaning process (unlike propofol, which must be shut off prior to extubation).**
- **Excellent option for patients who develop anxiety and tachypnea whenever sedation is lifted, making it difficult to extubate them.**
- **Dexmedetomidine may cause hypotension due to bradycardia.**

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Dexmedetomidine

Boluses **of dexmedetomidine should be avoided, as these can cause bradycardia in hemodynamic instability. Instead, the infusion can be started at a relatively high rate (e.g. 1-1.4 mcg/kg/min) *without* a bolus, and then down-titrated within 30-60 minutes.**

- **Dexmedetomidine can cause tolerance over ~4-5 days, with subsequent withdrawal when it is discontinued.[73] It may be inadvisable to continue dexmedetomedine infusions for longer periods of time. If tolerance occurs, dexmedetomidine may be transitioned to oral clonidine**

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Dexmedetomidine: A New Option for Intractable Distress in the Dying

- **Three case Reports by Soares LG, et al J Pain and Symptom Management July 2002:24:6-8**
- **Variable successes with this therapy**
- **Limited by need for continuous IV infusion and other treatment modalities may be required.**
- **Combination analgesic and sedative is an attractive option.**
- **Probably not useful for patients on high dose opiate therapy**

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Successful Use of Dexmedetomidine for the Treatment of Terminal Delirium

- **Fabina J , et al. Journal of Pain and Symptom Management February 2017:445**
- **Two cases of cancer patients receiving PCA Opiate therapy and benzodiazepine therapy and needing additional therapy.**
- **Dexmedetomidine replaced benzodiazepine therapy**
- **Better symptom control with dexmedetomidine. Significant reduction in opiate in one case and slight reduction in second case**
- **Case reports are interesting but need prospective controlled clinical studies to determine appropriate place in therapy.**

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Prescription volume and drug interactions

400,000 orders a month

- **Ondansetron/QT Prolonging Agents** 5109
- **Tapentadol; Tramadol/TCA's; Carbamazepine** 3876
- **ACEI's;ARBS/Trimethoprim** 2806
- **Alfentanyl;Fentanyl;Hydrocodone;Oxycodone/CYP 3A4 Inh** 2174
- **Vitamin K antgonists/SSRI's;SNRI's** 2803
- **Tetracyclines/Divalent &Trivalent Cations** 2050
- **Hydroxyzine,QT Prolonging Agents** 1837
- **Potassium Preparations/Potassium Sparing Diuretics** 1403
- **Azithromycin/QT Prolonging Agents** 1302
- **Fluconazole/Qt Prolonging Agents** 1284

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Table 4. Selected High-Risk Drugs

Drug	Potential Harm	Comment
Insulin and sulfonylureas	Hypoglycemia	May often be appropriate; however, aggressive glycemic control may often yield greater harms than benefits in older adults[54,71,72]
Warfarin	Gastrointestinal, intracranial bleeding	Although a high-risk drug, benefits of warfarin therapy often outweigh harms; maintenance of prothrombin time international normalized ratio in therapeutic range tightly linked to risk/benefit ratio[73]
Digoxin	Impairment of cognition, heart block	May have a third-line role in management of systolic heart failure; suboptimal choice for rate control in atrial fibrillation
Benzodiazepines	Falls	Associated with as much as a 60% increase in fall risk[74]
Diphenhydramine, other first-generation antihistamines	Impaired cognition, urinary retention in men	Poor choice as sleep aid due to anticholinergic effects, next-day sedation, impact on performance including driving; close medication reconciliation important because patients may also obtain over-the-counter drugs
Antipsychotics	Death, pneumonia	Elevated risk of death when used to treat behavioral complications of dementia, although in selected cases, benefits may exceed risks if consistent with patient goals of care[75]

Account for 1/3 of ED visits for ADE

JAMA. 2010;304(14):1592-1601. *Ann Intern Med.* 2007;147:755-765.

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Beers Criteria

- Potentially inappropriate medications for older adults.
- Originally conceived by Dr. Mark Beers
- Published in 1991, revised in 1997, 2002, and 2012.
- Consensus-based, but statistical association with adverse drug events
- Adopted for nursing home regulation.
- Does not account for the complexity of a patient's entire medication regimen.

J Am Geriatr Soc 60:616–631, 2012.

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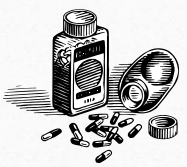
Beers Criteria: Benzodiazepines

- **Increased sensitivity for older adults**
  - Slowed metabolism, especially long-acting agents
  - Similar neurocognitive effects to alcohol
  - May cause a paradoxical reaction (increased agitation)
- **Increased risk of adverse clinical events**
  - Falls and fractures
  - Cognitive impairment
  - Delirium
- **Avoid if possible**
  - Appropriate if being used for seizures, alcohol withdrawal, severe anxiety, or periprocedural anesthesia
  - If necessary, use lowest dose possible



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J Am Geriatr Soc 60:616–631, 2012. See Table 2.

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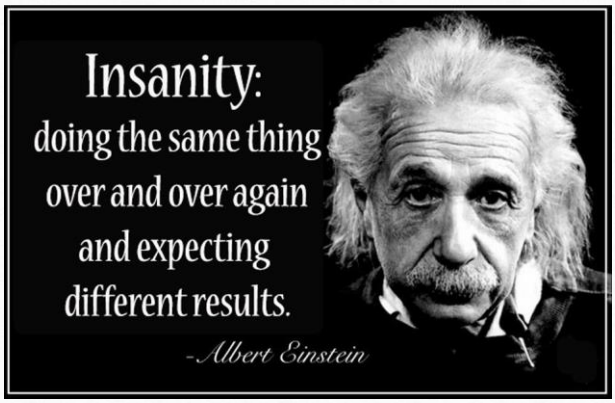

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Beers Criteria: Sedative-Hypnotics

- **Nonbenzodiazepine Hypnotics**
  - Eszopiclone (Lunesta)
  - Zolpidem (Ambien)
  - Zaleplon (Sonata)
- **Benzodiazepine-receptor agonists**
- **Adverse events similar to those of benzodiazepines**
- **Increased risk for delirium, falls fractures**

J Am Geriatr Soc 60:616–631, 2012. See Table 2.

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Points to Ponder

- **Review drug monitoring systems in your institutions**
- **Be "creatively critical" in discussing opportunities to improve care.**
- **Review and Revise Renal Drug dosing programs**
- **Partner with Hospital Administration and College(s) of Pharmacy.**
- **Share Best Practices**

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"We are what we repeatedly do. Excellence, then, is not an act, but a habit."

Aristotle

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Questions

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