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Non-pharmacologic and non-opioid therapy should be optimized before starting opioids for older adults in chronic pain.

Focus on Opioid Safety

- By Barbara Zarowitz

Opioids are controlled substances that have a useful and legitimate medical purpose to treat severe acute pain and chronic pain from several conditions, including active cancer or at the end of life. Guidelines from the American Pain Society and the American Academy of Pain Medicine state that chronic opioid therapy can be effective in carefully selected and monitored patients with chronic noncancer pain. However, opioids have a potential for abuse and have been associated with overdose deaths, emergency department visits and other adverse health consequences. Opioid medications are associated with dependence, tolerance, abuse and risk of accidental overdose. One study found that death rates for drug overdoses involving opioids were 7.8 per 100,000 adults aged 18 through 64 years in 2013, an increase from 4.5 per 100,000 in 2003.

Figure 1: Overprescribing of Opioids



Prescribers wrote 258.9 millions prescriptions for opioids in 2012, enough for every American adult to have a bottle of pills.

The US constitutes 4.6% of the world's population but consumes 80% of the world's opioid supply and 99% of the global hydrocodone supply.

2.1 million people suffer from opioid substance abuse in the U.S.

The cost of opioid abuse is estimated to be about \$53 - \$56 billion annually.

In 2016, the Centers for Disease Control and Prevention (CDC) released a guideline for opioid prescribing to assist providers in delivering safer, more effective chronic pain management for patients with pain outside of active cancer treatment, palliative care, and end-of-life care. Topics included in the guideline are listed in Table 1.

Table 1: Topics in the CDC Guideline for Prescribing Opioids for Chronic Pain

1) When to initiate or continue opioids for chronic pain
2) Opioid selection, dosage, duration, follow-up, and discontinuation
3) Assessing risk and addressing harms of opioid use, including the use of opioids in adults ≥ 65 years of age
4) Morphine Equivalent Dose (MED) of 50 mg/day as a threshold for increased risk of opioid overdose
5) General avoidance of opioid doses ≥ 90 mg MED
6) Tapering methodology for long-term high opioid dosages

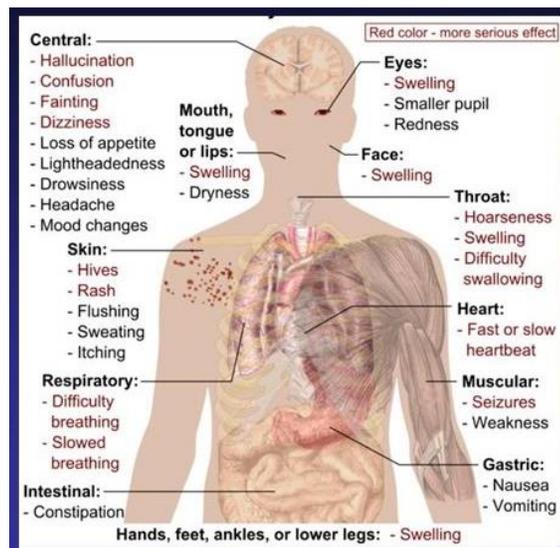
In March 2016, the Food and Drug Administration (FDA) announced required class-wide safety labeling changes for immediate-release (IR) opioid pain medications, similar to those required in 2013 for extended-release (ER) or long-acting (LA) formulations. A boxed warning will outline the serious risks of misuse, abuse, addiction, overdose and death. In addition, the American Medical Association has proposed mandatory education for prescribers of controlled substances, with a focus on opioid analgesics. Nearly 40 States have implemented Prescription Drug Monitoring Programs (PDMP) to curb growing opioid abuse. PDMPs maintain an electronic registry of patients, prescribers and pharmacies for each opioid prescription. Legislation to require health care professionals to query PDMP databases is being considered by several States. In addition, some Medicare Part D plans have begun imposing opioid prescribing restrictions.

Why is opioid overuse a problem in older adults residing in long-term care environments?

Figure 2: Serious Opioid Adverse Effects in Older Adults

Serious Opioid Adverse Effects in Older Adults

- Ileus/Constipation
- Nausea/Vomiting
- Sedation/Resp. Depression
- Cough Suppression
- Confusion/Delirium
- Pruritus
- Dry Mouth
- Sweats
- Urinary Retention
- Tolerance/Dependence



In addition to the serious opioid adverse effects noted in Figure 2, older adults often receive other medications that can increase the risk of these side effects. For example, antihistamines, skeletal muscle relaxants and benzodiazepines can increase the risk of delirium and falls. Medications with anticholinergic side effects, such as antihistamines, and drugs for overactive bladder can increase the risk of constipation, confusion, dry mouth, and urinary retention. Many older adults with dementia are unable to communicate adverse effects which can result in an exacerbation of behavioral symptoms.

Key Principles when Starting Opioid Therapy for Chronic Pain

Prescribe immediate-release opioids (oxycodone, hydromorphone, morphine) instead of extended-release (ER) or long-acting (LA) formulations

Avoid ER/LA opioids including: oxycodone CR, oxymorphone ER, hydromorphone ER, and morphine SR, as well as fentanyl and methadone

Initiate at the lowest starting dosage on product labeling for adults not already receiving opioids

Exercise caution when starting opioids in adults ≥ 65 years and for those with renal or hepatic impairment because decreased drug clearance can lead to accumulation of the opioid to toxic amounts.

Key Principles for Opioid Dosing for Pain

Carefully reassess evidence of individual benefits and risks before increasing the opioid dose

Aim for a morphine equivalent dose (MED) of ≤ 50 mg/day (see Table 2 for MED)

Prescribe no more than the minimum quantity needed for the expected duration of pain severe enough to require opioids (≤ 7 days is usually sufficient)

Avoid increasing the dose to ≥ 90 MED/day or carefully justify a decision to titrate dosage to ≥ 90 MED/day.

Table 2: Estimating Morphine Equivalent Doses (MED)

Opioid	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone (Zohydro, Norco, etc)	1
Hydromorphone (Dilaudid)	4
Methadone	
1 – 20 mg/day	4
21 – 40 mg/day	8
41 – 60 mg/day	10
≥ 61 – 80 mg/day	12
Morphine	1
Oxycodone (Oxycontin)	1.5
Oxymorphone (Opana)	3
Tapentadol (Nucynta)	0.4

Not all inclusive. Adapted from Von Korff M, Saunders K, Ray GT et al. Clin J Pain 2008;24: and Washington State Interagency Guideline on Prescribing Opioids for Pain (<http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf>)

Multiply the dose for each opioid by the conversion factor to determine the dose in MEDs. For example, tablets containing hydrocodone 5 mg and acetaminophen 325 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MED daily (1:1 conversion factor). Extended-release tablets containing oxycodone 20 mg daily would be equivalent to 30 MED daily (1:1.5 conversion factor).

The following cautions should be noted:

- 1) All doses are in **mg/day** except for transdermal fentanyl which is **mcg/hour**.
- 2) Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and pharmacokinetics.
- 3) Do NOT use the calculated dose in MED to determine the dose to use when converting one opioid to another. When converting opioids the new opioid is typically dosed at substantially lower than the calculated MED dose to avoid overdose due to incomplete cross-tolerance and individual variability in opioid kinetics.
- 4) Use particular caution with methadone dose conversions because the conversion factor increases at higher doses.
- 5) Use particular caution with fentanyl since it is dosed in mcg/hour instead of mg/day; absorption is affected by heat and other factors.
- 6) Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. MEDs are based on the degree of mu-receptor agonism; it is unknown if this drug is associated with overdose in the same manner as observed with pure mu receptor agonists.

Key Principles for Tapering Opioids in Chronic Pain

Taper the dose by about 10% per week

Once the smallest available dose is reached, extend the interval between doses

Opioids can be stopped when taken \leq once daily

Use a slow taper to minimize symptoms of opioid withdrawal (e.g., anxiety, drug craving insomnia, abdominal pain, diarrhea, sweating, tremor, tachycardia, vomiting).

Table 3: Outline of Opioid Safety Initiatives in Older Adults

Target	Intervention
Triple threat of opioids, and two CNS medications, e.g., antipsychotics, and benzos	Educate prescribers and nurses. Recommend discontinuation or replacement where appropriate.
Fall / injury risk	Recommend fall and prevention strategies. Consider gradual dosage reduction (GDR) to lowest opioid dose possible. Recommend discontinuation of concurrent medications that may increase fall risk.
Use of codeine, meperidine, methadone	Identify and eradicate use of <i>Unacceptable</i> medications per the <i>Geriatric Pharmaceutical Care Guidelines</i> .
NSAID use; NSAID use without PPI for gastroprotection	NSAID use should be limited to only those older adults in whom no safer or more effective form of therapy exists and for the shortest time possible. NSAIDs should be prescribed with an appropriate PPI.
Effectiveness of laxative use in patients receiving opioids > 10 days	Docusate, a stool softener, is ordered frequently in the absence of a stimulant laxative. Docusate is no more effective than placebo. Suggest appropriate bowel regimens (e.g., a stimulant laxative).
Apply pharmacogenetic principles to opioid selection where pharmacogenetic information is available	Tramadol, codeine, hydrocodone, oxycodone and methadone are metabolized by CYP2D6 for which several polymorphisms exist. Application of pharmacogenetic information may prevent under-treated pain and opioid adverse consequences.
Anticholinergic burden in residents receiving opioids (see Figure 3)	Combined effects of opioids with other medications having anticholinergic properties increases the risk of delirium, urinary retention, and constipation. The anticholinergic burden should be assessed and reduced as much as possible. Monitoring for adverse effects is recommended.
Naloxone in emergency kits	Assure the presence of naloxone injection in each facility's emergency kit.
Opioid drug interactions	Suggest discontinuation and/or replacement of interacting drugs where appropriate.
High risk patients	Exercise extra caution, evaluation and lower opioid doses in nursing home residents at high risk of opioid harm; sleep-disordered breathing, heart failure, obesity, renal or hepatic impairment, age ≥ 65 years, mental health conditions, and substance use disorders.

Figure 3: Estimating the Anticholinergic Burden [ACB (list is not all inclusive)]

ACB=3	<ul style="list-style-type: none"> • Antidepressants: amitriptyline (Elavil), amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine (Paxil), trimipramine • Antipsychotics: chlorpromazine, clozapine, olanzapine (Zyprexa), perphenazine, quetiapine (Seroquel), thioridazine, trifluoperazine • Antihistamines: brompheniramine, carbinoxamine, chlorpheniramine, clemastine, dimenhydrinate, diphenhydramine (Benadryl), hydroxyzine (Atarax), pyrilamine • Overactive Bladder: darifenacin (Enablex), oxybutynin, tolterodine
ACB=2	<ul style="list-style-type: none"> • Antidepressants: citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), mirtazapine (Remeron) • Anticonvulsants: carbamazepine (Tegretol), oxcarbazepine (Trileptal) • Miscellaneous: meperidine (Demerol), cyclobenzaprine (Flexeril), temazepam (Restoril)
ACB=1	<ul style="list-style-type: none"> • Antidepressants: bupropion (Wellbutrin), duloxetine (Cymbalta), trazodone • Antipsychotics: haloperidol, risperidone (Risperdal) • Gastrointestinal: cimetidine, lansoprazole (Prevacid), loperamide, ranitidine • Miscellaneous: morphine, alprazolam, diazepam, digoxin, colchicine, lithium, prednisolone, furosemide, warfarin

Add the anticholinergic burden (ACB) score of each medication together to estimate the total burden. A score of ≥ 3 is clinically significant. Consider alternative medication(s) which can lower ACB score.



Vancomycin Dosing and Monitoring: Don't Forget to Reevaluate

Though the following case did not occur in the long term care setting, the complexity of the patient and the events that occur with regard to assessment of renal function and medication monitoring are all too familiar.

The Case*†: A 61-year-old woman receiving palliative chemotherapy for non-small-cell lung cancer at a community hospital developed methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endophthalmitis originating from her port. Vancomycin 1.25 grams intravenously twice daily was initiated, and the patient was transferred to a large academic medical center for ophthalmologic consultation and further treatment. Vancomycin was continued upon transfer until she was found to have a rapidly rising serum creatinine (SCr). The initial SCr was 0.4 mg/dL at the community hospital; it had increased to 0.8 mg/dL on admission to the receiving facility and was apparently interpreted as "normal," since it still fell within "normal" range. The patient was recognized to be in acute renal failure when her creatinine reached 1.09 mg/dL the day after transfer. The vancomycin trough was 64 mcg/mL (target trough concentration = 15-20 mcg/mL for this complicated infection). The vancomycin blood concentration had not been checked previously throughout her treatment. As a result of her renal failure, the patient rapidly developed non-anion gap metabolic acidosis and, 5 days after transfer, required urgent dialysis for volume overload and worsening acid-base status. Urine and blood studies failed to identify a clear cause of her renal failure, and she required ongoing dialysis treatments.

Commentary and Key Take Away Points:

The course of action may appear reasonable based on what was known at the time (a single SCr value) and the assumption that the vancomycin dose given at the outside hospital was appropriate. To safeguard patients against drug-induced toxicity, several issues highlighted by this case deserve attention.

- Vancomycin is renally eliminated and has a narrow therapeutic index, with the potential for nephrotoxicity, particularly with concomitant nephrotoxins and with more aggressive dosing.
- Patients with end-stage liver disease or reduced muscle mass secondary to malnutrition or immobility can exhibit a lower than normal baseline SCr value. Patients with significant renal injury (e.g., significant elevations from baseline, as in this case) may still have "normal" SCr values.
- If the SCr value of 0.8 mg/dL upon admission had been compared with the patient's lower than normal initial SCr value of 0.4 mg/dL from the outside hospital, the fact that it doubled, would have been identified. This should have prompted an order for a serum vancomycin trough concentration prior to the next dose.
- Even patients without significant changes in SCr from baseline may experience nephrotoxicity from vancomycin. In these cases, a vancomycin trough concentration obtained at the time of admission could reveal excessive drug accumulation due to subclinical acute kidney injury (AKI).
- SCr is an insensitive and nonspecific marker for detecting AKI. Changes in values often occur only after significant renal damage. To facilitate early detection of AKI and allow prompt intervention, the Acute Kidney Injury Network has proposed standards for diagnosing AKI based on abrupt changes in SCr (increase > 0.3 mg/dL in 48 h) or urine output (< 0.5 mL/kg/hr for > 6 h)
- Medication records of patients transferring from outside facilities often do not include detailed therapeutic drug monitoring records. This case highlights the importance of assessing vancomycin therapy through trough monitoring.
- Consultation with a pharmacist is encouraged when dosing a narrow-therapeutic index drug, particularly if therapeutic drug monitoring is required.

* This content was adapted from AHRQ WebM&M (Morbidity & Mortality Rounds on the Web) with permission from AHRQ Patient Safety Network. The original commentary was written by Annie Wong-Beringer, PharmD, and was adapted for this piece by Carrie Allen, PharmD. (Citation: Wong-Beringer A. Failure to reevaluate. AHRQ WebM&M [serial online]. December 2010. Available at: <https://psnet.ahrq.gov/webmm/case/232>.) † References available upon request

Risk of Acute Kidney Injury With Some Newer Diabetes Drugs

From March 2013 to October 2015, the FDA has received 101 confirmed reports of acute kidney injury (AKI) in diabetics receiving canagliflozin- (i.e., Invokana and Invokamet) or dapagliflozin-containing medications (i.e., Faxiga and Xigduo XR), with some patients requiring hospitalization and others dialysis. In June 2016, the FDA required warnings about AKI to be made stronger for these medications. This change also follows the FDA's announcement in May regarding canagliflozin-containing medications and the potential increase in amputations.

Healthcare professionals are reminded to not only assess kidney function prior to and during therapy with canagliflozin or dapagliflozin, but also to consider the risk of acute kidney injury in patients who meet any of the following criteria:

decreased blood volume (e.g., dehydration)	chronic kidney disease	heart failure	use of diuretics (e.g., hydrochlorothiazide, furosemide)	use of non-steroidal anti-inflammatory drugs (NSAIDs)	use of Angiotensin-Converting Enzyme (ACE) inhibitors (e.g., lisinopril)	use of Angiotensin Receptor Blockers (ARBs) (e.g., losartan)
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Patients receiving these medications for their diabetes should be closely monitored for signs of acute kidney injury including decreased urine production and/or swelling in the legs or feet.

 **The Clinical Capsule** by Kori Hauersperger

Two New Agents Recommended in Heart Failure with reduced Ejection Fraction (HFrEF)

The 2016 ACC/AHA/HFSA HF treatment guidelines recommend using two newer agents in individuals with symptomatic New York Heart Association class II or III HF/EF (previously called systolic HF) to reduce HF-related hospitalizations and deaths.

Medication	Initial Dose and Titration	Recommendation for NYHA Class II or III HF/EF
Sacubitril/valsartan (Entresto) ARNI with an ARB	24 mg sacubitril / 26 mg valsartan twice daily if <u>no or low previous</u> ACEI or ARB use or CrCl < 30 mL/min OR 49 mg / 51 mg twice daily if current ACEI /ARB use Double the dose every 2 - 4 weeks, as tolerated MAX and target dose: 97 mg / 103 mg twice daily	Replace ACEI or ARB with sacubitril/valsartan in a regimen that may include a beta blocker and an aldosterone antagonist. - Stop ACEI 36 hours before initiating - Systolic blood pressure must be ≥ 95 mmHg - Avoid in those with history of angioedema or receiving aliskiren - Monitor BP, potassium, and creatinine
Ivabradine (Corlanor) sinoatrial node modulator	2.5 - 5 mg twice daily x 14 days then adjust to resting HR 50-60 bpm. After 14 days, decrease dose if HR < 50 bpm or increase dose by 2.5 mg twice daily HR > 60 bpm MAX dose: 7.5 mg twice daily	Add ivabradine to a regimen that includes a beta blocker at maximally tolerated dose - Requires: HR of ≥ 70 bpm at rest and LVEF ≤ 35% - Ensure beta blocker is at maximum tolerated dose by up-titration at least 4 weeks before starting ivabradine - Monitor BP, pulse and symptoms of HF

ACC = American College of Cardiology; ACEI = Angiotensin Converting Enzyme Inhibitor; AHA = American Heart Association; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; bpm = beats per minute; CrCl = creatinine clearance; HF/EF = HF with reduced ejection fraction; HFSA = Heart Failure Society of America; HR = heart rate; LVEF = left ventricular ejection fraction.
Yancy CW, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, *Journal of the American College of Cardiology* (2016).

 **Regulatory Recap – CMS Adverse Event Trigger Tool: Drug Toxicity Related to Acetaminophen**
- By Carrie Allen

The CMS Adverse Event Trigger Tool assigns questions as “surveyor probes” to guide in an investigation of potential adverse events and/or the situations that may lead to avoidable adverse events. The following surveyor probes from this document are of critical importance.

- Is there evidence of a system for ensuring residents with orders for routine or PRN acetaminophen do not receive more than 4 grams in a 24 hour period?
- Is there evidence of a system to ensure that medications that contain acetaminophen are flagged to alert medication nurses that the resident has more than one medication containing acetaminophen ordered?

**NEW Drug**

by Dave Pregizer

Xiidra™ Ophthalmic Solution

Brand Name (Generic Name)	Xiidra [(ZYE-druh); (lifitegrast) [lif i TEG rast]
How Supplied	foil pouch containing 5 low density polyethylene 0.2 mL single-use containers
Therapeutic Class	Lymphocyte function-associated antigen-1 (LFA-1) antagonist
Approved Indication	Treatment of the signs and symptoms of dry eye disease.
Usual Dosing	One drop twice daily in each eye (approximately 12 hours apart).
Common Drug Interactions	No drug interactions listed in the manufacturer's labeling.
Most Common Side Effects	Instillation site irritation, dysgeusia (taste disturbance) and decreased visual acuity.
Miscellaneous	Contact lenses should be removed prior to administration and may be reinserted 15 minutes following administration.
Website	www.Xiidra.com

**NEW Generic Medications**

Generic Name	Brand Name	Date Generic Available
Dofetilide 125 mcg, 250 mcg, and 500 mcg Capsule	Tikosyn® Capsule	6/14/16
Miglitol 25 mg, 50 mg, and 100 mg Tablet	Glyset® Tablet	6/6/16
Armodafinil 50 mg, 150 mg, and 250 mg Tablet	Nuvigil® Tablet	6/6/16

HealthLine Quiz

By Steve Law

1. Which is considered a serious opioid adverse effect in older adults?
 - a. Constipation
 - b. Confusion/Delirium
 - c. Urinary retention
 - d. Tolerance/Dependence
 - e. All of the above
2. A key principle for starting opioid dosing for chronic pain is to prescribe long-acting opioid formulations instead of immediate-release opioid formulations:
 - a. True
 - b. False
3. Which medication would be considered to have the highest anticholinergic burden score (ABS)?
 - a. Citalopram
 - b. Trazodone
 - c. Diphenhydramine
 - d. Ranitidine
4. If a patient is taking 40 mg of oxycodone per day, the morphine equivalent dose (MED) would be 60 mg per day.
 - a. True
 - b. False
5. There may be an increased risk of acute kidney injury in patients taking canagliflozin and dapagliflozin-containing medications:
 - a. True
 - b. False
6. If a patient is on the medication, ivabradine, heart rate must be monitored:
 - a. True
 - b. False
7. Which is FALSE concerning the new medication: Xiidra™ ophthalmic solution?
 - a. It is indicated for the treatment of the signs and symptoms of dry eye disease
 - b. It is a Lymphocyte function-associated antigen-1 (LFA-1) antagonist
 - c. It is dosed three times a day (morning, afternoon, and at bedtime)
 - d. A common side effect may be decreased visual acuity

***Please note, the HealthLine Quiz is designed to help readers retain information that is relevant to their care setting. It is not an approved source of continuing education credits for healthcare professionals.**

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Answers to the HealthLine Quiz: 1) E 2) B 3) C 4) A 5) A 6) A 7) C