PainWeek®

Complicated By: Using Comorbidities to Select Treatment Options

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Disclosure

- Abigail Brooks
  - Nothing to disclose
- Courtney Kominek
  - Consultant: American Society of Health-System Pharmacists
  - Honoraria: Practical Pain Management

- The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of any agency of the United States government, including the Department of Veterans Affairs, as well as employers, employee affiliates and/or pharmaceutical companies mentioned or specific drugs discussed.

Learning Objectives

- Explain pharmacokinetic changes that occur in renal and hepatic dysfunction
- Discuss pharmacologic considerations for renal dysfunction, hepatic dysfunction, pulmonary conditions, cardiac conditions, and psychiatric conditions including potential medication contraindications
- If given a patient case, provide pharmacotherapy recommendations taking into consideration a patient's chronic pain condition and comorbidities

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Chronic Obstructive Pulmonary Disease, Obstructive Sleep Apnea, and Chronic Kidney Disease

Case #1 – Complicated by:

Case #1

WA is a 66 yo male presenting to your outpatient pharmacy pain clinic for routine follow-up post hospital discharge 2 weeks ago for COPD exacerbation (second in last 6 months) and acute kidney injury. At discharge, patient was given home oxygen 1L via nasal cannula which he wasn't on prior, antibiotics, prednisone 10 mg daily with taper, and was instructed to follow-up with his primary care provider and pain clinic.

- PMH
  - T2DM, Diabetic peripheral neuropathy
  - HTN, Hyperlipidemia
  - Chronic kidney disease, stage 2 EGFR 63 mL/min
  - Lumbar spondylosis, s/p L4-L5 fusion in 2010
  - Osteoarthritis of knee
- Medications
  - Albuterol HFA 2 puffs q6h PRN
  - Aspirin 81 mg PO daily
  - Atorvastatin 40 mg PO daily
  - Budesonide/formoterol 2 inhalations BID
  - Empagliflozin 25 mg PO daily
  - **Gabapentin 600 mg PO TID**
  - Ibuprofen 600 mg PO TID PRN
  - Lisinopril 20 mg daily
  - Metformin 1000 mg PO q12h
  - **Morphine SA 30 mg PO q12h**
  - Prednisone 10 mg PO daily
  - Tiotropium 1 puff daily

Vitals

BP: 145/90
HR 80
Lipid panel wnl

Labs

Fasting glucose 220
EGFR and CrCl: 55 mL/min

1. What recommendations do you have for his opioid regimen?
2. What recommendations do you have for his nonopioid regimen?
3. What recommendations do you have for nonpharmacologic approaches?

Opioids and COPD

- Population-based, retrospective, cohort study
- Claims from 1/1/06-12/31/10 from regional managed care plan in SW U.S. with inpatient stay or 2 outpatient visits
- Exposures: COPD diagnosis
- Controls: no COPD diagnosis
- Results
  - Greater use of anticonvulsants, antidepressants, muscle relaxants, antirheumatic medications in COPD than nonCOPD ($p<0.001$)
  - Greater use of short-acting and long-acting opioids in COPD than nonCOPD ($p<0.001$)

Roberts MH, Mapel DW, Hartry A, Worley AV, Thomson H. Chronic pain and pain medication use in chronic obstructive pulmonary disease: a cross sectional study. Ann Thorac Soc. 2013;10(4):290-298.

Opioids and COPD

	Outpatient exacerbations	Emergency room visits for COPD or pneumonia	Hospitalization for COPD or pneumonia	ICU admission for COPD or pneumonia	COPD or pneumonia-related mortality	All-cause mortality
Short-acting opioids ≤30 MED			↑		↑	
Short-acting opioids > 30 MED	↑	↑	↑		↑	↑
Long-acting opioids ≤30 MED			↑		↑	↑
Long-acting opioids > 30 MED	↓		↑		↑	↑

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Vozoris NT, Wang X, Fischer HD, et al. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. Eur Resp J. 2016;48:683-693.

Opioids and Sleep Disordered Breathing

- Alter sleep architecture and sleep stage distribution
- Affect both obstructive sleep apnea (OSA) and central sleep apnea (CSA)
  - OSA: Alteration in airway muscles activity
  - CSA > OSA
  - CSA dose-related and can be reduced with opioid taper

Rosen IM, Aurora RN, Kirsch DB, et al. Chronic opioid therapy and sleep: an American Academy of Sleep Medicine position statement. J Clin Sleep Med. 2019;15(11):1671-1673.
Hassamal S, Miotto K, Wang T, Saxon AJ. A narrative review: the effects of opioids on sleep disordered breathing in chronic pain patients and methadone maintained patients. Am J Addiction. 2016;25:452-465.
Ryswyk EV, Antic NA. Opioids and sleep-disordered breathing. Chest. 2016;150(4):934-944.

Opioids and Sleep Disordered Breathing

- Nested case control study of Veterans Health Administration (VHA) patients prescribed 10/1/100-9/30/12
- Cases(n=817): dispensed at least 1 opioid by VHA and had claim for serious opioid-related toxicity or overdose
- Controls (n=8170): dispensed at 1 opioid by VHA and did not experience serious opioid-related toxicity or overdose
- Results – Sleep apnea
  - Cases 18%, Controls 8%, $p<0.001$

Zedler B, Xie L, Wang Li, et al. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med. 2014;15:1911-1929.

Buprenorphine Mechanism of Action

- Partial agonist of mu opioid receptors
- Antagonist at kappa opioid receptors
- Agonist at delta opioid receptors
- Partial agonist at opioid receptor-like 1 (ORL-1) receptor

Butrans package insert. Stamford, CT: Purdue Pharma LP; 2019 Oct.

Buprenorphine Patch Dosing – Conversion from Other Opioids

Morphine	< 30 mg	30-80 mg	> 80 mg
Hydrocodone	< 15 mg	15-40 mg	> 40 mg
Oxycodone	< 15 mg	15-40 mg	> 40 mg
Tramadol	< 300 mg	300-400 mg	NA
Codeine	< 90 mg	90-250 mg	> 250 mg
	⇩	⇩	⇩
Buprenorphine patch dose	5 mcg/hr patch q week	Taper to < 30 mg morphine equivalent then 10 mcg/hr patch q week	Buprenorphine patch may not be appropriate

Butrans package insert. Stamford, CT: Purdue Pharma LP; 2019 Oct.

Buprenorphine Buccal Dosing

Previous daily dose before taper	Buprenorphine buccal starting dose
< 30 mg PO MME	75 mcg qday or q12h
30-89 mg PO MME	Taper to < 30 mg PO MME, then 150 mcg q12h
90-160 mg PO MME	Taper to < 30 mg PO MME, then 300 mcg q12h
> 160 mg PO MME	Consider alternative opioid

Initial dose of morphine SA or oxycodone SA	Buprenorphine buccal dose
80-160 PO MME	300 mcg q12h
161-220	450 mcg q12h

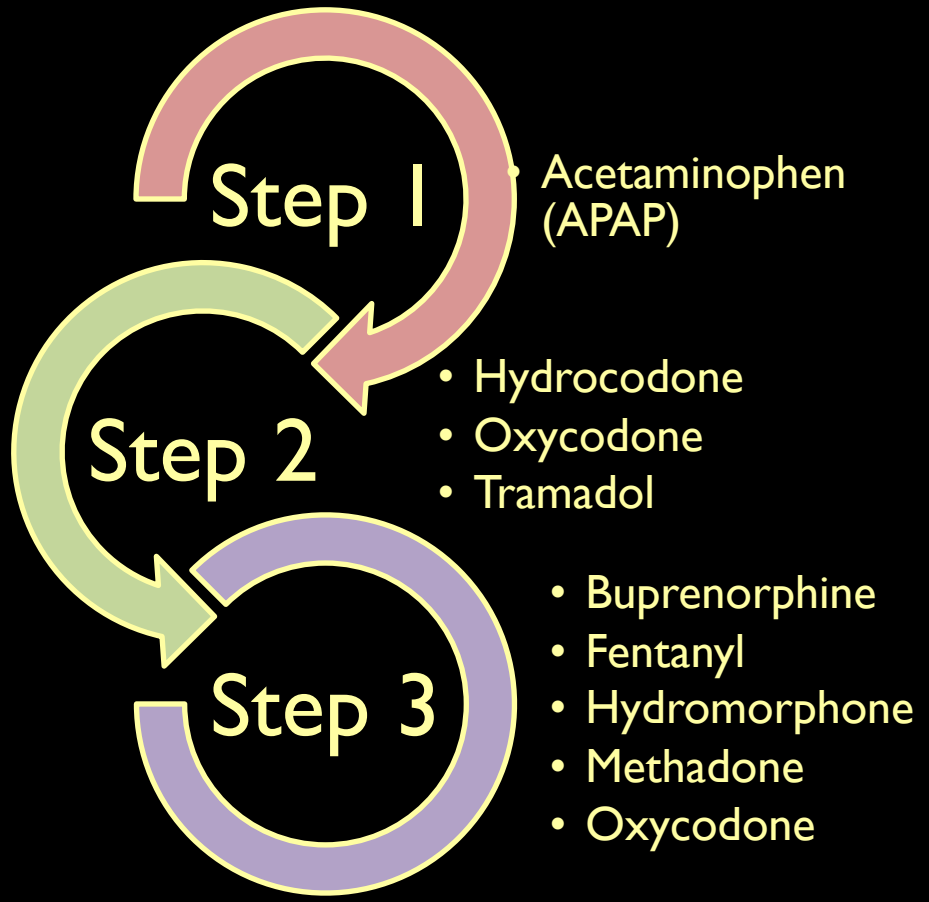
Belbuca package insert. Raleigh, NC; BioDelivery Sciences International, Inc: 2019 Dec.
Webster L, Gruener D, Kirby T, Xiang Q, Tzanis E, Finn A. Evaluation of the tolerability of switching patients on chronic full mu-opioid agonist therapy to buccal buprenorphine. Pain Med. 2017;17:899-907.

Considerations for CKD

- Metabolic pathway
- Metabolites
- Route of elimination
- Protein binding

Pham PC, Khaing K, Sievers TM, et al. 2017 update on pain management in patients with chronic kidney disease. Clin Kidney J. 2017;10(5):688-697.

Adapted WHO Pain Ladder



Barakzoy AS, Moss AH. Efficacy of the World Health Organization analgesic ladder to treat pain in end-stage renal disease. J Am Soc Nephrol. 2006;17:3198-3203.
Raina R, Krishnappa, Gupta M. Management of pain in end-stage renal disease patients: short review. Hemodialysis Internat. 2018;22:290-296.

Pain Medications in CKD/ESRD

*Exceptions: Stage 4 or 5 CKD and if dialysis is interrupted/stopped

Recommended	Caution	Avoid
Acetaminophen	Hydrocodone	Codeine
Buprenorphine	Oxycodone	Meperidine
Fentanyl	Tramadol	Morphine
Gabapentin/Pregabalin		Nonsteroidal anti-inflammatory drugs (NSAIDs)
Hydromorphone*		
Methadone		

Coalition for Supportive Care of Kidney Patients. Treating pain in advanced CKD and dialysis patients: clinical algorithm and preferred medications. 2016. Available at: https://www.kidneysupportivecare.org/pain-symptom-management/#:~:text=Treating%20Pain%20in%20Late%20Stage%20CKD%20%26%20Dialysis,to%20assist%20clinicians%20managing%20pain%20in%20dialysis%20patients. Accessed 25 July 2020.
Raina R, Krishnappa, Gupta M. Management of pain in end-stage renal disease patients: short review. Hemodialysis Internat. 2018;22:290-296.

Opioids to Avoid in CKD

Codeine

- Not recommended in CKD
- Renal clearance 90%
- Accumulation of metabolites can lead to respiratory depression

Meperidine

- Contraindicated in CKD due to accumulation of neurotoxic metabolites

Morphine

- Avoid CrCl < 30 mL/min and dialysis
- Accumulation of neurotoxic metabolites

Pham PC, Khaing K, Sievers TM, et al. 2017 update on pain management in patients with chronic kidney disease. Clin Kidney J. 2017;10(5):688-697.

Opioids for Use in CKD

Buprenorphine

- Hepatically metabolized to norbuprenorphine that has weak effect
- Renal clearance of parent and metabolites = 30%
- Safe for advanced CKD
- No dose adjustments needed
- Likely not dialyzed

Fentanyl

- Metabolized by CYP3A4 to inactive metabolites
- 75% eliminated in urine
- Impact of dialysis?
- Not dialyzed

Methadone

- Minimal accumulation
- Hepatic metabolism and elimination
- 20% eliminated by kidneys
- Compensation in ESRD through biliary-fecal elimination
- No dose adjustment in CKD needed
- Not routinely dialyzed
- Essentially kinetics similar in CKD compared to healthy patients
- Reserve for pain specialists

Pham PC, Khaing K, Sievers TM, et al. 2017 update on pain management in patients with chronic kidney disease. Clin Kidney J. 2017;10(5):688-697.
Atkinson TJ, Fudin J, Wegrzyn EL, Bettinger JJ. Dialysis, opioids, and pain management: where's the evidcenc. Practical Pain Management. 2014;14(8):49-57
Owsiany MT, Hawley CE, Triantafylidis Lk, Paik JM. Opioid management in older adults with chronic kidney disease: a review. Drugs. 2018;78:1459-1479.
Dean M. Opioids in renal failure and dialysis patients. J Pain Symptom Manage. 2004;28(5):497-504

Case #1 - Revisited

Opioid

- No change and monitor
  - Document risks and benefits
- Taper off opioids
  - Reduce my 15 mg/day qmonth or longer
- Convert to buprenorphine product
  - Patch: taper to morphine SA 15 mg PO BID by reducing in 15 mg/day increments THEN buprenorphine patch 10 mcg/hr qweek
  - Buccal: convert to 150 mcg q12h

Nonopioid

- Gabapentin
  - Requires renal dose adjustment to 600 mg PO BID (max 1400 mg/day in 2 divided doses)
- Future nonopioid options
  - Switch gabapentin to pregabalin
    - Max dose 300 mg/day in 2 or 3 divided doses
  - Trial duloxetine
    - Monitor for hypoglycemia, hypertension
    - Monitor renal function and avoid if CrCl < 30 mL/min
  - Topicals: capsaicin or lidocaine

Nonpharmacological

- Pulmonary rehabilitation
- Diabetes education
- Repeat sleep study
- Dietitian referral
- Physical therapy referral
- Interdisciplinary pain program
- Integrated health and wellness (acupuncture, tai chi, yoga, mediation)

Substance Use Disorder

Case #2 – Complicated by:

Case #2

- Ms. Wilson is a 75 YOF admitted for intractable hip pain s/p fall 2 days ago. Imaging confirms hip fracture requiring total hip replacement.

- PMH significant for:
  - AUD (currently following in SA outpt program), Remote h/o opioid abuse, PTSD, Nicotine dependence
  - HTN, Atrial fibrillation (currently on LTOC) , COPD, GERD
  - OA bilateral knees, Low back pain, Post-laminectomy syndrome
- Active outpt medications:
  - **Acetaminophen 500mg PO QID PRN pain**
  - Albuterol inhaler, Fluticasone/salmeterol inhaler
  - **Diclofenac gel – apply QID PRN knee pain**
  - **Duloxetine 60mg PO daily**
  - **Lidocaine 5% patch – apply daily for back pain**
  - Lisinopril 10mg PO daily
  - **Naltrexone 380mg IM injection Q4 weeks (last dose 2 weeks ago)**
  - Omeprazole 20mg PO QAM
  - Prazosin 2mg PO QHS
  - Warfarin (INR goal 2-3) (last administered last night)

1. For elective surgery, what is appropriate procedure for management of oral and long-acting injectable naltrexone?
2. For emergent surgery, what is appropriate procedure for long-acting injectable naltrexone?
3. What are some options for non-opioid pain management?
4. Appropriate opioid pain management plan?
5. As part of the discharge planning process, what risk mitigation strategies can be recommended?

Perioperative Pain Management in Patients with History of SUD

- Pain History
- Physical Exam
- Medication Reconciliation
- Physical Comorbidities
- Psychiatric Comorbidities
- Labs
- PDMP query

Chou R, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57.

Pre-surgical and Post-surgical Considerations for Managing Pain – APS Guidelines

Nonpharmacological Therapies

- Systemic Pharmacologic therapies
- Peripheral, Regional, and Neuraxial Analgesic Therapies
- Local, intra-articular, and topical therapies

Chou R, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016 Feb;17(2):131-57.

Perioperative Planning Considerations

- Stability of regimen
- Dosing regimen
- Buprenorphine formulation
- Severity of postsurgical pain
- Length of hospital stay
- Length of planned recovery
- Discharge plans

Low Severity Risk for Pain	Intermediate or Moderate Severity Risk for Pain	**High Severity Risk for Pain (Opioid Requirement)**
• Tooth extraction • Endoscopy • Arthroscopy • Colonoscopy • Bronchoscopy	• Laparoscopic procedures • Thoracoscopic procedures • Arthroscopic procedures • Neurosurgical procedures	• **Open intra-abdominal surgery** • **Open intra-thoracic surgery** • **Orthopedic procedures**

1. *Perioperative Pain Management Guidance for Patients on Chronic Buprenorphine Therapy Undergoing Elective or Emergent Procedure Supplemental Information*. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; April 2019.
2. *Perioperative Pain Management Guidance for Patients on Chronic Buprenorphine Therapy for Opioid Use Disorder Undergoing Elective or Emergent Procedures Buprenorphine for Opioid Use Disorder*. Washington, DC: Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives, Veterans Health Administration, Department of Veterans Affairs; March 2019.

AUD and Perioperative Care

If patient is undergoing elective surgery, what is the appropriate management of oral and long-acting injectable naltrexone?

- Stop naltrexone pre-surgery, consider initiating IR opioid for acute pain
  - >72 hrs for tablet
  - >4 weeks for injection (consider conversion to tablet to limit relapse)
- When naltrexone is no longer occupying the receptors, due to opioid receptor upregulation, patient may be more sensitive to opioids
- Patients who have been treated with naltrexone may respond to lower doses of opioids than previously used

Given need for emergent surgery at this time, what is appropriate procedure for long-acting injectable naltrexone?

- Synopsis of package insert guidance on the reversal of injectable naltrexone:
  - If opioid therapy is required as part of anesthesia or analgesia, patients should be continuously monitored in an anesthesia care setting by appropriately trained staff in a setting equipped and staffed for cardiopulmonary resuscitation
  - Reference Vivitrol Emergency Pain Management Card

1. Ward EN, Quaye AN, Wilens TE. Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018 Aug;127(2):539-547.
2. Alford, Daniel. Managing Acute and Chronic Pain with Opioid Analgesics in Patients on Medication Assisted Treatment (MAT). PCSS MAT Training. Last accessed 2/12/20.
3. Alkermes, Inc. (2019). *Vivitrol: package insert*. Waltham, MA. Rev. 9/2019. Last accessed 2/5/20.

AUD and Perioperative Care

Re-initiation of naltrexone - PCSS

- Oral can be restarted 3-6 days after last dose of IR opioid, 7-10 days after last dose of methadone
- Injectable can be restarted 3-4 weeks after the last dose of opioids and scheduled regularly for Q3-4 weeks

Re-initiation of naltrexone – package insert

- Injectable candidates should be opioid free for at least 7-14 days before starting therapy
- Oral candidates should be opioid free for at least 7-10 days (IR opioid), 7-14 days for buprenorphine or methadone

1. Alkermes, Inc. (2019). *Vivitrol: package insert*. Waltham, MA. Rev. 9/2019. Last accessed 2/5/20.
2. Mirante, Brian and Wyatt, Stephen. The naltrexone conundrum: Naltrexone's impact on pain management in the perioperative period. PCSS MAT Training. Last accessed 2/5/20.
3. Duramed Pharmaceuticals, Inc. (2013). *Revia: package insert*. Pomiona, NY. Last accessed 2/13/20.

Case #2 - Revisited

What are some options for non-opioid pain management modalities?

- Gabapentinoid vs. topiramate
- Increase acetaminophen dose
- Oral NSAID – avoid due to LTOC

- Appropriate opioid pain management plan?
  - Consult anesthesia
  - Avoid ER/LA opioids
  - IV opioid initially with transition to PO opioid
  - Increased sensitivity to opioids off naltrexone
  - Monitor for opioid withdrawal symptoms
  - Assess need for bowel regimen
  - Taper opioid while inpatient in preparation for discharge planning

Case #2 - Revisited

- As part of the discharge planning process, what risk mitigation strategies can be recommended?
  - OEND – naloxone education and kit distribution
  - Addiction Recovery Services clinic f/u appt
    - Skip next naltrexone injection depending on post-op treatment plan?
  - Orthopedic surgeon f/u appt
  - Ongoing pain management in the setting of physical therapy
  - Regular UDT, limiting days supply of opioids while prescribed
  - Tobacco cessation counseling/medications