What’s New in Pain and Palliative Care Medications?

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Objectives

- List new medications used to treat pain and non-pain symptoms approved by the FDA in 2014. For each drug the participant will be able to describe approved indications, common adverse effects and drug interactions.
- For each new pain/palliative care medication approved in 2014, describe the burden-to-benefit ratio and the role of the medication in caring for patients with pain or advanced illness.
- Analyze important drug alerts and news items and their relevance to drug therapies commonly used in hospice and palliative care patients.

Akynzeo (netupitant/palonosetron)

- Netupitant – selective antagonist of human substance P/neurokinin 1 (NK1) receptors (300 mg)
- Palonosetron – 5HT3 receptor antagonist (0.5 mg)
- Delayed emesis – largely associated with the activation of the tachykinin family NK1 receptors
  - Broadly distribute in the central and peripheral nervous systems
- Cisplatin-based chemotherapy regimens
- ~$500/capsule

<table>
<thead>
<tr>
<th></th>
<th>Netupitant + palonosetron</th>
<th>Palonosetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (no emetic episode and no use of rescue medication for the 25-120 hour period)</td>
<td>90.4%</td>
<td>80.1%</td>
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<tr>
<td>Complete response to the 0-24 hours interval (acute phase)</td>
<td>98.5%</td>
<td>89.7%</td>
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<tr>
<td>Complete response within 120 hours (overall phase)</td>
<td>89.6%</td>
<td>76.5%</td>
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- 1 capsule about 1 hour prior to chemo with oral dexamethasone 12 mg given 30 minutes before chemo
- Dexamethasone 8 mg po daily on Days 2-4 (with cisplatin-based)
Hetlioz (Tasimelteon)

- Melatonin receptor agonist indicated for the treatment of non-24-hour sleep-wake disorder in individuals who are totally blind.
- High affinity for MT1 and MT2 receptors in the suprachiasmatic nucleus of the brain; MT1 and MT2 are thought to synchronize the body’s melatonin and cortisol circadian rhythms with the day-night cycle in patients with non-24 hour disorder.
- In totally blind persons, the absence of light permits the circadian cycle to run longer than 24 hours.

Hetlioz (Tasimelteon)

- Dose: 20 mg/day PO taken before bedtime at the same time every night (do not take with food)
- Efficacy – mean total nighttime sleep was 28 minutes longer (on average; range 7-74 minutes)
- Adverse effects
  - Headache (17%)
  - Elevated transaminases (10%)
  - Nightmares or unusual dreams (10%)
- Do not use in severe hepatic impairment (Child-Pugh C)
- No dose adjustment needed in renal impairment

Hetlioz (Tasimelteon)

- Metabolized by 1A2, 3A4
  - Avoid concomitant strong 1A2 inhibitors (e.g., fluvoxamine)
  - Avoid strong 3A4 inhibitors (e.g., ketoconazole)
  - Avoid strong 3A4 inducers (e.g., rifampin)
  - Tasimelteon exposure decreased by smoking (induction of 1A2 levels)
  - Additive effect with alcohol
- 90% protein bound; elimination primarily renal
- Cost for 30 capsules is $7,020

Belsomra (Suvorexant)

- Orexin antagonist indicated for insomnia characterized by difficulties with sleep onset and/or sleep maintenance.
- Orexin, also called hypocretin, is a neurotransmitter that regulates arousal, wakefulness and appetite.
- The orexin neuropeptide signaling system is a central promotor of wakefulness
- Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R are thought to suppress wake drive
**Belsomra (Suvorexant)**

- Denotes first approved within a pharmacologic drug class.
- Dose: 10 mg po taken no more than once per night and within 30 min of going to bed, with at least 7 hr remaining before the planned time of awakening
- May increase to 20 mg; no benefit increasing to 30-40 mg po qd
  - 5 mg with 3A4 inhibitor (max 10 mg)
- Efficacy demonstrated objectively (polysomnography) and subjectively (patient reported sleep latency)
- $300/month

**Belsomra (Suvorexant)**

- Adverse effect
  - Somnolence, headache, dizziness, CNS depression
  - Daytime impairment, sleep paralysis, hallucinations
  - Complex sleep related behaviors (e.g., sleep-driving)
- Monitoring
  - Somnolence, CNS depression (DC with daytime somnolence)
  - Worsening insomnia or abnormal thinking and behavioral changes; complex sleep related behaviors
  - Suicidal ideations
  - Compromised respiratory function
- Drug interactions – alcohol, 3A4 inhibitors, CNS depressants

**Memantine/Donepezil (Namzaric) Combo**

- FDA approved fixed-dose combination of memantine XR and donepezil
- For moderate to severe Alzheimer’s related dementia in patients receiving stable doses of the two drugs
- Once-daily capsule
  - 28/10 (memantine/donepezil)
  - 14/10 (memantine/donepezil) for severe renal impairment

**Let’s “Wake” You Up!**

- Which of the following medications is indicated for non-24-sleep wake disorder in people who are totally blind?
  A. Belsomra (Suvorexant)
  B. Hetlioz (Tasimelteon)
  C. Memantine/donepezil combination (Namzaric)
  D. None of the above
Ionsys

- Used for the management of acute pain, in hospitalized patients.
- Patient-controlled iontophoretic transdermal system providing on-demand systemic delivery of fentanyl, an opioid agonist, for up to 24 hours or a maximum of 80 doses, whichever comes first.
- 40 mcg/activation

FDA Definitions of Abuse-Deterrent Formulations

- Physical/chemical barriers
  - Physical barriers prevent chewing, crushing, cutting, grating or grinding.
  - Chemical barriers can resist extraction of the opioid using common solvents such as water, alcohol, or other organic solvents
- Agonist/antagonist combinations
  - Opioid antagonist (e.g., naloxone) can interfere with, reduce or defeat the euphoria associated with abuse.
  - Antagonist can be sequestered and released only upon manipulation of the product

Practical Pain Management, August 2014, p. 15

FDA Definitions of Abuse-Deterrent Formulations

- Aversion
  - Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed is used
- Delivery system (including depot injectable formulations and implants)
  - Certain drug-release designs or the method of drug delivery can offer resistance to abuse.
  - Sustained-release depot injectable formulations administered as IM or SC implants can be more difficult to manipulate.

FDA Definitions of Abuse-Deterrent Formulations

- Prodrug
  - A prodrug that lacks opioid activity until transformed in the gastrointestinal tract can be unattractive for IV or intranasal routes of abuse
- Combination
  - Two or more of the above methods can be combined to deter abuse.

Practical Pain Management, August 2014, p. 15
Targiniq ER

- Oxycodone/naloxone, controlled release
- For management of chronic pain - severe enough to require daily, around-the-clock, long-term opioid treatment, in whom other treatment methods were unsuccessful
- NOT a “prn” analgesic
- Abuse-deterrent
  - When crushed and snorted, or crushed, dissolved and injected – naloxone blocks euphoric effects of oxycodone
  - Taking excessive doses orally still may occur

Targiniq ER

- Available as:
  - Supplied as 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg tablets for oral administration.
  - The tablet strengths, a 2:1 ratio in each, describe the amount of oxycodone and naloxone per tablet as the hydrochloride salts, respectively
- One tablet every 12 hours

Xartemis

- Bilayer combination – IR and ER oxycodone plus acetaminophen for acute pain in patients > 18 years old
- One tablet = 7.5 mg oxycodone/325 mg acetaminophen
- Dose: 2 tablets every 12 hours for 48 hours
- 3.75 mg oxy/325 mg aceta are immediate release
- 11.25 mg oxy/325 mg aceta are extended release over 12 hours
- Labeling does not include “abuse-deterrent” language, but sponsor will be working with FDA to characterize “abuse-deterrent features”
- $128.80 for 14 days


Hysingla ER

- Extended-release hydrocodone with abuse deterrent characteristics
- HY (hydrocodone bitartrate)
- SING (single entity)
- LA (long-acting)
- Available as 20, 30, 40, 60, 80, 100, 120 mg
  - “A proprietary extended-release solid oral dosage platform that uses a unique combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions.”
  - Deters chewing, injecting or snorting product

1 month supply:
- 20 mg - $230
- 120 mg - $1100
Zohydro ER

- Abuse-deterrent formulations get FDA nod
- Original formulation was approved by the FDA for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which no alternative treatment options are adequate.
- Abuse-deterrent technology – BeadTek – utilizes excipients that immediately form a viscous gel when crushed and dissolved in liquids or solvents
- Will transition to new formulation in second quarter of 2015.

Zohydro® ER with BeadTek™

- Multi-particulate formulation of coated carrier beads in hard gelatin capsules
- Additional beads containing polyethylene oxide (inert)

BeadTek™ Technology

- PEO beads are inactive when used as indicated
- When crushed and dissolved in liquids or solvents, the PEO is designed to form a viscous gel

Peripheral Opioid Antagonists

Block peripheral effects of opioids (mu antagonist) without crossing blood-brain barrier to reverse centrally mediated analgesia

- Methylnaltrexone (Relistor) - SC
- Alvimopan (Enterog) - PO
- Naloxegol (Movantik) - PO
Naloxegol (Movantik)

- Pegylated opioid antagonist (peripherally active mu opioid receptor antagonist – PAMORA)
- Naloxegol is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.
- Naloxegol is an antagonist of opioid binding at the mu-opioid receptor. When administered at the recommended dose levels, naloxegol functions as a peripherally acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids.

Naloxegol (Movantik)

- First orally administered PAMORA for OIC
- Dosing
  - DC all maintenance laxative therapies (can resume after 3 days if suboptimal response to naloxegol)
  - 25 mg po qd 1 hour before or 2 hours after first meal of the day (take in AM)
  - May reduce to 12.5 mg if not tolerated, or if taken with 3A4 inhibitors
- Serious adverse effects-opioid withdrawal (1-3% patients)

Naloxon (Movantik)

- Warnings/precautions
  - Risk of GI perforation in those with conditions associated with reduction in structural integrity of GI tract wall (e.g., PUD, diverticular disease, infiltrative GI tract malignancies, peritoneal mets)
  - Monitor for worsening GI pain; DC
  - Monitor for opioid withdrawal
- Adverse effects
  - Abdominal pain, diarrhea, nausea, flatulence, vomiting, headache, hyperhidrosis
- $500/month (25 mg po qd)

Naloxone

- Naloxone – semisynthetic derivative of thebaine, competitive antagonist at opioid receptors in the brain
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within
  - 1-2 minutes after IV administration
  - 2-5 minutes after IM or SC administration
- Half-life is 30-80 minutes; protective effect may wear off in 45 minutes after IV administration of a low dose
Naloxone

- **Dosing**
  - Naloxone hydrochloride 0.4 and 1 mg/ml solution for IV, IM or SC administration
  - Dose: 0.4-2 mg IV for adults
    - Can repeat every 2-3 minutes up to a total of 10 mg
  - Naloxone can be administered intranasally using a mucosal atomizer device
    - Syringe attached to a spray tip that fragments the medication into a fine mist
    - Dose is 2 mg (1 mg per nostril) which can be repeated in 3-5 minutes

Evzio (Naloxone)

- Opioid antagonist for IM or SC injection
  - 0.4 mg/0.4 ml; prefilled autoinjector
    - Electronic voice instruction system
  - Indicated for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression
  - Dose
    - < 1 year old: Pinch thigh muscle while administering; monitor injection site for residual needle parts
    - > 1 year old: Inject IM or SC into the anterolateral aspect of thigh (through clothing ok)
    - May give additional doses every 2-3 minutes until desired response or emergency medical assistance available

- **Adverse**
  - Post-op: nausea, vomiting, hypotension, tachycardia, edema
  - Also, needle retracted: pruritus, urticaria, post-op: respiratory depression
Honorable Mention

- **Obredon (hydrocodone/guaifenesin)**
  - New combination antitussive/expectorant
  - Hydrocodone 2.5 mg and guaifenesin 200 mg/5 ml
  - 18 years and older for symptomatic relief of cough and to loosen mucus associated with the common cold

- **Dyloject (diclofenac sodium) Injection**
  - Management of mild to moderate pain in adults and for moderate to severe pain alone or in combination with opioids
  - 15-30 minutes to administer full dose
  - 37.5 or 50 mg in acute post-operative pain

Rescheduling

- **Hydrocodone products rescheduled as CII**
- **Tramadol scheduled as CIV**
  - “weaker” opioid
  - Dual mechanism analgesic
  - Lowers seizure threshold
  - Serotonin syndrome
  - Hypoglycemia

I’ll take the combo to go...

- Nortriptyline-morphine compared to each as monotherapy
- Patients randomized 1:1:1
  - Average baseline pain rating 5.3
  - Combination morphine + nortriptyline pain rating 2.6
  - Nortriptyline alone 3.1
  - Morphine alone 3.4
- Brief pain inventory scores lower for combination

Acetaminophen Update

- **Meta analysis – 13 randomized trials on low back pain or hip or knee osteoarthritis**
- **Results showed acetaminophen is ineffective in low back pain, and provides minimal short term benefit for osteoarthritis.** (Machado GC et al. BMJ 2015;350:h1225)
- **Previously undocumented side effect of acetaminophen – diminishes intensity of positive and negative emotions.** (Durso et al. Psychol Sci 2015 Apr 10)

Gilron I. Pain March 5, 2015
Goals of Medication Management in Advanced Illness

• Provide quality care
  – Select medications based on patient- and drug-related variables
  – Achieve the therapeutic goal
  – Prevent adverse effects
• Conform to standards of practice
• Guided by evidence based when applicable
• Cost effective drug therapy
  – Cost of medication and monitoring

Prescribing Continuum

• Drug therapy initiation
• Dosage titration
• Changing/adding drugs
• Switching or stopping drugs

The Process of Deprescribing

• Deprescribing – “the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient’s care goals, current level of functioning, life expectancy, values and preferences.”
• Positive, patient-centered intervention with inherent uncertainties
• Requires shared decision-making, informed patient consent and close monitoring of effects
  – The same as when starting medications
The Process of Deprescribing

1. Ascertain that all drugs the patient is currently taking and the reasons for each one.
2. Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention.
3. Assess each drug for its eligibility to be discontinued.
4. Prioritize drugs for discontinuation.
5. Implement and monitor drug discontinuation regimen

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Step 1

- Ascertain that all drugs the patient is currently taking and the reasons for each one.
- Defined by the Joint Commission as:
  - "The process of comparing a patient’s medication orders to all of the medications that the patient has been taking. This reconciliation is done to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions. It should be done at every transition of care in which new medications are ordered or existing orders are rewritten. Transitions in care include changes in setting, service, practitioner or level of care.”

http://www.ihs.gov/ehr/index.cfm?module=medication_reconciliation

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Step 2

- Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention.

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Step 2

- Ascertain and assess risk according to:
  - Drug factors (number of drugs – single most important predictor)
  - Use of “high risk” drugs
    - Opioids, benzodiazepines, psychotropic drugs, NSAIDs, anticoagulants, digoxin, cardiovascular drugs, hypoglycemic agents, anticholinergic agents; NSAID + diuretic; ACE inhibitor and CKD
  - Patient factors
    - Age > 80 years old, cognitive impairment, multiple comorbidities, substance abuse, multiple prescribers, past or current nonadherence

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Step 3

• Assess each drug for its eligibility to be discontinued
  – No valid indication (drug use without indication)
  – Part of a prescribing cascade (drug-induced adverse effects)
  – Actual or potential harm of a drug > potential benefit (inappropriate drug therapy)
  – Disease and/or symptom control is ineffective or symptoms have completed resolved
  – Preventive drug is unlikely to confer any patient-important benefit over the patient’s remaining lifespan
  – Drugs are imposing unacceptable treatment burden (drug-induced adverse effects)

Say what?

• MJ is a 74 year old man admitted to hospice with an admitting diagnosis of end-stage lung cancer. His prognosis is less than 2 months. He has no active comorbid conditions except hypothyroidism.

• Which of the following medications would you feel comfortable stopping at this time?
  A. Atorvastatin
  B. Oral morphine long-acting tablets
  C. Oral morphine solution
  D. Senna
  E. Levothyroxine

Drugs are rarely indicated if they do not confer a

Patient Important Outcome

Un-useful Medications

• Unlikely to provide benefit
  – Medications for dementia in advanced disease
  – Riluzole for advanced ALS
  – Antimicrobial therapy

• Primary or secondary prevention
  – Dyslipidemia
  – Bisphosphonates

• Burden exceeds benefit
  – Anticoagulation
Step 4

- Prioritize drugs for discontinuation
- Deciding the order of discontinuation of drugs may depending on integrating 3 pragmatic criteria:
  - Those with the greater harm and least benefit
  - Those easiest to discontinue
    - Lowest likelihood of withdrawal reactions or disease rebound
  - Those that the patient is most willing to discontinue first
    - To gain buy-in to deprescribe other drugs
- Suggested approach is to rank drugs from high harm/low benefit to low harm/high benefit and discontinue the former in sequential order

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Step 5

- Implement and monitor drug discontinuation regimen
- Explain and agree with patient/caregiver on management plan
- Cease 1 drug at a time so that harms (withdrawal reactions or return of disease) and benefits (resolution of adverse drug effects) can be attributed to specific drugs and rectified if necessary
- Wean patients off drugs more likely to cause adverse withdrawal effects, instruct patient/caregiver what to look for and report in the event of such effects occurring, and what actions they can self-initiate if these occur
- Communicate plan to all HCP; document reasons for and outcomes of deprescribing

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Mrs. D.

- Slim Caucasian 82 yo woman admitted to hospice with a diagnosis of Alzheimer’s disease (FAST 7D).
- Lives with daughter, primary caregiver.
- Daughter tells you Mom can be somewhat combative, particularly when she takes her medication
  - Patient frequently has dry heaves after daughter wrestles her into taking her meds
- Patient naps frequently during the day, doesn’t want to go to bed at night, or remain in bed during the night.

Mrs. D.

- Daughter gives the patient “Simply Sleep” (diphenhydramine 25 mg), two tablets at bedtime
  - Doesn’t seem to be helping
  - In fact, seems to make patient a bit more agitated
- Patient had a stroke 3 years ago with some left-sided weakness and residual physical discomfort.
- Patient has never had an MI, and she’s been taking alendronate for bone health for about 6 years.
Mrs. D's Medication History

<table>
<thead>
<tr>
<th>Start date</th>
<th>Medication</th>
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<tbody>
<tr>
<td>6 years ago</td>
<td>Alendronate (Fosamax) 5 mg po once daily</td>
</tr>
<tr>
<td>4 years ago</td>
<td>Donepezil (Aricept) 23 mg once daily</td>
</tr>
<tr>
<td>6 months ago</td>
<td>Methadone 2.5 mg po q12h</td>
</tr>
<tr>
<td>6 months ago</td>
<td>Morphine oral solution, 5 mg po q2h prn additional pain (uses one dose about three times a week)</td>
</tr>
<tr>
<td>6 months ago</td>
<td>Senna, one or two tablets daily</td>
</tr>
<tr>
<td>3 years ago</td>
<td>Atorvastatin (Lipitor) 20 mg po qd</td>
</tr>
<tr>
<td>5 years ago</td>
<td>Multivitamin with iron daily</td>
</tr>
<tr>
<td>2 months ago</td>
<td>Simply Sleep (diphenhydramine 25 mg), 2 tablets at bedtime</td>
</tr>
</tbody>
</table>

Mrs. D.

- Drug factors?
  - Number of drugs
  - Use of “high risk” drugs
  - Past or current drug toxicity
- Patient factors?
  - Age > 80 years old
  - Cognitive impairment
  - Multiple comorbidities
  - Substance abuse
  - Multiple prescribers
  - Nonadherence

Mrs. D. – Prioritize Discontinuing Medications

1. Diphenhydramine
2. Donepezil
3. MVI
4. Alendronate
5. Atorvastatin
6. Senna
7. Morphine
8. Methadone
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