Symptom Management Jeopardy

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May 2025

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Opioid-Induced Constipation (OIC)

- Opioid receptors are throughout the digestive tract; influence motility, fluid absorption, sphincter tone
- OIC can occur with any opioid use, even when opioid is being used for dyspnea
- OIC occurs in 40%-80% of patients on opioids
- Patients do not become tolerant to this effect

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Opioid-Induced Constipation (OIC)

- Increasing fiber does not help most hospice patients
- Docusate (Colace®) generally not helpful
- Requires use of osmotic or stimulant laxative (Miralax® or senna/bisacodyl)
- Worsened by use of ondansetron, calcium channel blockers, anticholinergics, iron, calcium, anticonvulsants, antidepressants, diuretics, muscle relaxants, others
- Transdermal buprenorphine is associated with a lower risk of OIC as it bypasses the gastrointestinal tract and first-pass metabolism

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Dyspnea

- Pulse ox does NOT always correlate with the subjective complaint of shortness of breath
- Opioids are first line treatment; anxiolytics are add-on for anxiety component; anxiolytics alone not beneficial
- Nebulized morphine is NOT more beneficial for dyspnea; use oral/parenteral forms unless patient unable to take/tolerate

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MDI Drug Deposition in the Lungs

Published lung deposition rates

Accuhaler®	**7.6%**
Aerolizer®	**13%–20%**
Breezhaler®	**26.8%–39%**
Easyhaler®	**18.5%–31%**
Genuair®	**30.1%–51.1%**
Handihaler®	**9.8%–46.7%**
Ingelheim inhaler®	**16%–59%**
NEXThaler®	**39.4%–56%**
Spinhaler®	**11.5%**
Turbuhaler®	**14.2%–69.3%**
Twisthaler®	**36%–37%**

Rate increases to 11%–68% with the addition of a valved holding chamber or spacer

Baloira A, et al. Lung Deposition and Inspiratory Flow Rate in Patients with Chronic Obstructive Pulmonary Disease Using Different Inhalation Devices: A Systematic Literature Review and Expert Opinion. Int J Chron Obstruct Pulmon Dis. 2021 Apr 19;16:1021-1033. doi: 10.2147/COPD.S297980.

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Dry Powder Inhalers (DPIs)

- Most DPIs require a high inspiratory flow to overcome the device's resistance and to achieve effective drug delivery.
- The inspiratory airflow generated by the patient represents the only active force that can produce the disaggregation of the powdered drug for inhalation.
- Many patients with COPD, especially those with severe COPD (but also many patients with less severe disease), might not achieve the required inspiratory flow.
- Thus, DPIs might not be the best option when the required inspiratory rate cannot be assured.

- Albuterol sulfate (ProAir Digihaler, ProAir RespiClick)
- Aclidinium (Tudorza Pressair)
- Fluticasone furoate (Arnuity Ellipta)
- Fluticasone propionate (Flovent Diskus, ArmonAir Digihaler)
- Fluticasone propionate/salmeterol (Advair Diskus, Airduo Digihaler, Wixela Inhub)
- Fluticasone furoate/vilanterol (Breo Ellipta)
- Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)
- Mometasone (Asmanex Twisthaler)
- Umeclidinium (Incruse Ellipta)
- Umeclidinium bromide/vilanterol (Anoro Ellipta)
- Budesonide (Pulmicort Flexhaler)
- Budesonide/formoterol (Symbicort, Breyna)
- Tiotropium (Spiriva HandiHaler)

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Patient QOL: Nebulized Meds

Surveys of patient-reported symptom control, quality of life, and device preference with nebulizers vs. inhalers

First author, year	Study type	Sample size	Study findings
Barta, 2002 [46]	Patient survey (via postal questionnaire)	82 with COPD	Approximately 75% of patients reported greater symptom relief with nebulizers than inhalers; 98% reported that the benefits of nebulized therapy outweighed any disadvantages; nebulized treatment at home helped patients feel comfortable and more in charge of their own symptom control; compliance was generally excellent
Sharafkhaneh, 2013 [47]	Telephone survey of randomly selected patients and caregivers	400 patients with COPD and 400 caregivers	Most patients and caregivers (~ 80%) preferred therapy with nebulizer vs. inhalers for controlling symptoms and improving quality of life
Dhand, 2018 [48]	Online survey using the Harris Poll Online panel	254 patients with COPD	54% of patients with COPD preferred nebulizers to other inhalation devices
Hanania, 2018 [49]	Web-based, descriptive, cross-sectional US-based survey	499 with self-reported COPD	Most (35%) patients reported no device preference, whereas 33% preferred pMDIs, 12% preferred nebulizers, 10% preferred SMIs, and 9% preferred DPIs. Patients with more severe symptoms (mMRC score ≥ 2) were most likely to report using a nebulizer

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Inhalers vs. Nebs

- Nebulized medications tend to be a more efficient route of administration for patients with end-stage disease when compared to metered-dose or dry-powder inhalers
- Switching inhaled corticosteroids to oral corticosteroids may provide palliation of additional symptoms including suppressed appetite, inflammatory pain, fatigue, and acute pulmonary exacerbations
- Nebulized albuterol, ipratropium, and albuterol/ipratropium are the most cost-effective inhaler options
- Dexamethasone causes fewer mineralocorticoid effects than prednisone

NHPCO Deprescribing Toolkit, available at https://www.nhpco.org/wp-content/uploads/NHPCO_Deprescribing_Toolkit.pdf

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Opioid Naïve Dosing

- Taking less than 60 mg OME/day for less than a week
- Unintentional overdose may be more likely if opioid therapy is initiated with long-acting opioids (FIVE TIMES MORE LIKELY)
- **Start low and go slow**
- Dose and frequency adjustment may be necessary for the elderly or those with organ dysfunction.

ORAL OPIOID FORMULATION	SUGGESTED INITIAL DOSING FOR OPIOID-NAÏVE
Morphine Immediate-Release	5mg by mouth every 4 hours as needed
Oxycodone Immediate-Release	5mg by mouth every 4 hours as needed
Oxymorphone Immediate-Release	5mg by mouth every 4 hours as needed
Hydromorphone Immediate-Release	2mg by mouth every 4 hours as needed
Methadone	2.5mg by mouth every 8 hours

Miller M, Barber CW, Leatherman S, et al. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy. *JAMA Intern Med.* 2015;175(4):608–615.

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Pain Management: Subcutaneous (SQ) Opioids

- Opioids can be given SQ without access to a vein, at the same dose as IV, to achieve similar blood levels as IV
  - Morphine, hydromorphone, fentanyl can all be safely administered as SQ bolus doses or continuous SQ infusion
  - Methadone SQ infusions have been associated with more frequent local skin irritation; improved with frequent site rotation

PCNOW Fast Fact #28 Subcutaneous Opioid https://www.mypcnow.org/fast-fact/subcutaneous-opioid-infusions/

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Pain Management: Subcutaneous (SQ) Opioids

- SQ bolus injections onset of action around 5 minutes (faster for fentanyl)
- No data to suggest that cachectic, febrile, or hypotensive patients have problems with drug absorption
- Subcutaneous tissue can absorb up to 3 ml/hr
  - At low opioid requirements morphine is generally the drug of choice
  - Switch to hydromorphone for a high opioid requirement since it's more potent (smaller infusion volume)

PCNOW Fast Fact #28 Subcutaneous Opioid https://www.mypcnow.org/fast-fact/subcutaneous-opioid-infusions/

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Pain Management Pearls

- Absorption of fentanyl patches can be increased more than three-fold by heating pads, electric blankets, fever

- Opioids (except methadone, buprenorphine) do not provide much benefit for neuropathic pain

Ashburn, Michael A., et al. "The pharmacokinetics of transdermal fentanyl delivered with and without controlled heat." *The Journal of Pain* 4.6 (2003): 291-297.
Coluzzi, Paul H. "Sublingual morphine: efficacy reviewed." *Journal of pain and symptom management* 16.3 (1998): 184-192.

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Appetite

- Megestrol (Megace®) is approved for anorexia or cachexia associated with AIDS and advanced breast and endometrial cancer; has NOT been shown to provide significant weight gain for most hospice patients
  - Doses studied for appetite range 100-1600 mg daily
  - Has not been shown to increase quality of life
  - Instead, may want to try mirtazapine or prednisone/dexamethasone for increased appetite

Wong, Meagan, et al. "Megestrol for Palliative Care in Patients with Cancer." *American family physician* 101.9 (2020): online-online.

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Anxiety

- Steroids, decongestants, beta blockers, antihistamines, migraine medications, albuterol, caffeine can cause/worsen anxiety
- Opioid/benzodiazepine/alcohol/smoking/other drug withdrawal can cause anxiety
- Antidepressants can help, but often take several weeks
- Buspirone has onset of at least two weeks and cannot be used as-needed

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Medication Causes of Agitation/Delirium

Drug Class	Specific Drug Types	Examples
Anticholinergics	**H_1 receptor blockers** **Anti-Parkinson** **Phenothiazine**	**diphenhydramine, meclizine, hydroxyzine** **benztropine** **promethazine**
Antidepressants	Tricyclics SSRIs	amitriptyline, nortriptyline fluoxetine, paroxetine
Sedative	**Benzodiazepines**	**alprazolam, diazepam, temazepam**
Analgesic	**Opioids**	**codeine, morphine, hydromorphone, fentanyl, tramadol**
Antihypertensive/ antiarrhythmic	Beta blockers ACE inhibitors Calcium channel blockers Other	metoprolol, propranolol lisinopril, captopril amlodipine, nifedipine Digoxin
Antibiotics	Quinolones Macrolides	levofloxacin, ciprofloxacin azithromycin, clarithromycin
Anticonvulsants	Barbiturates	phenobarbital
Steroids	**Corticosteroids**	**dexamethasone, prednisone, prednisolone, methylprednisolone**

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Treating Agitation/Delirium

Antipsychotics

Medication	Initial Dosing
First generation	
Chlorpromazine	25mg PO/IM every 1 hour PRN
Haloperidol	0.5-1mg PO/SL/IM/SC every 1 hour PRN
Second generation	
Olanzapine	2.5mg PO daily
Quetiapine	25mg PO BID
Risperidone	0.5-1mg PO BID
Ziprasidone	20mg PO BID or 10mg IM every 2 hours

- First line for treatment of potentially reversible delirium
- Atypical (second generation) antipsychotics preferred in patients with Parkinson's Disease or neuromuscular disorders (less EPS side effects), but may not work as quickly as 1st generation antipsychotics
- Can use in combination with benzodiazepines if sedation is desired

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American Psychiatric Association. *Am J Psychiatry. 1999;156(5 suppl):1-20.*

Treating Agitation/Delirium

- **Benzodiazepines are mostly ineffective as monotherapy**
- **Benzodiazepines like lorazepam often make delirium WORSE**
    - Paradoxical reactions (excessive movement, increased talking, excitement) to BZDs may occur in older adults and severely ill patients
    - Exception: delirium due to withdrawal (alcohol, BZDs) or severe dyspnea/hypercapnia
- **Addition** of BZD may minimize EPS symptoms associated with antipsychotics and allow for lower doses (lorazepam 0.5 -1 mg PO/SL/IM/IV q 1h prn)

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Giving Medications Per Rectum

- Many tablets can be given rectally; however, the therapeutic effect of tablets is unpredictable
- Extent of absorption and timing of effect can vary greatly
- Insert about a finger's length into the rectum; blunt in inserted first improves retention
- Drugs administered through the rectum, especially opioids, are dosed similarly as when given orally (possible exception for seizure meds)
- 10 ml warm water can be inserted via syringe to assist dissolution of the suppository or suspension
- Keep volume of drug preparation less than 60 ml to avoid spontaneous expulsion before absorption

Opioids	Steroids	NSAIDs/APAP	Anxiolytics	Antipsychotics	Anti-Emetics	Seizure Meds
Morphine **Hydromorphone** Methadone Oxycodone Codeine Tramadol	Dexamethasone Hydrocortisone	**APAP** Diclofenac **Indomethacin** Ibuprofen Naproxen Aspirin	Lorazepam Midazolam Clonazepam Diazepam	Olanzapine Haloperidol Chlorpromazine	Ondansetron Metoclopramide **Prochlorperazine** **Promethazine**	Phenobarbital Levetiracetam Lamotrigine Valproic Acid Carbamazepine Phenytoin

PC NOW Fast Fact #257 Palliative Care Per Rectum available at https://www.mypcnow.org/fast-fact/palliative-care-per-rectum/

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Transmucosal Drug Delivery

- Sublingual, buccal
- Not all drugs will work! Have to be both lipophilic and water soluble; best if high potency
- Instilling volumes more than 2-3 mL will result in leakage out of sublingual space

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High Concentrate Oral Solutions

- Dexamethasone 1 mg/ml
- Prednisone 5 mg/ml
- Methadone 10 mg/ml
- Morphine 20 mg/ml
- Oxycodone 20 mg/ml
- Sertraline 20 mg/ml
- Haloperidol 2 mg/ml
- Lorazepam 2 mg/ml
- Diazepam 5 mg/ml
- Alprazolam 1 mg/ml

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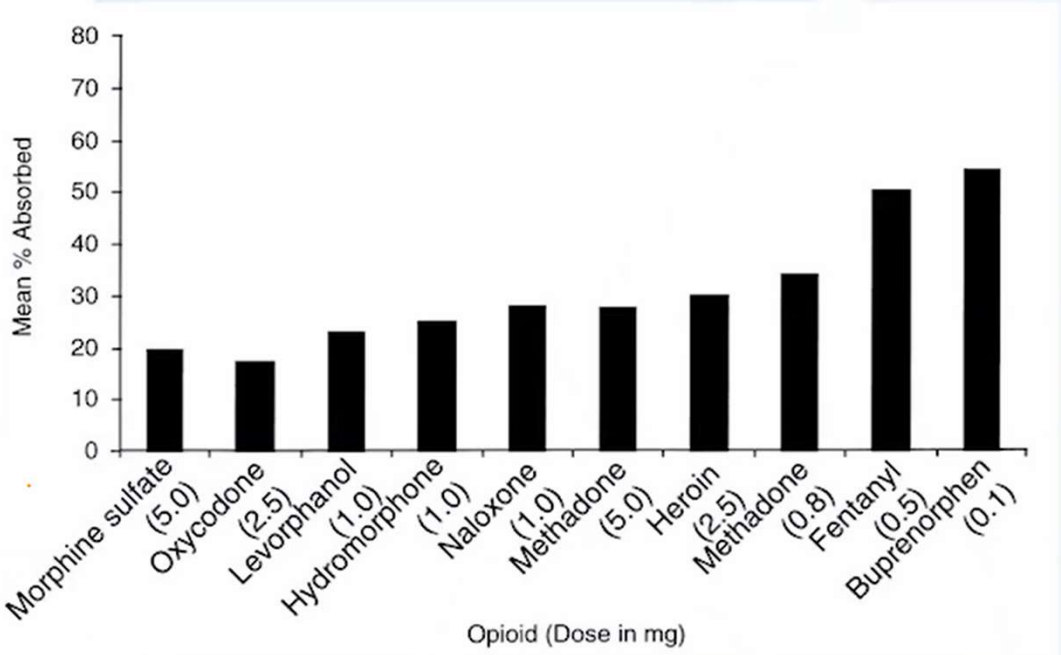
Transmucosal Opioid Absorption

How much actually gets absorbed transmucosally?



Coluzzi. *J Pain Symptom Manage*. 1998;16(3):184-192.

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Transdermal Drug Delivery

- Skin is designed to keep stuff out!
- Just because something can be made into a topical form doesn't mean it's going to be absorbed
- Medications found in ABH/R gel have NOT been found to be absorbed in sufficient quantity to provide clinical benefit

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Dehydration at End of Life

Dehydration is a natural, nonpainful process at end of life which may be a natural analgesic

With less fluid, there is

- Less urine and less need for a tube in their bladder to catch the urine
- Less swelling of the legs and feet (edema)
- Less fluid buildup in the stomach, so less nausea and vomiting
- Less water buildup in the lungs, so fewer breathing problems
- There may also be less noisy breathing that sometimes occurs when a person is dying

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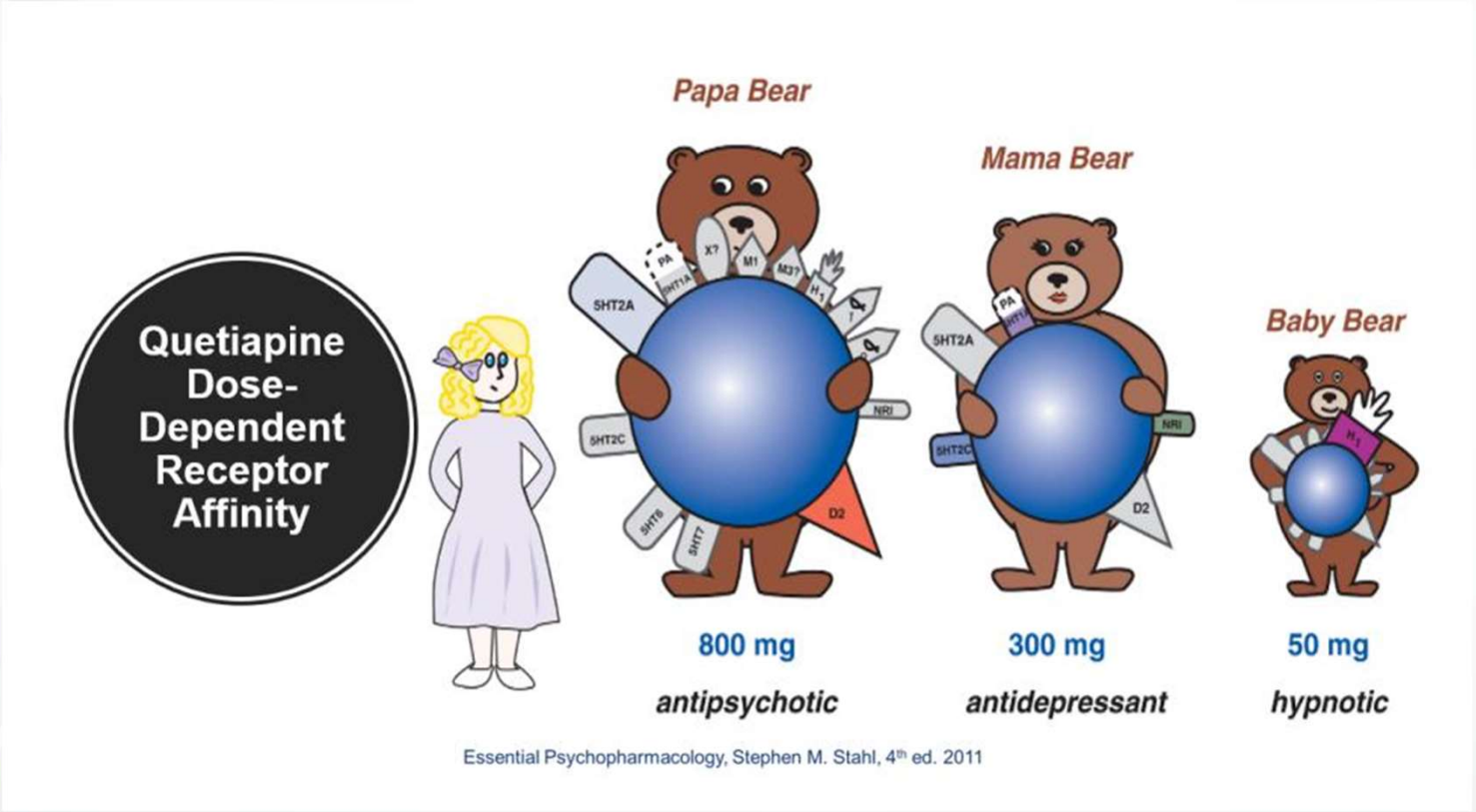
Dose-Dependent Activity



Essential Psychopharmacology, Stephen M. Stahl, 4th ed. 2011

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Questions?
Thanks!

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