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Medication Administration for the Enteral Nutrition Patient:
Some Key Points

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Disclosures

- The speaker has served as a consultant to:
  - American Regent
  - B Braun
  - CAPS
  - Pharmacosmos
  - UpToDate

Objectives

1. Highlight some aspects of the enteral medication process
2. Review the basis for the 'meal effect' and the potential 'EN effect' on medications
3. Describe general enteral medication administration approaches to limit EN-drug interactions

Outline

- The Enteral Medication Process
- Drug-Nutrition Interactions – the Meal Effect
- Enteral Nutrition-Drug Interactions
- Approaches to Patient Care

European Journal of Clinical Pharmacology
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REVIEW

Drug administration via feeding tubes—a procedure that carries risks: systematic identification of critical factors based on commonly administered drugs in a cohort of stroke patients

Jana Sommerfeldt[1] · Hannes Sartorius[1] · Bettina von Sarnowski[2] · Sandra Klein[3] · Christoph A. Ritter[1]

"Feeding tube administration of medications turned out to be a highly complex process with several unmet risks."

Eur J Clin Pharmacol 2024;80(11):1599

The Enteral Medication Process

- Providing medication through a patient's enteral feeding tube seems simple to the uninitiated
- But the improvised preparation and enteral administration of a drug product has significant implications for patient safety
- Clinicians should respect the complexity of drug formulations and their interactions that may otherwise derail expected therapeutic effects

The Enteral Medication Process

Guidance for a Safe Enteral Medication Process

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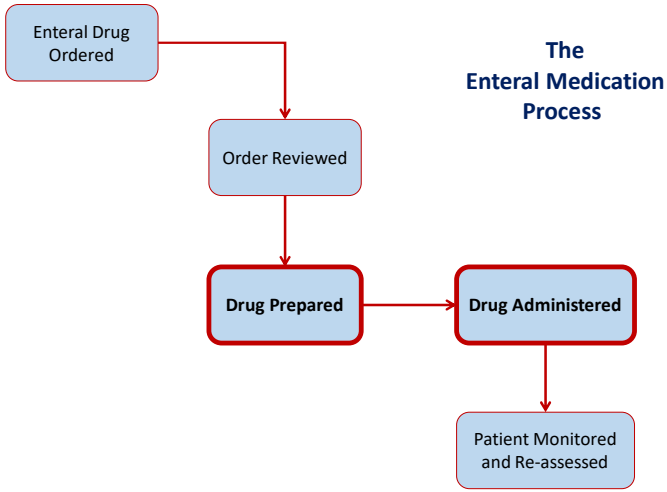
The Enteral Medication Process

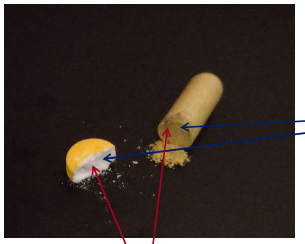
Drug Administered



The Enteral Medication Process

The Enteral Medication Process

- Oral Drug Products
  - Dosage Forms
    - Solid – tablets, capsules
    - Liquid – solutions, suspensions
  - Drug Formulation
    - Contents
      - Active drug
      - Excipients
    - Release characteristics
      - Immediate-release
      - Modified-release (e.g., enteric-coated, sustained- or extended-release)



Immediate-Release Oral Drug Products

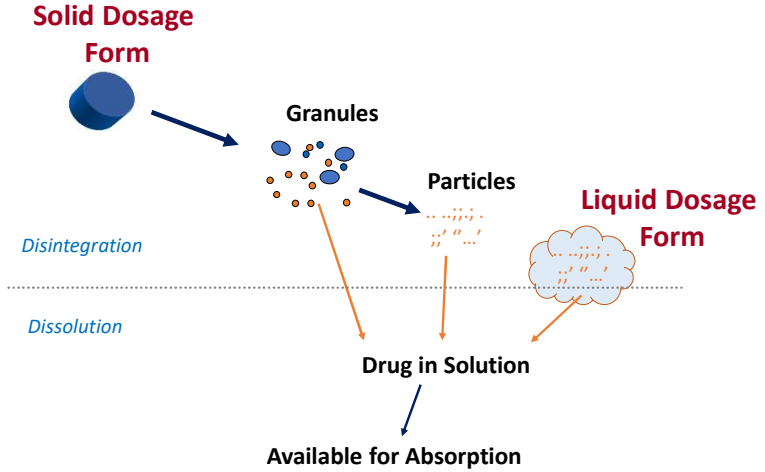
Drug

"Active Pharmaceutical Ingredient"

Excipients

Disintegrants, diluents, binders, lubricants …

Solvents, sweeteners, stabilizers, preservatives, …



The Enteral Medication Process

- Oral Bioavailability = net proportion of a dose that is delivered to the systemic circulation after absorption
  - Depends on:
    - Fraction absorbed from the gut lumen into the enterocytes
    - Extraction at the gut and at the liver (i.e., metabolism, efflux transport)
  - Determined by multiple factors:
    - Physicochemical properties (e.g., solubility, permeability)
    - Pharmaceutical elements (e.g., excipients in the formulation)
    - Physiologic influences (e.g., variability in gut function)

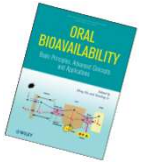
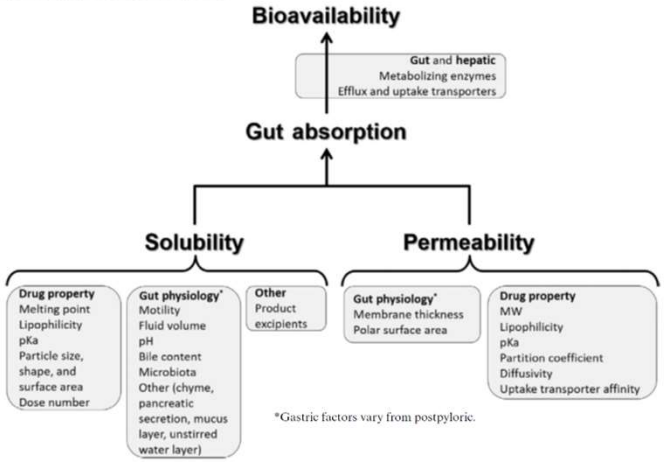


Figure 1. Determinants of drug bioavailability.



Nutr Clin Pract 2021;36:111

The Enteral Medication Process

Oral Administration

- Formulated product
- Taken intact with water
- Product-designed disintegration
- Drug dissolution
- Available for predictable absorption

Enteral Administration

- Formulation design broken
- Interaction between drug and excipients in confined space
- Dispersed in water
- Additional unintended interaction
- Dissolution vs complexation

The Enteral Medication Process

- Drug Preparation
  - Any alteration of a commercial dosage form
  - May affect GI absorption, bioavailability, clinical effect, safety

- Drug Administration
  - Involves the timing of drug delivery into the gut using an appropriate device
  - With respect to flushing protocols, other medication, and the EN regimen

The Enteral Medication Process

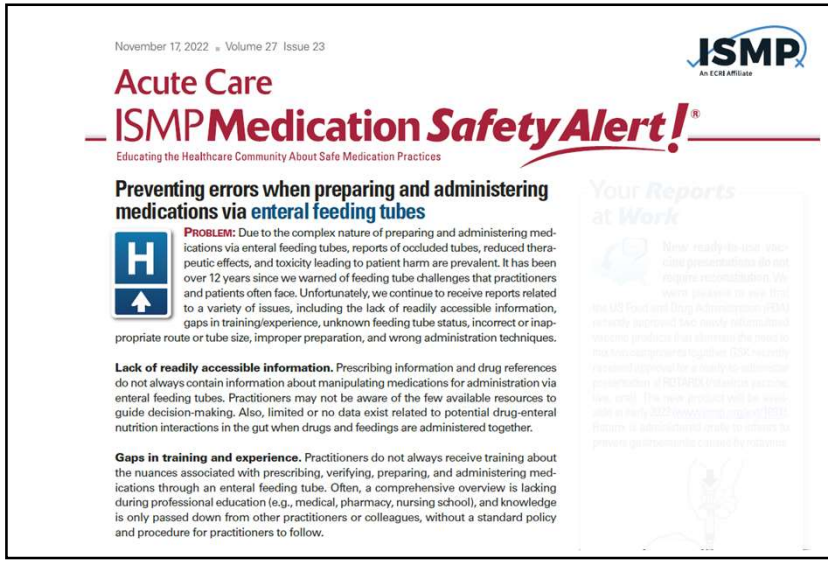
- Medication Errors
  - Can occur at each step
  - Several can occur in a single patient
  - Will affect the patient's care and outcomes
  - Depending on the degree of exposure, some drugs may pose a hazard to the caregiver preparing the medication

Clin Nutr 2002;21:531 / *Ann Pharmacother* 2003;37:1420 / *Nutr Clin Pract* 2003;18:402 / *J Res Pharm Pract* 2012;1:37

The Enteral Medication Process

- Enteral Drug Errors
  - Unsuitable drug formulation
  - Inappropriate gastrointestinal site
  - Improper preparation and/or administration method
- Clinical Consequences
  - Adverse drug effect
  - Therapeutic drug failure
  - Tube obstruction (clogging)

Ann Pharmacother 2003;37:1420 / *Nutr Clin Pract* 2003;18:402 / *JC J Qual Patient Safety* 2008;34:285 / *Crit Care Med* 2009;37(Suppl):A122 / *J Res Pharm Pract* 2012;1:37 / *Pharm Pract News* 2014;Apr:1



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Acute Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Preventing errors when preparing and administering medications via enteral feeding tubes

PROBLEM: Due to the complex nature of preparing and administering medications via enteral feeding tubes, reports of occluded tubes, reduced therapeutic effects, and toxicity leading to patient harm are prevalent. It has been over 12 years since we warned of feeding tube challenges that practitioners and patients often face. Unfortunately, we continue to receive reports related to a variety of issues, including the lack of readily accessible information, gaps in training/experience, unknown feeding tube status, incorrect or inappropriate route or tube size, improper preparation, and wrong administration techniques.

Lack of readily accessible information. Prescribing information and drug references do not always contain information about manipulating medications for administration via enteral feeding tubes. Practitioners may not be aware of the few available resources to guide decision-making. Also, limited or no data exist related to potential drug-enteral nutrition interactions in the gut when drugs and feedings are administered together.

Gaps in training and experience. Practitioners do not always receive training about the nuances associated with prescribing, verifying, preparing, and administering medications through an enteral feeding tube. Often, a comprehensive overview is lacking during professional education (e.g., medical, pharmacy, nursing school), and knowledge is only passed down from other practitioners or colleagues, without a standard policy and procedure for practitioners to follow.

The Enteral Medication Process

- Enteral drug *handling* errors
  - From surveys up to 97% of respondents are confident that their technique is appropriate/effective
    - While responses reveal otherwise, and 83% don't use guideline/protocol
  - Error rates approach 60-75% in observational studies

Preparation	
Mix meds together	49-70%
Crush tabs together	84-86%
Crush mod-release meds	15-87%
No diluting liquid meds	36-46%
No shaking suspension	51%
No protective equipment	100%

Administration	
Administer meds together	49-68%
Drug pwdr lost (underdosed)	70%
No flush (≥15 mL) pre med	57-99%
No flush (≥15 mL) post med	34%
No flush between meds	62-99%
Diluent other than water	18%
EN-drug interaction	22%

Pediatrics 1988;81:549 / *Heart Lung* 1996;25:318 / *Gastroenterol Nurs* 1997;20:118 / *Am J Crit Care* 1977;6:382 / *Am J Health-Syst Pharm* 2002;59:378 / *Nutr Clin Pract* 2005;20:354 / *Nutr Clin Pract* 2007;22:126 / *Pharm World Sci* 2008;30:907 / *JC J Qual Patient Safety* 2008;34:285 / *JPEN* 2009;33:122 / *Age Ageing* 2010;39:495 / *Nursing* 2013;43(12):26 / *Pharm Pract News* 2014;Apr:1 / *J Intellect Disab Res* 2015;59:215 / *J Res Pharm Pract* 2017;6:100 / *J Nutr Health Aging* 2017;21:904 / *Saud Pharmaceut J* 2024;32:101938

Outline

✓The Enteral Medication Process

- Drug-Nutrition Interactions – the Meal Effect
- Enteral Nutrition-Drug Interactions
- Approaches to Patient Care

Drug-Nutrition Interactions
The Meal Effect

Table 1 Types of drug-nutrition interaction.

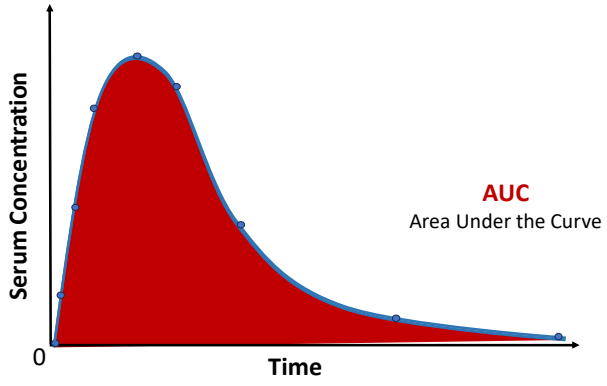
Precipitating factor	*Object of the interaction*	*Interaction term*
Meal	Drug	Food-drug
Diet component[a]	Drug	Diet-drug, nutrient-drug
Nutritional status	Drug	Nutritional status-drug
Drug	Nutritional status	Drug-nutrition (status)
Drug	Metabolic profile	Drug-metabolic (profile)
Drug	Nutrient	Drug-nutrient

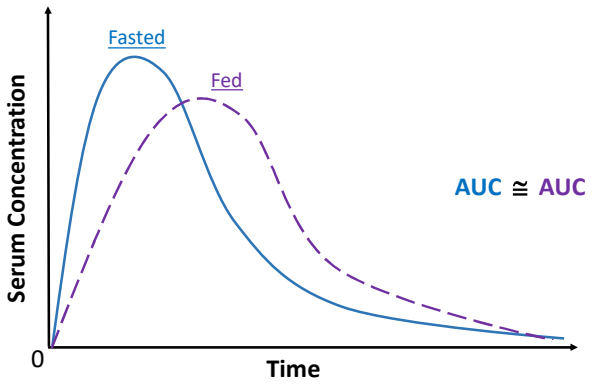
[a]Includes those found in dietary supplement products.

Encyclopedia of Human Nutrition, 4th edition. Elsevier, 2023;(vol 2):79-92.

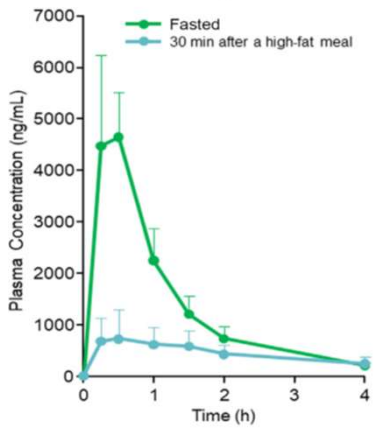
Drug-Nutrition Interactions
The Meal Effect

- Direct interaction between food and drug
- Indirectly as food changes gut conditions
  - Gastric emptying, proximal intestinal pH, bile flow, splanchnic blood flow, enterocyte function (permeability, transport, metabolism)
- Food may influence
  - Drug stability and solubility
  - The *rate* of drug absorption
  - The drug's *bioavailability*
    - Reflected in the **a**rea **u**nder the concentration-time **c**urve (AUC)





Edaravone (Radicava ORS) in Healthy Subjects – Meal Effect



Clin Ther 2022;44:1552

Drug-Nutrition Interactions
The Meal Effect

- U.S. Food & Drug Administration "test meal"
  - 800-1000 kcal, energy from fat ~50%
- Other meal types may have a different effect
- Clinical significance
  - AUC_{fed}:AUC_{fasted} outside 80-125%

Drug-Nutrition Interactions
The Meal Effect

Administer on Empty Stomach
- Bisphosphonates
- Ciprofloxacin
- Diltiazem
- Furosemide
- Levothyroxine
- PPIs
- Zafirlukast

Administer with Food
- Amoxicillin-clavulanate
- Carbamazepine
- Fenofibrate
- Labetalol
- Metoprolol
- Tamsulosin
- Trazadone

Outline

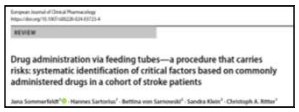
✓The Enteral Medication Process

✓Drug-Nutrition Interactions – the Meal Effect

- Enteral Nutrition-Drug Interactions
- Approaches to Patient Care

Enteral Nutrition-Drug Interaction

- Very limited data on EN-drug interactions
  - Unpredictable given all the variability
  - Requires much more study



- Site of interaction
  - In the enteral container or access device, within the gut lumen, at the gut mucosal epithelium
- Central issue
  - Whether or not to hold the EN (beyond the time to flush-administer drug-flush) in order to avoid an interaction

Nutr Clin Pract 2005;20:618 / *Am J Health Syst Pharm* 2008;65:2347 / *Am J Health Syst Pharm* 2009;66:1458 / *Anaesthesiol Intens Ther* 2014;46:307 / *Nutr Hosp* 2014;30:514 / *JPEN* 2017;41:15 / *Nutr Clin Pract* 2021;36:111

Enteral Nutrition-Drug Interaction

- Apply Meal Effect Data?
  - A liquid meal has a different influence on gut physiology compared with a solid meal of similar nutrient content
    - Better drug dissolution in the stomach with a solid meal
  - And continuous feeds into the stomach or small bowel are even less representative of a meal effect
  - The interaction potential goes beyond extrapolating from meal effect data
- Risks are to bioavailability *and* tube patency

Pharmaceut Res 2007;24:1118 / *Am J Health Syst Pharm* 2009;66:1458 / *Mol Pharmaceutics* 2019;16:573 /

Enteral Nutrition-Drug Interaction

- Bioavailability
  - EN composition, volume/rate may influence drug absorption
  - Drug interaction with EN components may be more likely than with a more complex meal matrix
  - Holding EN
    - Long enough to flush tube-administer med-flush tube again
    - Longer only to avoid a potentially clinically relevant interaction
  - Proximity to EN can be based on general meal effect data when no other data available

Enteral Nutrition-Drug Interaction

- Tube Patency
  - Clogged feeding tubes a 'never event'?
    - Inpatient – over 80% receive 1+ meds that can clog tube, but obstruction rates rarely reported (up to 60%, with over ½ requiring replacement)
    - Outpatient – obstruction rates of 30% in 1 year, 59% in 2 years
    - 62% of common liquid drug formulations are prone to clog with EN in vitro
  - Follow best practices
  - Generally avoid
    - Low pH liquid or those with alcohol content; modified-release meds
    - EN with casein and fiber content because of obstruction risk

Clin Nutr 2000;19:15 / *Age Ageing* 2010;39:495 / *JPEN* 2013;37:689 / *Eur J Clin Nutr* 2020;74:261 / *J Clin Nurs* 2020;29:4614 / *Sci Rep* 2023;13:21727

Riluzole (Rilutek, Tiglutik)

- Meal Effect
  - High-fat meal → ↓AUC 20% (tab), ↓AUC 9% (susp)
  - Therefore take 1 h pre/2h post meal
- Enteral Preparation
  - Tablet – film-coating may increase clogging risk
  - Suspension – osmolality/viscosity not described, consider dilution with water (1:1)
- Enteral Administration
  - Suspension – 30 mL water flush pre/post; compatible with silicone and polyurethane tubes

Drug Design Dev Ther 2017:11 59 / *Clin Ther* 2019;41:2490

Edaravone (Radicava ORS)

- Meal Effect
  - High-fat meal → ↓AUC 61%
  - Therefore take after overnight (8-10 h) fast, wait 1 h for food

Meal	Drug Timing	AUC
800-1000 kcal, 55-65 g fat	1 h before	↓ 15%
800-1000 kcal, 55-65 g fat	with	↓ 61%
800-1000 kcal, 55-65 g fat	4 h later	↓ 24%
800-1000 kcal, 55-65 g fat	8 h later	NS change
400-500 kcal, 11-14 g fat	2 h later	↓ 21%
250 kcal, low/no fat	2 h later	↓ 10%

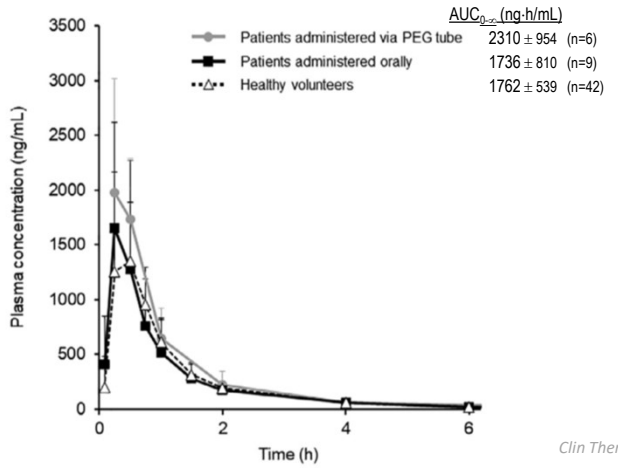
Clin Ther 2022;44:1552 / *Clin Pharmacol Drug Dev* 2023;12:77 / *Clin Ther* 2023;45:1251

Edaravone (Radicava ORS)

- Enteral Preparation
  - Osmolality/viscosity not described, consider dilution with water
- Enteral Administration
  - Suspension – 30 mL water flush pre/post;
  - Compatible with silicone, polyvinylchloride and polyurethane tubes ≥12 Fr

Clin Ther 2022;44:1552 / *Clin Pharmacol Drug Dev* 2023;12:77 / *Clin Ther* 2023;45:1251

Edaravone in Patients with ALS – Oral vs PEG



Clin Ther 2023;45:1251

Dextromethorphan/Quinidine (Nuedexta)

- Meal Effect
  - Neither active drug affected by food intake
  - Therefore take without regard to meals
- Enteral Preparation
  - Disperse capsule contents in 10-20 mL water
- Enteral Administration
  - Water flush pre/post include rinse of dosing syringe

Outline

✓The Enteral Medication Process

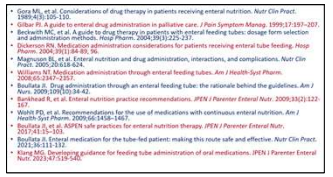
✓Drug-Nutrition Interactions – the Meal Effect

✓Enteral Nutrition-Drug Interactions

•Approaches to Patient Care

Approaches to Patient Care

- Incorporate available guidance on enteral medication use into practice
  - ASPEN *JPEN* 2017 – Section 8
  - *Nutr Clin Pract* 2021



- Seek resources for questions on specific medication
  - Literature compilations
  - Human expertise
- Systematically review and then address any ongoing errors and consequences

Meds That Should Not Be Crushed

Crushing pills can improve ease of administration, but some shouldn't be crushed. Crushing **extended-release** meds can result in administration of a large dose all at once. Crushing **delayed-release** meds can alter the mechanism designed to protect the drug from gastric acids or prevent gastric mucosal irritation. Crushing **sublingual or buccal** tabs can alter effectiveness. Crushing pills **based on certain technologies** (i.e., amorphous solid dispersion or nanocrystals) can alter bioavailability.[8] Crushing **bitter-tasting** meds can be unpleasant for the patient. Crushing **irritating or hazardous** meds can be harmful to the individual crushing the meds. (If hazardous meds [e.g., carcinogenic] must be crushed, follow USP Chapter <800> standards in healthcare settings or advising outpatients on proper procedures. Hazardous meds below explicitly state not to crush in the product information. The NIOSH hazardous meds list is at https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf?id=10.26616/NIOSHPUB2016161.

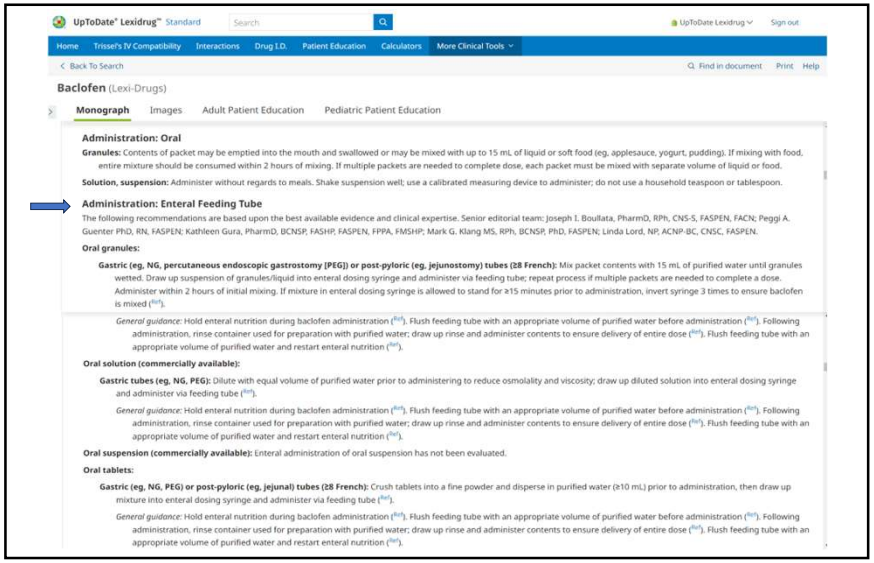
*This table has some **common** meds that should not be crushed; many more may not be listed. Brand names are representative and may not be all-inclusive. The most current product labeling for US and Canadian products was used to confirm information, in addition to listed references.*

Modified-release: Indicates extended-release or delayed-release formulation.[7]

Medications That Should Not Be Crushed[1-4,8,10]

Generic Name	Brand Name	Dosage Form	Comments
Acamprosate	*Campral*	Tablet	• Modified-release
Acetaminophen	*Tylenol Arthritis Pain Extended-Release* (US)	Tablet	• Modified-release
Albuterol	*ProAir ER* (US)	Tablet	• Modified-release
Alendronate	*Fosamax*	Tablet	• Irritant (oropharyngeal)
Alfuzosin	*Uroxatral* (US), *Xatral* (Canada)	Tablet	• Modified-release
Alprazolam	*Xanax XR* (US)	Tablet	• Modified-release
Ambrisentan	*Letairis* (US), *Volibris* (Canada)	Tablet	• Teratogenic
Amoxicillin/Clavulanate	*Augmentin XR* (US)	Tablet	• Modified-release • Scored tablets can be split
Apremilast	*Otezla* (US)	Tablet	• Antineoplastic
Aprepitant	*Emend* (US)	Capsule	• Nanocrystal
Aspirin	*Ecotrin*	Tablet	• Modified-release • Irritant (gastric)

Pharmacist's Letter Feb 2023 [Resource #390224]



Approaches to Patient Care

- Human Expertise
  - Caregiver training videos
  - Clinical pharmacist
- Multidisciplinary programs reduced the number of enteral medication errors *and* tube obstructions
  - Promoted practice guidelines
  - Held training sessions for caregivers
  - Established/used a database of oral dosage forms
  - Had pharmacists offer patient-specific recommendations
    - Evaluating each drug for appropriateness via enteral tube
    - Recommending ways to simplify a patient's drug regimen

Qual Saf Health Care 2006;15:44 / *BMJ Open* 2020;9:e000882 / *Crit Care Nurs* 2022;42:54

Some Take Home Points

- The prescriber, dietitian, pharmacist, and nurse share responsibility for safe drug use in enterally fed patients
- EN-drug interaction risk will direct the timing of enteral drug administration with the EN regimen
- Best practices should allow for therapeutic drug effect and nutrient delivery without additional risk
- Feeding tube obstruction should be a "(near) never event" if using best practices

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