What Did They do to Us!? Part II

UNDERSTANDING PHARMACOKINETICS, PHARMACODYNAMICS AND DRUG-DRUG INTERACTIONS

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UNIVERSITY OF VIRGINIA HEALTH SYSTEM

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Name	Role	Relationship	Company
Chloé LeBegue-Polley	Consultant	Owner	CLP Consulting, LLC
Chloé LeBegue-Polley	Joint Patent Holder	Patent Holder	University of South Carolina-Live Biotherapeutics

No one else in a position to control the content of this educational activity has disclosed a relevant financial interest or relationship with any commercial interest.

Activity Code (Part 2)

Activity Code: **150958**

Instructions for claiming credits/contact hours can be found here.

Objectives

Part 1:

1. Differentiate between pharmacokinetics and pharmacodynamics
2. Understand common pathways for drug-drug interactions

Part 2:

1. Learn how to utilize high quality drug-drug interaction resources
2. Identify drug-drug interactions common in the oncology setting
3. Patient case

Using Lexicomp as a Reference

KNOWLEDGELINK

UVAHealth

Internal Search...

CONNECT - RECENT NEWS

Heroic Work and Unique Expertise: 2024 National CRNA Week Is Jan. 21-27

January 19, 2024

"Reflect on the heroic work and unique expertise of CRNAs and residents while recognizing the power and resilience of our community."

Research in Motion | Hongji Zhang, PhD

January 19, 2024

"As a cancer immunologist, my research revolves around understanding the

WORKDAY | KRONOS | IT HELP

EMAIL | DATA | MC POLICYTECH

UVA HEALTH'S 2022-2032 STRATEGIC PLAN

Finance (ePro) | People Search | In Hospital Maps | Lexicomp

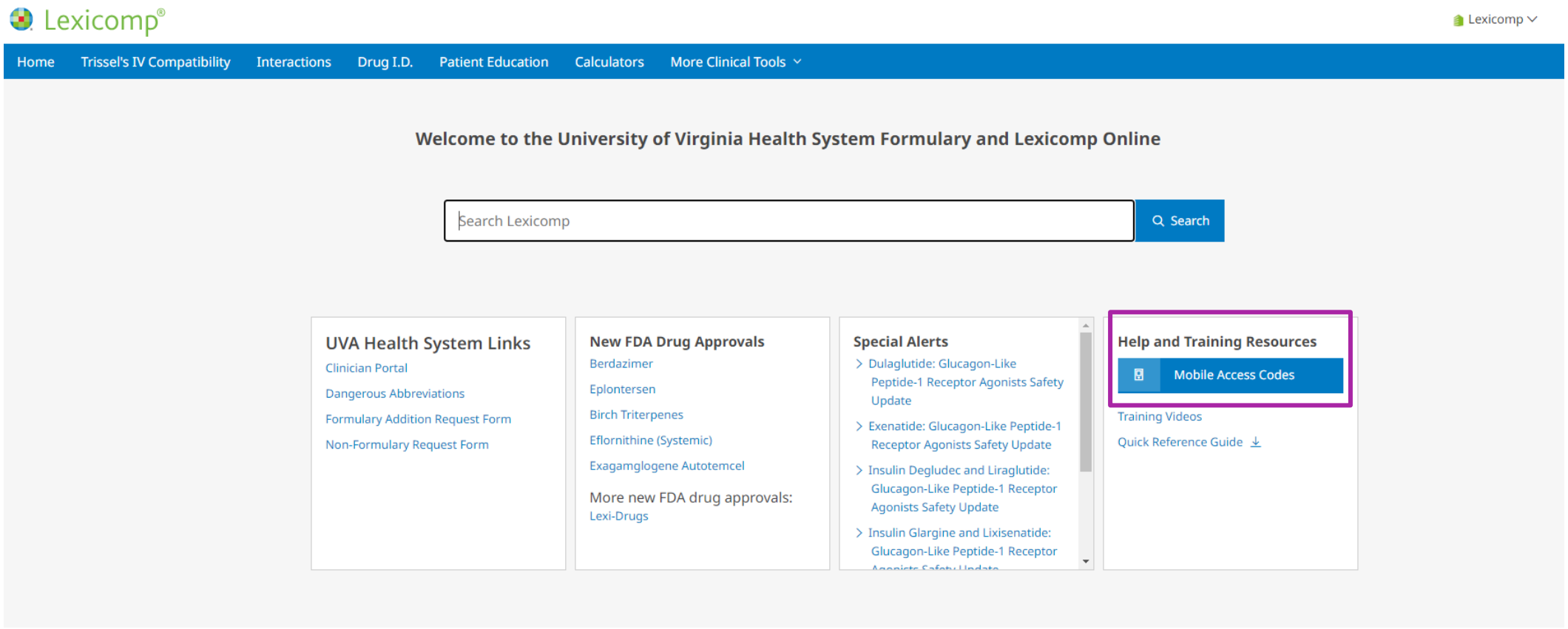
CLINICAL LINKS

*ordered by most used

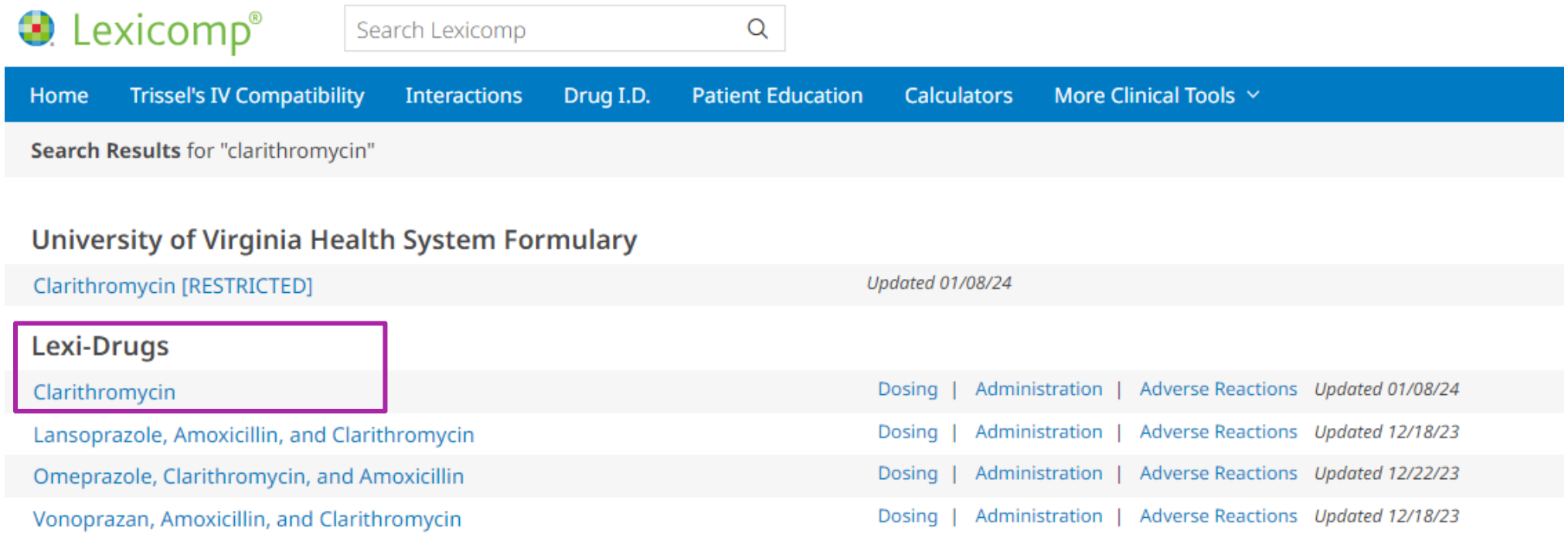
- Lexicomp Reference
- Up-To-Date
- PubMed
- Lippincott Procedures
- Epic Learning Library
- Hill-Rom Smart Client
- NPGO Practice News
- Patient Education
- Pharmacy Services
- Pharmacy - Peds Intranet
- Clinical Nutrition Tools
- Ambulatory Operations
- Clinical Career Ladder
- Children's Hospital Intranet
- New Medical Device Request

View Full Clinician Portal

Using Lexicomp as a Reference



Using Lexicomp as a Reference



Using Lexicomp as a Reference

Clarithromycin (Lexi-Drugs)

Outline Alphabetical

Expand All

- Dosing: Hepatic Impairment: Pediatric
- Calculations
- Uses
- Clinical Practice Guidelines
- Administration and Storage Issues
- Patient Counseling Points
- Medication Safety Issues
- Warnings & Precautions
- Reproduction, Pregnancy, & Lactation
- Adverse Reactions
- Interactions
- Patient & Therapy Management
- Preparations
- Pharmacology & Pharmacokinetics
- Dental Information
- Pearls & Related Information

Metabolism/Transport Effects

Substrate of CYP3A4 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** CYP3A4 (strong), OATP1B1/1B3 (SLCO1B1/1B3), P-glycoprotein/ABCB1

Drug Interactions

Open Interactions

Note: Interacting drugs may **not be individually listed below** if they are part of a group interaction (eg, individual drugs within "CYP3A4 Inducers [Strong]" are NOT listed). For a complete list of drug interactions by individual drug name and detailed management recommendations, use the Lexicomp drug interactions program by clicking on the "Open Interactions" button above.

Abemaciclib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Abemaciclib. Management: In patients taking abemaciclib at a dose of 200 mg or 150 mg twice daily, reduce the dose to 100 mg twice daily when combined with strong CYP3A4 inhibitors. In patients taking abemaciclib 100 mg twice daily, decrease the dose to 50 mg twice daily. *Risk D: Consider therapy modification*

Acalabrutinib: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Acalabrutinib. *Risk X: Avoid combination*

Ado-Trastuzumab Emtansine: CYP3A4 Inhibitors (Strong) may increase serum concentrations of the active metabolite(s) of Ado-Trastuzumab Emtansine. Specifically, strong CYP3A4 inhibitors may increase concentrations of the cytotoxic DM1 component. Management: Avoid concomitant use of ado-trastuzumab emtansine and strong CYP3A4 inhibitors when possible. Consider alternatives that do not inhibit CYP3A4 or consider administering after CYP3A4 inhibitor discontinuation. Monitor for toxicities if combined. *Risk D: Consider therapy modification*

Afatinib: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Afatinib. Management: If combined, administer the P-gp inhibitor simultaneously with, or after, the dose of afatinib. Monitor closely for signs and symptoms of afatinib toxicity and if the combination is not tolerated, reduce the afatinib dose by 10 mg. *Risk D: Consider therapy modification*

ALfentanil: CYP3A4 Inhibitors (Strong) may increase the serum concentration of ALfentanil. Management: If use of alfentanil and strong CYP3A4 inhibitors is necessary, consider dosage reduction of alfentanil until stable drug effects are achieved. Frequently monitor patients for respiratory depression and sedation when these agents are combined. *Risk D: Consider therapy modification*

Alfuzosin: CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. *Risk X: Avoid combination*

Aliskiren: P-glycoprotein/ABCB1 Inhibitors may increase the serum concentration of Aliskiren. *Risk C: Monitor therapy*

Using Lexicomp as a Reference

Selected Items

Drug(s)

Enter Drug Name | Add

✕ **Clarithromycin** — Single Drug Analysis

✕ **Midazolam** — Single Drug Analysis

Allergies

Interaction Checking | Interaction Analysis | Interaction Monograph | Clarithromycin

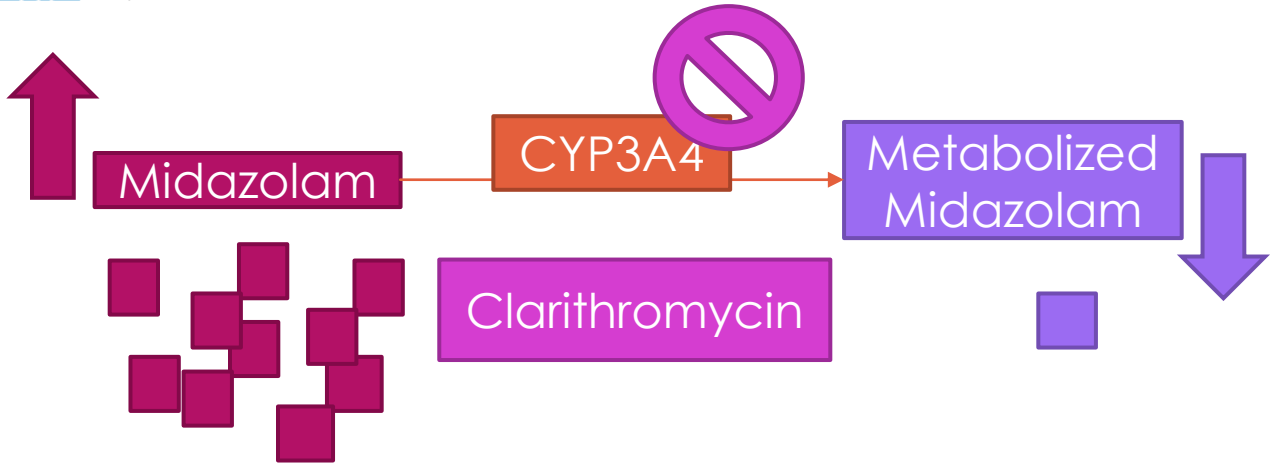
Title Midazolam / CYP3A4 Inhibitors (Strong)

Dependencies:

Route: The magnitude and clinical consequences of this interaction appears greater with oral midazolam compared with other routes of midazolam administration.

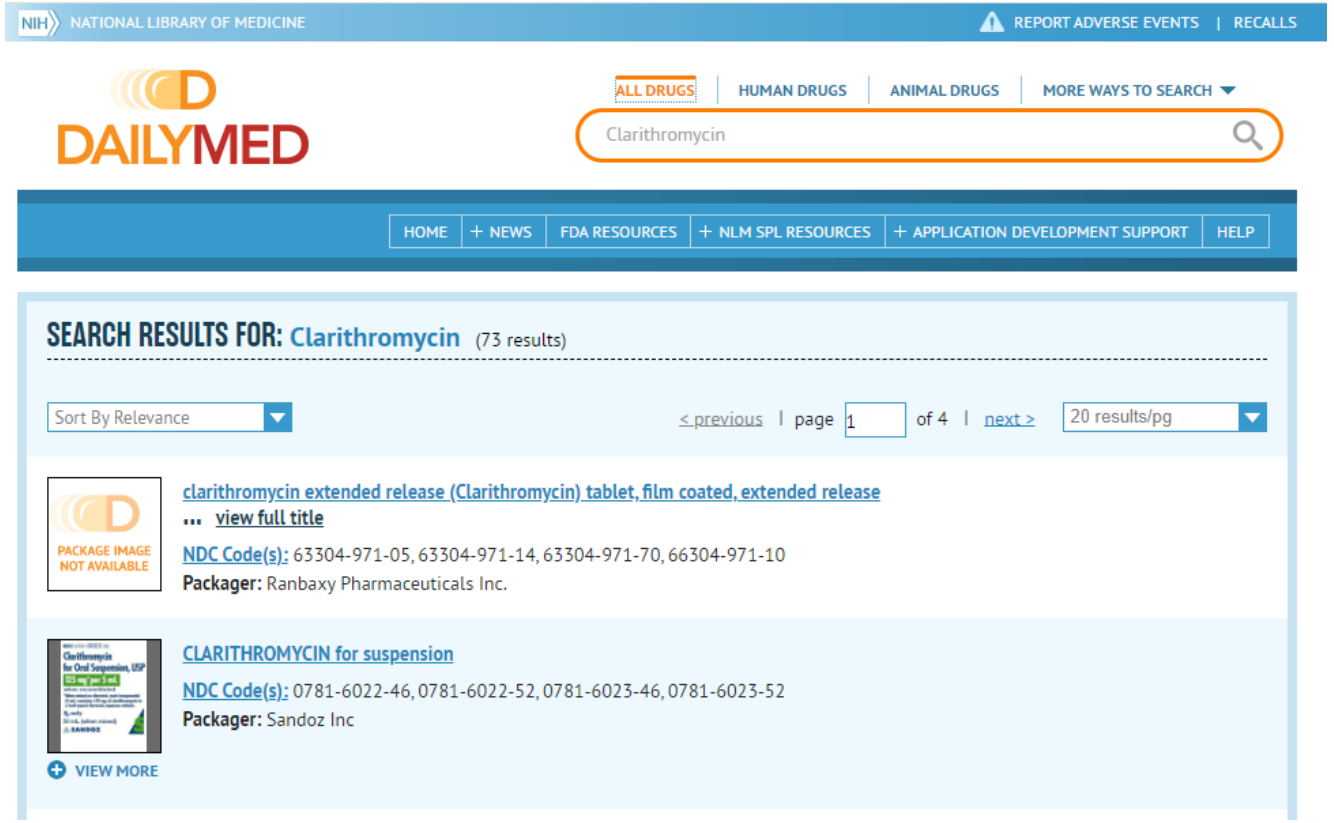
Risk Rating D: Consider therapy modification

Summary CYP3A4 Inhibitors (Strong) may increase the serum concentration of Midazolam. **Severity** Major **Reliability Rating** Excellent



Package Insert as a Reference

Package Insert as a Reference



Package Insert as a Reference

CLARITHROMYCIN - clarithromycin tablet
Ajanta Pharma USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CLARITHROMYCIN TABLETS safely and effectively. See full prescribing information for CLARITHROMYCIN TABLETS.

CLARITHROMYCIN tablets, for oral use
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Contraindications (4)	5/2023
Drug Interactions (7)	5/2023

INDICATIONS AND USAGE

Clarithromycin tablets are a macrolide antimicrobial indicated for mild to moderate infections caused by designated, susceptible bacteria in the following:

- Acute Bacterial Exacerbation of Chronic Bronchitis in Adults (1.1)
- Acute Maxillary Sinusitis (1.2)
- Community-Acquired Pneumonia (1.3)
- Pharyngitis/Tonsillitis (1.4)
- Uncomplicated Skin and Skin Structure Infections (1.5)
- Acute Otitis Media in Pediatric Patients (1.6)
- Treatment and Prophylaxis of Disseminated Mycobacterial Infections (1.7)
- *Helicobacter pylori* Infection and Duodenal Ulcer Disease in Adults (1.8)

Limitations of Use
To reduce the development of drug-resistant bacteria and maintain the effectiveness of clarithromycin and other antibacterial drugs, clarithromycin tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.9)

DOSAGE AND ADMINISTRATION

- Adults: Clarithromycin tablets 250 mg or 500 mg every 12 hours for 7–14 days (2.2)
- *H.pylori* eradication (in combination with lansoprazole/amoxicillin, omeprazole/amoxicillin, or omeprazole): Clarithromycin tablets 500 mg every 8 or 12 hours for 10–14 days. See full prescribing information (FPI) for additional information. (2.3)
- Pediatric Patients: Clarithromycin 15 mg/kg/day divided every 12 hours for 10 days (2.4)
- Mycobacterial Infections: Clarithromycin tablets 500 mg every 12 hours; Clarithromycin tablets 7.5 mg/kg up to 500 mg every 12 hours in pediatric patients (2.5)
- Reduce dose in moderate renal impairment with concomitant atazanavir or ritonavir-containing regimens and in severe renal impairment (2.6)

DOSAGE FORMS AND STRENGTHS

- Tablets: 250 mg and 500 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to clarithromycin or any macrolide drug (4.1)
- Cisapride and pimozide (4.2)
- History of cholestatic jaundice/hepatic dysfunction with use of clarithromycin (4.3)
- Colchicine in renal or hepatic impairment (4.4)
- Lomitapide, lovastatin, and simvastatin (4.5)
- Ergot alkaloids (ergotamine or dihydroergotamine) (4.6)
- Lurasidone (4.7)

WARNINGS AND PRECAUTIONS

7 DRUG INTERACTIONS

Clarithromycin tablets should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively

metabolized by this enzyme. Adjust dosage when appropriate and monitor serum concentrations of drugs primarily metabolized by CYP3A closely in patients concurrently receiving clarithromycin.

Table 8: Clinically Significant Drug Interactions with Clarithromycin Tablets

Drugs That Are Affected By Clarithromycin Tablets		
Drug(s) with Pharmacokinetics Affected by clarithromycin tablets	**Recommendation**	**Comments**
Antiarrhythmics: Disopyramide Quinidine Dofetilide Amiodarone Sotalol Procainamide	Not Recommended	Disopyramide, Quinidine: There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidineor disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs *[see Warnings and Precautions (5.2)]*. Serum concentrations of these

Case Report: DDI

- 2006: 14 year old Caucasian male presented with cervical lymphadenopathy
- Labs unremarkable, chest x-ray normal
- Right cervical node biopsy disclosed classic Hodgkin lymphoma
- Subject was treated with VAMP + radiation
  - Vinblastine
  - Doxorubicin
  - Methotrexate
  - Prednisone

Bashir H, Motl S, Metzger ML, et al. Itraconazole-enhanced chemotherapy toxicity in a patient with Hodgkin lymphoma. *J Pediatr Hematol Oncol*. **2006**;28(1):33-35.

Case Report: DDI

- After the first VAMP cycle, he developed flu-like symptoms
  - Fever, chills, malaise, cough, neutropenia
  - Resolved with hospitalization and abx
- After the second VAMP cycle, he presented with febrile neutropenia
  - No cultures revealed pathogens
  - Diagnostic imaging revealed left paramedian pulmonary infiltrate → PNA
- Empiric antimicrobial coverage during Cycle 3
  - Vancomycin
  - Imipenem
  - Ceftriaxone
  - Itraconazole

Bashir H, Motl S, Metzger ML, et al. Itraconazole-enhanced chemotherapy toxicity in a patient with Hodgkin lymphoma. *J Pediatr Hematol Oncol*. **2006**;28(1):33-35.

Case Report: DDI

- On C3D10, subject hospitalized for fever, neutropenia (ANC 40/mm3), severe mucositis with spontaneous bleeding
  - Inability to eat or drink
  - Severe abdominal cramps
  - Lower back and lower extremity neuropathic pain w/ paresthesia
    - Morphine PCA pump required for pain control
- Dx: severe bone marrow toxicity and neuropathy
- Held VAMP and **dc'd itraconazole starting on C3D15**
  - Neutrophil recovery on C3D18

Bashir H, Motl S, Metzger ML, et al. Itraconazole-enhanced chemotherapy toxicity in a patient with Hodgkin lymphoma. *J Pediatr Hematol Oncol*. **2006**;28(1):33-35.

Case Report: DDI

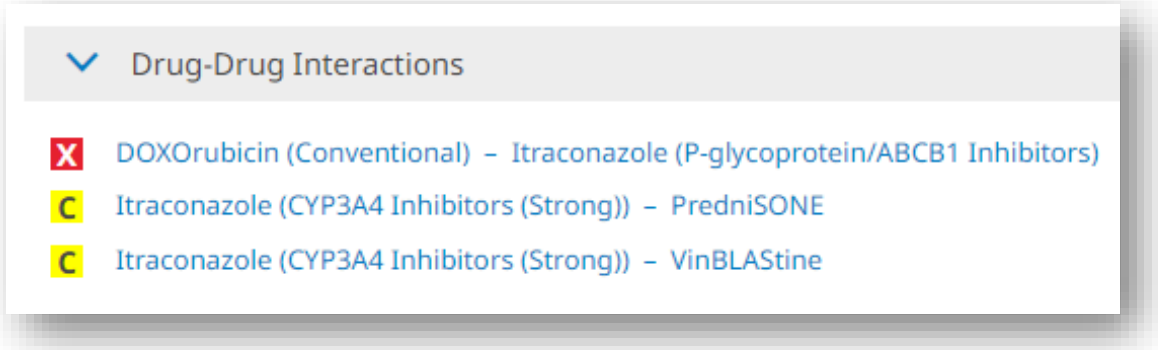
- Pain and malaise recovered over the next 2 weeks
- Side effects did not recur with standard doses of VAMP with Cycle 4
- Subject remained in remission at time of article writing

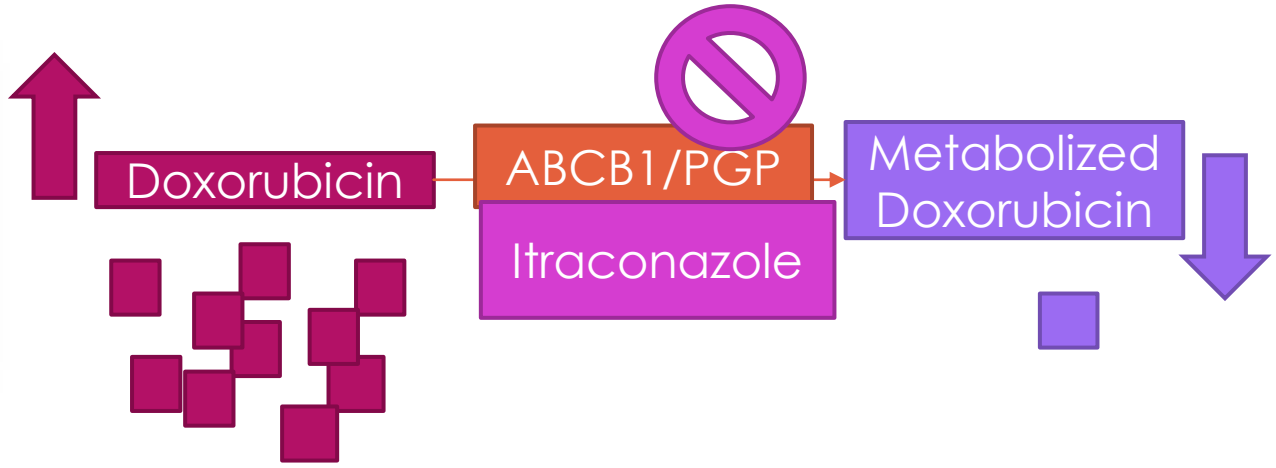
What happened to the patient during Cycle 3?

Bashir H, Motl S, Metzger ML, et al. Itraconazole-enhanced chemotherapy toxicity in a patient with Hodgkin lymphoma. *J Pediatr Hematol Oncol*. **2006**;28(1):33-35.

Case Report: DDI

- Itraconazole-enhanced chemotherapy toxicity





Bashir H, Motl S, Metzger ML, et al. Itraconazole-enhanced chemotherapy toxicity in a patient with Hodgkin lymphoma. *J Pediatr Hematol Oncol*. 2006;28(1):33-35.

Common Oncology Issues

CYP ✓

QT

HDI

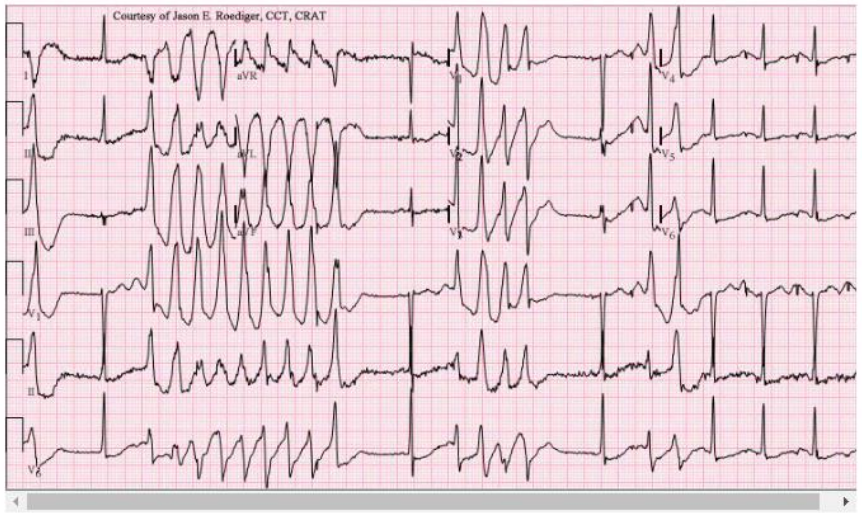
INR

pH

Lohr LK, Blake KT, Chan CM, Sturm S, Walsh GT. Managing Drug Interactions With Oral Anticancer Treatments. *J Adv Pract Oncol*. 2023;14(5):419-438. doi:10.6004/jadpro.2023.14.5.7

The QT Interval

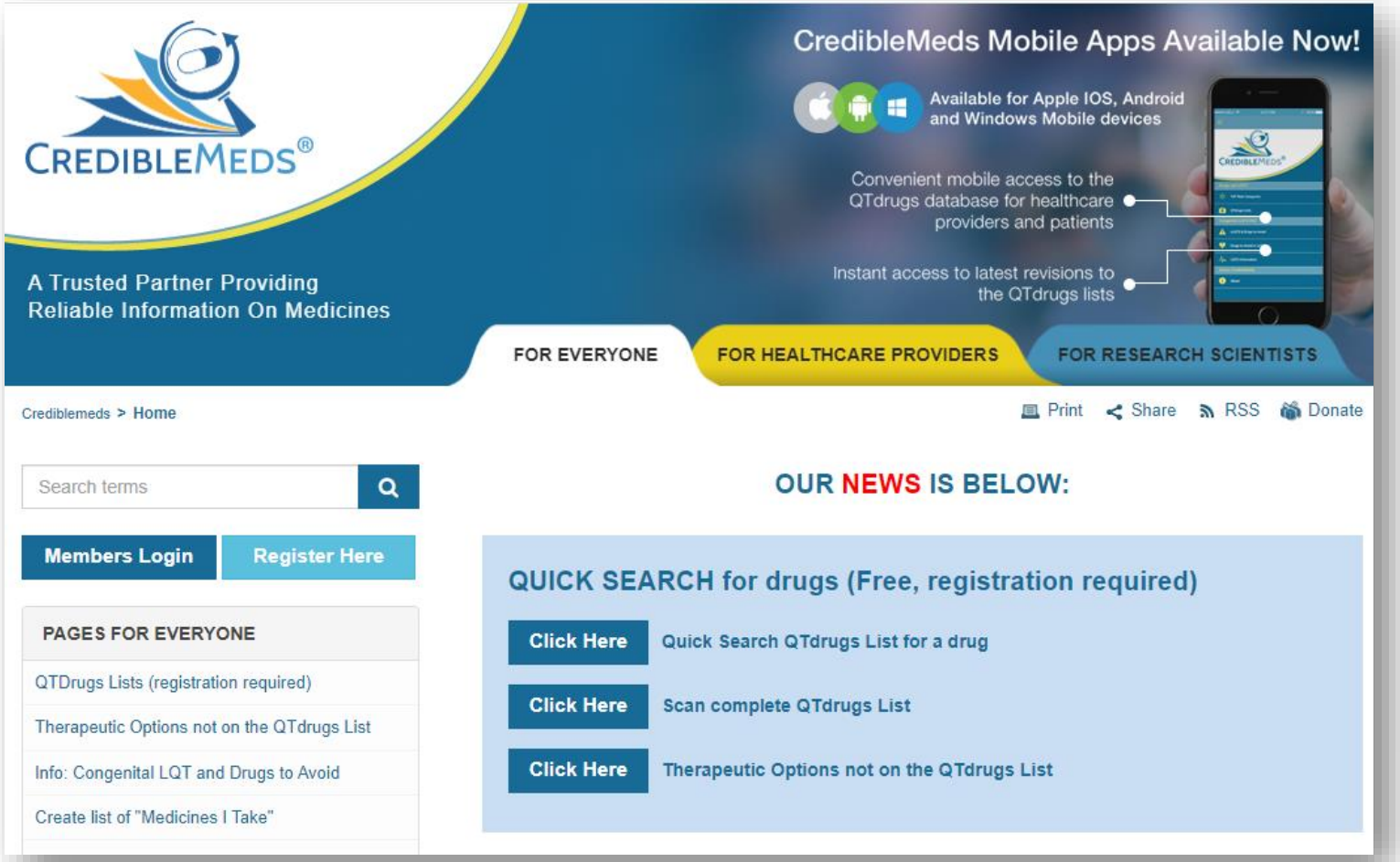
- The period between the beginning of the QRS complex and the end of the T wave on an ECG
- QT interval prolongation
  - Related to ion exchange (repolarizing K+, depolarizing Ca2+, Na+)
- Risk Factors
  - Female
  - Older
  - Multiple QT prolonging agents
- Consequences of QT prolongation
  - Life threatening ventricular arrhythmia
    - Torsades de pointes (TdP)
    - QT > 500 msec, QTc > 470 msec



Torsade de Pointes. Torsades de pointes with prolonged QT interval (12-lead ECG of torsades de pointes (TdP) in a 56-year-old white female with low blood potassium (2.4 mmol/L) and low blood magnesium (1.6 mg/dL). Courtesy of Wikimedia Commons [Author Jason E Roediger, CCT, CRAT, https://commons.wikimedia.org/wiki/File:Torsades_de_Pointes_TdP.png].

Wolters Kluwer Clinical Drug Information, Drug Monographs: Drug-Induced Prolongation of the QT Interval and Torsades de Points
https://hemonc-mhmedical-com.proxy1.library.virginia.edu/drugs.aspx?gbosID=238628#monoNumber=238628&sectionID=213812653&tab=tab0
Image: https://emedicine.medscape.com/article/1950863-overview?form=fpf

Credible Meds Reference



Resources for Healthcare Professionals

This section of CredibleMeds® includes tools to assist physicians, nurses, pharmacists and other healthcare professionals who play central roles in medication safety.

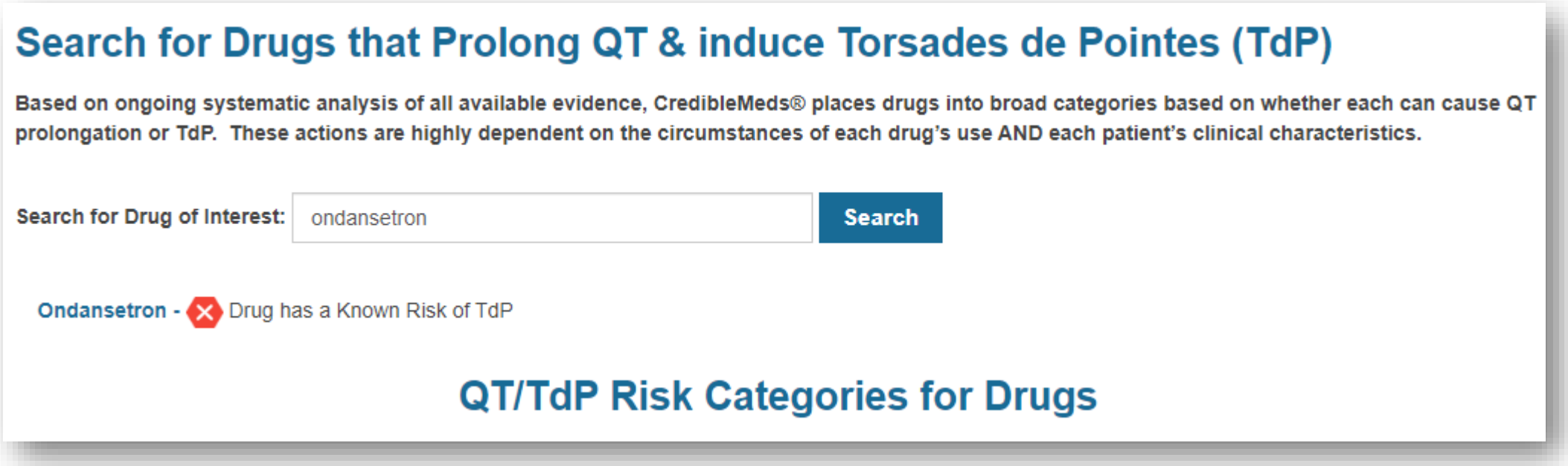
QT Drugs List: This portal includes QTdrugs.org, a list of drugs categorized by their potential to cause QT prolongation and/or torsades de pointes (TdP). Click on a drug and see if the FDA-approved label mentions contraindicated concomitant meds or recommends ECG monitoring.

ADECA™ RISK CATEGORIES

Categories of TdP risk for drugs on the QTdrugs List:

- Drugs with **known risk** of TdP
- Drugs with **possible risk** of TdP
- Drugs with **conditional risk** of TdP - i.e., drugs that can cause TdP under certain conditions or which create conditions that foster TdP

Credible Meds Reference



Common Oncology Issues

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pH

Lohr LK, Blake KT, Chan CM, Sturm S, Walsh GT. Managing Drug Interactions With Oral Anticancer Treatments. *J Adv Pract Oncol*. 2023;14(5):419-438. doi:10.6004/jadpro.2023.14.5.7

Herb-Drug Interactions

- A single herb contains multiple **phytoconstituents** that may be biologically active and capable of modulating physiological actions, similar to therapeutic drugs, through complex synergistic and/or antagonistic effects
  - Some herbs act as laxatives or antacids and affect absorption
  - Modify the volume of distribution of protein-bound medications by binding plasma proteins
  - Modify the expression of drug metabolizing enzymes (CYPs)
  - Act as inhibitors or inducers
    - Herbal induction of CYPs may take several days, but inhibition is often immediate
    - Prodrugs may be induced AND inhibited by HDIs
  - Alter excretion by damaging kidneys or acting as a diuretic

Borse SP, Singh DP, Nivsarkar M. Understanding the relevance of herb-drug interaction studies with special focus on interplays: a prerequisite for integrative medicine. *Porto Biomed J*. 2019;4(2):e15. Published 2019 Mar 1. doi:10.1016/j.pbj.0000000000000015

Herb-Drug Interactions

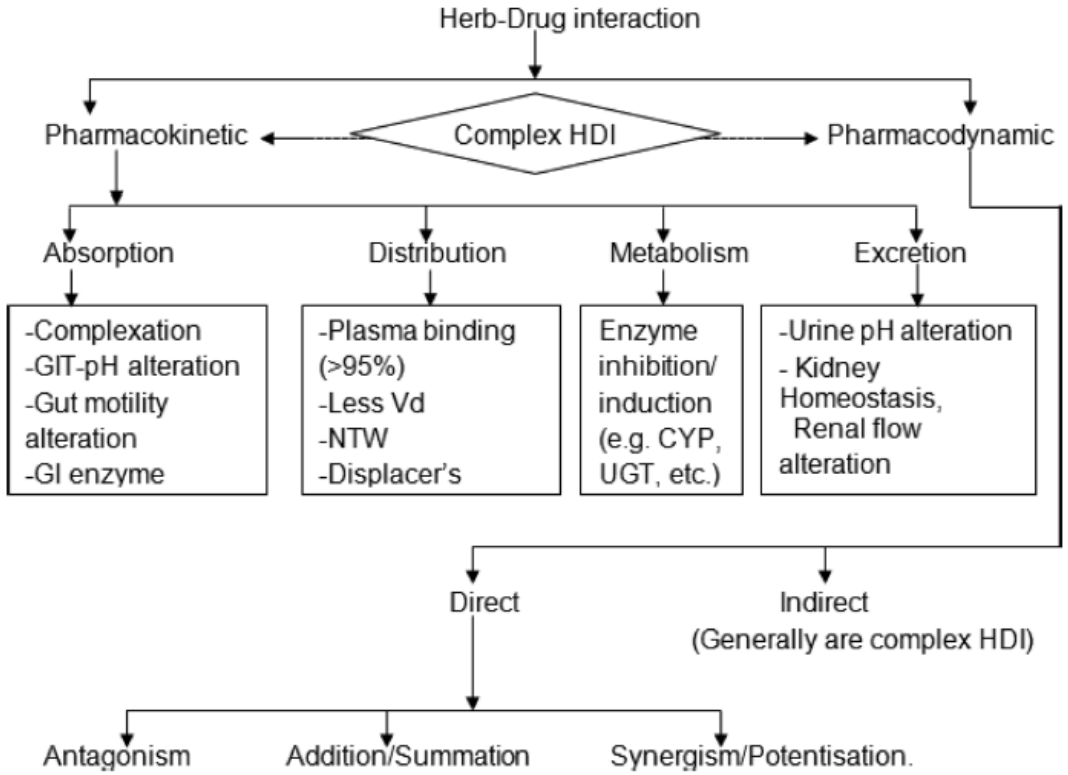


Figure 2. Mechanism of herb-drug interactions. CYP = cytochrome, GIT = gastrointestinal tract, Vd = volume of distribution, UGT = UDP-glucuronosyltransferase.

Borse SP, Singh DP, Nivsarkar M. Understanding the relevance of herb-drug interaction studies with special focus on interplays: a prerequisite for integrative medicine. *Porto Biomed J*. 2019;4(2):e15. Published 2019 Mar 1. doi:10.1016/j.pbj.0000000000000015

Example HDI

Interactions

St John's wort has been shown to induce several drug metabolising enzymes including some cytochrome P450 isoenzymes (in particular CYP3A4) and the transport protein P-glycoprotein. Clinically important interactions resulting in decreased plasma concentrations of the interacting drug have been reported with ciclosporin, digoxin, HIV-protease inhibitors, NNRTIs, oral contraceptives, tacrolimus, theophylline, and warfarin. There is also a possibility of an interaction between St John's wort and antiepileptics. In addition, stopping St John's wort may result in increased, and possibly toxic, concentrations of the interacting drug.

In many countries, including the UK and USA, preparations of St John's wort are not required to be licensed as medicines, and the amount of active ingredient may vary widely between preparations. Changing preparations may therefore alter the degree of enzyme induction.

Use of St John's wort with drugs known to act on serotonergic neurotransmitters may result in synergistic interactions and an increased risk of adverse effects may also occur. Examples include the SSRIs and nefazodone (see Antidepressants, Refer to) and the selective serotonin ($5\text{-}HT_1$) agonists (see under Sumatriptan, Refer to) used to treat migraine.

Title Hormonal Contraceptives / CYP3A4 Inducers (Moderate)

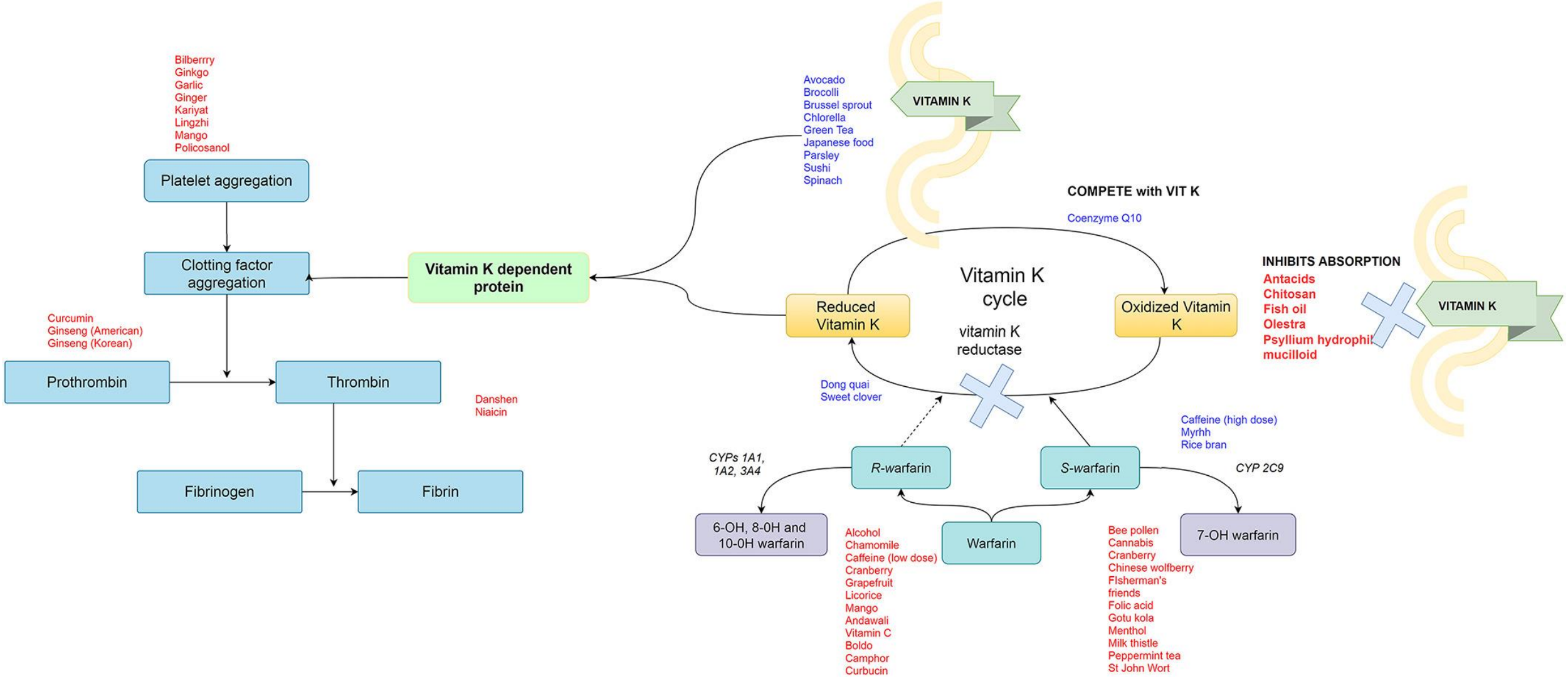
Risk Rating D: Consider therapy modification

Summary CYP3A4 Inducers (Moderate) may decrease the serum concentration of Hormonal Contraceptives. **Severity** Major **Reliability Rating** Good

Patient Management Contraceptive failure is possible. If a moderate CYP3A4 inducer must be used in a patient taking hormonal contraceptives, advise patients to use an alternative method of contraception or a back-up method during coadministration, and to continue back-up contraception for 28 days after discontinuing the moderate CYP3A4 inducer to ensure contraceptive reliability. It is important to note that breakthrough bleeding, though an important sign regarding the diminished effect of many hormonal contraceptives, might not be present in spite of the occurrence of an interaction.

When using levonorgestrel as an emergency contraceptive, recommendations outside of the United States suggest doubling the dose of levonorgestrel to 3 mg in women who have used enzyme inducing drugs in the previous 4 weeks.

HDI and INR



Tan CSS, Lee SWH. Warfarin and food, herbal or dietary supplement interactions: A systematic review. Br J Clin Pharmacol. 2021; 87: 352–374. https://doi-org.proxy1.library.virginia.edu/10.1111/bcp.14404

Common Oncology Issues

CYP ✓

QT ✓

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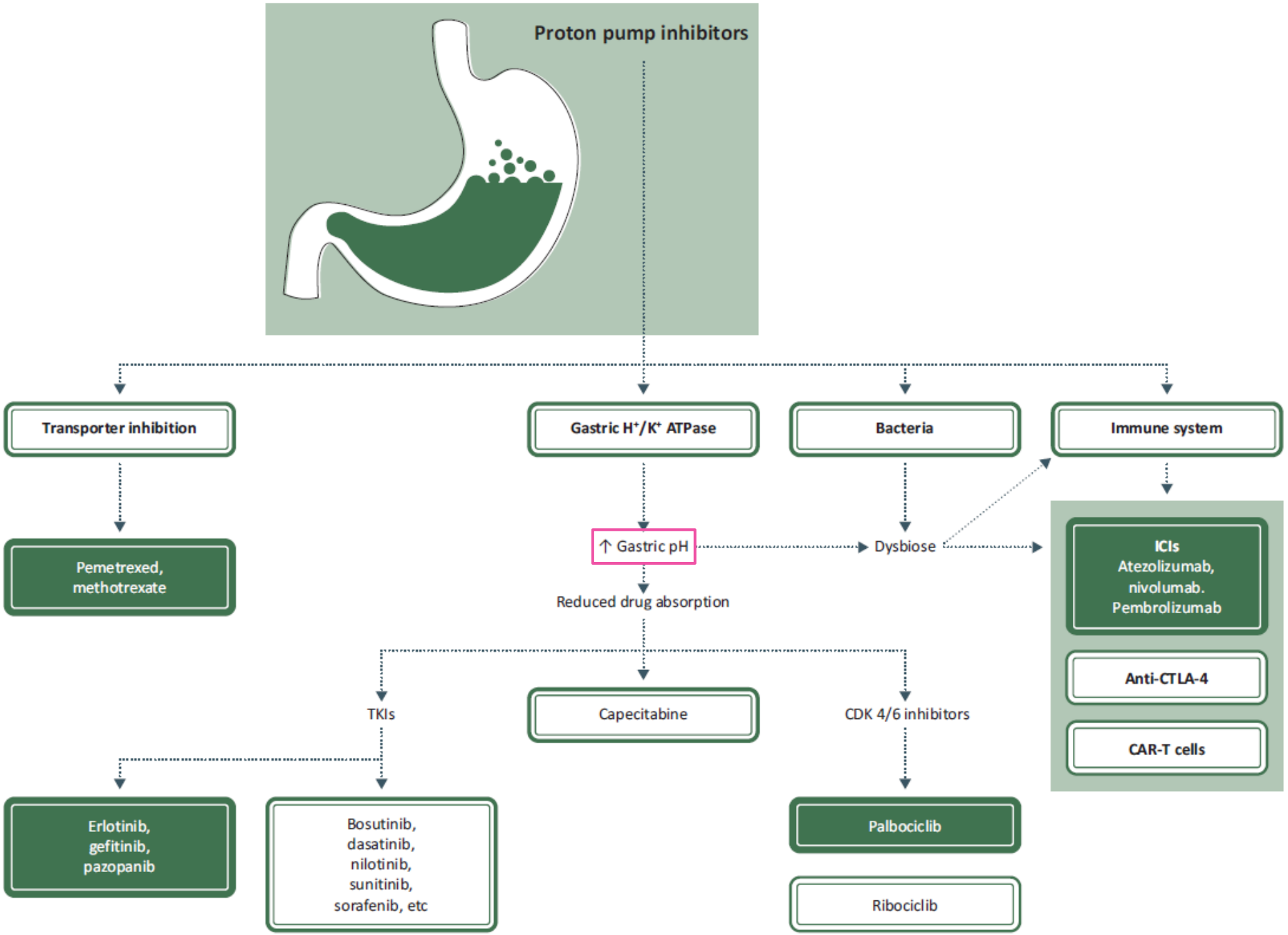
pH

Lohr LK, Blake KT, Chan CM, Sturm S, Walsh GT. Managing Drug Interactions With Oral Anticancer Treatments. *J Adv Pract Oncol*. 2023;14(5):419-438. doi:10.6004/jadpro.2023.14.5.7

Gastric Acid Suppressants (pH)

- Author's study showed that > 25% of cancer patients receiving anticancer treatment use PPIs
- Suppression of gastric acidity can decrease the absorption, and thus the efficacy, of certain targeted therapies
- TKIs (tyrosine kinase inhibitors) are weakly basic → co-administration with a gastric acid suppressant decreases bioavailability
  - Dasatinib, erlotinib, gefitinib, pazopanib, lapatinib, nilotinib, sunitinib and vandetanib display pH-dependent solubility and absorption
- PPI use changes the composition of the gastric and intestinal microbiome, which has an impact on the response to immunotherapy
  - The microbiome can modulate the host's antitumor response and the response to ICIs, anticytotoxic T-lymphocyte-associated protein 4 and CAR-T therapy

Raoul JL, Moreau-Bachelard C, Gilabert M, Edeline J, Frénel JS. Drug-drug interactions with proton pump inhibitors in cancer patients: an underrecognized cause of treatment failure. ESMO Open. 2023 Feb;8(1):100880. doi: 10.1016/j.esmoop.2023.100880. Epub 2023 Feb 8. PMID: 36764092; PMCID: PMC10024146.



Raoul JL, Moreau-Bachelard C, Gilabert M, Edeline J, Frénel JS. Drug-drug interactions with proton pump inhibitors in cancer patients: an underrecognized cause of treatment failure. ESMO Open. 2023 Feb;8(1):100880. doi: 10.1016/j.esmoop.2023.100880. Epub 2023 Feb 8. PMID: 36764092; PMCID: PMC10024146.

When to Consider Potential DDIs

- When a subject is first enrolling to a new protocol
- When any changes are made to a subject's medication regimen
  - Drugs, herbs, dietary supplements, etc.
- When a subject is experiencing side effects
  - Exacerbation of expected chemotherapy side effects
  - Bleeding
- When a medication is not having its intended effect

Call to Action

- Reducing the frequency of drug-drug interactions is an important initiative for patient safety on clinical trials
- CRCs play a huge role in both data integrity and patient safety on a micro and macro level
  - PK studies inform Investigator's Brochure
- Utilize your resources
- **How can we work together to reduce DDIs at the Cancer Center?**

Poll Question

- Describe how CRCs assist with subject safety on clinical trials in regards to prevention of DDIs.
  - **a.** Documenting concomitant medications at appropriate intervals
  - **b.** Alerting study team to potentially harmful new medications
  - **c**. Ensuring PKs are taken at the appropriate time
  - **d.** All of the above

Poll Question

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INVESTIGATIONAL DRUG SERVICES - ONCOLOGY

Activity Code (Part 2)

Activity Code: **150958**

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