In the name of ALLAH

DRUG INTERACTION
CLINICAL CONSIDERATIONS

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BASIC CONCEPTS

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- **What is a drug interaction?**

  An interaction is said to occur when the effects of one drug are changed by the presence of another drug, herbal medicine, food, drink or by some environmental chemical agent.

- **How seriously should interactions be regarded and handled?**

- **Mechanisms of drug interactions:**
  - Pharmacokinetic
  - Pharmacodynamic

Risk Factors for Drug Interactions[1,12–33]

Category	Risk Factor	Potential Effect
Patient characteristics Demographics	Age (< 5 years and ≥ 65 years)	Alterations in drug distribution; ↓ clearance which may result in drug accumulation
	Female gender	↓ ability to metabolize compared to males
Social factors	Nutrition	Affects cytochrome p450 activity (e.g., grapefruit juice inhibits CYP 3A4 activity)
	Smoking	Affects cytochrome p450 activity (i.e., induces CYP 1A2)
	Alcohol	Affects cytochrome p450 activity specifically CYP 2E1
Organ dysfunction	↓ renal function	↓ clearance, which may result in ↑ serum concentrations of drug and accumulation
	↓ hepatic function	↓ metabolism, which may result in ↑ serum concentrations and accumulation of the parent drug and/or metabolite
	Heart Failure (HF)	↑ risk due to number of medications prescribed with comorbidities
	Chronic obstructive pulmonary disease (COPD)	↑ risk due to number of medications prescribed with comorbidities
Metabolic and endocrine	Obesity	↑ distribution of lipophilic drugs
	Fatty liver	Altered metabolism
	Hypoproteinemia	↑ serum drug concentration
Genetic[a]	Genetic polymorphisms (ultrarapid, extensive, intermediate, or poor metabolizers)	Altered metabolism
Acute medical conditions	Dehydration	↑ serum drug concentrations
	Hypotension	↓ clearance
	Hypothermia	↓ clearance
	Infection	↑ catabolism

Risk Factors for Drug Interactions[1,12–33]

Category	Risk Factor	Potential Effect
Drug characteristics	Narrow therapeutic index (NTI)	↑ risk of dose-related adverse drug events
	Highly protein bound	↑ free fraction (active drug) from protein displacement
	Small volume of distribution	Drug confined to the plasma
	Cytochrome p450 substrate	↓↑ serum drug concentration with coadministration inducer or inhibitor precipitant drug
	P-glycoprotein substrate	↓↑ serum drug concentration with coadministration inducer or inhibitor precipitant drug
Other factors	Polypharmacy	Risk of adverse drug interactions ↑ with increase in number of medicines
	Number of prescribers	Number of prescribed drugs ↑ with multiple prescribers
	Number of pharmacies utilized	Number of prescribed drugs ↑ with multiple pharmacies; Pharmacist may not have knowledge of all drugs prescribed to patient
	Self-prescribing	OTC medicines interacting with prescribed medicines
	Duration of hospital stay	Susceptible to hospital-acquired conditions and subsequent drug therapy

BASIC CONCEPTS

- Pharmacokinetic interactions
  - **Drug absorption interactions**
  - **Drug distribution interactions**
  - **Drug metabolism interactions**
  - **Drug excretion interactions**

BASIC CONCEPTS

- Drug absorption interactions
  - **Effects of changes in gastrointestinal pH**

    H2-RA + Ketoconazole
  - **Adsorption, chelation and other complexing mechanisms**

    Quinolone + Calcium carbonate
  - **Changes in gastrointestinal motility**

    Propantheline + Acetaminophen
  - **Induction or inhibition of drug transporter proteins**

    Digoxin + Rifampin

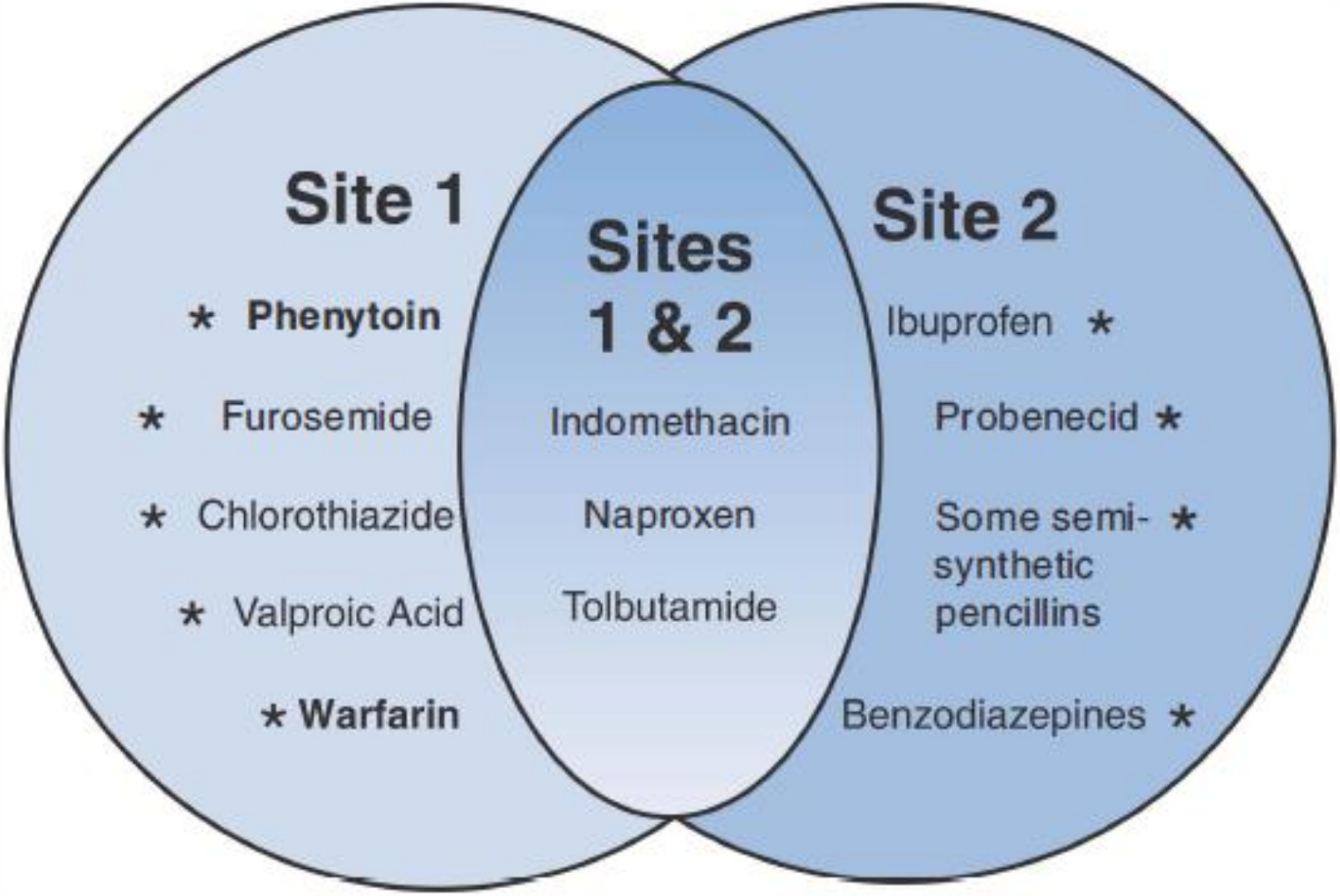
- Drug distribution interactions
  - **Protein-binding interactions**

    Coumarins + Phenytoin
  - **Induction or inhibition of drug transport proteins**

    Protease inhibitors + Azoles

BASIC CONCEPTS

Albumin: Two High Affinity Binding Sites



- Drug metabolism interactions
  - **Changes in first-pass metabolism**

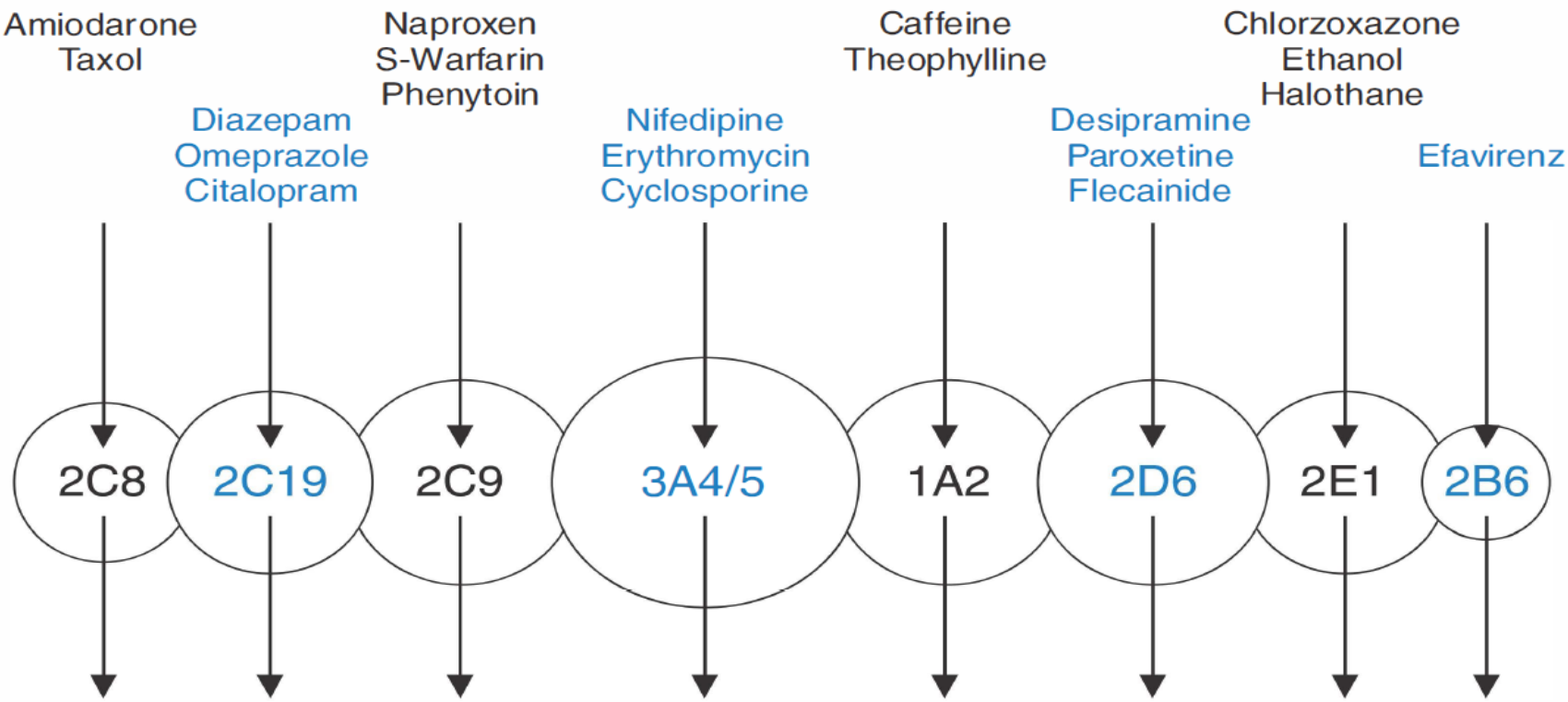
    Hydralazine + Propranolol
  - **Enzyme induction**

    Rifampin + Cyclosporin
  - **Enzyme inhibition**

    Sildenafil + Ritonavir

BASIC CONCEPTS

SUBSTRATES



INHIBITORS

Gemfibrozil
Fluvoxamine
Fluconazole
Itraconazole
Clarithromycin
Ritonavir
Amiodarone
Quinidine
Paroxetine
Disulfiram

INDUCERS

Rifampin
Carbamazepine
Rifampin
Omeprazole
Ethanol
Rifampin

BASIC CONCEPTS

- Drug excretion interactions
  - **Changes in urinary pH**

    Aspirin + Antacids
  - **Changes in active renal tubular excretion**

    Methotrexate + Salicylates
  - **Changes in renal blood flow**

    Lithium + NSAIDs
  - **Biliary excretion and the entero-hepatic shunt**

    Hormonal contraceptives + Antibacterials

    Glibenclamide + Cyclosporine
  -

BASIC CONCEPTS

- Pharmacodynamic interactions
  - **Additive or synergistic interactions**
  - **Antagonistic or opposing interactions**
  - **Drug or neurotransmitter uptake interactions**

❑ Additive or synergistic interactions

- ✓ **The serotonin syndrome**
- ✓ Antipsychotics + Antimuscarinics
- ✓ Antihypertensives + Drugs that cause hypotension
- ✓ Beta-agonist bronchodilators + Potassium-depleting drugs
- ✓ CNS depressants + CNS depressants
- ✓ Drugs that prolong the QT interval + Other drugs that prolong the QT interval
- ✓ Nephrotoxic drugs + Nephrotoxic drugs
- ✓ ACE inhibitors + Potassium-sparing diuretics

BASIC CONCEPTS

- **Antagonistic or opposing interactions**
  - ✓ Coumarins + Vitamin K
  - ✓ Antidiabetics + Glucocorticoids
  - ✓ Levodopa + Antipsychotics

BASIC CONCEPTS

- **Drug or neurotransmitter uptake interactions**

  Tricyclic antidepressants + Inotropes and Vasopressors

BASIC CONCEPTS

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- **Drug-herb interactions**

  St John's wort (*Hypericum perforatum*)

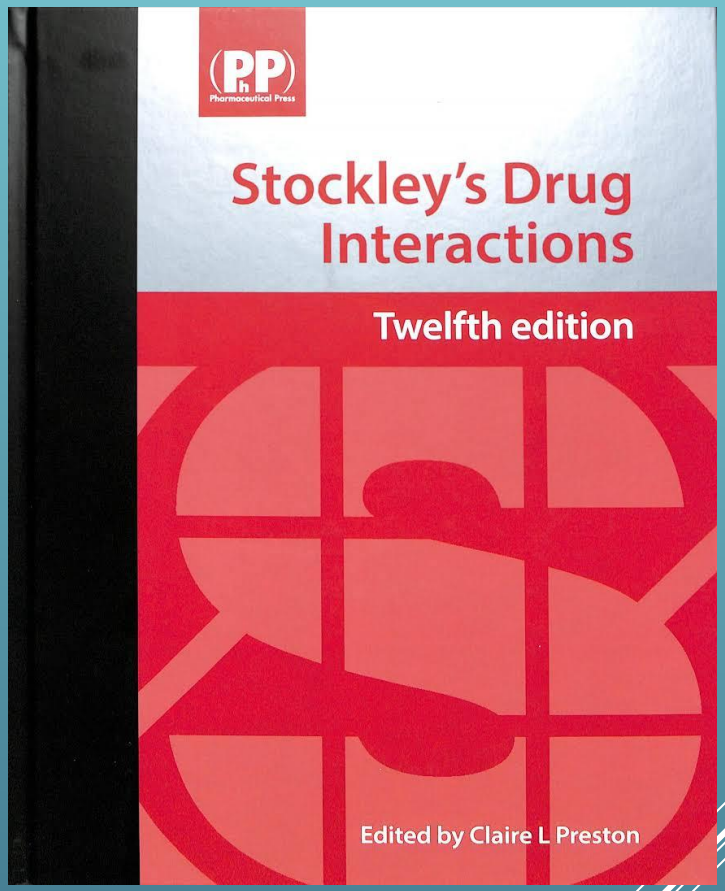
- **Drug-food interactions**

  Cruciferous vegetables and charcoal-broiled meats

  Grapefruit juice

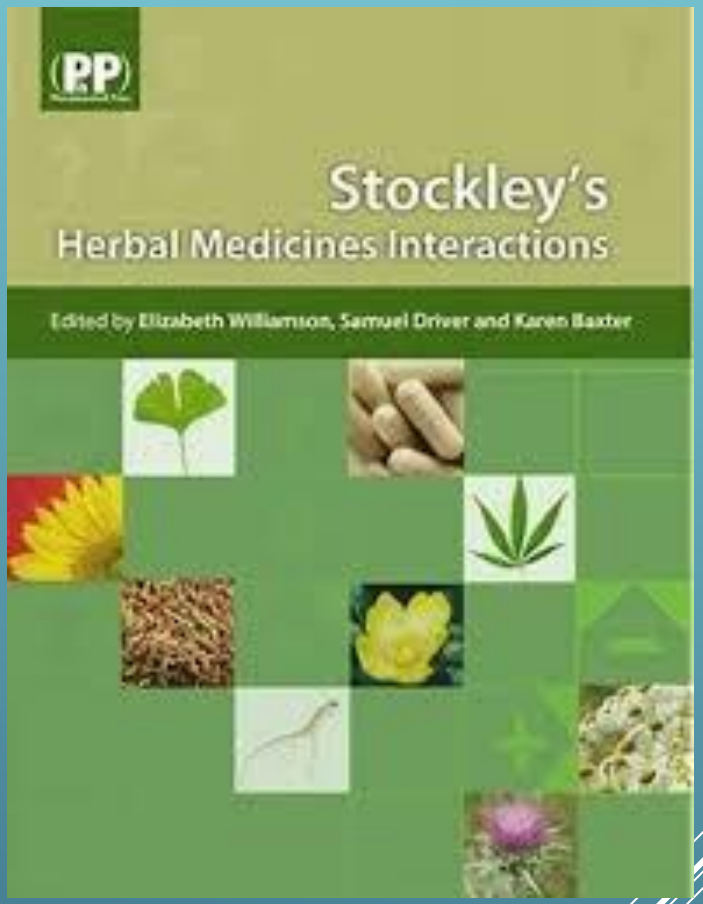
REFERENCES & DATABASES

Stockley’s Drug Interactions



REFERENCES AND DATABASES

Stockley’s Herbal Medicines Interactions



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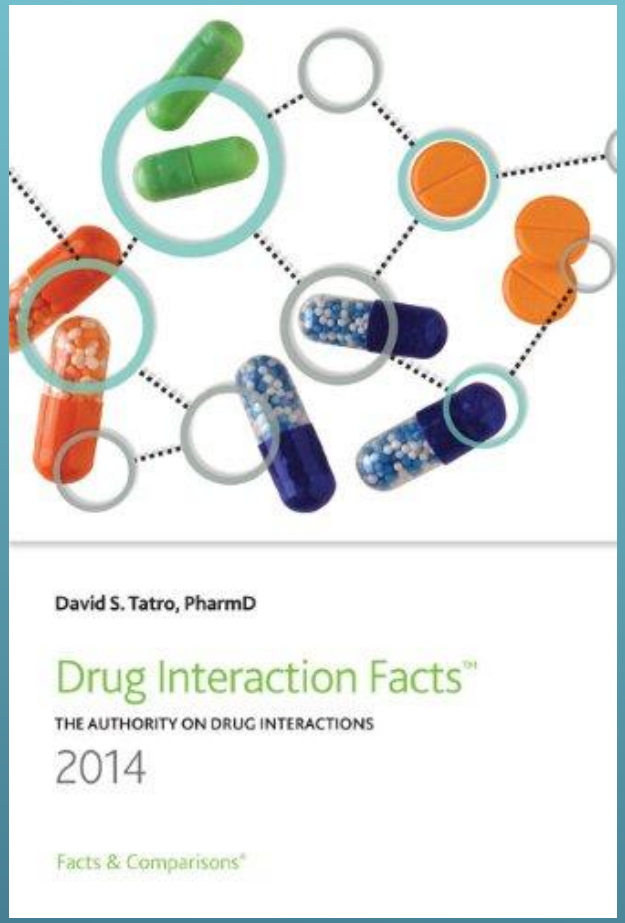

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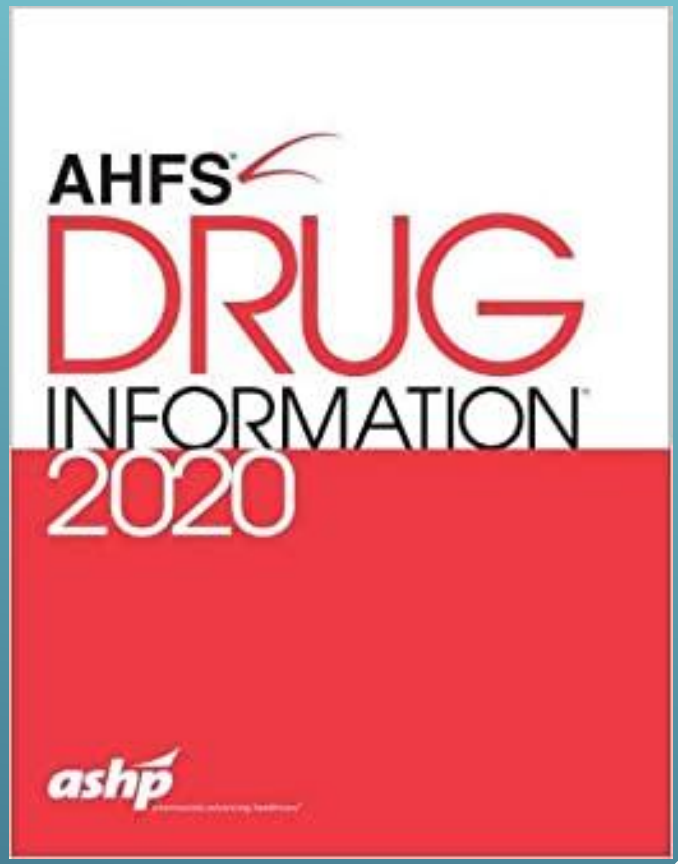
AHFS Drug Information



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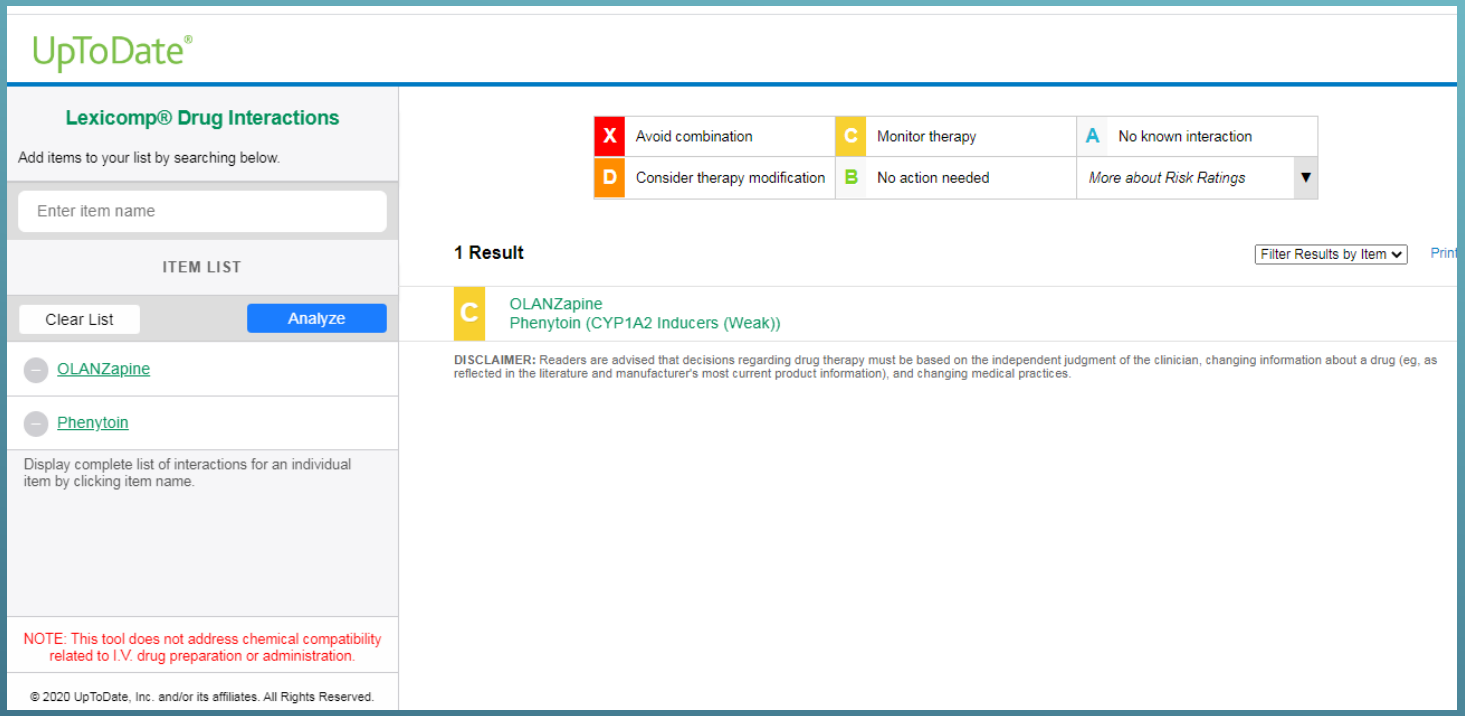
Lexicomp Drug Interaction



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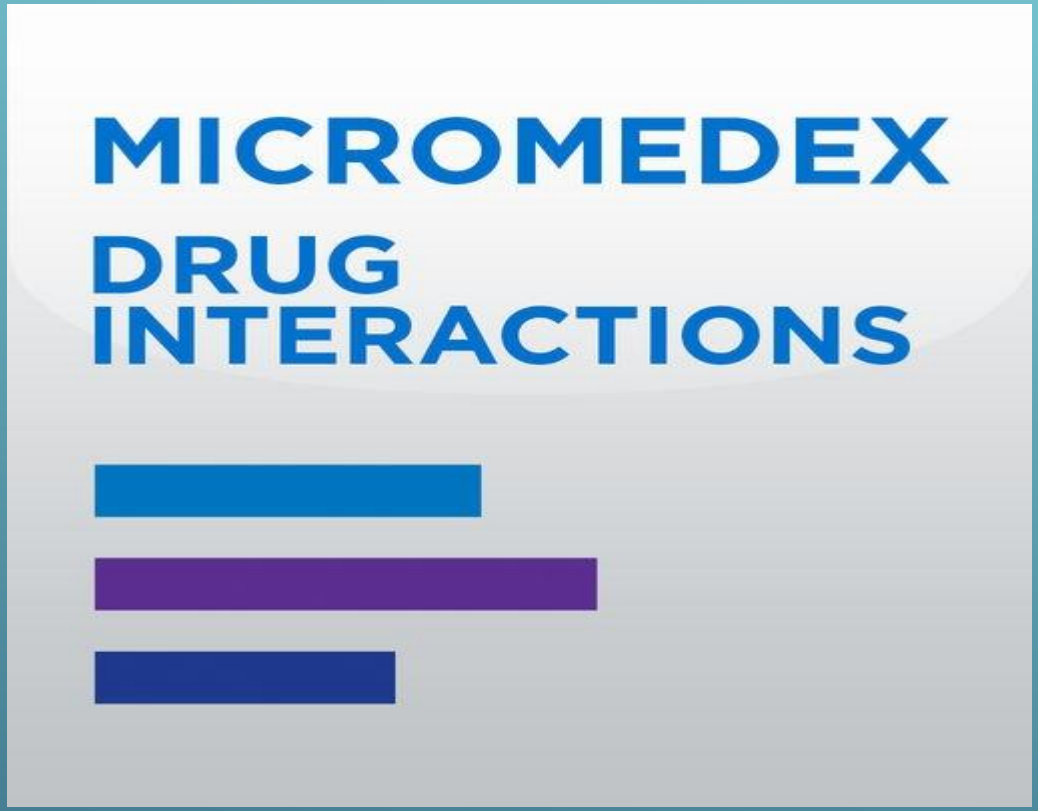

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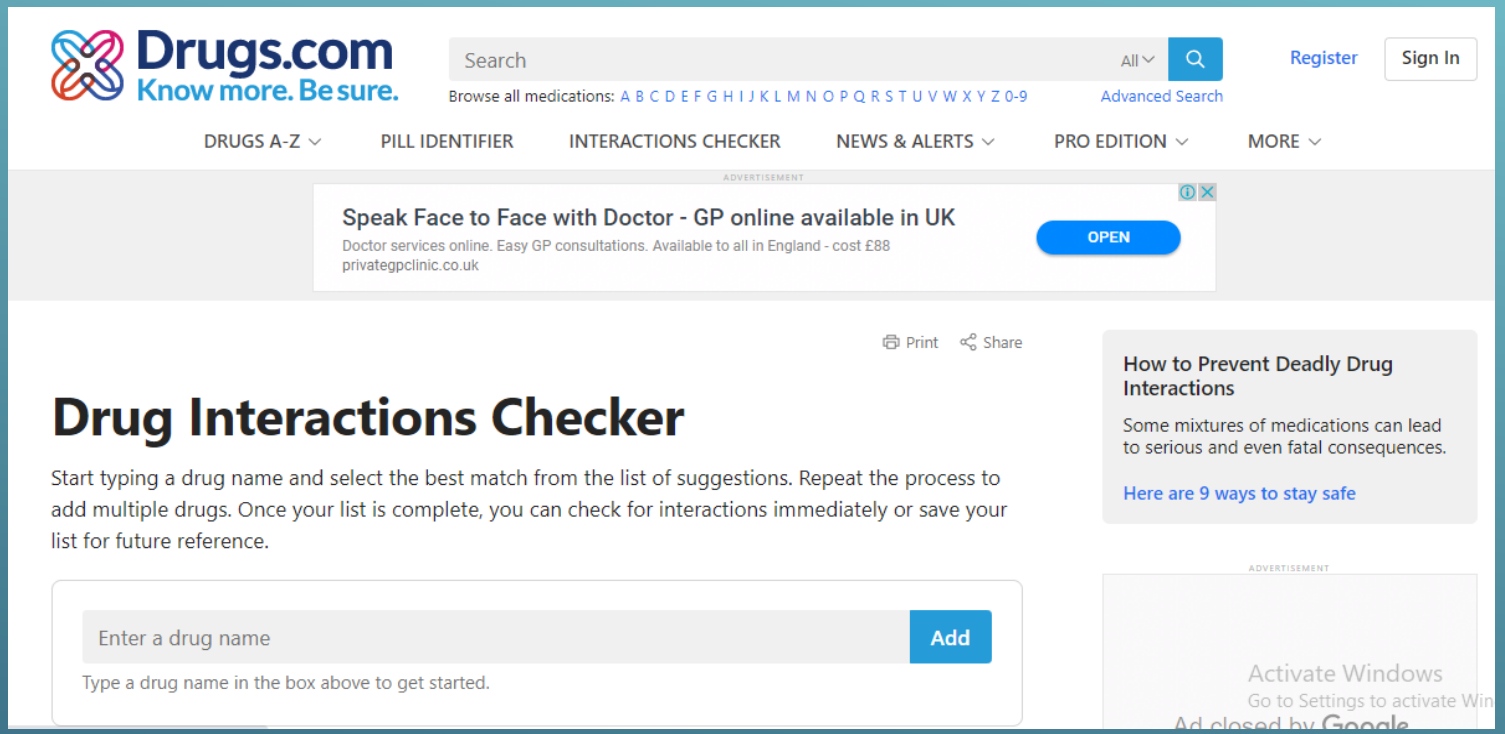

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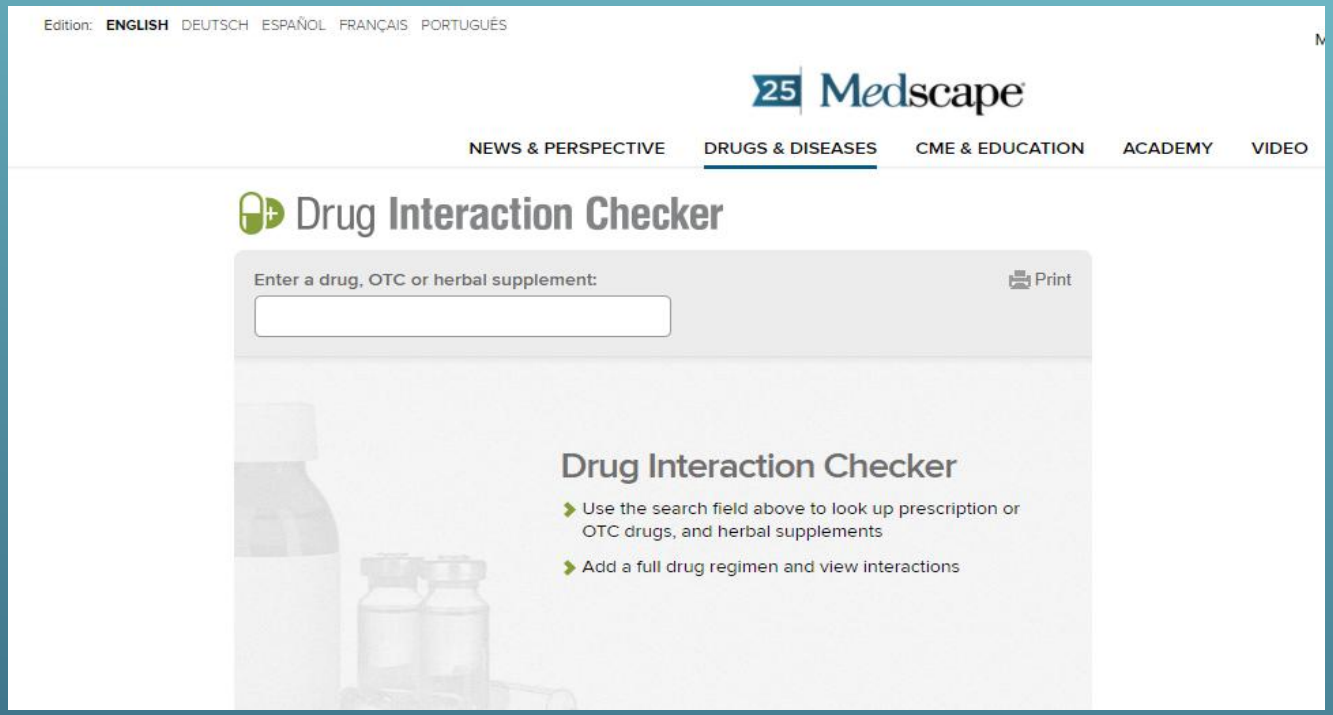

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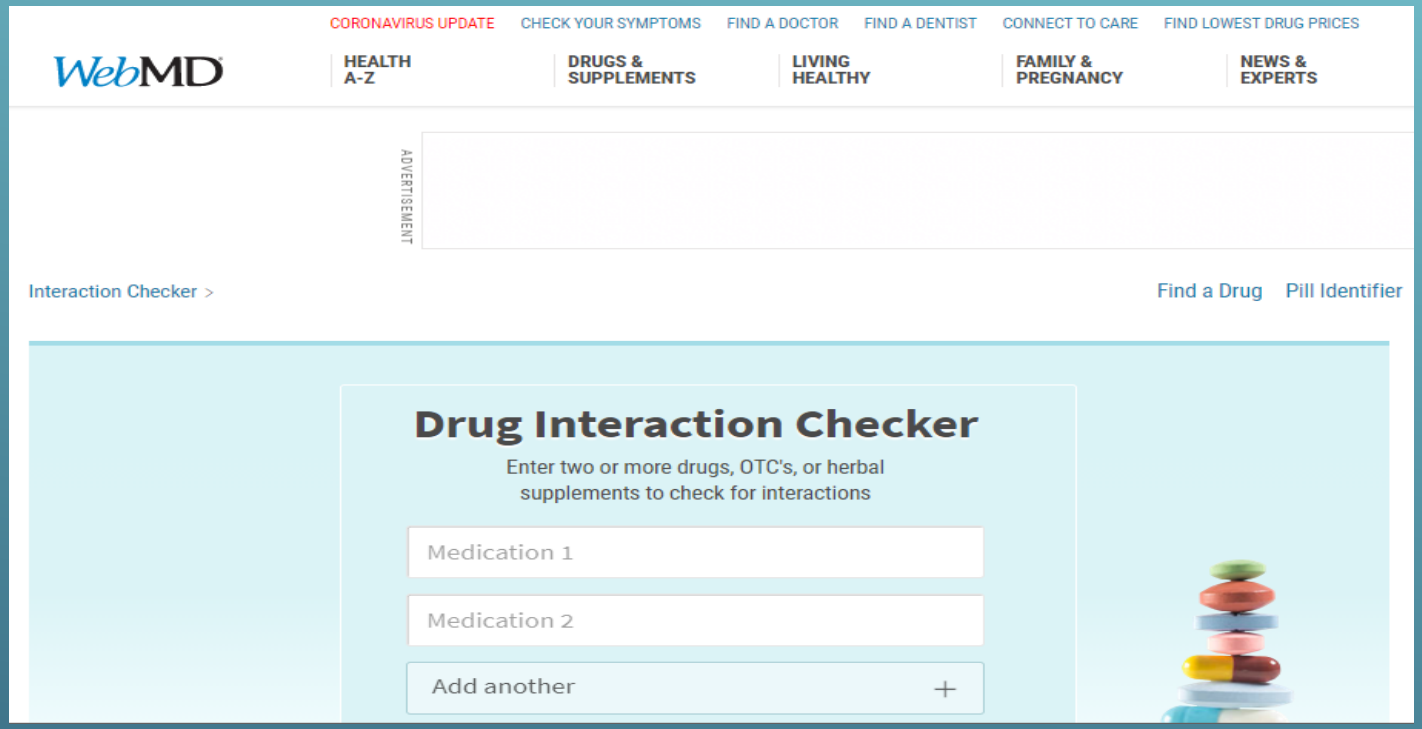

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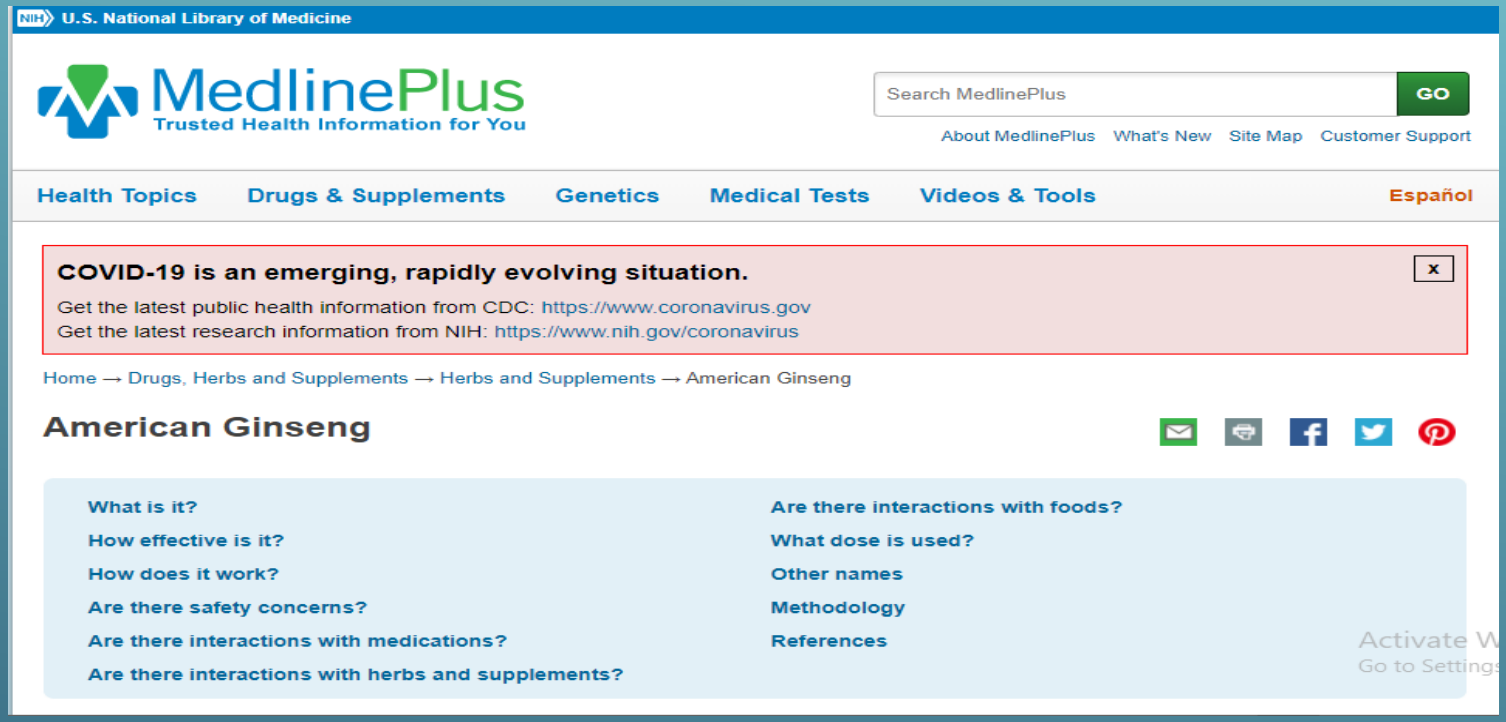


REFERENCES AND DATABASES

SPECIAL DRUG INTERACTIONS

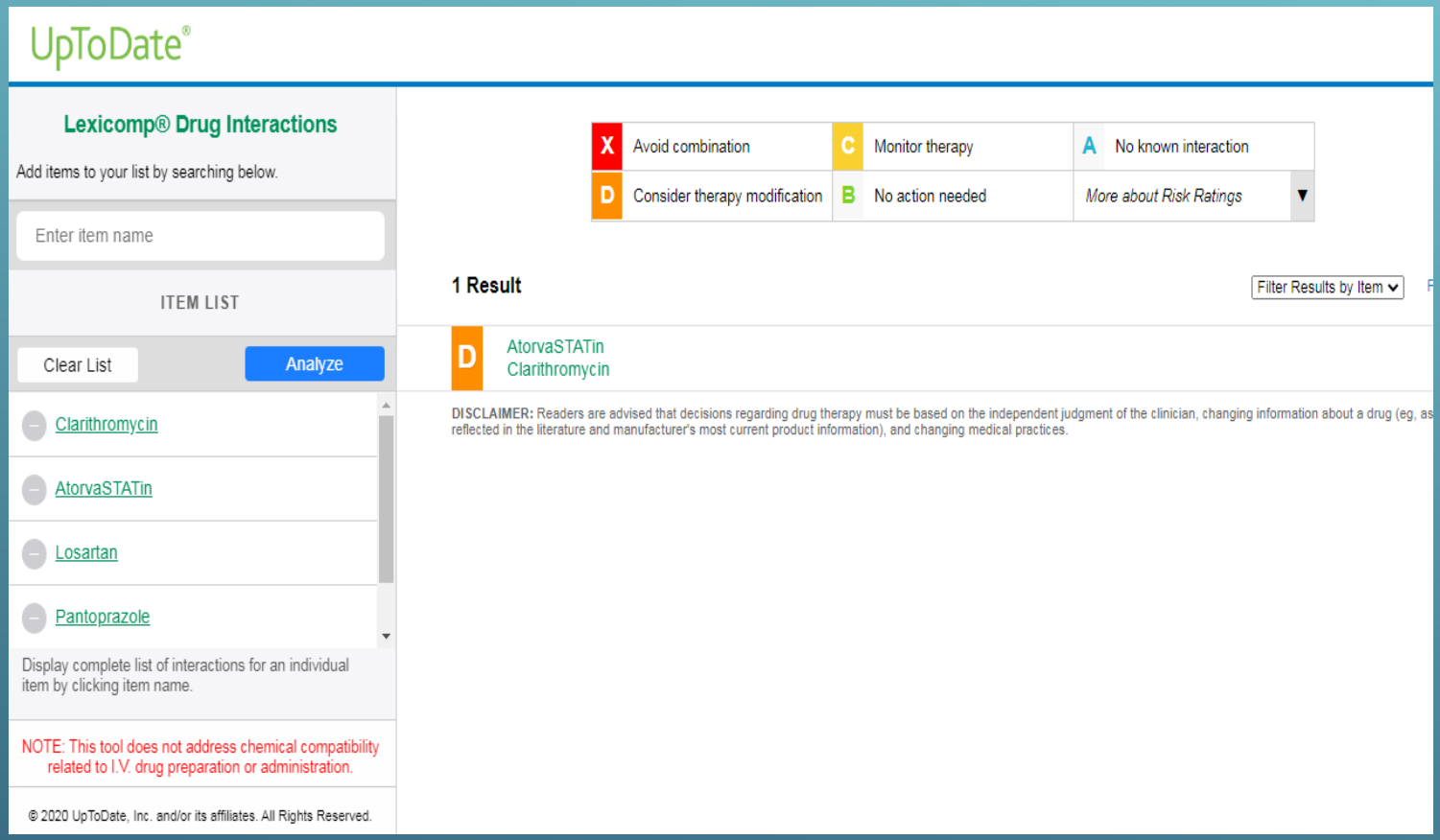
CASE #1

CASE 1

- A 56 years old woman comes to your pharmacy
- PMH: HTN and Dyslipidemia
- DH: Losartan 50 mg BD and Atorvastatin 20 mg QD
- Her physician has diagnosed *Helicobacter pylori* infection and has prescribed following medications;

tab clarithromycin 500 mg	BD
cap amoxicillin 500 mg	2* BD
tab pantoprazole 40 mg	BD

You as a pharmacist checked her drug interactions



What is your decision for this patient?

STATIN INTERACTIONS

- Statins that depend on the cytochrome P-450 (CYP) 3A4 enzyme system to be metabolized are most vulnerable to this interaction (lovastatin, simvastatin, and to a lesser extent atorvastatin).
- Rosuvastatin and pravastatin have the lowest potential for interaction with medications that inhibit the CYP metabolic pathways.
- Gemfibrozil interferes with the glucuronidation of statins, thereby interfering with their renal clearance. This impact may be minimal or up to a three to fourfold increase in statin levels depending upon the specific agent.

	Do Not Use	Use with Caution
Lovastatin/ Simvastatin	Protease Inhibitors Azoles (except fluconazole) Macrolides (except azithromycin) Gemfibrozil Danazol Cyclosporine Emtricitabine Tenofovir Red yeast rice	Amiodarone Amlodipine Diltiazem, Verapamil Fluconazole Efavirenz Fenofibrate Imatinib Ticagrelor Grapefruit juice
Atorvastatin	Posaconazole Voriconazole Red yeast rice	Protease Inhibitors Macrolides (except azithromycin) Other Azoles Gemfibrozil Verapamil, Diltiazem Digoxin Imatinib Cyclosporine, Tacrolimus
Rosuvastatin	Red yeast rice	Protease Inhibitors Clarithromycin Gemfibrozil Cyclosporine, Tacrolimus Antacids

Atorvastatin + Clarithromycin

- **Risk Rating** D: Consider therapy modification
- **Summary** Clarithromycin may increase the serum concentration of Atorvastatin.
- **Patient Management:** Limit atorvastatin to a maximum dose of 20 mg/day when used with clarithromycin. If this combination is used, monitor patients more closely for evidence of atorvastatin toxicity (eg, muscle aches or pains, renal dysfunction)

CASE 1

STATIN INTERACTIONS

- When statin-fibrate combination therapy is indicated, fenofibrate is preferred
- Under any circumstance, the use of gemfibrozil should be avoided in combination with lovastatin, pravastatin, and simvastatin.

CASE #2

CASE 2

- A 33 years old man comes to emergency ward with tremor, akathisia and hyperthermia
- PMH: Depression, Insomnia
- HH: opium addiction
- DH: sertraline 100 mg QD zolpidem 10 since 2 years ago, Methadone 20 mg BD since last week
- What’s your idea about possible diagnosis as a GP?

SEROTONIN SYNDROME

- Serotonin syndrome, also referred to as serotonin toxicity, is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system.
- It is seen with therapeutic medication use, inadvertent interactions between drugs, and intentional self-poisoning.
- Although classically described as the triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities, serotonin syndrome is actually a spectrum of clinical findings ranging from benign to lethal

Table 3. Mechanisms of Serotonin Syndrome and the Drugs Associated with Each

Mechanism	Associated Drugs
Inhibit Serotonin Uptake	**Amphetamines/weight loss drugs:** phentermine **Antidepressants:** bupropion, nefazodone, trazodone **Antiemetics:** granisetron, ondansetron **Antihistamines:** chlorpheniramine **Certain opiates:** levomethorphan, levorphanol, meperidine, methadone, pentazocine, pethidine, tapentadol, tramadol **Drugs of abuse:** cocaine, MDMA ("Ecstasy") **Herbal supplements:** St. John's wort (*Hypericum perforatum*) **Over-the-counter cold remedies:** dextromethorphan **SNRIs:** desvenlafaxine, duloxetine, venlafaxine **SSRIs:** citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline **TCAs:** amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine
Inhibit Serotonin Metabolism	**Anxiolytics:** buspirone **Herbal supplements:** St. John's wort (*Hypericum perforatum*) **MAOIs:** furazolidone, isocarboxazid, linezolid, methylene blue, phenelzine, selegiline, Syrian rue, tranylcypromine **Triptans:** almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
Increase Serotonin Synthesis	**Amphetamines/weight loss drugs:** phentermine **Dietary supplements:** L-tryptophan **Drugs of abuse:** cocaine

Table 3. Mechanisms of Serotonin Syndrome and the Drugs Associated with Each

Mechanism	Associated Drugs
Increase Serotonin Release	**Antidepressants:** mirtazapine **Amphetamines/weight loss drugs:** phentermine **Certain opiates:** meperidine, oxycodone, tramadol **Drugs of abuse:** MDMA ("Ecstasy") **Over-the-counter cold remedies:** dextromethorphan **Parkinson disease treatment/amino acid:** L-dopa
Activate Serotonin Receptors	**Anxiolytics:** buspirone **Antidepressants:** mirtazapine, trazodone **Antimigraines:** dihydroergotamine, triptans **Certain opiates:** fentanyl, meperidine **Drugs of abuse:** LSD **Mood stabilizers:** lithium **Prokinetic agents:** metoclopramide
Inhibit CYP450 Microsomal Oxidases	**CYP2D6** **Inhibitors:** fluoxetine, sertraline **Substrates:** dextromethorphan, oxycodone, phentermine, risperidone, tramadol **CYP3A4** **Inhibitors:** ciprofloxacin, ritonavir **Substrates:** methadone, oxycodone, venlafaxine **CYP2C19** **Inhibitors:** fluconazole **Substrates:** citalopram

SEROTONIN SYNDROME

- Prevention of serotonin syndrome begins with awareness by physicians and patients of the potential for toxicity from serotonergic drugs.[1]
- Avoiding the combined use of serotonin-augmenting drugs is essential. Physicians should modify prescribing practices to minimize coprescription of drugs known to have a high probability of inducing serotonin syndrome.

Serotonergic Agents (High Risk) + Methadone

- **Risk Rating** C: Monitor therapy
- **Summary** Methadone may enhance the serotonergic effect of Serotonergic Agents (High Risk). This could result in serotonin syndrome.
- **Patient Management** Monitor for signs and symptoms of serotonin syndrome/serotonin toxicity (eg, hyperreflexia, clonus, hyperthermia, diaphoresis, tremor, autonomic instability, mental status changes) when these drugs are combined.
- Patients with other risk factors (eg, higher drug concentrations/doses, greater numbers of serotonergic agents) are likely at greater risk for these potentially life-threatening toxicities.

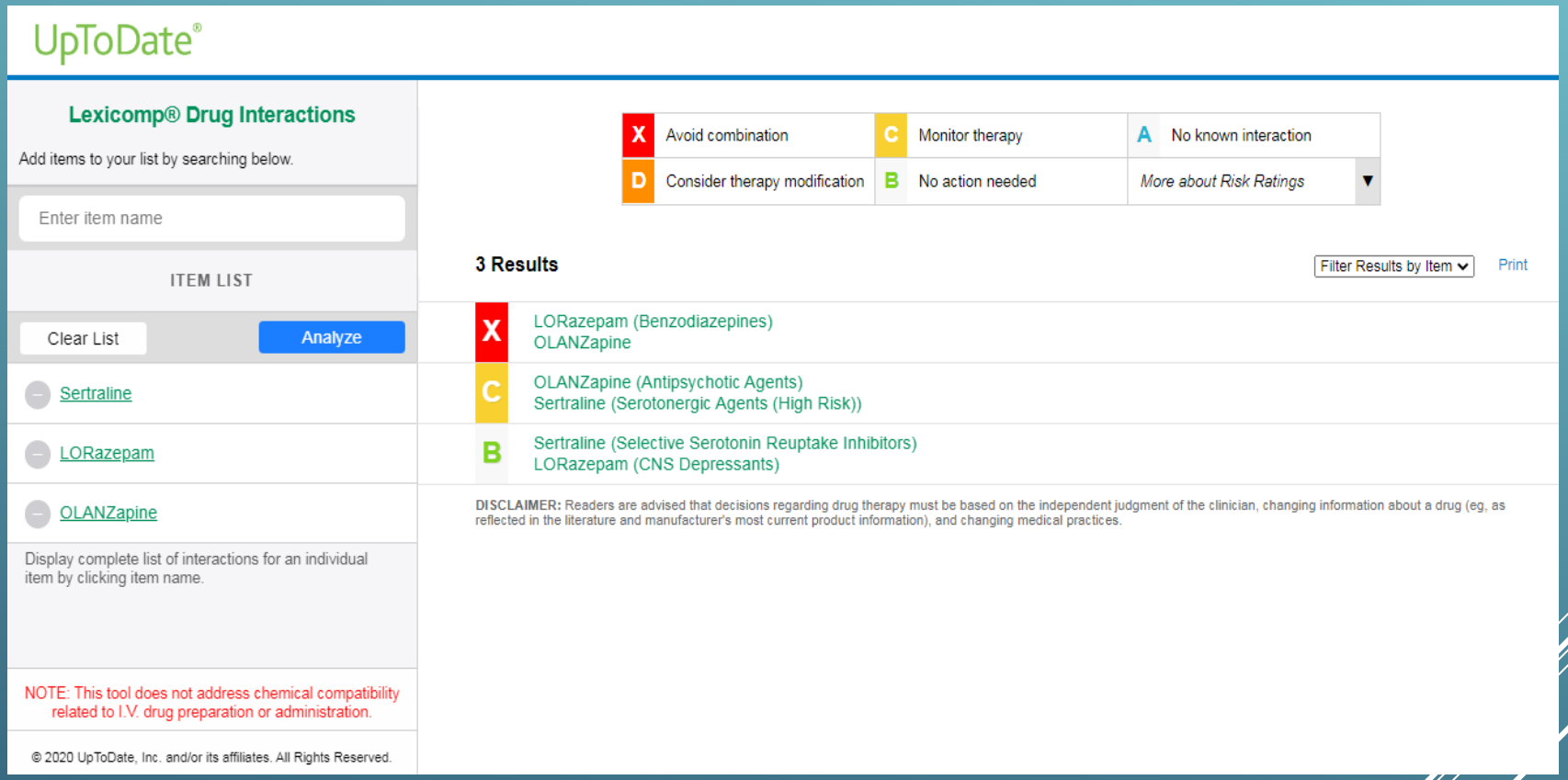
CASE 2

CASE #3

CASE 3

- A 52 years old woman calls with you in drug and poison information center and asks about her drugs interaction.
- PMH: GAD, OCD
- DH: tab Sertraline 50 mg QD, tab Lorazepam 1 mg QHS, and tab Olanzapine 2.5 mg QD since 5 years ago.

You check Lexicomp Drug Interaction database and find following result:



What's your advice to this woman about her medications?

Benzodiazepines + Olanzapine

- **Route**: Clinical significance and severity of this interaction may be lower with oral olanzapine and/or oral benzodiazepines.
- Olanzapine prescribing information specifically recommends avoiding the (route-specific) combination of IM olanzapine with a parenteral benzodiazepine.
- **Risk Rating** X: Avoid combination
- **Summary** Olanzapine may enhance the adverse/toxic effect of Benzodiazepines.

CASE 3

OLANZAPINE + BENZODIAZEPINE

- **Patient Management**

  Olanzapine prescribing information recommends to avoid concomitant use of parenteral benzodiazepines and intramuscular (IM) olanzapine due to risks of additive adverse effects (e.g., cardiorespiratory depression, excessive sedation). Additive pharmacologic effects might also be expected with oral use of these agents, but specific recommendations for management are lacking.

CASE #4

CASE 4

A 68 years old woman comes to your pharmacy with following prescription:

tab ciprofloxacin 250 mg BD

tab levothyroxine 0.1 mg QD

tab calcium-D QD

tab raloxifen 60 mg QD

tab ferfolic QD

What is your advice to this patient as a pharmacist?

Medication	Advice when coadministered with polyvalent cations
Ofloxacin	Administer 2 hours before or 2 hours after polyvalent cations
Moxifloxacin	Administer 4 hours before or 8 hours after polyvalent cations
Ciprofloxacin	Administer 2 hours before or 6 hours after polyvalent cations
Gemifloxacin	Administer 3 hours before or 2 hours after polyvalent cations
Nalidixic acid	Administer 2 hours before or 2 hours after polyvalent cations
Levofloxacin	Administer 2 hours before or 2 hours after polyvalent cations
Tetracycline	Administer 4 hours before or 2 hours after polyvalent cations
Doxycycline	Administer 4 hours before or 2 hours after polyvalent cations
Alendronate	Administer 30 mins before or 2 hours after polyvalent cations
Penicillamine	Administer 1 hours before or 1 hours after polyvalent cations
Levothyroxine	Administer 4 hours before or 4 hours after polyvalent cations
Mycophenolate	Administer 2 hours before polyvalent cations

- Levothyroxine 7 AM, at least 30 mins before breakfast
- Ciprofloxacin 11 AM, 4 hours after levothyroxine and 2 hours before Calcium-D
  11 PM
- Calcium-D 1 PM, 2 hours after ciprofloxacin and at least 2 hours before ferfolic
- Ferfolic 3 PM, 2 hours after Calcium-D
- Raloxifen 7 PM, 12 hours interval with levothyroxine

CASE 4


Thanks for your attention