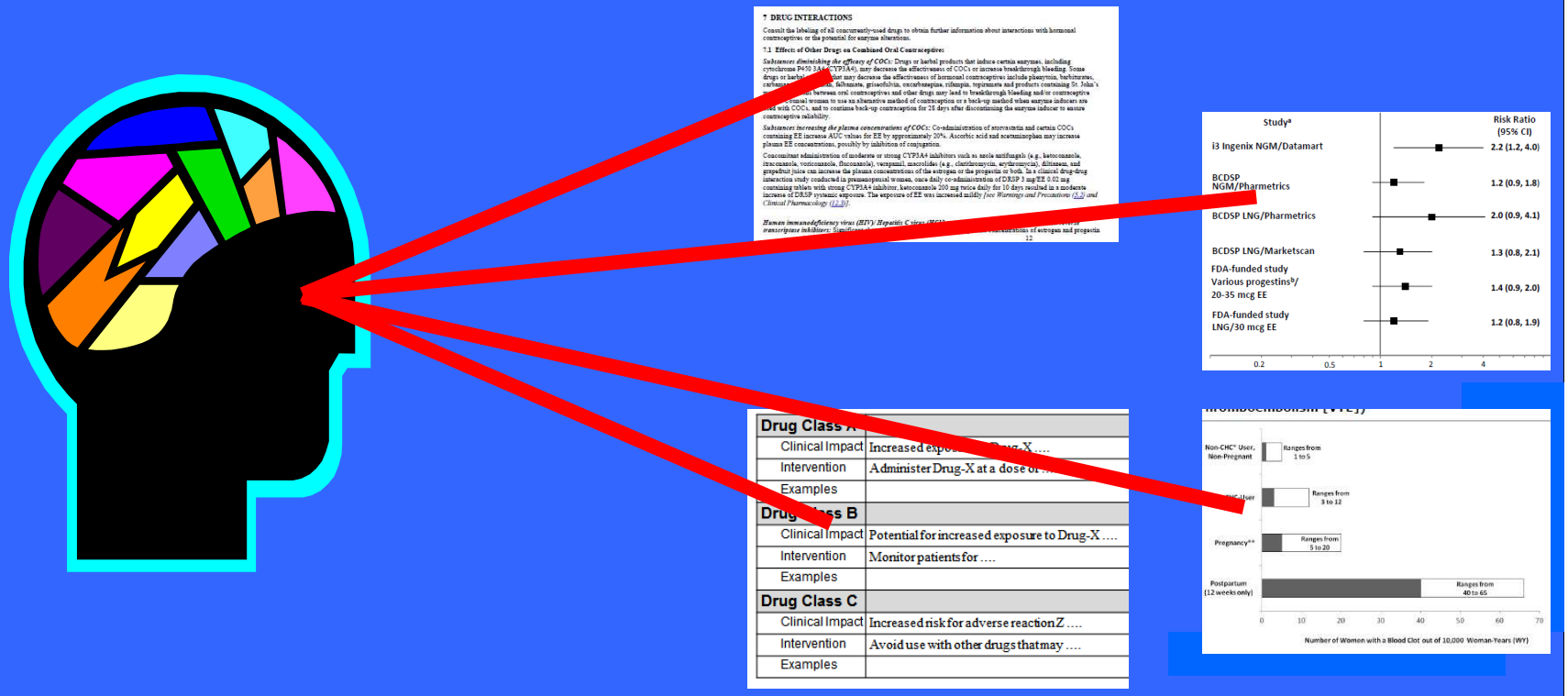
Drug Interactions with Hormonal Contraceptives

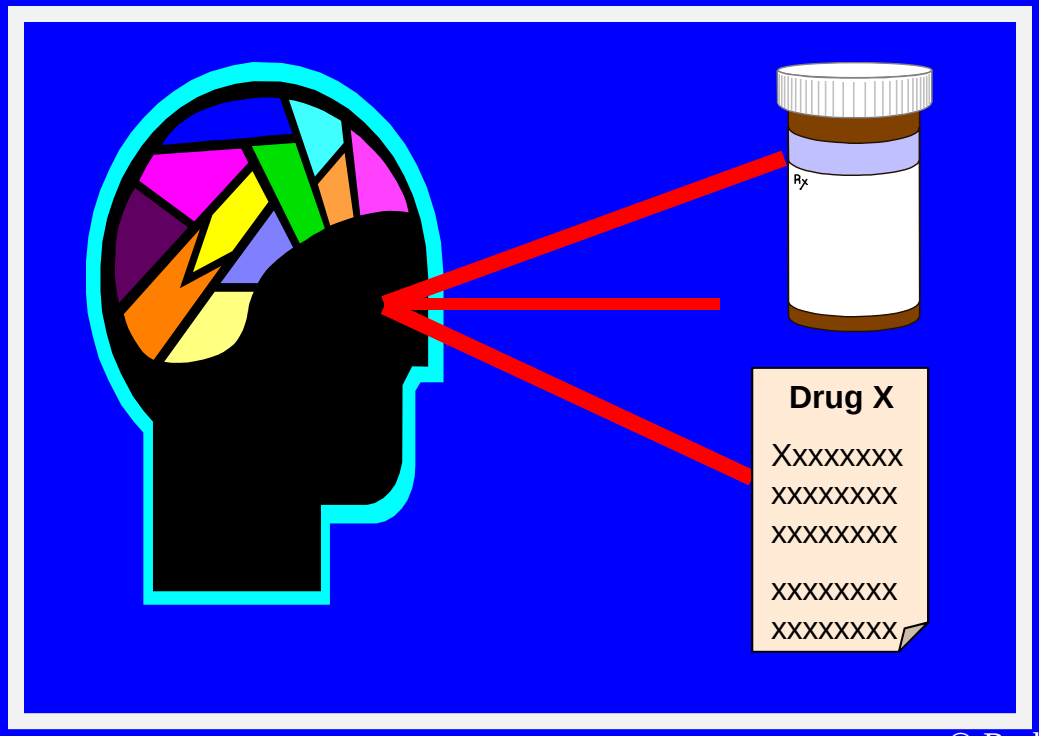
Alternative Displays & Effects on Cognition



Ruth S. Day / Duke University

FDA DDI-HC Meeting / Nov. 9, 2015

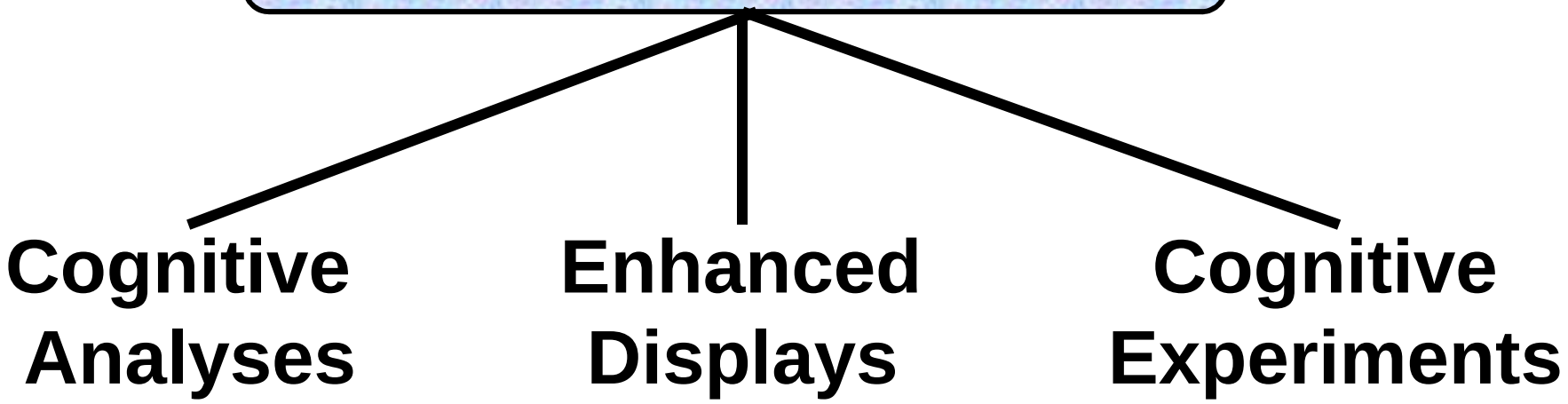
Medical Cognition Laboratory



Rx

Comprehension, memory, and use of drug information.

Basic Approach

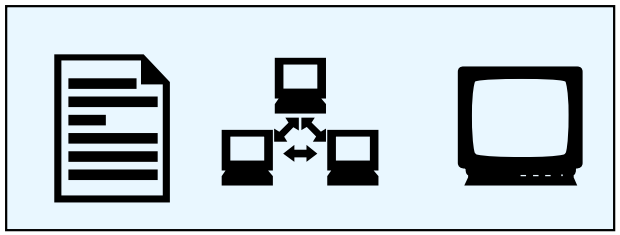


Basic Approach

Cognitive Analyses

Enhanced Displays

Cognitive Experiments

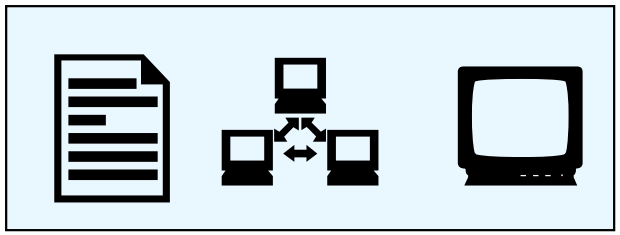


--Obtain quantitative measures

--Calculate "cognitive accessibility"

Basic Approach

Cognitive Analyses



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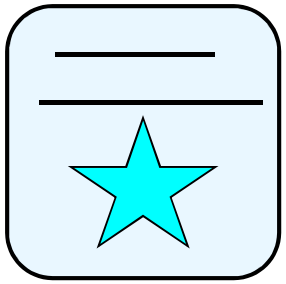


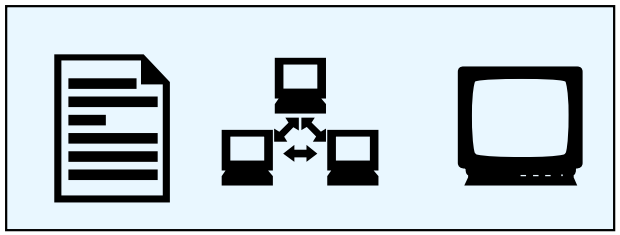
--Same info

--Based on cognitive principles

Cognitive Experiments

Basic Approach

Cognitive Analyses



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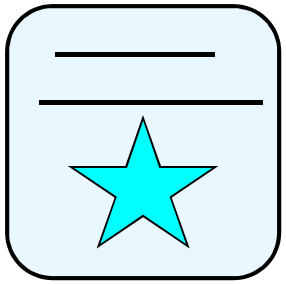

--Same info

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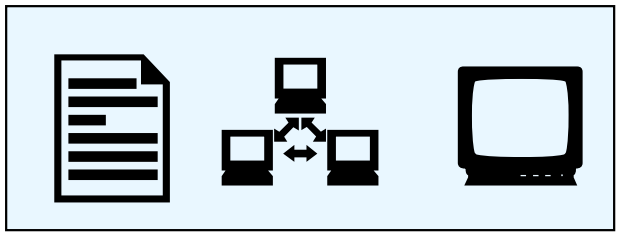
Cognitive Experiments

Test effects on:

--Attention
--Comprehension
--Memory
--Problem Solving
--Decision Making
--Behavior

Basic Approach

Cognitive Analyses



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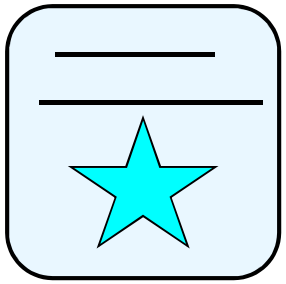

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--Attention
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--Behavior

Health Outcomes

Ruth Day

Basic Approach

Today

Cognitive Analyses

DDI for HC

--Labeling for:

--sample HC's

--sample DI drugs (antivirals)

Basic Approach

Today

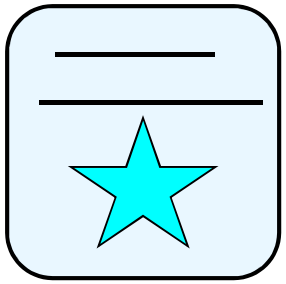
Cognitive Analyses

--Labeling for:

--sample HC's

--sample DI drugs (antivirals)

Enhanced Displays



--Key info

--Based on cognitive principles

Basic Approach

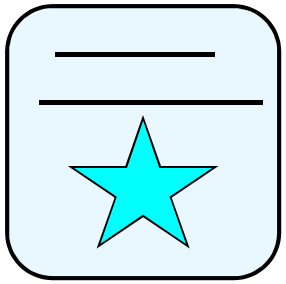
Today

Cognitive Analyses

DDI for HC

--Labeling for:
- --sample HC's
- --sample DI drugs (antivirals)

Enhanced Displays



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Cognitive Experiments

Test effects on:

- --Attention
- --Comprehension
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- --Behavior

Health Outcomes

Ruth Day

DDI Labeling

–Drug Interactions (Section 7)
–Clinical Pharmacology (Section 12)
–Dosage and Administration (Section 2)

--Patient Counseling (Section 17)

Cognitive Accessibility

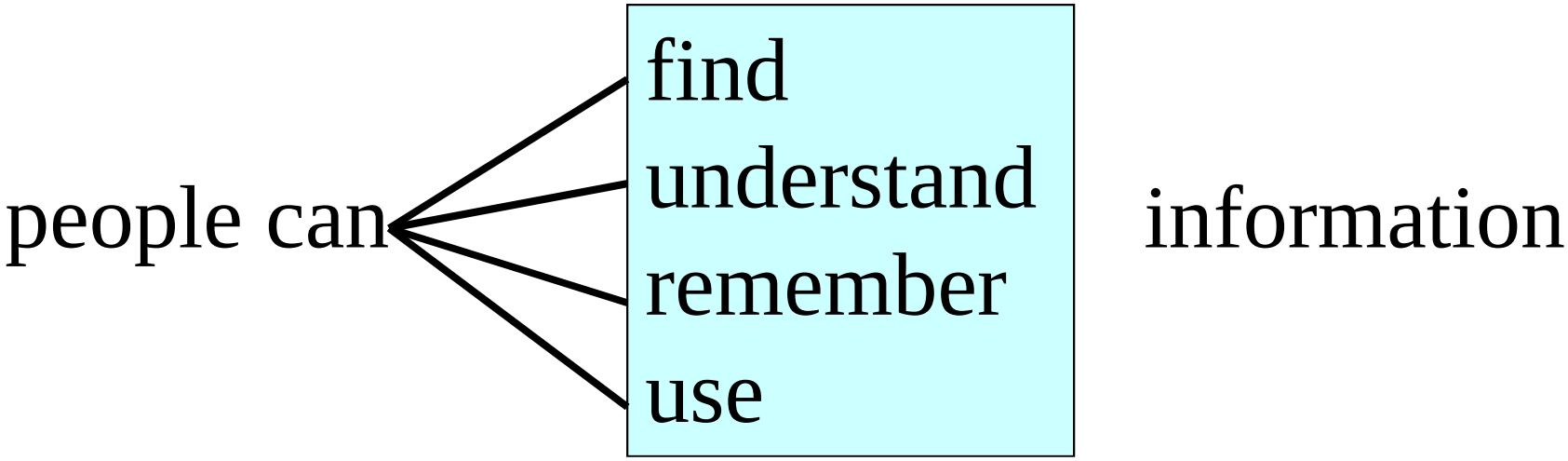
Ruth Day

Cognitive Accessibility

The ease with which

Cognitive Accessibility

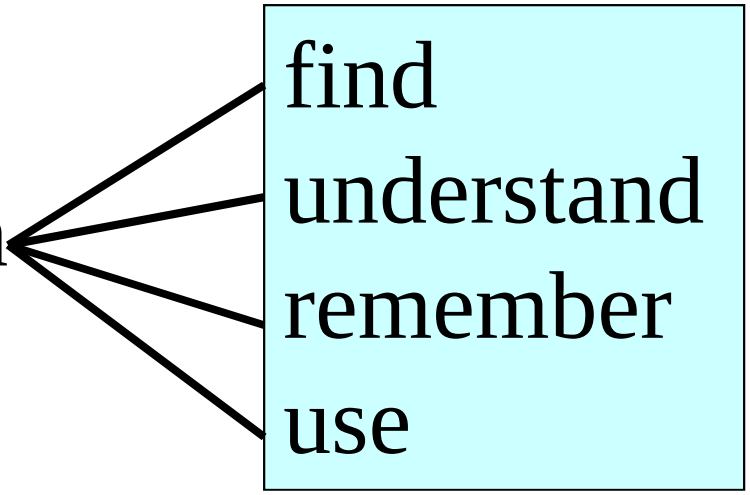
The ease with which



Cognitive Accessibility

The ease with which

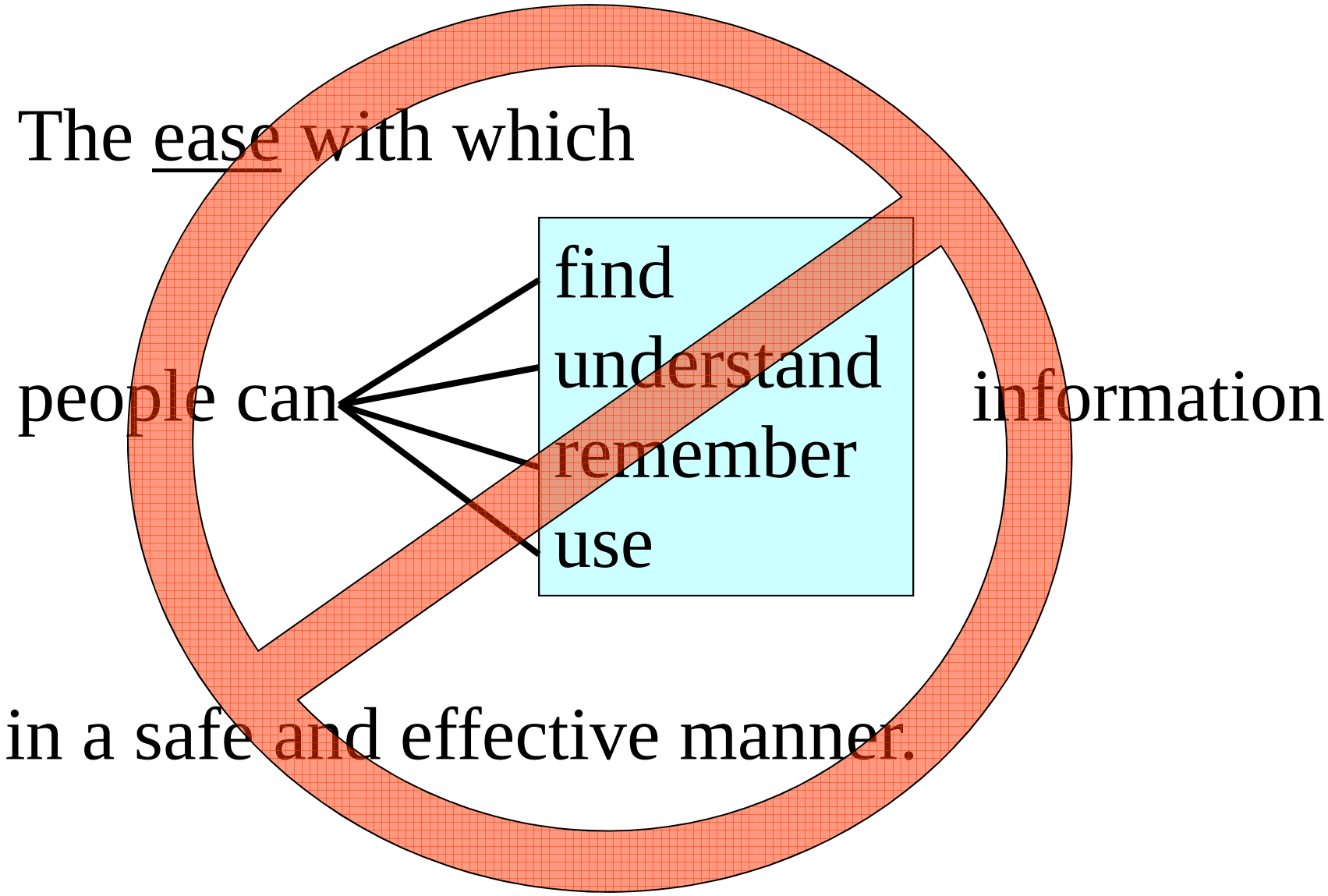
people can



information

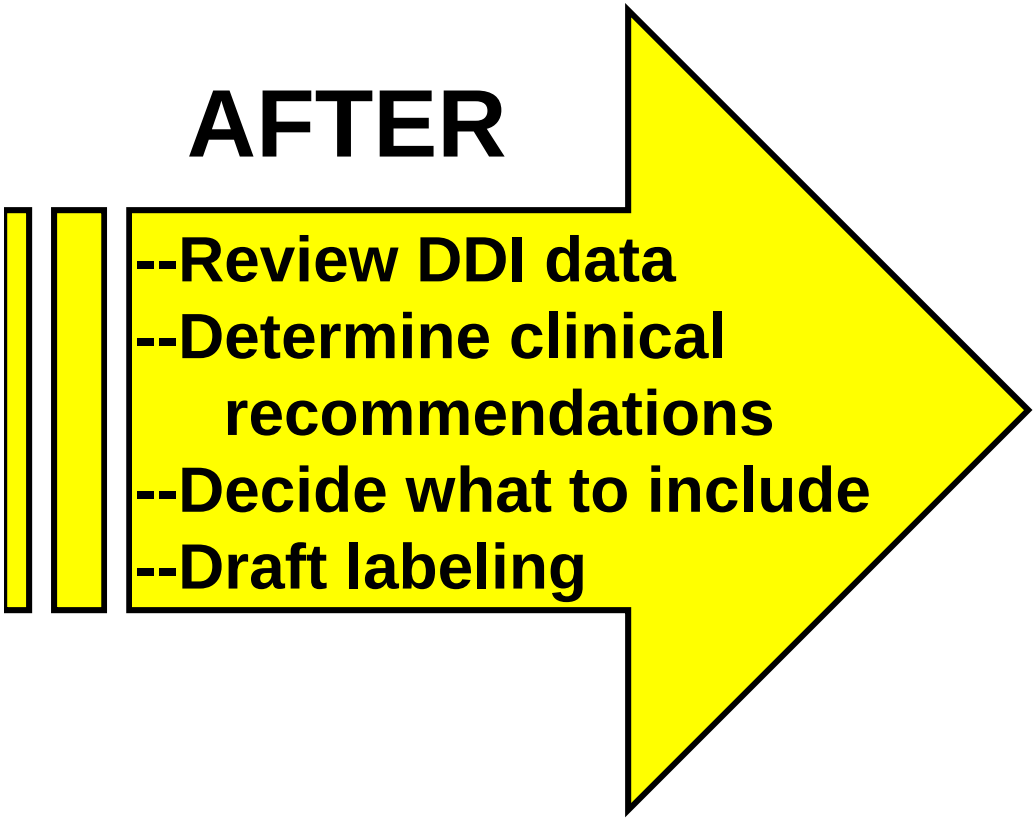
in a safe and effective manner.

Cognitive IN-Accessibility

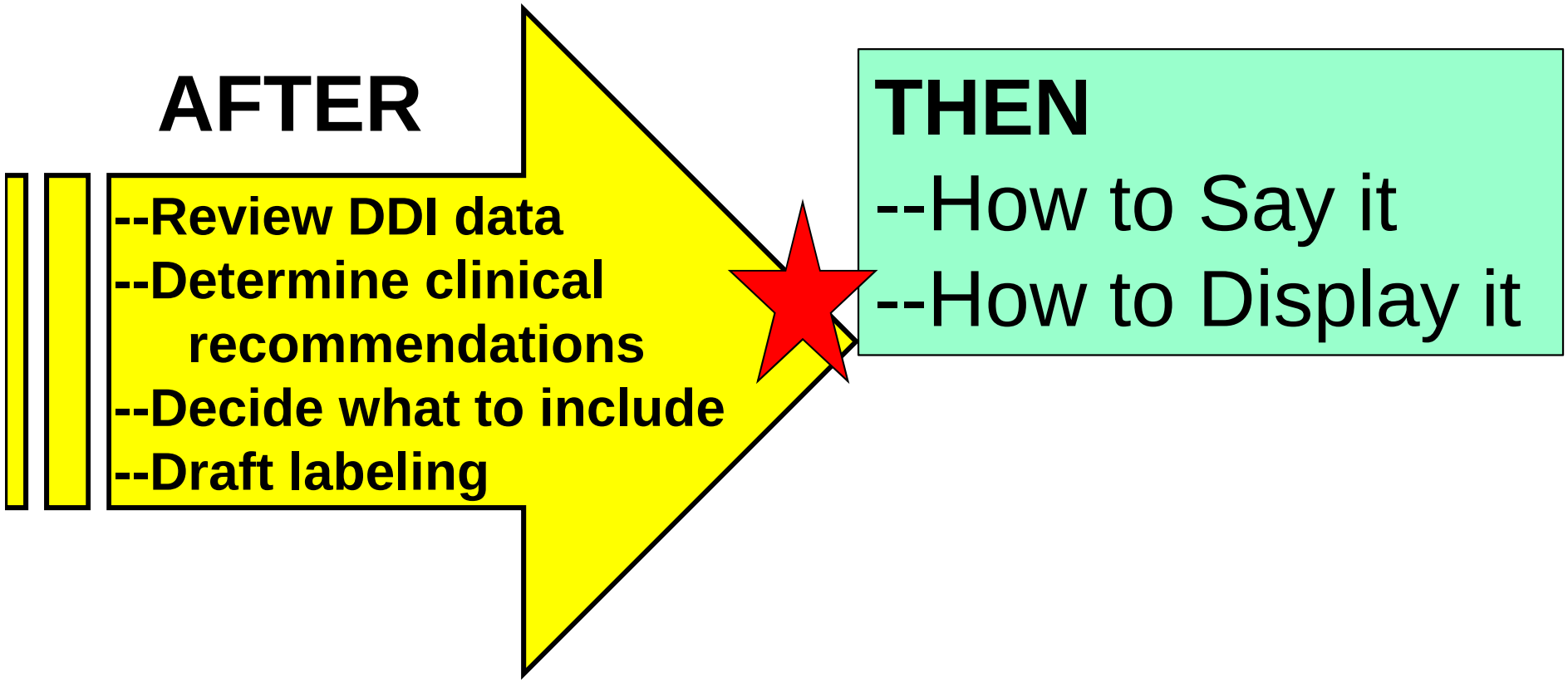


Ruth Day

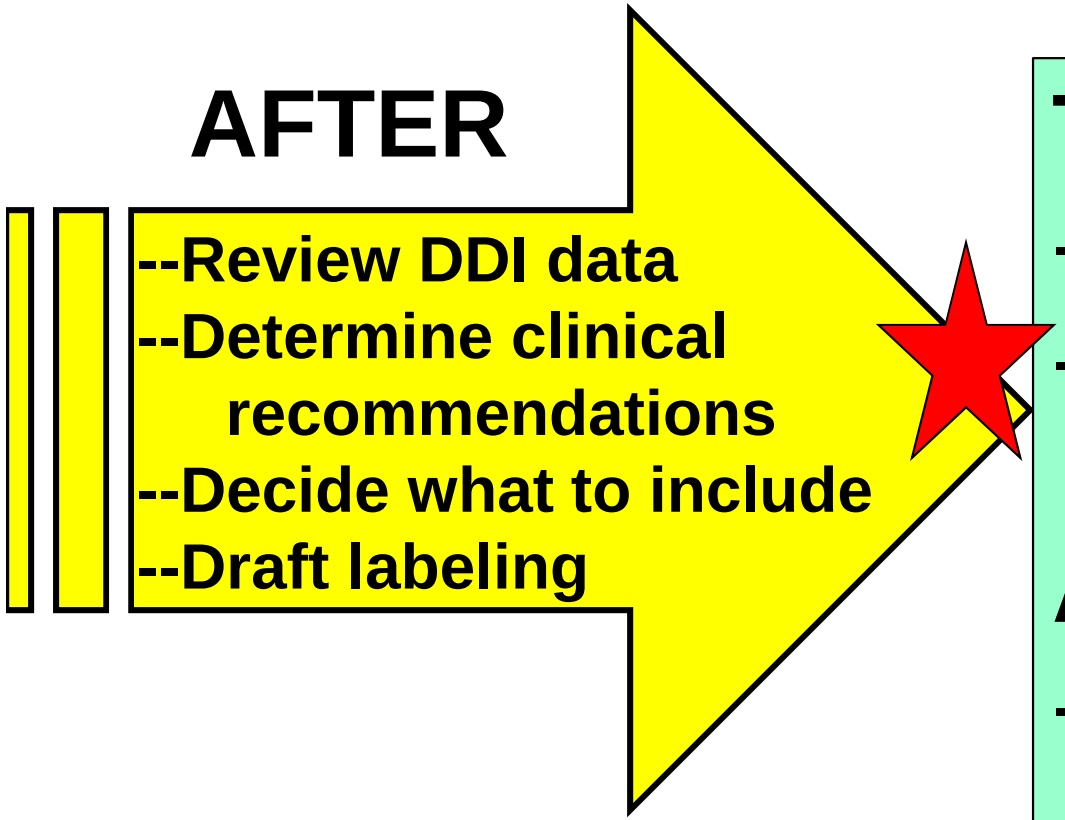
Time Zone


AFTER
--Review DDI data
--Determine clinical recommendations
--Decide what to include
--Draft labeling

Time Zone


AFTER
--Review DDI data
--Determine clinical recommendations
--Decide what to include
--Draft labeling
THEN
--How to Say it
--How to Display it

Time Zone



THEN

--How to Say it

--How to Display it

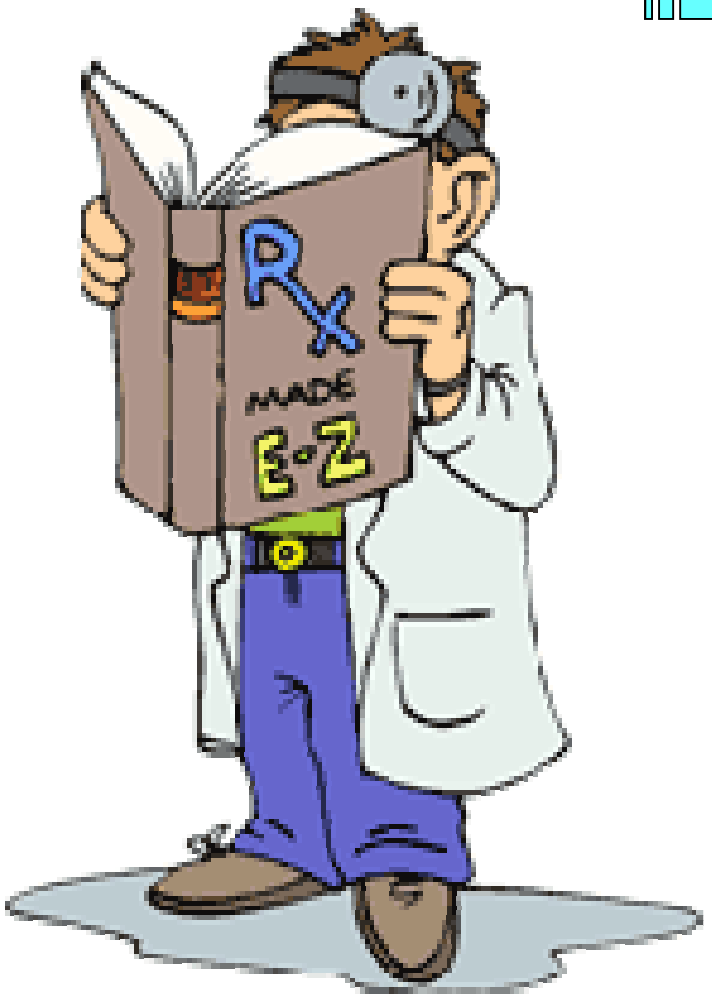
AND

--for whom

--for what tasks

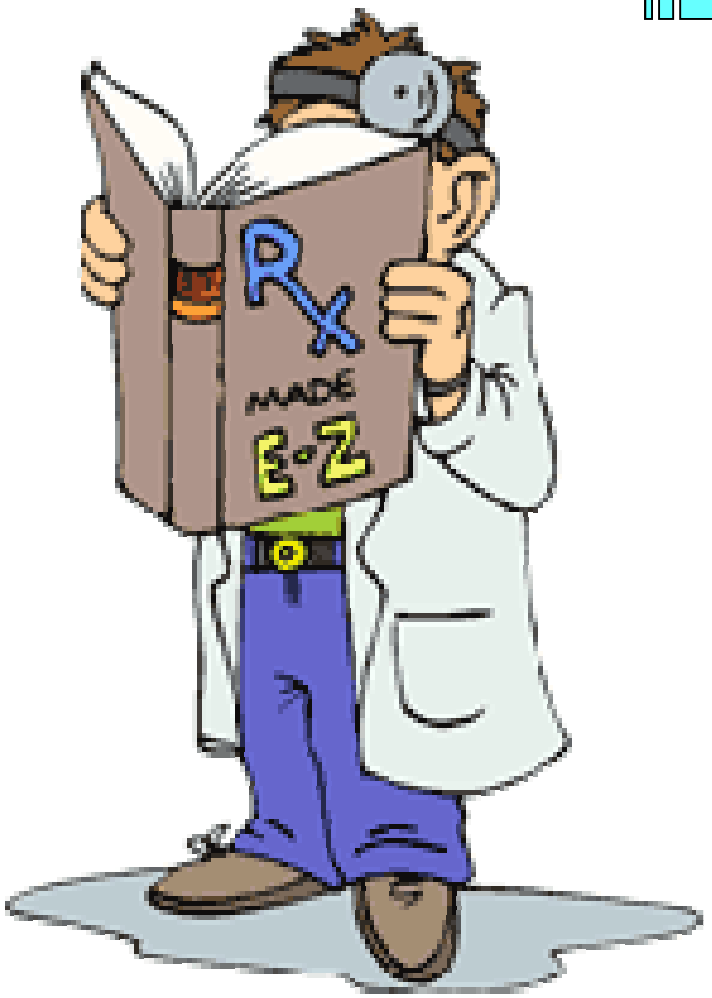
Basic Problem

Providers ⇒ **DDI Labeling** ⇒ FDA



Basic Problem

Providers → **DDI Labeling** → FDA



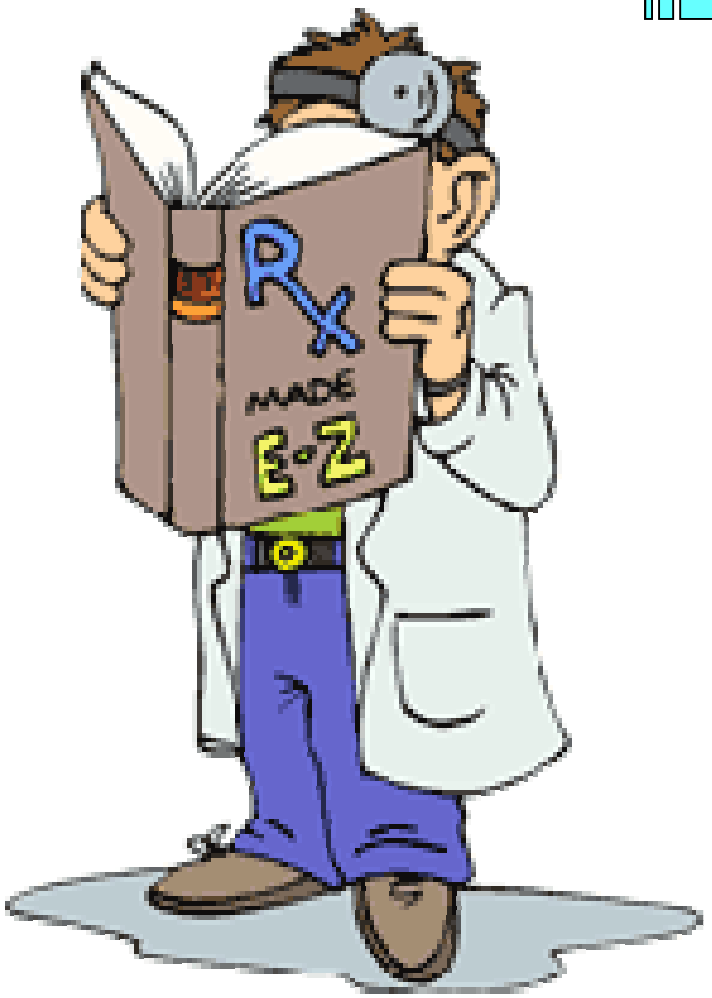
--Don’t read labeling

--Too much information

--Not clinically friendly

Basic Problem

Providers → **DDI Labeling** → FDA



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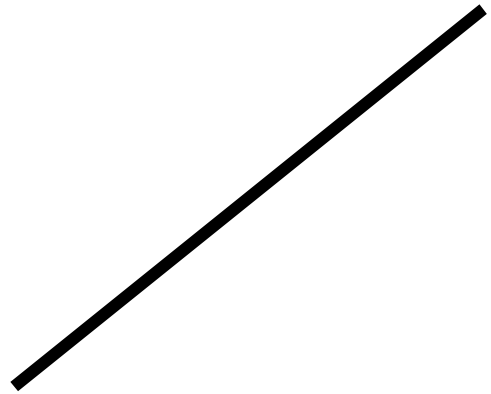
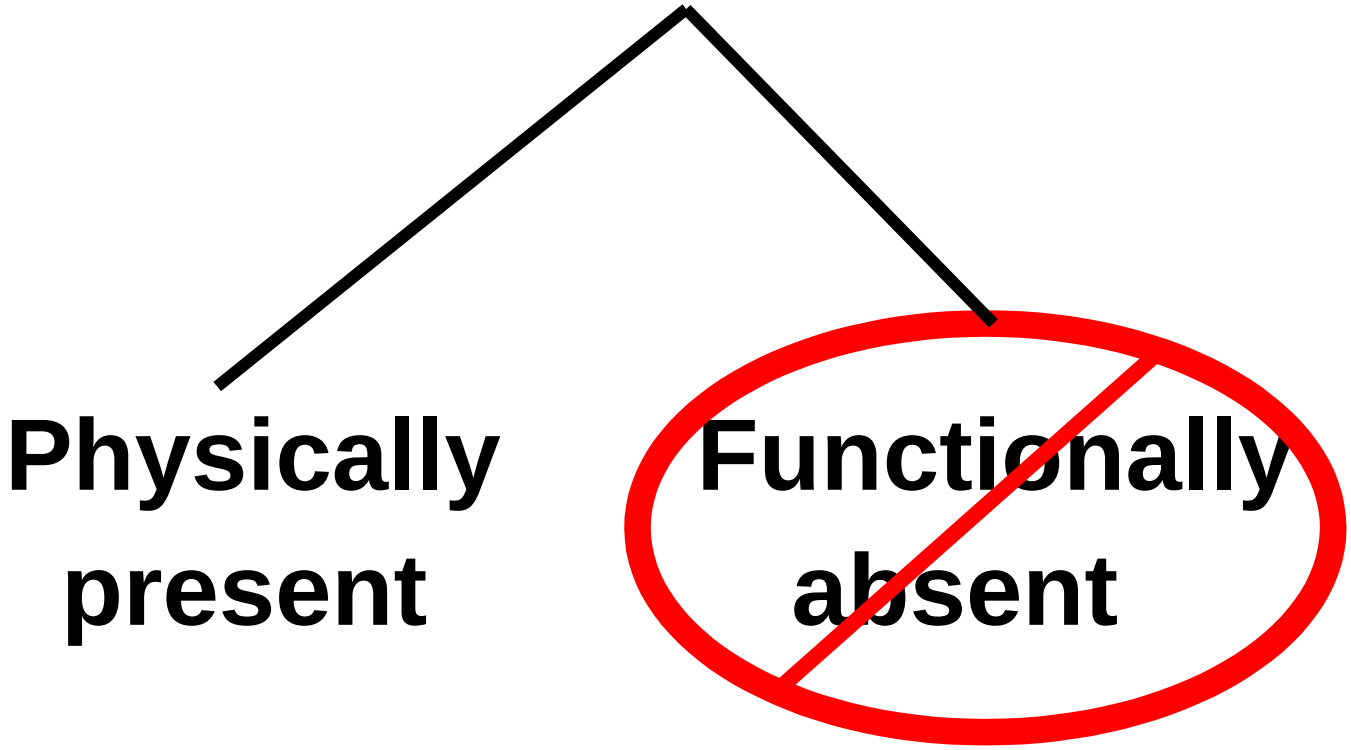
Cognitive accessibility ?

DDI Information

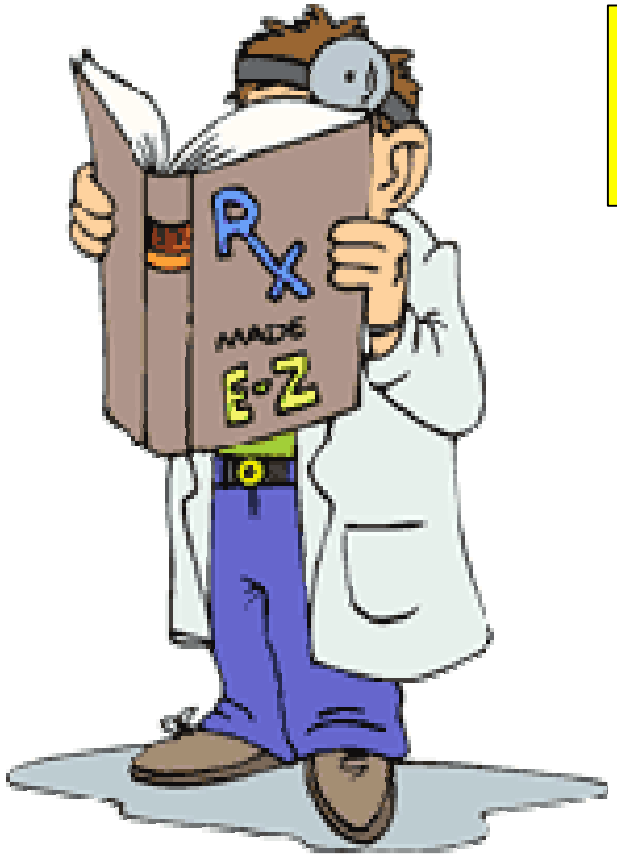


Physically present

DDI Information



Basic Problem

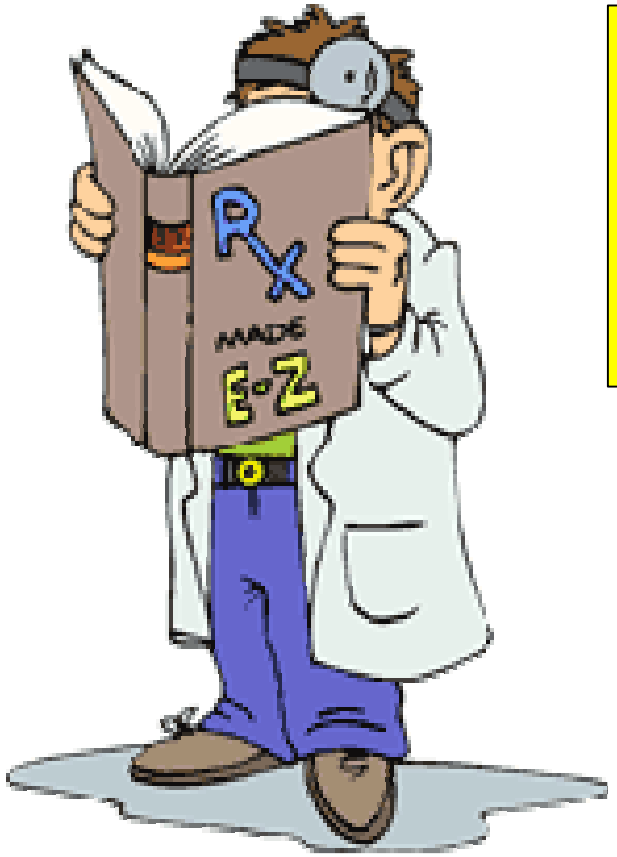


Questions
--What do they want?

Drug List

Drug-A
Drug-B
Drug-C
Drug-D
Drug-E

Basic Problem

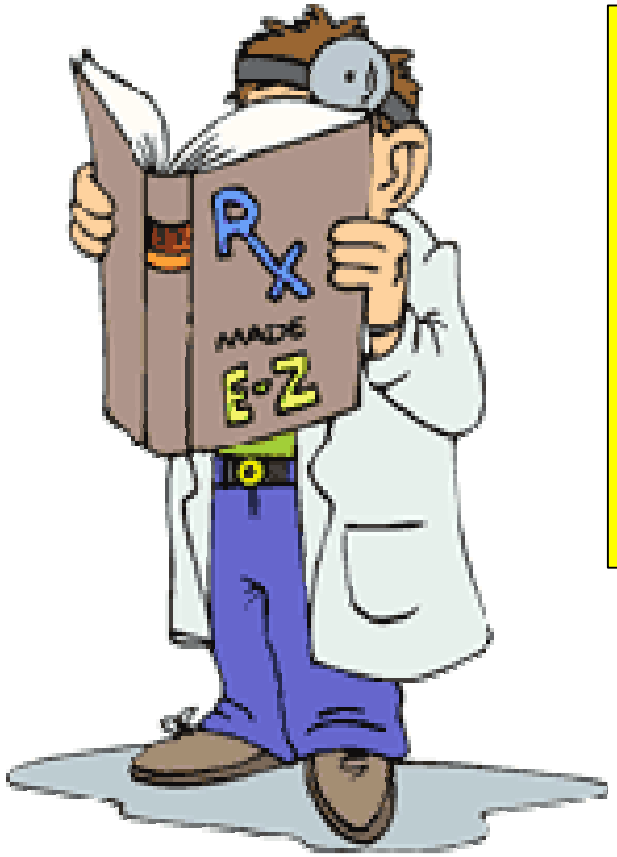


Questions
--What do they want?
--What do they **need**?
--When do they need it?

Drug List

Drug-A
Drug-B
Drug-C
Drug-D
Drug-E

Basic Problem



Questions

--What do they want?

--What do they **need**?

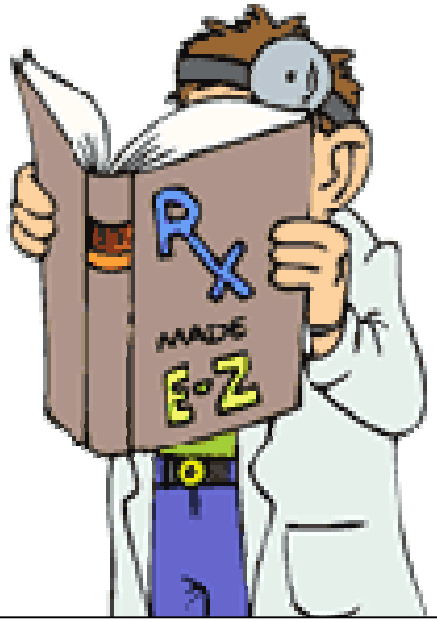
--When do they need it?

--Can they get along without (some of) it?

Drug List

Drug-A
Drug-B
Drug-C
Drug-D
Drug-E

Basic Problem



Questions
--What do they want?
--What do they **need**?
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without (some of) it?

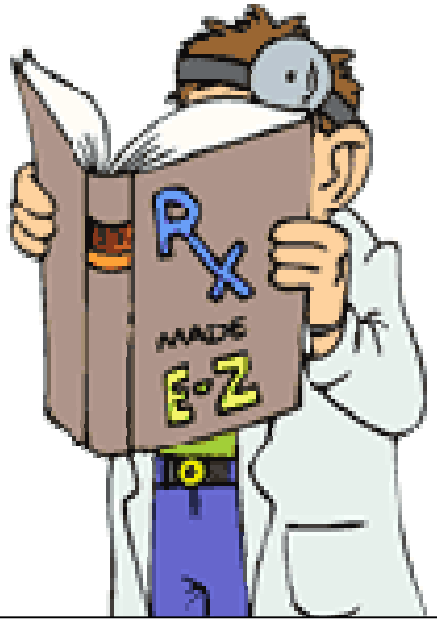
Drug List

Drug-A
Drug-B
Drug-C
Drug-D
Drug-E

How to get HCP's to
--Look at the labeling
--Engage them
--Help them find,
understand,
remember, & use the info

Ruth Day

Basic Problem



Questions
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Drug List

Drug-A
Drug-B
Drug-C
Drug-D
Drug-E

How to get HCP's to
--Look at the labeling
--Engage them
--Help them find, understand, remember, & use the info

Real-world situations
--Careful read
--Skim
--Search & find
--Remember
--Use

Ruth Day

Cognitive Tasks

Cognitive Tasks

Task	Time Needed	Label Support?
Read for general knowledge	A lot	Content = Good Cognitive Accessibility = Could be better

Cognitive Tasks

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Cognitive Tasks

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Find whether a specific drug is listed	Too much	Could be better Could → errors

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Remember	Too much	Poor
(etc.)		

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Find whether a specific drug is listed	Too…	
Remember	Too…	
(etc.)		

How to

--reduce time
--reduce effort
--increase comprehension
--increase memory
--facilitate problem solving
--facilitate decision making

Ruth Day

Alternative Displays

Alternative Displays

Text

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 **Effects of Other Drugs on Combined Oral Contraceptives**

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentrations of the estrogen or the progestin or both. In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

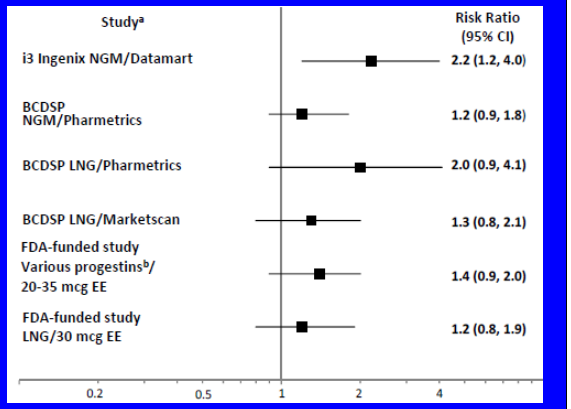
Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin

12

Table

Epidemiologic Study[A]	Comparator Product	Risk Ratios (95% CI)
i3 Ingenix NGM Study in Ingenix Research Datamart[1,6,7,8]	NGM/35 mcg EE[B]	2.2[C] (1.2-4.0)[D]
BCDSP[E] NGM Study in Pharmetrics database[2,3,5]	NGM/35 mcg EE	1.2 (0.9-1.8)[F]
BCDSP[E] LNG Study in Pharmetrics database[4]	LNG[G]/30 mcg EE	2.0 (0.9-4.1)[H]
BCDSP[E] LNG Study in Marketscan database[4]	LNG/30 mcg EE	1.3 (0.8-2.1)[I]
FDA-funded Study in Kaiser Permanente and Medicaid databases[J, K, 9]	"All progestins[L]"/20-35 mcg EE	1.4 (0.9-2.0)
	LNG/ 30 mcg EE	1.2 (0.8-1.9)

Figure



Alternative Displays

Text

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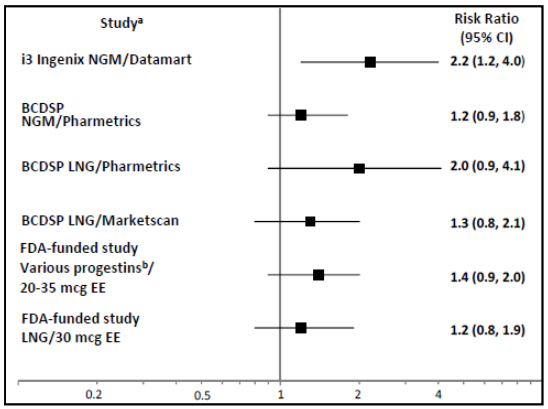
Figure

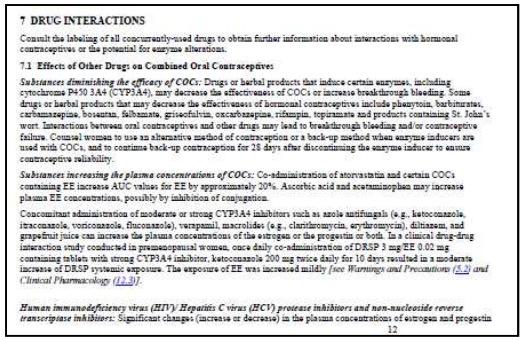


Which is best?

Ruth Day

Alternative Displays

Text



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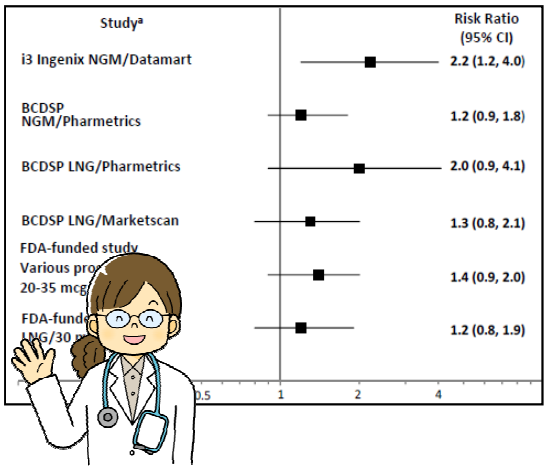


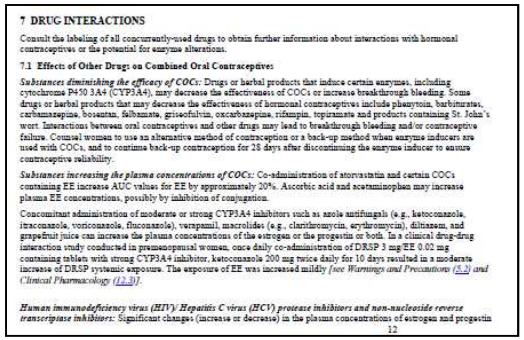
Which is best?

--for whom?

Ruth Day

Alternative Displays

Text



7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

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Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentrations of the estrogen or the progestin or both. In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

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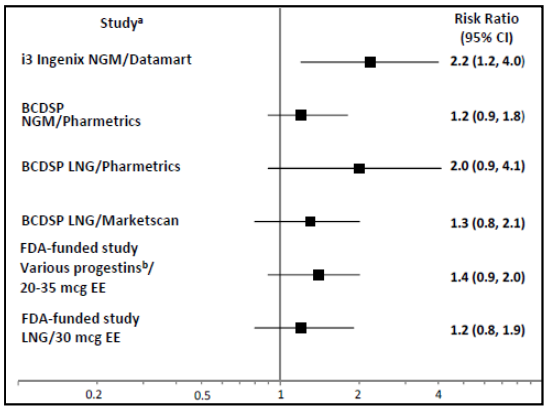
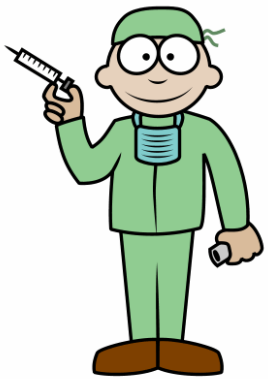
Figure



Which is best?

--for whom?

--what situation?



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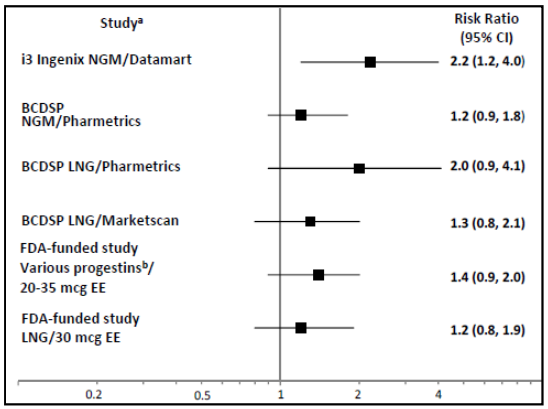

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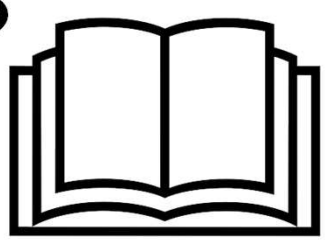
--for whom?

--what situation?

--what task?



Ruth Day

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Ruth Day

Viberzi (IBS-D)

Developed by Joe Grillo
FDA (OCP, OTS)

with input from Ruth Day

Table 2: Established and Other Potentially Clinically Relevant Interactions Affecting VIBERZI

OATP1B1 Inhibitors	
Clinical Impact:	Increased exposure to eluxadoline when coadministered with [see *Clinical Pharmacology (12.3)*]
Intervention:	Administer VIBERZI at a dose of 75 mg twice daily [see *Dosage and Administration (2)*] and monitor patients for impaired mental abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions [see *Adverse Reactions (6.1)*].
Examples:	cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, saquinavir, tipranavir), rifampin, eltrombopag
Strong CYP Inhibitors*	
Clinical Impact:	Potential for increased exposure to eluxadoline [see *Clinical Pharmacology (12.3)*]
Intervention:	Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions [see *Adverse Reactions (6.1)*].
Examples:	ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazole, (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2D6)
Drugs that Cause Constipation	
Clinical Impact:	Increased risk for constipation related adverse reactions and potential for constipation related serious adverse reactions
Intervention:	Avoid use with other drugs that may cause constipation (see below); loperamide may be used occasionally for acute management of severe diarrhea but avoid chronic use. Discontinue loperamide immediately if constipation occurs.
Examples:	alosetron, anticholinergics, opioids

*As a precautionary measure due to incomplete information on the metabolism of eluxadoline

Ruth Day

Drug Class A	
Clinical Impact	
Intervention	
Examples	
Drug Class B	
Clinical Impact	
Intervention	
Examples	
Drug Class C	
Clinical Impact	
Intervention	
Examples	

Modified version

General template

Ruth Day

Drug Class A	
Clinical Impact	Increased exposure to Drug-X ….
Intervention	Administer Drug-X at a dose of ….
Examples	
Drug Class B	
Clinical Impact	Potential for increased exposure to Drug-X ….
Intervention	Monitor patients for ….
Examples	
Drug Class C	
Clinical Impact	Increased risk for adverse reaction Z ….
Intervention	Avoid use with other drugs that may ….
Examples	

Drug Class A	
Clinical Impact	Increased exposure to Drug-X ….
Intervention	Administer Drug-X at a dose of ….
Examples	aaaa, bbbb, cccc, dddd ….
Drug Class B	
Clinical Impact	Potential for increased exposure to Drug-X ….
Intervention	Monitor patients for ….
Examples	eeee, ffff, gggg, hhhh ….
Drug Class C	
Clinical Impact	Increased risk for adverse reaction Z ….
Intervention	Avoid use with other drugs that may ….
Examples	kkkk, mmmm, pppp, rrrr …..

Drug Class A	
Clinical Impact	Increased exposure to Drug-X ….
Intervention	Administer
Examples	aaaa, bbbb,
Drug Class B	
Clinical Impact	Potential fo
Intervention	Monitor pa
Examples	eeee, ffff, g
Drug Class C	
Clinical Impact	Increased r
Intervention	Avoid use with other drugs that may ….
Examples	kkkk, mmmm, pppp, rrrr …..

Schema

(organizing structure)

--easy to see at a glance

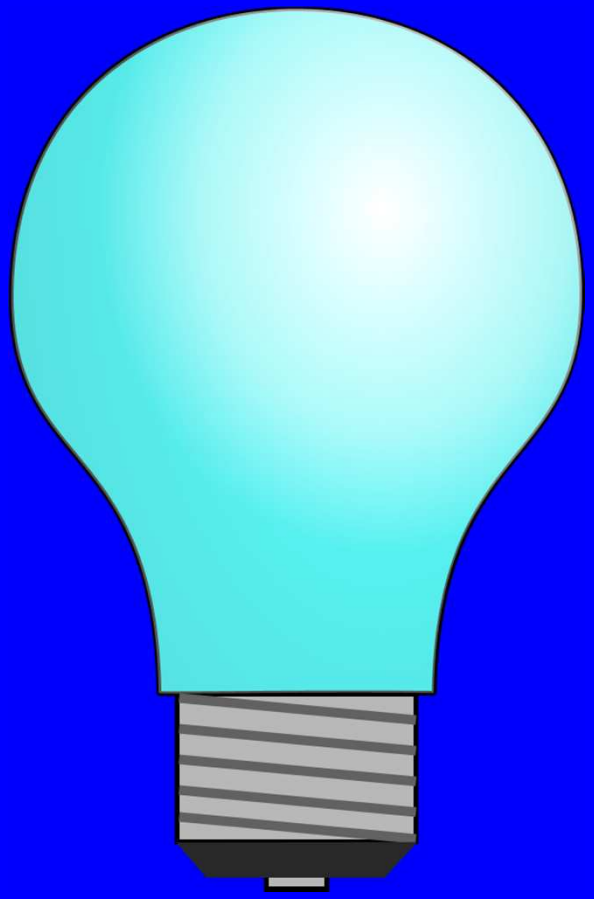
--easy to understand

--facilitates memory

--facilitates acquisition of new information

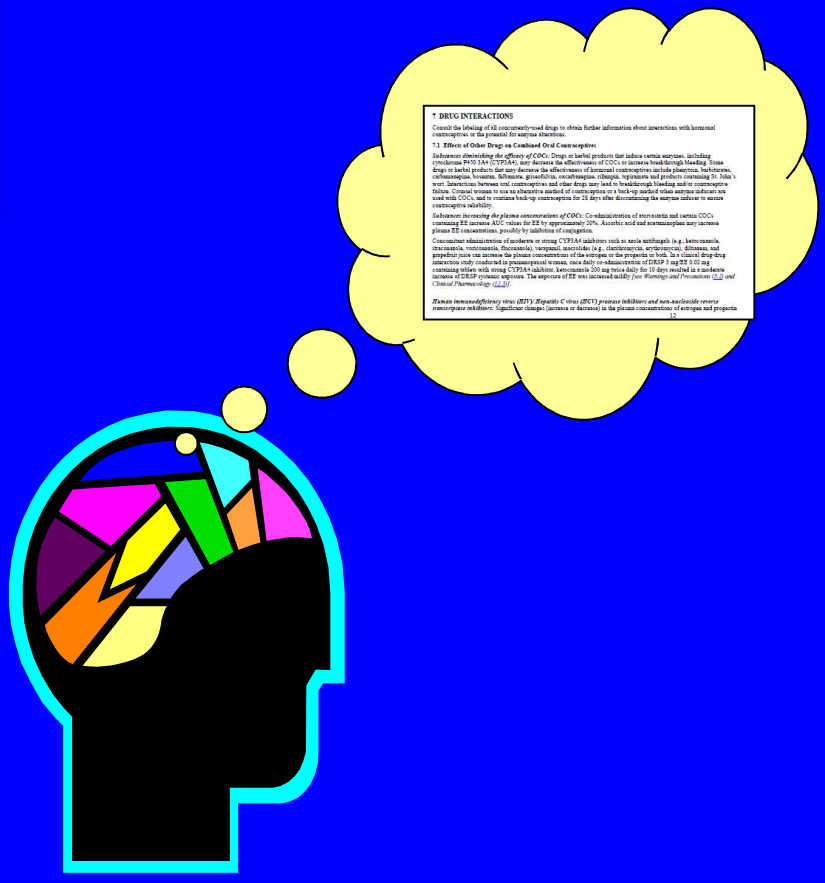
“Wall Charts”

“Wall Charts”



“Wall Charts”

Stimulate Thinking



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Wall Charts

Problem: Information Load

--lots of information, often complex

--how grasp key information quickly?

--how remember (at least something) later?

--how find it again when needed?

Wall Charts

Problem: Information Load

--lots of information, often complex
--how grasp key information quickly?
--how remember (at least something) later?
--how find it again when needed?

Suggestion: "Wall Chart"

--key elements
--quick reminder
--focus on drugs that interact
--simple (like DDI "highlights")

Wall Charts

Problem: Information Load

--lots of information, often complex

--how grasp key info

--how remember (at

--how find it again w

Focus on

--main drugs that interact with HC

--their status within a simple schema

Suggestion: "Wa

--key elements

--quick reminder

--focus on drugs that interact

--simple (like DDI "highlights")

Wall Charts

Examples

	Safety Effect	Efficacy Effect
Drug Class A	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class B	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class C	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx

Wall Charts

	Adverse Reactions	Exposure Effects
Drug Class A	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples (↑) --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class B	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: (↓) --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class C	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: (↑) --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx

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Wall Charts

	Established Interaction	Potential Interaction
Drug Class A	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class B	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class C	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx

Wall Charts

	Potential for **HC** to affect other drugs	Potential for **Other Drugs** to affect HC
Drug Class A	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class B	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Drug Class C	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx

Wall Charts

	x	x
Health Condition A	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Health Condition B	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx
Health Condition C	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx	Examples: --xxxx --xxxx --xxxx --xxxx --xxxx --xxxx

Wall Charts

Drug Class/ Health Cond	X	X
HIV Drug-1: Drug-2: Drug-3:		
AntiViral Drug-1: Drug-2: Drug-3		
AntiEpileptic Drug-1: Drug-2: Drug-3		

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Wall Charts

	Effect	Intervention
Drug Class A Drug-1: Drug-2: Drug-3:		
Drug Class B Drug-1: Drug-2: Drug-3:		
Drug Class C Drug-1: Drug-2: Drug-3:		

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Wall Charts

	HC Effect: on Other Drugs	Other Drugs: Effects on HC
Drug Class A Drug-1: Drug-2: Drug-3:		
Drug Class B Drug-1: Drug-2: Drug-3		
Drug Class C Drug-1: Drug-2: Drug-3		

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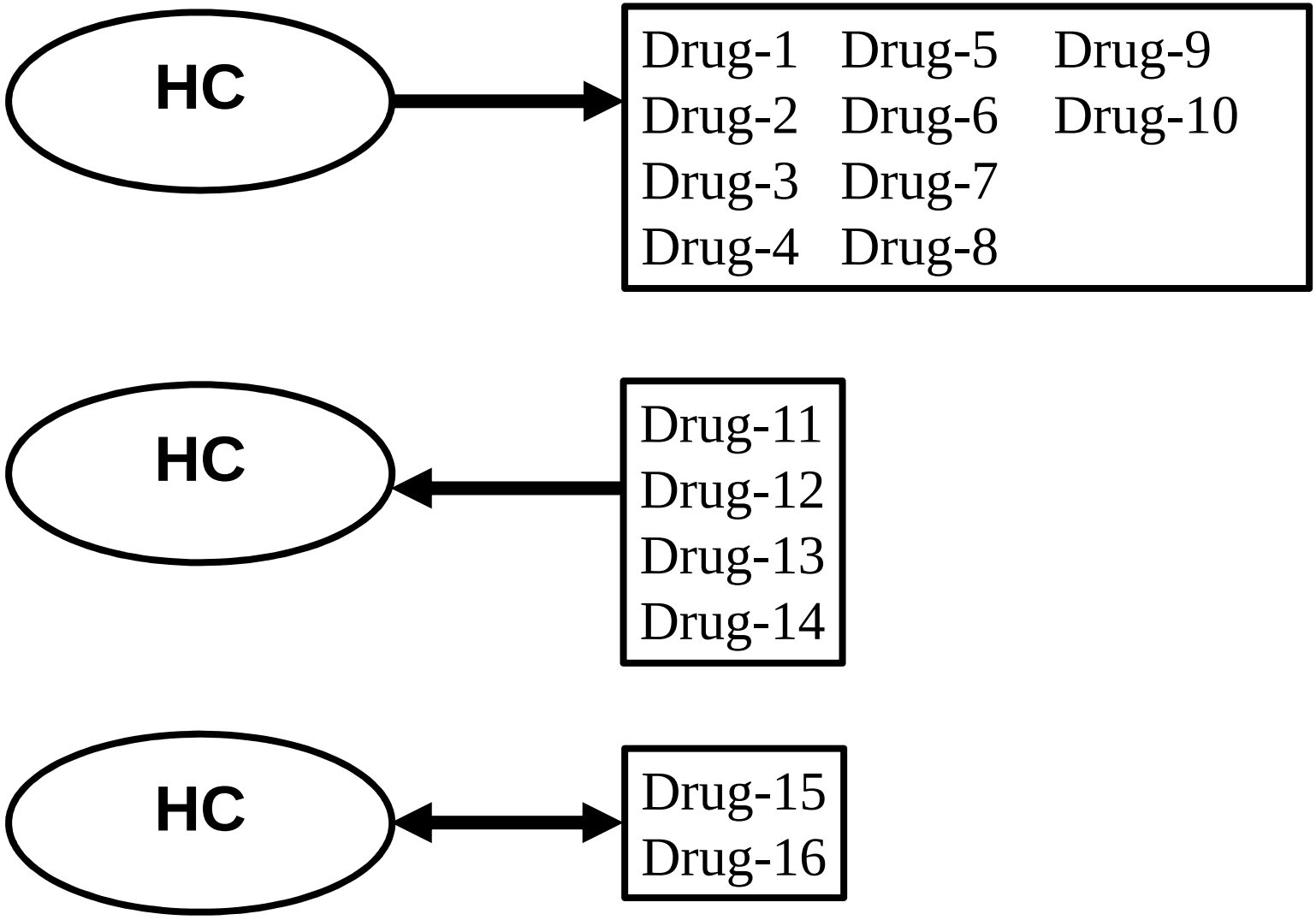
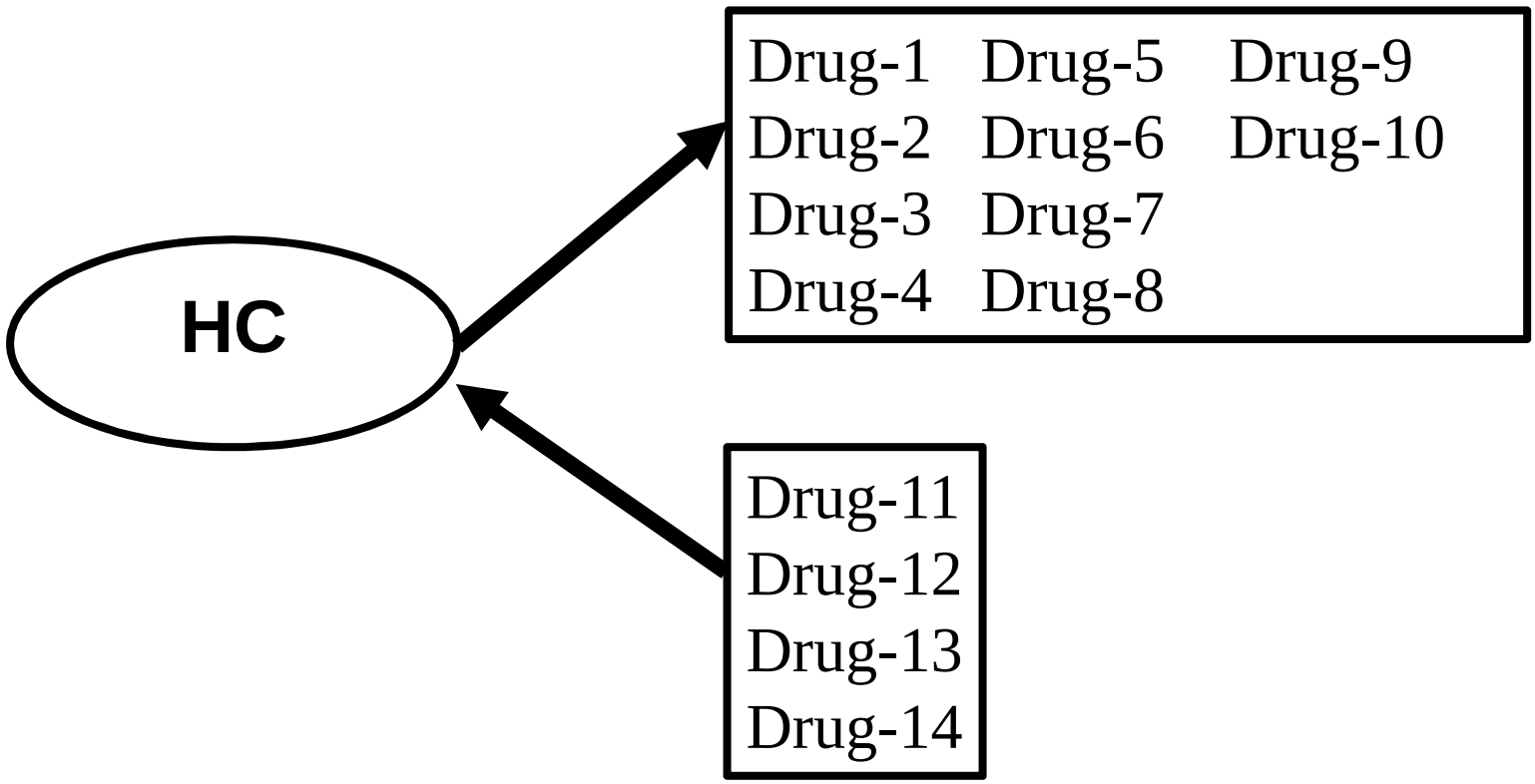
Wall Charts

Type of Effect	Likely	Rare
Teratogenic		
Lactation		
Exposure Changes		

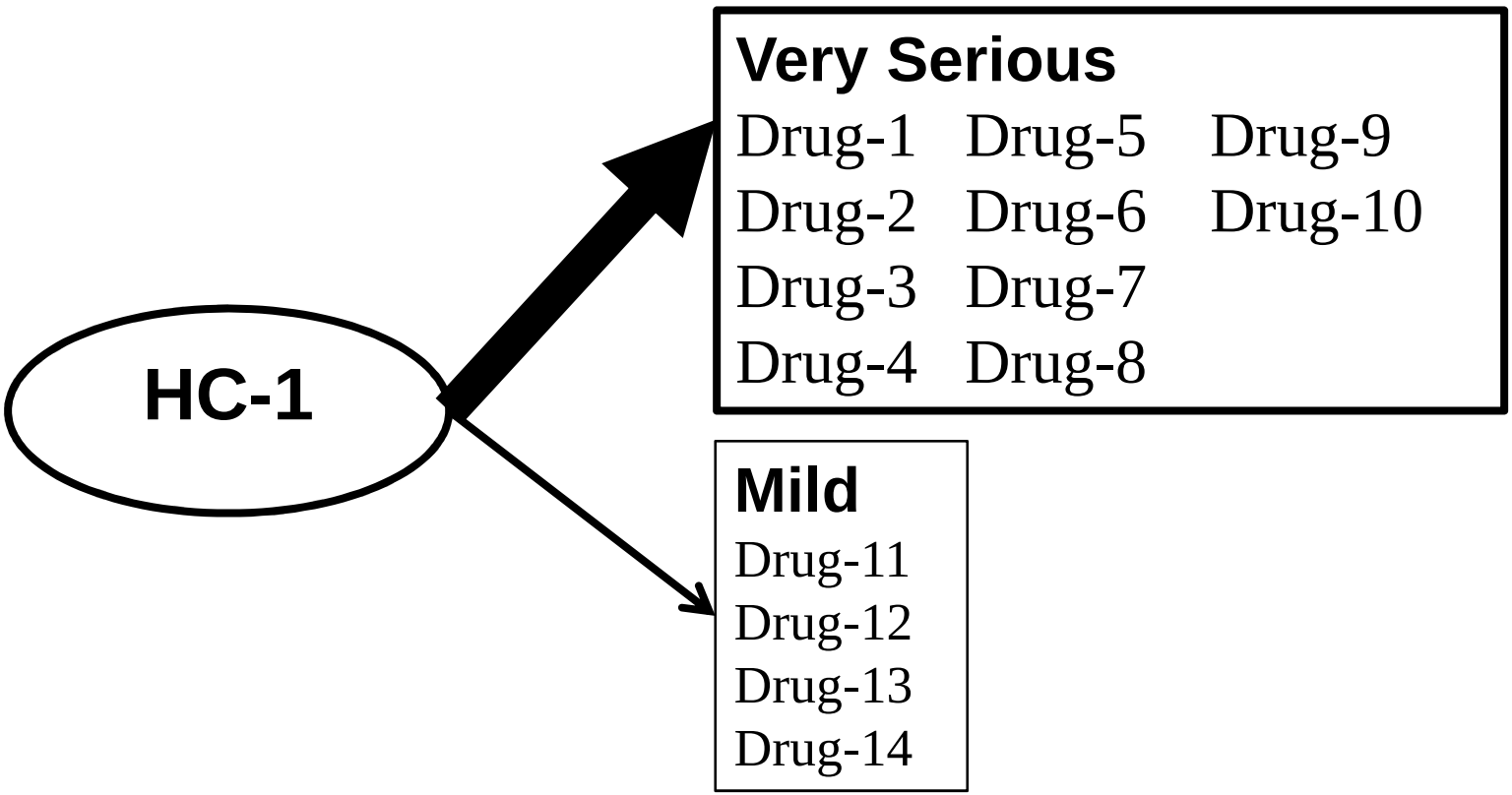
Wall Charts


HC
Drug-1 Drug-5 Drug-9
Drug-2 Drug-6 Drug-10
Drug-3 Drug-7
Drug-4 Drug-8
HC
Drug-11
Drug-12
Drug-13
Drug-14
HC
Drug-15
Drug-16

Wall Charts


HC
Drug-1
Drug-2
Drug-3
Drug-4
Drug-5
Drug-6
Drug-7
Drug-8
Drug-9
Drug-10
Drug-11
Drug-12
Drug-13
Drug-14

Wall Charts


HC-1
Very Serious
Drug-1 Drug-5 Drug-9
Drug-2 Drug-6 Drug-10
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Drug-4 Drug-8
Mild
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Drug-14

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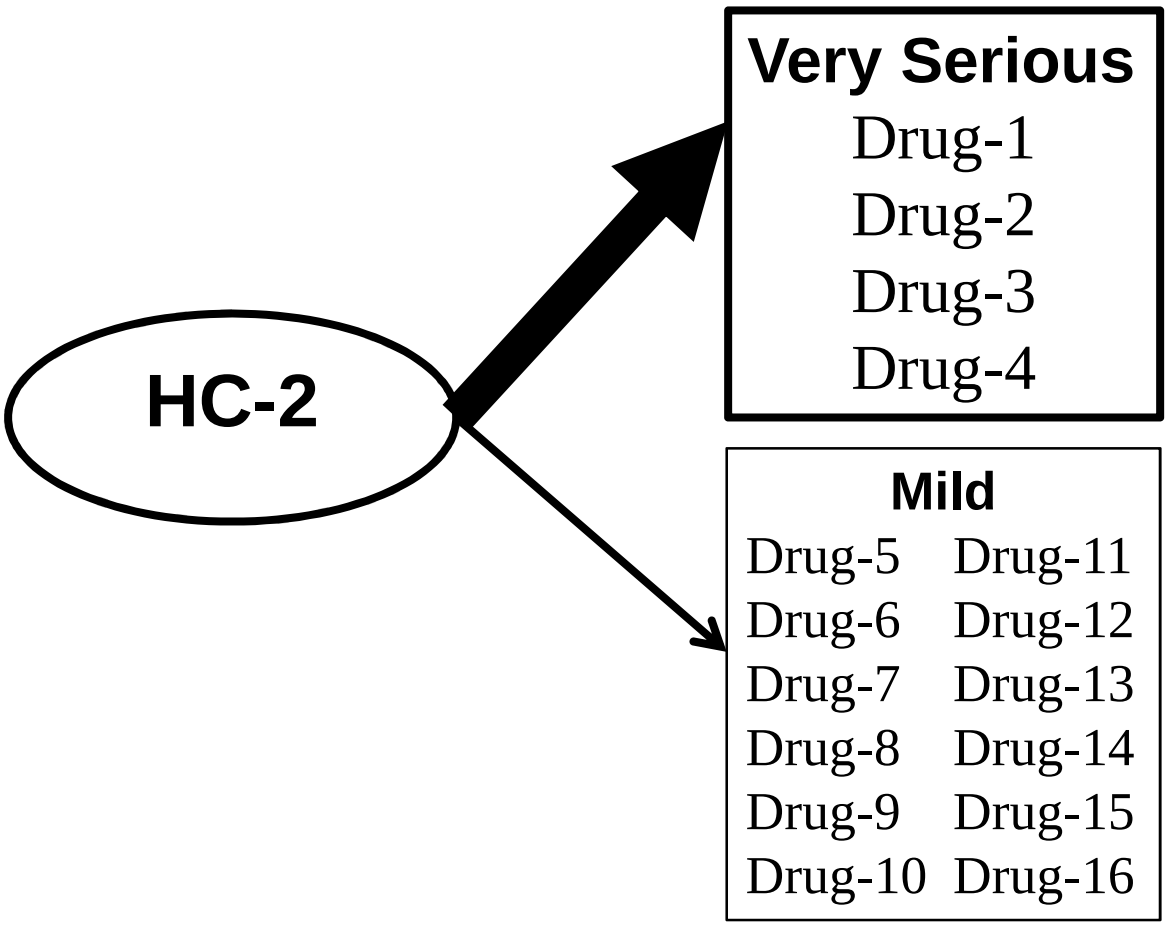
HC-2
Very Serious
Drug-1
Drug-2
Drug-3
Drug-4
Mild
Drug-5
Drug-6
Drug-7
Drug-8
Drug-9
Drug-10
Drug-11
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Drug-14
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Drug-16

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transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

COCs Increasing the Plasma Concentrations of CYP450 Enzymes: In clinical studies, administration of a hormonal contraceptive containing EE did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g., midazolam) while plasma concentrations of CYP2C19 substrates (e.g., omeprazole and voriconazole) and CYP1A2 substrates (e.g., theophylline and tizanidine) can have a weak or moderate increase.

Clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations *[see Clinical Pharmacology (12.3)]*.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Beyaz with other drugs that may increase serum potassium concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

7.3 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

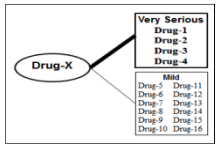
7.4 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate concentrations by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

7.5 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity. Folates may mask vitamin B12 deficiency. *[See Warnings and Precautions (5.12) and Drug Interactions (7.2).]*

7.6 Overview: Main Drugs that Interact with Drug-X



Embedded Wall Chart

7.6 Main Drugs that Interact with HC-1

7.6 Main Drug Classes that Interact with HC-1

Ruth Day

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

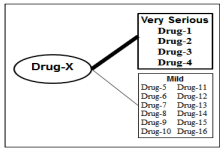
Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentrations of the estrogen or the progestin or both. In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin

7.6 Overview: Main Drugs that Interact with Drug-X



transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

COCs Increasing the Plasma Concentrations of CYP450 Enzymes: In clinical studies, administration of a hormonal contraceptive containing EE did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g., midazolam) while plasma concentrations of CYP2C19 substrates (e.g., omeprazole and voriconazole) and CYP1A2 substrates (e.g., theophylline and tizanidine) can have a weak or moderate increase.

Clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations *[see Clinical Pharmacology (12.3)]*.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Beyaz with other drugs that may increase serum potassium concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

7.3 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

7.4 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate concentrations by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

7.5 Interference with Laboratory Tests

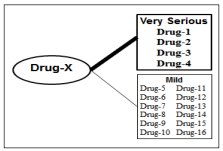
The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity. Folates may mask vitamin B12 deficiency. *[See Warnings and Precautions (5.12) and Drug Interactions (7.2).]*

Embedded Wall Chart

Ruth Day

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.



7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentrations of the estrogen or the progestin or both. In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin

transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

COCs Increasing the Plasma Concentrations of CYP450 Enzymes: In clinical studies, administration of a hormonal contraceptive containing EE did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g., midazolam) while plasma concentrations of CYP2C19 substrates (e.g., omeprazole and voriconazole) and CYP1A2 substrates (e.g., theophylline and tizanidine) can have a weak or moderate increase.

Clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations *[see Clinical Pharmacology (12.3)]*.

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Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Beyaz with other drugs that may increase serum potassium concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

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7.5 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity. Folates may mask vitamin B12 deficiency. *[See Warnings and Precautions (5.12) and Drug Interactions (7.2).]*

Embedded Wall Chart

Ruth Day

7 DRUG INTERACTIONS

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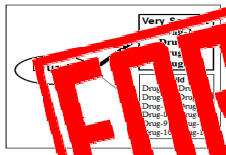
Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside [illegible] transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of [illegible] progestin

7.6 Overview: Main Drugs that Interact with Drug-X



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Embedded Wall Chart

Prime Real Estate

If you had some,
to foster key take-away message,

--what would it be?

--how would you display it?

Ruth Day

Embedded Wall Chart

7 DRUG INTERACTIONS

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Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside ***transcriptase inhibitors:*** Significant changes (increase or decrease) in the plasma concentrations of ... progestin

7.6 Overview: Main Drugs that Interact with Drug-X

FOR SALE!

transcriptase inhibitors.

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Prime Real Estate

If you had some,
to foster key take-away message,

--what would it be?

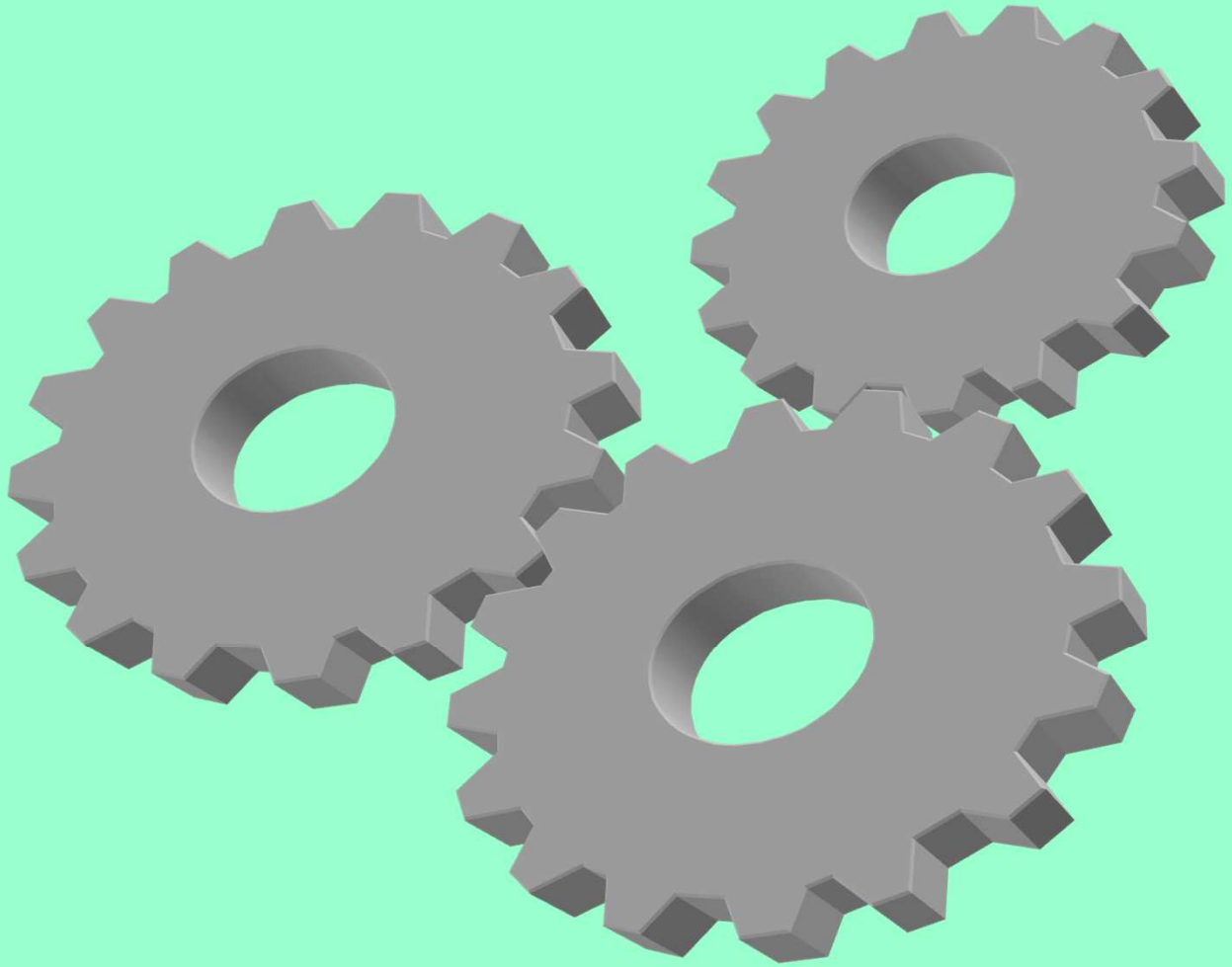
--how would you display it?

And if you lost that space

--how would you enhance
the existing space
--to increase comprehension, memory,
and safe/effective use?

Ruth Day

LET'S SHIFT GEARS



Drug Interactions

Patient Counseling

Section 17

Ruth Day

Drug Interactions

Patient Counseling

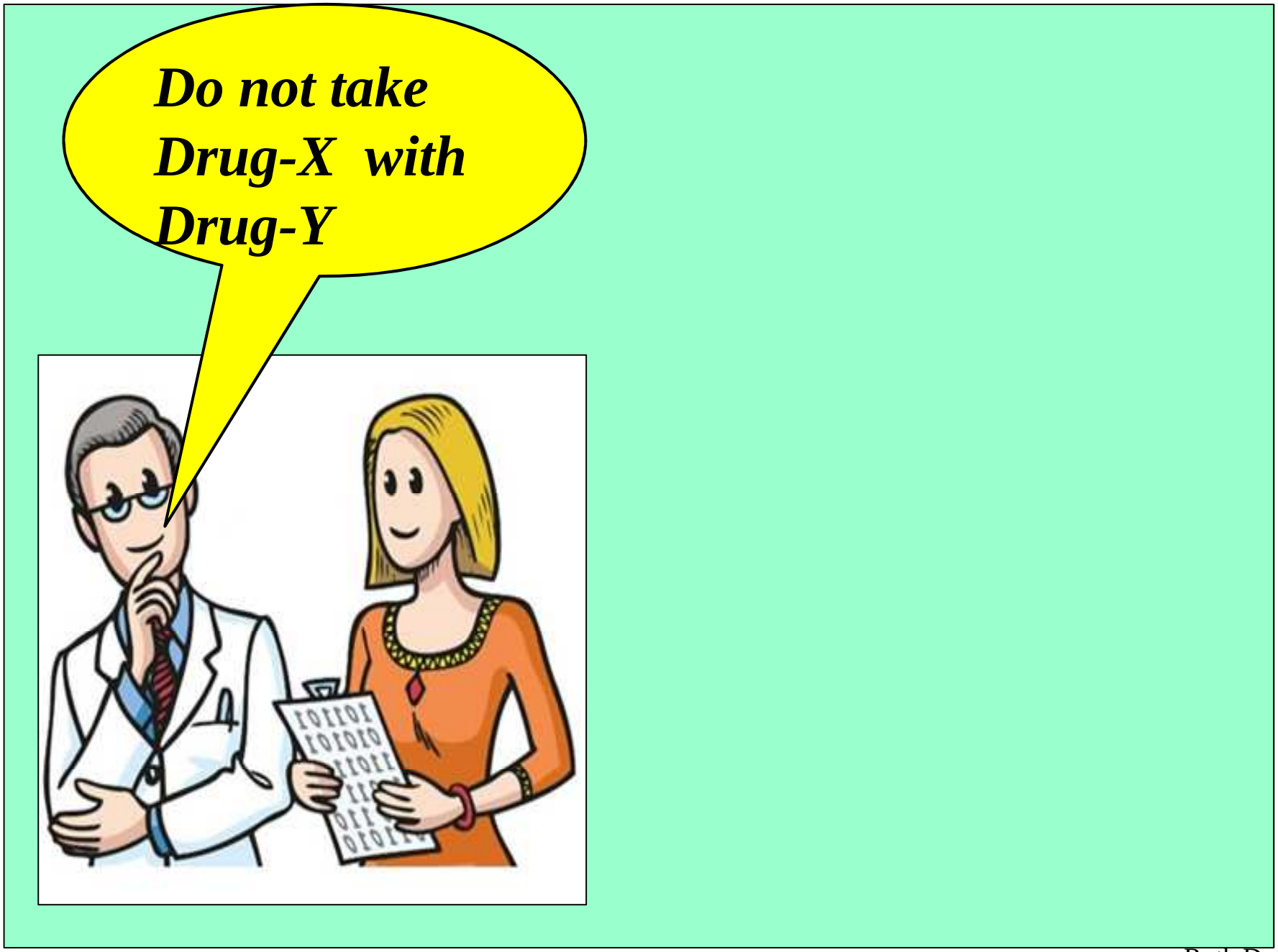
Section 17

--Written for providers:
(what to tell patients)

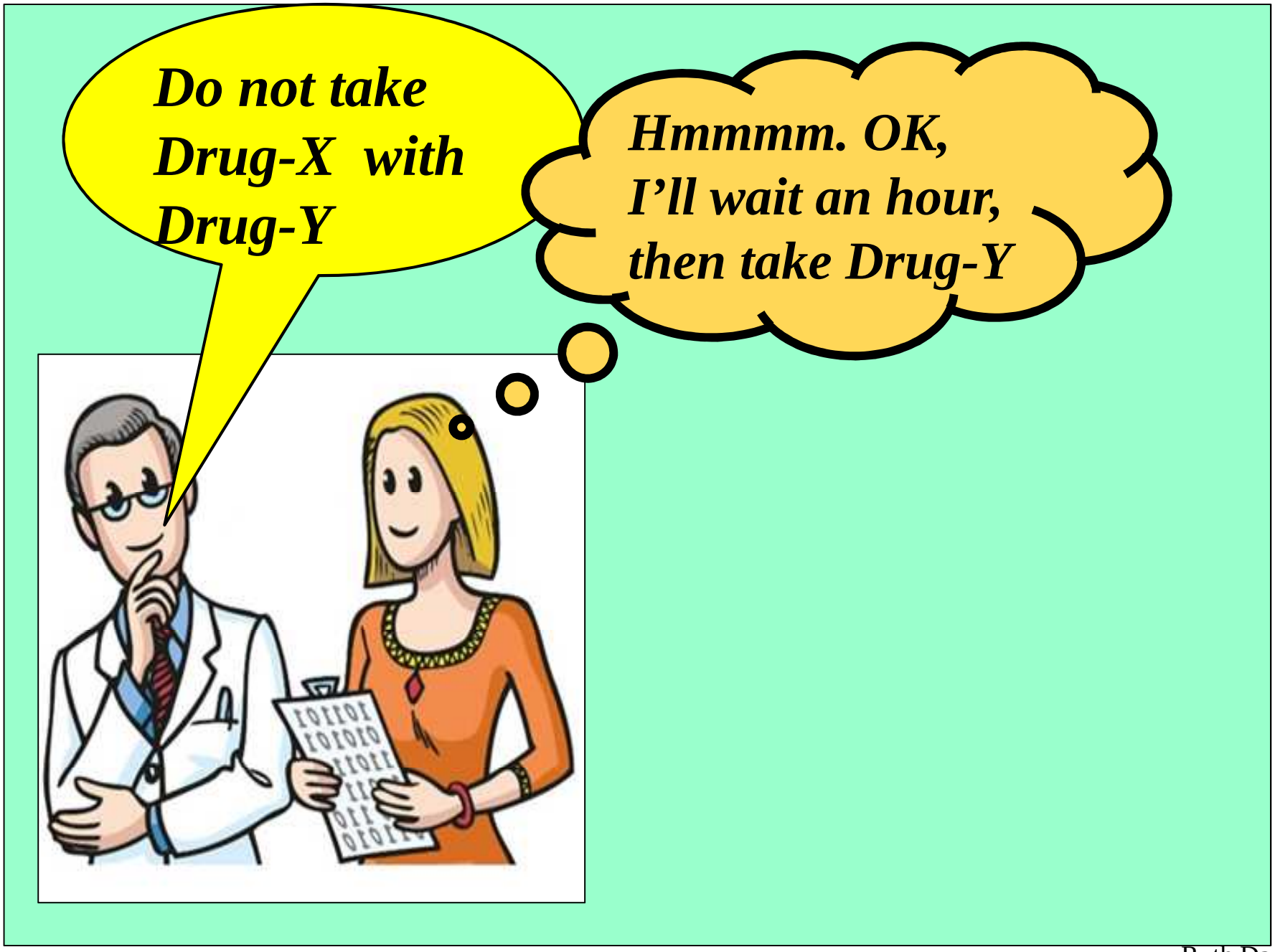
--NOT the
"FDA Approved
Patient Labeling"

--Instead, for
provider-patient
communication

Ruth Day



Ruth Day


Do not take Drug-X with Drug-Y
Hmmmm. OK, I'll wait an hour, then take Drug-Y

Ruth Day

Do not take Drug-X with Drug-Y

Hmmmm. OK, I'll wait an hour, then take Drug-Y

Sure, plain language.
But: multiple interpretations.

1) "Not at the same time, but wait a while, then it's OK"

2) "Never take Drug-Y during the course of treatment with Drug-X."

Alternative Meanings Test

Ruth Day

Sample Section 17

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

• Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
• Counsel patients that the increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC.
• Counsel patients about the information regarding the risk of VTE with DRSP-containing COCs compared to COCs that contain levonorgestrel or some other progestins.
• Counsel patients that Drug-X does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
• Counsel patients on Warnings and Precautions associated with COCs.
• Counsel patients that Drug-X contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Drug-X in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition or taking strong CYP3A4 inhibitors.
• Inform patients that Drug-X is not indicated during pregnancy. If pregnancy occurs during treatment with Drug-X, instruct the patient to stop further intake. However, women should be advised on the continued need of sufficient folate intake.
• Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See “What to Do if You Miss Pills” section in FDA-Approved Patient Labeling.
• Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
• Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
• Counsel any patient who starts COCs postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken a pink tablet for 7 consecutive days.
• Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
• Counsel patients to report whether they are taking folate supplements. Drug-X contains the equivalent of 0.4 mg (400 mcg) of folic acid.
• Counsel patients to maintain folate supplementation if they discontinue Drug-X due to pregnancy

Ruth Day

Sample Section 17

17 PATIENT COUNSELING INFORMATION

See "FDA-approved patient labeling (Patient Information)."

• Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.

• Counsel [redacted] arting a COC or restarting [redacted]

• Counsel [redacted] to COCs that contain lev[redacted]

• Counsel [redacted] l diseases.

• Counsel [redacted]

• Counsel [redacted] lvised to inform their healt[redacted] nce of these conditions[redacted] if they are currently [redacted] ACE inhibitors, angiotensi[redacted] ong CYP3A4 inhibitors.

• Inform p[redacted] Drug-X, instruct the patient[redacted] ate intake.

• Counsel [redacted] in the event pills are missed[redacted]

• Counsel [redacted] vith COCs.

• Counsel [redacted] duction. This is less likely[redacted]

• Counsel [redacted] ethod of contraception until she has taken a pink tablet for 7 consecutive days.

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• Counsel patients to report whether they are taking folate supplements. Drug-X contains the equivalent of 0.4 mg (400 mcg) of folic acid.

• Counsel patients to maintain folate supplementation if they discontinue Drug-X due to pregnancy

Many Sec. 17's look like this.
Have improved over the years.

Mostly plain language.

But cognitive accessibility could be improved.

Ruth Day

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

- Counsel patients that ….
- Counsel patients that ….
- Counsel patients about …
- Counsel patients that ….
- Counsel patients on ….
- Counsel patients that ….
- Inform patients that ….
- Counsel patients to ….

  Counsel patients to ….
- Counsel any patient who ….
- Counsel patients that ….
- Counsel patients to ….
- Counsel patients to ….

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

- Counsel patients that ….
- Counsel patients that ….
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- Counsel patients on ….
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- Counsel patients to ….

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- Counsel any patient who ….
- Counsel patients that ….
- Counsel patients to ….
- Counsel patients to ….

Effortful reading.

What are the topics?

Where is DDI?
Or anything else?

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

- Counsel patients that ….
- Counsel patients that ….
- Counsel patients about … **[DDI]**
- Counsel patients that ….
- Counsel patients on ….
- Counsel patients that . **[1 DDI + 1 Precaution + 8 DDI’s]**
- Inform patients that … .
- Counsel patients to ….

  Counsel patients to … **[~ DDI]**
- Counsel any patient who
- Counsel patients that
- Counsel patients to … **[~ DDI]**
- Counsel patients to

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

Uh-oh.
DDI in several locations.

- Counsel patients that ….
- Counsel patients that ….
- Counsel patients about … **[DDI]**
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Uh-oh.
DDI in several locations.

Cognitive Violations:
--No clustering
--No chunking
--No explicit coding

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- Inform patients that … .
- Counsel patients to ….

  Counsel patients to … **[~ DDI**
- Counsel any patient who
- Counsel patients that
- Counsel patients to … **[~ DDI**
- Counsel patients to

Uh-oh.
DDI in several locations.

Cognitive Violations:
--No clustering
--No chunking
--No explicit coding

Ruth Day

Enhanced Version

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

Counsel patients that:

Topic-A: xxxxxxxxxx

Topic-B: xxxxxxxxxx

Topic-C: xxxxxxxxxx

Drug Interactions:

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Topic-E: xxxxxxxxxx

Topic-F: xxxxxxxx

Ruth Day

Enhanced Version

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

Counsel patients that:

Topic-A: xxxxxxxxxx

Topic-B: xxxxxxxxxx

Topic-C: xxxxxxxxxxx

Drug Interactions:

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--

Topic-E: xxxxxxxxxx

Topic-F: xxxxxxxx

Cognitive Principles Used:

--Clustering

--Chunking

--Explicit coding

Enhanced Version

17 PATIENT COUNSELING INFORMATION

See "FDA-approved patient labeling (Patient Information)."

Counsel patients that:

Topic-A: xxxxxxxxxx

Topic-B: xxxxxxxxxx

Topic-C: xxxxxxxxxxx

Drug Interactions:

--

--

--

Topic-E: xxxxxxxxxx

Topic-F: xxxxxxxx

Cognitive Principles Used:

--Clustering

--Chunking

--Explicit coding

Therefore

--decrease effort

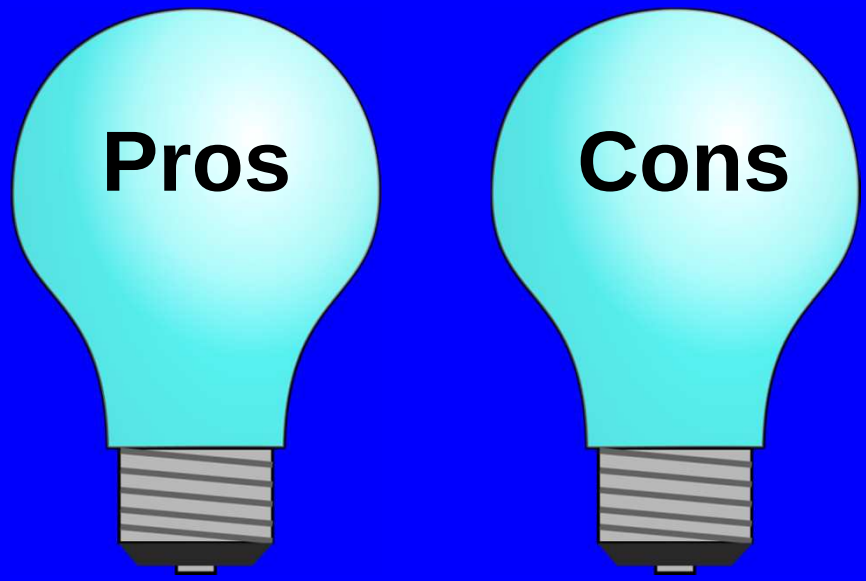
--speed processing

--increase processing

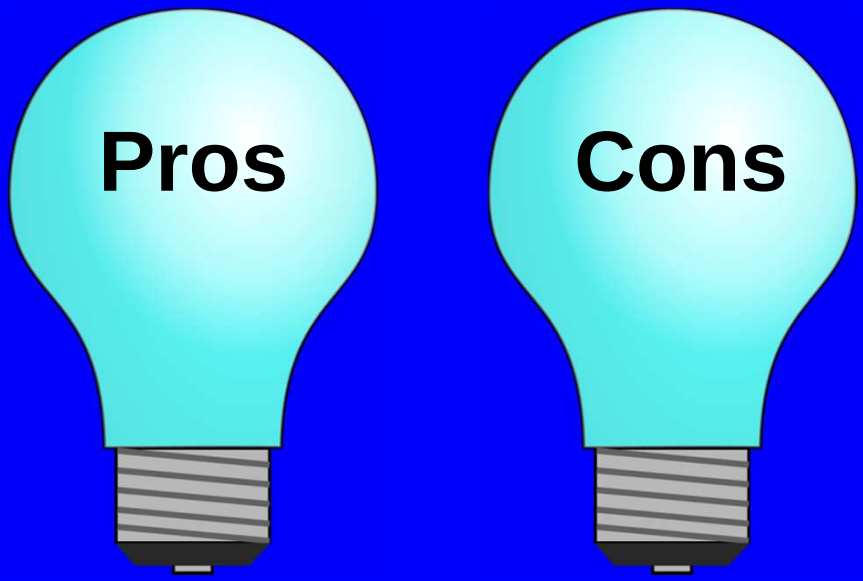
--boost memory

Ruth Day

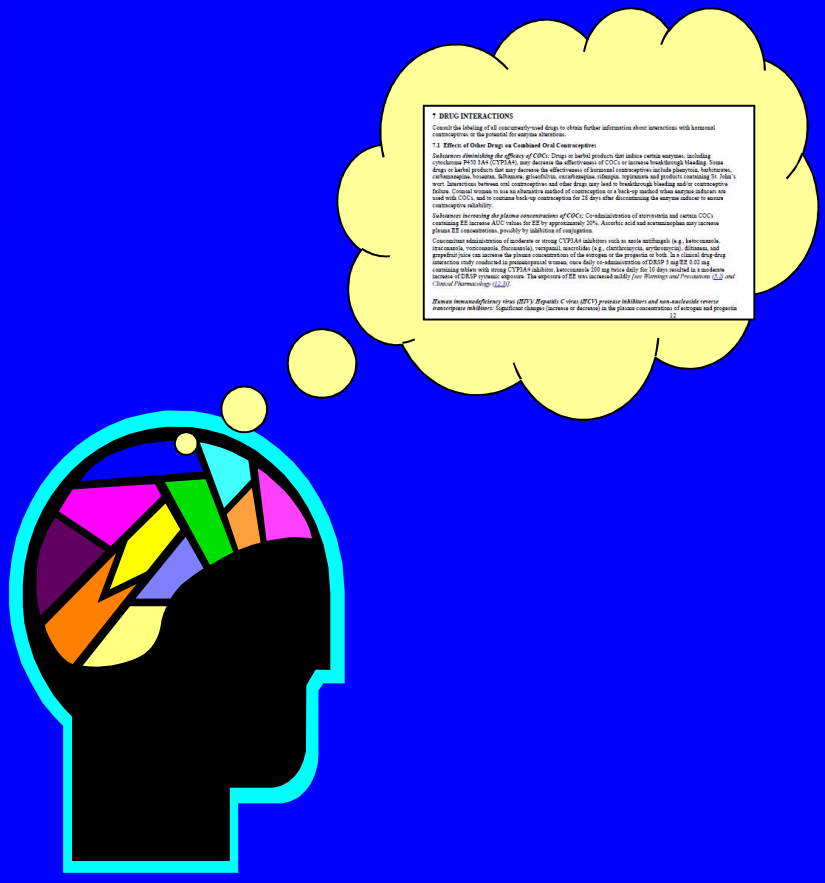
Lots of Ideas



Lots of Ideas



Stimulate Thinking



7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 **Effect of Other Drugs on Combined Oral Contraceptives**

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, ritonavir, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

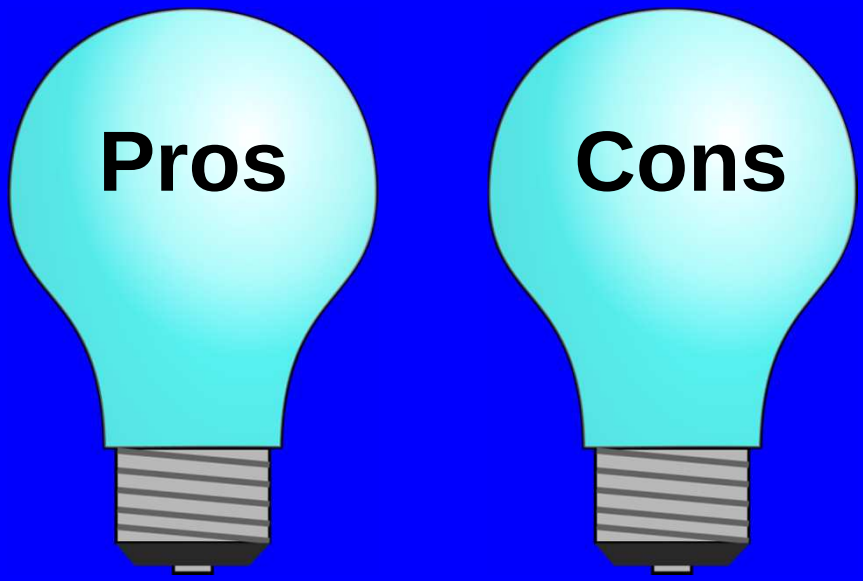
Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentration of the estrogen or the progestin or both. In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

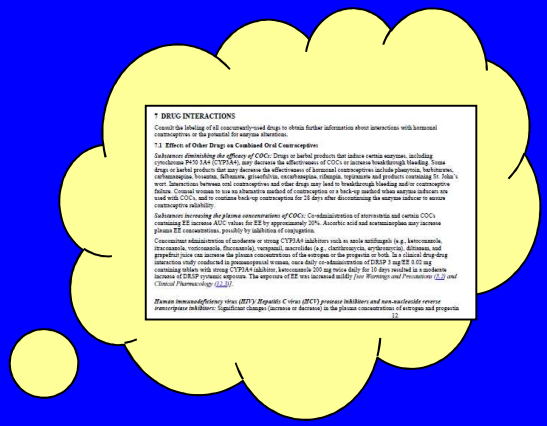
Human immunodeficiency virus (HIV) Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentration of estrogen and progestin

12

Lots of Ideas



Stimulate Thinking



7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

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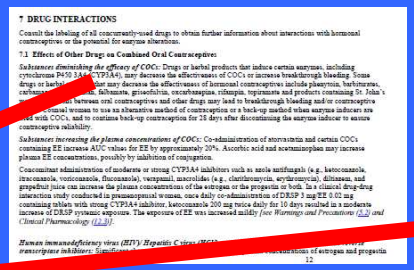
Human immunodeficiency virus (HIV) Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentration of estrogen and progestin

12

Cognitive Accessibility

Drug Interactions with Hormonal Contraceptives

Alternative Displays & Effects on Cognition



7 DRUG INTERACTIONS

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7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal [illegible] that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, [illegible], felbamate, griseofulvin, oxcarbazepine, rifampin, topiramate and products containing St. John's [illegible]. Breakthrough bleeding and spotting between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Advise women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increases AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

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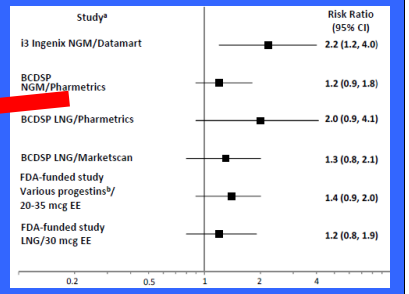
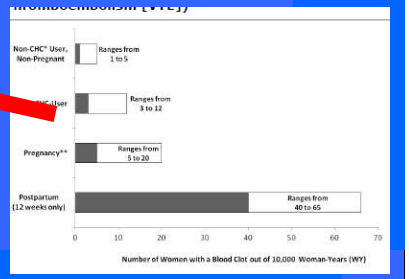
Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) [illegible] transcriptase inhibitors: [illegible] concentrations of estrogen and progestin

12



Drug Class A	
Clinical Impact	Increased exposure to Drug-X ....
Intervention	Administer Drug-X at a dose of ...
Examples	
Drug Class B	
Clinical Impact	Potential for increased exposure to Drug-X ....
Intervention	Monitor patients for ....
Examples	
Drug Class C	
Clinical Impact	Increased risk for adverse reaction Z ....
Intervention	Avoid use with other drugs that may ....
Examples	



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