Drug Interactions with Hormonal Contraceptives Alternative Displays & Effects on Cognition

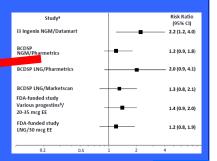


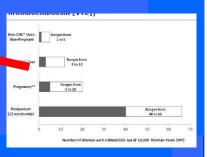
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linical Pharmacology (<u>1.34</u>). Lunan instantodyleiensy virus (IIII) Hepaitis C virus (IIII) anscriptuse inhibitors: Significan

Drug Class A	
Clinical Impact	Increased expo.
Intervention	Administer Drug-X at a dose or
Examples	
Drug has 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	

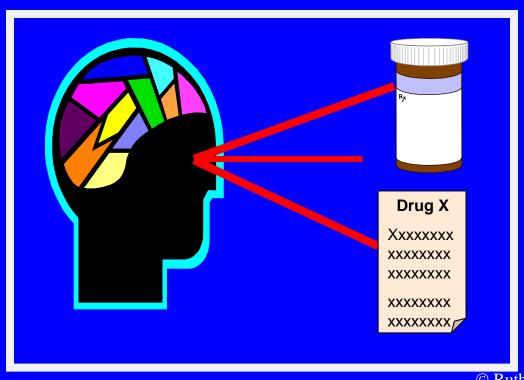




Ruth S. Day / Duke University

FDA DDI-HC Meeting / Nov. 9, 2015

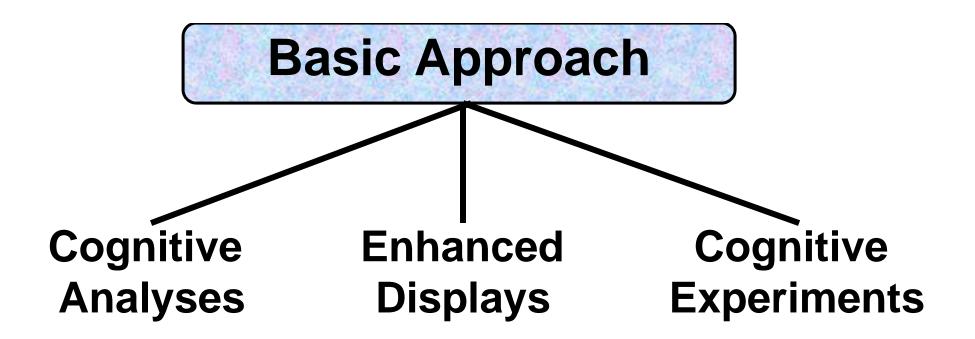
Medical Cognition Laboratory

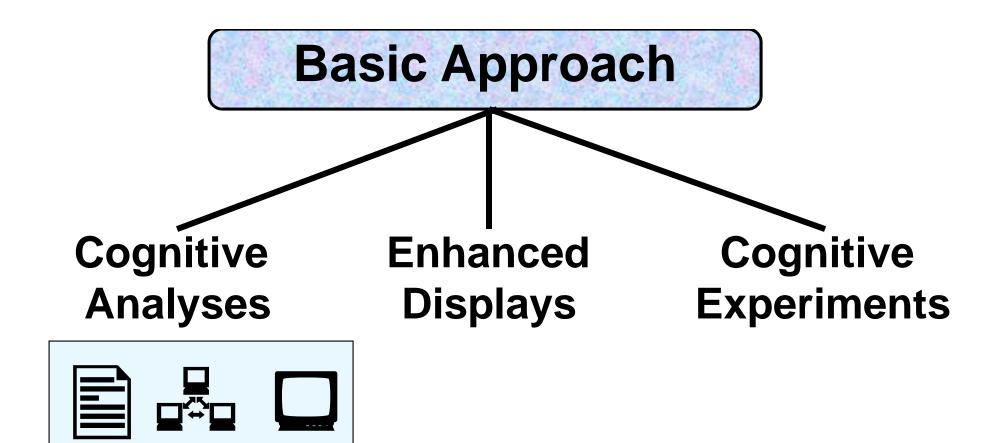


Rx

© RuthDay

Comprehension, memory, and use of drug information.





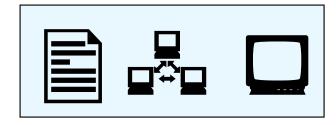
- --Obtain quantitative measures
- --Calculate "cognitive accessibility"

Basic Approach

Cognitive Analyses

Enhanced Displays

Cognitive Experiments



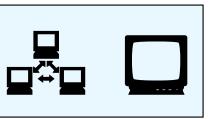
- --Obtain quantitative measures
- --Calculate "cognitive accessibility"



- --Same info
- --Based on cognitive principles

Basic Approach

Cognitive Analyses



- --Obtain quantitative measures
- --Calculate "cognitive accessibility"

Enhanced Displays



- --Same info
- --Based on cognitive principles

Cognitive Experiments

Test effects on:

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

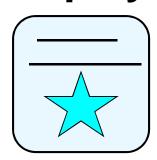
Basic Approach

Cognitive Analyses



- --Obtain quantitative measures
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Enhanced Displays



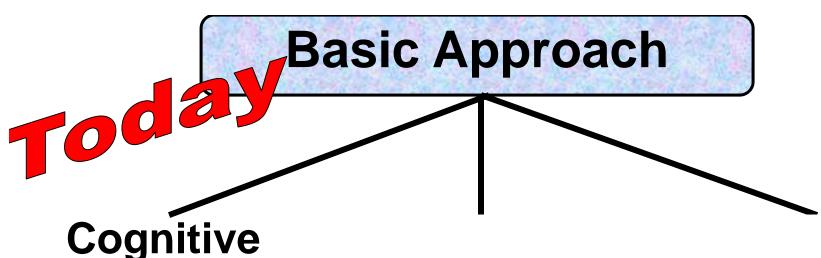
- --Same info
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Cognitive Experiments

Test effects on:

- --Attention
- -- Comprehension
- --Memory
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- -- Decision Making
- --Behavior

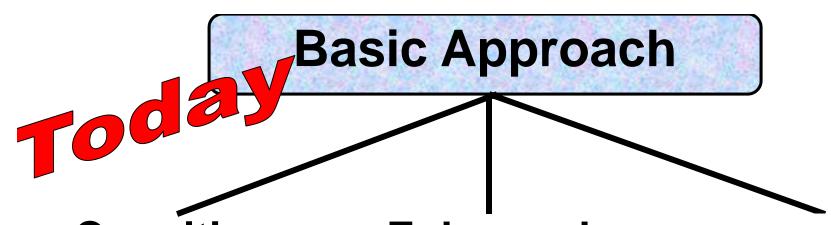
Health Outcomes



Cognitive Analyses



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

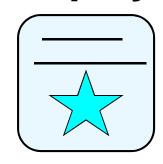


Cognitive Analyses

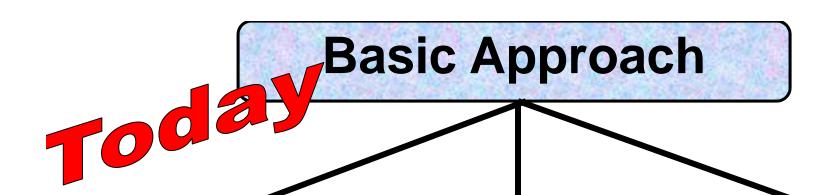


- --Labeling for:
 - --sample HC's
 - --sample DI drugs (antivirals)

Enhanced Displays



- --Key info
- --Based on cognitive principles



Cognitive Analyses



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

Enhanced Displays



- --Key info
- --Based on cognitive principles

Cognitive Experiments

Test effects on:

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

Health Outcomes

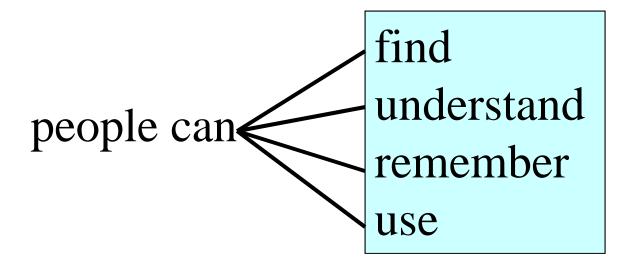
DDI Labeling

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

--Patient Counseling (Section 17)

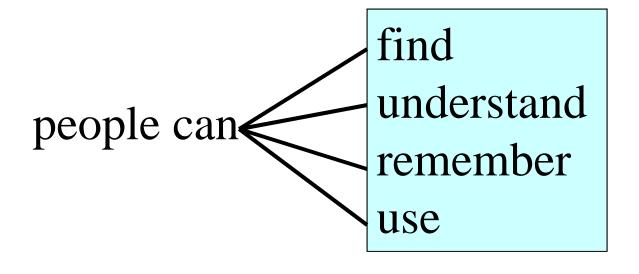
The ease with which

The ease with which



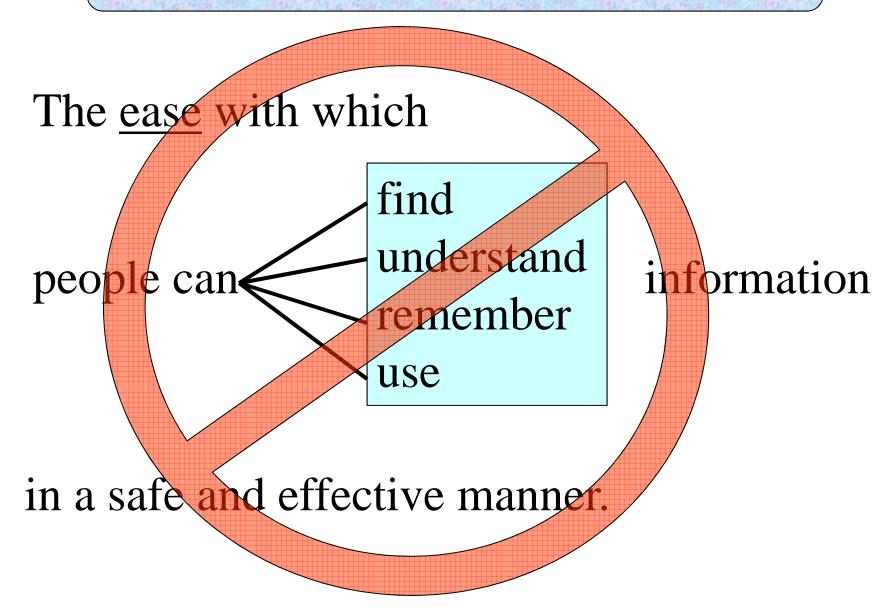
information

The ease with which



information

in a safe and effective manner.



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

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- --Review DDI data
- --Determine clinical recommendations
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THEN

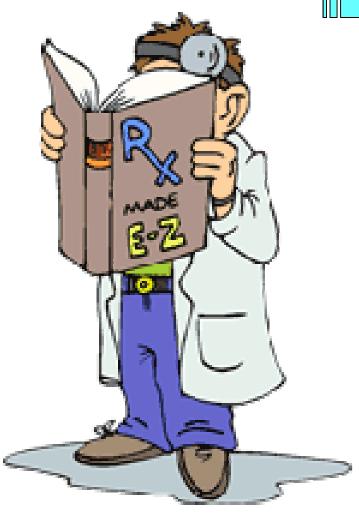
- --How to Say it
- --How to Display it

AND

- --for whom
- --for what tasks

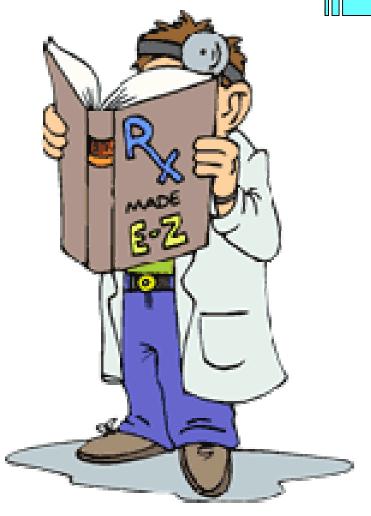










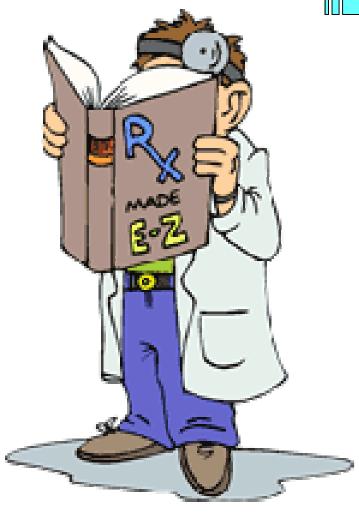


- --Don't read labeling
- -- Too much information
- --Not clinically friendly

Providers



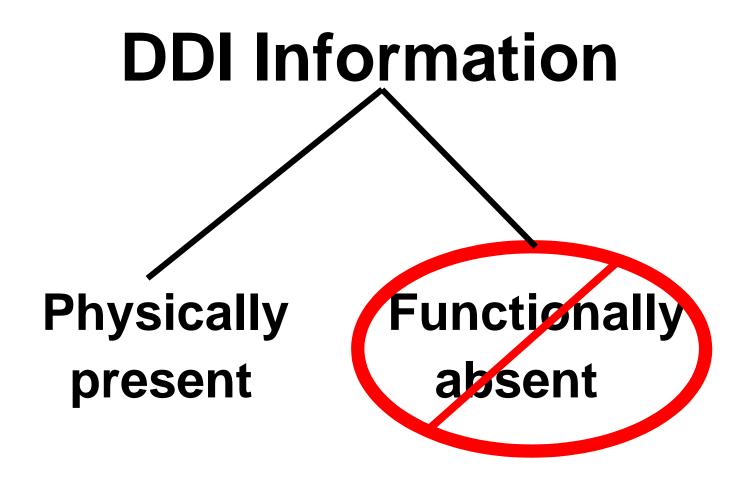


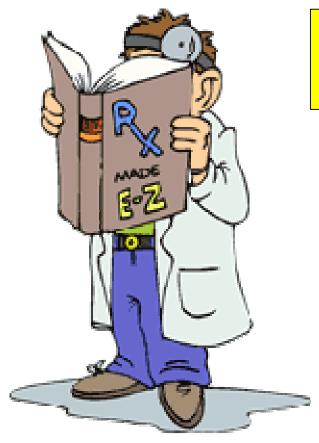


- --Don't read labeling
- --Too much information
- --Not clinically friendly

Cognitive accessibility?

DDI Information Physically present





Questions

--What do they want?

Drug List

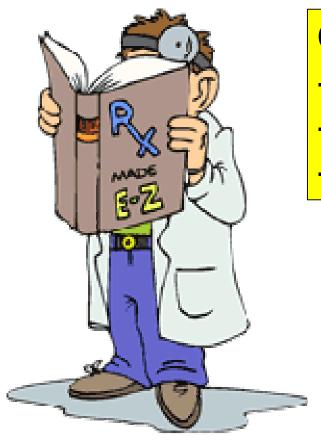
Drug-A

Drug-B

Drug-C

Drug-D

Drug-E



Questions

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

Drug List

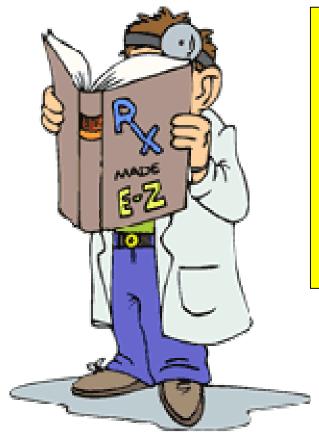
Drug-A

Drug-B

Drug-C

Drug-D

Drug-E



Questions

- --What do they want?
- --What do they **need**?
- --When do they need it?
- --Can they get along without (some of) it?

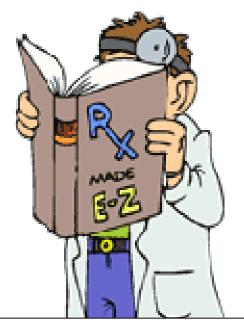
Drug List

Drug-A

Drug-B

Drug-C Drug-D

Drug-E



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

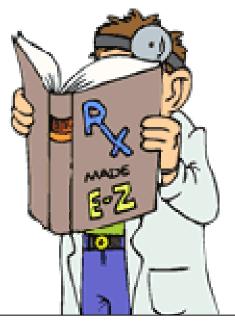
Drug-B Drug-C

Drug-D

Drug-E

How to get HCP's to

- --Look at the labeling
- -- Engage them
- --Help them find, understand, remember, & use the info



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

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



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

Task	Time Needed	Label Support?
Read for general knowledge	A lot	Content = Good Cognitive Accessibility = Could be better
Solve a problem	Moderate to a lot	Content = Good Cognitive Accessibility = Variable

Task	Time Needed	Label Support?
Read for general knowledge	A lot	Content = Good Cognitive Accessibility = Could be better
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Find whether a specific drug is listed	Too much	Could be better Could → errors

Task	Time Needed	Label Support?
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Solve a problem	Moderate to a lot	Content = Good Cognitive Accessibility = Variable
Find whether a specific drug is listed	Too much	Could be better Could → errors
Remember	Too much	Poor
(etc.)		

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(etc.)		

Task	Time Needed		Label Support?
Read for general knowledge	A lot		Content = Good Cognitive Accessibility = Could be better
Solve a problem	Mod to a	How	to ice time
Find whether a specific drug is listed	Тоо	reduce effortincrease comprehensionincrease memory	
Remember	Тоо		
(etc.)			itate problem solving itate decision making



Text

Table

Figure

* DDIC INTEDACTIONS

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

7.1 Effects of Other Drugs on Combined Oral Contraceptives

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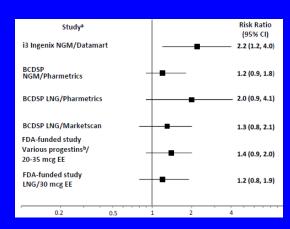
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palamia d. concentrations, pouvoir of minorous or configuration.

Concentration affirmations of moderate or trong CFF2A4 hishibitors such as anole satisfungais (e.g., lestoconazole, intencenazole, voriconazole, florenazole), vorigonazole, florenazole), vorigonazole, florenazole), vorigonazole, florenazole), vorigonazole, florenazole), vorigonazole, florenazole), vorigonazole, florenazole, properturi juice ana minorase da platuna concentrations of the surrigonar to both in a citization of the grant properturi pro

Human immunodeficiency virus (HIV) Hapatitis C virus (HCV) protease inhibitors and non-mucleoside reverse transcripture inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin 12

Epidemiologic Study ^A	Comparator Product	Risk Ratios (95% CI)
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L		



Text

Table

Figure

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Substances diministrings the effices of COCC: Drays or otheral products that induce certain susymes, including cytochrome P4'90.344 (CVP344), may decrease the affectiveness of COCs or increases breadfutrough bleeding Sometrays or large large or health products that may decrease the affectiveness of Demmenal commengeries includes large-grown, hardwineness, carbannespains, boseanna, Shibanate, griscofishus, occarbanapains, integrate products of the product of the commence of the commenc

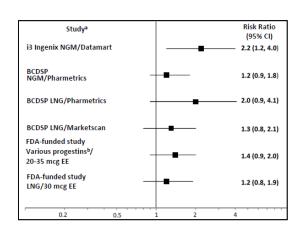
Subtameer increasing the plasma concentrations of COGs: Co-administration of atomastatin and certain COGs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and aceteminopless may increase plasma EE concentrations, possibly by inhibition of conjugation.

patama in concentration, provincy by manerous or conjugation.

Concominate silaministration of modesters or trong CVP3A4 highlyters such as asole antifungals (e.g., lastoconazole, intercensole, voriconazole, from or trong CVP3A4 highlyters such as asole antifungals (e.g., clariformycia, dilinasen, and papeluri juice and increase the plantase concentrations of the surgest or the president for both in a clinical drug-drug interaction endry conducted in presentation manes, conc daily co-deministration of DNS page 22 of 0.2 ag containing without with energy CVP3A highlyting, absorbanced One gratic shifty for 10 days resulted as a modestra to the containing without with energy CVP3A highlyting, absorbanced on 20 ag mater shifty for 10 days resulted as a modestra to the containing without propose. The exposure of EE was increased mility for Humango and Processions (2.2) of Clinical Pharmacology (2.2.2).

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

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Which is best?

Text

Table

Figure

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

As Exercise to trace long-to-a Commission Unit Learning products that induce certain surginus, including cyrechman PMO 3.84 (CVP344), may decrease the effectiveness of COCs or increase breatherings blooding Some derings or barbon products that may decrease the effectiveness of CPCs or increase breatherings blooding Some derings or Learning to the CPC of the CPC

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Human immunodeficiency virus (HIV) Hepainis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptuse inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and properties.

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Permanente and Me databases^{J, K, 9}



| Studya | Risk Ratio (95% CI) | | i3 Ingenix NGM/Datamart | 2.2 (1.2, 4.0) | | BCDSP | NGM/Pharmetrics | 1.2 (0.9, 1.8) | | BCDSP LNG/Pharmetrics | 2.0 (0.9, 4.1) | | BCDSP LNG/Marketscan | 1.3 (0.8, 2.1) | | FDA-funded study | 20-35 mgg | 1.4 (0.9, 2.0) | | FDA-funded study | 1.2 (0.8, 1.9) | |

Which is best?

--for whom?

Text

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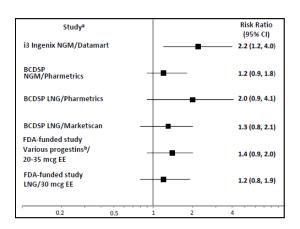
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Which is best?

- --for whom?
- --what situation?







Text

Table

Figure

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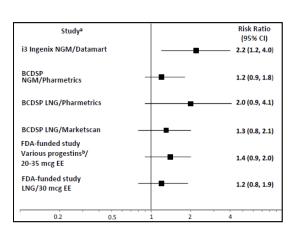
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Which is best?

--for whom?

--what situation?

--what task?







Ruth Day

Tables

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TS)

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

OATPIBI Inhibito	irs	Addition to the
Clinical Impact:	Increased exposure to eluxadoline when coadministered with Clinical Pharmacology (12.3)]	Developed by
Intervention:	Administer VIBERZI at a dose of 75 mg twice daily [see Do. Administration (2)] and monitor patients for impaired mental needed to perform potentially hazardous activities such as dri operating machinery and for other eluxadoline-related advers Adverse Reactions (6.1)].	Joe Grillo FDA (OCP. OTS
Examples:	cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinav saquinavir, tipranavir), rifampin, eltrombopag	with input from
Strong CYP Inhibit	ors [±]	Ruth Day
Clinical Impact:	Potential for increased exposure to eluxadoline [see Clinical . (12.3)]	Pharmacology
Intervention:	Monitor patients for impaired mental or physical abilities nee potentially hazardous activities such as driving a car or opera for other eluxadoline-related adverse reactions [see Adverse]	ting machinery and
Examples:	ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazol clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2	
Drugs that Cause C	onstipation	
Clinical Impact:	Increased risk for constipation related adverse reactions and p constipation related serious adverse reactions	potential for
Intervention:	Avoid use with other drugs that may cause constipation (see may be used occasionally for acute management of severe dischronic use. Discontinue loperamide immediately if constipations	arrhea but avoid
Examples:	alosetron, anticholinergics, opioids	
		

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

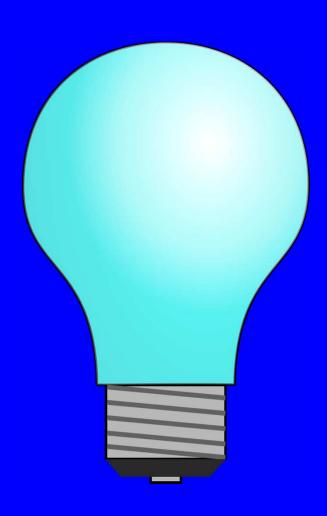
Drug Class A		
Clinical Impact		
Intervention	Modified version	
Examples	General template	
Drug Class B		
Clinical Impact		
Intervention		
Examples		
Drug Class C		
Clinical Impact		
Intervention		
Examples		

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 e	xposure to Drug-X
Intervention	Administer	Schema
Examples	aaaa, bbbb,	(organizing structure)
Drug Class B		easy to see at a glance
Clinical Impact	Potential fo	
Intervention	Monitor pa	
Examples	eeee, ffff, g	facilitates memory
Drug Class C		facilitates acquisition of
Clinical Impact	Increased r	new information
Intervention	Avoid use with other drugs that may	
Examples	kkkk, mmmm, pppp, rrrr	



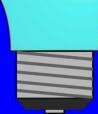


Good Idea?

Bad Idea?

Stimulate Thinking





oult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal monetrees or the potential for engrase alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Salamann desimaling the effects of COCs. Deep as belief product that induce cents acquest, stability, synchrone POC AC COCS and the effect of COCs of the second product of the contract stability of the contract stability of the cocs of the cocs

Substances increasing the plasma concentrations of COCs: Co-administration of atomistation and curain COC containing EE increase AUC values for EE by approximately 20%. Accordic acid and acateminophen may increase about EE measurements, notable for admissioning an acid and acateminophen may increase about EE measurements.

Concentrate administration of moderns or strong CVFDA4 inhibitors such as note sufficiently (e.g., lastrocassols, increassols, ventionassols, increassols, ventionassols, despensal, such as noted to the contraction of the c

Human immunodeficiency virus (HIV) Hepatids C virus (HCV) processe inhibitors and non-nucleoside reverse



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?

Problem: Information Load

- --lots of information, often complex
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Suggestion: "Wall Chart"

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

Problem: Information Load

- --lots of information, often complex
- --how grasp key info Focus on
- --how remember (at
- --how find it again w

- --main drugs that interact with HC
- Suggestion: "Wa
 - --key elements
 - --quick reminder
 - --focus on drugs that interact
 - --simple (like DDI "highlights")

--their status within a simple schema

xamp	Safety Effect	Efficacy Effect	
Drug	Examples:	Examples:	
Class A	xxxxxxxx	xxxxxxxx	
Class A	XXXXXXXX	xxxxxxxx	
	xxxxxxxx	xxxxxxxx	
Drug	Examples:	Examples:	
Class B	XXXXXXXX	xxxxxxxx	
Class D	XXXXXXXX	xxxxxxxx	
	xxxxxxxx	xxxxxxxx	
Drug	Examples:	Examples:	
Class C	xxxxxxxx	xxxxxxxx	
Class C	XXXXXXXX	xxxxxxxx	
	XXXXXXXX	XXXXXXXX	

	Adverse Reactions	Exposure Effects
Drug Class A	Examples:xxxxxxxxxxxxxxxx	Examples ()xxxxxxxxxxxxxxxx
Drug Class B	Examples:xxxxxxxxxxxxxxxxxxxxxxxx	Examples: (↓)xxxxxxxxxxxxxxxxxxxx
Drug Class C	Examples:xxxxxxxxxxxxxxxx	Examples: (

Ruth Day

	Established Interaction	Potential Interaction
Drug Class A	Examples:xxxxxxxxxxxxxxxx	Examplesxxxxxxxxxxxxxxxx
Drug Class B	Examples:xxxxxxxxxxxxxxxx	Examples:xxxxxxxxxxxxxxxx
Drug Class C	Examples:xxxxxxxxxxxxxxxxxxxx	Examples:xxxxxxxxxxxxxxxx

Ruth Day

	Potential for HC to affect other drugs	Potential for Other Drugs to affect HC	
Drug	Examples:	Examples	
Class A	xxxxxxxx	xxxxxxxx	
Class A	xxxxxxxx	xxxxxxxx	
	xxxxxxxx	xxxxxxxx	
Drug	Examples:	Examples:	
Class B	xxxxxxxx	XXXXXXXX	
Class D	xxxxxxxx	xxxxxxxx	
	XXXXXXXX	xxxxxxxx	
Drug	Examples:	Examples:	
Class C	xxxxxxxx	xxxxxxxx	
Class C	xxxxxxxx	xxxxxxxx	
	xxxxxxxx	XXXXXXXX Ruth Day	

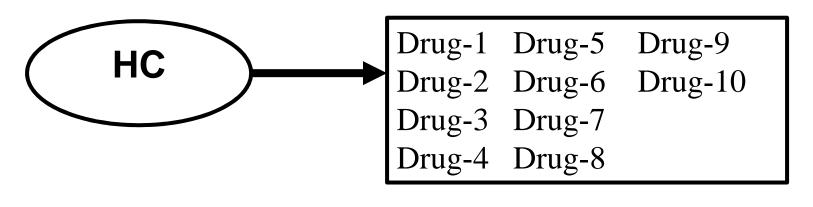
		X			X
Health	Examples:		Examples		
Condition A	XXXX	XXXX		xxxx	XXXX
	XXXX	XXXX		XXXX	XXXX
	XXXX	XXXX		XXXX	XXXX
Health	Examples:		Examples:		
Condition B	XXXX	XXXX		XXXX	XXXX
	XXXX	XXXX		XXXX	XXXX
	XXXX	XXXX		XXXX	XXXX
Health	Examples:		Examples:		
Condition C	XXXX	XXXX		XXXX	XXXX
	XXXX	XXXX		XXXX	XXXX
	XXXX	XXXX		XXXX	XXXX

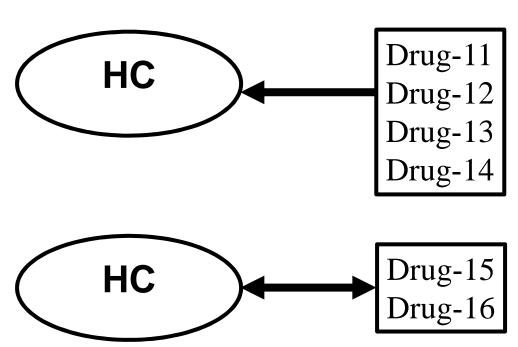
Drug Class/ Health Cond	X	X
HIV		
Drug-1:		
Drug-2:		
Drug-3:		
AntiViral		
Drug-1:		
Drug-2:		
Drug-3		
AntiEpileptic		
Drug-1:		
Drug-2:		
Drug-3		

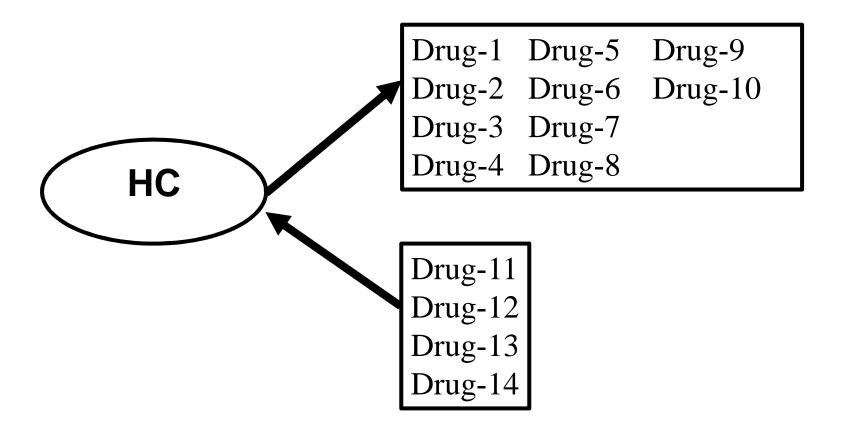
	Effect	Intervention
Drug Class A		
Drug-1:		
Drug-2:		
Drug-3:		
Drug Class B		
Drug-1:		
Drug-2:		
Drug-3:		
Drug Class C		
Drug-1:		
Drug-2:		
Drug-3:		

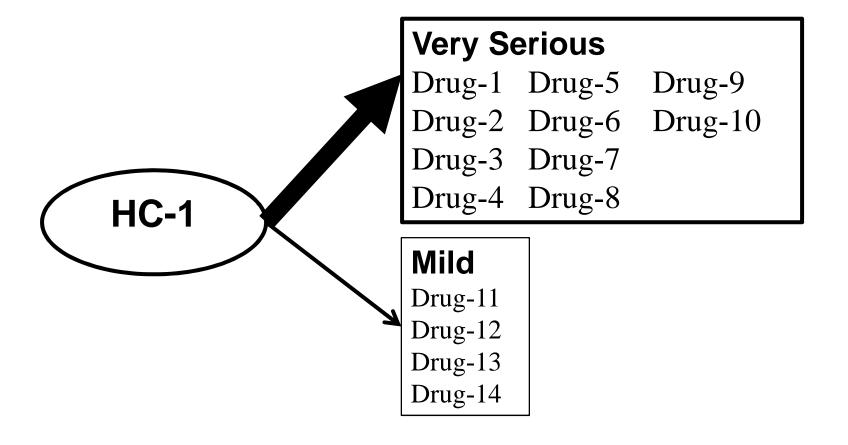
	HC Effect: on Other Drugs	Other Drugs: Effects on HC
Drug Class A		
Drug-1:		
Drug-2:		
Drug-3:		
Drug Class B		
Drug-1:		
Drug-2:		
Drug-3		
Drug Class C		
Drug-1:		
Drug-2:		
Drug-3		

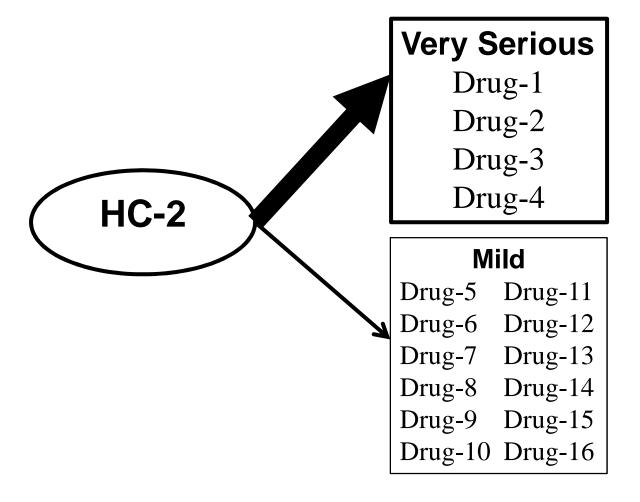
Type of Effect	Likely	Rare
Teratogenic		
Lactation		
Exposure Changes		











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 (CYP9A4), may decrease the effectiveness of COCs or increase breakthrough bloeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phosphoin, burbinaries carbanasepine, bosentan, felbamate, griscofialtin, oxcarbazepine, ritimpin, topiramete and products containing St. John wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bloeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when anyme inducer 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 in physical paper or a containing EE increase AUC values for EE by in physical paper or an expension of the paper of the physical paper of the paper of

Concomitant administration of moderate or strong CYP3A4 inhibitors such as anole antifungals (e.g., ketoconazole, iraconazole, voriconazole, fluconazole, vorapamil, macrolides (e.g., clarifaromycin, enythromycin), dilitasem, and grapefluit jnice can increase the plasma concentrations of the estrogen or the progestin or both In clinical drug-drug interaction study conducted in prememopausal 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 middly (see Warnings and Precontions (5.2) as Clinical Pharmacology (12.3)].

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

transcriptase inhibitors,

Antibiotics: There have been reports of prognancy 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 plasms concentrations of lamortigine, likely due to induction of lamortigine glucuronidation. This may reduce sairure control; therefore, dosage adjustments of lamortigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyma 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., oneprazole and voriconazole) and CYP1A1 substrates (e.g., theophylline and transidine) can have a weak or moderate increase.

Clinical studies did not indicate an inhibitory potential of DRSP towards human CVP 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 Beyar with other drugs that may increase serum potassium concentration [see Warnings and Procuntions (5.2) and Clinical Pharmacology (2.23).

7.3 Effects of Folstes on Other Drugs

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

7.4 Effects of Other Drugs on Folster

Several drugs have been reported to reduce foliate concentrations by inhibition of the dihydrofoliate reductate enzyme (e.g., methotreams and sulfatalazins) or by reducing foliate absorption (e.g., dobotyvamine), or via unknown mechanisms (e.g., antispilppics such as carbamasepine, phenytoin, phenobarbital primidone and valprice caid).

7.5 Interference with Laboratory Test

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glacose tolerance, and binding proteins. DRSP causes an increase in plasma remin activity and plasma addosterone induced by its mild anti-mineralocorticoid activity. Foliates may mask vitamin B12 deficiency. [See Warrangs and Procautions (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

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 afficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P410 3A4 (CYPSA4), may decrease the effectiveness of COCs or increase breakthrough bloeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phosphoin, burbinaries carbanaseptine, bosentan, felbanate, griscofulvin, oxcarbaseptine, ritimpin, topizamete and products containing St. John wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bloeding and/or contraceptive failure. Counted women to use an alternative method of contraception or a back-up method when enzyme inducer 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 axole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole, voraconazole, fluconazole, voraconazole, fluconazole, voraconazole, fluconazole, voraconazole, fluconazole, voraconazole, fluconazole, voraconazole, fluconazole, voraconazole fluconazole, continuous despetados productes de planta concentrations of the estrogen or the progestin or both is clinical drug-drug interaction study conducted in premiseopeural 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 Procautions (5.2) as Clinical Pharmacology (12.3)].

Human immunodeficiency virus (HIV) Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptuse 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 Inbelling 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 continuing 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., omegrazole and voriconazole) and CYP1A1 substrates (e.g., deeply-like and inanidus) 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 Serian Potassium Concentration: There is a potential for an increase in serian potassium concentration in women taking Beyra with other drugs that may increase serian potassium concentration [see Warnings and Precautions (§2) and Clinical Pharmacology (123).

7.3 Effects of Folstes on Other Drug:

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.

4 Effects of Other Drugs on Folstes

Several drugs have been reported to reduce foliate concentrations by inhibition of the dihydrofolate reductase enzyme (e.g., methorsense and sulfasalazino) or by reducing foliate absorption (e.g., cholostyramine) or via unknown mechanisms (e.g., antispilepics such as carbamasepine, phenytoin, phe

7.5 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, gincose tolerance, and binding proteins. DRSP causes an increase in plasma reain activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity. Folates may mask vitamin B12 deficiency. [See Warnings and Precautions (2.1.2) and Drug Interactions (2.2.3)

Embedded Wall Chart

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

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

Concomitant administration of moderate or strong CYP3A4 inhibitors such as axole antifungals (e.g., letoconazole, itraconazole, voriconazole, fluconazole, fluconazole, fluconazole propestin or both. In a clinical drug-drug interaction study conducted in prememopassial women, once daily co-administration of DKSP 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 DKSP systemic exposure. The exposure of EE was increased mildly face Warnings and Precautions (5.2) an 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

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transcriptase inhibitor

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Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Beyra with other drugs that may increase serum potassium concentration [see Warnings and Procuntings (3.2) and Clinical Pharmacology (2.23).

7.3 Effects of Folstes on Other Drug:

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Embedded Wall Chart

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

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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) protease inhibitors and non-nucleoside contranscriptase inhibitors: Significant changes (increase at decrease) in the plasma concentrations of the contraction of

7.6 Overview: Main Drugs that Interact with Drug-X



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Potential to Increase Serian Potesstam Concentration: There is a potential for an increase in serian potestium concentration in women taking Beyen with other drugs that may increase serian potestium concentration [see Warnings and Precautions (3,2) and Clinical Pharmacology (12,3)].

7.3 Effects of Folstes on Other Drug:

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 Folster

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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, gincoss tolerance, and binding proteins. DRSP causes an increase in plasma reain activity and plasma addosterone induced by its mild anti-mineralocorticoid activity. Folates may mask vitamin B12 deficiency. [See Warnings and Procuntions (2.2.1) and Drug Interactions (2.2.1)

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?

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 COCr: 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 commongivers include phenytoin, barbinurates, carbanasepine, bosentan, followante, griscofishine, oxcarbasepine, rifampin, topiramete and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counted 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 18 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorva statin 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 axole antifungals (e.g., ketocomazole, itracomazole, voricomazole, flucomazole), vorapamil, macrolides (e.g., clarifaromycin, scythromycin), dilinasem, 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 premanopamial women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketocomazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly face Warnings and Procuntous (5.2) and Clinical Pharmacology (12.3)].

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7.6 Overview: Main Drugs that Interact with Drug-X



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7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing FE 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 sainure control; therefore, dorage adjustments of lamotrigine may be necessary. Consult the Inbelling 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., omegrazole and voriconazole) and CYP1A3 substrates (e.g., facephylline and intantidue) 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 Beyar with other drugs that may increase serum potassium concentration [see Warmings and Procuntions [5.2] and Clinical Pharmacology (12.3).

7.3 Effects of Folstes on Other Drug:

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

7.4 Effects of Other Drugs on Folstes

Several drugs have been reported to reduce foliate concentrations by inhibition of the dihydrofoliate reductase enzyme (e.g., methorwants and sulfasalazine) or by reducing foliate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antispileptics such as carbamasepine, phenytoin, phenobarbiral, primidene 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 reain activity and plasma addosterone induced by its mild anti-mineralocorticoid activity. Folates may mask vitamin B12 deficiency. [See Warnings and Precautions (2.1.2) and Drug Interactions (2.2.1.7)

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?

And if you lost that space

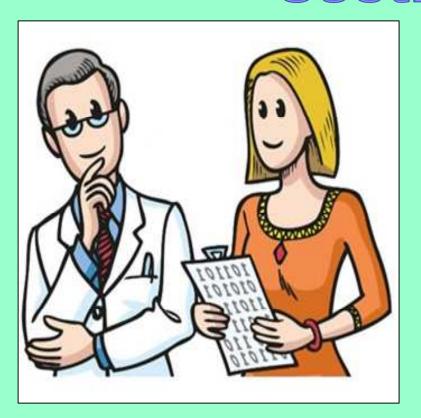
- --how would you enhance the existing space
- --to increase comprehension, memory, and safe/effective use?

LET'S SHIFT GEARS

Drug Interactions Patient Counseling Section 17

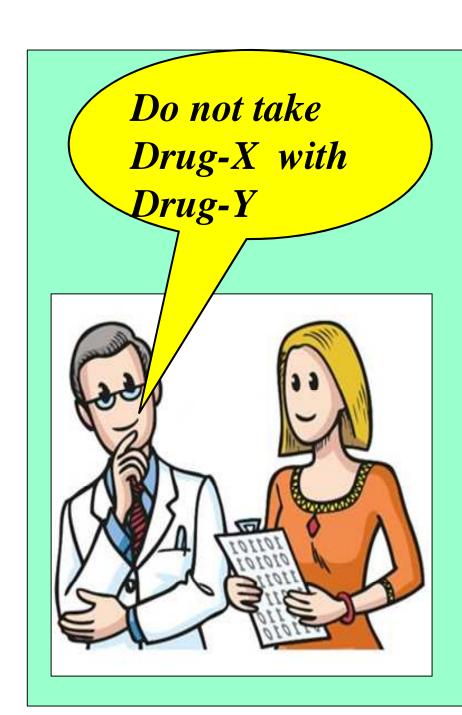


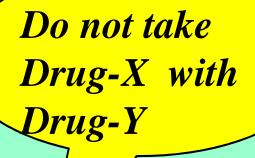
Drug Interactions Patient Counseling Section 17



- --Written for providers: (what to tell patients)
- --NOT the

 "FDA Approved
 Patient Labeling"
- --Instead, for provider-patient communication





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



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

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

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 restarting

- Counsel contain lev
- Counsel
- Counsel
- Counsel their healtl conditions currently cangiotensi inhibitors.
- Inform p the patient
- Counsel are missed
- Counsel
- Counsel less likely
- Counsel

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

Mostly plain language.

But cognitive accessibility could be improved.

arting a COC or

to COCs that

l diseases.

vised to inform nce of these if they are ACE inhibitors, ong CYP3A4

Drug-X, instruct ate intake.

in the event pills

vith COCs. duction. This is

ethod of

contraception until she has taken a pink tablet for 7 consecutive days.

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

Ruth Day

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

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

Effortful reading.

What are the topics?

Where is DDI?
Or anything else?

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

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

• Counsel patients that

Uh-oh.

• Counsel patients that

- **DDI** in several locations.
- 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

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

• Counsel patients that

Uh-oh.

• Counsel patients that

DDI in several locations.

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

Cognitive Violations:

- --No clustering
- --No chunking
- --No explicit coding

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 ... [~ DD
- 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

Enhanced Version

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

Counsel patients that:

Topic-A: xxxxxxxxx

Topic-B: xxxxxxxxxx

Topic-C: xxxxxxxxxx

Drug Interactions:

Topic-E: xxxxxxxxxx

Topic-F: xxxxxxxx

Enhanced Version

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

Counsel patients that:

Topic-A: xxxxxxxxxx

Topic-B: xxxxxxxxxx

Topic-C: xxxxxxxxxx

Drug Interactions:

__

--

__

Topic-E: xxxxxxxxxx

Topic-F: xxxxxxxx

Cognitive Principles Used:

- --Clustering
- --Chunking
- -- Explicit coding

Enhanced Version

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

Counsel patients that:

Topic-A: xxxxxxxxx

Topic-B: xxxxxxxxxx

Topic-C: xxxxxxxxxx

Drug Interactions:

__

__

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Topic-E: xxxxxxxxxx

Topic-F: xxxxxxxx

Cognitive Principles Used:

- --Clustering
- --Chunking
- -- Explicit coding

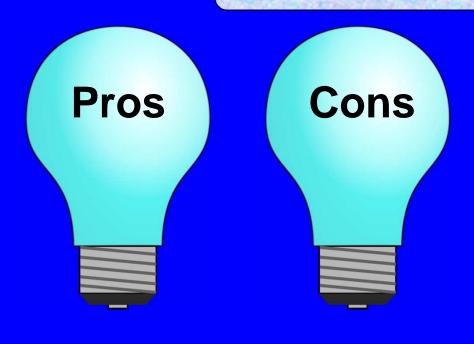
Therefore

- --decrease effort
- --speed processing
- --increase processing
- --boost memory

Ruth Day



Lots of Ideas



Lots of Ideas



Cons

Stimulate Thinking

* DRUG INTERACTIONS

oult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal

Effects of Other Drugs on Combined Oral Contraceptives

Substances increasing the plasme concentrations of COCs: Co-administration of atomistation and certain COCs containing EE increases AUC values for EE by approximately 30%. Ascerbic acid and acatemine plasm may increase above EE concentration, and this to include the descriptions.

leuna EE concentrations, possibly by inhibition of conjugation. oncomitant administration of moderate or strong CVPLA4 inhibitors

Concentrate relatable revision of modern we strong CVFAM shifthers such as such asterdamph (a.g., histocampale, intercampale, softcampale, florecampale, softcampale, and relative (a.g., and continuous), and relative (a.g., and and approximate photos and an expert of the program of the program of the an elizated disperfugiate action only otherwise in generating and worse, care chips or exhibiting the continuous grades with a reng cVFAM shiftent, inconcentrate 200 any note of the 10 days resulted in a modern account of the continuous of CVFAM shiftent and an elizated continuous and a

Human immunodeficiency virus (HIV) Hepatids C virus (HCV) processe inhibitors and non-nucleoside reverse



Lots of Ideas



Cons

Stimulate Thinking

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about inseractions with hormone

Effects of Other Drugs on Combined Oral Contraceptives

Substances increasing the plasme concentrations of COCs: Co-administration of atomistantin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascerbic acid and acetaminephan may increase where EE concentration most oblig inhibition of construction.

pleans EE concurrations, possibly by inhibition of conjugation.

Concentrate administration of moderate or strong CVFIA4 inhibit

Concerning statistication fundament or trong CFDAs thickness such as sufficiently (e.g., between the increasate), encounted by respect, according to go, indevenous, encounted by respect, ancestories or go, indevenous, encounters or distances or despreyation to both. In a clinical desprise, interaction only conducted in generational resum, near each oper-continuous or desprise or both. In a clinical desprise, interaction only conducted in generation areas, near each oper-continuous and conduction and proceed on the continuous and conduction of the conduction of the

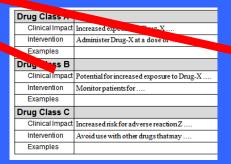
Haman immunodeficiency virus (HIV) Hepatids C virus (HCV) protease inhibitors and non-nucleotide reverse

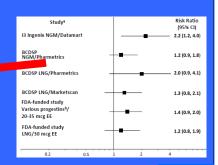
Cognitive Accessibility

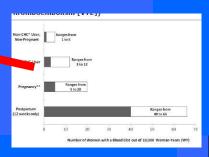
Drug Interactions with Hormonal Contraceptives Alternative Displays & Effects on Cognition











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