GYÓGYSZERES INTERKACIÓK
ENZIMEK, SZUBSZTRÁTOK, INDUKTOROK, INHIBÍTOROK

SZALAI GÁBOR

KISKUNHALASI SEMMELWEIS KÓRHÁZ

INTENZÍV OSZTÁLY

D: Drug selection

O: Over or underdose

C: Compliance

U: Undertreated

M: Monitoring

E: Education

N: Not classifiable

T: Toxicity/ADRs

MEDICATION-RELATED PROBLEM		
Category	**Subcategory**	**Code**
Drug selection (Problems relating to the choice of medicine prescribed or taken)	Duplication	D1
	Drug interaction	D2
	Wrong drug	D3
	Incorrect strength	D4
	Inappropriate dosage form	D5
	Contraindication apparent	D6
	No indication apparent	D7
	Other drug selection problem	D0

RECOMMENDATIONS		
Category	**Subcategory**	**Code**
Change of therapy	Dose increase	R1
	Dose decrease	R2
	Drug change	R3
	Drug formulation change	R4
	Drug brand change	R5
	Dose frequency/schedule change	R6
	Prescription not dispensed	R7
	Other changes to therapy	R8

Guidelines for pharmacists performing clinical interventions
Pharmaceutical Society of Australia 2018

KLINIKAI GYÓGYSZERÉSZ „VEZÉRFONALA”

Letter	Definition
M	Medication reconciliation
A	Antibiotics or anti-infectives
I	Indications for medications
D	Drug dosing
E	Electrolytes, hematology, and other laboratory results
N	No drug interactions, allergies, duplications, side effects
S	Stop dates

EMMI SZAKMAI IRÁNYELV
AZ ALAPSZINTŰ GYÓGYSZERÉSZI GONDOZÁS KERETÉBEN VÉGZETT GYÓGYSZERBIZTONSÁGI ELLENŐRZÉSRŐL
2013.04.01. – 2014.05.01.

- **klinikailag jelentős interakciók** feltárása
  - melynek eredményeként a terápiás hatás megváltozik: csökken vagy elmarad, illetve fokozott, ami miatt nemkívánt gyógyszerhatás jön létre (fejlesztőcsoport által készített definíció)

„An interaction is clinically significant if concomitant use of the drugs leads to safety, efficacy, or tolerability concerns greater than those present when the drugs are administered alone.” -FDA-

https://kollegium.aeek.hu/Download/Download/477

KLINIKAILAG JELENTŐS INTERAKCIÓBAN GYAKRAN RÉSZT VEVŐ GYÓGYSZEREK I.

- **kis terápiás szélességű gyógyszerek, melyeknek terápiás hatása/toxicitása jelentősen változik kis koncentráció- vagy hatásváltozás esetén is**
  - antikoaguláns gyógyszerek:
    - K-vitamin antagonisták: acenokumarol, warfarin
    - dabigatran, rivaroxaban
  - immunszuppresszánsok: ciklosporin, takrolimus, sirolimus, metotrexat
  - szulfanilureák
  - egyes antiarrhythmiás szerek
    - amiodaron, propafenon, digoxin
  - teofillin
  - lítium-karbonát

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KLINIKAILAG JELENTŐS INTERAKCIÓBAN GYAKRAN RÉSZT VEVŐ GYÓGYSZEREK II.

- **gyógyszerek, melyek más, együttesen szedett gyógyszerek hatását befolyásolják**
  - **gyógyszermetabolizáló enzim-gátlók**:
    - egyes makrolid antibiotikumok: eritromicin, klaritromicin
    - ciprofloxacin
    - metronidazol
    - azol antifungális szerek: itrakonazol, vorikonazol, posakonazol, flukonazol
    - immunszuppresszánsok: ciklosporin, takrolimus
    - egyes SSRI antidepresszánsok: fluoxetin, paroxetin, szertralin
    - amiodaron
    - omeprazol

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KLINIKAILAG JELENTŐS INTERAKCIÓBAN GYAKRAN RÉSZT VEVŐ GYÓGYSZEREK III.

- **gyógyszermetabolizáló enzim-induktorok**:
  - rifampicin
  - karbamazepin, fenitoin,
  - hypericum extractum

- **felszívódást befolyásoló komplexképzők**
  - antacidok, szukralfát
  - kalcium-, magnézium- és vastartalmú készítmények

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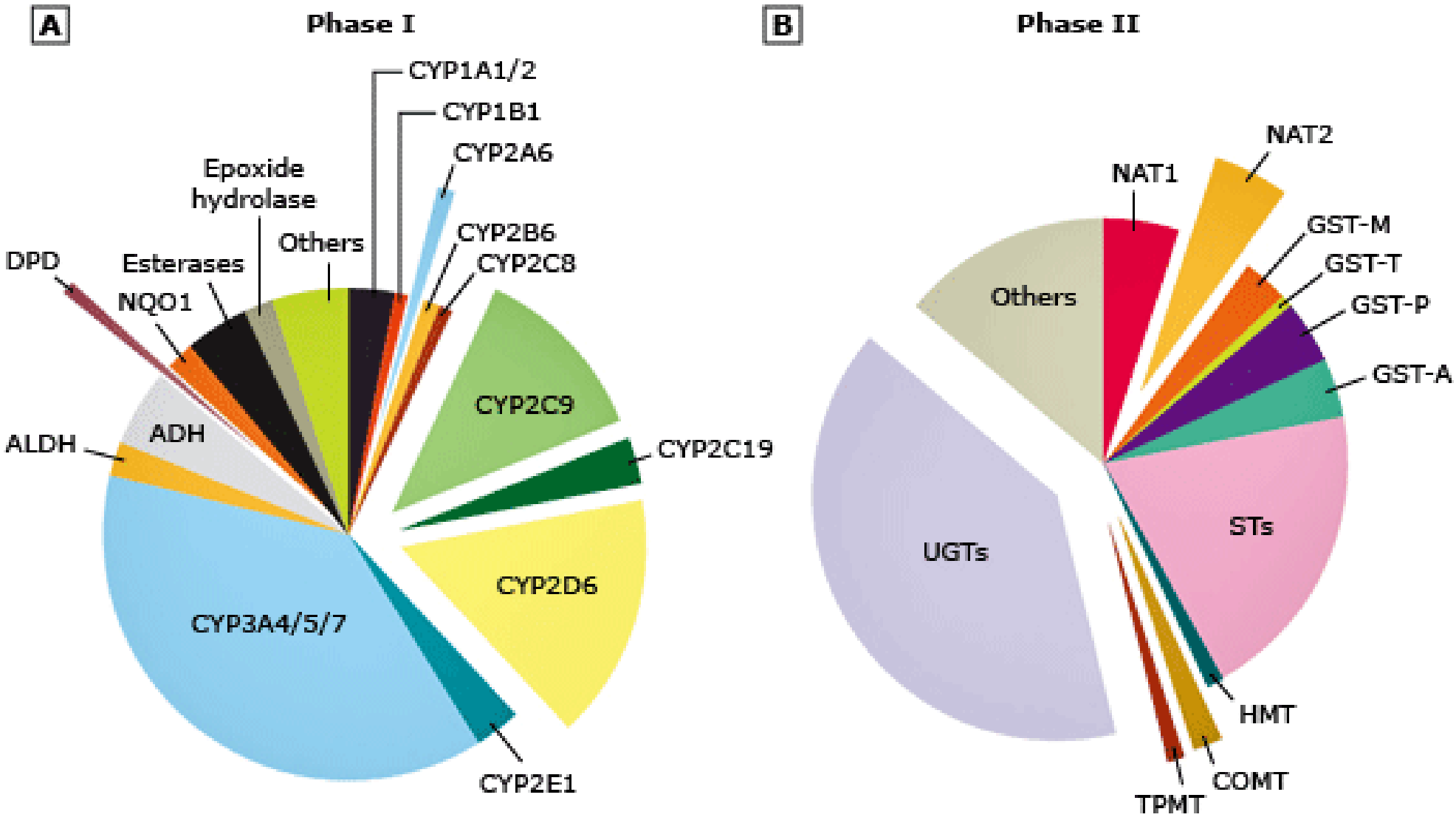

A
Phase I
CYP1A1/2
CYP1B1
CYP2A6
Epoxide hydrolase
Others
CYP2B6
CYP2C8
DPD
Esterases
NQO1
CYP2C9
CYP2C19
ALDH
ADH
CYP2D6
CYP3A4/5/7
CYP2E1
B
Phase II
NAT2
NAT1
GST-M
GST-T
GST-P
Others
GST-A
STs
UGTs
HMT
TPMT
COMT

	Sensitive substrates	Moderate sensitive substrates
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine	clozapine, pirfenidone, ramosetron, theophylline
CYP2B6	bupropion[(a)]	efavirenz
CYP2C8	repaglinide[(b)]	montelukast, pioglitazone, rosiglitazone
CYP2C9	celecoxib[(c)]	glimepiride, phenytoin, tolbutamide, S-warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole[(d)], rabeprazole, voriconazole
CYP2D6	atomoxetine, desipramine, dextromethorphan, eliglustat[(e)], nebivolol, nortriptyline, perphenazine, tolterodine, R-venlafaxine	encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine, S-venlafaxine

	Sensitive substrates	Moderate sensitive substrates
CYP3A	Substrates with ≥10-fold increase in AUC by co-administration of strong inhibitors: alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir[f], ebastine, everolimus, ibrutinib, lomitapide, lovastatin[b], midazolam, naloxegol, nisoldipine, saquinavir[f], simvastatin[b], sirolimus, tacrolimus, tipranavir[f], triazolam, vardenafil	alprazolam, aprepitant, atorvastatin[b], colchicine, eliglustat[e], pimozide, rilpivirine, rivaroxaban, tadalafil
	Substrates with 5- to 10-fold increase in AUC by co-administration of strong inhibitors: budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir[f], isavuconazole, ivabradine, lemborexant, lurasidone, maraviroc, mobocertinib, quetiapine, sildenafil, ticagrelor, tolvaptan, venetoclax	

CYP3A4

TABLE 6–1. Some drugs metabolized by 3A

Antidepressants

Amitriptyline[1]
Citalopram[2]
Clomipramine[1]
Doxepin[1]
Fluoxetine[2]
Imipramine[1]
Mirtazapine[4]
Nefazodone
Reboxetine
Sertraline[2]
Trazodone[3]
Trimipramine[1]
Venlafaxine[6]

Antipsychotics

Aripiprazole[6]
Chlorpromazine[2]
Clozapine[2]
Haloperidol[2]
Perphenazine[2]
Pimozide[5]
Quetiapine[2]
Risperidone[6]
Ziprasidone[2]

Sedative-hypnotics

Benzodiazepines

Clonazepam[2]
Diazepam[2]
Flunitrazepam[2]
Nitrazepam[6]

Triazolobenzodiazepines

Alprazolam[2]
Estazolam
Midazolam[11]
Triazolam[11]

Other sedative-hypnotics

Eszopiclone[2]
Zaleplon[2,7]
Zolpidem[2]
Zopiclone[2]

Psychotropic drugs, other

Buspirone[11]
Donepezil[2]
Galantamine[2]

Other drugs

Analgesics

Alfentanil
Buprenorphine[2]
Codeine (10%, *N*-demethylated)
Fentanyl
Hydrocodone[6]
Meperidine[2]
Methadone[7]
Propoxyphene[8]
Sufentanil

Antiarrhythmics[5]

Amiodarone[2,7]
Lidocaine[2]
Mexiletine[2]
Propafenone[2]
Quinidine[2]

Antiepileptics

Carbamazepine[2]
Ethosuximide[2]
Felbamate[2]
Tiagabine[2]
Zonisamide[2]

CYP3A4

TABLE 6–1. Some drugs metabolized by 3A *(continued)*

Other drugs *(continued)*

Antifungals
- Fluconozale[2]
- Itraconazole[2]
- Ketoconazole[2]
- Miconazole
- Voriconazole[2]

Antihistamines
- Astemizole[9]
- Desloratidine[2]
- Ebastine[2]
- Loratadine[7]
- Terfenadine[9,11]

Antimalarials
- Chloroquine[2]
- Halofantrine[2]
- Primaquine[2]

Antineoplastics
- Busulfan
- Cyclophosphamide[2]
- Daunorubicin
- Docetaxel[2]
- Doxorubicin[2]

Antineoplastics (continued)
- Etoposide[2]
- Ifosfamide[2]
- Paclitaxel[2]
- Tamoxifen[2]
- Teniposide[2]
- Trofosfamide[2]
- Vinblastine[2]
- Vincristine[2]
- Vindesine[2]
- Vinorelbine[2]

Antiparkinsonian drugs
- Bromocriptine[2]
- Pergolide[2,9]
- Tolcapone[2]

Antiprogesterone agents
- Lilopristone
- Mifepristone
- Onapristone
- Toremifene[2]

Antirejection drugs
- Cyclosporine[2]
- Sirolimus (Rapamune)[2]
- Tacrolimus

Calcium channel blockers
- Amlodipine
- Diltiazem[2]
- Felodipine[11]
- Lercanidipine
- Nicardipine
- Nifedipine[11]
- Nimodipine
- Nitrendipine
- Verapamil[2]

HMG-CoA reductase inhibitors (statins)
- Atorvastatin
- Cerivastatin[9]
- Lovastatin[2,11]
- Simvastatin[2,11]

Macrolide/ketolide antibiotics
- Clarithromycin
- Dirithromycin
- Erythromycin
- Telithromycin[2]
- Troleandomycin[9]

CYP3A4

TABLE 6–1. Some drugs metabolized by 3A *(continued)*

Other drugs *(continued)*

Nonnucleoside reverse transcriptase inhibitors
- Delavirdine[2]
- Efavirenz[2]
- Nevirapine[2]

Protease inhibitors (antivirals)
- Amprenavir[2]
- Atazanavir[2]
- Indinavir[2]
- Lopinavir[2]
- Nelfinavir[2]
- Ritonavir[2]
- Saquinavir[2]

Proton pump inhibitors
- Esomeprazole[10]
- Lansoprazole[10]
- Omeprazole[10]
- Pantoprazole[10]
- Rabeprazole[2]

Steroids
- Budesonide
- Cortisol
- Dexamethasone[2]
- Estradiol
- Ethinyl estradiol[2]
- Fluticasone[2]
- Gestodene
- Hydrocortisone
- Methylprednisolone[2]
- Prednisone[2]
- Progesterone[2]
- Testosterone[2,11]

Triptans
- Almotriptan[2]
- Eletriptan[2,11]

Miscellaneous drugs
- Bosentan[2]
- Cevimeline[2]
- Cilostazol[2]
- Cisapride[2,9]

Miscellaneous drugs (continued)
- Colchicine[2]
- Conivaptan
- Cyclobenzaprine[2]
- Dextromethorphan[11]
- Diclofenac[2]
- Ergots
- Granisetron
- Levomethadyl[6,9]
- Meloxicam[2]
- Montelukast[2]
- Nateglinide[2]
- Ondansetron[2]
- Pioglitazone[2]
- Ranolazine[2]
- Sibutramine
- Sildenafil[2,11]
- Vardenafil[2]
- Vesnarinone

CYP2D6

TABLE 5–1. Some drugs metabolized by 2D6

Antidepressants	Antipsychotics	Other drugs	
Tricyclic antidepressants[1]	Aripiprazole[3]	*Analgesics*	*Miscellaneous drugs*[3]
Amitriptyline	Chlorpromazine[3]	Codeine[5]	Benztropine[2]
Clomipramine	Clozapine[4]	Hydrocodone[3]	Cevimeline[3]
Desipramine[2]	Fluphenazine[3]	Methadone[4]	Cinacalcet[3]
Doxepin	Haloperidol[3]	Oxycodone[3]	Chlorpheniramine
Imipramine	Perphenazine[3]	Tramadol[3,6]	Delavirdine[2]
Nortriptyline[2]	Quetiapine[3,4]		Debrisoquin[3,8]
Trimipramine	Risperidone[3]	*Cardiovascular drugs*	Dexfenfluramine[3]
	Thioridazine[3]	Alprenolol[2]	Dextromethorphan[3,8]
Other antidepressants	Zuclopenthixol	Bufuralol[3,8]	Diphenhydramine[3]
Duloxetine[3]		Carvedilol[3]	Donepezil[3]
Fluoxetine[3]	*Other psychotropics*	Diltiazem[9]	Indoramin
Fluvoxamine[3]	Amphetamines	Encainide[2]	Loratadine[3]
Maprotiline[3]	Atomoxetine	Flecainide[3]	Metoclopramide[2]
Mirtazapine[3]		Metoprolol[2,8]	Ondansetron[3]
Minaprine		Mexiletine[3]	Perhexilene[3]
Moclobemide		Nebivolol[2]	Tacrine[3]
Paroxetine		Propafenone[3]	Tamoxifen[3]
Sertraline[3]		Propranolol[7]	Tropisetron
Venlafaxine[3]		Timolol[2]	

CYP2D6 POLIMORFIZMUS

Table 1 Assignment of likely CYP2D6 phenotypes based on diplotypes

Likely phenotype	Activity score	Genotypes[a]	Examples of *CYP2D6* diplotypes
CYP2D6 Ultrarapid Metabolizer (~1–2% of patients)[b]	>2.0	An individual carrying duplications of functional alleles	**1/*1xN*, **1/*2xN*, **2/*2xN*[c]
CYP2D6 Normal Metabolizer (~77–92% of patients)	2.0–1.0[d]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0–2.0	**1/*1*, **1/*2*, **1/*4*, **1/*5*, **1/*9*, **1/*41*, **2/*2*,**41/*41*
CYP2D6 Intermediate Metabolizer (~2–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10*,**4/*41*, **5/*9*
CYP2D6 Poor Metabolizer (~5–10% of patients)	0	An individual carrying only no functional alleles	**3/*4*,**4/*4*, **5/*5*, **5/*6*

https://cpicpgx.org/guidelines/

CYP2D6 CPIC guidelines

CPIC guideline for atomoxetine based on *CYP2D6* genotype

CPIC guideline for opioids based on *CYP2D6*, *OPRM1*, and *COMT* genotype

CPIC guideline for ondansetron and tropisetron based on *CYP2D6* genotype

CPIC guideline for tamoxifen based on *CYP2D6* genotype

CPIC guideline for selective serotonin reuptake inhibitors based on *CYP2D6* and *CYP2C19* genotype

CPIC guideline for tricyclic antidepressants based on *CYP2D6* and *CYP2C19* genotype

https://cpicpgx.org/gene/cyp2d6/

Table of Pharmacogenetic Associations

Pharmacogenetic tests, along with other information about patients and their disease or condition, can play an important role in drug therapy. When a health care provider is considering prescribing a drug, knowledge of a patient's genotype may be used to aid in determining a therapeutic strategy, determining an appropriate dosage, or assessing the likelihood of benefit or toxicity.

Valbenazine	CYP2D6	poor metabolizers	Results in higher systemic active metabolite concentrations and higher adverse reaction risk (QT prolongation). Dosage reductions may be necessary.
Venlafaxine	CYP2D6	poor metabolizers	Alters systemic parent drug and metabolite concentrations. Consider dosage reductions.
Vortioxetine	CYP2D6	poor metabolizers	Results in higher systemic concentrations. The maximum recommended dose is 10 mg.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#section1

CYP2C9

TABLE 8–1. Some drugs metabolized by 2C9

Angiotensin II blockers

Candesartan

Irbesartan

Losartan[1] (pro-drug)

Antidepressants

Fluoxetine[1]

Sertraline[1]

Hypoglycemics, oral[2]

Sulfonylureas

Chlorpropamide

Glimepiride

Glipizide

Glyburide[1,7]

Nateglinide[1,7]

Rosiglitazone[2]

Tolbutamide

Gliclazid

NSAIDs[3]

Aceclofenac

Celecoxib

Diclofenac[1,3,7]

Flurbiprofen[3]

Ibuprofen[1,3,7]

Indomethacin[3,7]

Lornoxicam

Mefenamic acid

Meloxicam[1]

Piroxicam

Tenoxicam

Valdecoxib[1]

Other drugs

Bosentan[1,7]

Dapsone[2,3]

Fluvastatin[4,7]

Mestranol[5] (pro-drug)

Phenobarbital

Phenytoin[3]

Tamoxifen[1]

Tetrahydrocannabinol[1]

Torsemide[7]

S-Warfarin[6]

Acenokumarol

Note. NSAID=nonsteroidal anti-inflammatory drug.

[1]Metabolized by other P450 cytochromes as well.

[2]Most glitazones are metabolized by 2C8 and 3A4.

[3]Also metabolized by phase II enzymes.

[4]This is an exception among the statin drugs, most of which are partly or wholly metabolized by 3A4.

[5]Pro-drug metabolized to active ethinyl estradiol.

[6]*S*-Warfarin is the more active isomer of warfarin.

[7]Handled by transporters as well.

CYP2C9 POLIMORFIZMUS

Table 1 Assignment of likely CYP2C9 phenotypes based on genotypes

Likely phenotype[a,b]	Activity score	Genotypes	Examples of diplotypes
Normal metabolizer	2	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	1.5 1	An individual carrying one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR two decreased function alleles	*1/*2 *1/*3, *2/*2
Poor metabolizer	0.5 0	An individual carrying one no function allele plus one decreased function allele; OR two no function alleles	*2/*3 *3/*3
Indeterminate	n/a	An individual carrying allele combinations with uncertain and/or unknown function alleles	*1/*7, *1/*10, *7/*10, *1/*57

https://cpicpgx.org/guidelines/

CYP2C9 CPIC guidelines

CPIC guideine for NSAIDs based on *CYP2C9* genotype

CPIC guideline for phenytoin based on *CYP2C9* and *HLA-B* genotype

CPIC guideline for warfarin based on *CYP2C9*, *VKORC1* and *CYP4F2* genotype

https://cpicpgx.org/gene/cyp2c19/

CYP2C19

TABLE 9–1. Some drugs metabolized by 2C19

Antidepressants	Barbiturates	Proton pump inhibitors	Other drugs
Amitriptyline[1]	Hexobarbital	Esomeprazole[3]	Carisoprodol
Citalopram[1]	Mephobarbital[1]	Lansoprazole	Cilostazol[1]
Clomipramine[1]	Phenobarbital[1]	Omeprazole[3]	Cyclophosphamide[1] (pro-drug)
Fluoxetine[1,2]		Pantoprazole	Diazepam[1]
Imipramine[1]		Rabeprazole[4]	Flunitrazepam[2]
Moclobemide[1]			Ifosfamide[1] (pro-drug)
Sertraline[1]			Mephenytoin
Trimipramine[1]			Nelfinavir[1]
			Phenytoin[1]
			Progesterone[1]
			Proguanil[1] (pro-drug)
			Propranolol[3]
			R-warfarin[1]
			Tolbutamide
			Voriconazole[1]

[1]Also metabolized by other cytochromes.
[2]2C19 is a minor pathway.
[3]Also metabolized by 3A4.
[4]Cytochromes are a lesser pathway compared with other proton pump inhibitors.

CYP2C19 POLIMORFIZMUS

Table 1b Assignment of CYP2C19 predicted phenotypes

Likely phenotype	Genotypes	Examples of *CYP2C19* diplotypes
Ultrarapid metabolizer (~5–30% of patients)[d]	An individual carrying two increased function alleles or one normal function allele and one increased function allele	**17/*17, *1/*17*
Extensive metabolizer (~35–50% of patients)	An individual carrying two normal function alleles	**1/*1*
Intermediate metabolizer (~18–45% of patients)	An individual carrying one normal function allele or one increased function allele and one no function allele	**1/*2, *1/*3, *2/*17*[e]
Poor metabolizer (~2–15% of patients)	An individual carrying two no function alleles	**2/*2, *2/*3, *3/*3*

https://cpicpgx.org/guidelines/

CYP2C19 CPIC guidelines

CPIC guideline for clopidogrel based on *CYP2C19* genotype

CPIC guideline for voriconazole based on *CYP2C19* genotype

CPIC guideline for selective serotonin reuptake inhibitors based on *CYP2D6* and *CYP2C19* genotype

CPIC guideline for tricyclic antidepressants based on *CYP2D6* and *CYP2C19* genotype

CPIC guideline for proton pump inhibitors based on *CYP2C19* genotype

https://cpicpgx.org/gene/cyp2c19/

Table of Pharmacogenetic Associations

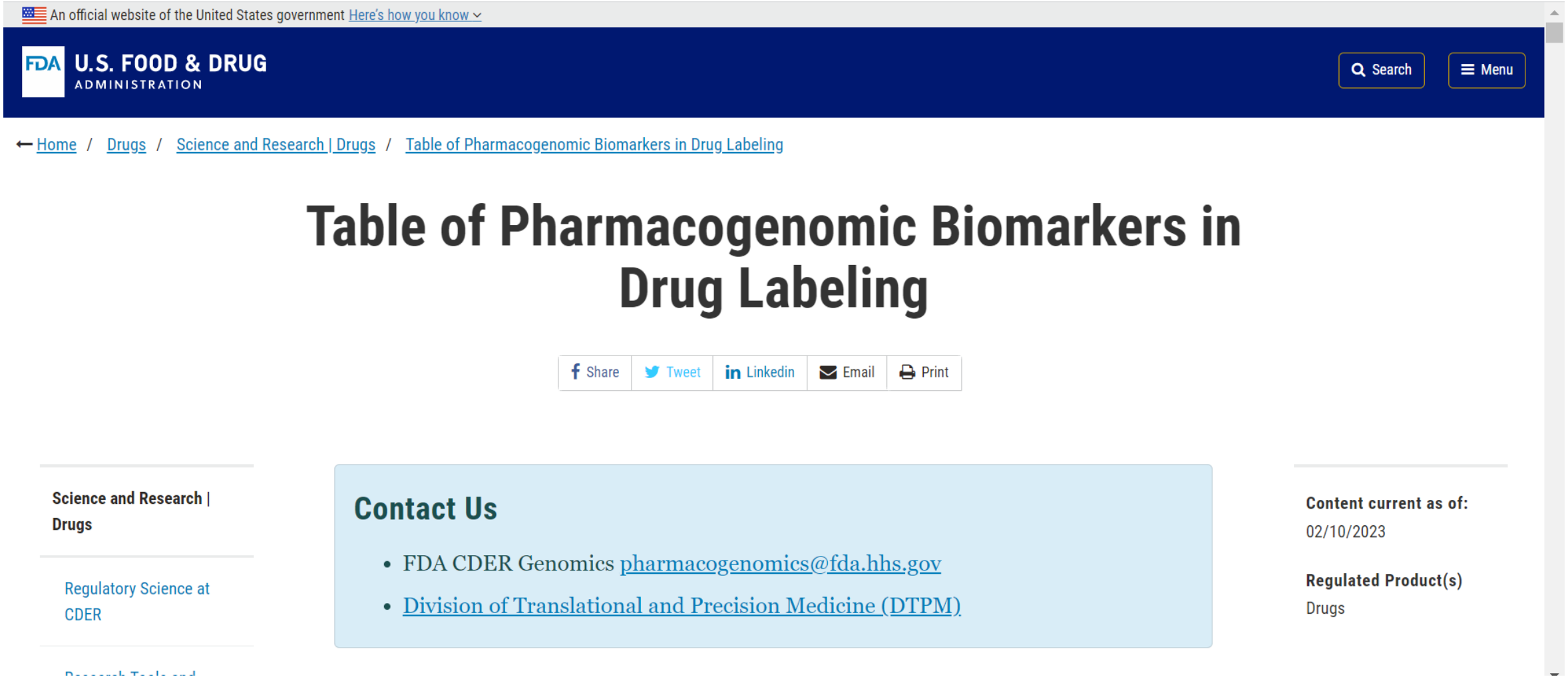
Pharmacogenetic tests, along with other information about patients and their disease or condition, can play an important role in drug therapy. When a health care provider is considering prescribing a drug, knowledge of a patient's genotype may be used to aid in determining a therapeutic strategy, determining an appropriate dosage, or assessing the likelihood of benefit or toxicity.

Citalopram	CYP2C19	poor metabolizers	Results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dose is 20 mg.
Clobazam	CYP2C19	intermediate or poor metabolizers	Results in higher systemic active metabolite concentrations. Poor metabolism results in higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.
Clopidogrel	CYP2C19	intermediate or poor metabolizers	Results in lower systemic active metabolite concentrations, lower antiplatelet response, and may result in higher cardiovascular risk. Consider use of another platelet P2Y12 inhibitor.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#section1

Table 2 Antiplatelet therapy recommendations based on CYP2C19 phenotype when considering clopidogrel for cardiovascular indications

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b] - ACS and/or PCI[c]	Classification of recommendation[b] - non-ACS, non-PCI cardiovascular indications[d]
CYP2C19 ultrarapid metabolizer	Increased clopidogrel active metabolite formation; lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
CYP2C19 rapid metabolizer	Normal or increased clopidogrel active metabolite formation; normal or lower on-treatment platelet reactivity; no association with higher bleeding risk	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	No recommendation
CYP2C19 normal metabolizer	Normal clopidogrel active metabolite formation; normal on-treatment platelet reactivity	If considering clopidogrel, use at standard dose (75 mg/day)	Strong	Strong
CYP2C19 likely intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard dose clopidogrel (75 mg) if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[e]	No recommendation[e]
CYP2C19 intermediate metabolizer	Reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	No recommendation
CYP2C19 likely poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong[e]	Moderate[e]
CYP2C19 poor metabolizer	Significantly reduced clopidogrel active metabolite formation; increased on-treatment platelet reactivity; increased risk for adverse cardiac and cerebrovascular events	Avoid clopidogrel if possible. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong	Moderate



https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

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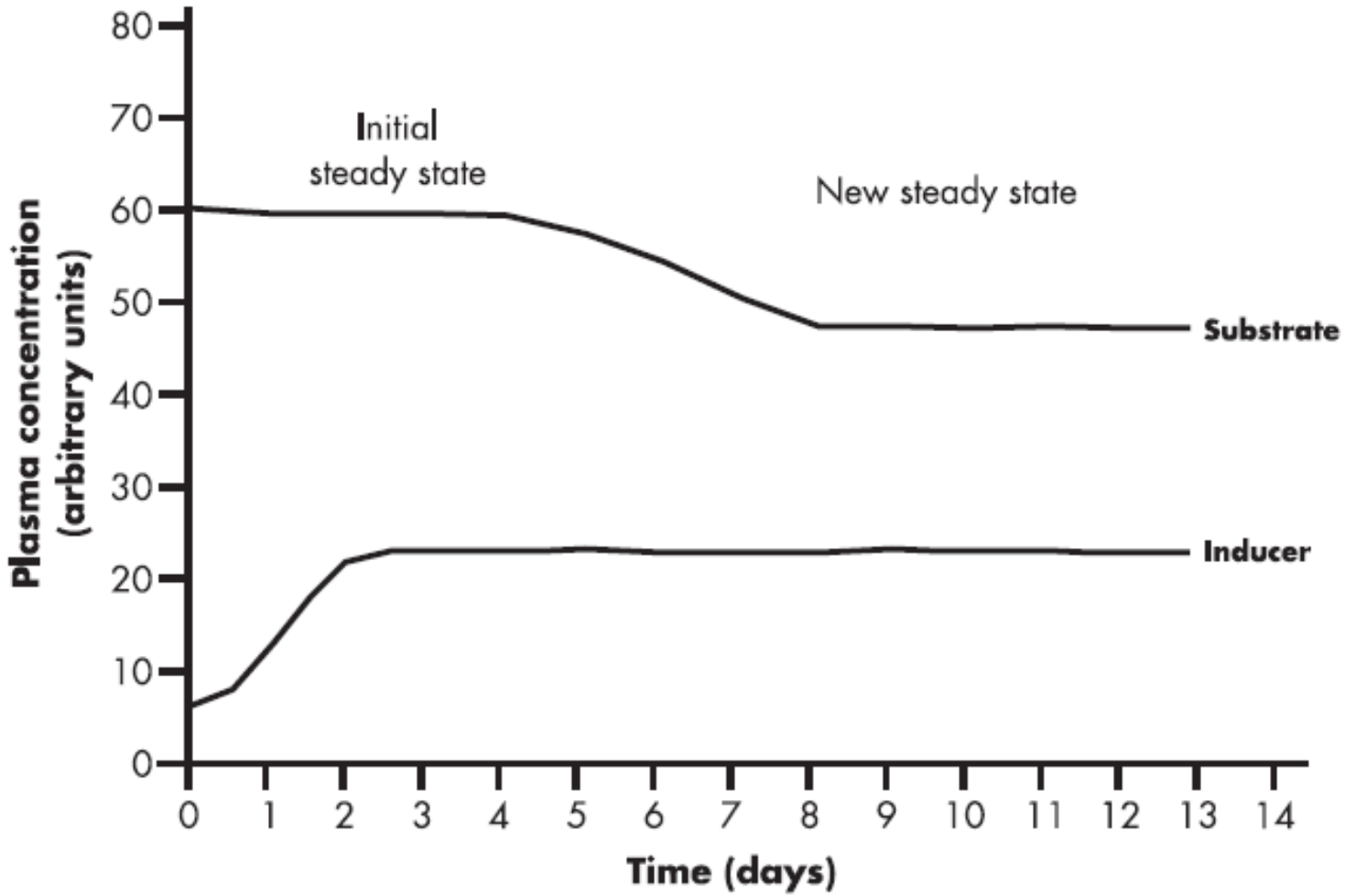
Személyre szabott gyógyszerbiztonság

ENZIM INDUKCIÓ



ENZIM INDUKTOROK

- **erős induktor**:

  érzékeny index CYP szubszrát ↓AUC ≥ 80%

- **közepes induktor**:

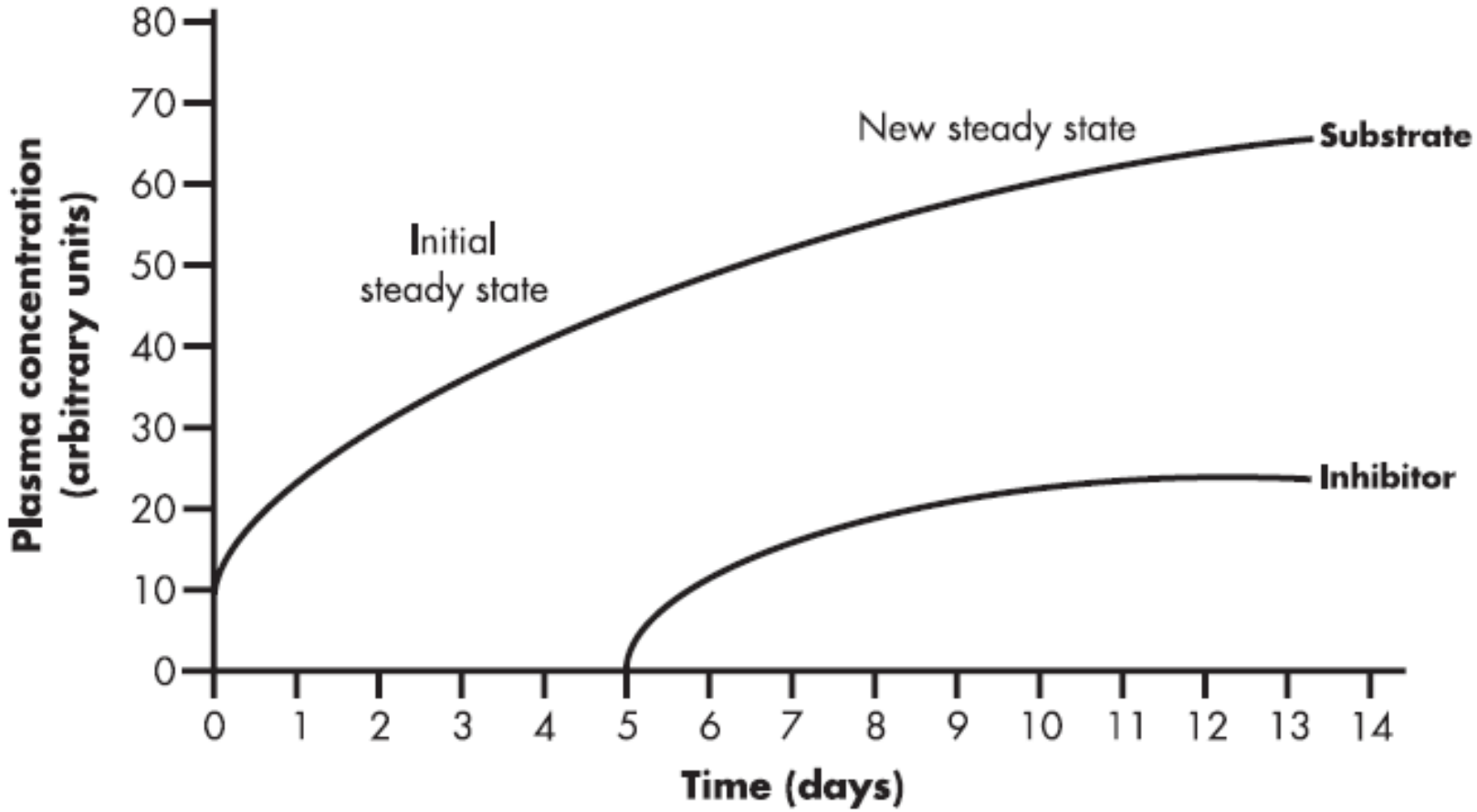
  érzékeny index CYP szubszrát ↓AUC ≥ 50%, de < 80%

- **gyenge induktor**:

  érzékeny index CYP szubszrát ↓AUC ≥ 20%, de < 50%

	Strong inducers	Moderate inducers	Weak inducers
CYP1A2	-	phenytoin[a], rifampin[b], smoking, teriflunomide	-
CYP2B6	carbamazepine[c]	efavirenz[d], rifampin[b]	isavuconazole, lemborexant, lorlatinib, nevirapine, ritonavir[e,f]
CYP2C8	-	rifampin[b]	-
CYP2C9	-	enzalutamide[g], rifampin[b]	apalutamide[h], aprepitant, carbamazepine[c], dabrafenib, lorlatinib, ritonavir[e,f]
CYP2C19	rifampin[b]	apalutamide[h], efavirenz[d], enzalutamide[g], phenytoin[a]	ritonavir[e,f]
CYP3A	apalutamide[h], carbamazepine[c], enzalutamide[g], ivosidenib[i], lumacaftor, mitotane, phenytoin[a], rifampin[b], St. John's wort[j]	bosentan, cenobamate[k], dabrafenib, efavirenz[d], etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib	armodafinil, elagolix, mobocertinib, modafinil[l], rufinamide, vemurafenib, zanubrutinib

ENZIM INHIBÍCIÓ



ENZIM INHIBÍTOROK

- **erős inhibítor**:

  érzékeny index CYP szubszrát ↑AUC ≥ 5x

- **közepes inhibítor**:

  érzékeny index CYP szubszrát ↑AUC ≥ 2x, de < 5x

- **gyenge inhibítor**:

  érzékeny index CYP szubszrát ↑AUC ≥ 1.25x, de < 2x

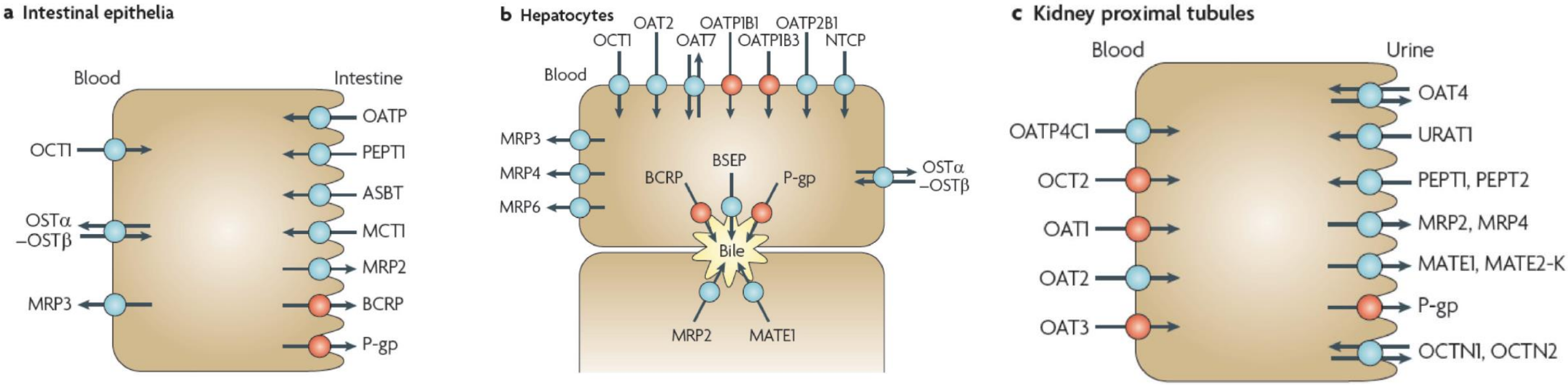
	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine[a]	methoxsalen, mexiletine, oral contraceptives, vemurafenib	acyclovir, allopurinol, cimetidine, peginterferon alpha-2a, piperine, zileuton
CYP2B6	-	-	clopidogrel[b], tenofovir, ticlopidine[c], voriconazole[d]
CYP2C8	gemfibrozil[e]	clopidogrel[b], deferasirox, teriflunomide	trimethoprim
CYP2C9	-	amiodarone[h], fluconazole[f], miconazole, piperine	ceritinib, diosmin, disulfiram, fluvastatin, fluvoxamine[a], voriconazole[d]
CYP2C19	fluconazole[f], fluoxetine[g], fluvoxamine[a], ticlopidine[c]	cenobamate, felbamate, voriconazole[d]	omeprazole
CYP2D6	bupropion, fluoxetine[g], paroxetine, quinidine[h], terbinafine	abiraterone, cinacalcet, duloxetine, lorcaserin, mirabegron, rolapitant	amiodarone[h], celecoxib, cimetidine, clobazam, cobicistat, escitalopram, fluvoxamine[a], labetalol, sertraline, vemurafenib

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP3A4	The inhibitors below cause a ≥10-fold increase in AUC of sensitive substrate(s): cobicistat[h], danoprevir and ritonavir[j], elvitegravir and ritonavir[j], grapefruit juice[k], indinavir and ritonavir[j], itraconazole[h], ketoconazole[h], lopinavir and ritonavir[h,j], paritaprevir and ritonavir and ombitasvir (and/or dasabuvir)[j], posaconazole, ritonavir[h,i,j], saquinavir and ritonavir[h,j], tipranavir and ritonavir[j], telithromycin, troleandomycin, voriconazole[d]	aprepitant, ciprofloxacin, conivaptan[l], crizotinib, cyclosporine, diltiazem[m], dronedarone[h], erythromycin[h], fluconazole[f], fluvoxamine[a], grapefruit juice[k], imatinib, isavuconazole, tofisopam, verapamil[h]	chlorzoxazone, cilostazol, cimetidine, clotrimazole, fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine[h], ticagrelor[h]
	The inhibitors below cause a 5- to 10-fold increase in the AUC of sensitive substrate(s): ceritinib, clarithromycin[h], idelalisib, nefazodone, nelfinavir	-	-

Table 1 Representative Drugs Having Large and Clinically Important Effects on the Human CYP Enzymes

	Inhibition of	Induction of
Azole antifungals		
Ketoconazole	CYP3A	
Itraconazole	CYP3A	
Fluconazole	CYP3A, CYP2C9	
Voriconazole	CYP3A	
Terbinafine	CYP2D6	
Antidepressants		
Fluoxetine	CYP2D6	
Paroxetine	CYP2D6	
Fluvoxamine	CYP1A2, CYP2C19	
Nefazodone	CYP3A	
Bupropion	CYP2D6	
Anticonvulsants		
Carbamazepine		CYP3A
Anti-infectives		
Erythromycin	CYP3A	
Clarithromycin	CYP3A	
Ciprofloxacin	CYP1A2	
Rifampin		CYP3A
Viral protease inhibitors		
Ritonavir	CYP3A	
Saquinavir	CYP3A	
Amprenavir		CYP3A
Nonnucleoside reverse transcriptase inhibitors		
Delavirdine	CYP3A	
Nevirapine		CYP3A
Efavirenz		CYP3A
Cardiovascular agents		
Quinidine	CYP2D6	
Diltiazem	CYP3A	
Verapamil	CYP3A	

TRANSZPORTFEHÉRJÉK



P-gp vagy MDR1: permeábilis glikoprotein vagy multidrog rezisztencia 1 fehérje
BCRP: mellrák rezisztencia fehérje
OATP1B1/1B3: szerves anion-transzportáló polipeptid transzporter
OAT1/OAT3: szerves anion transzporter
MATE1/2: multisrog és toxin ….
OCT2: szerves kation transzporter

Transporter	Gene	Substrate
P-gp	ABCB1	dabigatran etexilate[a], digoxin, edoxaban, fexofenadine[b,c,d]
BCRP	ABCG2	rosuvastatin[b,c], sulfasalazine[e]
OATP1B1, OATP1B3	SLCO1B1, SLCO1B3	atorvastatin[f,g,h], bosentan[g], docetaxel[d,g,i], elagolix[g,h], fexofenadine[c,d,g], glecaprevir[f,g,h], glyburide[j], grazoprevir[g,h], letermovir, paclitaxel[d,g,k], pitavastatin, pravastatin[c,d], repaglinide[k], rosuvastatin[c,f], simvastatin acid[h]
OAT1, OAT3	SLC22A6, SLC22A8	adefovir[l,m], baricitinib[n], bumetanide[n], cefaclor[n], ceftizoxime[n], ciprofloxacin, famotidine[n], furosemide, methotrexate[n], oseltamivir carboxylate[m,n], benzylpenicillin (penicillin G)[n], tenofovir[l,m]
MATE1, MATE-2K, OCT2	SLC47A1, SLC47A2, SLC22A2	metformin

P-gp SZUBSZTRÁTOK

- bilastin
- colchicin
- **dabigatran etexilate, edoxaban,**
- **digoxin**
- doxorubicin (konvencionális), etoposid/etoposid-foszfát, topotecan
- **everolimus, sirolimus, tacrolimus**
- morphin, naldemedine, naloxegol
- **risperidon**
- afatinib, pazopanib, relugolix, talazoparib

OATP1B1/1B3 SZUBSZTRÁTOK

- **atorvastatin, fluvastatin, rosuvastatin, simvastatin, ezetimib**
- valsartan, olmesartan
- repaglinid
- fexofenadtin
- glecaprevir, pibrentasvir, grazoprevir, voxilaprevir
- irinotecan
- letermovir
- **methotrexat**

Transporter	Gene	Inhibitor
P-gp[a]	ABCB1	amiodarone, clarithromycin[b], cobicistat, cyclosporine[b,c], dronedarone, erythromycin, itraconazole, ketoconazole, lapatinib[c], lopinavir and ritonavir, quinidine, ranolazine, saquinavir and ritonavir, verapamil
BCRP	ABCG2	curcumin, cyclosporine A[b,d], darolutamide[b,e], eltrombopag[b], febuxostat[e], fostamatinib[d], rolapitant[d,f], teriflunomide[b,e]
OATP1B1, OATP1B3	SLCO1B1, SLCO1B3	atazanavir and ritonavir, clarithromycin[d], cyclosporine[c,d], gemfibrozil[e], lopinavir and ritonavir, rifampin (single dose)[d]
OAT1, OAT3	SLC22A6, SLC22A8	probenecid, teriflunomide[b,c]
MATE1, MATE2-K, OCT2	SLC47A1, SLC47A2, SLC22A2	cimetidine, dolutegravir, isavuconazole, pyrimethamine, ranolazine, trilaciclib, vandetanib

X	**Avoid Combination** Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. Concurrent use of these agents should generally be avoided.
D	**Consider Therapy Modification** Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the risks resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, or choosing alternative agents.
C	**Monitor Therapy** Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications often outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in some patients.
B	**No Action Needed** Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
A	**No Known Interaction** Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents