LE ADR RICONOSCONO 2 CAUSE PRINCIPALI

- variabilità individuale su base genetica nelle risposte ai farmaci
- interazioni tra farmaci (DDi)

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La variabilità individuale nelle risposte ai farmaci su base genetica

risiede in variazioni di sequenza esistenti a carico dei geni codificanti per le proteine coinvolte nella risposta ad un determinato trattamento farmacologico

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POLIMORFISMI GENETICI

- **SNPs**
  (SINGLE NUCLEOTIDE POLYMORPHISMS)

- **CNV**
  (COPY NUMBER VARIATION)

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- **Geni codificanti per il bersaglio terapeutico primario, come per esempio recettori o enzimi**
- **Geni codificanti per proteine coinvolte nel metabolismo del farmaco**
- **Geni codificanti per proteine coinvolte nell'assorbimento, distribuzione ed escrezione del farmaco**

What is an SNP?

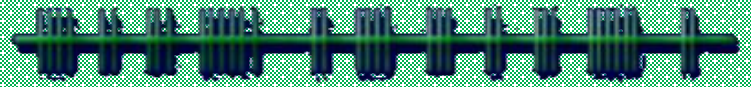
Different people can have a different nucleotide or base at a given location on a chromosome

...GGTAACTG...

...GGCAACTG...

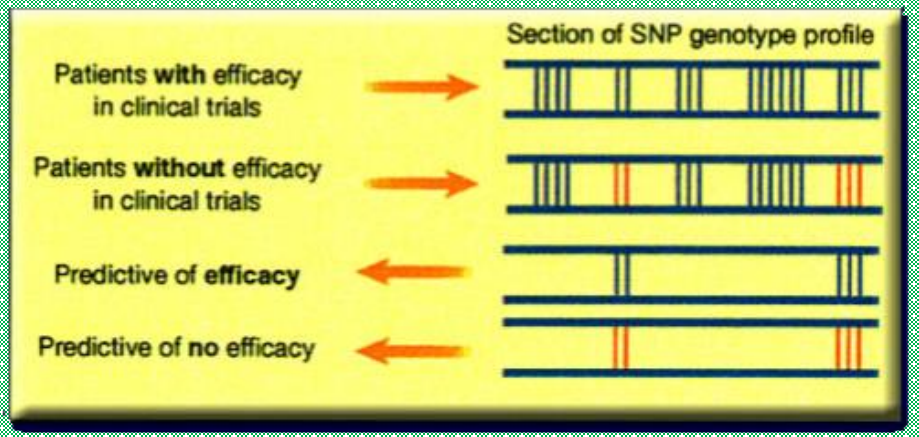
What is an SNP map?

Location of SNPs on human DNA



Human DNA

How can an SNP map be used to predict medicine response?



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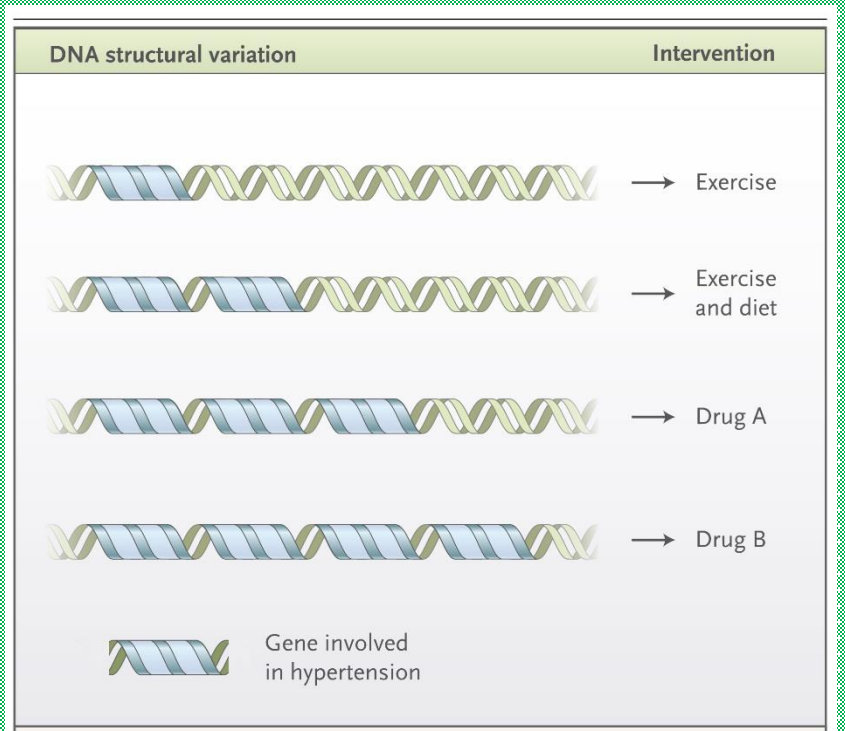

Figure 1. A Model of Copy-Number Variation and Treatment of Hypertension.

A hypothetical scenario is shown. In this model, four approaches to treating hypertension depend on the number of copies of a gene conferring a risk of hypertension that are carried by the affected person. The optimal clinical intervention for a person with one, two, three, or four copies of this gene is exercise, exercise and diet, administration of drug A, or administration of drug B, respectively.

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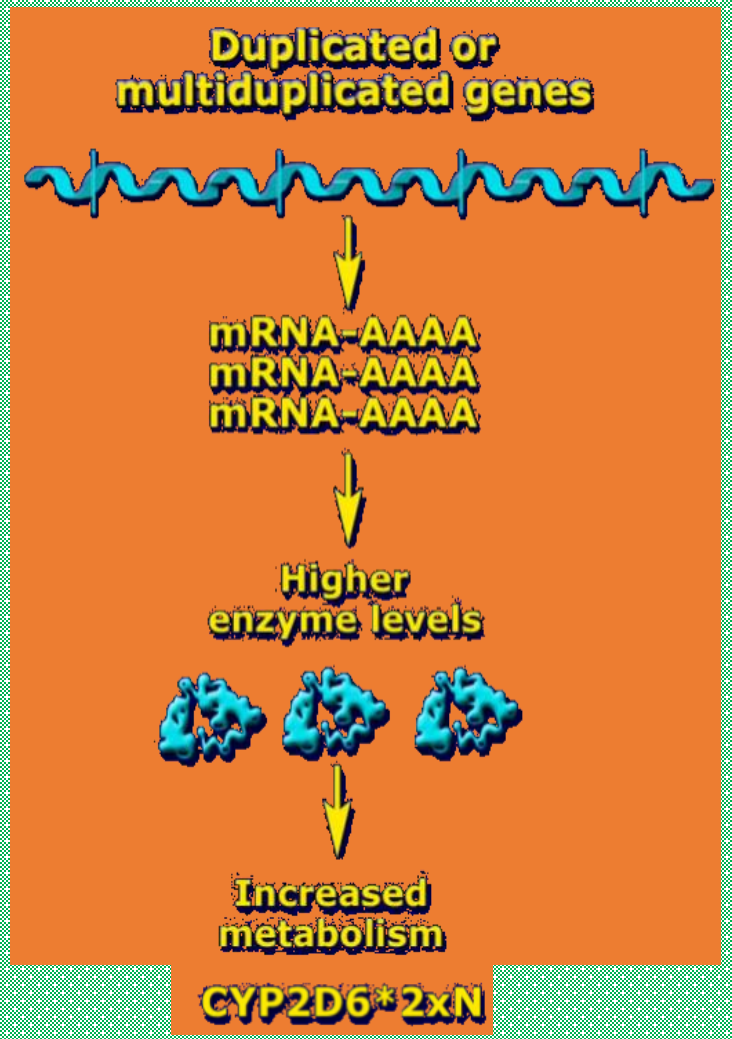

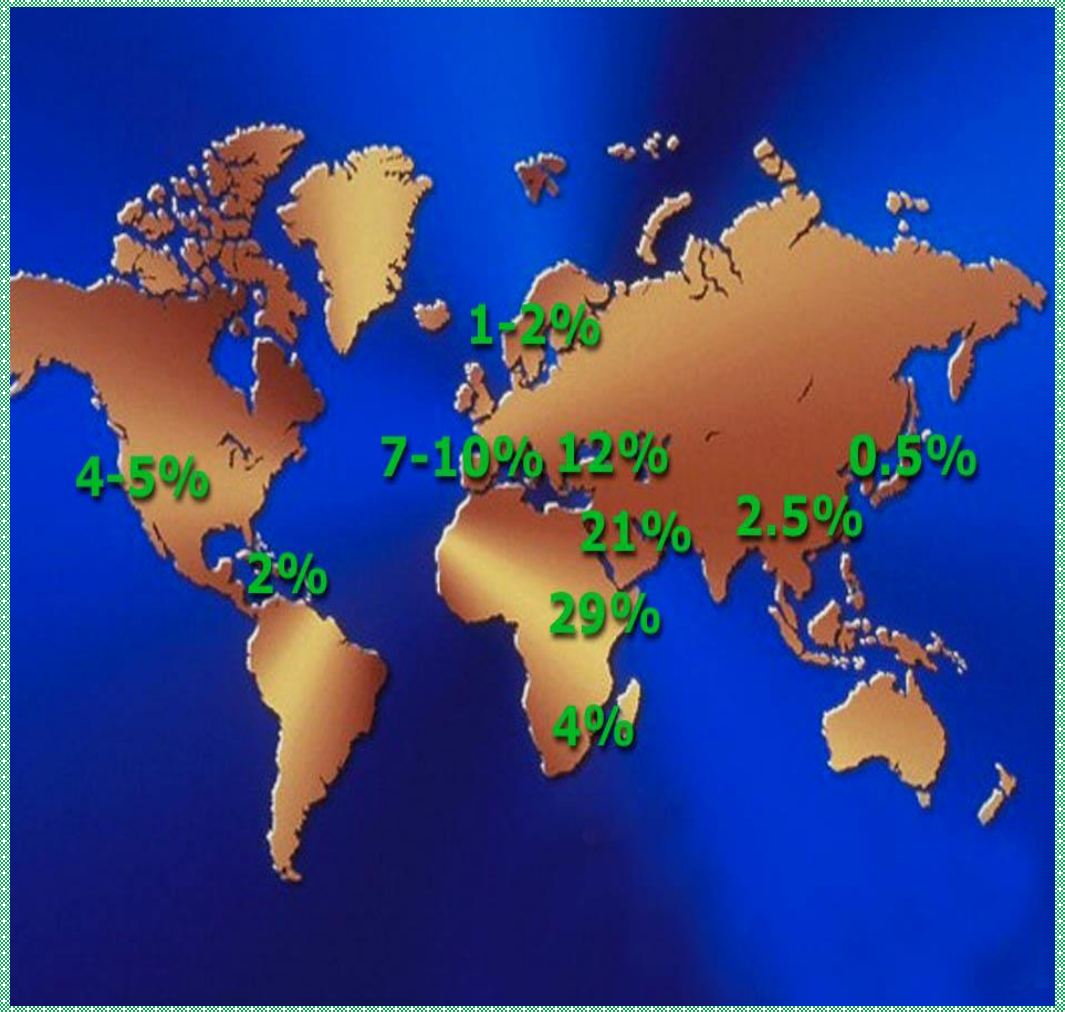

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The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Structural Genomic Variation and Personalized Medicine

Charles Lee, Ph.D., and Cynthia C. Morton, Ph.D.

N ENGL J MED (2008) 358: 740-1

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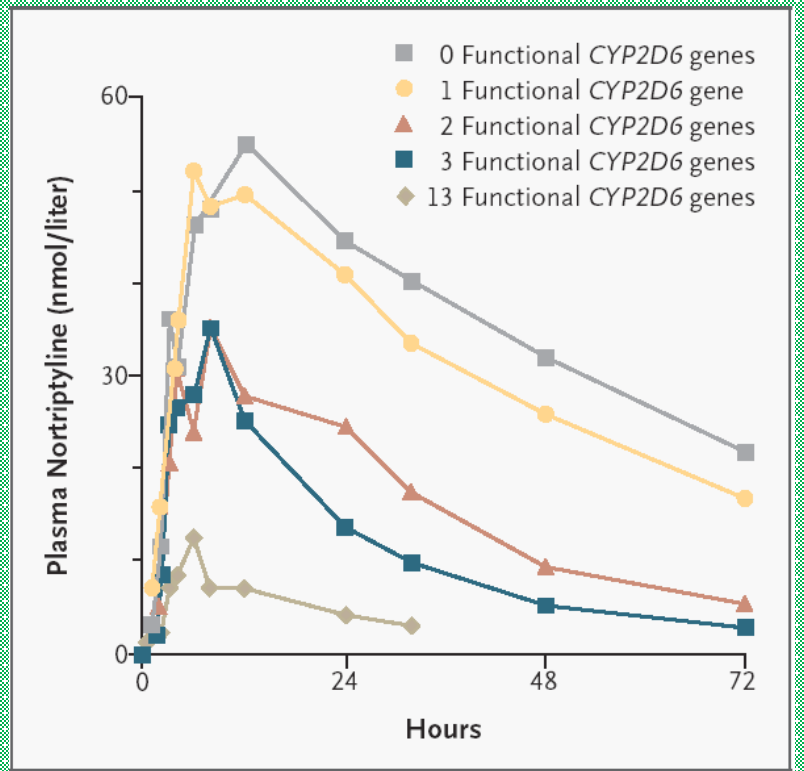

Figure 4. Pharmacogenetics of Nortriptyline.

Mean plasma concentrations of nortriptyline after a single 25-mg oral dose are shown in subjects with 0, 1, 2, 3, or 13 functional *CYP2D6* genes. Modified from Dalén et al.[23] with the permission of the publisher.

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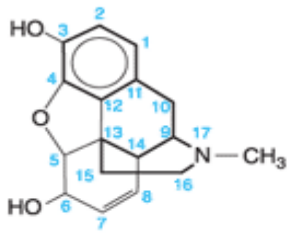

MORPHINE

NONPROPRIETARY NAME	CHEMICAL RADICALS AND POSITION* 3	6	17	OTHER CHANGES†
Morphine	—OH	—OH	—CH_3	—
Heroin	—$OCOCH_3$	—$OCOCH_3$	—CH_3	—
Hydromorphone	—OH	=O	—CH_3	(1)
Oxymorphone	—OH	=O	—CH_3	(1), (2)
Levorphanol	—OH	—H	—CH_3	(1), (3)
Levallorphan	—OH	—H	—$CH_2CH{=}CH_2$	(1), (3)
Codeine	—OCH_3	—OH	—CH_3	—
Hydrocodone	—OCH_3	=O	—CH_3	(1)
Oxycodone	—OCH_3	=O	—CH_3	(1), (2)
Nalmefene	—OH	$=CH_2$	—CH_2 	(1), (2)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	(1), (2)
Naltrexone	—OH	=O	—CH_2 	(1), (2)
Buprenorphine	—OH	—OCH_3	—CH_2 	(1), (4)
Butorphanol	—OH	—H	—CH_2 	(1), (2), (3)
Nalbuphine	—OH	—OH	—CH_2 	(1), (2)

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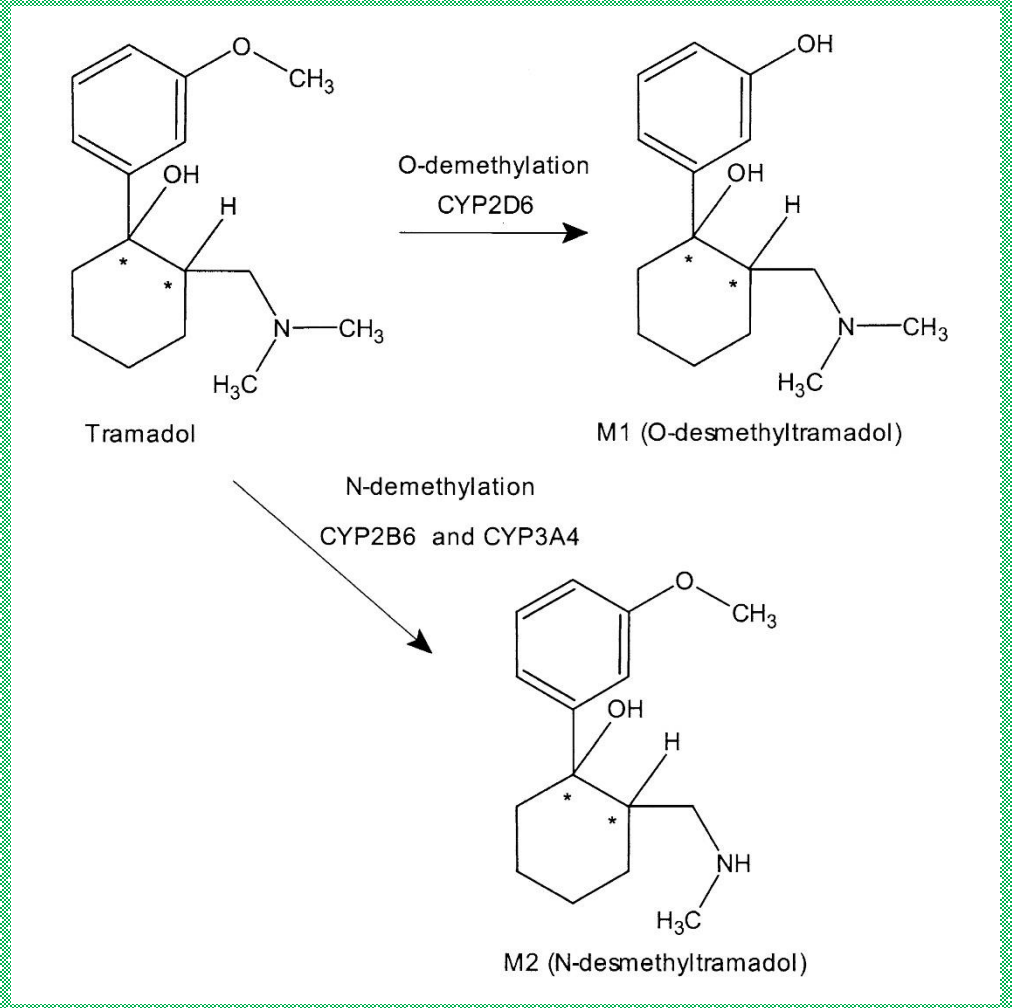

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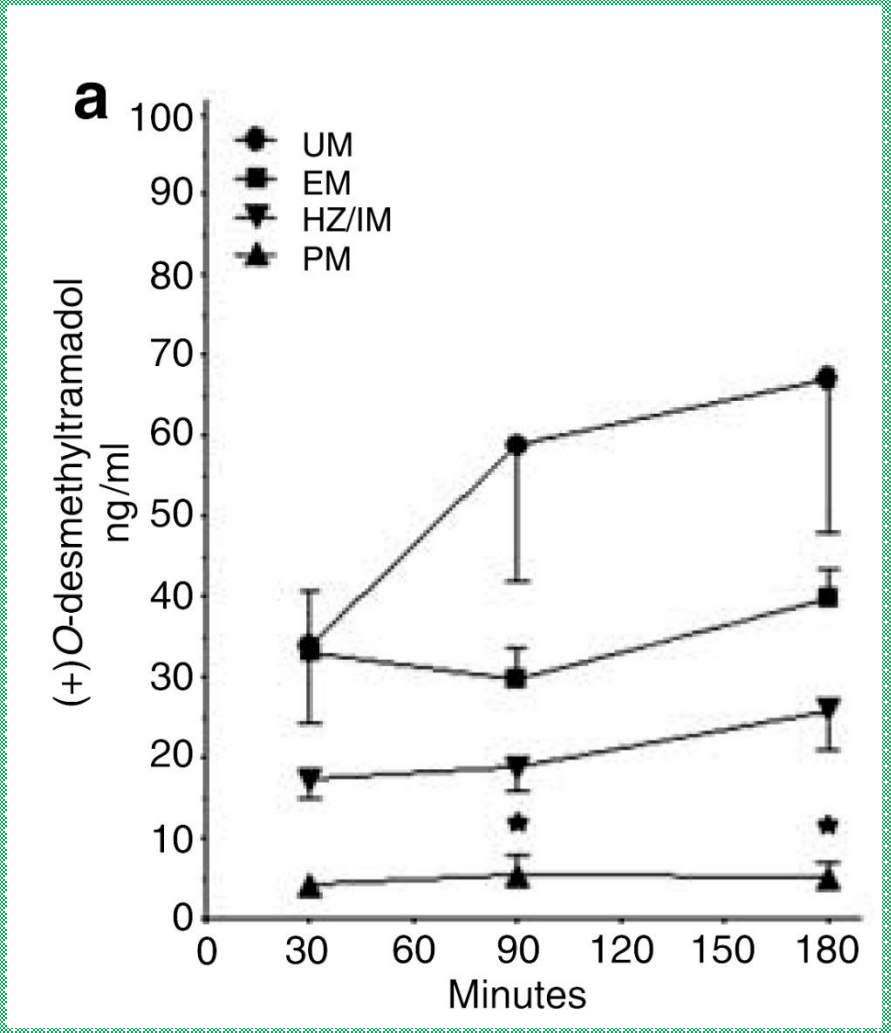

Clinical Pharmacology & Therapeutics (2007) 82: 41-47

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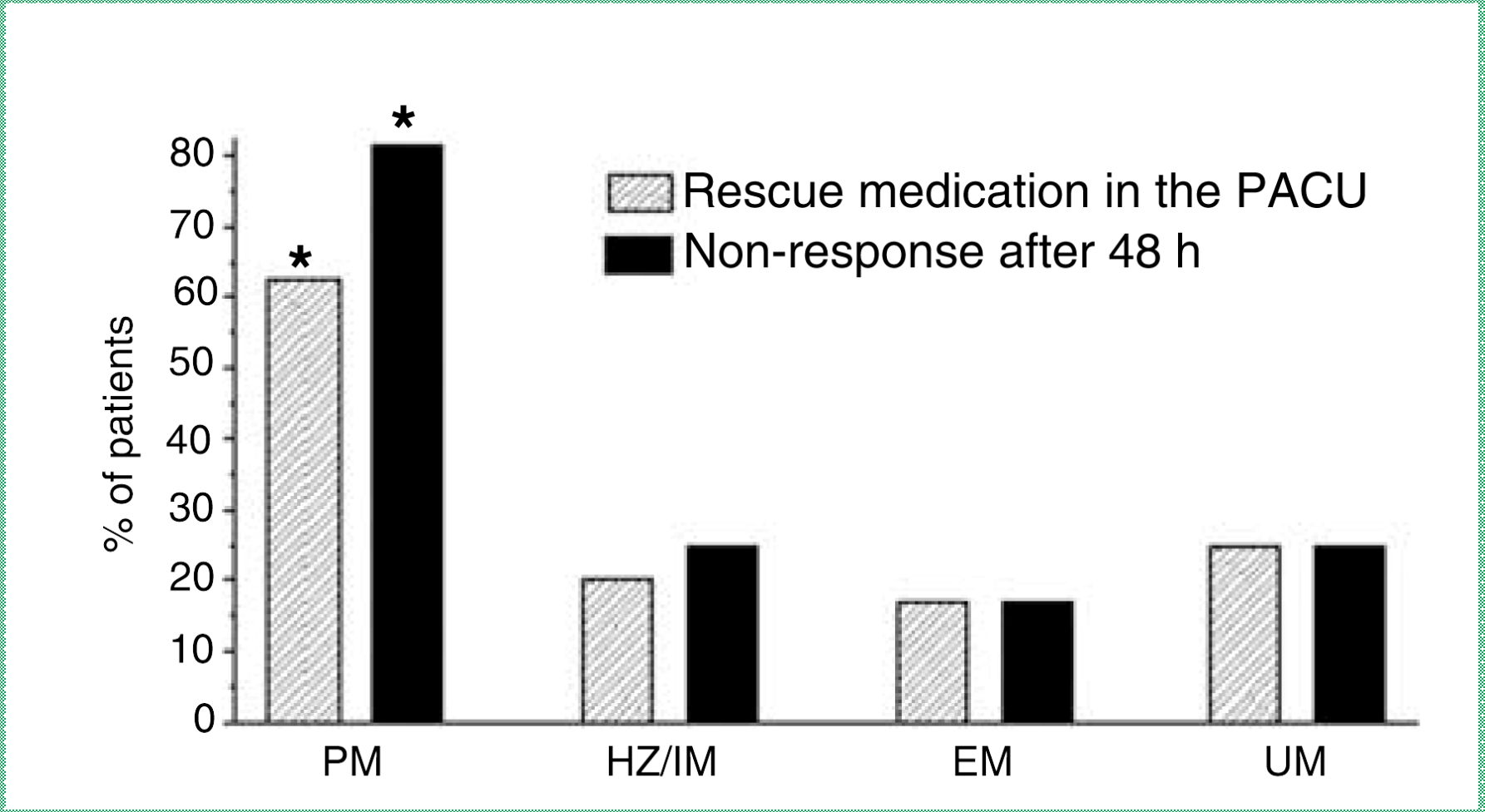

Clinical Pharmacology & Therapeutics (2007) 82: 41-47

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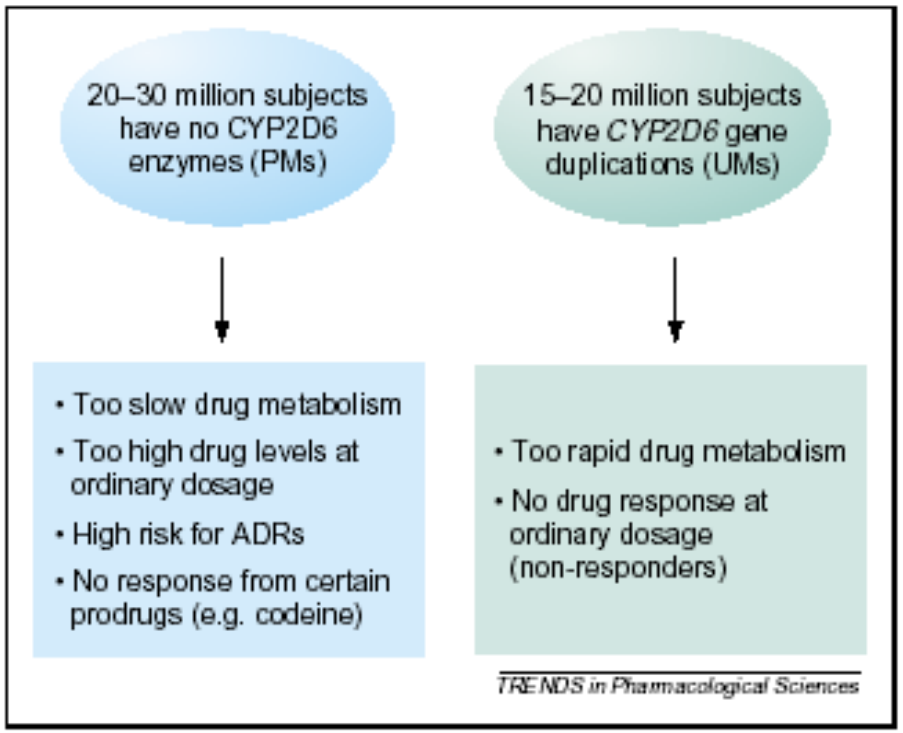

Figure 2. The consequences of outlier cytochrome P450 CYP2D6-dependent drug metabolism. 35–50 million Europeans are either poor metabolizers (PMs) (i.e. lack the functional enzyme) or ultrarapid metabolizers (UMs) (i.e. have multiple gene copies of *CYP2D6*, resulting in elevated enzyme levels), with respect to CYP2D6. As a result of the use of population-based dosing, drug treatment can result in many different effects in these subjects. Abbreviation: ADRs, adverse drug reactions.

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Table 2 An estimation of the number of ultrarapid CYP2D6 metabolisers in Western Europe carrying two or more active *CYP2D6* genes on one allele. The overall percentage in the population is 5.45%

	Million inhabitants	*Frequency UMs*	*Million UMs*
Austria	8	0.04	0.32
Belgium	10	0.03	0.3
Denmark	5	0.01	0.05
England	60	0.03	1.8
Finland	5	0.01	0.05
France	60	0.04	2.4
Germany	82	0.04	3.28
Greece	10	0.1	1
Holland	15	0.03	0.45
Italy	57	0.1	5.7
Norway	5	0.01	0.05
Portugal	10	0.1	1
Spain	40	0.1	4
Sweden	9	0.01	0.09
Total	376		20.49

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BJP BRITISH JOURNAL OF PHARMACOLOGY

BPS BRITISH PHARMACOLOGICAL SOCIETY

British Journal of Pharmacology (2010), 160, 919–930

0007-1188/10
www.brjpharmacol.org

RESEARCH PAPER

Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety

CF Samer[1,2], Y Daali[1,2], M Wagner[3], G Hopfgartner[3], CB Eap[4,5], MC Rebsamen[2,6], MF Rossier[2,6], D Hochstrasser[2,6], P Dayer[1,2] and JA Desmeules[1,2]

Interazioni farmacologiche

Su base farmacodinamica

Su base farmacocinetica (A D M E)

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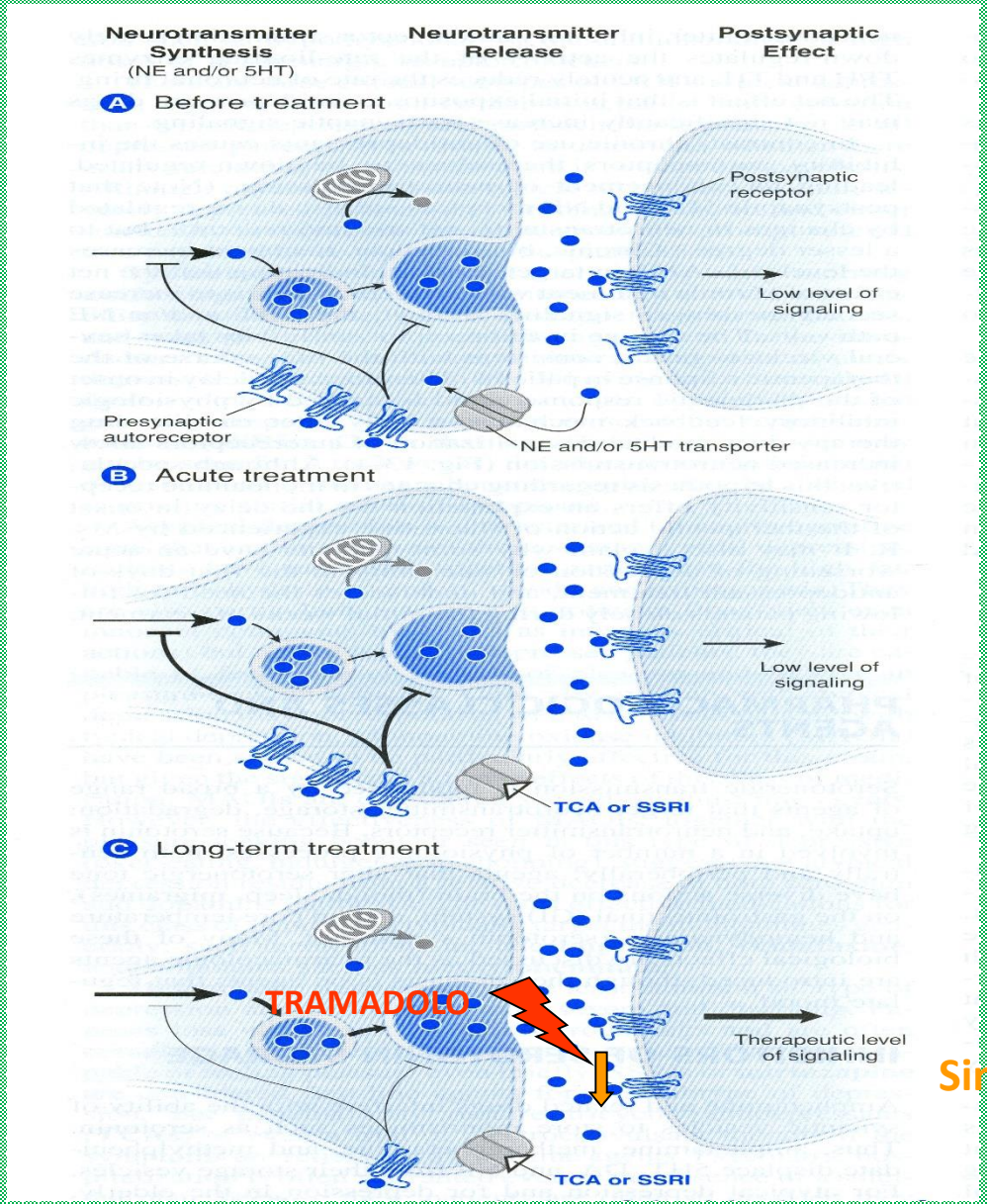


Toxic level of signalling

Sindrome serotoninegica

Patrizia Romualdi

Serotonin syndrome with fluoxetine plus tramadol

S Kesavan MRCP G M Sobala MD MRCP

J R Soc Med 1999;**92**:474–475

The serotonin syndrome is a rare but potentially fatal reaction to the combination of a serotonergic agent and a selective serotonin reuptake inhibitor (SSRI) antidepressant[1]. It arises most often when a monoamine oxidase inhibitor is given with an SSRI[2]. Tramadol is an analgesic commonly used in patients with chronic pain, who are often receiving an SSRI as well. Tramadol inhibits the reuptake of serotonin and the serotonin syndrome has been reported when it was given with the SSRIs paroxetine and sertraline[3,4]. We report a case with fluoxetine.

Int J Legal Med
DOI 10.1007/s00414-010-0536-3

ORIGINAL ARTICLE

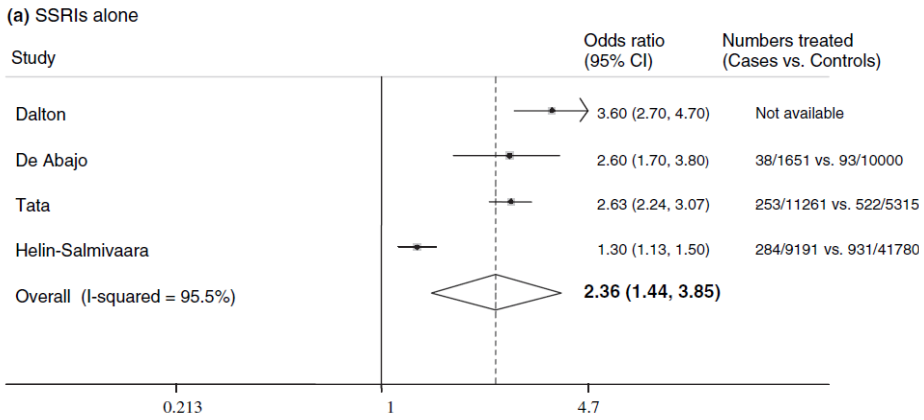
Deaths involving contraindicated and inappropriate combinations of serotonergic drugs

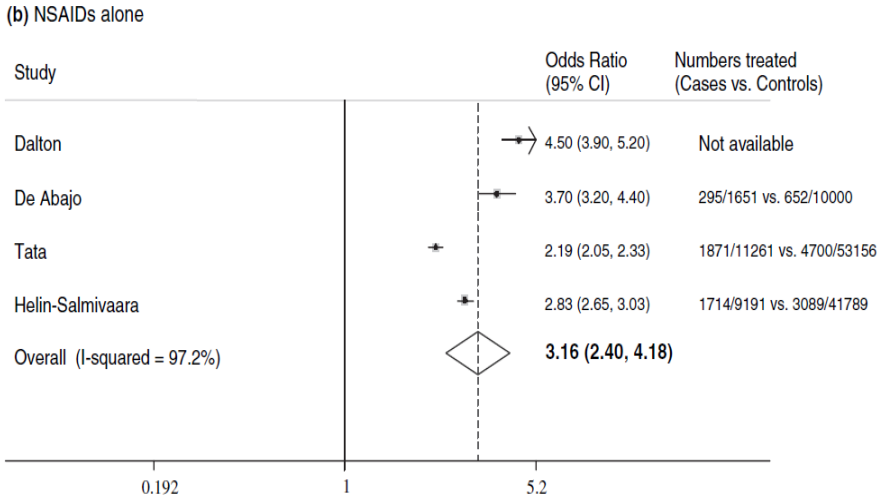
Jennifer L. Pilgrim · Dimitri Gerostamoulos · Olaf H. Drummer

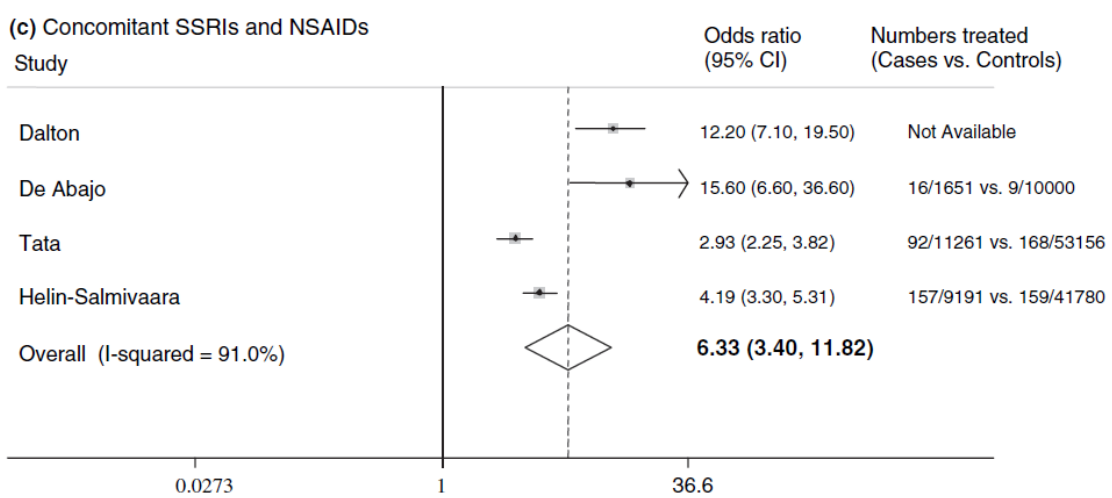
Received: 5 August 2010 / Accepted: 18 November 2010

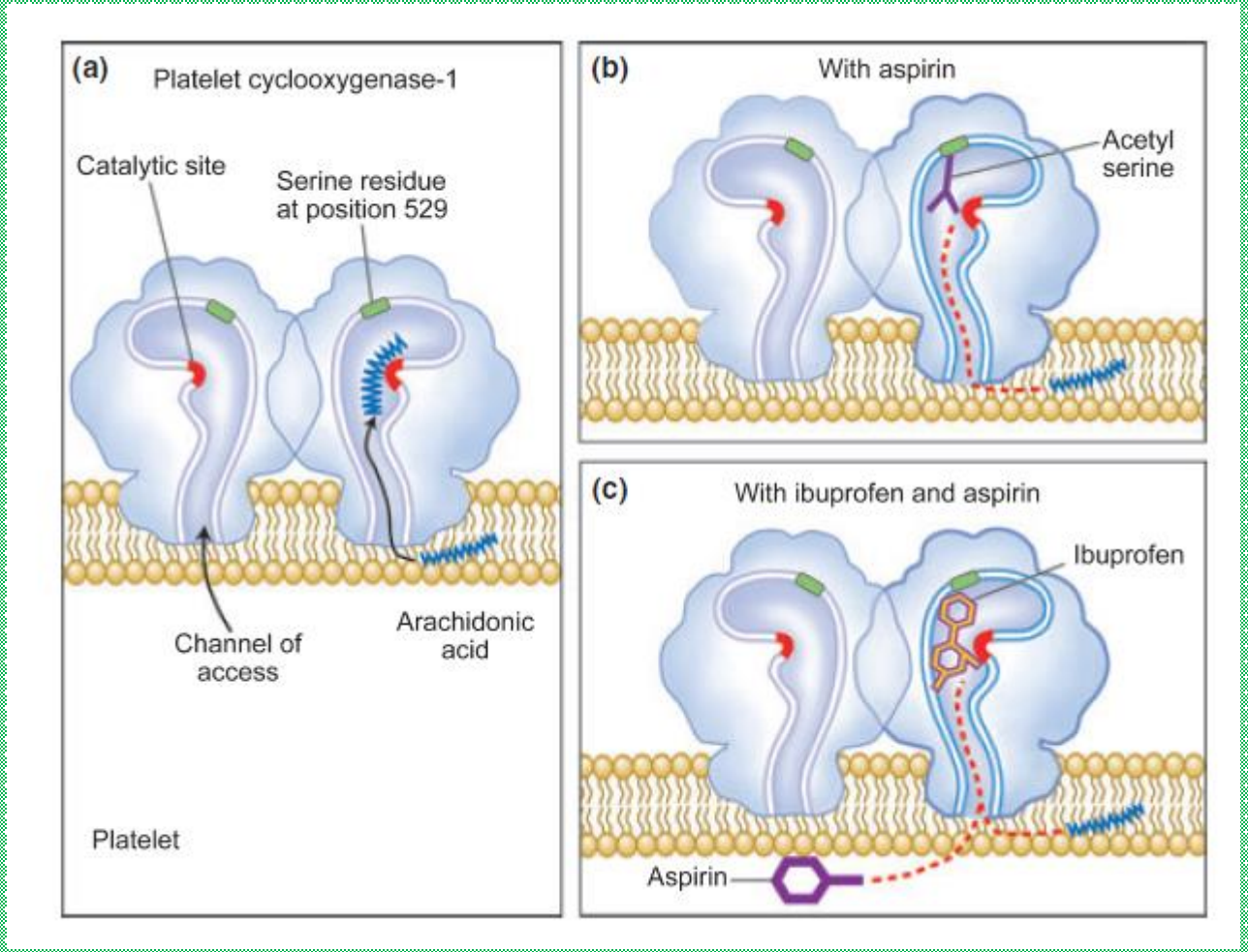
Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs

Y. K. LOKE*, A. N. TRIVEDI† & S. SINGH†









from J Intern Med 2010; 268: 51-529

FANS CHE INIBISCONO L'AZIONE DELL'ASPIRINA SULLA FUNZIONE PIASTRINICA

IBUPROFEN

NAPROXEN

INDOMETACINA

FANS CHE NON INIBISCONO L'AZIONE DELL'ASPIRINA SULLA FUNZIONE PIASTRINICA

SULINDAC

DICLOFENAC

COXIB

A proposito del metabolismo..

Table 1 | **Examples of drugs withdrawn because of CYP-related DDIs**

Drug name (generic)	Therapeutic use	Safety problem	Year withdrawn
Seldane (terfenadine)	Allergy	QTc prolongation	1998
Posicor (mibefradil)	Hypertension	QTc prolongation	1998
Duract (bromfenac)	Nonsteroidal anti-inflammatory drug	Toxicity	1998
Hismanal (astemizole)	Allergy	QTc prolongation	1999
Propulsid (cisapride)	Heartburn	QTc prolongation	2000
Lotronex (alosetron)	Irritable bowel syndrome	Toxicity	2000
Baycol (cerivastatin)	Hyperlipidaemia	Toxicity	2001
Serzone (nefazodone)	Antidepressant	QTc prolongation	2003

CYP, cytochrome P450; DDIs, drug–drug interactions.

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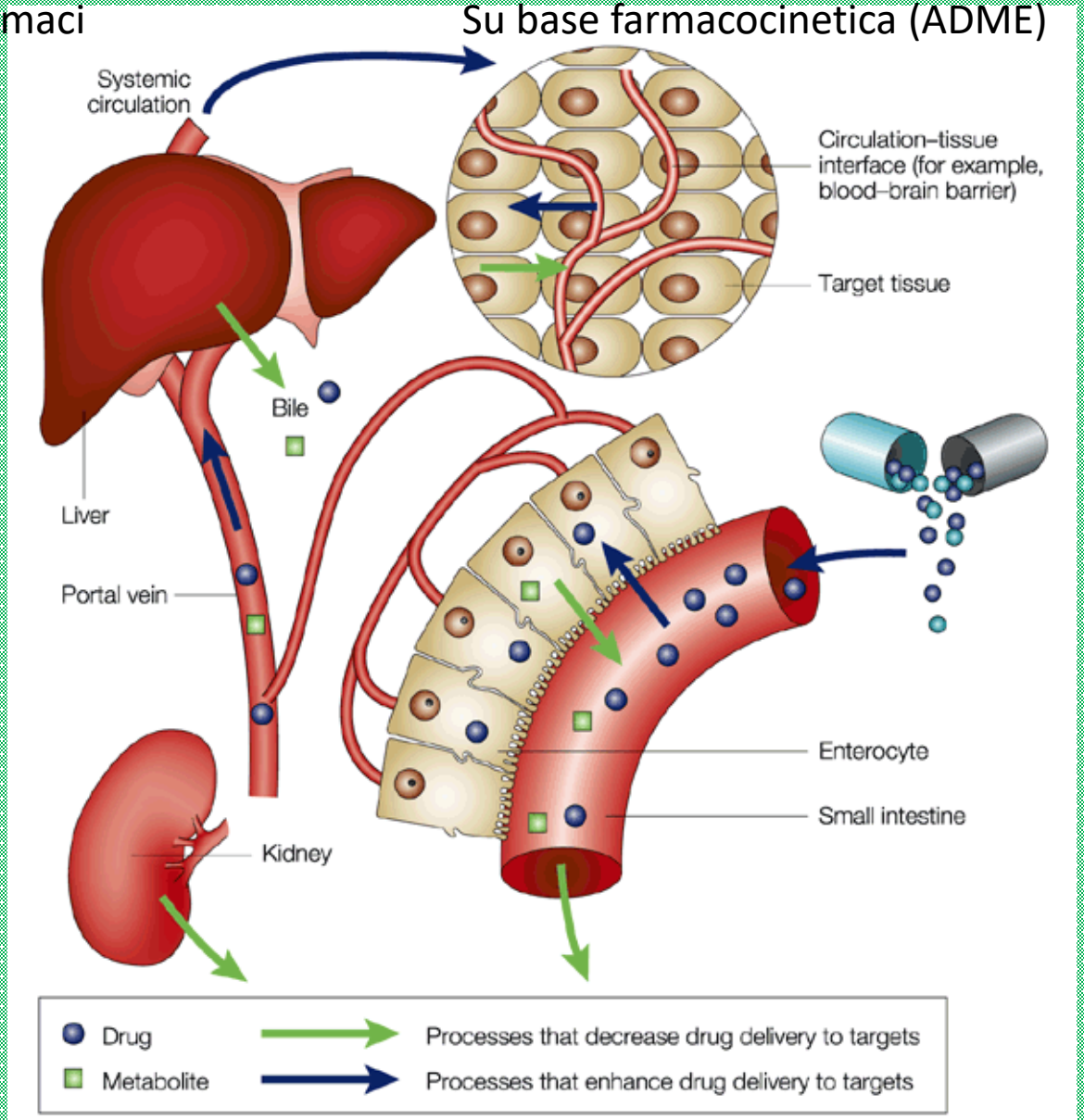
from Nature Review Drug Discovery 2005

Interazioni tra farmaci

Su base farmacocinetica (ADME)



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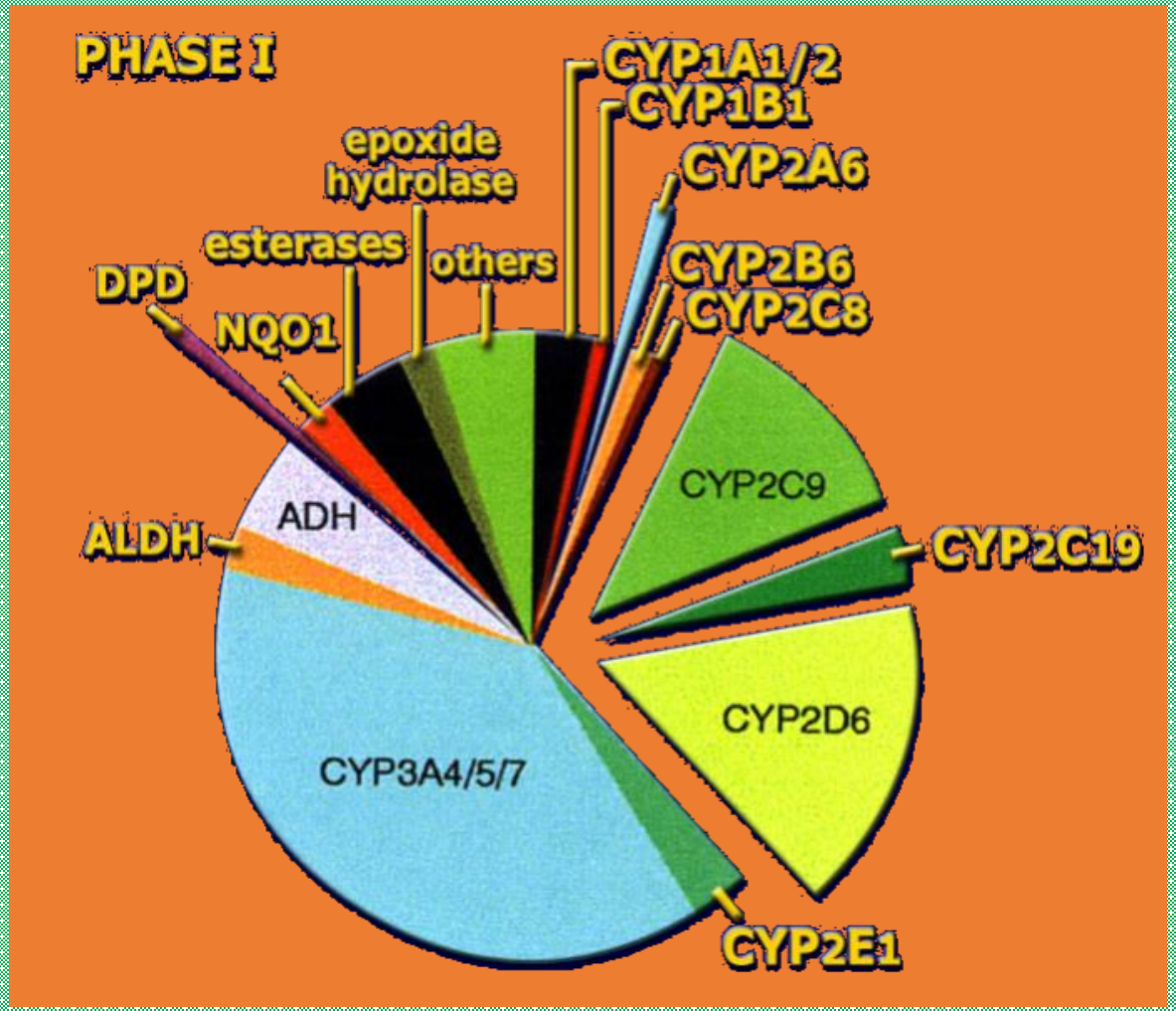
Nature Reviews | Drug Discovery



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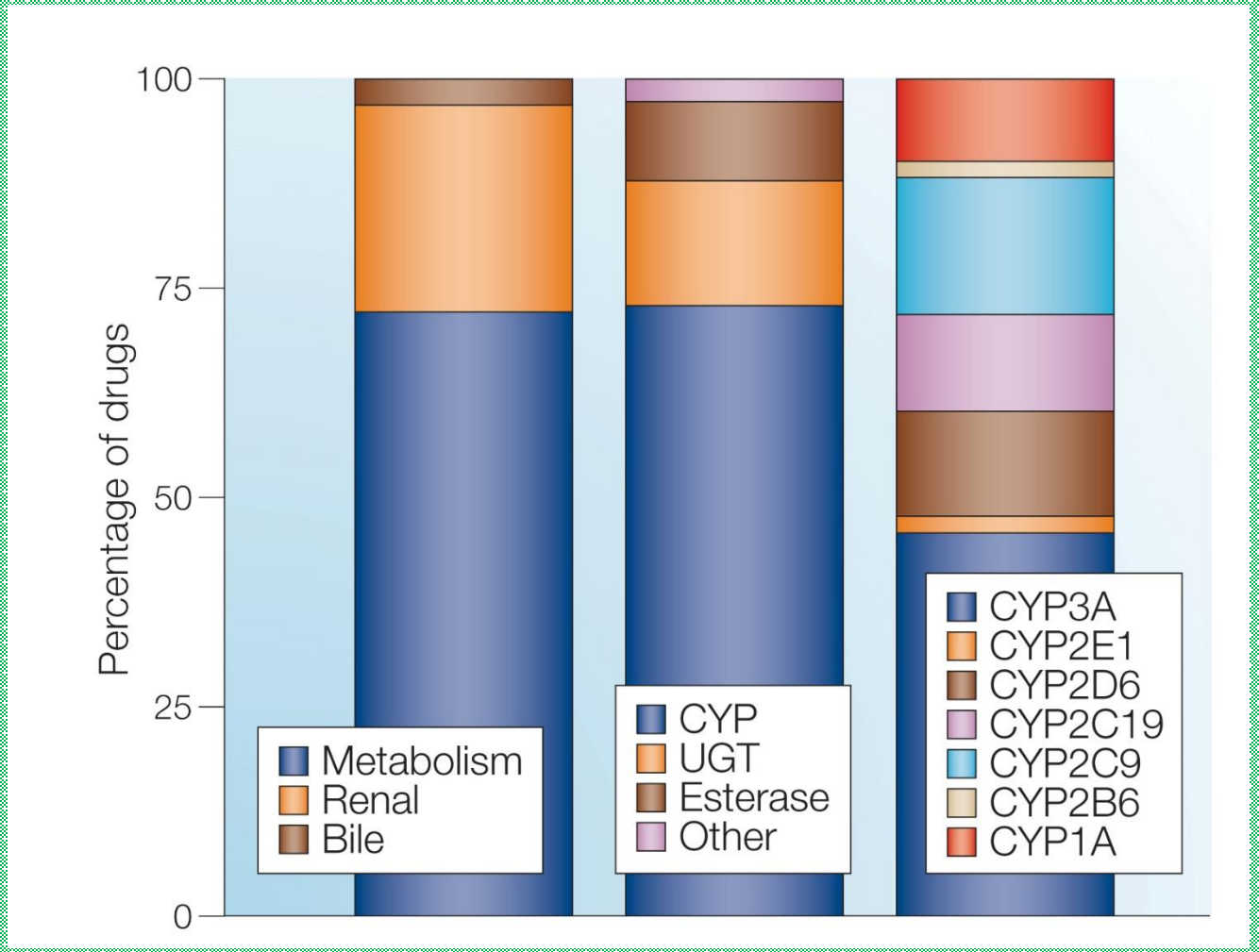

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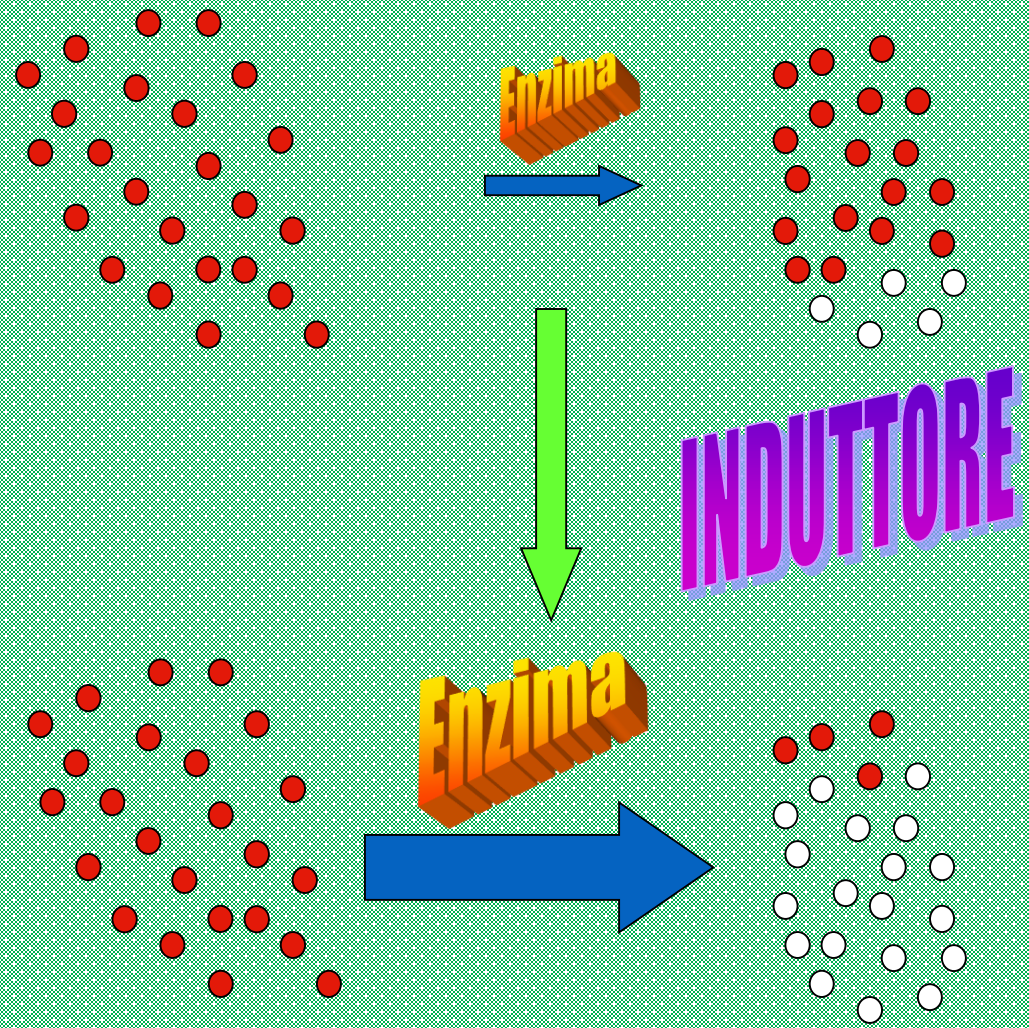
from Nature Review Drug Discovery 2005

Induzione...



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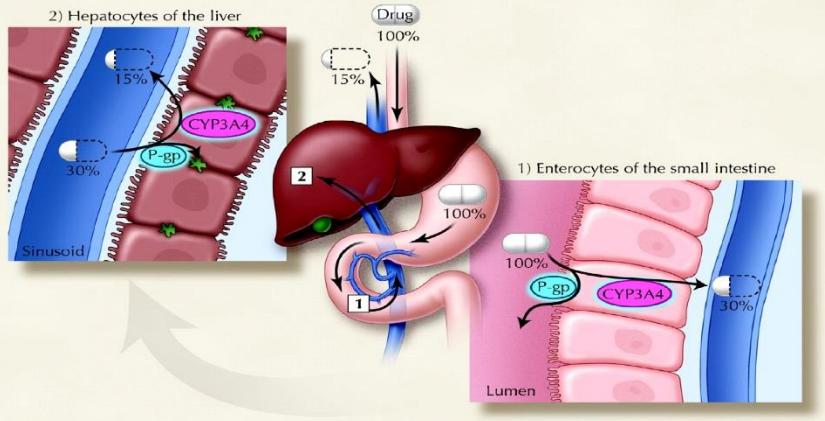
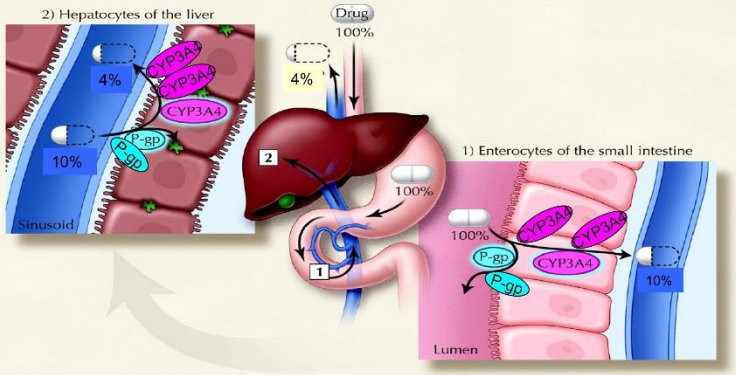
Interplay between hepatic and intestinal CYP3A4/5 in the determining drug availability



(Bailey and Dresser, CMAJ **170**:1531, 2004)

Effect of enzyme induction on the interplay between hepatic and intestinal CYP3A4/5 in the determining drug availability



(Bailey and Dresser, CMAJ **170**:1531, 2004)

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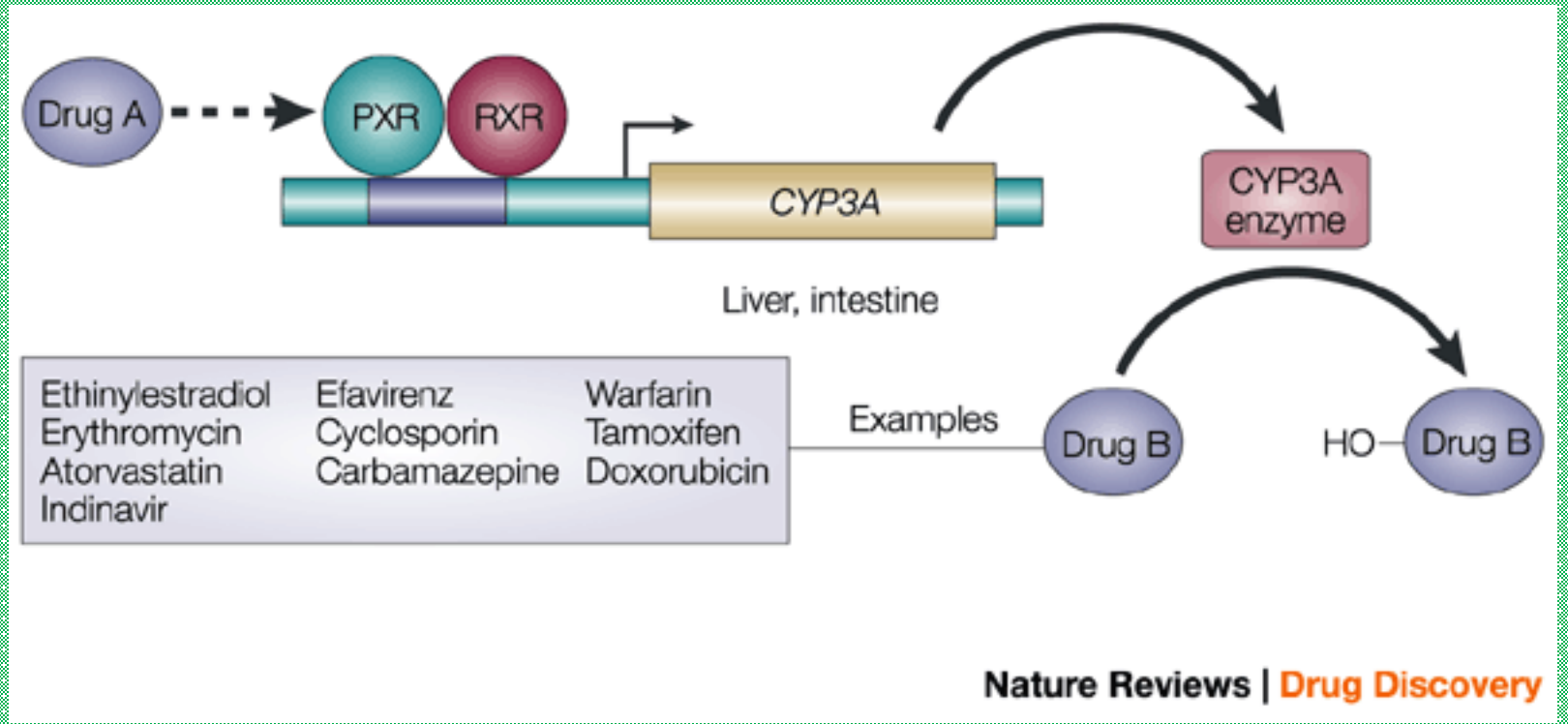

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inibizione

Table 1 Major substrates and inhibitors for CYP2D6

Major classes of drugs as substrates
- Antidepressants
  - Tricyclic antidepressants
  - Serotonin reuptake inhibitors
- Neuroleptics
- Beta-blockers
- Antiarrhytmics

Specific drugs as substrates
- Alprenol
- Amiflamine
- Aprindine
- Atenolol
- Bufuralol
- Bupranolol
- Chlorpropamide
- Clomipramine
- Clozapine
- Codeine
- Debrisoquine
- Desimipramine
- Desmethylcitalopram
- Dextromethorphan
- Dihydrocodeine
- Encainide
- Ethylmorphine
- Flecainide
- Flunarizine
- Fluperlapine
- Guanoxan
- Haloperidol
- Hydrocodone
- Imipramine
- Indoramin
- Maprotiline
- Methoxyamphetamine
- Methoxyphenamine
- Metiamide
- Metoprolol
- Mexiletine
- Nortriptyline
- Ondansetron
- Otycodone
- Perhexiline
- Perphenaxine
- Phenacetin
- Phenformin
- Propafenone
- Propranolol
- Quinidine
- Risiperidone
- Thioridazine
- Timolol
- Tomoxetine
- Tropisetron
- Zuclopenthixol

Inhibitors, drugs
- Chinidin
- Fluoxetin
- Levomepromazine
- Lobelin
- Methadone
- Paroxetine
- Quinidine
- Trifluperidol

Inhibitors, alkaloids[a]
- Ajmalicine
- Ajmalicine
- Berberine
- Coniine
- Ergotamine
- Gramine
- Harmaline
- Laudanosine
- Sempervirine
- Vincamine
- Vinblastine

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CYP3A4 substrates	CYP3A4 inhibitors	CYP3A4 inducers
Benzodiazepines	Amiodarone	Barbiturates
Buprenorphine	Cimetidine	Carbamazepine
Buspirone	Ciprofloxacin	Dexamethasone
Caffeine	Diltiazem	Efavirenz
Ca channel blocker	Erythromycin	Griseofulvin
Codeine	Fluconazole	Phenytoin
Fentanyl	Fluoxetine, fluvoxamine	Primidone
Haloperidol	Grapefruit juice	Rifabutin
HMG Co A reductase	Indinavir, nelfinavir, ritonavir, saquinavir	St. John's wort
Indinavir, nelfinavir, ritonavir, saquinavir	Itraconazole	
Lidocaine	Norfloxacin	
Macrolide		
Methadone		
Odansetron		
Quinine		
Androgenic steroids and corticosteroids		
Tamoxifen		
Taxol, vincristine		
Trazodone		
Zolpidem		

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Inhibition of Cytochrome P450 3A by Clarithromycin Uniformly Affects the Pharmacokinetics and Pharmacodynamics of Oxycodone in Young and Elderly Volunteers

Antti Liukas, MD, Nora M. Hagelberg, MD, PhD,* Kristiina Kuusniemi, MD, PhD,* Pertti J. Neuvonen, MD, PhD,† and Klaus T. Olkkola, MD, PhD**

(*J Clin Psychopharmacol* 2011;31: 302–308)

Tossicita' da ossicodone

EFFETTI DELLA RIFAMPICINA SU FARMACI METABOLIZZATI DAL CYP3A4

Table I. Effect of Rifampicin on the Oral AUC of Drugs that are Metabolized Predominately by CYP3A4

Drug	Type of Clearance (CL)[a]	Rifampicin (mg/day)	AUC (ng h/mL)		Fold Induction[b]	Ref.
			Before RIF	After RIF		
Cyclosporine	Low	600 mg × 11 days	8986	2399	3.7	(2)
Tacrolimus	Low	600 mg × 18 days	351	112	3.1	(179)
Methadone	Low	600 mg × 5 days	1128	262	4.3	(125)
Alprazolam	Low	450 mg × 4 days	224	28	8.0	(126)
Diazepam	Low	600 mg × 7 days	4430	1040	4.2	(127)
Zolpidem	Low	600 mg × 5 days	1202	336	3.6	(128)
Zopiclone	Low	600 mg × 5 days	473	86	5.5	(129)
Quinidine	Moderate	600 mg × 7 days	8000	910	8.8	(185)
Midazolam	Moderate	600 mg × 5 days	612	25	24.0	(130)
Triazolam	Moderate	600 mg × 5 days	14.8	0.74	20.0	(131)
Nifedipine	High	600 mg × 7 days	280	18	15.5	(124)
Indinavir	High	600 mg × 8 days	18.8[c]	1.2[c]	16.0	(199)
(*S*)-Verapamil	High	600 mg × 12 days	152	5	30.0	(9)
(*R*)-Verapamil	High	600 mg × 12 days	724	14	52.0	(9)

AUC: area under plasma concentration–time curve; RIF: rifampicin.
[a] Type of clearance: low clearance < 200 mL/min; moderate clearance > 500 mL/min; high clearance > 1000 mL/min.
[b] Fold induction: the ratio of AUC before and after rifampicin.
[c] μg h/mL.

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LE INTERAZIONI TRA FARMACI

DAL PUNTO DI VISTA DELLA TERAPIA oncologica

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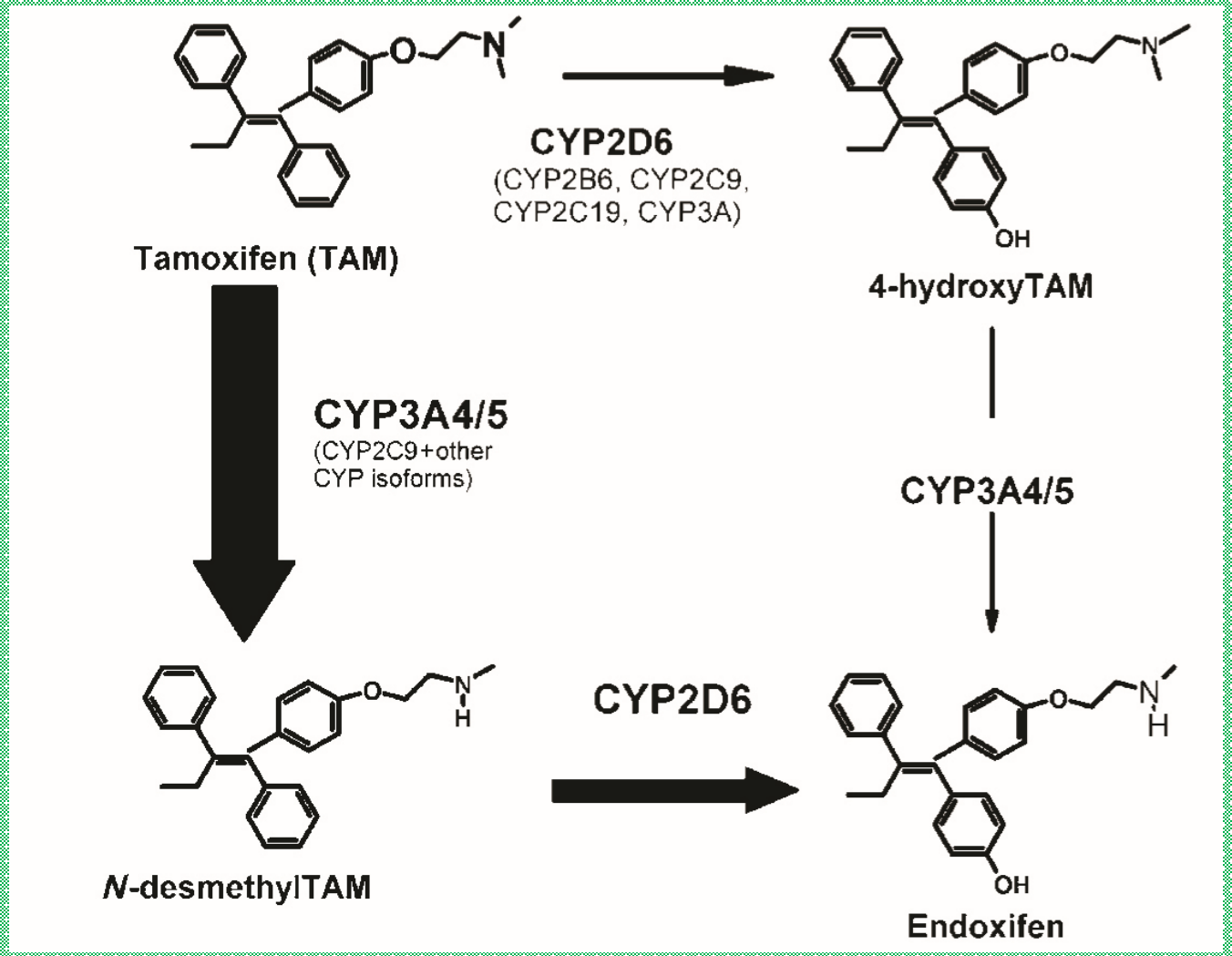

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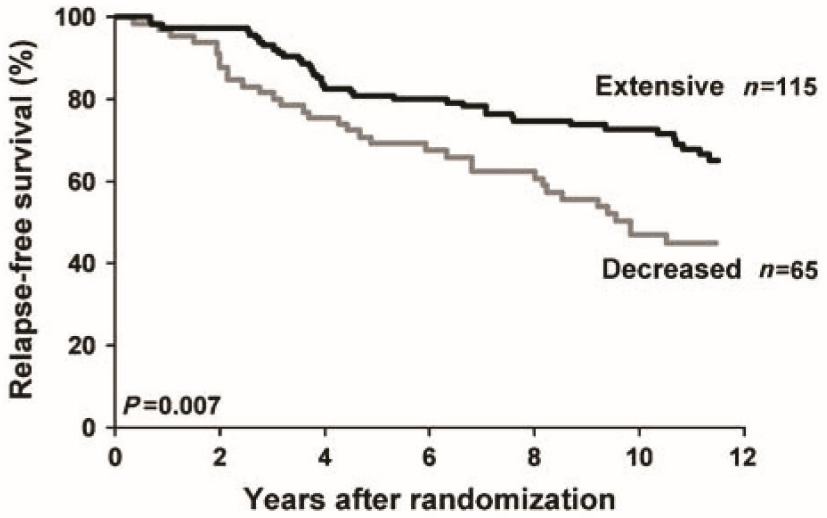

Figure 2 Kaplan–Meier estimates of RFS based on CYP2D6 metabolism (extensive vs. decreased). Reprinted with permission from Goetz, M.P. *et al. Breast Cancer Res. Treat.* **101**, 113–121 (2007).

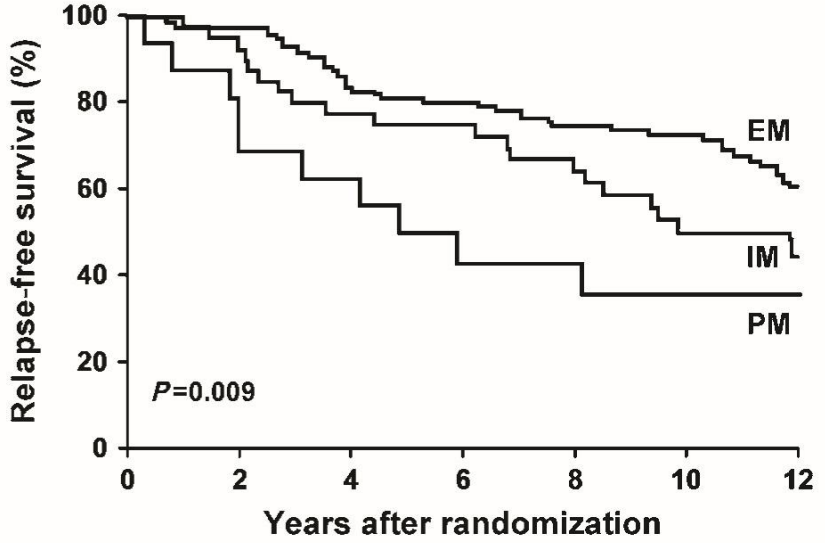

Figure 3 Kaplan–Meier estimates of RFS based on metabolizer status (extensive, intermediate, or poor). Reprinted with permission from Goetz, M.P. *et al. Breast Cancer Res. Treat.* **101**, 113–121 (2007).

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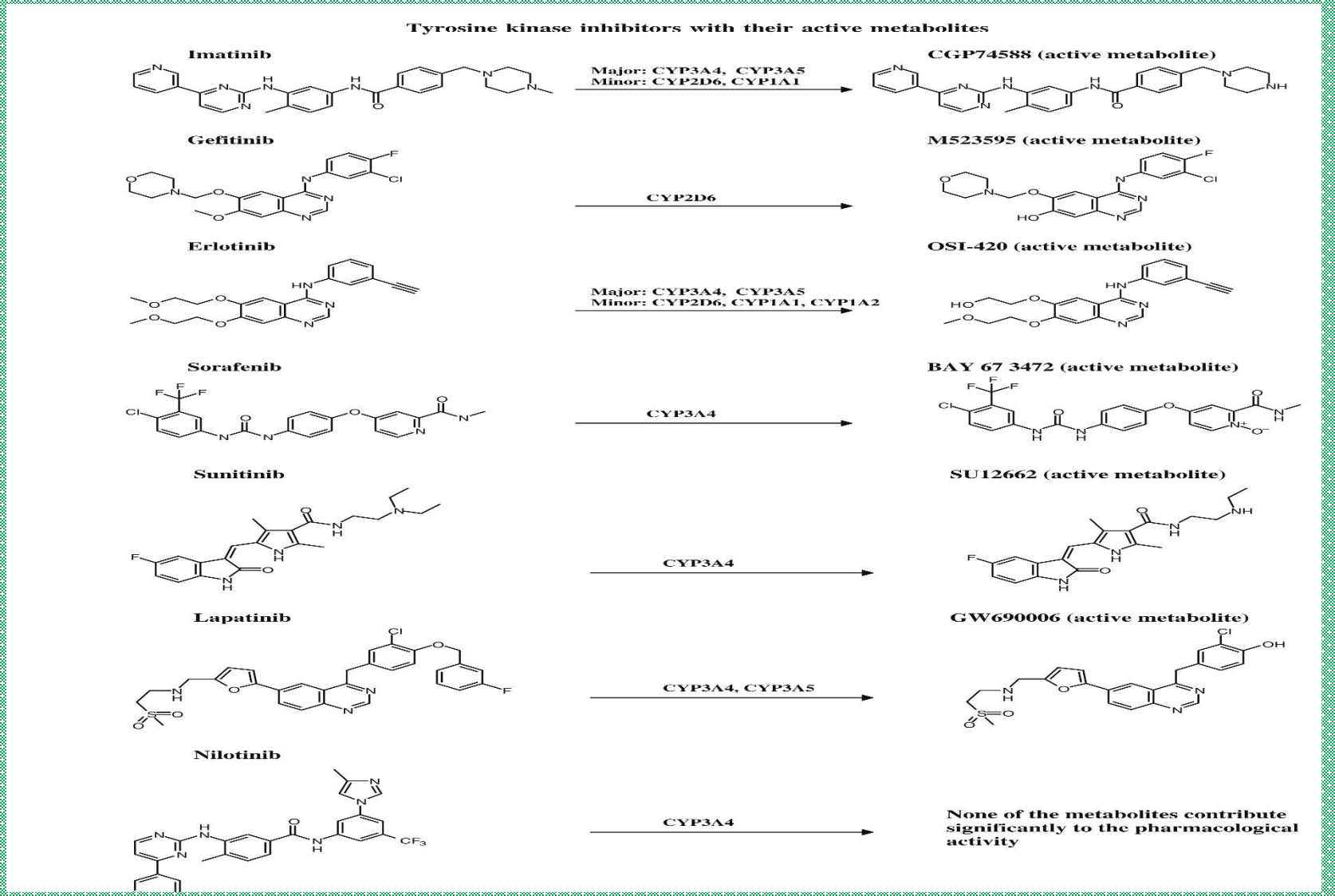

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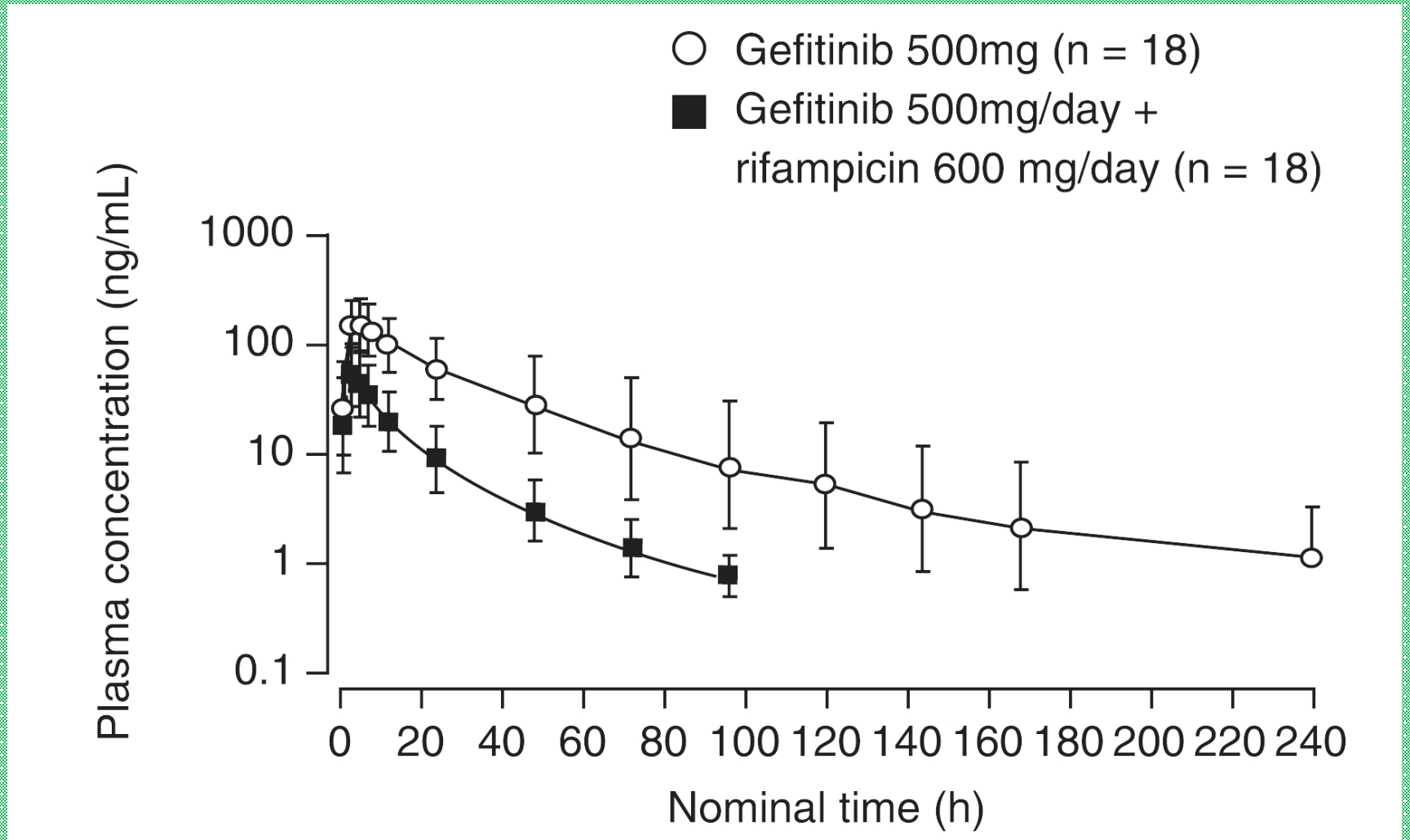

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Clin Pharmacokinet 2005; 44 (10) pp 1067-1081

Table 1 Clinically relevant CYP450-mediated interactions in the ICU [14–16, 18–22]

Substrate	Inhibitor	Inducer
CYP1A2		
Theophylline	Fluvoxamine	Rifampicin
Haloperidol	Ciprofloxacine	Carbamazepine
	Cimetidine	Tobacco
CYP2C9		
Warfarin	Metronidazole	Rifampicin
Phenytoin	Isoniazide	Phenobarbital
Ibuprofen, Diclofenac, Naproxen	Fluconazole, Voriconazole	Phenytoin
Voriconazole	Amiodarone	Carbamazepine
CYP2C19		
Citalopram	Fluoxetine, Paroxetine,	Rifampicin
Phenytoin	Voriconazole	Carbamazepine
Diazepam		Phenytoin
Voriconazole		Phenobarbital
CYP2D6		
Codeine, Tramadol	Paroxetine, Sertraline, Fluoxetine	
Paroxetine	Amiodarone	
Haloperidol	Quinidine	
Carvedilol, Metoprolol, Propranolol		
CYP3A4		
Fentanyl, Sufentanyl	Clarithromycine, Erythromycine	Rifampicin
Clarithromycin, Erythromycin	Fluconazole, Itraconazole,	Rifabutin
Warfarin	Voriconazole, Posaconazole	Carbamazepine
Carbamazepine	Diltiazem, Verapamil	Phenytoin
Haloperidol	Amlodipine, Nifedipine	Phenobarbital
Midazolam, Alprazolam, Diazepam	Amiodarone	Efavirenz,
Amlodipine, Felodipine, Nifedipine		Nevirapine
Diltiazem, Verapamil		
Atorvastatin, Simvastatin, Cerivastatin		
Methylprednisolone, Hydrocortisone		
Cyclosporine, Tacrolimus		
Nelfinavir, Ritonavir, Saquinavir		

....MEGLIO UN FARMACO

CHE NON E' METABOLIZZATO DAL CYP450 2D6 E 3A4 ?

Patrizia Romualdi

INTERAZIONI DEI PRINCIPALI FARMACI UTILIZZATI IN MEDICINA INTERNA E/O ONCOLOGIA CON GLI ANALGESICI OPPIACEI ORALI

Terapia	CYP2D6	CYP3A4	Somministrato contemporaneamente a			
			Codeina[1,3,8]	Tramadolo[2,3]	Ossicodone[1,3]	Idromorfone[3]
Cardiovascolare						
Amiodarone[4]		●	●	●	●	●
Amlodipina[5]		●	●	●	●	●
Atorvastatina[4,6]		●	●	●	●	●
Carvedilolo[7]	●		●	●	●	●
Diltiazem[4]		●	●	●	●	●
Losartan[4]		●	●	●	●	●
Lovastatina[4,6]		●	●	●	●	●
Metoprololo[7]	●		●	●	●	●
Nicardipina[9]		●	●	●	●	●
Nifedipina[4,6]		●	●	●	●	●
Nimodipina[10]		●	●	●	●	●
Propranololo[4,7]	●		●	●	●	●
Simvastatina[4,6]		●	●	●	●	●
Timololo[7]	●		●	●	●	●
Verapamil[4]		●	●	●	●	●
Warfarin[4]		●	●	●	●	●
Antinfiammatoria						
Celecoxib[4]	●		●	●	●	●
Antipiretica/Analgesica						
Paracetamolo[11,12]	●	●	●	●	●	●
Gastroenterologica						
Cimetidina[4,13]	●		●	●	●	●
Esomeprazolo[4]		●	●	●	●	●
Granisetrone[14]		●	●	●	●	●
Ondansetrone[15]	●	●	●	●	●	●
Omeprazolo[16]		●	●	●	●	●
Patologie del SNC						
Aloperidolo[17]	●	●	●	●	●	●
Alprazolam[4,6]		●	●	●	●	●
Carbamazepina[4]		●	●	●	●	●
Diazepam[4]		●	●	●	●	●
Donepezil[17]	●	●	●	●	●	●
Fluoxetina[17,18]	●	●	●	●	●	●
Imipramina[17]		●	●	●	●	●
Mirtazapina[4,17]	●		●	●	●	●
Paroxetina[17,18]	●		●	●	●	●
Sertralina[18]	●		●	●	●	●
[illegible]olam[4,6]		●	●	●	●	●
[illegible]faxina[17]	●		●	●	●	●
[illegible]idem[6]		●	●	●	●	●

● Inibitore isoenzima ● Substrato isoenzima ● Nessuna interazione ● Possibile interazione ● Interazione altamente probabile

Patrizia Romualdi

INTERAZIONI DEI PRINCIPALI FARMACI UTILIZZATI IN MEDICINA INTERNA E/O ONCOLOGIA CON GLI ANALGESICI OPPIACEI ORALI

Terapia	CYP2D6	CYP3A4	Somministrato contemporaneamente a			
			Codeina[1,3,8]	Tramadolo[2,3]	Ossicodone[1,3]	Idromorfone[3]
Antifettiva						
Claritromicina[4]		●	●	●	●	●
Eritromicina[4]		●	●	●	●	●
Itraconazolo[4]		●	●	●	●	●
Ketoconazolo[4]		●	●	●	●	●
Antineoplastica						
Anastrozolo[20]		●	●	●	●	●
Busulfan[4]		●	●	●	●	●
Ciclofosfamide[21]		●	●	●	●	●
Docetaxel[4]		●	●	●	●	●
Doxorubicina[21]		●	●	●	●	●
Erlotinib[4]		●	●	●	●	●
Etoposide[22]		●	●	●	●	●
Gefitinib[4]		●	●	●	●	●
Imatinib[23]		●	●	●	●	●
Irinotecan[4]		●	●	●	●	●
Lapatinib[19]		●	●	●	●	●
Sorafenib[24]		●	●	●	●	●
Sunitinib[25]		●	●	●	●	●
Paclitaxel[4,21]		●	●	●	●	●
Tamoxifene[21,23,26,27]	●	●	●	●	●	●
Vinblastina[21]		●	●	●	●	●
Vinorelbina[28]		●	●	●	●	●

● Inibitore isoenzima ● Substrato isoenzima ● Nessuna interazione ● Possibile interazione ● Interazione altamente probabile

Patrizia Romualdi

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REVIEW

Clinically significant drug–drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review

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Background: Opioids are the most frequently used drugs to treat pain in cancer patients. In some patients, however, opioids can cause adverse effects and drug–drug interactions. No advice concerning the combination of opioids and other drugs is given in the current European guidelines.

Objective: To identify studies that report clinically significant drug–drug interactions involving opioids used for pain treatment in adult cancer patients.

Design and data sources: Systematic review with searches in Embase, MEDLINE, and Cochrane Central Register of Controlled Trials from the start of the databases (Embase from 1980) through January 2014. In addition, reference lists of relevant full-text papers were hand-searched.

Results: Of 901 retrieved papers, 112 were considered as potentially eligible. After full-text reading, 17 were included in the final analysis, together with 15 papers identified through hand-searching of reference lists. All of the 32 included publications were case reports or case series. Clinical manifestations of drug–drug interactions involving opioids were grouped as follows: 1) sedation and respiratory depression, 2) other central nervous system symptoms, 3) impairment of pain control and/or opioid withdrawal, and 4) other symptoms. The most common mechanisms eliciting drug–drug interactions were alteration of opioid metabolism by inhibiting the activity of cytochrome P450 3A4 and pharmacodynamic interactions due to the combined effect on opioid, dopaminergic, cholinergic, and serotonergic activity in the central nervous system.

Conclusion: Evidence for drug–drug interactions associated with opioids used for pain treatment in cancer patients is very limited. Still, the cases identified in this systematic review give some important suggestions for clinical practice. Physicians prescribing opioids should recognize the risk of drug–drug interactions and if possible avoid polypharmacy.

Keywords: opioids, pain, cancer patients, drug–drug interactions