# ΑΝΑΓΚΑΙΟΤΗΤΑ ΚΑΙ ΠΡΟΟΠΤΙΚΕΣ ΟΡΓΑΝΩΣΗΣ ΠΙΣΤΟΠΟΙΗΜΕΝΩΝ ΠΡΟΓΡΑΜΜΑΤΩΝ ΣΥΝΕΧΟΥΣ ΦΑΡΜΑΚΕΥΤΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ ΣΤΗΝ ΕΛΛΑΔΑ:

## *ΤΟ ΠΑΡΑΔΕΙΓΜΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΣΥΛΛΟΓΟΥ ΡΟΔΟΠΗΣ*

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Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης

Σέρρες, 8 Μαΐου 2010

# ΦΑΡΜΑΚΕΥΤΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

ΣΥΝΘΗΚΕΣ ΕΠΑΓΓΕΛΜΑΤΙΚΟΥ ΧΩΡΟΥ

ΦΑΡΜΑΚΕΥΤΙΚΗ ΕΡΕΥΝΑ

ΦΑΡΜΑΚΕΥΤΙΚΗ ΑΓΩΓΗ

ΑΝΑΠΤΥΞΗ ΝΕΩΝ ΦΑΡΜΑΚΩΝ


ΠΡΟΓΡΑΜΜΑΤΑ ΣΠΟΥΔΩΝ ΦΑΡΜΑΚΕΥΤΙΚΗΣ ΕΚΠΑΙΔΕΥΣΗΣ

**Table 1.** Response rates to a major drug in selected therapeutic areas.

| Therapeutic area | Efficacy (%) |
|---|---|
| Alzheimer's disease | 30 |
| Analgesics (COX-2) | 80 |
| Asthma | 60 |
| Cardiac arrhythmia | 60 |
| Depression (SSRI) | 62 |
| Diabetes | 57 |
| HCV | 47 |
| Incontinence | 40 |
| Migraine (acute) | 52 |
| Migraine (prophylaxis) | 50 |
| Oncology | 25 |
| Osteoporosis | 48 |
| Rheumatoid arthritis | 50 |
| Schizophrenia | 60 |

COX-2: cyclooxygenase-2

SSRI: selective serotonin re-uptake inhibitors

# ΠΡΟΣΑΡΜΟΓΗ ΔΟΣΗΣ

ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΕΣ ΠΑΡΑΜΕΤΡΟΙ

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ΚΛΙΝΙΚΕΣ ΠΑΡΑΜΕΤΡΟΙ

ΦΥΤΟΘΕΡΑΠΕΥΤΙΚΑ ΤΟΞΙΚΑ

ΣΥΜΜΟΡΦΩΣΗ ΑΣΘΕΝΗ

**Ας δούμε όμως στην κλινική πράξη πως αυτά τα στοιχεία ενσωματώνονται με συγκεκριμένα παραδείγματα φαρμάκων**

# Το παράδειγμα των στατινών: Η απόσυρση της σεριβαστατίνης το 2001

↓

# Ανάλυση των δεδομένων φαρμακοεπαγρύπνησης

# Οι *στατίνες* είναι αναστολείς της αναγωγάσης του 3-υδροξυ-3-μεθυλογλουταρυλο- συνενζύμου Α (HMG-CoA)

Διαφορές των στατινών στο επίπεδο του μεταβολισμού

**Ηπατικός μεταβολισμός**

| *Στατίνη* | *Κύριο ισοένζυμο* |
|---|---|
| Ατορβαστατίνη (*Lipitor*) | CYP3A4 |
| Λοβαστατίνη (*Mevacor*) | CYP3A4 |
| Πραβαστατίνη (*Pravachol*) | None |
| Σεριβαστατίνη (*Baycol*) | CYP3A4/CYP2C8 |
| Σιμβαστατίνη (*Zocor*) | CYP3A4 |
| Φλουβαστατίνη (*Lescol*) | CYP2C9 |
| Ροζουβαστατίνη (Crestor) | (~10%) CYP2C9 |

Μπορεί αυτή η διαφοροποίηση στο επίπεδο του μεταβολισμού να οδηγήσει στην εμφάνιση ADRs κατά τη συγχορήγησή τους με συγκεκριμένα φάρμακα ή και τρόφιμα, **και αν ΝΑΙ**, είναι δυνατόν να προβλεφθούν και με ποιό τρόπο;

## Συγκεντρώσεις *στατινών* στο αίμα μετά την εμφάνιση φαρμακευτικών αλληλεπιδράσεων (*ADRs*)

| Στατίνη | *Φάρμακο* | Συγκέντρωση στατίνης * |
|---|---|---|
| - Σιμβαστατίνη (40mg) | *Ιτρακοναζόλη* | ↑5,5x - Ραβδομυόλυση |
| | *Κυκλοσπορίνη* | ↑13x |
| - Λοβαστατίνη (40mg) | *Ερυθρομυκίνη* | ↑ 3x - Ραβδομυόλυση |
| - Λοβαστατίνη (80mg) | *Κυκλοσπορίνη* | ↑ 5x - Ραβδομυόλυση |
| - Λοβαστατίνη (60mg) | *Ερυθρομυκίνη* | ↑ 8x - Ραβδομυόλυση |
| | *Διλτιαζέμη* | |

Ήδη το FDA (Δεκέμβριος, 1997) μετά την αναφορά 6 περιστατικών ραβδομυόλυσης σε ασθενείς μετά τη συγχορήγηση σιμβαστατίνης και *μιμπεφραδίλης* είχε εκδώσει προειδοποίηση (warning label).

Worz, CR. and Bottorff, M. (2001). The role of cytochrome P450-mediated drug-drug interactions in determining the safety of statins. Expert Opin. Pharmacother., 2(7): 1119-1127.

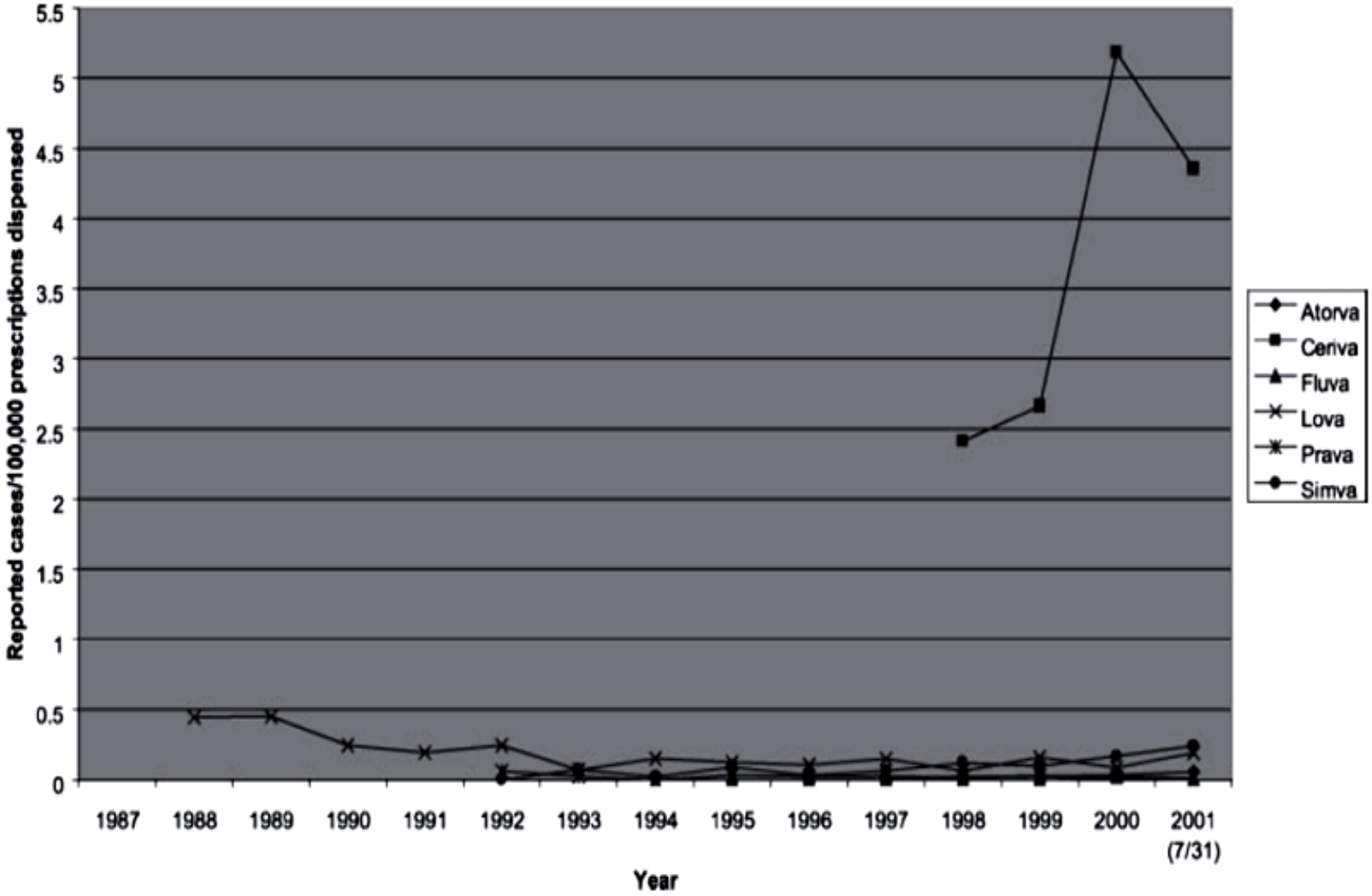



Figure 2. Domestic reporting rates of rhabdomyolysis associated with statins (1988–July 2001). *Cases were U.S. patients with myalgia, myopathy or gait disturbance + clinical diagnosis of rhabdomyolysis + CPK > 10 000 IU/L and reported to the FDA. **Date reflects date report was received by FDA, not date of occurrence of event, which is not consistently reported

Table 4. Reporting rates (per 100 000 Rxs) for U.S. cases of rhabdomyolysis associated with statins: all cases* reported through 7/31/01

| Calendar years analyzed | Lovastatin: 1988–July 2001 | Pravastatin: 1992–July 2001 | Simvastatin: 1992–July 2001 | Fluvastatin: 1994–July 2001 | Atorvastatin: 1997–July 2001 | Cerivastatin: 1998–July 2001 |
|---|---|---|---|---|---|---|
| All cases | | | | | | |
| Cases | 180 | 19 | 136 | 1 | 51 | 479 |
| #Rxs (000's)† | 99 485 | 83 673 | 120 188 | 38 119 | 149 706 | 11 172 |
| Crude reporting rate/ 100 000Rx | 0.18 | 0.02 | 0.11 | 0.00 | 0.03 | 4.29 |
| Monotherapy | | | | | | |
| Cases | 120 | 17 | 99 | 1 | 45 | 200 |
| Estimated #Rxs (000's)‡ | 97 336 | 82 000 | 118 986 | 37 791 | 147 610 | 11 038 |
| Crude reporting rate/ 100 000Rx | 0.12 | 0.02 | 0.08 | 0.00 | 0.03 | 1.81 |
| Combination with gemfibrozil | | | | | | |
| Cases | 60 | 2 | 37 | 0 | 6 | 279 |
| Estimated #Rxs (000's)† | 2109 | 1422 | 962 | 316 | 1198 | 22 |
| Crude reporting rate/ 100 000Rx | 2.84 | 0.14 | 3.85 | 0.00 | 0.50 | 1248.66 |

~60%

*Cases identified in the AERS database with a CPK > 10 000 IU/L, signs and symptoms (myalgia, myopathy, gait disturbance) and clinical diagnosis of rhabdomyolysis.

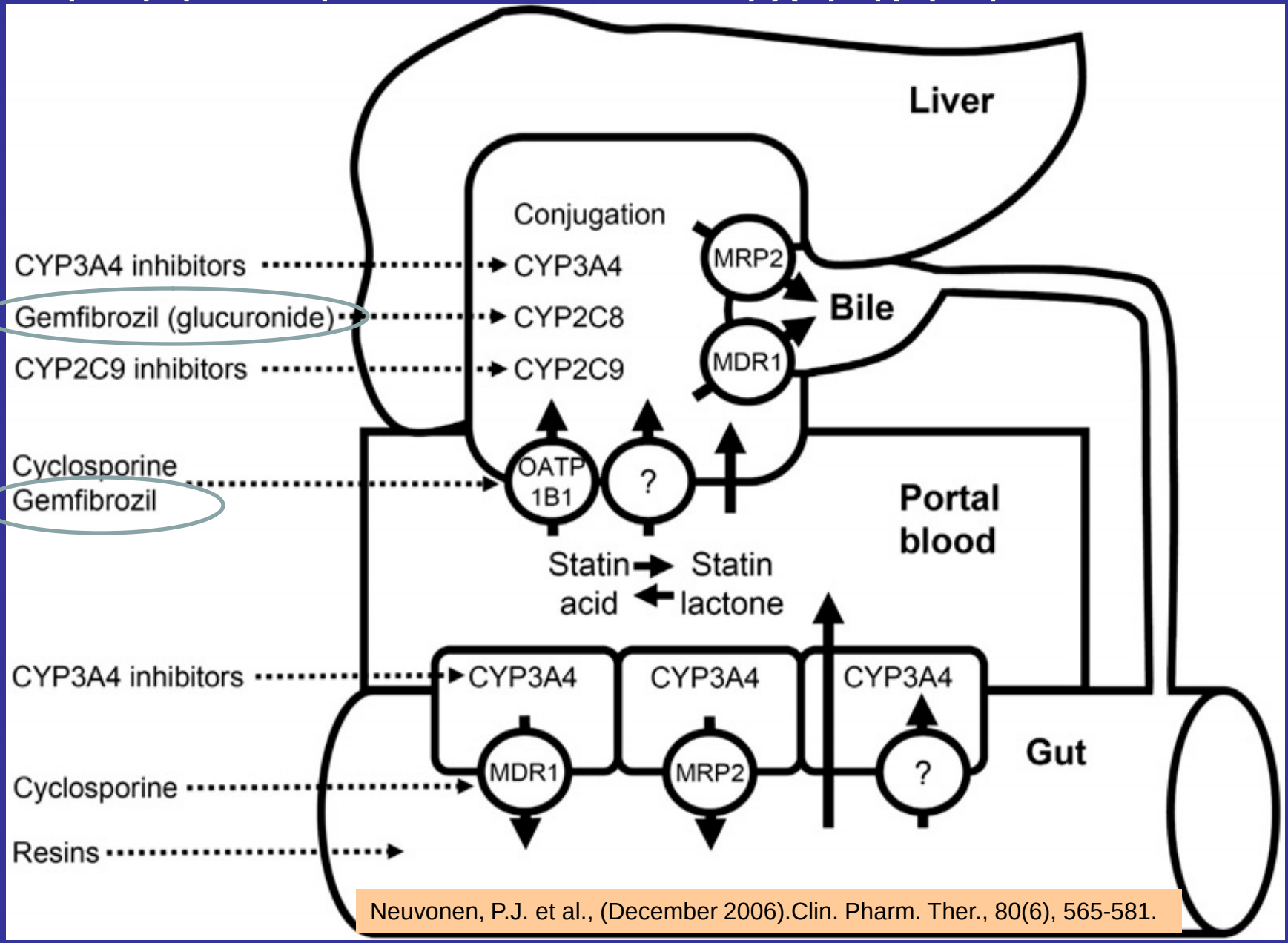
†All dispensed Rxs for all years the drug was marketed between 1988–July 2001 (IMS HEALTH NPA*Plus*™, excluding Long Term Care).

‡Estimate of Rxs for statin therapy, with or without concomitant gemfibrozil therapy, based on percentage of mentions (IMS HEALTH NDTI™) summed across all years of marketing for each drug and applied to Rxs for all years each drug was marketed (IMS HEALTH NPA*Plus*™).

§This analysis does not include concomitant therapy with fenofibrate, which was prevalent in 0–1% of mentions across statins, or clofibrate, which occurred only in 0.04% of lovastatin mentions. Few cases of rhabdomyolysis were reported for any statin + fenofibrate or clofibrate; they are not included in this analysis.

Η γκεμφιβροζίλη είναι αναστολέας του CYP2C9 και CYP2C8

# Ένζυμα και μεταφορείς που εμπλέκονται στην εμφάνιση των ADRs κατά τη χορήγηση των στατινών




Neuvonen, P.J. et al., (December 2006).Clin. Pharm. Ther., 80(6), 565-581.

# The Grapefruit Challenge

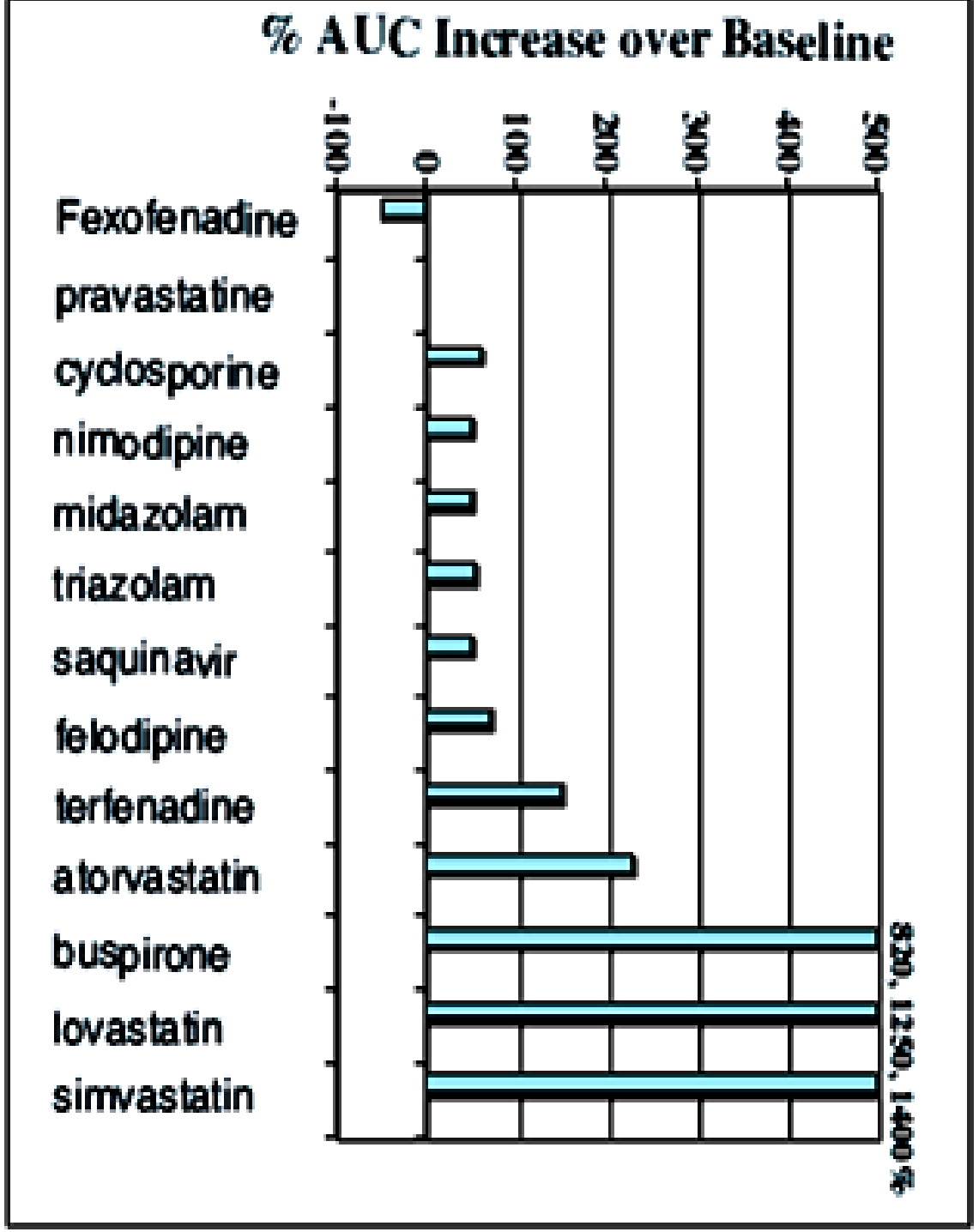
*The juice inhibits a crucial enzyme, with possibly fatal consequences.*

Αλληλεπίδραση μεταξύ ατορβαστατίνης (Lipitor)
και χυμού γκρέϊπφρουτ που προκάλεσε συμπτώματα ραβδομυόλυσης σ' έναν άνδρα ηλικίας 59 ετών στις Η.Π.Α.

By Amy M. Karch, AJN ▼ December 2004 ▼ Vol. 104, No. 12

## Drugs That Interact with Grapefruit Juice

- **α- and β-adrenergic blocker:** carvedilol
- **Androgen hormone inhibitor:** finasteride
- **Anthelmintic:** albendazole
- **Antiarrhythmics:** amiodarone, quinidine
- **Antibiotics:** clarithromycin, erythromycin, troleandomycin
- **Anticoagulant:** warfarin
- **Antiepileptic:** carbamazepine
- **Antifungal:** itraconazole
- **Antihistamine:** fexofenadine
- **Antihyperlipidemics:** atorvastatin, fluvastatin, lovastatin, simvastatin
- **Antineoplastics:** cyclophosphamide, etoposide, ifosfamide, tamoxifen, vinblastine, vincristine
- **Antitussive:** dextromethorphan
- **Antivirals:** amprenavir, indinavir, nelfinavir, ritonavir, saquinavir
- **Anxiolytics:** alprazolam, buspirone, midazolam
- **Calcium channel blockers:** diltiazem, felodipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil
- **Erectile dysfunction drugs:** sildenafil, tadalafil
- **Hormone replacement drugs:** cortisol, estradiol, methylprednisolone, progesterone, testosterone
- **Hypnotic–sedative:** triazolam
- **Immunosuppressants:** cyclosporine, sirolimus, tacrolimus
- **Opioid analgesics:** alfentanil, fentanyl, sufentanil
- **Selective serotonin reuptake inhibitors:** fluvoxamine, sertraline
- **Xanthine:** theophylline




% AUC Increase over Baseline

*Figure 2. Examples of AUC changes over baseline when the drug was given with grapefruit juice.* 12-20

Hua

drug

569.

TOM LYNCH, PharmD, and AMY PRICE, MD, *Eastern Virginia Medical School, Norfolk, Virginia*

*American Family Physician*
*Volume 76, Number 3 • August 1, 2007*


**Table 2. Examples of Common Drug-Drug Interactions Involving the Cytochrome P450 Enzyme System**

| *Drug(s)/product* | *Enzyme inhibitor or inducer* | *Drug(s)* | *Metabolizing enzyme* | *Possible clinical effect* |
|---|---|---|---|---|
| Amiodarone (Cordarone) | CYP2C9 and CYP3A4 inhibitor | Warfarin (Coumadin) | CYP2C9 | Increased risk of bleeding caused by increased warfarin level[19] |
| Carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin) | CYP3A4 inducer | Ethinyl estradiol-containing contraceptives | CYP3A4 | Unplanned pregnancy caused by reduced estradiol level[20] |
| Clarithromycin (Biaxin), erythromycin, telithromycin (Ketek) | CYP3A4 inhibitor | Simvastatin (Zocor), verapamil (Calan) | CYP3A4 | Myopathy or rhabdomyolysis caused by increased simvastatin level[21]<br>Hypotension and QT interval prolongation caused by increased verapamil level[22] |
| Diltiazem (Cardizem), verapamil | CYP3A4 inhibitor | Prednisone | CYP3A4 | Immunosuppression caused by increased prednisolone serum levels[23] |
| Fluoxetine (Prozac), paroxetine (Paxil), | CYP2D6 inhibitor | Risperidone (Risperdal), tramadol (Ultram) | CYP2D6 | Increased risk of extrapyramidal adverse effects caused by increased risperidone level[24]; decrease in analgesic effect caused by low level of active metabolite[25] |
| Grapefruit juice | CYP3A4 inhibitor | Buspirone (Buspar) | CYP3A4 | Dizziness and serotonin syndrome caused by increased buspirone level[26] |
| Metronidazole (Flagyl) | CYP2C9 inhibitor | Warfarin | CYP2C9 | Increased risk of bleeding caused by increased warfarin level[27] |
| Terbinafine (Lamisil) | CYP2D6 inhibitor | Amitriptyline | CYP2D6 | Dry mouth, dizziness, and cardiac toxicity caused by prolonged increase in amitriptyline and nortriptyline (Pamelor) levels[28] |

*CYP=cytochrome P.*

*Information from references 19 through 28.*

# Pharmacogenetics and cytochrome P450

It is well understood that administering

## Drug interactions
## Adverse drug reactions (ADRs)
## Clinical practice

REVIEW ARTICLE

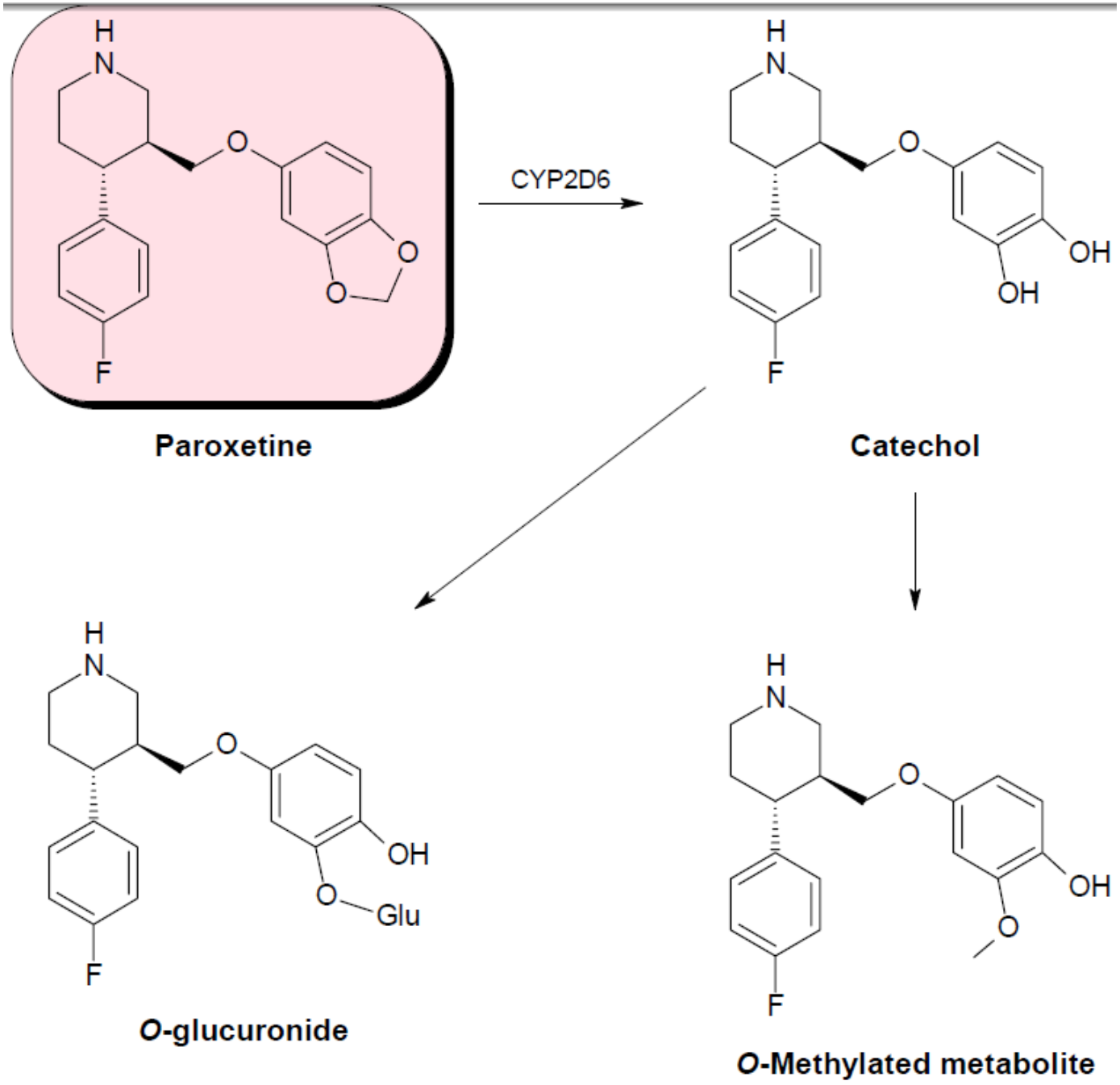
Clin Pharmacokinet 2009; 48 (11): 689-723
0312-5963/09/0011-0689/$49.95/0

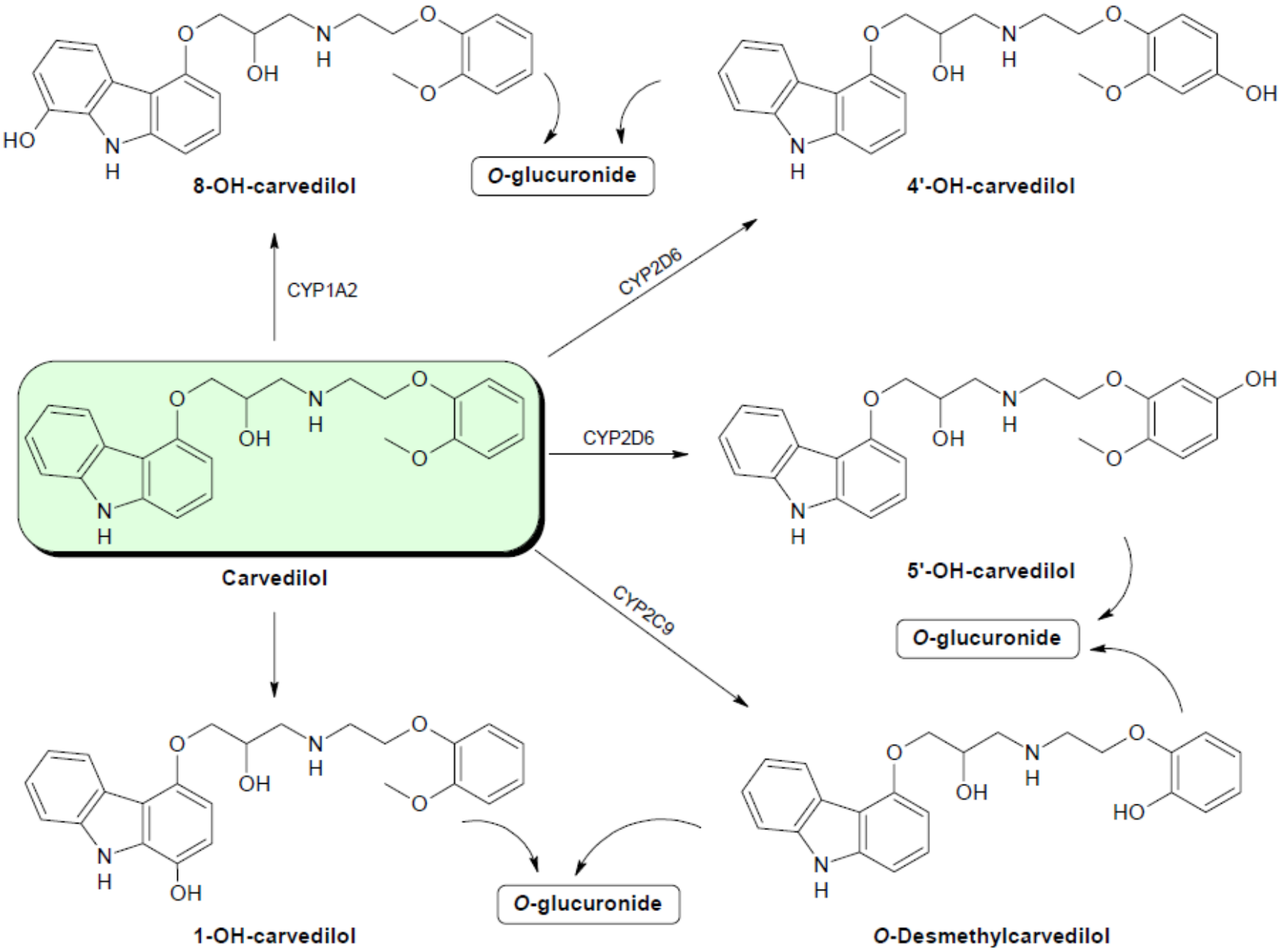


# Polymorphism of Human Cytochrome P450 2D6 and Its Clinical Significance

## Part I

*Shu-Feng Zhou*


H
N
O
O
O
F
CYP2D6
Paroxetine
H
N
O
OH
OH
F
Catechol
H
N
O
OH
O
Glu
F
O-glucuronide
H
N
O
OH
O
F
O-Methylated metabolite


8-OH-carvedilol
O-glucuronide
4'-OH-carvedilol
CYP1A2
CYP2D6
CYP2D6
Carvedilol
5'-OH-carvedilol
CYP2C9
O-glucuronide
1-OH-carvedilol
O-glucuronide
O-Desmethylcarvedilol

Ενσωμάτωση αυτών των γνώσεων στην κλινική πράξη αλλά και στην εκπαίδευση

**Φάρμακα που αλληλεπιδρούν με καρδιαγγειακά φάρμακα στο επίπεδο του μεταβολισμού**

| CYP2D6 | CYP3A4 | CYP2C9 | CYP2C19 |
|---|---|---|---|
| **Υποστρώματα** | | | |
| Προπρανολόλη (*Interal*)<br>Μετοπρολόλη (*Lopresor*)<br>Τιμολόλη (*Nyolol*)<br>Καρβεδιλόλη (*Dilatrend*) | Διλτιαζέμη(*Tildiem*)<br>Βεραπαμίλη (*Isoptin*)<br>Νιφεδιπίνη (*Adalat*) (κ.λ.π. αναστολείς καναλιών $Ca^{++}$)<br>Λοζαρτάνη (*Cozaar*)<br>Κυκλοσπορίνη | Λοζαρτάνη | Προπρανολόλη |
| **Επαγωγείς (ενισχύουν τη δράση του ενζύμου)** | | | |
| Κανένα | Ριφαμπικίνη<br>Αλκοόλη<br>Φαινοβαρβιτάλη (*Gardenal*)<br>Φαινυτοϊνη (*Epanutin*)<br>Καρβαμαζεπίνη (*Tegretol*) | Ριφαμπικίνη<br>Φαινοβαρβιτάλη | |
| **Αναστολείς (μειώνουν τη δράση του ενζύμου)** | | | |
| Κινιδίνη (*Kinidin/Durules*)<br>Φλουοξετίνη(*Fluoxetine/Bio*)<br>Νορφλουξετίνη<br>Παροξετίνη(*Seroxat*)<br>Αμιωδαρόνη<br>Σιμετιδίνη<br>Χλωμιπραμίνη (*Anafranil*)<br>Αλοπεριδόλη (*Aloperidine*)<br>Αρκετά αντι-ϊικά<br>Μιμπεφραδίλη (*Posicor*) | Κετοκοναζόλη<br>Ιτρακοναζόλη<br>Χυμός γκρέϊπφρουτ<br>Σιμετιδίνη<br>Κλαριθρομυκίνη<br>Ερυθρομυκίνη<br>Διλτιαζέμη<br>Βεραπαμίλη<br>Μιμπεφραδίλη | Φλουκοναζόλη<br>Σιμετιδίνη (*Tagamet*)<br>Αμιωδαρόνη (*Angoron*) | Φλουκοναζόλη<br>Φελβαμάτη<br>Ομεπραζόλη*<br>Φλουοξετίνη<br>Τικλοπιδίνη |

*Ομεπραζόλη (Probitor)

Flockhart D.A. & Tanus-Santos J.E.(2002). Arch. Intern. Med. 162: 405-412.

Προσβλέποντας στο μέλλον της φαρμακογονιδιωματικής προσέγγισης για εξατομίκευση των δοσολογικών σχημάτων στην κλινική πράξη

GENOTYPING…
HAPLOTYPING...

PHARMACOTYPING…

ΑΠΟ ΤΟ ΠΑΡΟΝ ΣΤΟ… ΜΕΛΛΟΝ

Στις **22 Αυγούστου 2005** ο Αμερικανικός Οργανισμός Ελέγχου Φαρμάκων και Τροφίμων (FDA) ενέκρινε την κυκλοφορία ενός **φαρμακογενετικού τεστ** που επιτρέπει την κατάλληλη επιλογή της δοσολογίας του φαρμάκου **ιρινοτεκάνη** (Camptosar), βελτιώνοντας έτσι τη φαρμακευτική αγωγή του συγκεκριμένου σκευάσματος. Το συγκεκριμένο τεστ επιτρέπει την ανίχνευση **μιας μετάλλαξης** στο γονίδιο UGT1A1 (UGT1A1*28), η ύπαρξη της οποίας οδηγεί **σε τοξικότητα** κατά τη χορήγηση της **συνηθισμένης δοσολογίας της ιρινοτεκάνης**.

Στις **23 Δεκεμβρίου 2004** ο Αμερικανικός Οργανισμός Ελέγχου Φαρμάκων και Τροφίμων (FDA) ενέκρινε την κυκλοφορία του πρώτου **φαρμακογενετικού τεστ** (*AmpliChip Cytochrome P450 Genotyping Test*) που επιτρέπει με απλό τρόπο, (λήψη αίματος του ασθενή), την ανίχνευση **29 γενετικών πολυμορφισμών στο γονίδιο CYP2D6 και 2 αντίστοιχων μεταλλάξεων στο γονίδιο CYP2C19**. Τα γονίδια αυτά εμπλέκονται στο μεταβολισμό αρκετών φαρμάκων, ενώ η ύπαρξη αυτών των γενετικών πολυμορφισμών οδηγεί σε εμφάνιση ανεπιθύμητων ενεργειών κατά τη λήψη της συνηθισμένης δοσολογίας αυτών των σκευασμάτων. Με τη χρήση του τεστ προσαρμόζεται ανάλογα η δοσολογία και έτσι βελτιώνεται η φαρμακευτική αγωγή.

## Table 2. US FDA or EMEA drug pharmacogenomic labeling: tumoral status*.

| Drug | Gene target | Information | Tumoral phenotype |
|---|---|---|---|
| Erlotinib | *EGFR* | No response<br>Test not required | No tumoral *EGFR* expression |
| Cetuximab | *EGFR* | No response<br>Test required | No tumoral *EGFR* expression |
| Panitumumab | *EGFR* | No response<br>Test required | No tumoral *EGFR* expression |
| Trastuzumab | *HER2* | No response<br>Test required | No tumoral *HER2* expression |
| Tamoxifene | *ER* | No response<br>Test required | No tumoral *ER* expression |
| Anastrozole | *ER* | No response<br>Test required | No tumoral *ER* expression |
| Exemestane | *ER* | No response<br>Test required | No tumoral *ER* expression |
| Letrozole | *ER* | No response<br>Test required | No tumoral *ER* expression |
| Cetuximab | *K-RAS* | No response<br>Test required | Tumoral *K-RAS* mutations |
| Panitumumab | *K-RAS* | No response<br>Test required | Tumoral *K-RAS* mutations |
| Imatinib | *c-Kit* | No response<br>Test required | Absence of activating tumoral *c-Kit* mutations |

**Data taken from* [104,105].
*EMEA: European Medicines Agency.*

**Table 3. Pharmacogenomics risk factors for adverse drug reactio**

| Drug | Gene target | ADR |
|---|---|---|
| Carbamazepine | *HLA-B*1502* | Stevens–Johnson syndrome (Asian) |
| Allopurinol | *HLA-B*5801* | Stevens–Johnson syndrome |
| 6-mercaptopurine | *TMPT* | Neutropenia |
| Abacavir | *HLA-B*5701* | Hypersensitivity |
| Flucloxacillin | *TNF-α -238G/A* | Cholestatic hepatitis |
| Irinotecan (high doses) | *UGT1A1*28* | Severe neutropenia |
| Nevirapine | *HLA-DRB1*0101* | Hypersensitivity |
| Flucloxacillin | *HLA-DRB1-DQB1* | Cholestatic hepatitis |
| Simvastatin | *SLC01B1*5* | Myopathy |
| Nevirapine | *HLA Cw8-B14* | Hypersensitivity |
| Warfarin | *VKORC1* and *CYP2C9* | Oral anticoagulant overdose |
| NSAID | *GSTM1* and *GSTT1* | Cytolytic hepatitis |
| Diclofenac | *UGT2B7*2* | Hepatotoxicity |
| Diclofenac | *ABCC2 C-24T* | Hepatotoxicity |
| Izoniazid | *NAT2* | Cytolytic hepatitis |
| Ximelagatran | *HLA-DRB1*0701* | Cytolytic hepatitis |
| Tacrine | *GSTM1* and *GSTT1* | Cytolytic hepatitis |

*ADR: Adverse drug reaction; NSAID: Nonsteroidal anti-inflammatory drug.*

**Table 1. US FDA or EMEA drug pharmacogenomic labeling: constitutive genetic variants.**

| Drug | Gene target | Information | Outcome |
|---|---|---|---|
| Thioridazine | *CYP2D6* | ADRs: W&P<br>Test not required | QT prolongation, torsades de pointes |
| Codeine | *CYP2D6* | ADRs: W&P<br>Test not required | Apnea among children from breastfeeding mothers |
| Atomoxetine | *CYP2D6* | ADRs: W&P<br>Test not required | Dose reduction for PMs |
| Tamoxifene | *CYP2D6–CYP2C19* | Lower response rate: W&P<br>Test not required | Loss of efficiency among PMs and with CYP2D6 inhibitors |
| Voriconazole | *CYP2C19* | ADRs: W&P<br>Test not required | Hepatotoxicity |
| Warfarin | *CYP2C9* | ADRs: W&P<br>Individualized dosing: W&P<br>Test not required | Risk of bleeding |
| Warfarin | *VKORC1* | ADRs: W&P<br>Individualized dosing: W&P<br>Test not required | Risk of bleeding |
| Irinotecan | *UGT1A1* | ADRs: W&P<br>Individualized dosing<br>Test not required | Diarrhea, neutropenia |
| Azathioprine and 6-mercaptopurine | *TPMT* | ADRs: W&P Individualized dosing<br>Test not required | Neutropenia |
| Capecitabine | *DPD* | ADRs: contraindication<br>Test not required | Orodigestive – neutropenia |
| Maraviroc | *CCR5* | Nonresponse<br>Test required | For CCR5-negative patients |
| Rasburicase | *G6PD* | ADRs: contraindication<br>Test not required | Hemolysis in G6PD-deficient patients |
| Carbamazepine | *HLA-B*1502* | ADRs: W&P<br>Test not required | Severe immunoallergic cutaneous |
| Abacavir | *HLA-B*5701* | ADRs: W&P<br>Test not required | Hypersensitivity reactions |

*W&P section of the summarized product characteristics* [104,105].
*ADR: Adverse drug reaction; EMEA: European Medicines Agency; PM: Poor metabolizer; W&P: Warnings and precautions.*

ΟΛΕΣ ΑΥΤΕΣ ΟΙ ΣΥΓΧΡΟΝΕΣ ΕΞΕΛΙΞΕΙΣ ΠΟΥ ΟΔΗΓΟΥΝ ΤΗ ΦΑΡΜΑΚΕΥΤΙΚΗ ΠΕΡΙΘΑΨΗ ΚΑΙ ΩΣ ΕΚ ΤΟΥΤΟΥ ΠΩΣ ΚΑΘΟΡΙΖΟΥΝ ΚΑΙ ΤΟ ΡΟΛΟ ΤΩΝ ΦΑΡΜΑΚΟΠΟΙΩΝ ΣΤΟ ΣΥΣΤΗΜΑ ΠΕΡΙΘΑΛΨΗΣ;

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**FACULTY:**
***Gerald Gianutsos, PhD, JD***
*Associate Professor of Pharmacology*
*University of Connecticut School of Pharmacy*
*Storrs, Connecticut*

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## GOAL:

To provide pharmacists with an understanding of the diversion and abuse of prescription drugs and the legal issues designed to limit diversion.

## OBJECTIVES:

After completing this activity, participants should be able to:

1. **Describe** the demographics of prescription drug abuse.*
2. **Identify** the dangers associated with the nonmedical use of prescription drugs.*
3. **Recognize** the patient characteristics and techniques that may suggest the possibility of diversion.*
4. **Discuss** the legal risks and responsibilities that arise from the diversion of drugs.*
5. **Implement** strategies to reduce diversion.

*Also applies to pharmacy technicians.

---

Imagine a cocktail of morphine, Demerol (meperidine), codeine, chlorpheniramine, Placidyl (ethchlorvynol), and Valium (diazepam). These and other drugs were found in "significant quantities" in the tissues of Elvis Presley upon his death in 1977 from a suspected drug overdose.[1]

More than 30 years later, the actor Heath Ledger, who was found dead from a drug overdose, had Vicodin (hydrocodone), OxyContin (oxycodone), diazepam, and alprazolam in his bloodstream.[2] What is especially noteworthy in these two high-profile cases was that none of these substances are

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Alberts on Neurology, April 2010

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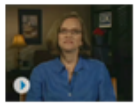
Medscape Psychiatry Minute, April 2010



CDC Commentary: Screening for Autism and Developmental Delays -- Learn the Signs Georgina Peacock, MD, MPH, reminds us that autism spectrum disorder can be diagnosed at 18 months or younger and gives some tips on how to screen for developmental delays.

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Incidentally, I was involved as a consultant in a similar program with the Italian government some years back when the Italian Ministry of Health decided it wanted to make continuing education mandatory for all Italian pharmacists as a condition of license renewal. If I can be of further assistance to you or the association in your venture, please do not hesitate to contact me.

Cordially,

*Harold*

Harold E. Cohen, R.Ph.
*SVP, Publisher & Editor-in-Chief*
*U.S. Pharmacist*

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Κωδικός:

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2 Πόντους

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Ημερομηνία:30/4/2010

Θέμα: Αλληλεπιδράσεις Φαρμάκων (ΦΑ)

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**ΠΕΡΙΛΗΠΤΙΚΗ ΣΥΝΟΨΗ ΤΩΝ ΦΑΡΜΑΚΕΥΤΙΚΩΝ ΑΛΛΗΛΕΠΙΔΡΑΣΕΩΝ.Άρθρο-2**

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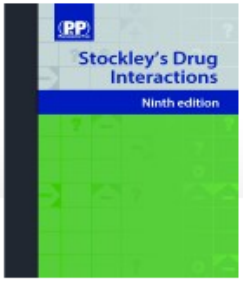

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ΑΡΧΙΚΗ | ΟΡΓΑΝΩΣΗ ΠΡΟΓΡΑΜΜΑΤΩΝ | ΥΛΙΚΟ για ΣΦΕ | ΠΙΣΤΟΠΟΙΗΜΕΝΑ ΣΥΝΕΔΡΙΑ | ΣΥΝΔΕΣΜΟΙ | ΕΠΙΚΟΙΝΩΝΙΑ

Διαδικτυακές διευθύνσεις για έλεγχο αλληλεπιδράσεων φαρμάκων
Διαδικτυακές διευθύνσεις με λίστες των φαρμάκων
Πηγές για τη φαρμακοεπαγρύπνηση στο διαδίκτυο
Διαδικτυακές διευθύνσεις ρυθμιστικών οργανισμών για τα φάρμακα
Διαδυκτυακές διευθύνσεις για φάρμακα και θέματα υγείας στα Ελληνικά
Ασφάλεια Φαρμάκων σε Άτομα με Ανεπάρκεια του Ενζύμου G6PD
Φυτοθεραπευτικά Σκευάσματα και τα Φαρμακευτικά Φυτά

ΣΦΕ Είσοδος

Όνομα:

Κωδικός:

Είσοδος

Καινούριος χρήστης;

ΣΦΕ Τα Νέα στη ΣΦΕ

Διαδικτυακά Προγράμματα Συνεχούς Φαρμακευτικής Επιμόρφωσης στο Διεθνή Χώρο

ΔΙΑΔΙΚΤΥΟ

Μήνυμα του Συλλόγου

**Πηγές για τη φαρμακοεπαγρύπνηση στο διαδίκτυο**

1. **Εθνικός Οργανισμός Φαρμάκων (ΕΟΦ)**

   Διαδικτυακή διεύθυνση: http://www.eof.gr/web/guest/home

   ΕΟΦ- Φαρμακοεπαγρύπνηση: http://www.eof.gr/web/guest/pharmacovigilance

2. **World Health Agency (WHO)**

   Διαδικτυακή διεύθυνση: www.who.int

   *Ασφάλεια ασθενών*: www.who.int/patientsafety/en/

   *WHO Drug Information*: http://www.who.int/medicines/publications/druginformation/en/index.html

   *The International Pharmacopoeia (Ph.Int.)*: http://www.who.int/medicines/publications/pharmacopoeia/overview/en/index.html

3. **Pharmacovigilance in the European Economic Area**

   Διαδικτυακή διεύθυνση: http://eudravigilance.emea.eu.int/human/index.asp

4. **Food and Drug Administration (FDA)**

   Διαδικτυακή διεύθυνση: www.fda.gov

   *Ασφάλεια ασθενών*: www.fda.gov/cder/drug/MedErrors/ (Center for Drug Evaluation & Research-CDER)

   *Εκπαίδευση καταναλωτών*: http://www.fda.gov/cder/consumerinfo/DPAdefault.htm

   *Αναφορά-Καταγραφή-Ανάλυση ιατρικών λαθών*: www.fda.gov/medwatch/

   Φαρμακοεπαγόμενη ηπατοτοξικότητα: http://www.fda.gov/cder/livertox/

**Διαδικτυακές διευθύνσεις για αλληλεπιδράσεις και ανεπιθύμητες ενέργειες των φαρμάκων**

**(Drug interaction and ADRs-Related Educational Web Links)**

1. CDER- Preventable Adverse Drug Reactions: A Focus on Drug Interactions

   http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm

2. The University of Arizona Center for Education and Research on Therapeutics

   http://www.arizonacert.org/

3. The University of Arizona Center for Education and Research on Therapeutics-Educational Toolbox - Drugs that Prolong the QT Interval and/or Induce Torsades de Pointes Ventricular Arrhythmia

   http://www.arizonacert.org/medical-pros/education/index.html

4. Important Drug Interaction Information

   http://www.azcert.org/consumers/interaction-advisory.cfm

**Διαδικτυακά Προγράμματα Συνεχούς Φαρμακευτικής Επιμόρφωσης στο Διεθνή Χώρο**

1. Medscape CME Pharmacists

   http://cme.medscape.com/pharmacists

2. Pharmacy Times CME Programs

   http://www.pharmacytimes.com/

3. U.S. Pharmacist Continuing Education

   http://www.uspharmacist.com/continuing_education/

4. Pharmacist Continuing Education / iMedisearch

   http://www.rphworld.com/pharmacist/links-12-titleA.html

5. The Pharmacists' Learning Assistance Network (P.L.A.N.®) / Continuing Education Programs

   http://www.acpe-accredit.org/pharmacists/programs.asp

6. Education, Pharmacy, Continuing

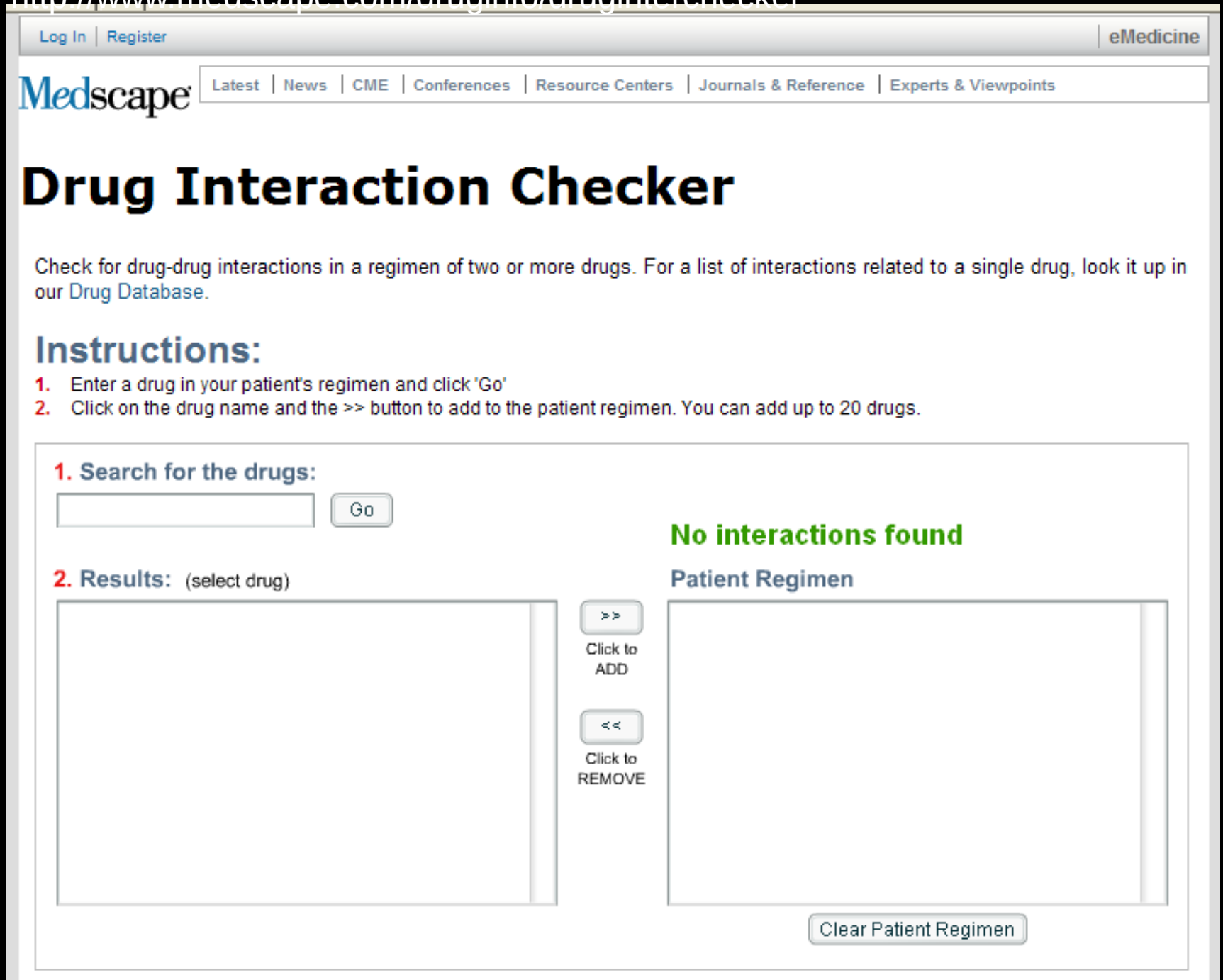
   http://www.intute.ac.uk/healthandlifesciences/cgi-bin/browse.pl?id=95665&gateway=omni

7. The Centre for Pharmacy Postgraduate Education (CPPE)

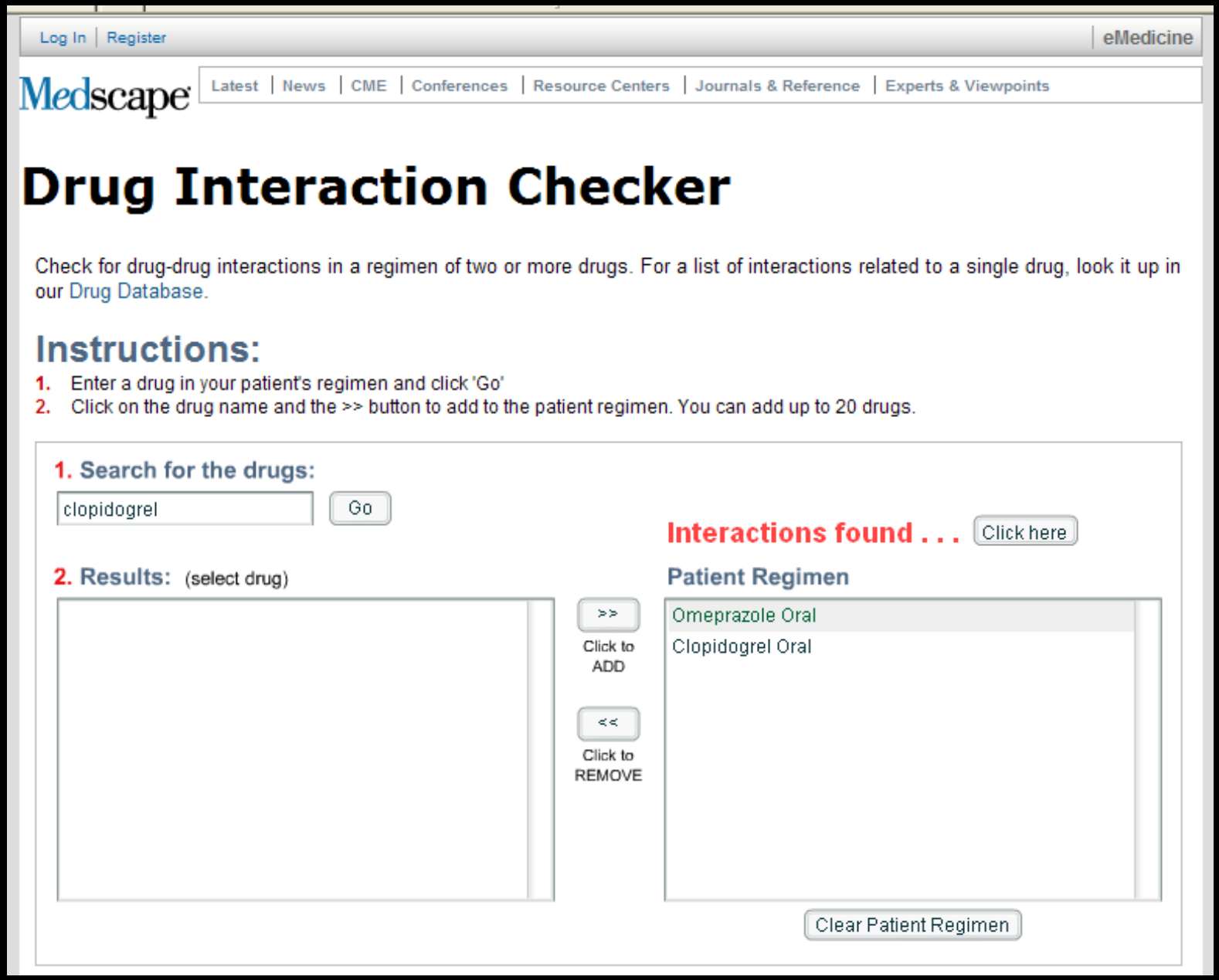
   http://www.cppe.ac.uk/

8. College of Pharmacy Practice (CPP)

http://www.medscape.com/druginfo/druginterchecker



# Συγχορήγηση Κλοπιδογρέλης με ομεπραζόλη



# Multi-Drug Interaction Checker

Print this for your patient

## Patient Regimen

CLOPIDOGREL ORAL
OMEPRAZOLE ORAL

## Interactions

**Severe Interaction**
CLOPIDOGREL/PROTON PUMP INHIBITORS; CIMETIDINE
Clopidogrel Oral and Omeprazole Oral may interact based on the potential interaction between CLOPIDOGREL and PROTON PUMP INHIBITORS; CIMETIDINE.

## Clopidogrel/Proton Pump Inhibitors; Cimetidine

This information is generalized and not intended as specific medical advice. Consult your healthcare professional before taking or discontinuing any drug or commencing any course of treatment.

MONOGRAPH TITLE: Clopidogrel/Proton Pump Inhibitors; Cimetidine

SEVERITY LEVEL: 2-Severe Interaction: Action is required to reduce the risk of severe adverse interaction.

MECHANISM OF ACTION: Some proton pump inhibitors(1-3) and cimetidine(3) may inhibit the metabolism of clopidogrel to its active metabolite by CYP P-450-2C19.

CLINICAL EFFECTS: Concurrent use of proton pump inhibitors(1-3) or cimetidine(3) may result in decreased clopidogrel effectiveness.

PREDISPOSING FACTORS: None determined.

PATIENT MANAGEMENT: The US manufacturer of clopidogrel states that concurrent use of inhibitors of CYP P-450-2C19 such as the proton pump inhibitors and cimetidine should be avoided. Consider the use of other H2 blockers or antacids in patients receiving clopidogrel.(3)

DISCUSSION: In a study in healthy subjects, concurrent omeprazole (20 mg daily) decreased the effects of clopidogrel (75 mg daily) on platelets.(4)

A retrospective review of post-stent patients compared patients who took clopidogrel with a proton pump inhibitor (PPI, n=4521, exact agent not specified) to patients who took clopidogrel without a PPI (9862). Stent patients without a preceding cardiovascular event who took a PPI had a 32.5% incidence of a major cardiovascular event within one year of stent placement compared to a 21.2% incidence in patients not receiving a PPI. Stent patients with a preceding cardiovascular event who took a PPI had a 39.8% incidence of a major cardiovascular event within one year of stent placement compared to a 26.2% incidence in patients not receiving a PPI.(5)

In contrast to this, another retrospective review found that clopidogrel reduced adverse effects after 1 year by similar degrees in patients taking PPIs and those not taking PPIs.(6)

In a study in healthy subjects, lansoprazole tended to lower clopidogrel-induced inhibition of platelet aggregation. In subjects with a high rate of platelet aggregation inhibition following clopidogrel, lansoprazole decreased clopidogrel-induced platelet aggregation inhibition.(7)

In a study in patients with coronary artery disease, esomeprazole and pantoprazole had no effects on platelet response to clopidogrel.(8)

In a retrospective review of 13,636 patients who received clopidogrel following an acute myocardial infarction, concurrent use of a PPI other than pantoprazole (exact PPI not specified) was associated with an increased risk of reinfarction.(9)

A retrospective review of claims data examined patients younger than 65 years of age who were compliant with clopidogrel therapy. Patients were assigned to one of three groups: control (no PPI use), low PPI exposure, or high PPI exposure (based on compliance of PPI therapy, not defined in article). Specific PPIs were not identified. Initial comparisons found rates of myocardial infarction of 1.38% in the control group, 3.08% in the low exposure group, and 5.03% in the high exposure group. When subsets with identical co-morbid conditions was analyzed, myocardial infarction rates were 2.60% (95% CI 1.01-4.19) in the control group, 10% in the low exposure group (95% CI 3.81-16.19), and 11.38% in the high exposure group (95% CI 8.69-14.07) (10).

CI=1.22-1.57), and 29.2% (hazard ratio 1.61, 95% CI=1.41-1.88), respectively. The sample size of rabeprazole was not sufficient to analyze independently.(12)

A post-hoc analysis of the PRINCIPLE-TIMI 44 trial and the TRITON-TIMI trial examined the effects of PPI use on the pharmacodynamic effects and clinical efficacy of clopidogrel. The PRINCIPLE-TIMI 44 trial examined 201 patients undergoing cardiac catheterization with planned percutaneous coronary intervention, 53 of which were taking a PPI at randomization. Patients receiving a PPI had significantly lower rates of inhibition of platelet aggregation at 0.5 hours, 2 hours, 6 hours, and 18-24 hours post-loading dose of clopidogrel. After 15 days of maintenance therapy, there were significantly more non-responders in the group receiving PPI (50% versus 7.9%). The TRITON-TIMI trial examined 13,608 patients who underwent cardiac catheterization with planned percutaneous coronary intervention, 4529 of which were taking a PPI at randomization. Patients received clopidogrel treatment for 6-15 months. There were no significant differences in occurrence of cardiovascular death, non-fatal MI, or non-fatal stroke between patients taking PPIs at randomization and those not; however, use of PPIs was only assessed at randomization and not during the study.(13)

In a cross-over study in 72 healthy subjects, simultaneous administration of omeprazole (80 mg daily) and clopidogrel (300 mg loading dose, followed by 75 mg daily) decreased the AUC of the active metabolite of clopidogrel by 46% following the loading dose and by 42% during maintenance dosing. Clopidogrel-induced inhibition of platelet aggregation was decreased by 47% following the loading dose and by 30% during the maintenance dose. In a cross-over study in 72 healthy subjects, administration of omeprazole (another CYP P-450-2C19 inhibitor, 80 mg daily) 12 hours after clopidogrel (300 mg loading dose, followed by 75 mg daily) produced similar effects.(3)

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4.Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, Mansourati J, Mottier D, Abgrall JF, Boschat J. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol 2008 Jan 22;51(3):256-60.

5.Aubert RE, Epstein RS, Teagarden JR, Xia F, Yao J, Desta Z, Skaar T, Flockhart DA. Abstract 3998: Proton pump inhibitiors effect on clopidogrel effectiveness: the clopidogrel Medco outcomes study. Circulation 2008;118:S815.

6.Dunn SP, Macaulay TE, Brennan DM, Campbell CL, Charnigo RJ, Smyth SS, Berger PB, Steinhubl SR, Topol EJ. Abstract 3999: Baeline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel

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Αποτέλεσμα, εφαρμογή
και υλοποίηση του προγράμματος

Ε Κ Β Α Σ Η

Η αναγκαιότητα υλοποίησης προγραμμάτων συνεχούς φαρμακευτικής εκπαίδευσης είναι πιεστική, παράλληλα με την ενίσχυση της αποτελεσματικότητας και της ασφάλειας της φαρμακευτικής αγωγής στην κλινική πράξη

Εγχειρήματος ?

ΣΥΜΠΕΡΑΣΜΑΤΑ