32nd Annual meeting : American College of Clinical Pharmacology
Exposure-Response (E-R) Relationships - From Research to Clinic: Adjusting Dosage Regimens to Manage Risks
September 21, 2003, Tampa, FL

# Effect of *Pharmacogenetics* and *Drug-Drug Interactions* on Exposure-Response: What Needs to be Done?

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## Examples of Poor or Non-Responders (%)

| | |
|---|---|
| Asthma | 40-75 |
| Cancer | 70-100 |
| Depression | 20-40 |
| Diabetes | 50-75 |
| Duodenal U | 20-70 |
| Hyperlipidemia | 30-75 |
| Hypertension | 10-70 |
| Migraine | 30-60 |
| OA/RA | 20-50 |
| Schizophrenia | 25-75 |

< BM Silber, in "Pharmacogenomics", Ed Kalow/Meyer/Tyndale, Marcell Dekker 2001>

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## Genetics x Environment

NEJM 2003 April 10; 348:1442-1448

- 1/3 patients with resistant epilepsy
- ABCB1 (MDR2) 3435T genotyping
- CC:TT odds ratio 2.66

Science 2003 Jul 18;301:386-9

- 5-HT T gene
- short form with more depressed symptoms… in response to stressful life events

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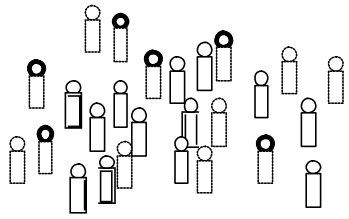
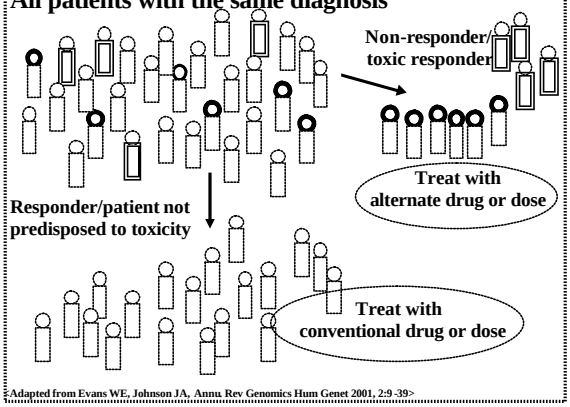
## The Empirical Strategy for Drug Therapy



**Treat all patients with the same diagnosis with the same medications**

Adapted from Evans WE, Johnson JA, Annu. Rev Genomics Hum Genet 2001, 2:9-39>

## All patients with the same diagnosis




Adapted from Evans WE, Johnson JA, Annu. Rev Genomics Hum Genet 2001, 2:9-39>

## *Adverse Drug Reactions: Pharmacogenetics*

- Analysis of 18 ADR studies (1995-2000)
  - 59% of all drugs causing ADRs metabolized by polymorphic enzymes
    - only 5 of 27 have narrow therapeutic indices
  - 7% of other randomly selected drugs from Top 200 are substrates for polymorphic enzymes

< *Phillips KA et al, JAMA;2001;286:2270-2279*>

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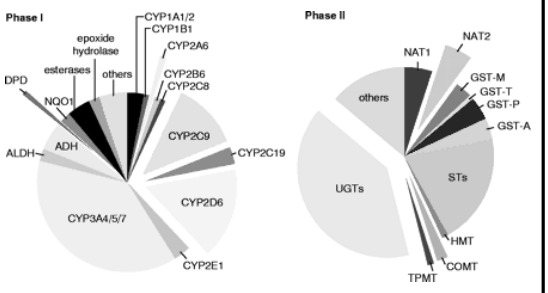
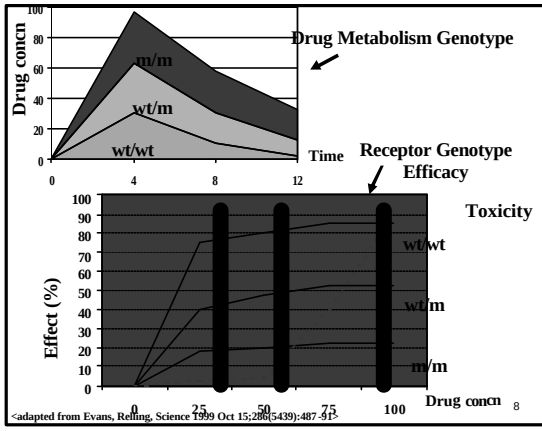
## Contribution of Genetic Polymorphisms to Drug Metabolism




<Evans, Relling, Science 1999 Oct 15;286(5439):487-91>






<adapted from Evans, Relling, Science 1999 Oct 15;286(5439):487-91>

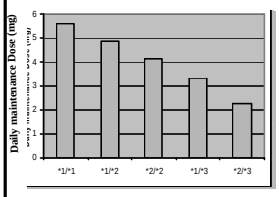


## Metabolism/transporter genotypes



## Marketed Drugs

***CYP2C9***
*Warfrin Study*




***CYP2C19***
*Lansoprazole Study*

- **Gastroesophageal reflux disease (GERD)**

homEM: 45.8%*
**het EM: 67.9%**
**PM: 84.6%**

*** lower with GERD grades C or D**

< Adapted from Higashi MK et al, JAMA 2002; 287:1690>< Furuta et al, Clin Pharmacol Ther, October 2002>



## Marketed Drugs (cont'd)

***CYP3A5/P-gp***
***tacrolimus/cyclosporine*** *(Zheng HX et al)*

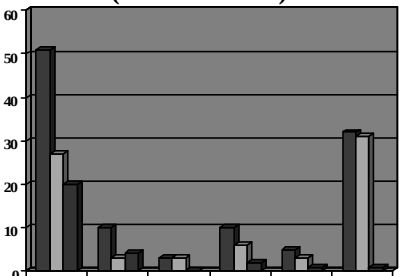
***P-gp/OATP***
***digoxin/fexofenadine/pravastatin***
*(Hoffmeyer et al.; Ameyaw MM; Kim R et al, JohneA et al)*

***UGT1A1***
***irinotecan*** *(Mathijssen RHJ, et al, Iyers, L, et al., )*

***TPMP***
***6-mercaptopurine*** *(Krynetski and Evans)*



## IND/NDA Reviews (70 submissions)



| | 2D6 | 2C19 | 2C9 | 3A | 1A2 | Others |
|---|---|---|---|---|---|---|
| Total | 51 | 10 | 3 | 10 | 5 | 32 |
| Genotyping | 27 | 3 | 3 | 6 | 3 | 31 |
| Phenotyping | 20 | 4 | 0 | 2 | 1 | 1 |

Others: P-gp, transferase & others

<Chou W, Huang, S-M, Sahajwalla C, Lesko, LJ, presented at the ASCPT meeting, April 2003>



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## Applications

- **To stratify the patient groups; population analysis- labeling claims**
- **To explain the variability- post hoc**
- **To determine the genetic basis of adverse events/efficacy**
- **To use enriched populations for efficacy trials**

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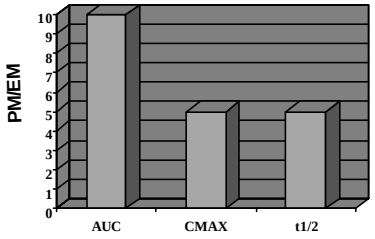
## *CYP2D6*

- **Atomoxetine (Strattera)**
- **Attention-deficit/hyperactivity disorder**




< Atomoxetine (Strattera) labeling, 2002>

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## *Atomoxetine*

| ADR | PM | EM |
|---|---|---|
| decreased appetite | 23% | 16% |
| insomnia | 13% | 7% |
| sedation | 4% | 2% |
| depression | 6% | 2% |
| tremor | 4% | 1% |
| early morning awakening | 3% | 1% |
| pruritus | 2% | 1% |
| mydriasis | 2% | 1% |

< Atomoxetine (Strattera) labeling, 2002>

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- **Laboratory Tests**

- **Poor metabolizers (PM) of CYP2D6.. 10-fold higher AUC**

**Laboratory tests are available to identify CYP2D6 PMs** ***…….higher blood levels in PMs lead to higher rate of some adverse effects of STRATTERA***

**< STRATTERA- Atomoxetine laeling>**

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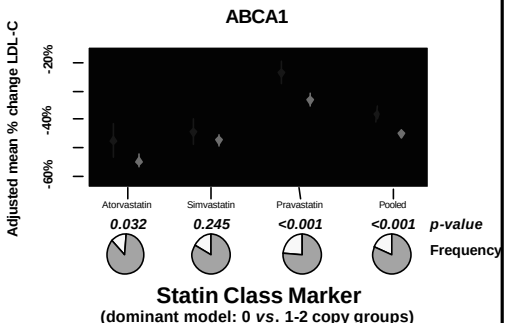
## LDL-C Class-wide HAP™ Marker




< Ruano G , et al, XIV International Symposium on Drugs Affecting Lipid Metabolism, July 12, 2003; abstract in 52nd Annual American College of Cardiology (Scientific Session March 30 - April 2, 2003, Chicago, IL)> >

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## Exposure and gene expression

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- **CDER/FDA pharmacogenetics working group**

  **Lesko*, Huang (OCPB)**

  **Collins, Sistare (OTR), Wang (OB)**

  **Meyer, Pazdur, Williams, Leighton (OND)**

  **Hackett, Mansfield; Essayan; MacGregor (CDRH, CBER, NCTR)**

*** Chair of the working group**

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- **Guidance Development**

  **"Safe Harbor" –(Genomic Data Submission) guidance - Draft by 2003;**

  **Nov 13-14, 2003 BIO/DIA/FDA/PhRMA/PWG workshop; info at www://diahome.org**

  **May 2002 workshop proceedings in Lesko LJ et al, J Clin Pharmacol 43, April 2003**

  **"Pharmacogenetics and pharmacogenomics: clinical and non-clinical studies and in vitro diagnostic tests in marketing applications for human drug products and biologicals" - Draft by 2004**

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## CDER/FDA Perspectives

- **Genomic data will enrich applications**
- **Encourage- while science develops- "safe harbor" presentation to agency**
- **Transparency of regulatory implications**
- **Establishment of an interdisciplinary WG**

**<Lesko and Woodcock, Pharmacogenomics J, 2002>**
**<Galson, S, FDA/Drusafe PhRMA/PWG workshop on pharmacogenetics/pharmacogenomics in drug development and regulatory decision-making; Rockville, MD, May 16, 2002>**
**<Galson, S, Industrial Drug Development Conference, Austin, TX, Feb 25, 2003>**

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## Drug-drug Interactions

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## Post-marketing dosage changes 1980-1999 (n= 499)

- **71% evaluable**
- **21% had dosage changes**
- **79% safety-related reduction**
- **changes included: specific populations and drug interaction sections**

*Cross J, et al, Pharmacoepidemiology Drug Safety, September, 2002*

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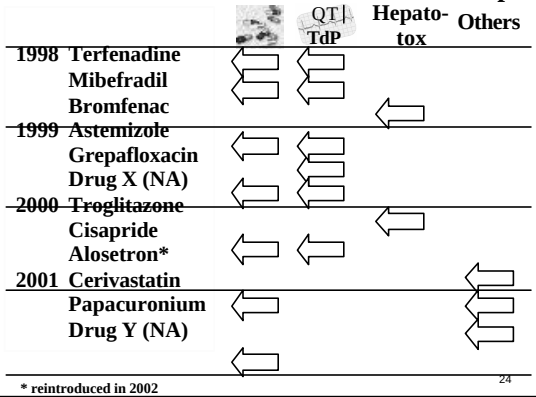
## Recent US Market Withdrawal/NA -Examples




*** reintroduced in 2002**

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## Elderly populations

- **... Patients ..with ACE inhibitors .. with .. hyperkalemia (n = 523) were ~ 20 times more likely to have a... potassium-sparing diuretic in the previous week**
- **...Patients .with digoxin toxicity (n = 1051) were about 12 times more likely to have ... clarithromycin in the previous week...**

*<JAMA, 2003;289 (13):1652 >*

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## Rosuvastatin (Crestor)

| Co-administration | Rosuvastatin AUC | Cmax |
|---|---|---|
| Cyclosporine | 7x | 11x |
| Gemfibrozil | 2x | 2x |

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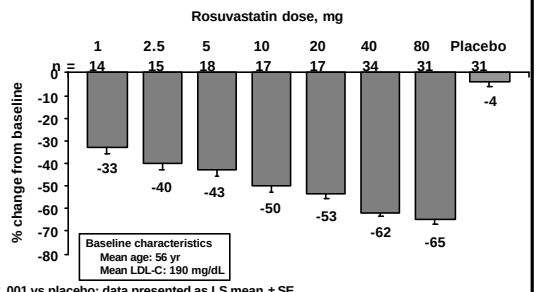
## *LDL-C: % Change From Baseline*

***Rosuvastatin (*Crestor®*) vs Placebo***

***Trials 8 and 23 Pooled (Wk 6)***




*P* < .001 vs placebo; data presented as LS mean ± SE.

**<Crestor® Clinical Development Efficacy, Dr. James Blasetto, MD, MPH, AstraZeneca July 9, 2003>**
**http://cdernet.cder.fda.gov/ACS/index.html**

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## Incidence of CK elevations and myopathy seen in phase II/III

| | (mg) | CK>10xULN | MYOPATHY (all cases) |
|---|---|---|---|
| **Baycol** | 0.4 | 1.6% | 1.0-1.6% |
| | 0.8 | 2.1% | 0.9-1.0% |
| | Pbo | 0% | 0% |
| **Rosuva** | 5 | 0.4% | 0.2% |
| | 10 | 0.2% | 0.1% |
| | 20 | 0.2% | 0.1% |
| | 40 | 0.4% | 0.2% |
| | 80 | 1.9% | 1.0% |
| **All marketed STATINS** [a] | 5-80 | 0.03-0.9% | 0-0.5% |

- **Data from Tables 10, 11 FDA briefing packet[a]**

**<Crestor® William Lubas, MD, PhD, CDER, FDA, Advisory Committee meeting, July 9, 2003>**
**http://cdernet.cder.fda.gov/ACS/index.html**

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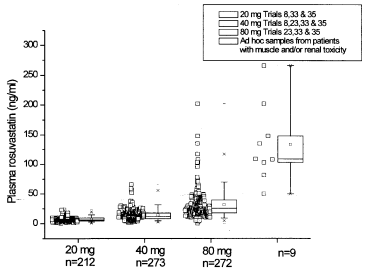
## Plasma rosuvastatin concentrations by dose and in 6 patients with rhabdomyolysis or renal toxicity




**<Crestor® William Lubas, MD, PhD, CDER, FDA, Advisory Committee meeting, July 9, 2003>**
**http://cdernet.cder.fda.gov/ACS/index.html**

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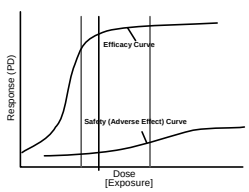
## Dosage and Administration

- **Approved 5-40 mg**
- **5 mg for….taking cyclosporine** ***[7-fold inc]***
- **10 mg for....combination with gemfibrozil** ***[2-fold]***




**<Data from Crestor® approved labeling: http://www.fda.gov/cder/approval/index.htm; 8/14/2003>**

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## Vardenafil (Levitra)
## - CYP3A4/5, 2C9 substrate

| Vardenafil 5mg | Vardanafil AUC | Cmax |
|---|---|---|
| Ritonavir (600 BID) | 49x | 13x |
| Ketoconazole (200 QD) | 10x | 4x |
| Indinavir (800TID) | 16x | 7x |
| Erythromycin (500TID) | 4x | 3x |

<Levitra® approved labeling; http://www.fda.gov/cder/approval/index.htm; 2003>

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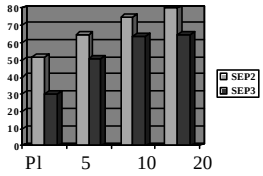
## Exposure-response data

- No-linear pharmacokinetics for >40 mg
- Efficacy data 5, 10, 20 mg
- QT/QTc changes 10, 80 mg




| | uncorrected | Fridericia | Indiv |
|---|---|---|---|
| V 10 mg | -2 | 8 | 4 |
| V 80 mg | -2 | 10 | 6 |
| Moxi 400 | 3 | 8 | 7 |

<Data from Levitra ® approved labeling; http://www.fda.gov/cder/approval/index.htm; 2003>

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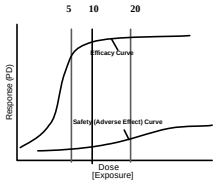
## Dosage and Administration

- Approved starting dose 10 mg (to 20 or 5 mg)
- < 2.5 mg in 72 hr….taking ritonavir *[Cmax 13x]*
- < 2.5 mg daily....taking indinavir, ketoconazole 400mg daily, itraconazole 400 mg daily *[Cmax 7x]*
- < 5 mg daily....taking ketoconazole/itraconazole 200 mg daily, or erythromycin *[Cmax 3-4x]*




<Data from Levitra ® approved labeling; http://www.fda.gov/cder/approval/index.htm; 2003>

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## Pharmacogenetics

## X

## Drug-drug interactions

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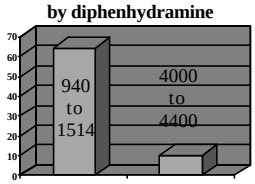
## Drug Interactions: CYP2D6 substrates

**Metoprolol**
**% AUC increase by diphenhydramine**




Hamelin *et al*. Clin Pharmacol Ther 2000;67:466-77

**Atomoxetine**

- *Drug-Drug Interactions:* Dosage adjustment ...in EMs ….. ... with CYP2D6 inhibitors, eg, paroxetine, fluoxetine, and quinidine ….. In vitro studies suggest that ….. P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine

**Tolterodine**

- ketoconazole increased AUC by 2.2 fold in PM

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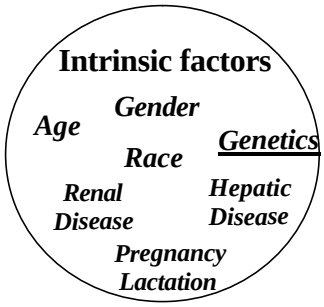
## Extrinsic factors

Drug-drug interaction  Smoking/Diet

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## Conclusion

- **It is critical to evaluate various extrinsic and intrinsic factors that affect the pharmacokinetics and -dynamics of drugs**
- **Quantitative tools are available and continue to be developed to evaluate exposure-response relationship**
- **Improved understanding and development of various in vitro and in vivo tools can aid in assessment and management of drug risks**

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