



Stanford - South Africa

Biomedical Informatics Program



Drug interactions and adverse drug reactions (ADRs)

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Drug Interactions

- Pharmacogenomics can often explain drug interactions.

PK: if metabolic pathways are shared, two drugs may change each other's rates of metabolism (saturate pathway, upregulate pathway, compete for binding)



Drug Interactions

PD: Common target (less likely) or common pathway (more likely) can mean “double hit” to the pathway which may change drug response significantly.

May also hit two parallel pathways, leading to major blockage vs. minor blockage of overall flux through pathway.



Flockhart CYP interactions

(<http://www.druginteractions.com/>)

2C19

Proton Pump Inhibitors:

lansoprazole
omeprazole
pantoprazole
E-3810

Anti-epileptics:

diazepam=>Nor
phenytoin(O)
S-mephenytoin
phenobarbitone

amitriptyline
carisoprodol
citalopram
clomipramine
cyclophosphamide
hexobarbital
imipramine
N-DeME
indomethacin
R-mephobarbital

2C9

NSAIDs:

diclofenac
ibuprofen
meloxicam
S-naproxen=>Nortimolol
piroxicam
suprofen

Oral

Hypoglycemic Agents:
tolbutamide
glipizide

Angiotensin II Blockers:

losartan
irbesartan

Sulfonylureas:

glyburide/
glibenclamide
glipizide

2D6

Beta Blockers:

carvedilol
S-metoprolol
propafenone

Antidepressants:

amitriptyline
clomipramine
desipramine
imipramine
paroxetine

Antipsychotics:

haloperidol
perphenazine
risperidone=>9OH
thioridazine

alprenolol
amphetamine
aripiprazole
atomoxetine



More of same...

proguanil
propranolol
teniposide
R-warfarin=>8-OH
fluoxetine
fluvastatin
glyburide
nateglinide
phenytoin=>4-OH
rosiglitazone
tamoxifen
torsemide
S-warfarin
debrisoquine
dexfenfluramine
dextromethorphan
duloxetine
encainide
flecainide
fluoxetine
fluvoxamine
lidocaine
metoclopramide
methoxyamphetam
mexillettine
minaprine
nebivolol
nortriptyline
ondansetron
perhexiline
phenacetin
phenformin
propranolol
sparteine
tamoxifen
tramadol
venlafaxine



Includes links to literature

2D6 Substrates

alprenolol: [PubMed](#)

Polymorphic drug oxidation in humans.

Eichelbaum M

[Fed Proc 1984 May 15;43\(8\):2298-2302](#)

Competitive inhibition of sparteine oxidation in human liver by beta-adrenoceptor antagonists and other cardiovascular drugs.

Otton SV, Inaba T, Kalow W

[Life Sci 1984 Jan 2;34\(1\):73-80](#)

amitriptyline: [PubMed](#)

Amitriptyline metabolism: association with debrisoquin hydroxylation in nonsmokers.

Mellstrom B, Sawe J, Bertilsson L, Sjoqvist F

[Clin Pharmacol Ther. 1986 Apr; 39\(4\): 369-371](#)

Amitriptyline pharmacokinetics and clinical response: II. Metabolic polymorphism assessed by hydroxylation of debrisoquine and mephenytoin.

Baumann P, Jonzier-Perey M, Koeb L, Kupfer A, Tinguely D, Schopf J

[Int Clin Psychopharmacol. 1986 Apr; 1\(2\): 102-112](#)

amphetamine: [PubMed](#)

The metabolic fate of amphetamine in man and other species.

Dring LG, Smith RL, Williams TR

[Biochem J 1970;425-435](#)

Introduction: human genetic variations in oxidative drug metabolism.

Smith RL

[Xenobiotica 1986;16:361-365](#)



Terminologies for adverse events

- MESH
- SNOMED
- WHO-ART
- ME_dDRA (Medical Dictionary for Regulatory Activities)

Very important for coding and standardization.



Most common major drug ADRs

- QT prolongation (heart problems)
- Liver failure
- Severe dermatological rash

- Many other minor ADRs
 - Minor rash
 - Abdominal discomfort
 - Dry mouth
 - Drowsiness or activation
 - Headache



US FDA AERS

([http://...search Google \"FDA AERS\"](http://...search Google \))

- Adverse Events Reporting System
- 420,000 adverse events reported 2004
 - 90% from manufacturers (electronic or paper)
 - 30% serious (death, disability, hospitalization)
 - Estimate 10% of AERS reported
- FDA generates 600-650 studies/year reviewing events
- There are 40+ FDA evaluators assigned to product classes who do studies, they also followup individual cases.



Data available (publicly!)

1. DEMOyyQq.TXT contains patient demographic
2. DRUGyyQq.TXT contains drug/biologic information
3. REACyyQq.TXT contains all MedDRA terms for event
4. OUTCyyQq.TXT contains patient outcomes for the event
5. RPSRyyQq.TXT contains report sources
6. THERyyQq.TXT contains drug therapy start and end dates
7. INDIyyQq.TXT contains MedDRA terms for the indications for use



Raw Data Files not pretty

```
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4264430 Demographic

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\$WT\$WT_COD\$REPT_DT\$OCCP_COD\$DEATH_D
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B0316252A\$GLAXOSMITHKLINE\$38\$YR\$F\$Y\$\$\$
20040106\$CN\$\$\$\$



4264430 Drugs taken

4264430\$1004494592\$PS\$BUPROPION HCL\$1\$ORAL
4264430\$1004494593\$SS\$ETHANOL\$2\$UNKNOWN
4264430\$1004494594\$C\$FLUOXETINE\$1\$UNKNOWN
4264430\$1004494595\$C\$FLURAZEPAM\$1\$UNKNOWN
4264430\$1004494596\$C\$LORAZEPAM\$1\$UNKNOWN
4264430\$1004494597\$C\$IBUPROFEN\$2\$UNKNOWN
4264430\$1004494598\$C\$ALBUTEROL\$1\$INHALATION

ISR\$DRUG_SEQ\$ROLE_COD\$DRUGNAME\$VAL_VBM\$ROUTE\$DOSE_VB
M\$DECHAL\$RECHAL\$LOT_NUM\$EXP_DT\$NDA_NUM



4264430 Outcome

4264430\$DE\$

DE Death

LT Life-Threatening

HO Hospitalization - Initial or Prolonged

DS Disability

CA Congenital Anomaly

RI Required Intervention to Prevent
Permanent Impairment/Damage

OT Other



4264430 reaction to drugs

4264430\$ALCOHOL POISONING\$

4264430\$COMA\$

4264430\$COMPLETED SUICIDE\$

4264430\$PULMONARY CONGESTION\$

4264430\$PULMONARY OEDEMA\$



4264430 report source

4264430\$CSM\$

FGN	Foreign
SDY	Study
LIT	Literature
CSM	Consumer
HP	Health Professional
UF	User Facility
CR	Company Representative
DT	Distributor
OTH	Other



4264430 Indications for use

- NO DATA FOR THIS CASE

- OTHER CASES:

4270153\$1004519893\$IILL-DEFINED DISORDER

4270171\$1004519925\$EX-SMOKER

4280108\$1004562380\$PULMONARY TUBERCULOSIS

4280202\$1004562721\$SMOKING CESSATION THERAPY

4280525\$1004563796\$OESOPHAGEAL CARCINOMA

4281601\$1004567517\$PULMONARY TUBERCULOSIS

4305706\$1004657419\$TONGUE NEOPLASM MALIGNANT STAGE UNSP.

4315801\$1004696076\$OVARIAN CANCER

4328626\$1004751505\$PROSTATE CANCER

4328627\$1004751507\$BREAST CANCER



4264430 Duration of use

No data for this case

ISR\$DRUG_SEQ\$START_DT\$END_DT\$DUR\$DUR_COD

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4280202\$1004562726\$20031222\$\$\$\$
4280525\$1004563796\$20021002\$\$\$\$





PRESCRIPTIONS *Go Personal*

