Pharmacogenomics

Matthew Taylor MD PhD
matthew.taylor@ucdenver.edu
Pills That Increase Your Intelligence

By Donald G. Cooley

Can you feed your brain some special food to make it smarter? Scientists have always laughed at the idea. Now they aren't quite so cocksure. Maybe your brain does have faster speed and quicker get-away when it runs on certain fuels. New scientific discoveries indicate that brain power can be stepped up by swallowing little white pills, a dozen you eat every day. Let's look into the strange story of one particular brain. It wasn't a very good brain. In fact, it belonged to a fourteen-year-old imbecile boy who had an intelligence quotient of 42 (the average I. Q. is 100). Every year the boy grew twelve months older, but his mental age increased only four and a half months. He kept running an intelligence deficit. Then he was fed little white pills, a dozen...
Variety is the Spice of Life
Current Model: ~One-Size-Fits-All Pharmacology

Patients with Disease

MD prescribes medication

Some benefit, some (many) do not, medication stopped in those who survive their adverse events

Fueled by trial and error
Definitions

• **Pharmacogenetics:**
  – the study of differences in drug response due to allelic variation in genes affecting drug metabolism, efficacy, and toxicity
  – Variable response due to individual gene(s)

• **Pharmacogenomics:**
  – the genomic approach to pharmacogenetics, is concerned with the assessment of common genetic variants in the aggregate for their impact on the outcome of drug therapy.
  – Variable response due to multiple loci across the genome
How might genes affect the prescriptions doctors write?
Pharmacogenetics Case

• Full-term 7-day-old male infant → difficulty feeding and lethargy

• Mother c/o episiotomy pain → MD prescribes codeine/paracetamol (30mg/500mg) 2 bid → constipation + somnolence → 1 bid

• Day 12: infant has ↓ appetite + grey skin

Koren, et al Lancet 2006; 368: 704
Codeine Metabolism

Codeine (ProDrug)

- CYP2D6: 10%
  - Codeine
  - CYP2D6
  - 10%

- CYP3A4: 80%
  - Codeine
  - CYP3A4
  - 80%

- Codeine Metabolism:
  - Glucuronide
  - Norcodeine
  - Morphine

- ACTIVE
- INACTIVE
Breast Milk → Gene Drug Interaction

- Morphine
  - 70 ng/mL (nl 0-12)
- Genotype CYP2D6
  - CYP 2D6*2A // CYP 2D6*2A×2

Breast Milk → fatal morphine overdose

**Codeine** (ProDrug) → CYP2D6 → Morphine (normal levels)

Morphine (ACTIVE) → CYP2D6
Adverse Drug Reactions

Incidence of Adverse Drug Reactions in Hospitalized Patients

A Meta-analysis of Prospective Studies

Jason Lazarou, MSc; Bruce H. Pomeranz, MD, PhD; Paul N. Corey, PhD

Objective.—To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients.

Data Sources.—Four electronic databases were searched from 1966 to 1996.

Study Selection.—Of 153, we selected 39 prospective studies from US hospitals.

METHODS

Definitions

One step we took to reduce heterogeneity was to exclude any data that did not use the following specific definitions:

Table 4.—Estimated Number of Hospital Patients in 1994 With ADRs, in Thousands (95% CI)*†

<table>
<thead>
<tr>
<th></th>
<th>ADRIn</th>
<th>ADRAd</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>All severities</td>
<td>3607 (2618-4596)</td>
<td>1547 (1033-2060)†</td>
<td>4986 (3976-5995)</td>
</tr>
<tr>
<td>Serious</td>
<td>702 (635-770)</td>
<td>1547 (1033-2060)</td>
<td>2216 (1721-2711)</td>
</tr>
<tr>
<td>Fatal</td>
<td>63 (41-85)</td>
<td>43 (15-71)</td>
<td>106 (76-137)§</td>
</tr>
</tbody>
</table>

*ADR indicates adverse drug reaction; CI, confidence interval; ADRIn, an ADR occurring in patients while in the hospital; and ADRAd, an ADR causing admission to the hospital.
†Based on 33 125 492 US admissions in 1994: estimates use values from Table 3 (eg, for all severities ADRIn: 33 125 492 × 0.1089 = 3 607 000 patients with an ADR).
‡By definition all ADRAds are serious, hence there are no data for nonserious ADRs in this category.
§From these numbers, we estimated that ADRs were the fourth to sixth leading cause of death in the United States.
Principles of Drug Therapy

Physician Prescribes a Medication $\rightarrow$ Something Good Happens

A $\rightarrow$ B

- MD Prescribes Medication $\rightarrow$ Something (good) Happens
- Medication Prescribed $\rightarrow$ Biological Effect
Realities of Drug Therapy

Physician Prescribes a Medication → Anything goes

A → B

MD Prescribes Medication

Pt Takes Drug

Pt Doesn’t Take Drug

No Effect

+ Effect

Side Effect

No Effect

+ and Side Effect

Side Effect

No Effect

+ / - Effect

Drug – Drug Interaction

Prescription Changes

Diagnoses Changes

Medication Prescribed → Medication Taken → Biological Effect
**Realities of Drug Biology**

Physician Prescribes a Medication ➔ Anything goes

A ➔ B

**Pharmacokinetics:** Relationship between drug dose and [drug]; absorption, distribution, delivery, removal (phase I and II reactions)

**Pharmacodynamics:** Relationship between drug concentrations and ‘drug effects’; interaction with drug targets (cells, receptors, enzymes); interactions with other drugs / biological compounds

Disease / Med List Changes ➔ Biological Effect ➔ Medication Absorbed ➔ Medication Taken ➔ Medication Prescribed

(C D E F X Y Z #%)
Most major drugs are effective in only 25 to 60 percent of patients.

Wilkinson. NEJM 2005;352: 2211-21

Response Rate (Drug Efficacy) for Various Conditions

Physicians’ Desk Reference, 54th Edn., 2000
The CYP450 Complex

- Gene products active in liver and intestinal epithelium
- 3 main families (CYP1, CYP2, CYP3)
  - 6 main genes (CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) → Phase I for ~90% of common drugs
- CYP3A4 → ~40% of all common drugs
  - Less genetic variation in CYP3A4 than other CYPs

- Important Point:
  - Most CYPs function to inactivate drugs, but rarely are needed for activation
  - CYP2D6: codeine → morphine is classic example
Phenotypes and Genotypes

Ethnic Variation Exists in Genotypes and Phenotypes

Expected Mutations*
- Frameshift
- Splicing
- Nonsense
- Missense (some)

* Based on assumption that gene in question is responsible for drug inactivation/elimination

Expected Mutations*
- Increased copy number
- Missense (some)
Nortriptyline Metabolism

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.
Acute lymphoblastic leukemia of childhood

Azathioprine

6-Mercaptopurine

Cures ALL

Myelosuppression

Thiopurine-S-methyltransferase (TPMT) activity ~0.5%

Increasing TMPT Activity →

Percent of population

≈Toxic metabolite elimination by TPMT

Standard AZ or 6MP doses to TMPT$^L$/TMPT$^L$ → fatal myelosuppression; (10% of dose needed)

It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter.

— FDA-approved labeling for warfarin (Coumadin) NDA 9-218/5-105
"If it were not for the great variability among individuals medicine might as well be a science and not an art."

– William Osler 1892
Genomic Model: Pharmacogenetic Stratification

MD genotypes her patients

Patients with Disease

Give Drug  High Dose  Low Dose  Alternate Drug
Pharmacogenetics and genomics

- Application of multiple genome wide markers (genetic, RNA, epigenetic, other biomarkers, etc.) to impact therapy
cDNA Microarray for Prognosis
Gene Expression Profiling, Rosenwald NEJM 2002

Diffuse Large-B-cell Lymphoma

Common cause of adult lymphoma

Chemo. cures in range of 35-40%

Prognostic Predictors: Age, ECOG performance status, tumor stage, LDH level, extent of extranodal disease → International Performance Index (IPI)

Can differences in gene expression add to the prognostic information provided by IPI?
Objectives: Pharmacogenetics

• At the conclusion of this lecture you should be able to:
  – Define pharmacogenetics and pharmacogenomics
  – Explain the two major elements of response to drugs, pharmacokinetics and pharmacodynamics,
  – Describe the central role of the CYP450 enzyme system in drug metabolism
  – Understand key specific pharmacogenetic examples
  – Appreciate the truism of the axiom *Variety is the spice of life!*

Matthew.taylor@ucdenver.edu