Case Studies in Pharmacogenetics

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Agenda

- Case studies
- Review considerations

Case Studies

Drug	Gene	Key Issue	Timing
Efavirenz	CYP2B6	Safety	Post-approval*
Atomoxetine	CYP2D6	Safety	**Pre-approval**
Valproate (VPA)	**POLG**	Safety	Post-approval
Clopidogrel	CYP2C19	**Efficacy**	Post-approval†

* After adult approval but before pediatric approval

† No approved uses in children

Efavirenz-CYP2B6 Interaction

- **Indication(s):** Combination with other antiretroviral agents for the treatment of HIV type 1 infection in adults and in pediatric patients at least 3 months old and weighing at least 3.5 kg

- **Mechanism(s):** Non-nucleoside reverse transcriptase inhibitor

- **Major warnings:** Hypersensitivity, DDI, QT prolongation, neuro-psychiatric events (including convulsion), hepatotoxicity, rash

Efavirenz-CYP2B6 Interaction

- CYP3A and CYP2B6 are the major isozymes responsible for efavirenz metabolism; evidence for auto-induction
- Common reduced or loss-of-function alleles include Q172H/K262R (*6), I328T (*18); about 6-12% of white, 14-38% of black/AA, and 1-4% of Asian individuals are poor metabolizers
- Relative to normal metabolizers, CYP2B6 poor metabolism has been shown to result in:
  - Higher concentrations (~2-fold higher AUC)
  - Higher virologic suppression and immunologic response, lower rates of failure (not consistently)
  - Marginally higher rates of hepatic and CNS adverse events

Efavirenz-CYP2B6 Interaction

Key Issues and Challenges

- Uncertain effect of genotype on clinical benefits and adult adverse events; CNS-related toxicities appear to resolve with continued dosing
- Balance between reducing adverse event risk and maintaining antiviral efficacy through dose adjustments, including the low barrier to resistance
- Guidelines recommend that for children above 3 years of age the dose should be weight-based, and for selected children under 3 years of age who require treatment with efavirenz, CYP2B6 genotype should be assessed and doses adjusted to prevent toxicity

Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.

Efavirenz-CYP2B6 Interaction

Labeling

- Clinical Pharmacology
  - The mean Cmax of efavirenz in subjects with CYP2B6 *6/*6 genotype…was 2.25-fold the mean Cmax observed in subjects with CYP2B6 *1/*1 genotype
  - A positive relationship between efavirenz concentration and QTc prolongation was observed

Valproate-POLG Interaction

- **Indication(s):** Complex partial seizures (10 years and above), simple and complex absence seizures (above 10 kg); migraine prophylaxis, manic episodes in bipolar disorder

- **Mechanism(s):** Mechanism not established, may be related to increased brain concentrations of GABA

- **Major warnings:** Hepatotoxicity, birth defects, pancreatitis, suicidal behavior/ideation, bleeding/hematopoietic disorders, hyperammonemia/hyperammonemic encephalopathy, hypothermia, multiorgan hypersensitivity/drug reaction with eosinophilic and systemic symptoms, somnolence
  - Valproate-induced liver failure (VILF) is a severe, potentially fatal adverse event; 1/10,000 in general population, 1/500 under 2 years of age

Includes valproic acid products such as divalproex

Valproate-POLG Interaction

- POLG replicates mtDNA; mutations result in a range of disorders from fatal encephalopathy to organ-specific disorders in adults (e.g., migraine)
  - Frequently manifests as treatment-refractory epilepsy in infants; sometimes associated with hepatic dysfunction
- FDA reviewed published literature and FAERS reports for VILF, natural history of POLG and other mitochondrial disorders
  - VPA resulted in liver failure in 61 of 65 patients with POLG-related disorder; estimated 20-40% develop hepatopathy in the absence of VPA
  - VPA resulted in hepatotoxicity in 3 of 26 patients with non-POLG disorders (e.g., MELAS, MERRF)
- Over 200 POLG mutations have been reported
  - 2/3 of cases with VILF have at least one copy of either A467T or W748S
  - Carriage of POLG mutations otherwise present in <1% of the population

Valproate-POLG Interaction

Key Issues and Challenges

- Evidence derived from published and reported case reports or case series without systematic capture of drug exposure or hepatic pathology
- POLG mutations result in a wide spectrum of mitochondrial disorders that are of variable penetrance and age-dependent
- Detecting clinically-suspected mitochondrial disease to permit genotype screening is based on a constellation of clinical factors
- Screening certain alleles captures most but not all at-risk individuals
- Unclear impact of more common variations (i.e., E1143G, Q1236H) and predictive utility in older children and adults

Valproate-POLG Interaction

Labeling

- Boxed Warning
  - Life-threatening adverse reactions…Hepatotoxicity…Children under the age of two years and patients with mitochondrial disorders are at higher risk
- Contraindications
  - Known mitochondrial disorders caused by mutations in mitochondrial DNA Polymerase γ (POLG)
  - Suspected POLG-related disorder in children under 2 years of age
- Warnings and Precautions
  - Reports of severe hepatotoxicity in children and adolescents
  - Characteristics of clinical presentation of POLG-related disorders
  - Screen per clinical practice; common culprits are A467T and W748S
  - Closely monitor liver function in children over 2 years of age

Atomoxetine-CYP2D6 Interaction

- **Indication(s):** Treatment of Attention-Deficit/Hyperactivity Disorder

- **Mechanism(s):** Selective norepinephrine reuptake inhibitor

- **Major warnings:** Suicidal ideation, liver injury, cardiovascular events, hemodynamic effects, psychosis/mania, bipolar disorder, aggressive behavior/hostility, allergic reactions, urinary hesitancy/retention, priapism, CYP2D6 drug- and gene-interaction

Atomoxetine-CYP2D6 Interaction

- Primary route of atomoxetine elimination is CYP2D6 metabolism
- Numerous alleles result reduce or abolish function, duplications can increase metabolic capacity; about 5-10% of white, 2-5% of black/AA, and <1% of Asian individuals are poor metabolizers
- Relative to normal metabolizers, CYP2D6 poor metabolism has been shown to result in:
  - Higher concentrations (10-fold higher AUC, 5-fold higher C_{max}, ~5-fold increase in $t_{1/2}$)
  - Higher rates of adverse events (insomnia 11% vs. 6%, weight loss 7% vs. 4%, constipation 7% vs. 4%, depression 7% vs. 4%, tremor 5% vs. 1%)

Atomoxetine-CYP2D6 Interaction

Key Issues and Challenges

- Evidence from pre-market clinical trial experience identified substantial differences in PK and consistently higher rates of adverse events in CYP2D6 poor metabolizers
- Multiple strengths are available and drug is titrated to a target dose; escalation from lowest starting dose in *known* PMs depends on persistence of symptoms and tolerability
- Prescribing recommendations for genotype are analogous to drug-drug interactions with CYP2D6 inhibitors
- PK and safety findings stratified by CYP2D6 phenotype throughout labeling

Atomoxetine-CYP2D6 Interaction

Labeling

- Dosage and Administration
  - Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 poor metabolizers
- Warnings and Precautions
  - Effects on blood pressure, heart rate, PK by CYP2D6 metabolizer status
  - Ethnic distribution of poor metabolizer phenotype
  - Laboratory tests are available to identify CYP2D6 poor metabolizers; dosage adjustment may be necessary
- Adverse Reactions
  - All AE rates stratified by metabolic status
- Use in Specific Populations
  - Notes no ethnic differences, but PMs are more common in Caucasians
- Clinical Pharmacology
  - All PK particulars stratified by CYP2D6 metabolizer status

Clopidogrel-CYP2C19 Interaction

- **Indication(s):** Acute coronary syndrome; recent MI, recent stroke, established peripheral artery disease
- **Mechanism(s):** P2Y12 inhibition of platelet aggregation
- **Major warnings:** Impaired CYP2C19 function, bleeding, increased risk of CV events with temporary discontinuation, thrombotic thrombocytopenic purpura, hypersensitivity (cross-reactivity)

Clopidogrel-CYP2C19 Interaction

- Clopidogrel is a prodrug activated by multiple CYP450 enzymes, including CYP2C19; esterases eliminate most of the parent
- Common loss-of-function alleles include I331V (*2) and W212X (*3); about 2% of white, 4% of black/AA, and 15% of (Southeast) Asian individuals are poor metabolizers
- Relative to normal metabolizers, CYP2C19 poor metabolism has been shown to result in:
  - Lower active metabolite C_{max} (~60% lower)
  - Lower antiplatelet activity (variable difference across assays)
  - Higher rates of cardiovascular events (~3-fold higher for stent thrombosis [among intermediate and poor vs. normal])

Clopidogrel-CYP2C19 Interaction

Key Issues and Challenges

- Evidence from published and sponsor-conducted PK/PD studies demonstrated a gene-drug interaction across multiple measures of exposure and response
- Outcomes data from published studies (retrospective observational cohorts and clinical trial substudies) supported presence of interaction
- Active metabolite is difficult to measure and was not well-characterized; pharmacodynamic measures have unclear relationship with clinical outcomes and are variable
- Altered dosing does not appear to compensate for reduced exposure; alternative treatment options became available
- Treatment context is often acute (in adults) making test turnaround important; many approaches to implement testing

Clopidogrel-CYP2C19 Interaction

- Boxed Warning
  - Diminished antiplatelet effect in patients with two loss of function alleles of the CYP2C19 gene
  - Less of the active metabolite and so reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of CYP2C19
  - Tests are available; consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.
- Warnings and Precautions
  - Diminished antiplatelet activity in patients with impaired CYP2C19 function; metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19; drug interactions analogous
- Clinical Pharmacology
  - Pharmacogenomics: Ethnic distribution, tests are available, PK/PD trial results

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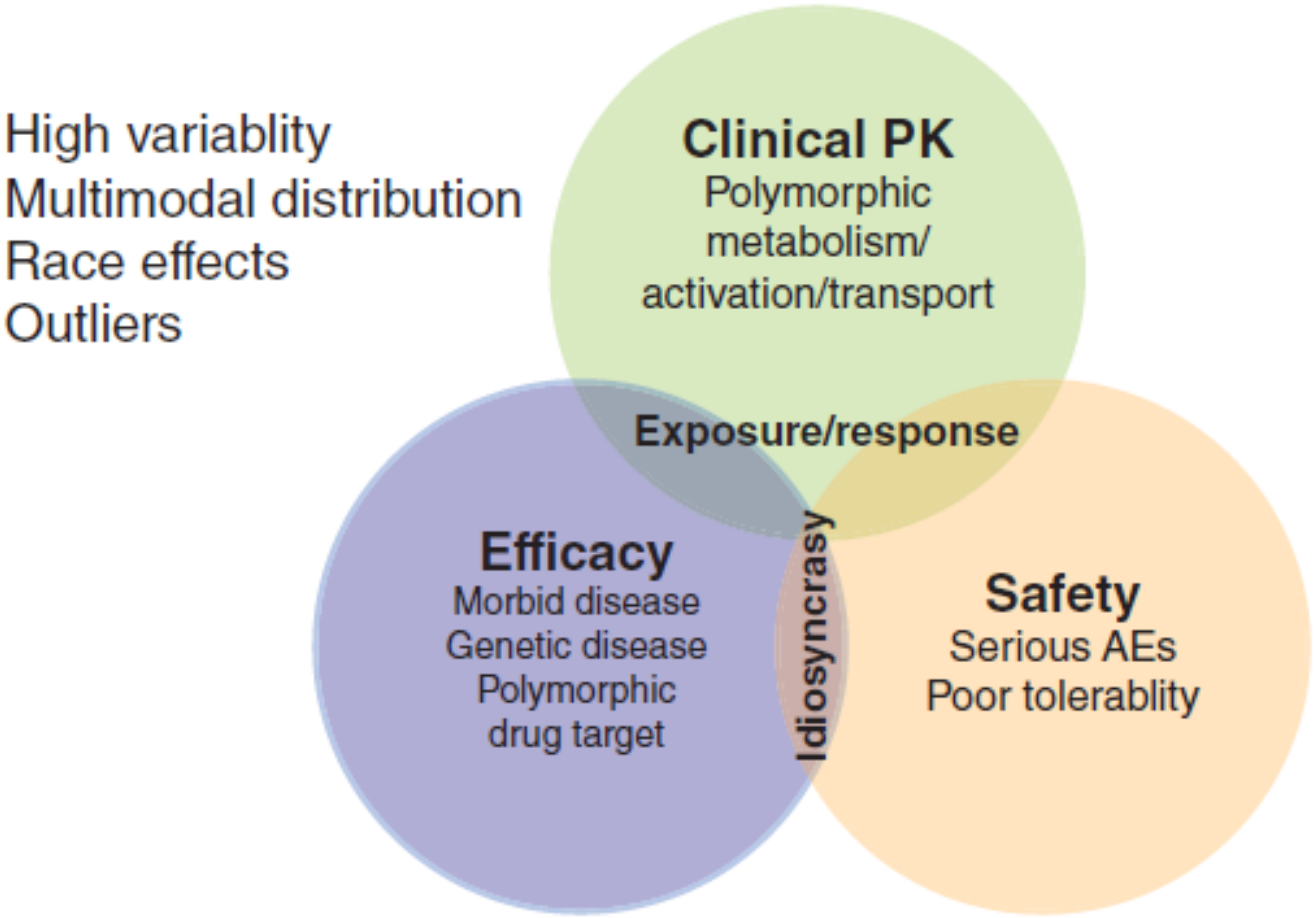
Review Considerations

Signals Prompting Investigation of Gene-Drug Interactions



PMID: 24548989

Experience to Date with Labeling Gene-Drug Interactions

- Data emerge mostly in post-marketing setting, often external to sponsor's clinical trials
- Clinical events are usually severe and gene-drug interaction is highly replicated with significant increase in relative risk
- Many gene-drug interactions are extensions of known clinical pharmacology (e.g., drug interactions)
- Prospective validation trials are exceptional; totality of evidence must be considered (PK-PD-outcome)

Considerations for Establishing the Clinical Validity of a Gene-Drug Interaction

- Sources
  - Sponsor-conducted trials
  - Published literature
- Types of evidence (suitable for…)
  - Case reports/series (severe toxicity, outliers)
  - Retrospective case-control studies (severe toxicity, outliers)
  - Pro/retrospective cohort studies (efficacy, safety, PK)
  - Enriched/stratified experimental studies (PK, efficacy, safety)
- Causal inference
  - Mechanistic information/biological plausibility
  - Consistency across studies, populations, designs
  - Gene-dose response, concentration-response (e.g., for PK-related issues)
  - Magnitude of interaction and statistical significance

Factors Guiding the Strength of Prescribing Recommendations

- Points of uncertainty
  - Effectiveness of genotyping to optimize benefit/risk (utility)
  - Quality of studies to establish validity (design, assay, statistics)
  - Gaps in empirical evidence (e.g., inference from PK-outcome relationship vs. direct subgroup analysis of outcomes)
  - Generalizability to diverse racial/ethnic populations
- Considerations
  - Severity of the outcome
  - Treatment context (benefit/risk of alternative treatments, clinical monitoring tools, dosage forms)
  - Clinical performance attributes in the context of event rate
  - Test accessibility and feasibility, likelihood of prescriber uptake

Approaches to Incorporate Genetic Testing Recommendations

- Labeling is often silent on testing recommendations
  - Reference to '*known status*' and '*consider*' accommodates clinical judgment, uncertainty
  - Implicit that testing is essential when included in *Indications and Usage* or *Contraindications*
- When recommended, various approaches have been used
  - Test everyone (eliglustat, abacavir)
  - Test a targeted, at-risk subset (carbamazepine, valproic acid)
  - Test above a certain dose threshold (pimozide, tetrabenazine)
- Other considerations
  - Specific alleles are generally referenced except for CYP2D6 and NAT
  - Population prevalence is not uniformly described

Summary

- Goal is to improve health by identifying patients at risk for outcomes that skew benefit/risk through diagnostic testing
- Case examples illustrate that:
  - proactively characterizing and managing gene-drug interaction liabilities is feasible for outcomes and genetic factors that are common
  - rare events may have a clear genetic etiology, but rarity complicates assessment of validity and utility
- Prescribing recommendations balance uncertainty with the information that is needed to inform prescribers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