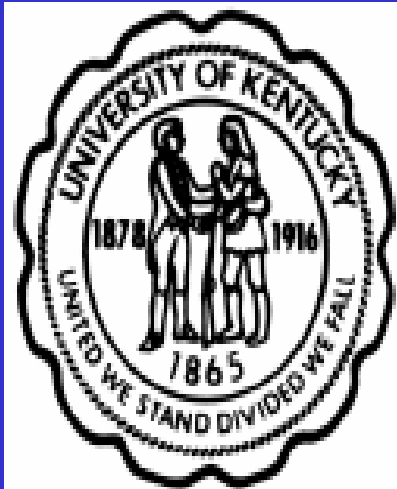


Pharmacogenomics Case
Studies in
Psychiatry/Neurology
Jose de Leon, MD

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Disclosure

In the past three years, Dr. de Leon has

1. been on the advisory boards of Bristol-Myers Squibb and Roche Molecular Systems;
2. received researcher-initiated grants from Eli Lilly and Roche Molecular Systems, Inc.;
3. lectured supported by Eli Lilly (once), Bristol-Myers Squibb (once), Janssen (twice) and by Roche Molecular Systems (six times).

Educational Objectives

At the conclusion of this presentation, the participant should:

1. Start to appreciate the role of genotyping for cytochrome P450 (CYP) poor metabolizers (PMs) in the clinical environment.
2. Start to appreciate the role of genotyping for CYP ultrarapid metabolizers (UMs) in the clinical environment.

0. Basic CYP pharmacology principles

0. Basic CYP pharmacology principles

0.1. Metabolized drugs

0.2. Pro-drugs (activated)

0.1. Metabolized drugs: Hypothesis

- Narrow therapeutic window drugs:
 - PMs have increased risk of adverse drug reactions (ADRs).
 - CYP2D6 PMs: ADRS on TCAs, typical antipsychotics and risperidone.
- Wide therapeutic window drugs:
 - UMs have increased risk of lack of response.
 - CYP2C19 EMs with two alleles: omeprazole.
 - CYP2C19 EMs with two alleles: citalopram.
 - CYP2D6 EMs with two alleles: atomoxetine.

0.2. Pro-drugs

■ Tamoxifen:

- CYP2D6 PMs do not respond.

■ Codeine-like drugs:

- Codeine, oxycodone, hydrocodone and possibly tramadol are pro-drugs (activated by CYP2D6).
- Codeine is transformed to morphine by CYP2D6 and morphine is the analgesic.
- CYP2D6 PMs lack analgesic response to codeine.
- CYP2C19 UMs may develop intoxication with these drugs.

1. Case Studies

1.1. Case Study 1

Case 1

(CNS Spectrums 11:757-60, 2006)

50-year-old Caucasian female nurse with depressive disorder with psychotic features:

- Her depressive disorder started at age 45.

Case 1

(CNS Spectrums 11:757-60, 2006)

- First admission reported:
 - She discontinued venlafaxine due to drowsiness and nausea.
 - She discontinued amitriptyline due to balance problems when walking.
 - She discontinued paroxetine; she did not report ADRs.
 - Her psychiatrist discontinued sertraline; she did not report ADRs.

Case 1

(CNS Spectrums 11:757-60, 2006)

- Treatment during first admission (3 days):
 - At admission: escitalopram (10 mg/d) and quetiapine (100 mg/day)
 - At discharge: escitalopram (10 mg/d) and trazadone (50 mg at night)
 - No trazadone given at hospital

Case 1 (*CNS Spectrums* 11:757-60, 2006)

- Treatment during second admission (14 months later; lasted 7 days):
 - At admission: escitalopram (10 mg/d) in spite of feeling sedated
 - Escitalopram was discontinued due to sedation
 - Mirtazapine initiated at 15 mg/d and increased to 45 mg/d; hydroxyzine at 50 mg/d PRN for anxiety
 - Patient was discharged on these two medications

Case 1

(CNS Spectrums 11:757-60, 2006)

- Not admitted to any Kentucky state hospital for 2 years. She may be stable on mirtazapine.
- No success in contacting her.

Can you explain
Case Study 1?

Case 1

(CNS Spectrums 11:757-60, 2006)

- Her genotype was CYP2D6 PM (*4/*4)
and CYP2C19 PM (*2/*2)
according to the AmpliChip CYP450 Test.

1.1 Case 1: Identification of double PMs (*Psychosomatics* 47:75-85, 2006).

Suspecting PMs for both:

- Very rare: (<1%) in all races
- Poor tolerance for most antidepressants (ADs), particularly for tricyclic antidepressants (TCAs)

1.1 Case 1: Dosage modifications for ADs (*Psychosomatics* 47:75-85, 2006).

Treating PMs for both:

- Avoid ADs dependent on CYP2D6 or CYP2C19
- Use ADs not dependent on CYP2D6 or CYP2C19:
 - Bupropion: metabolized by CYP2B6.
 - Mirtazapine: CYP2D6 is a minor pathway and is not metabolized by CYP2C19.

Case 1: Amitriptyline

(*CNS Spectrums* 11:757-60, 2006)

- Patient had ADRs on amitriptyline.
- Amitriptyline metabolism:
 - Major metabolic pathway for amitriptyline is demethylation to nortriptyline (active) by CYP2C19.
 - Nortriptyline is mainly metabolized by CYP2D6 to 10-OH-nortriptyline that is inactive.
- Kirchheiner et al. (2004) (*Mol Psychiatry* 9:442-473, 2004) recommended 50% of usual amitriptyline dosages for CYP2D6 PMs and 60% for CYP2C19 PMs.
- Double PMs should have a major problem metabolizing amitriptyline.

Case 1: Venlafaxine

(CNS Spectrums 11:757-60, 2006)

- Patient had ADRs on venlafaxine.
- Venlafaxine metabolism:
 - Major metabolic pathway is to 0-desmethylvenlafaxine
 - Performed by CYP2D6 and CYP3A4
 - 0-desmethylvenlafaxine and at least one other metabolite are further metabolized by CYP2D6.
- Kirchheiner et al. (2004) recommended 60% of usual venlafaxine dosages for CYP2D6 PMs.
- Double PMs have no CYP2D6 and cannot use CYP2C19 as an alternative pathway.

Case 1: Citalopram (CNS Spectrums 11:757-60, 2006)

- Patient had an ADR (sedation) on citalopram.
- Citalopram activity resides in the S-enantiomer, escitalopram.
- Citalopram is mainly metabolized by CYP2C19 to N-desmethylocitalopram.
- Escitalopram is metabolized by CYP2C19 and also by CYP2D6 and CYP3A4.
- An escitalopram study suggested those with one active allele of CYP2C19 have two-fold concentration increases when compared with two alleles. CYP2D6 alleles did not appear important (Ther Drug Monitor 2006;28:102-5).
- Double PMs have no CYP2C19 and cannot use CYP2D6 as an alternative pathway.

Case 1: Mirtazapine (CNS Spectrums 11:757-60, 2006)

■ No ADRs with mirtazapine.

- Mirtazapine is metabolized by demethylation, oxidation and conjugation. CYP2D6, CYP1A2 and CYP3A4 are involved.
- Mirtazapine is a racemic compound. CYP2D6 does not influence the (R)(-) enantiomer (glucuronidation) but influences the (S)(+) enantiomer.
- Due to a wide therapeutic window and glucuronidation component the CYP2D6 polymorphism has no clinical relevance.
- No clinically relevant interactions between paroxetine (a CYP2D6 inhibitor) and mirtazapine are known.
- Kirchheiner et al. (2004) recommended no mirtazapine dose modifications for CYP2D6 PMs.

Case 1: Frequency of double PMs (CNS Spectrums 11:757-60, 2006)

- Are you going to see many studies on double PMs (CYP2D6 and CYP2C19)? No.
- In our study in the first 1576 psychiatric patients there was only 1. The prevalence was 0.06 (95% CI 0.01-0.41%) or 0.07 (95% CI 0.01-0.41%) in Caucasians.
- To obtain 30 double PMs we will need to genotype approximately 47,280 patients.

1.2. Case Study 2

Case 2

(J Clin Psychopharm 23:420-421, 2003)

44-year-old healthy Caucasian male:

- Oxycodone was prescribed after dental surgery.
 - He took 2 doses of 10 mg (no other meds).
 - After that he felt very unusual: could not sleep and felt “super alert” (but in no danger).
 - During the long night, he woke up his wife and called his brother, a physician.

Can you explain
Case Study 2?

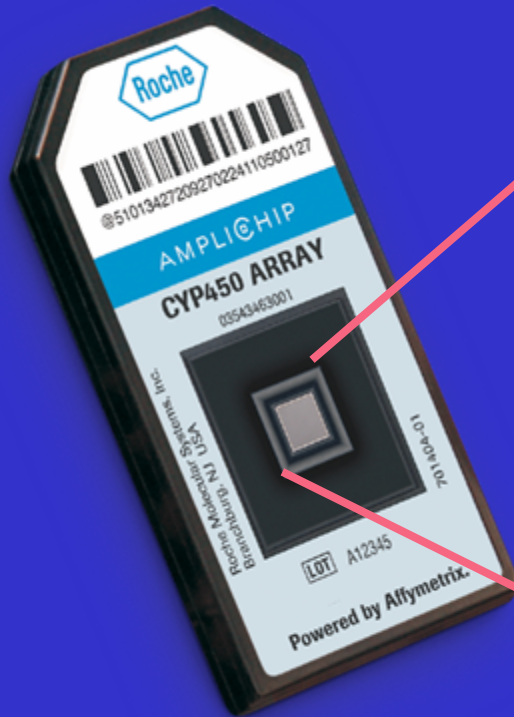
Case 2

(J Clin Psychopharm 23:420-421, 2003)

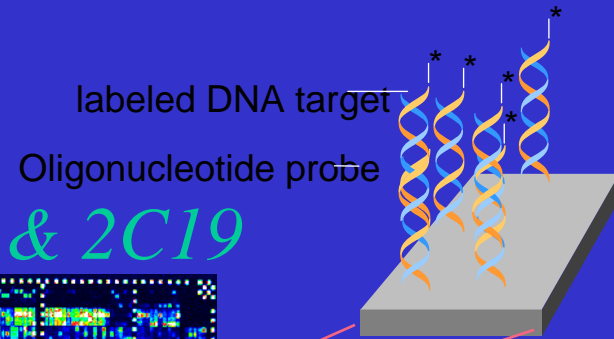
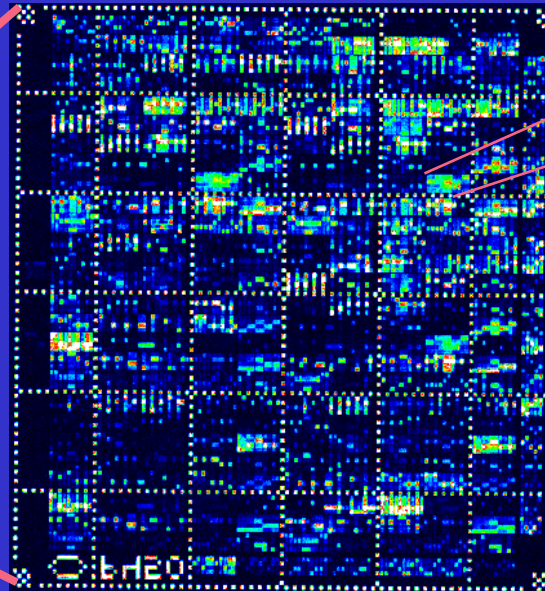
- He was genotyped for CYP2D6, and found to be a UM.
- Hydrocodone is activated by CYP2D6.
- As codeine, oxycodone and hydrocodone are metabolized by CYP2D6, we recommended that he avoid them.

3. CYP Genotyping

3.1. Genotyping equipment: AmpliChip CYP450 Test



CYP450 2D6 & 2C19



To address the relevant genetic variations, each array contains over 15,000 different probes complementary to sense and anti-sense P450 genomic DNA. Probes range in length from 18mer to 22mer

3.1. Genotyping equipment: AmpliChip CYP450 Test

- Approved by the FDA
- Uses Affymetrix technology
- Tests for:
 - 20 CYP2D6 alleles (*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *19, *20, *29, *35, *36, *40, 41)
 - 7 CYP2D6 duplications (*1xn, *2xn, *4xn, *10xn, 17xn, *35xn, and *41xn)
 - 3 CYP2C19 alleles (*1, *2, *3)
- Tests for wild-type allele
- Software to classify in 4 phenotypes

3.1. AmpliChip CYP450 Test references

1. **Long review article:** de Leon J, et al. The AmpliChip CYP450 genotyping test: integrating a new clinical tool. *Mol Diag Ther* 10:135-151, 2006.
2. **Short review article:** de Leon J. The AmpliChip CYP450 test: personalized medicine has arrived in psychiatry. *Exp Rev Mol Diag* 6:277-286, 2006.
3. **Risperidone study:** de Leon J, et al. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. *J Clin Psychiatry* 66:15-27, 2005.
4. **Clinical guidelines:** de Leon J, et al. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19 . *Psychosomatics* 47:75-85, 2006.

Thank you