

Lack of patient response to antidepressants? Can pharmacogenetics tell us why?

Joseph S. Bertino Jr., Pharm.D.

Scientific Director

Ordway Research Institute Drug Development Center

Albany, NY



Clinical Case

- **Patient is a 32 year old white female**
- **Longstanding history of depression (> 10 years)**
- **Patient has no history of suicide attempts**
- **No other pertinent past medical history**
- **No concurrent diseases**

Medication Review

- Patient has been on the following medications over the last 10 years:
 - Amitriptyline, imipramine and nortriptyline all dose up to 150 mg daily for 12 weeks on average. No response. Patient never had measurable concentrations of these TCAs
 - Trazodone 150 mg daily. Patient had GI intolerance and discontinued medication after 3 weeks
 - Fluoxetine 20 mg each morning. Patient had GI intolerance and discontinued medication after 2 weeks
 - Sertraline 50 mg each morning. Patient experienced GI intolerance and agitation and discontinued medication after 3 weeks

Clinical Presentation

- Patient admitted to inpatient psychiatry unit for:
 - Treatment of depression
 - Observation taking medications to assure compliance
- Clinical Pharmacology Consulted for dosing

Clinical Presentation

- **History unremarkable other than depression**
- **Patient smokes 15 cigarettes daily x 15 years**
- **Current medications nortriptyline 75 mg bid for 4 weeks**
- **Physical examine unremarkable**
- **HAM-D score = 20 (severe depression)**

Clinical Presentation

- **Serum nortriptyline concentrations reported:**
 - **Day 7 predose = unmeasurable**
 - **Day 14 predose = unmeasurable**
 - **Day 21 predose = unmeasurable**
 - **Day 27 predose = 5 ng/ml (therapeutic = 75-150)**

Hospital Course

Nortriptyline DOT and Dose

- Days 1-7: 125 mg bid
- Days 8-15: 175 mg bid
- Days 16-24: 250 mg bid
- Days 25-32: 300 mg bid

Serum Concentration

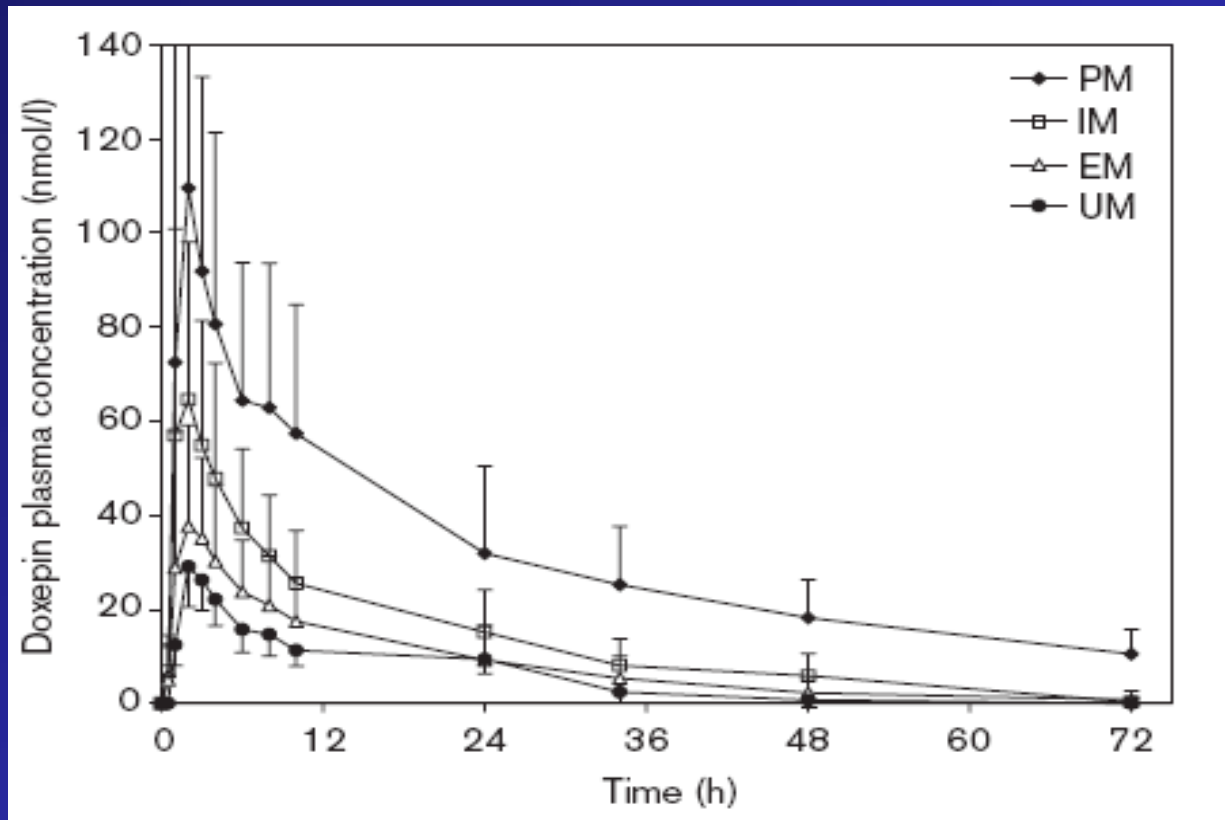
- Predose day 7 = 30 ng/ml
- Predose day 15 = 52 ng/ml
- Predose day 24 = 87 ng/ml
- Predose day 32 = 121 ng/ml

Hospital Course

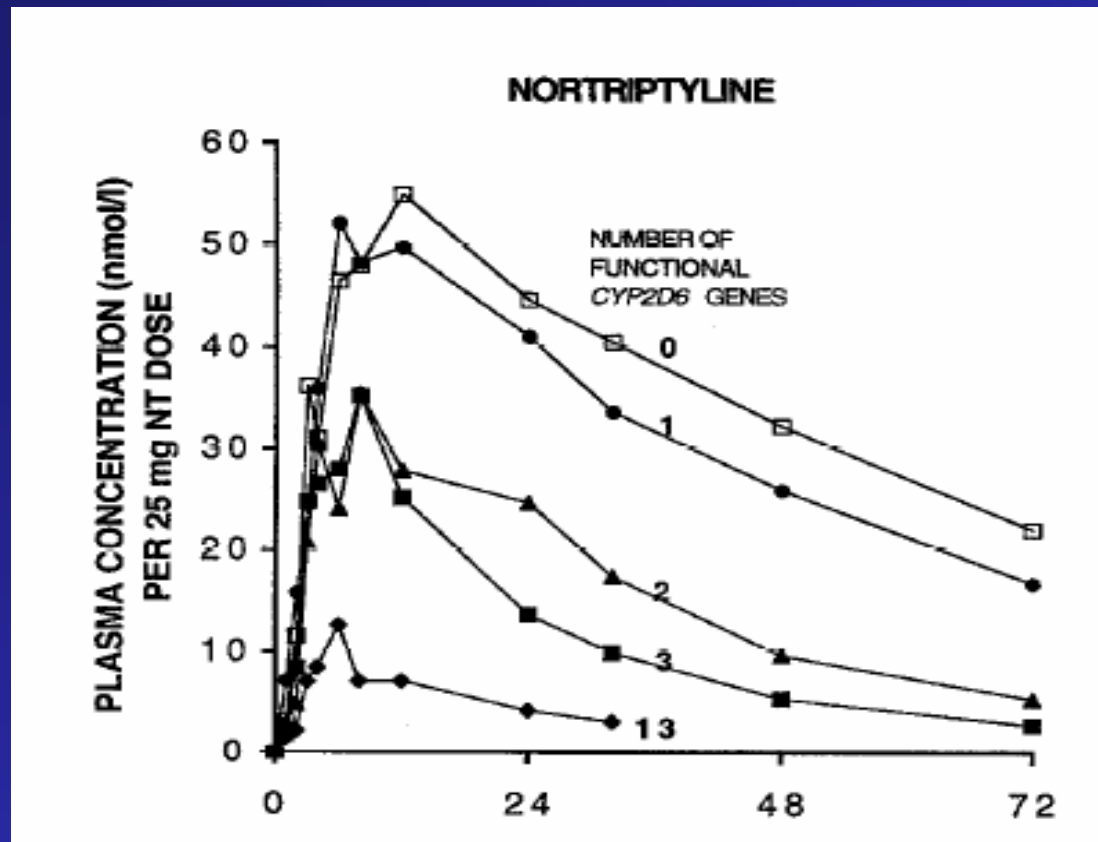
- DNA obtained for CYP2D6 genotyping
 - *1/*2x3
- Patient discharged on Day 37, final nortriptyline dose = 300 mg bid
- Patient instructed to avoid CYP2D6 inhibitors, given comprehensive list
- HAM-D score 14, mood improving
- Planned followup in 1 week with psych

Possible causes of nonresponse to drugs

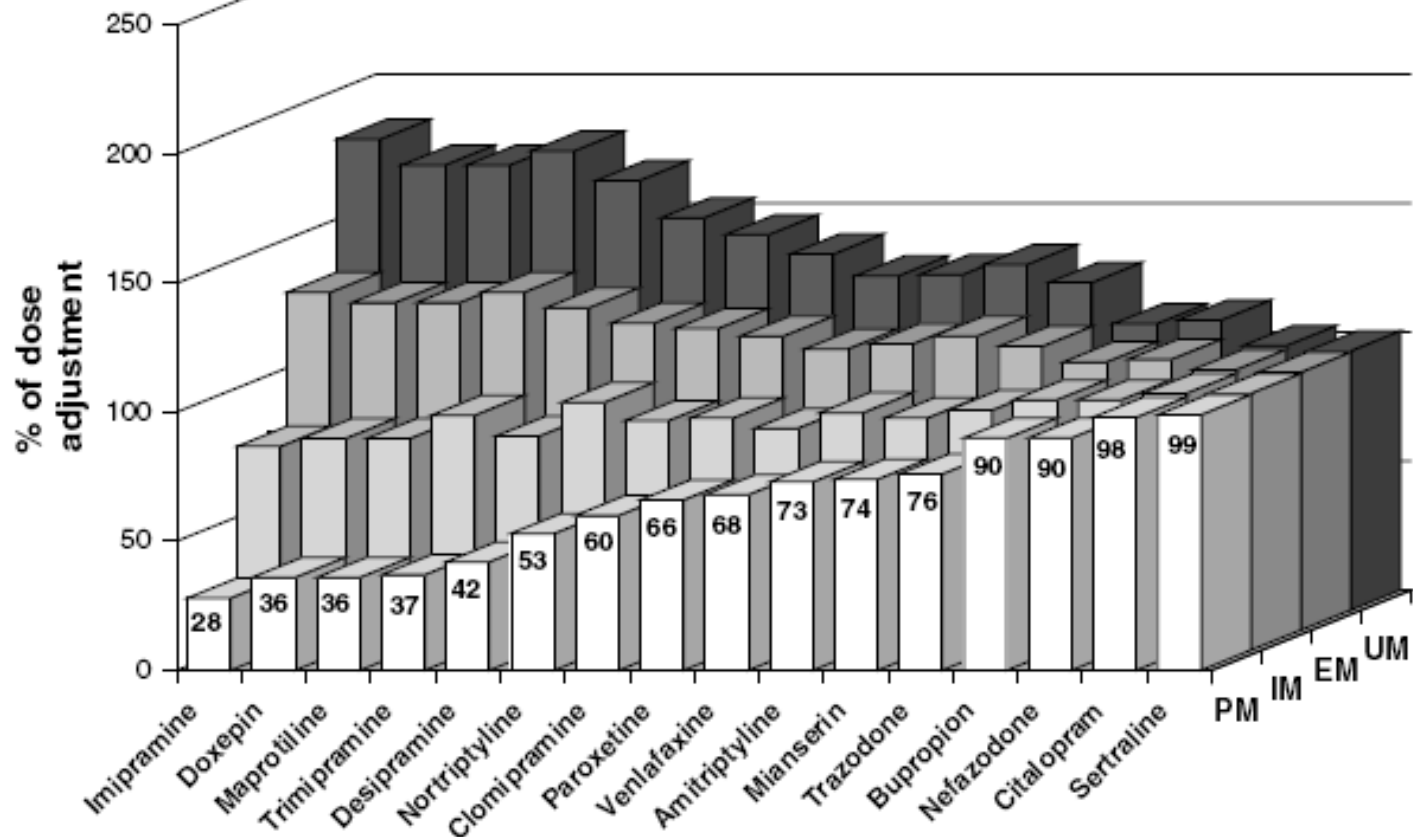
- **Noncompliance**
 - **Can't afford**
 - **Won't take**
 - **Can't take**
- **Malabsorption**
- **Drug interactions**
 - **GI interaction**
 - **Metabolic interaction**
- **Genetic explanations**
 - **Polymorphism of drug metabolizing enzymes**
 - **Polymorphism of receptors**



Kircheiner et al, Pharmacogenetics and genomics 2005;15:579



Dalen CP&T 1998;63:444-452



Kirchheiner et al. Mol Psych 2004;9-442-473

Incidence of CYP2D6 UM Genotype

- American • 4.3%
- Turkish • 8.7%
- African American • 4.9%
- Ethiopian • 29%
- Saudi Arabian • 21%
- Columbian • 1.7%

Bernard et al. *Oncologist* 2006;11:126-135

Issues to Consider

- **Lack of concentration-effect relationships**
- **Lack of data on receptor polymorphism**
- **Presence of active metabolites that are metabolized through different DMEs**
- **AHRQ report on SSRIs**