# Adding Value to Pharmacogenetics

How to implement pharmacogenetics in rural health care?

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No Disclosures

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## Outline

I. Introduction to Pharmacogenetics

II. Integrated model of pharmacogenetic testing and consultations

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I. Introduction to pharmacogenetics

PHARMACOGENETICS BASICS ⟶ How does it work?

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I. Introduction to pharmacogenetics

EVIDENCE ⟶ Does it work?

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I. Introduction to pharmacogenetics

CLINICAL UTILITY ⟶ Is there a benefit?

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I. Introduction to pharmacogenetics

COST EFFECTIVENESS → How much it costs to improve outcome?

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I. Introduction to pharmacogenetics

CLINICAL VIGNETTE

Clopidogrel (Plavix)

Prodrug

Poor metabolizer

Genetic polymorphism

CYP2C19

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CLINICAL VIGNETTE
ANTIPLATELET MEDICATIONS

65-year-old male with coronary artery disease underwent elective percutaneous coronary angioplasty (PTCA) and stenting using a drug eluting stent (DES).

Dual antiplatelet therapy (DAT) was initiated with **clopidogrel** 300 mg PO x1 with baby aspirin, followed by 75 mg PO daily and daily baby aspirin.

After 2 months, he noticed palpitations during exercise which turned out to be ischemia-induced ventricular ectopy on stress testing.

Re-catherization showed in-stent restenosis of 90% and the lesion is re-treated with another DES.

**Clopidogrel was discontinued** and replaced by another platelet inhibitor, Ticagrelor 180 mg PO x 1 followed by 90 mg PO daily.

He had normal stress testing at 6- and 12-month post intervention.

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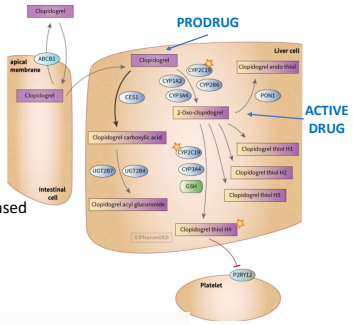
## Clopidogrel

Individuals who are **poor metabolizers (PM)** due to a **genetic polymorphism** have **reduced ability to activate clopidogrel** and are at increased risk for stent thrombosis.

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## FDA Black Box Warning

**WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE *CYP2C19* GENE**

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Tests are available to identify patients who are CYP2C19 poor metabolizers.
- Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

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## CYP2C19 Alleles & Genotypes

| Allele | SNP | CYP2C19 Function |
|---|---|---|
| *1 | N/A | Normal function |
| *2 | 681G>A | No function |
| *3 | 636G>A | No function |
| *17 | -808C>T | Increased function |

| Genotype | Phenotype |
|---|---|
| *1/*1 | Normal Metabolizer (NM) |
| *1/*2, *1/*3 | Intermediate Metabolizer (IM) |
| *2/*2, *2/*3 | Poor Metabolizer (PM) |
| *1/*17 | Rapid Metabolizer (RM) |
| *17/*17 | Ultra-rapid Metabolizer (UM) |

| Race | PMs | IMs | RM/UM |
|---|---|---|---|
| Whites | 2% | 25% | 40% |
| Blacks | 4% | 30% | 45% |
| Asian | 14% | 50% | <5% |

- Genetic polymorphisms account only for 5.2-12% of the variation of platelet aggregation inhibition by clopidogrel in PCI patients, with other factors collectively explaining >80% of the variation.

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## Clopidogrel Genetic Testing Recommendations

1. ***Genetic testing might be considered*** to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. (Level of Evidence: C)
2. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with ***an alternate P2Y12 inhibitor (e.g., prasugrel or ticagrelor) might be considered***. (Level of Evidence: C)
3. The ***routine clinical use of genetic testing*** to screen patients treated with clopidogrel who are undergoing PCI ***is not recommended***. (Level of Evidence: C)

Levine GN, et al. Circulation 2011;124:e574-651.

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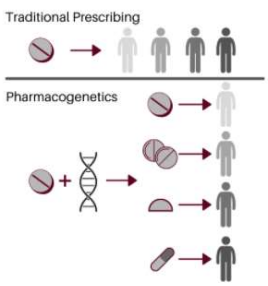
## The promise of Pharmacogenetics




Average patient

Individual patient

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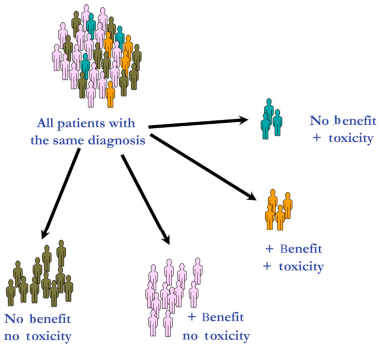


From: Genomic and Precision Medicine, 3rd Edition; eds. Ginsburg, Willard, David. Academic Press

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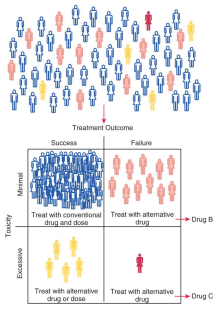


Adapted from Yaffe SJ, Aranda JV: Neonatal and pediatric pharmacology, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins

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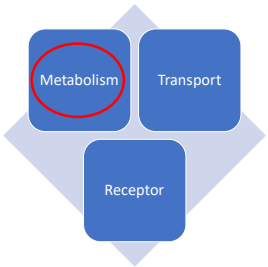


Individual drug response profile

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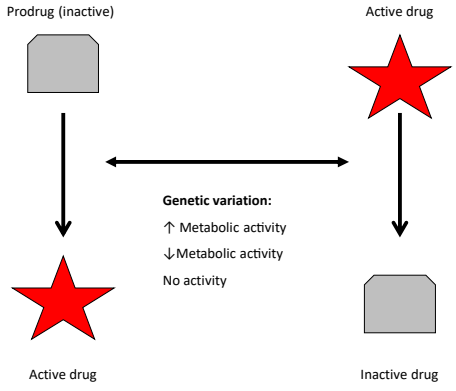


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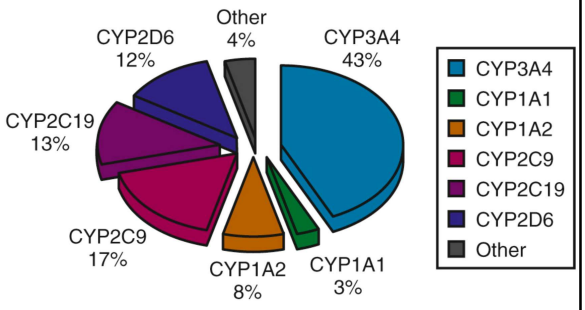
## Cytochrome P-450 (CYP) drug metabolizing enzymes




From: Thompson & Thompson Genetics in Medicine, 8th edition; eds. Willard, McInnes, Nussbaum. Elsevier Health Sciences

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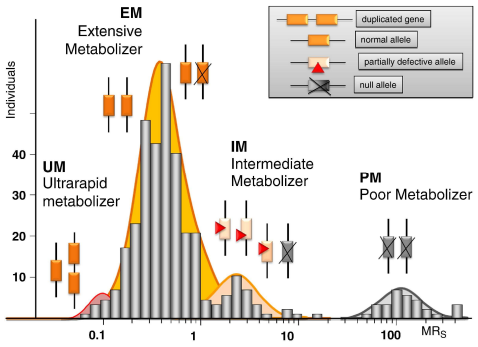
## Alleles (genotype) and effect on metabolizing enzyme activity (phenotype)




Zanger UM, Schwab M. Pharmacol Ther. 2013 Apr;138(1):103-41. PMID: 23333322.

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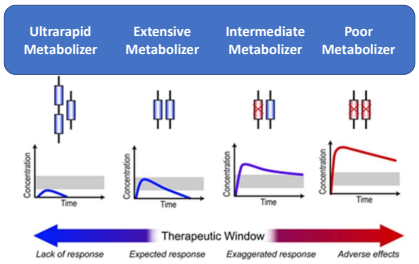


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## Evidence for pharmacogenetics-guided therapy in psychiatry

Prospective RCTs comparing PG guided vs non-guided pharmacotherapy, treatment as usual (TAU).

| Genotyping method | Study design | Outcome |
|---|---|---|
| CYP1A2, CYP2D6, CYP2C19 (Genesight I) | Open label, prospective cohort, n = 25 genotyping guided vs n = 26 TAU (Hall-Flavin et al. (2012)) | Genotyping leads to more reduction in depression scores |
| CYP1A2, CYP2D6, CYP2C19 (Genesight II) | Open label, prospective cohort, n = 114 genotyping guided vs n = 113 TAU (Hall-Flavin et al. (2013)) | Genotyping leads to more reduction in depression symptoms |
| CYP1A2, 2C9, 2C19, 2D6, SCL6A4, 5HTR2A | RCT, double-blind, n = 26 guided vs n = 25 TAU (Singh (2015)) | Genotyping results in higher response and remission rates |
| CYP2D6, CYP2C19, ABCB1, not otherwise specified | RCT, double-blind, n = 74 genotyping guided vs n = 74 TAU (Winner et al. (2012)) | Genotyping 2.52 times more likely to remit |
| CYP2D6 and others, not specified (Neuro Pharmagen) | RCT, double-blind, N = 155 guided vs n = 161 TAU (Perez et al. (2017)) | Genotyping results in higher response rate and better tolerability |
| CYP1A2, 2C9, 2C19, 2D6, 3A4, 3A5, SCL6A4, COMT, HTR2A, MHFR (NeuroIDgenetix) | RCT, n = 352 genotyping guided vs n = 333 TAU (Bradley et al. (2018)) | Genotyping leads to higher response rates and remission rates in patients with depression or anxiety. |
| CYP1A2, 2C9, 2C19, 2B6, 2D6, HTR2A, SCL6A4 | Prospective double-blind RCT, n = 1167 in total (Greden et al. (2019)) | Genotyping leads to higher response and remission rates in depressed patients |

van Westrhenen et al. Front Pharmacol. 2021 Apr 12;12:640032. PMID: 33995044;

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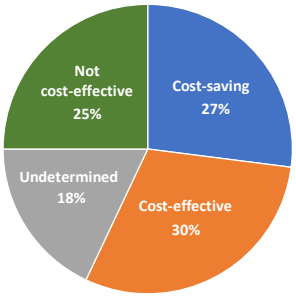
## Cost-effectiveness of PGx-guided therapy




*Modified from:* Verbelen et al., Pharmacogenomics J. 2017 Oct;17(5):395-402. PMID: 28607506

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CPIC®
Clinical Pharmacogenetics Implementation Consortium

- Develops and publishes guidelines for multiple drug-gene pairs focusing on the question of what might be an appropriate drug dose adjustment given the availability of genetic data.
- Does not address the question of when or how such genetic testing should be done.

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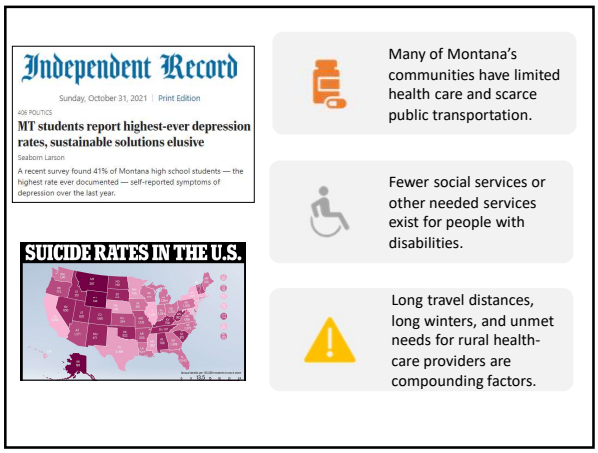


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## Clinical utility of pharmacogenetics in psychiatry

- Pharmacotherapy in psychiatry is hampered by side-effects and lack of effectivity.
- Only 30% of patients who suffer from psychiatric disorders remain compliant with their medication and reach full and stable remission.
- 30–50% of patients with major depressive disorder do not respond to their first antidepressant.
- Remission rates for SSRI's are as low as 37%.
- About 25,000 patients in US present to the emergency department each year due to antidepressant-induced adverse events.
- A major factor for side effects and lack of efficacy is the relation between dosage and systemic exposure to the drug.

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## II. Integrated model of pharmacogenetic testing and consultations

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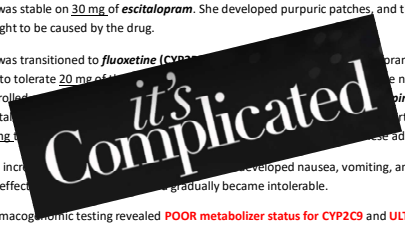
## CLINICAL VIGNETTE
## ANTIANXIETY MEDICATIONS

- A 19-year-old female presented with generalized anxiety disorder (GAD) and panic disorder. She was stable on 30 mg of ***escitalopram***. She developed purpuric patches, and these were thought to be caused by the drug.
- She was transitioned to ***fluoxetine*** (CYP2… …pram. She was able to tolerate 20 mg of … …e not optimally controlled … ***…pirone*** **(CYP3A4)** at total … …rtial substrate) 0.5 mg … …se additions.
- With incr… …developed nausea, vomiting, and fatigue. Side effect… …gradually became intolerable.
- Pharmacogenomic testing revealed **POOR metabolizer status for CYP2C9** and **ULTRARAPID metabolizer status for CYP2D6.**
- She is started ***venlafaxine extended release*** (**2D6**, 2C19, 3A4). Venlafaxine works well for her. She was stabilized on 150 mg with concomitant ***clonazepam*** (3A4 partial substrate) and continues to do well with optimal control of both anxiety and panic symptoms.

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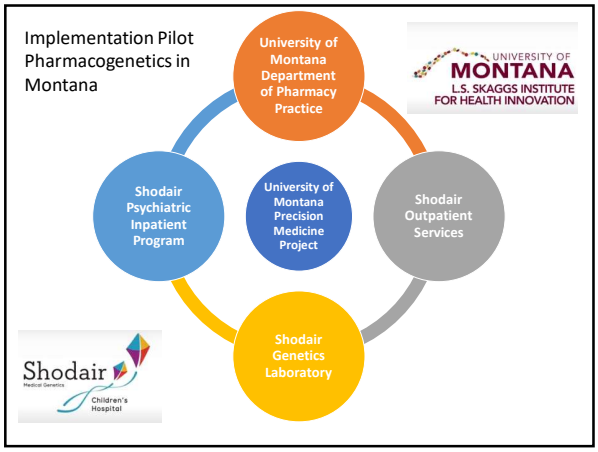


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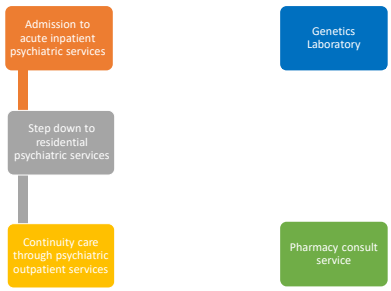
## Components of pharmacogenetics implementation

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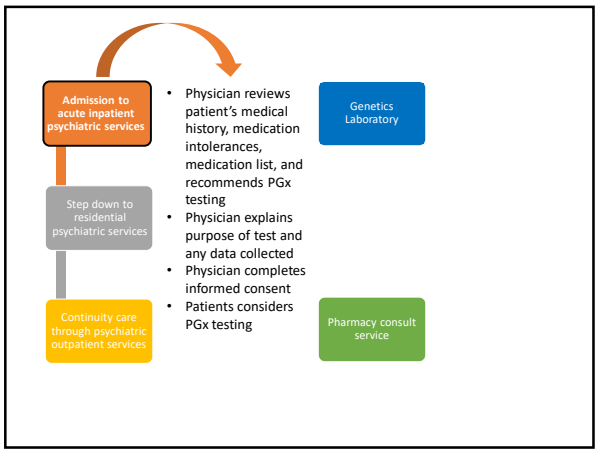


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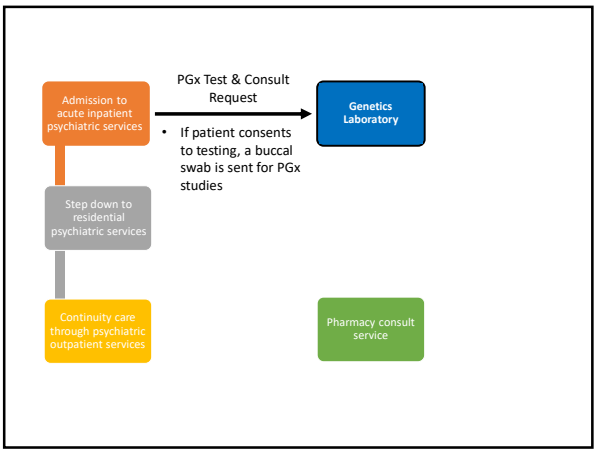


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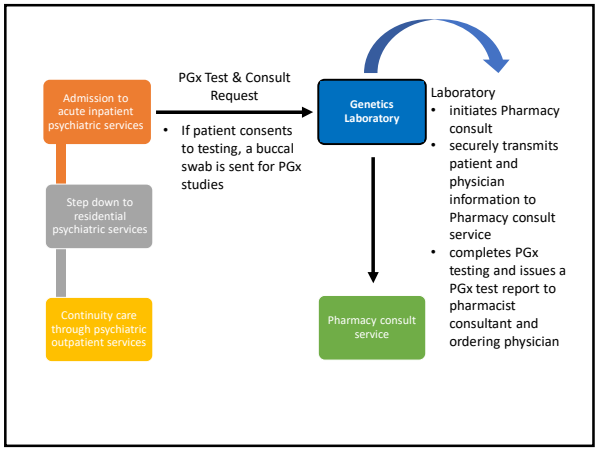


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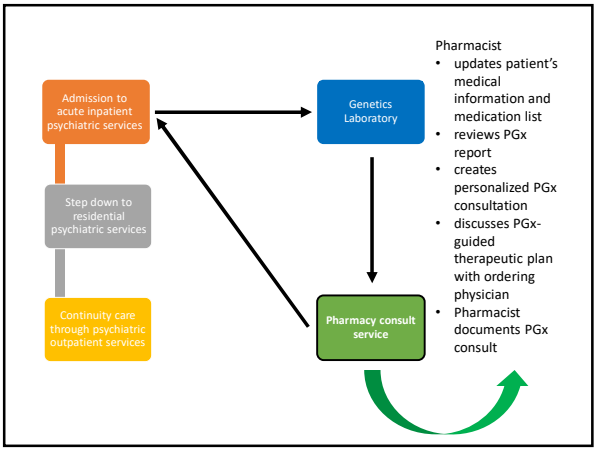


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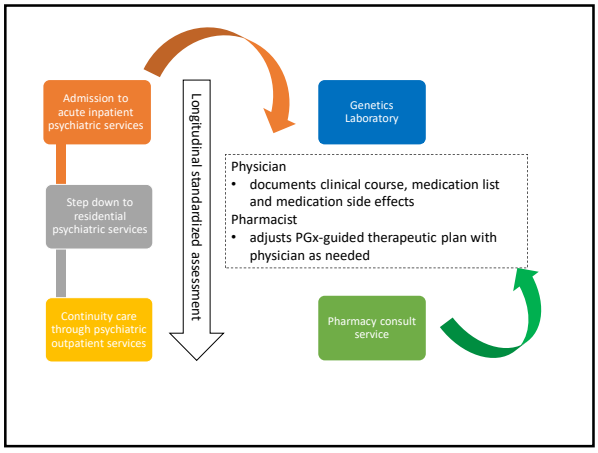


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CLINICAL VIGNETTE

## ANTIANXIETY MEDICATIONS

- A 19-year-old female presented with generalized anxiety disorder (GAD) and panic disorder. She was stable on 30 mg of ***escitalopram***. She developed purpuric patches, and these were thought to be the cause for the purpura.
- She was transitioned to ***fluoxetine* (CYP2D6**, CYP2C19**)** after tapering escitalopram. She was able to tolerate 20 mg of the medication; however, her anxiety symptoms were not optimally controlled on this dose of fluoxetine. After an initial concomitant trial with ***buspirone* (CYP3A4)** at total daily doses of 30 to 60 mg, she was transitioned to ***clonazepam*** (3A4 partial substrate) 0.5 mg to be used twice daily. The anxiety symptoms did not respond to these additions.
- With increase in dose of ***fluoxetine*** to 40 mg, she developed nausea, vomiting, and fatigue. Side effects continued to persist and gradually became intolerable.
- Pharmacogenomic testing revealed **POOR metabolizer status for CYP2C9** and **ULTRARAPID metabolizer status for CYP2D6.**
- She is started ***venlafaxine extended release*** (**2D6**, 2C19, 3A4). Venlafaxine works well for her. She was stabilized on 150 mg with concomitant ***clonazepam*** (3A4 partial substrate) and continues to do well with optimal control of both anxiety and panic symptoms.

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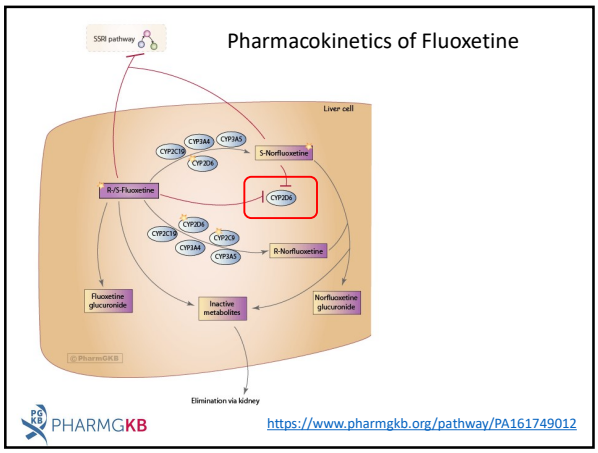
Pharmacokinetics of Fluoxetine
SSRI pathway
Liver cell
CYP3A4
CYP3A5
CYP2C19
CYP2D6
S-Norfluoxetine
R-/S-Fluoxetine
CYP2D6
CYP2D6
CYP2C19
CYP2C9
CYP3A4
CYP3A5
R-Norfluoxetine
Fluoxetine glucuronide
Inactive metabolites
Norfluoxetine glucuronide
Elimination via kidney
PHARMGKB
https://www.pharmgkb.org/pathway/PA161749012

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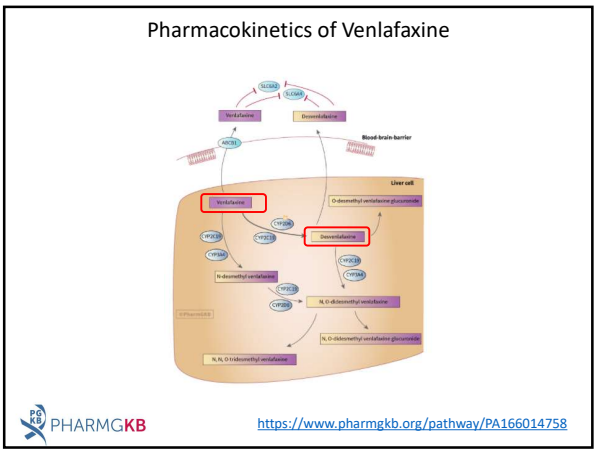
Pharmacokinetics of Venlafaxine
Venlafaxine
O-desmethylvenlafaxine
Blood-brain barrier
Liver cell
Venlafaxine
O-desmethylvenlafaxine glucuronide
Desvenlafaxine
N-desmethylvenlafaxine
N, O-didesmethylvenlafaxine
N, O-didesmethylvenlafaxine glucuronide
N, N, O-tridesmethylvenlafaxine
PHARMGKB
https://www.pharmgkb.org/pathway/PA166014758

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Thank you!
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