Fitzgerald
Colibri Healthcare

Pharmacogenomics& Precision Medicine for Mental Healthcare

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Disclosure

Josh Hamilton is a:

- consultant & speaker for Myriad Neuroscience (pharmacogenomics),
- paid ambassador, Point of Care Network (POCN)

All relevant financial relationships have been mitigated.

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Objectives

- At the end of this presentation, the participant will be able to:

1. Conceptualize mental illness in the context of epi/**genetics and neurobiology**, with an emphasis on mental disorders.
2. Discuss contemporary approaches to **management** of mental disorders, including practical applications for nurse practitioners *(Rx)*.
3. Apply concepts of **pharmacogenomics** to the selection, prescription and management of **drug therapy** for mental disorders *(Rx)*.

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Tips

- References
  - Listed throughout and at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

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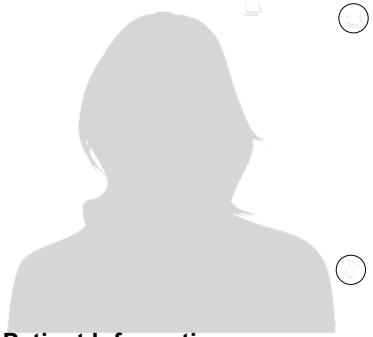
The Case of Mrs. O



Visit Notes – History of depression and anxiety

Diagnoses:
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- Mood disorder due to GMC
- Fibromyalgia
- Celiac Disease

Patient Information:
- 34-year-old Caucasian female

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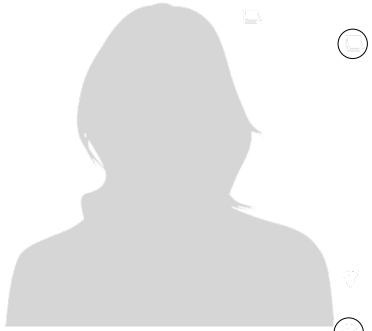

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Previous Medications
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Major Depressive Disorder (MDD) Etiology

Evolving theories:
- Differences in regional neuron density
- Effect of stress on neurogenesis & neuronal cell apoptosis
- Alterations in feedback pathways (PFC-limbic)
- Role of proinflammatory mediators

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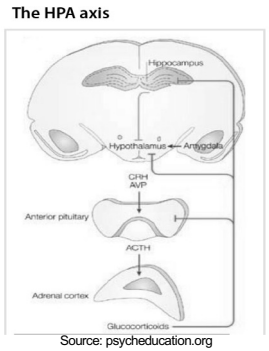
Chronic Stress



Source: psycheducation.org

Leading cause of depression

Exposure to stress for >21 days:

- Overactivity of HPA axis
- Glucocorticoid receptor (GR) resistance
  - ↓ suppression of proinflammatory cytokines

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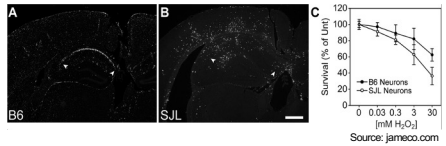
Hippocampus

- Closely associated with limbic system
- Greatest density of GRs
- Stress >21 days: Apoptosis
  - hippocampal cell atrophy; loss of negative feedback inhibition to hypothalamus
  - HPA axis dysregulation



Source: jameco.com

- SSRIs, SNRIs and TCAs stimulate hippocampal neurogenesis

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Pathological Energy Flow

- In stress: Adrenal hormones cause "selective shunting" of energy to limbic system.
- Decreased metabolism in cerebral cortex and hippocampus
  - Normally energy-demanding in rest states
  - Undergo rapid atrophy when de-energized

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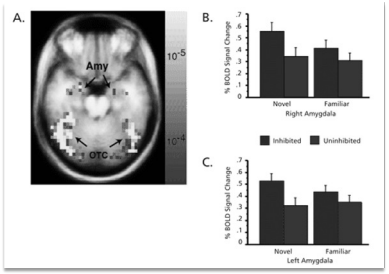
Functional Neuroimaging

- Inefficient info processing in dorsolateral PFC
- Increased activity at amygdala
- Provocative testing of amygdala:
  - Induced sadness (over-reactive)
  - Induced happiness (under-reactive)



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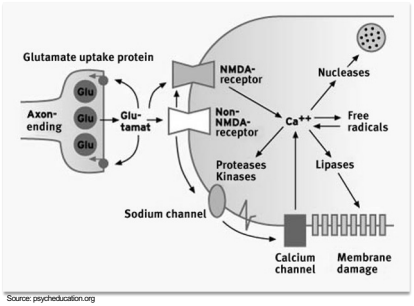
Glutomate Excitotoxicity

- Hypoxia & hypoglycemia leads to glutamate accumulation in ECF ➔ nerve-cell death (excitotoxicity)
- Results in decreased grey matter density in frontal lobes



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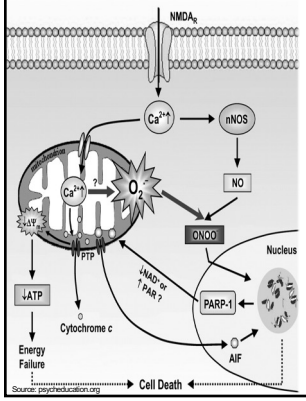
NMDA Receptors



- Excessive glutamatergic activation leads to excitotoxicity
- More than one type (excitatory/inhibitory)
- New drug development focuses on:
  - Inhibition of glutamate binding
  - Ion channel blockade
  - Binding inhibition at terminal regulatory domain
  - Ketamine derivatives

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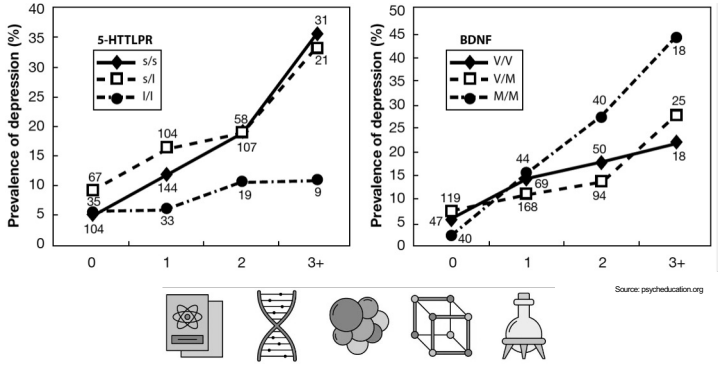
Epigenetics: Stress & Depression



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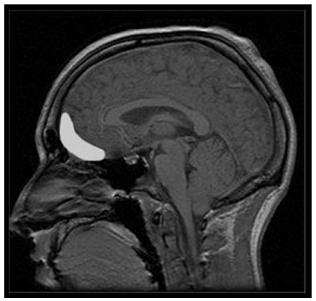
Depressive Disorders

- Depressed mothers & their children
- Anxious comorbidity
  - Orbitofrontal volume
  - Right hemispherical anomalies



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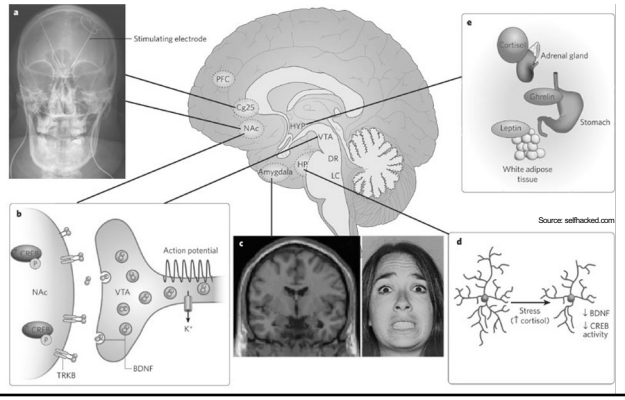
So…It's Complicated!



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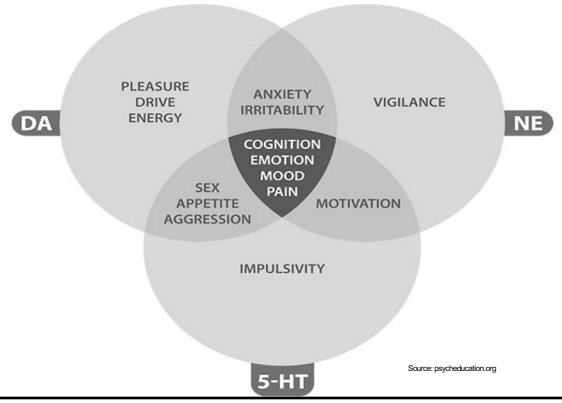
"Mapping" Depression



Source: psycheducation.org

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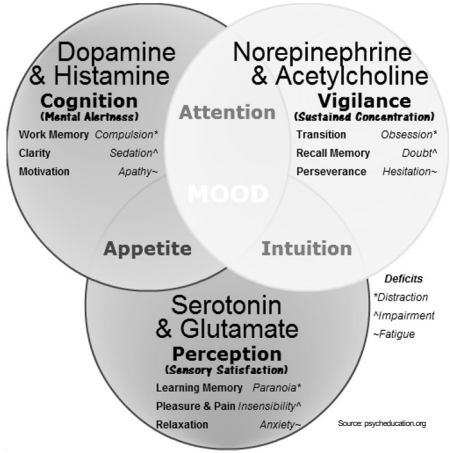

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Pharmacotherapy for Depression

- Goal is complete remission
- Placebo effect is growing
- A closer look at STAR*D
- "Common pathway" for effective tx?

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Symptom-Based Selection

- Build a multi-agent "portfolio"
- Treat all residual symptoms to sustained remission
  1. **Construct** symptoms into a diagnosis
  2. **Deconstruct** into specific symptom list
  3. **Match** symptoms to brain circuits
  4. **Consider** known neuropharmacology of circuits
  5. **Match** agents to neuropharmacology
  6. **Fine tune**

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A Few Words About Genetics…

- Potential for diagnosis & treatment
- Genetic complexity of psych illness
- Response isn't "all or none"
- Predict non/response & side-effects
- CYP-450 genotypes
- "Equipoise"

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Potential Genetic Equipoise

Gene	Protein	Biological Function	Therapeutic Implications
SLC 6A4 variation	SERT	Serotonin reuptake	Poor response, slow response, poor tolerability to SSRIs/SNRIs
$5HT_{2c}$ variation	$5HT_{2c}$ receptor	Regulates DA & NE release	Poor response, poor tolerability to atypical antipsychotics
DRD_2 variation	D_2 receptor	Mediates positive symptoms of psychosis, movements in Parkinsonism	Poor response, poor tolerability to atypical antipsychotics
COMT Val variation	COMT enzyme	Regulates DA levels in PFC; metabolizes DA & NE	Reduced executive functioning
MTHFR T variation	MTHFR enzyme	Regulates L-methylfolate levels & methylation	Reduced executive functioning, especially with Val COMT (T with Val)

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Case Study

The Case of Ms. O.

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Miss O.'s PGx Testing Results

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®) **desvenlafaxine** (Pristiq®) **levomilnacipran** (Fetzima®) **selegiline** (Emsam®) **vilazodone** (Viibryd®)	**amitriptyline** (Elavil®) [3,7] **citalopram** (Celexa®) [3,4] **clomipramine** (Anafranil®) [3,7] **desipramine** (Norpramin®) [1] **doxepin** (Sinequan®) [3,7] **duloxetine** (Cymbalta®) [2,7] **escitalopram** (Lexapro®) [3,4] **fluvoxamine** (Luvox®) [2,4,7] **imipramine** (Tofranil®) [3,7] **mirtazapine** (Remeron®) [3,7] **nortriptyline** (Pamelor®) [1] **paroxetine** (Paxil®) [1,4] **sertraline** (Zoloft®) [3,4] **trazodone** (Desyrel®) [3,7] **venlafaxine** (Effexor®) [1] **vortioxetine** (Brintellix®) [1]	**fluoxetine** (Prozac®) [1,4,6]

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All psychotropic medications require clinical monitoring.

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What to do with Ms. O.?

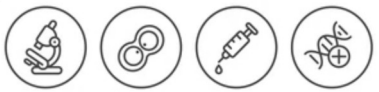
PGx Consultation

Elected to start levomilnacipran (Fetzima) (no gluten)

Outcomes

- 6-week medication titration
- Denies medication side-effects
- Significant improvement in HAM-A, BDI-II scores

PGx-GUIDED TREATMENT PLANNING



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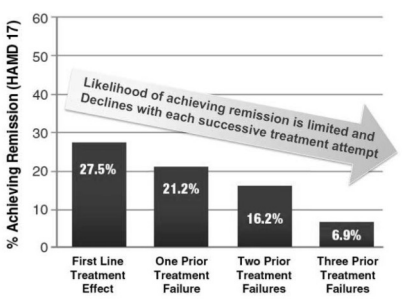
STAR*D: Diminishing Returns



Source: Rush AJ, et al. Am J Psychiatry. 2006.

- **Less than 40% of patients achieve remission with initial drug treatment.**
- **With each additional medication trial, the chance of remission decreases, *while treatment intolerance increases.***

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The FDA & Pharmacogenomics

aripiprazole	"The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose."	CYP2D6 PM
citalopram	"The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers."	CYP2C19 PM
thioridazine	"The use of thioridazine in patients known to have reduced activity of P450 2D6 is contraindicated."	CYP2D6 IM or PM
vortioxetine	"The maximum recommended dose of TRINTELLIX® is 10 mg/day in known CYP2D6 poor metabolizers."	CYP2D6 PM

(Not endorsed by the FDA)

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Why Patients Fail Treatment

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Pharmacogenomics

Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person.

National Human Genome Research Institute

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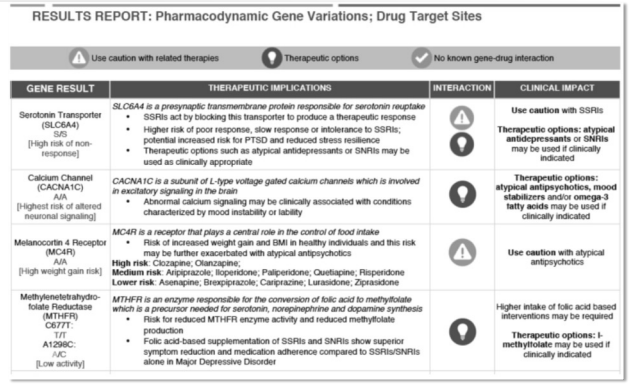
Example PGX Test Report #1



RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Serotonin Transporter (SLC6A4) S/S [High risk of non-response]	*SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • Higher risk of poor response, slow response or intolerance to SSRIs; potential increased risk for PTSD and reduced stress resilience • Therapeutic options such as atypical antidepressants or SNRIs may be used as clinically appropriate		**Use caution** with SSRIs **Therapeutic options: atypical antidepressants** or **SNRIs** may be used if clinically indicated
Calcium Channel (CACNA1C) A/A [Highest risk of altered neuronal signaling]	*CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain* • Abnormal calcium signaling may be clinically associated with conditions characterized by mood instability or lability		**Therapeutic options: atypical antipsychotics, mood stabilizers** and/or **omega-3 fatty acids** may be used if clinically indicated
Melanocortin 4 Receptor (MC4R) A/A [High weight gain risk]	*MC4R is a receptor that plays a central role in the control of food intake* • Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics **High risk**: Clozapine; Olanzapine; **Medium risk**: Aripiprazole; Iloperidone; Paliperidone; Quetiapine; Risperidone **Lower risk**: Asenapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone		**Use caution** with atypical antipsychotics
Methylenetetrahydro-folate Reductase (MTHFR) C677T: T/T A1298C: A/C [Low activity]	*MTHFR is an enzyme responsible for the conversion of folic acid to methylfolate which is a precursor needed for serotonin, norepinephrine and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • Folic acid-based supplementation of SSRIs and SNRIs show superior symptom reduction and medication adherence compared to SSRIs/SNRIs alone in Major Depressive Disorder		Higher intake of folic acid based interventions may be required **Therapeutic options: l-methylfolate** may be used if clinically indicated

Genomind PGx Pro: actual patient report

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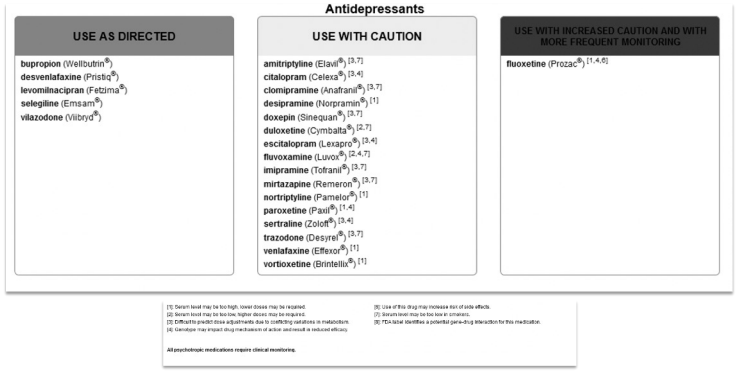
Example PGx Test Report #2



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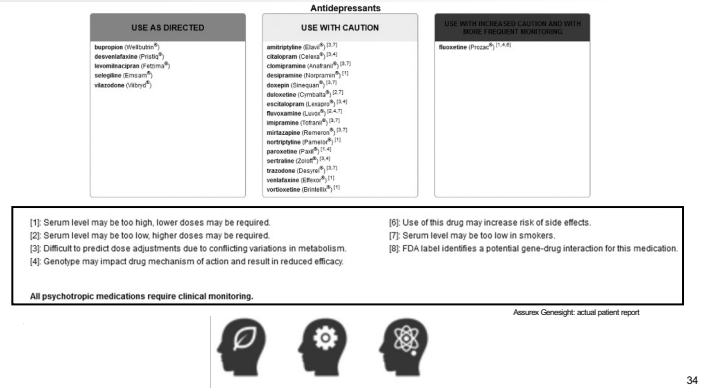
Clinical Considerations



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Assurex Genesight: actual patient report

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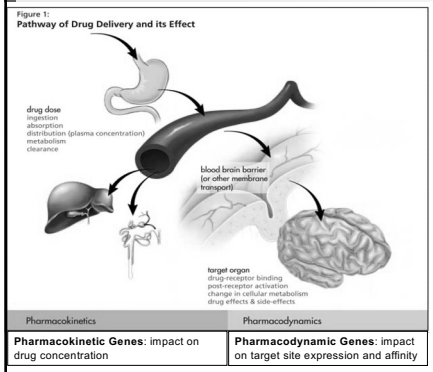
Integrative Genetic Profile



Pharmacokinetic Genes: impact on drug concentration

Pharmacodynamic Genes: impact on target site expression and affinity

Huang, A., *Pathway of Drug Delivery and its Effect*. 2008: 28th Canadian Geriatrics Society Annual Meetings: Academic Career Day. www.geriatricsandaging.ca/2008CGS

In addition to traditional strategies, **PD genes can inform potential alternative therapy options** to which a patient is more likely to respond.

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Pharmacogenomic Genes: Depression

PHAMACODYNAMIC (PD)	PHARMACOKINETIC (PK)
SLC6A4 – serotonin transporter	CYP-2D6
5HTR2A – serotonin 2A receptor	CYP-2C19
HLA-B*1502 – human leukocyte antigen	CYP-2C9
HLA-A*3101 – human leukocyte antigen	CYP-1A2
	CYP-2B6
	CYP-3A4
	UGT-1A4
	UGT-2B15

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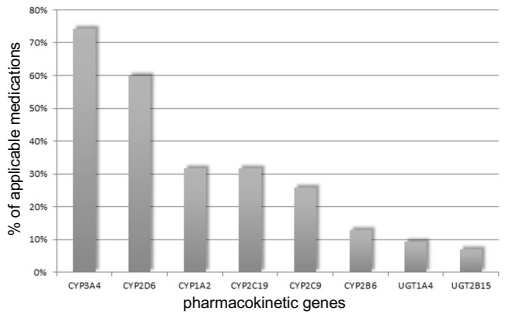
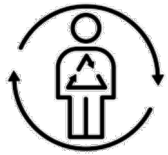
Medication Metabolism
% of medication substrates for CYP450 and UGT enzymes





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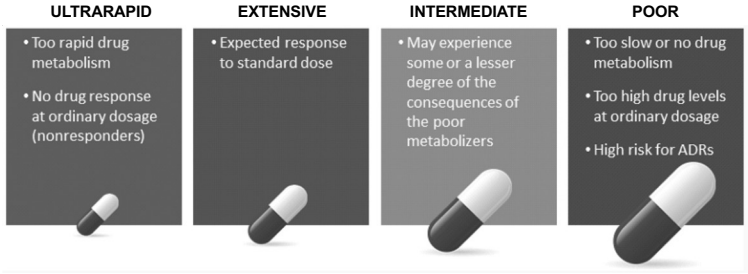
Genetics & Medication Serum Levels



Source: psycheducation.org

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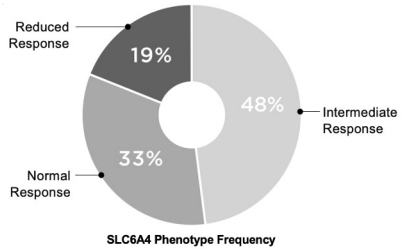
SSRI Efficacy & the SLC6A4 Gene



S/S variant:

lower **remission** rates

S/S and **S/L** variants:

lower **response** rates

Serretti A, et al. Mol Psychiatry. 2007.
Porcelli S, et al. Eur. Neuropsychopharmacol. 2012.

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Human Leukocyte Antigen (HLA)

MEDICATION	HLA-A*3101	HLA-B*1502
carbamazepine (Tegretol)	X	X
oxcarbazepine (Trileptal)		X

SEVERITY OF SKIN REACTIONS		
ODDS RATIOS	**HLA-A*3101**	**HLA-B*1502**
Less severe skin reactions	8.58	Not predictive
Stevens-Johnson TEN	5.65	80.7

Tegretol [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.
Trileptal [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.
Grover S, et al. Pharmacogene Genomics. 2014.

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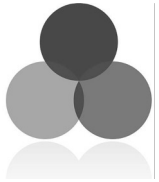
Combinatorial PGx Testing



PK GENES

CYP2D6

CYP2D6 + CYP2C19

CYP2D6 + CYP2C19 + CYP1A2

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4+ CYP2B6

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4+ CYP2B6 + UGT1A4

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9 + CYP3A4+ CYP2B6 + UGT1A4 + UGT2B15

PD GENES

SLC6A4

HTR2A

HLA-B*1502

HLA-A*3101

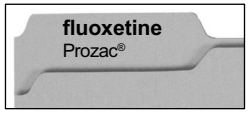
331,776

Composite Phenotypes

41

41

Specific Genetic Pathways



3A4 | 2D6 | 2C9 | 2C19 | SLC6A4

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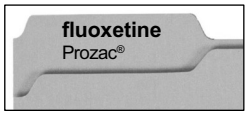
Genetic Significance for Each Unique Medication



3A4 | 2D6 | 2C9 | 2C19 | SLC6A4

43

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Genetic Significance for Each Unique Medication

HIGH: 2C19

NORMAL: SLC6A4

3A4 | 2D6 | 2C9

LOW

44

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Integration & Categorization

CLINICAL IMPACT

fluoxetine
(Prozac®)

Clinical Considerations

Potential elevated serum drug level
Increased risk of side-effects

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Clinical Studies

2*	2	1	1
prospective double blind randomized controlled trials[1]	prospective open label clinical outcome trials[2,3]	retrospective health economic outcomes trial[4]	prospective health economic outcomes project[5]

*One of these is the largest ever pharmacogenomics depression trial. The data was presented at the 2018 American Psychiatric Association's (APA) annual meeting.

1. Winner JG, et al. Discovery Medicine 2013. 2. Hall-Flavin DK, et al. Transl Psychiatry 2012. 3. Hall-Flavin DK, et al. Pharmacogenetics and Genomics .2013.

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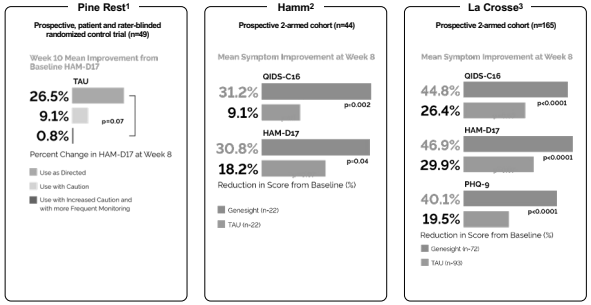
Guided Study Foundation



1. Winner JG, et al. Discov Med 2013 Nov; 16(89):219-27. (Pine Rest). 2. Hall-Flavin DK, et al. Transl Psychiatry 2012 Oct; 2(10): e172. (Hamm) 3. Hall-Flavin DK, et al. Pharmacogenet Genomics 2013 Oct; 23(10):535-48. (La Crosse)

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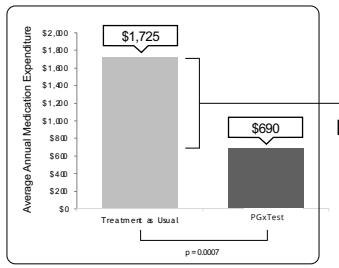
Economic Utility | Rx Expenditures

Total medication costs were reduced when treatment was guided by the pharmacogenomic test.



Winner JG, et al. Curr Med Research & Opin. 2015.

$1,035
Avg annual savings per patient

PGx-guided treatment helped to increase adherence and reduce polypharmacy

46%
Patients stayed on a new medication 46% longer when guided by the PGx test

20%
20% of patients were on fewer medications

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Largest Mental Health PGx Study

- ✓To evaluate the impact of the pharmacogenomic test on psychiatric treatment response in patients with major depressive disorder
- ✓Double-blind randomized controlled trial
- ✓1,167 patients at 60 different study sites
- ✓Patients with moderate to severe depression entered failing at least one psychotropic medication.

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Study Design

	Blinding up to week 12
Patients	**Blinded**
Clinicians	**Unblinded** to enable treatment changes guided by GeneSight
Central Raters	**Blinded**

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Two Study Arms

Genomics-Guided Arm and Treatment as Usual Arm Over the Course of the Study

				Study Unblinded	
	4 weeks	8 weeks		12 weeks	24 weeks
GeneSight-Guided Arm	Clinician had access to GeneSight report	Clinician had access to GeneSight report	Unblinding occurred after week 8	Clinician had access to GeneSight report	Clinician had access to GeneSight report
Treatment as Usual Arm	Clinician had no access	Clinician had no access		Clinician had access to GeneSight report	Clinician had access to GeneSight report

Both the Genomics-Guided Arm and Treatment as Usual Arms Received Active Therapy

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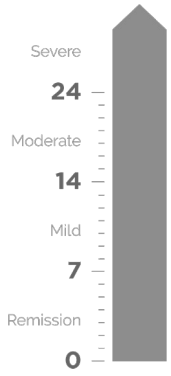
Hamilton Depression (HAM-D17) Rating Scale



Remission: HAM-D17 score ≤ 7 (e.g., 20 to 6)

Response: ≥ 50% reduction in HAM-D17 score (e.g., 20 to 10)

Symptom Improvement in HAM-D17 Score: change in HAM-D17 score from baseline to week 8

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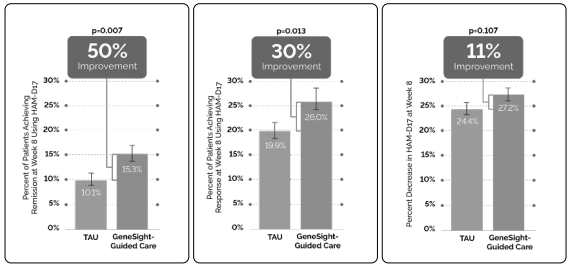
Remission & Response

Treatment guided by the pharmacogenomic test resulted in a 50% improvement in remission rates and a 30% increase in response rates at week 8 compared to TAU. Symptom improvement in the genomics-guided group trended toward significance at week 8, compared to TAU.



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Incongruent Medications

The pharmacogenomic test has the **greatest potential** to improve patient outcomes for those taking **genetically suboptimal medications**.

Therefore, a sub-analysis was performed on the 213 patients that entered the study on an incongruent (red category) medication in **both** arms.

Congruent = Taking a medication in the **green** or **yellow** category.

Incongruent = Taking a medication in the **red** category.

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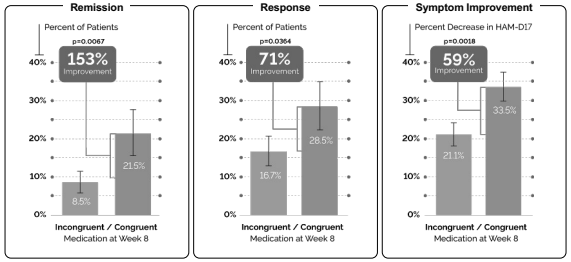
Switching Rx to Optimize Therapy

Significant improvements in symptom reduction, response, and remission were seen when patients were switched to a genetically optimal medication



How will you know which 20% will be on a sub-optimal medication?

55

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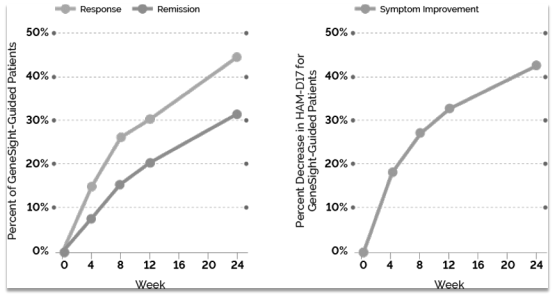
Durability

Clinical utility was durable over 6 months. Remission rates continued to increase and doubled during the open-label period.



1. Winner JG, et al. Discov Med 2013 Nov; 16(89):219-27. (Pine Rest). 2. Hall-Flavin DK, et al. Transl Psychiatry 2012 Oct; 2(10): e172. (Hamm) 3. Hall-Flavin DK, et al. Pharmacogenet Genomics 2013 Oct; 23(10):535-48. (La Crosse)

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Guided Study Conclusions

- ✓Genomics-guided treatment showed a statistically significant and clinically meaningful improvement in remission and response over unguided treatment as usual
- ✓The effect on response and remission continued to improve and was durable over 6 months
- ✓First phase 3 study comparing two active treatment arms to show statistically significant improvement (superiority) in remission and response rates of one arm over the other

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Case Study

The Case of Ms. P.

Patient Information:

- 35-year-old Caucasian female

Visit Notes

- Complex mood instability & anxiety
- Mixed personality pathology
- Extensive provider/medication history
  - Bipolar I DO, MRED, moderate
  - Anxiety state, unspecified
  - Adjustment DO w/mixed anx & dep mood
  - Partner relational problem
  - Borderline personality disorder
  - Migraine, unspecified
  - Postconcussion syndrome

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Case Study

The Case of Ms. P.

Patient Information:

- 35-year-old Caucasian female

Pre-PGx Testing Medications

- citalopram (Celexa®) 20 mg daily
- buspirone (BuSpar®) 5 mg BID
- lamotrigine (Lamictal®) 150 mg daily
- diazepam (Valium®) 5 mg QID PRN
- topiramate (Topamax®) 25 mg BID
- ondansetron (Zofran®) 4 mg QID PRN
- Intolerant to SGAs and SNRIs.

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Ms. P.'s PGx Test Results

Clinician: Joshua M Hamilton

Report Date: 6/12/2014

NORMAL FOLIC ACID CONVERSION	REDUCED FOLIC ACID CONVERSION	SIGNIFICANTLY REDUCED FOLIC ACID CONVERSION ✓

Note: Serum levels of folate may be too low. Folate supplementation or higher daily intake of folic acid may be required.

Patient Genotype and Phenotype

MTHFR	Reduced Activity	T/T

This individual is homozygous for the T allele of the C677T polymorphism in the MTHFR gene. This genotype is associated with significantly reduced folic acid metabolism, significantly decreased serum folate levels, and significantly increased homocysteine levels.

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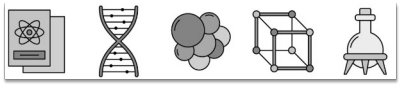
What to do with Ms. P.?

Testing Insights

- Current medications are genetically compatible
- Add l-methylfolate (Deplin) 15/90.314 mg daily



Outcomes

- 6-week follow-up appointment:
- Self-reporting target symptom improvement
  - Noteworthy change in GBI depression cluster (improved)
  - Significant decrease in HAM-A score

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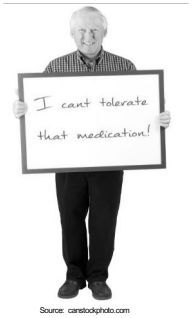
Precision Medicine: Personalized Care



Source: canstockphoto.com

Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person.

- National Institutes of Health
- National Human Genome Research Institute

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"Questions?"

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End of Presentation
Thank you for your time and attention.

Josh Hamilton,
DNP, RN/PMH-BC, FNP-C, PMHNP-BC, CNE, CTMH, CLNC, FAANP

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Additional Reading

- Grover S, et al. (2014). Pharmacogene Genomics.
- Hall-Flavin DK, et al. (2012). Translational Psychiatry. 2(10): e172.
- Hall-Flavin DK, et al. (2013). Pharmacogenetic Genomics. 23(10):535-48.
- Porcelli S, et al. (2012). European Neuropsychopharmacolology.
- Rush AJ, et al. (2006). American Journal of Psychiatry.
- Serretti A, et al. (2007). Molecular Psychiatry.
- Winner JG, et al. (2013). Discovery Medicine.
- Winner JG, et al. (2015). Current Medical Research & Opinion.

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Image Sources

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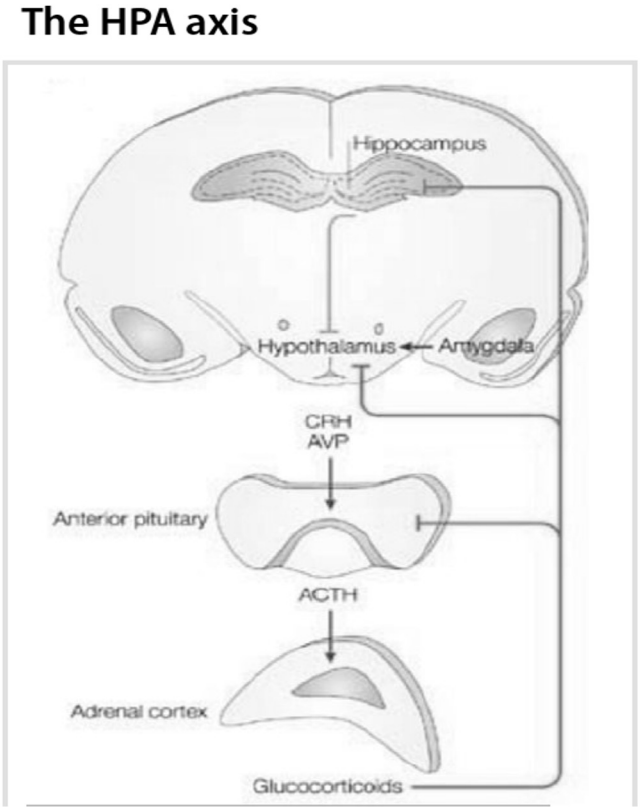
Chronic Stress



Source: psycheducation.org

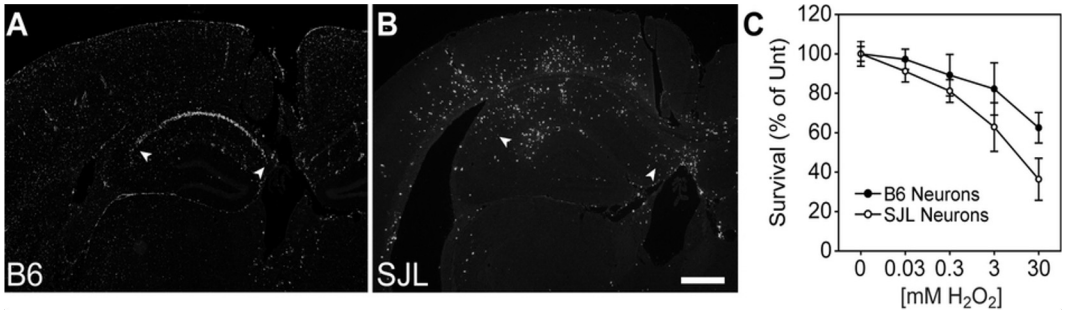
Leading cause of depression

Exposure to stress for >21 days:

- Overactivity of HPA axis
- Glucocorticoid receptor (GR) resistance
  - ↓ suppression of proinflammatory cytokines

Hippocampus

- Closely associated with limbic system
- Greatest density of GRs
- Stress >21 days: Apoptosis
  - hippocampal cell atrophy; loss of negative feedback inhibition to hypothalamus
  - HPA axis dysregulation

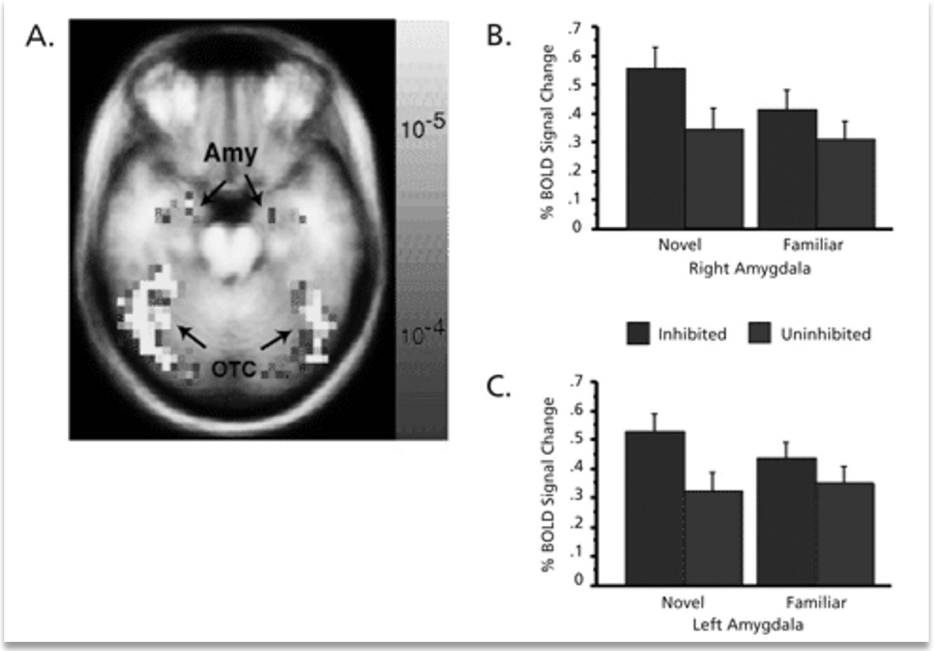


Source: jameco.com

- SSRIs, SNRIs and TCAs stimulate hippocampal neurogenesis

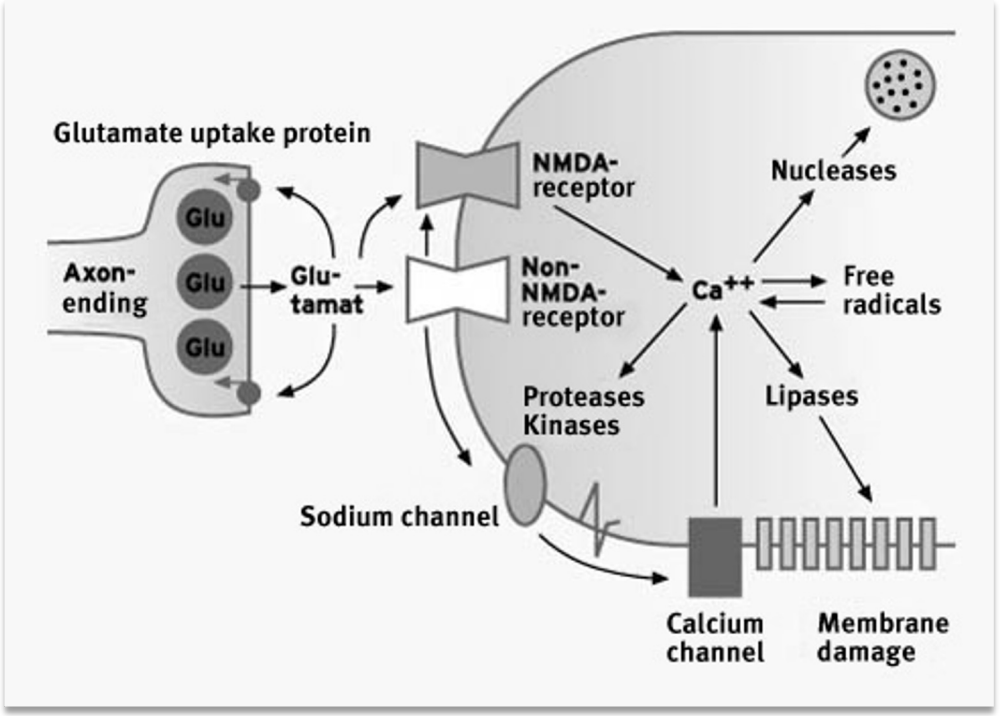
Functional Neuroimaging

- Inefficient info processing in dorsolateral PFC
- Increased activity at amygdala
- Provocative testing of amygdala:
  - Induced sadness (over-reactive)
  - Induced happiness (under-reactive)



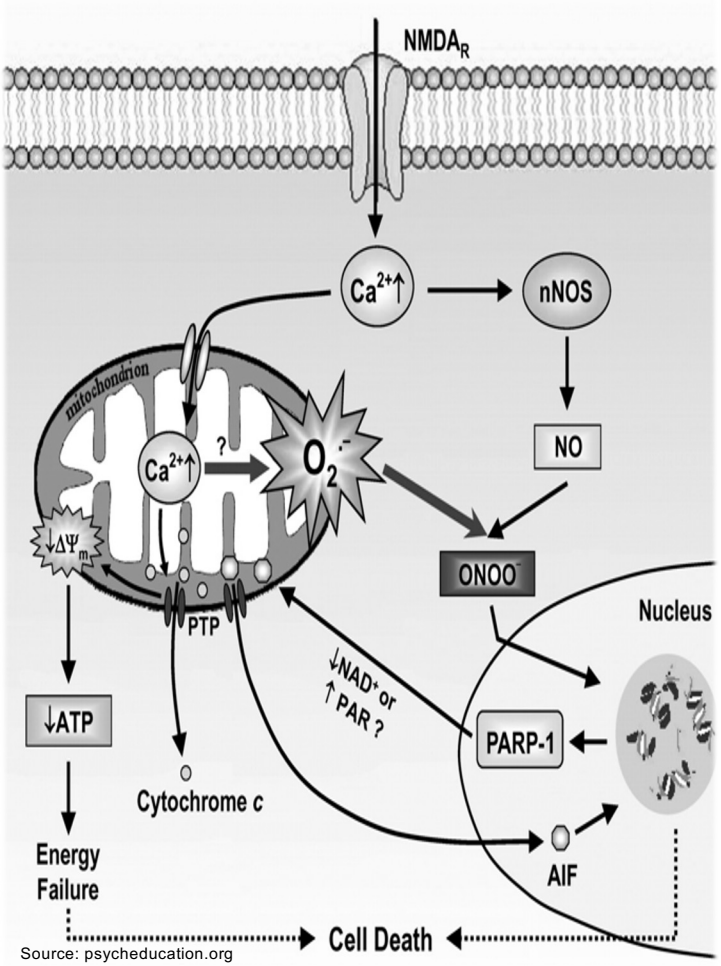
Glutomate Excitotoxicity

- Hypoxia & hypoglycemia leads to glutamate accumulation in ECF ➔ nerve-cell death (excitotoxicity)
- Results in decreased grey matter density in frontal lobes



Source: psycheducation.org

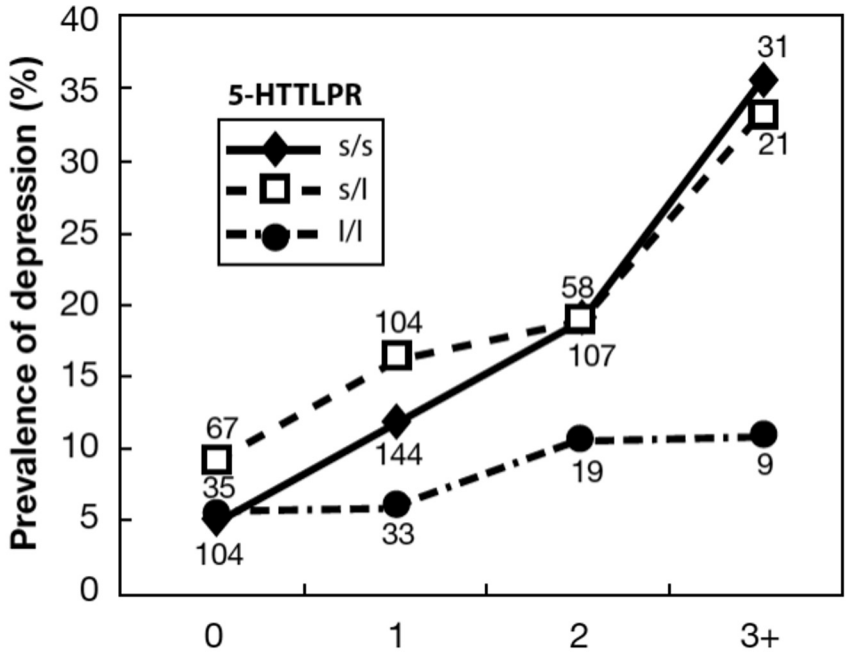
NMDA Receptors

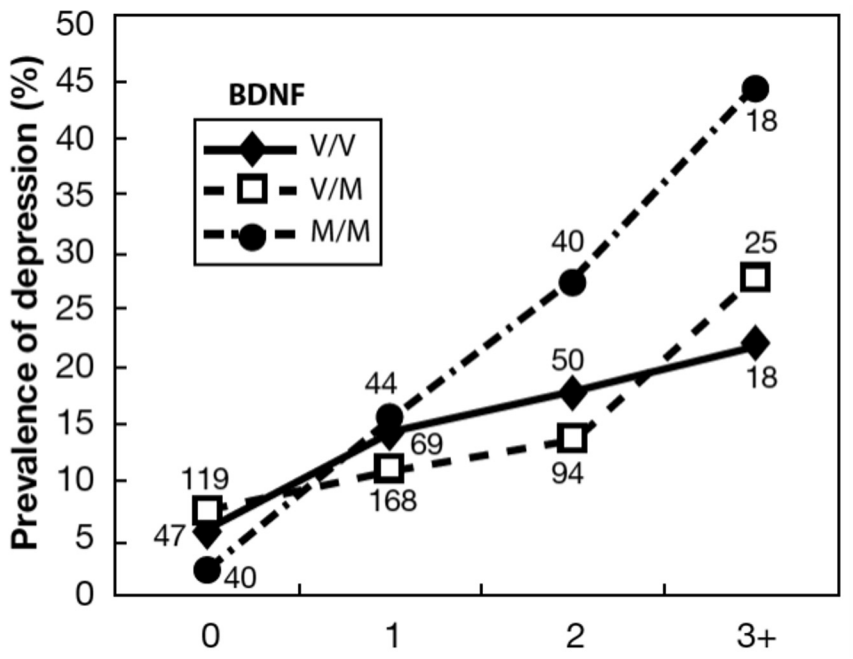


Source: psycheducation.org

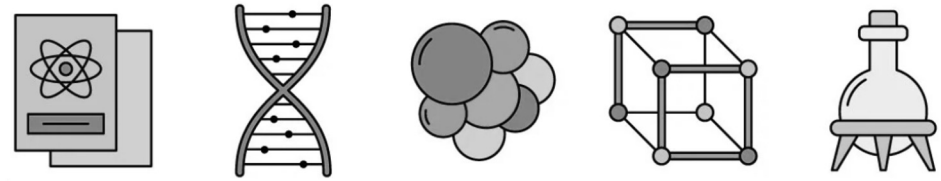
- Excessive glutamatergic activation leads to excitotoxicity
- More than one type (excitatory/inhibitory)
- New drug development focuses on:
  - Inhibition of glutamate binding
  - Ion channel blockade
  - Binding inhibition at terminal regulatory domain
  - Ketamine derivatives

Epigenetics: Stress & Depression

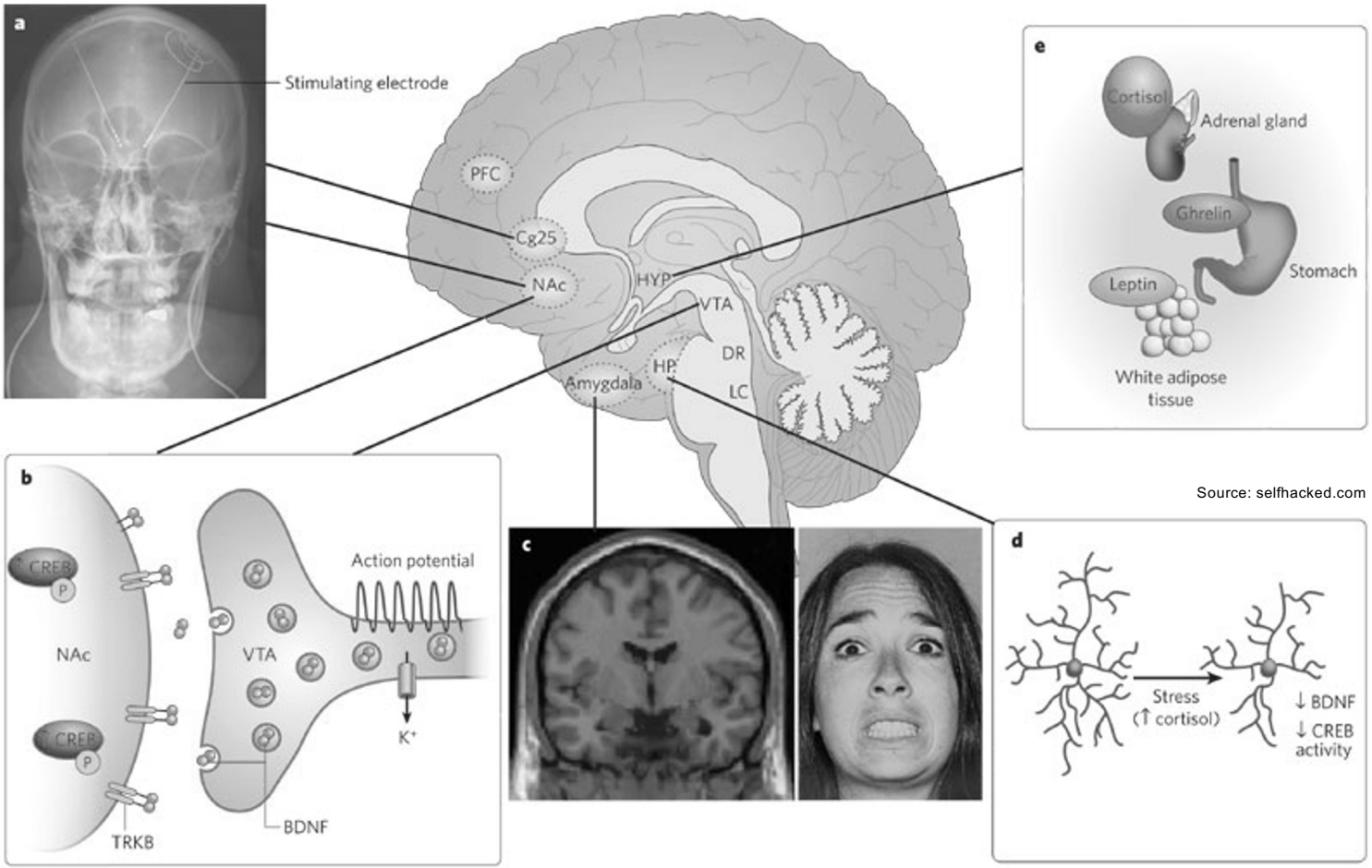




Source: psycheducation.org

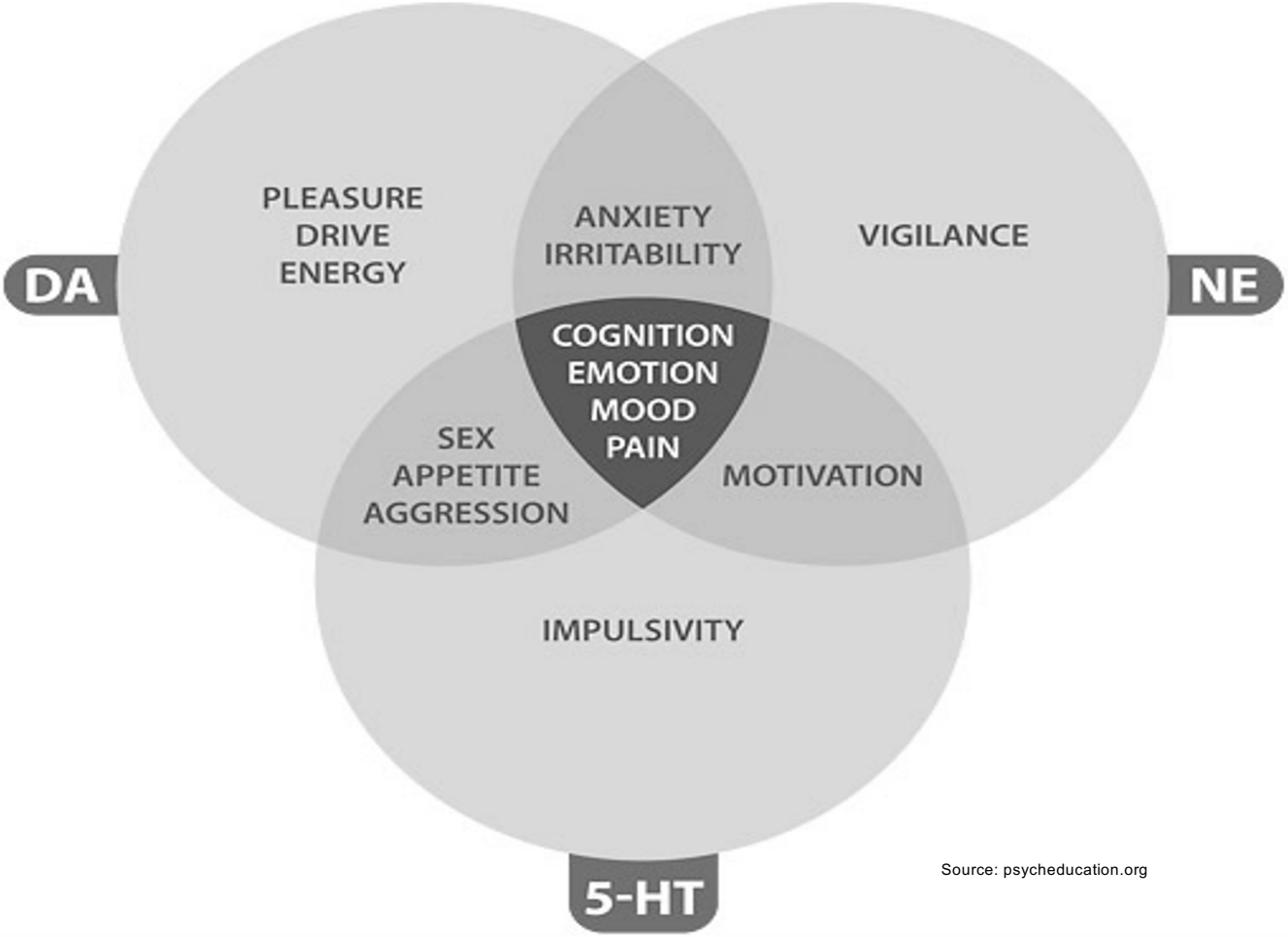


So…It's Complicated!

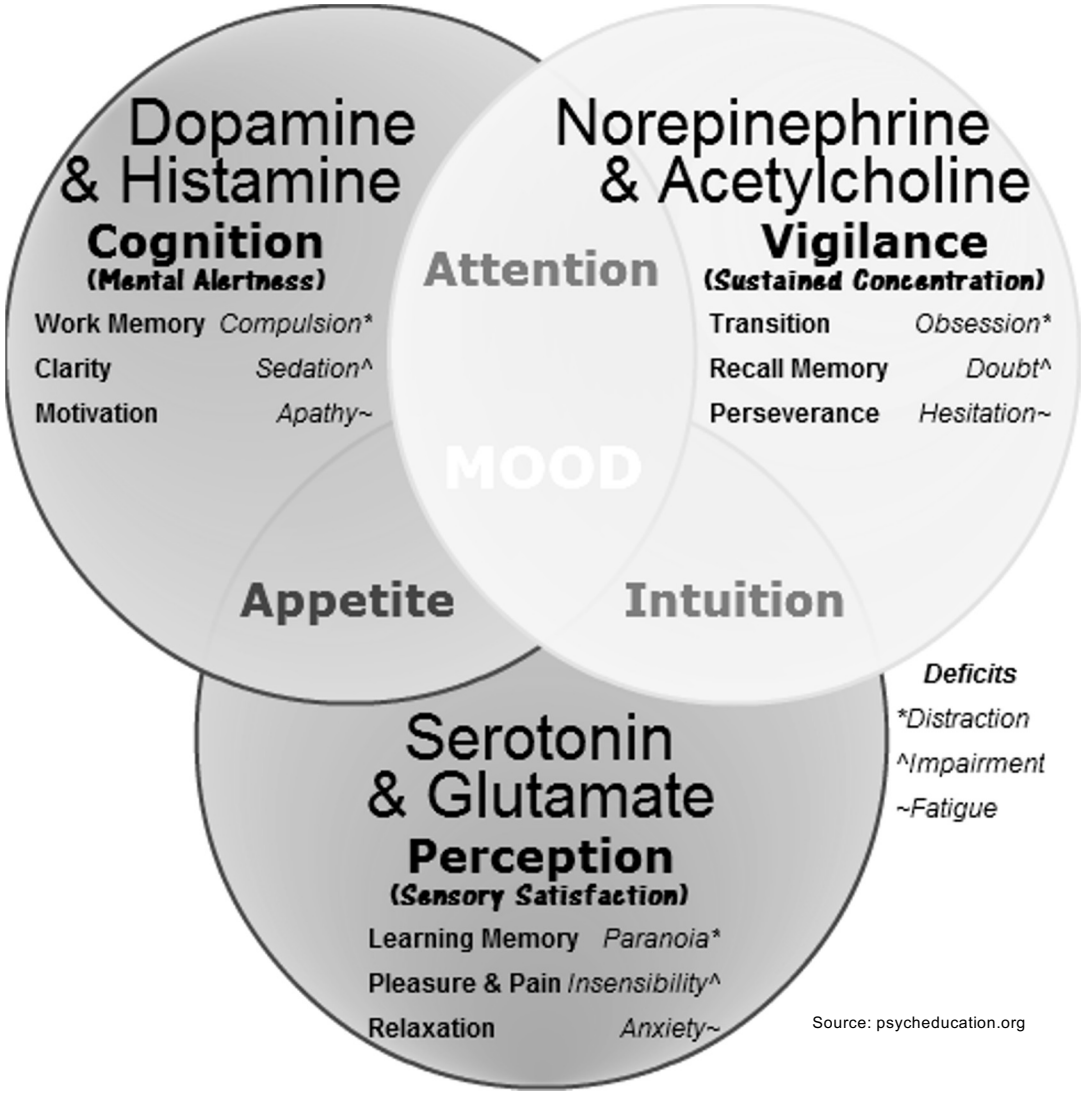


Source: selfhacked.com

“Mapping” Depression



Source: psycheducation.org



Source: psycheducation.org

Potential Genetic Equipoise

Gene	Protein	Biological Function	Therapeutic Implications
SLC 6A4 variation	SERT	Serotonin reuptake	Poor response, slow response, poor tolerability to SSRIs/SNRIs
$5HT_{2c}$ variation	$5HT_{2c}$ receptor	Regulates DA & NE release	Poor response, poor tolerability to atypical antipsychotics
DRD_2 variation	D_2 receptor	Mediates positive symptoms of psychosis, movements in Parkinsonism	Poor response, poor tolerability to atypical antipsychotics
COMT Val variation	COMT enzyme	Regulates DA levels in PFC; metabolizes DA & NE	Reduced executive functioning
MTHFR T variation	MTHFR enzyme	Regulates L-methylfolate levels & methylation	Reduced executive functioning, especially with Val COMT (T with Val)

Miss O.’s PGx Testing Results

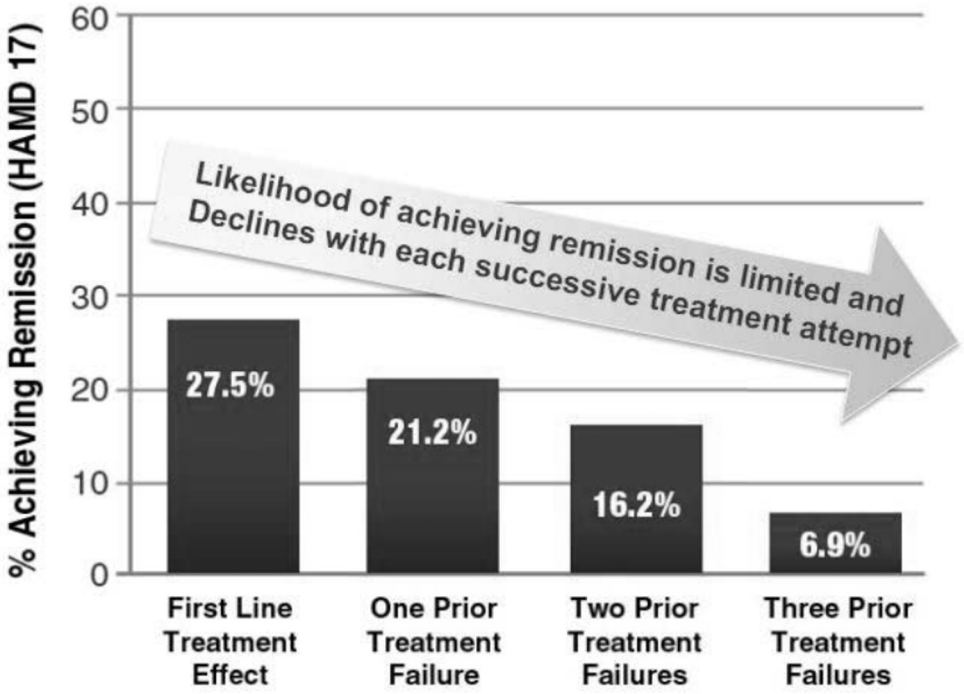
Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	**amitriptyline** (Elavil®) [3,7]	**fluoxetine** (Prozac®) [1,4,6]
desvenlafaxine (Pristiq®)	**citalopram** (Celexa®) [3,4]	
levomilnacipran (Fetzima®)	**clomipramine** (Anafranil®) [3,7]	
selegiline (Emsam®)	**desipramine** (Norpramin®) [1]	
vilazodone (Viibryd®)	**doxepin** (Sinequan®) [3,7]	
	duloxetine (Cymbalta®) [2,7]	
	escitalopram (Lexapro®) [3,4]	
	fluvoxamine (Luvox®) [2,4,7]	
	imipramine (Tofranil®) [3,7]	
	mirtazapine (Remeron®) [3,7]	
	nortriptyline (Pamelor®) [1]	
	paroxetine (Paxil®) [1,4]	
	sertraline (Zoloft®) [3,4]	
	trazodone (Desyrel®) [3,7]	
	venlafaxine (Effexor®) [1]	
	vortioxetine (Brintellix®) [1]	

[1]: Serum level may be too high, lower doses may be required.
[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[7]: Serum level may be too low in smokers.
[8]: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.

STAR*D: Diminishing Returns



- **Less than 40% of patients achieve remission with initial drug treatment.**
- **With each additional medication trial, the chance of remission decreases, *while treatment intolerance increases.***

Source: Rush AJ, et al. Am J Psychiatry. 2006.

The FDA & Pharmacogenomics

 aripiprazole	"The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose."	CYP2D6 PM
 citalopram	"The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers."	CYP2C19 PM
 thioridazine	"The use of thioridazine in patients known to have reduced activity of P450 2D6 is contraindicated."	CYP2D6 IM or PM
 vortioxetine	"The maximum recommended dose of TRINTELLIX® is 10 mg/day in known CYP2D6 poor metabolizers."	CYP2D6 PM

(Not endorsed by the FDA)

Example PGX Test Report #1

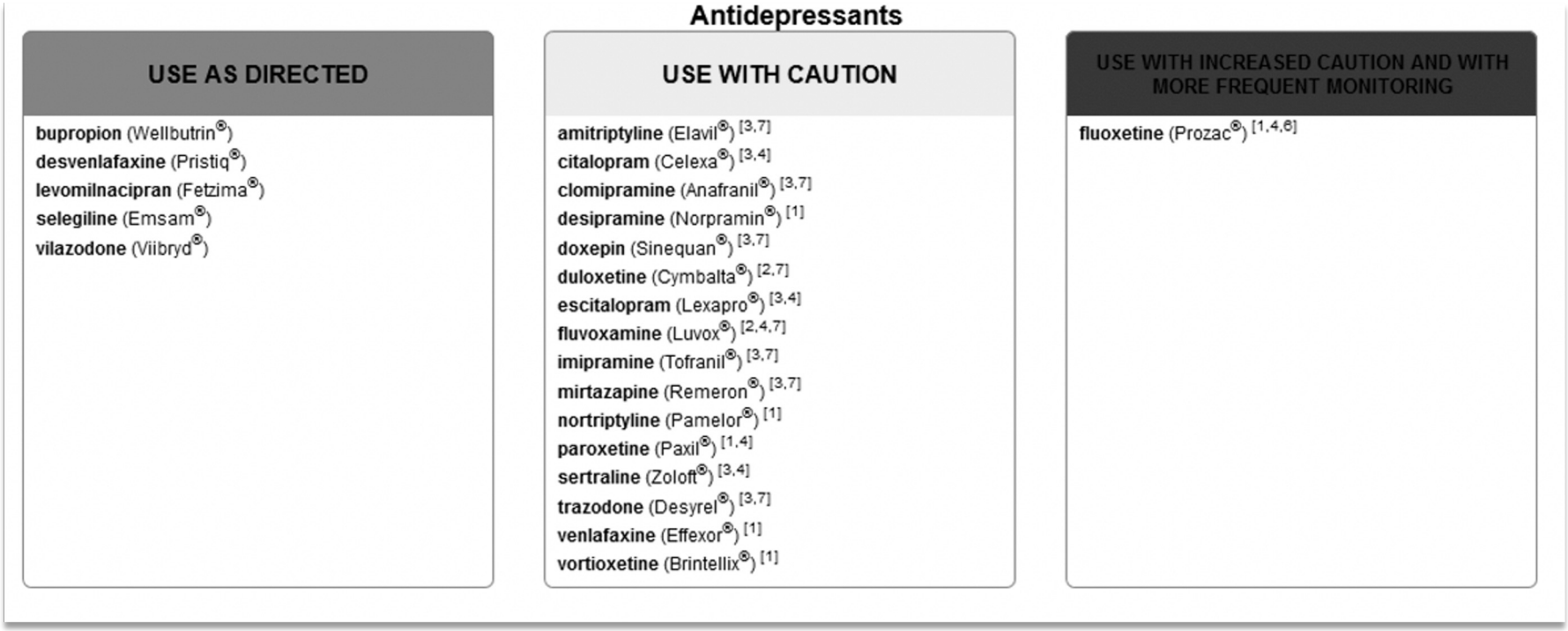
RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Serotonin Transporter (SLC6A4) S/S [High risk of non-response]	*SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • Higher risk of poor response, slow response or intolerance to SSRIs; potential increased risk for PTSD and reduced stress resilience • Therapeutic options such as atypical antidepressants or SNRIs may be used as clinically appropriate		**Use caution** with SSRIs **Therapeutic options: atypical antidepressants** or **SNRIs** may be used if clinically indicated
Calcium Channel (CACNA1C) A/A [Highest risk of altered neuronal signaling]	*CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain* • Abnormal calcium signaling may be clinically associated with conditions characterized by mood instability or lability		**Therapeutic options: atypical antipsychotics, mood stabilizers** and/or **omega-3 fatty acids** may be used if clinically indicated
Melanocortin 4 Receptor (MC4R) A/A [High weight gain risk]	*MC4R is a receptor that plays a central role in the control of food intake* • Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics **High risk**: Clozapine; Olanzapine; **Medium risk**: Aripiprazole; Iloperidone; Paliperidone; Quetiapine; Risperidone **Lower risk**: Asenapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone		**Use caution** with atypical antipsychotics
Methylenetetrahydrofolate Reductase (MTHFR) C677T: T/T A1298C: A/C [Low activity]	*MTHFR is an enzyme responsible for the conversion of folic acid to methylfolate which is a precursor needed for serotonin, norepinephrine and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • Folic acid-based supplementation of SSRIs and SNRIs show superior symptom reduction and medication adherence compared to SSRIs/SNRIs alone in Major Depressive Disorder		Higher intake of folic acid based interventions may be required **Therapeutic options: l-methylfolate** may be used if clinically indicated

Genomind PGx Pro: actual patient report

Example PGx Test Report #2



Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	**amitriptyline** (Elavil®) [3,7]	**fluoxetine** (Prozac®) [1,4,6]
desvenlafaxine (Pristiq®)	**citalopram** (Celexa®) [3,4]	
levomilnacipran (Fetzima®)	**clomipramine** (Anafranil®) [3,7]	
selegiline (Emsam®)	**desipramine** (Norpramin®) [1]	
vilazodone (Viibryd®)	**doxepin** (Sinequan®) [3,7]	
	duloxetine (Cymbalta®) [2,7]	
	escitalopram (Lexapro®) [3,4]	
	fluvoxamine (Luvox®) [2,4,7]	
	imipramine (Tofranil®) [3,7]	
	mirtazapine (Remeron®) [3,7]	
	nortriptyline (Pamelor®) [1]	
	paroxetine (Paxil®) [1,4]	
	sertraline (Zoloft®) [3,4]	
	trazodone (Desyrel®) [3,7]	
	venlafaxine (Effexor®) [1]	
	vortioxetine (Brintellix®) [1]	

[1]: Serum level may be too high, lower doses may be required.
[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[7]: Serum level may be too low in smokers.
[8]: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.

Clinical Considerations

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	**amitriptyline** (Elavil®) [3,7]	**fluoxetine** (Prozac®) [1,4,6]
desvenlafaxine (Pristiq®)	**citalopram** (Celexa®) [3,4]	
levomilnacipran (Fetzima®)	**clomipramine** (Anafranil®) [3,7]	
selegiline (Emsam®)	**desipramine** (Norpramin®) [1]	
vilazodone (Viibryd®)	**doxepin** (Sinequan®) [3,7]	
	duloxetine (Cymbalta®) [2,7]	
	escitalopram (Lexapro®) [3,4]	
	fluvoxamine (Luvox®) [2,4,7]	
	imipramine (Tofranil®) [3,7]	
	mirtazapine (Remeron®) [3,7]	
	nortriptyline (Pamelor®) [1]	
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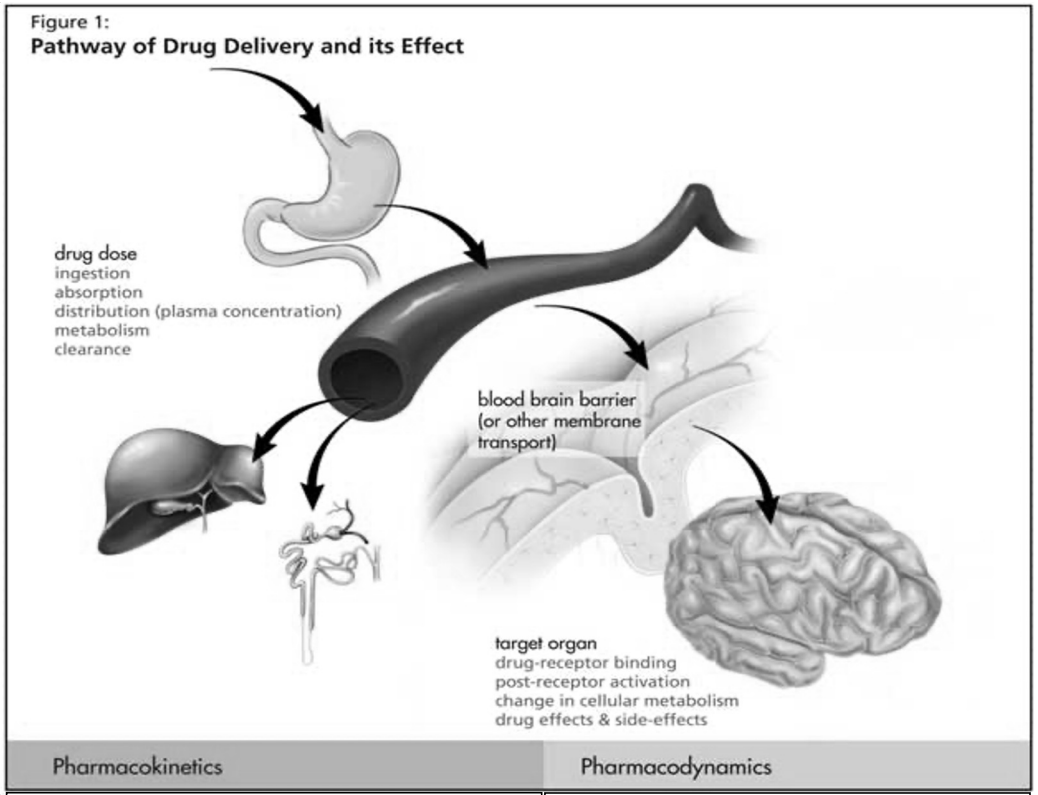
[7]: Serum level may be too low in smokers.
[8]: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.

Assurex Genesight: actual patient report

Integrative Genetic Profile

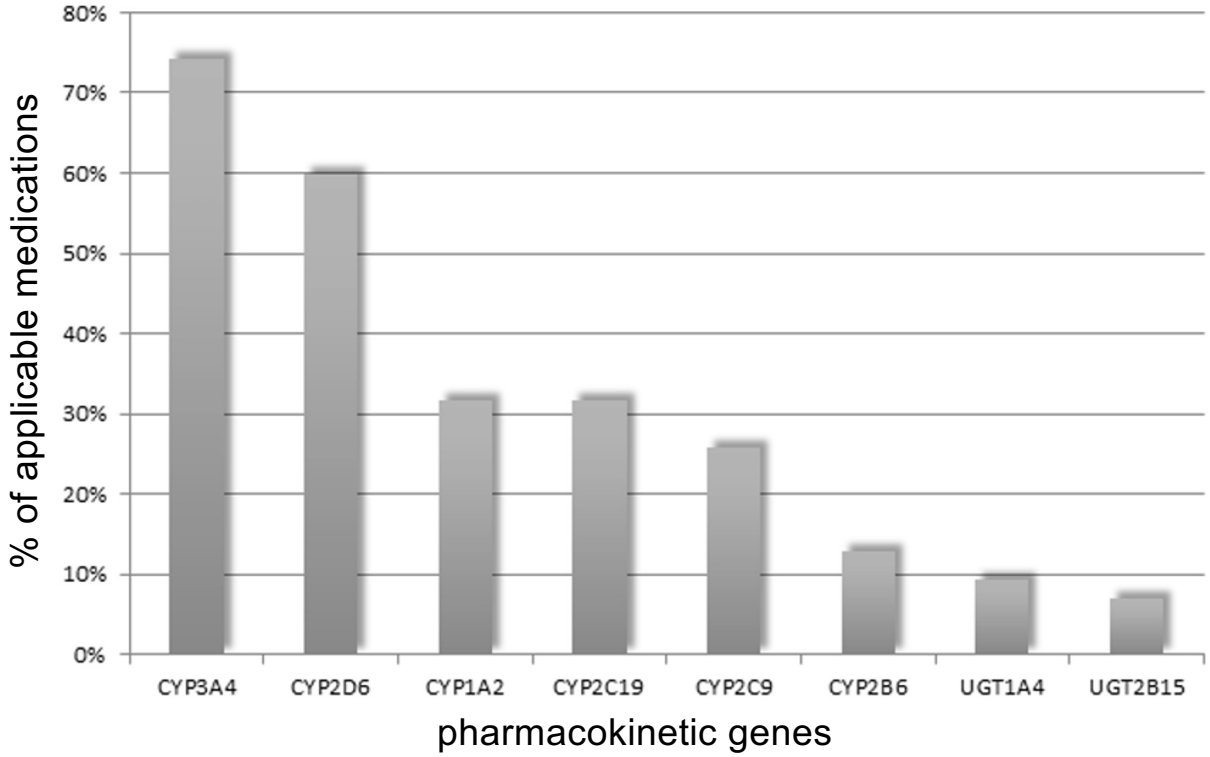


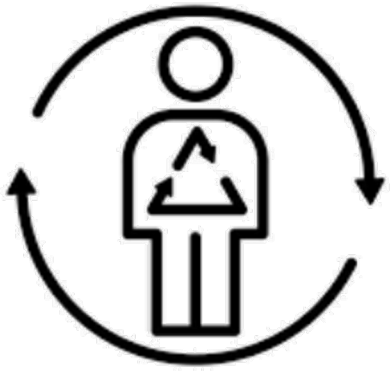
Pharmacokinetic Genes: impact on drug concentration	**Pharmacodynamic Genes**: impact on target site expression and affinity

Huang, A., *Pathway of Drug Delivery and its Effect*. 2008: 28th Canadian Geriatrics Society Annual Meetings: Academic Career Day. www.geriatricsandaging.ca/2008CGS

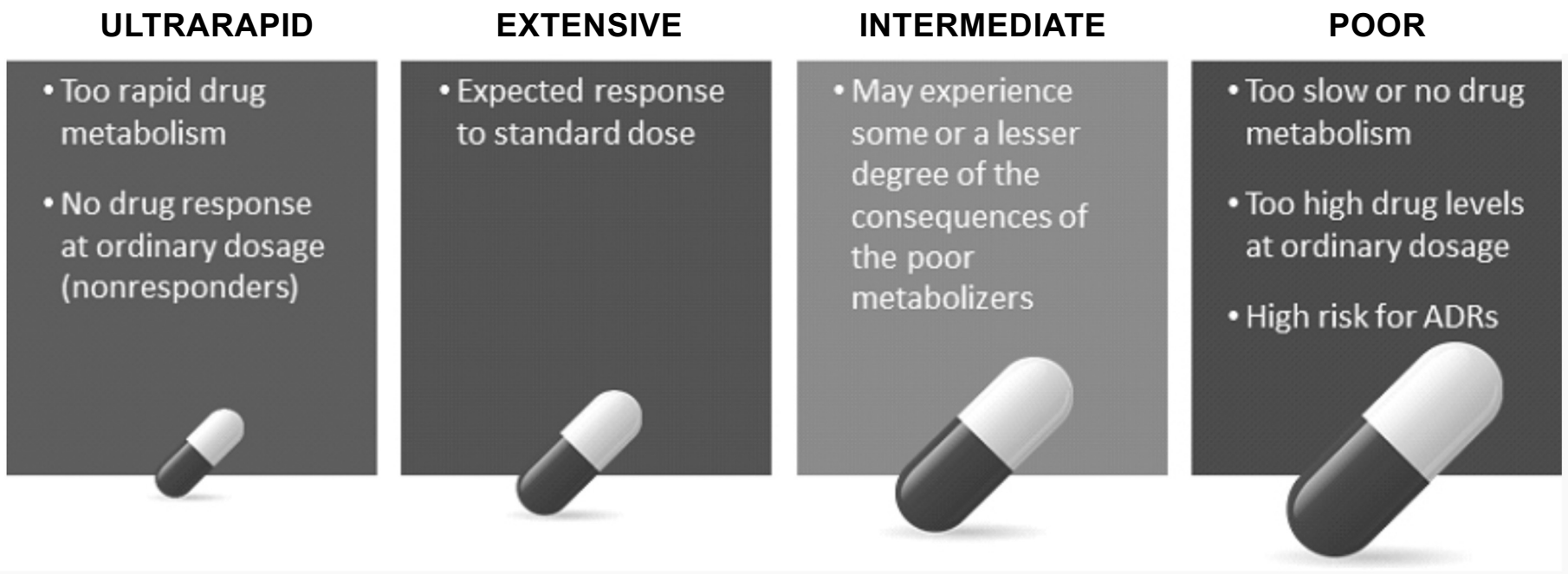
In addition to traditional strategies, **PD genes can inform potential alternative therapy options** to which a patient is more likely to respond.

Medication Metabolism
% of medication substrates for CYP450 and UGT enzymes



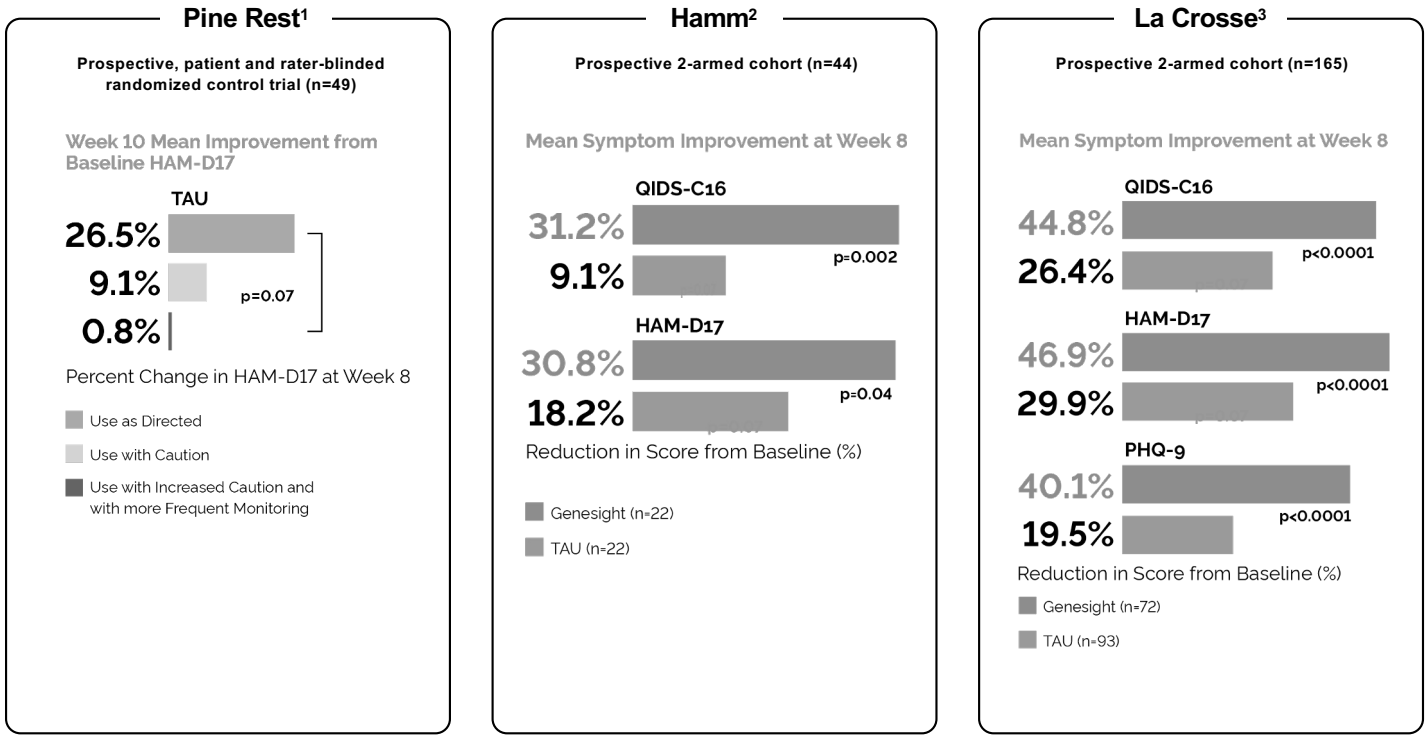


Genetics & Medication Serum Levels



Source: psycheducation.org

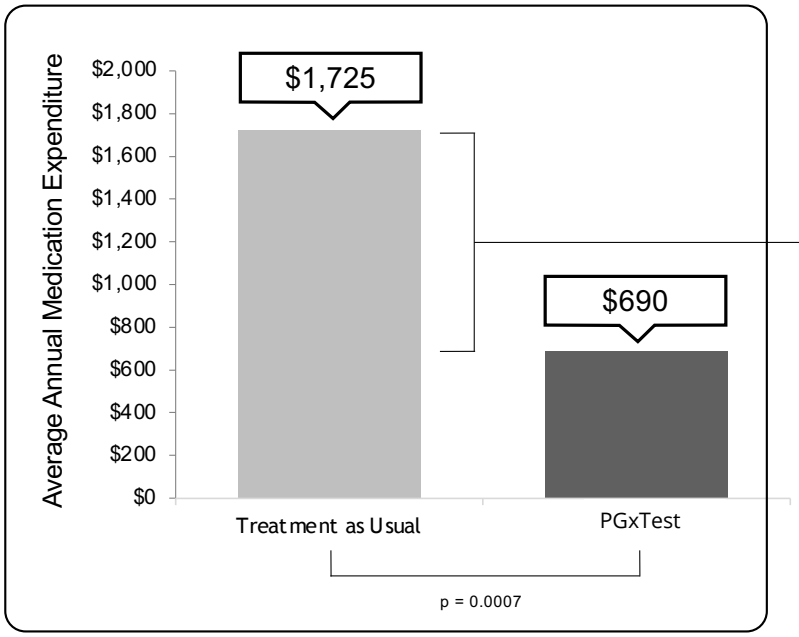
Guided Study Foundation



1. Winner JG, et al. Discov Med 2013 Nov; 16(89):219-27. (Pine Rest). 2. Hall-Flavin DK, et al. Transl Psychiatry 2012 Oct; 2(10): e172. (Hamm) 3. Hall-Flavin DK, et al. Pharmacogenet Genomics 2013 Oct; 23(10):535-48. (La Crosse)

Economic Utility | Rx Expenditures

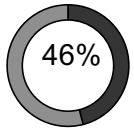
Total medication costs were reduced when treatment was guided by the pharmacogenomic test.



Winner JG, et al. Curr Med Research & Opin. 2015.

$1,035
Avg annual savings per patient

PGx-guided treatment helped to increase adherence and reduce polypharmacy

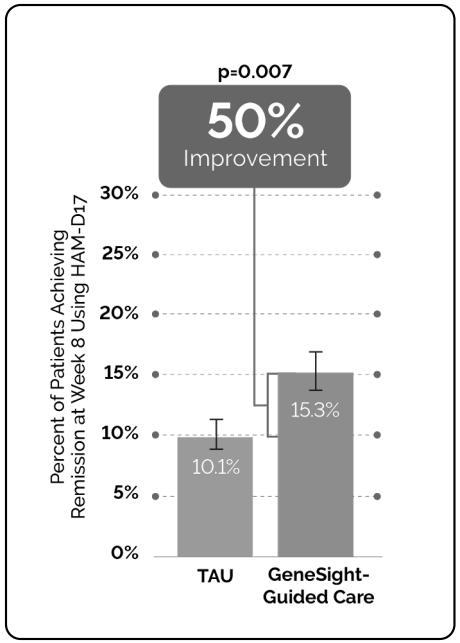


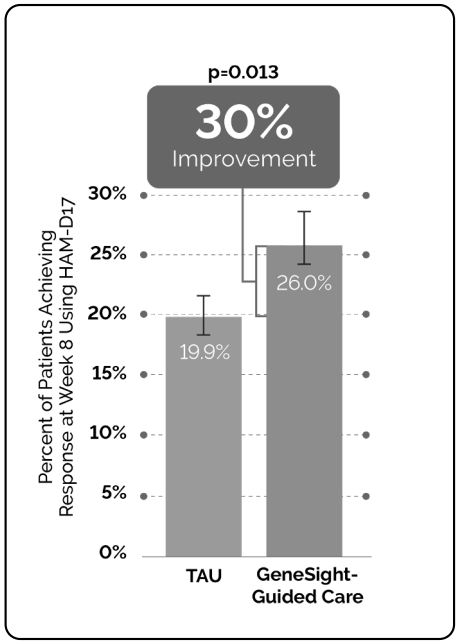
Patients stayed on a new medication 46% longer when guided by the PGx test

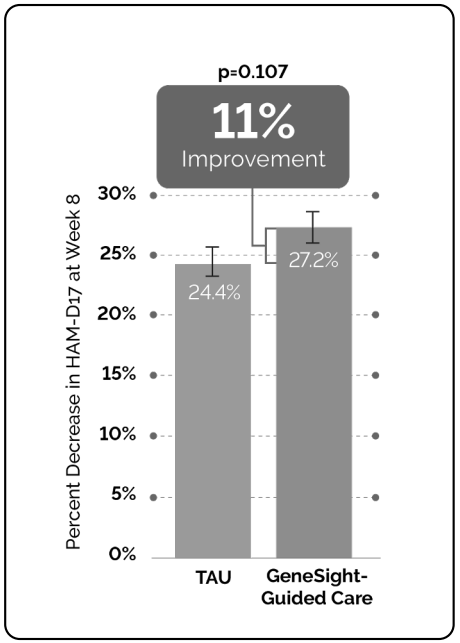
20% of patients were on fewer medications

Remission & Response

Treatment guided by the pharmacogenomic test resulted in a 50% improvement in remission rates and a 30% increase in response rates at week 8 compared to TAU. Symptom improvement in the genomics-guided group trended toward significance at week 8, compared to TAU.

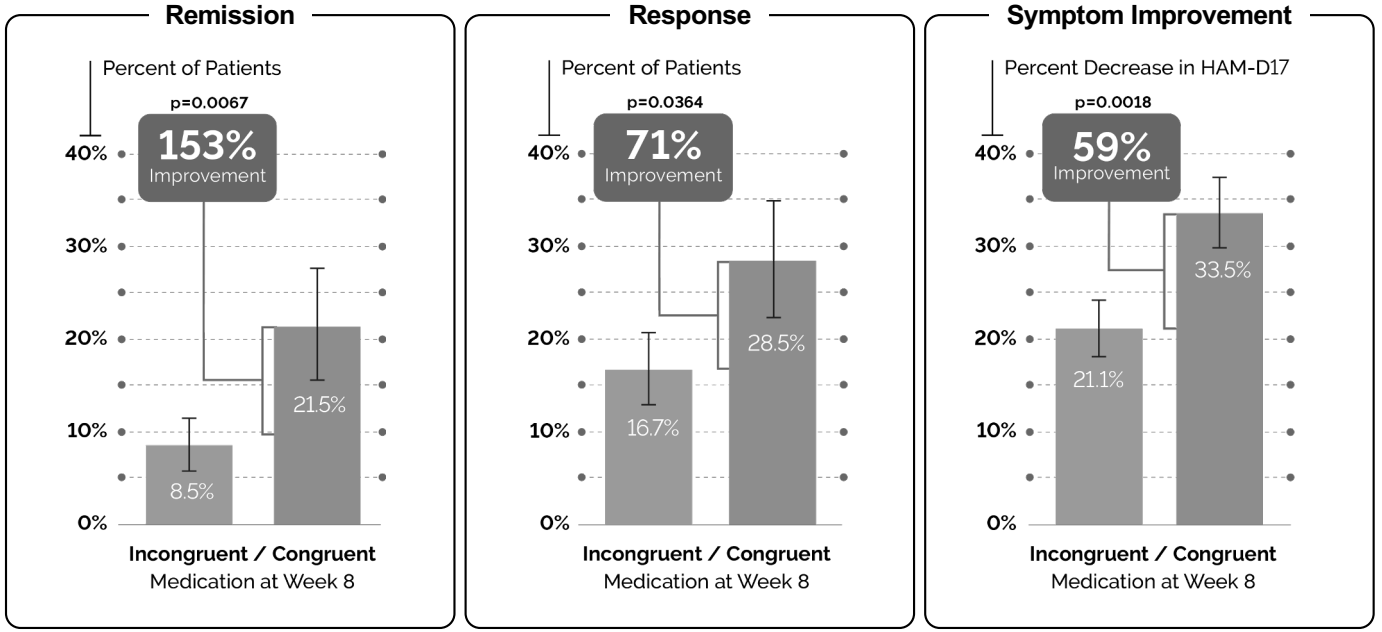






Switching Rx to Optimize Therapy

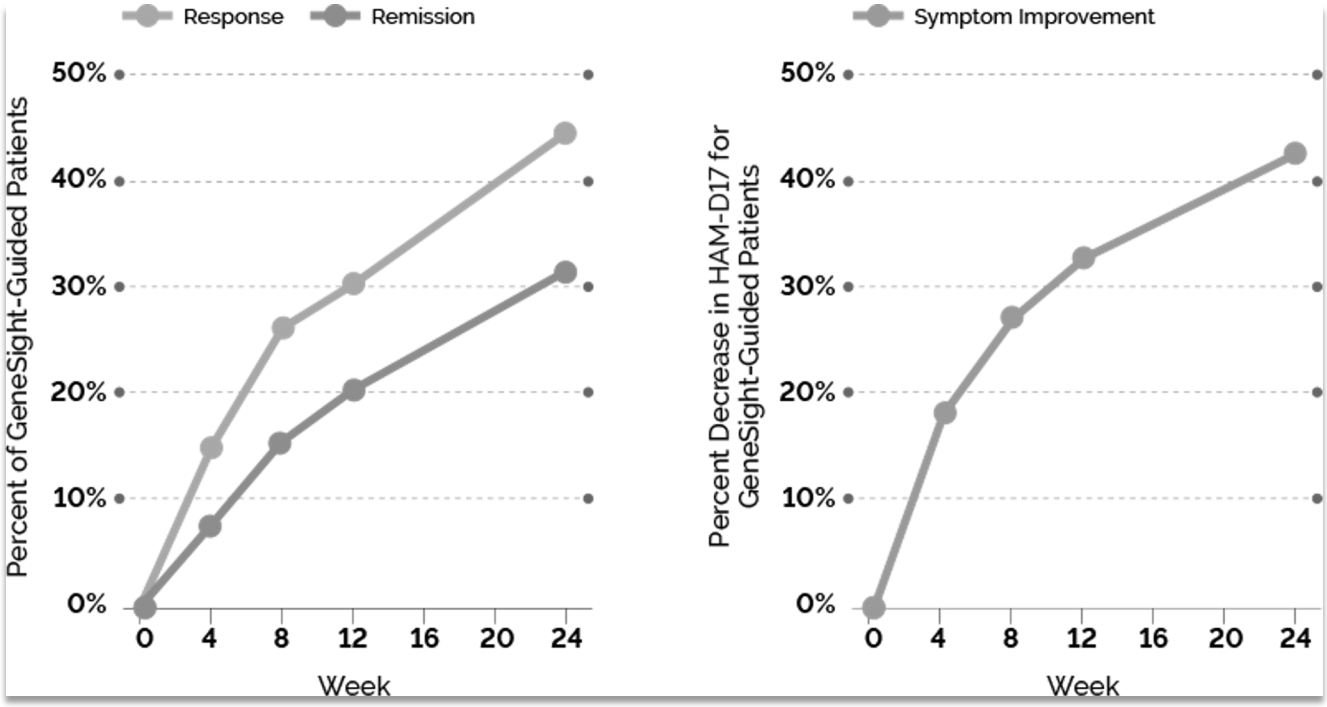
Significant improvements in symptom reduction, response, and remission were seen when patients were switched to a genetically optimal medication



How will you know which 20% will be on a sub-optimal medication?

Durability

Clinical utility was durable over 6 months. Remission rates continued to increase and doubled during the open-label period.



1. Winner JG, et al. Discov Med 2013 Nov; 16(89):219-27. (Pine Rest). 2. Hall-Flavin DK, et al. Transl Psychiatry 2012 Oct; 2(10): e172. (Hamm) 3. Hall-Flavin DK, et al. Pharmacogenet Genomics 2013 Oct; 23(10):535-48. (La Crosse)

Ms. P.'s PGx Test Results

Clinician: Joshua M Hamilton **Report Date:** 6/12/2014

NORMAL FOLIC ACID CONVERSION	REDUCED FOLIC ACID CONVERSION	SIGNIFICANTLY REDUCED FOLIC ACID CONVERSION
		✓

Note: Serum levels of folate may be too low. Folate supplementation or higher daily intake of folic acid may be required.

Patient Genotype and Phenotype

MTHFR	Reduced Activity	T/T
This individual is homozygous for the T allele of the C677T polymorphism in the MTHFR gene. This genotype is associated with significantly reduced folic acid metabolism, significantly decreased serum folate levels, and significantly increased homocysteine levels.		

Fitzgerald
Colibri Healthcare

Anxiously Awaited: Neurobiology & Personalized Treatment of Anxiety

Josh Hamilton,
DNP, RN/PMH-BC, FNP-C, PMHNP-BC, CNE, CTMH, CLNC, FAANP

1

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Chief Clinical Officer
The Hamilton Group Behavioral Health
AANP Nevada State Representative
josh@askjoshhamilton.com

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Disclosure

Josh Hamilton is a:

- consultant & speaker for Myriad Neuroscience (pharmacogenomics)
- paid ambassador for Point of Care Network (POCN)

All relevant financial relationships have been mitigated.

3

3

Neurobiology of Anxiety: Not just a Bunch of GABA

- At the end of this presentation, the participant will be able to:
  1. Conceptualize mental illness in the context of epi/genetics and neurobiology, with an emphasis on anxiety disorders.
  2. Develop a working knowledge of **updated diagnostic criteria** and **disease models** to improve case identification and diagnosis of anxiety disorders.
  3. Discuss contemporary approaches to **management** of anxiety disorders, including practical applications for nurse practitioners *(Rx)*.
  4. Explore evidence- and eminence-based **polypharmaceutical approaches** to selection and monitoring of treatments for anxiety *(Rx)*.
  5. Apply concepts of **pharmacogenomics** to the selection, prescription and management of **drug therapy** for anxiety disorders *(Rx)*.

4

Tips

- References
  - Listed throughout and at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

5

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Moving right along…

Source: Public Domain at mashable.com

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Source:https://www.flickr.com

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7

The brain doesn't care about the new DSM!

Symptom-based treatment strategy:

1. Deconstruct into component symptoms
2. Match to brain circuits/NTs
3. Select therapies rationally

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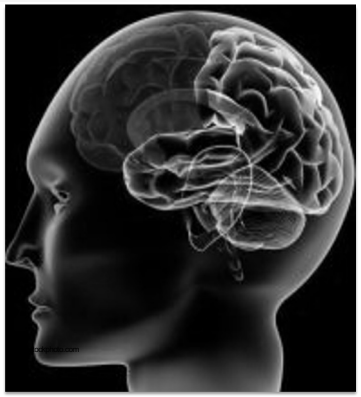
Neuroanatomy of Anxiety

- **Amygdala**: processing emotionally salient stimuli
- **Medial PFC**: modulation of affect
- **Hippocampus**: memory encoding & retrieval
- **CTSC**: "Worry loops"



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Stress Diathesis & Anxiety

- Neurohormonal responses to stress:
  - Pituitary➔adrenal cortisol
  - Catecholamine production
  - CRF produced in hypothalamus
  - Increased HPA activity➔stress reactivity

Feedback loop in hippocampus (glucocorticoid/CRF receptor proteins)

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FEAR: Neurobiological Regulators

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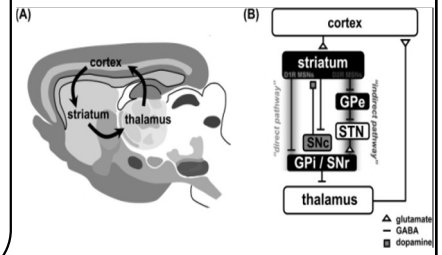
Worry

- CTSC feedback loops ("worry loops") in PFC
- Apprehension
- Obsession
- Catastrophizing
- Anxious Misery
- Ruminations and delusions?



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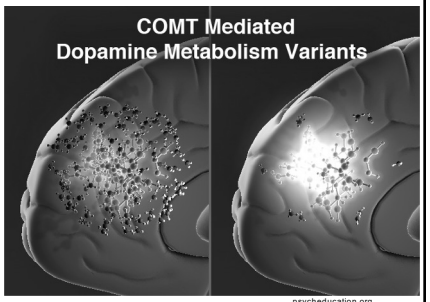
WORRY: Neurobiological Regulators

- 5HT
- GABA
- DA (COMT)
- NE
- Glutamate
- Voltage-gated ion channels



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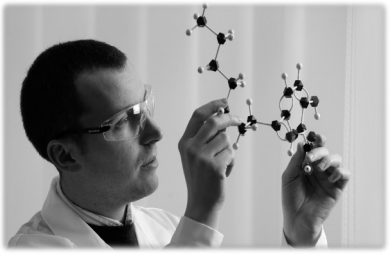
Pharmacotherapeutics for Anxiety



$\alpha_2\delta$ ligands
- gabapentin
- pregabalin

Serotonergics
- SERT inhibitors
- buspirone (BuSpar®)

Noradrenergics
- α_1 blockers
- NET inhibitors

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"Mother's Little Helpers"

BZDs effective to ↓ anxiety sx
- risk of dependence; use with caution
- PRN basis or scheduled (depending upon specific patient)
- *Avoid alprazolam!*

Caution with history of addiction
- Especially if active AOD abuse or dependence

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BZD Comparisons

	Action	(hrs)			Equivalent
Long-Acting					
Chlordiazepoxide (Librium)	Int	2-4	5-30 (parent) 3-100 (metab)	Oxidation	10mg
Diazepam (Valium)	Rapid	1	20-50 (parent) 3-100 (metab)	Oxidation	5mg
Flurazepam (Dalmane)	Rapid	0.5-2	47-100 (metab)	Oxidation	30mg
Intermediate Acting					
Alprazolam (Xanax)	Int	0.7-1.6	6-20 (parent)	Oxidation	0.5mg
Clonazepam (Klonopin)	Int	1-4	18-39 (parent)	Oxidation	0.25mg
Lorazepam (Ativan)	Int	1-1.5	10-20 (parent)	Conjugation	1mg
Oxazepam (Serax)	Slow	2-3	3-21 (parent)	Conjugation	15mg
Temazepam (Restoril)	Slow	0.75-1.5	10-20 (parent)	Conjugation	30mg
Short Acting					

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BZD Conversions

Benzodiazepine	Equivalent Diazepam mg
Alprazolam	10
Chlordiazepoxide	0.4
Clonazepam	2.5
Flurazepam	0.6
Lorazepam	5
Oxazepam	1
Temazepam	1

For example, the equivalent diazepam dose for 12 mg daily of lorazepam would be 12*5 = 60 mg daily
(typical administered in 3-4 divided doses)

Miller NS, Gold MS, Management of withdrawal syndromes and relapse prevention in drug and alcohol dependence. Am Fam Physician. 1998 Jul;58(1):139-46

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Generalized Anxiety Disorder

Source: MS Clip Art

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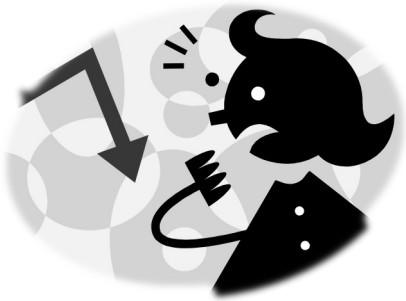
Panic Disorder



Source: MS Clip Art

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Panic Disorder Etiology

- Drug/Alcohol
- Genetics
- Social learning
- Cognitive theories
- Neurobiology/conditioned fear
- Psychosocial stressors
  - Prior separation anxiety

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Treatment of Panic Disorder

- ≥70% treatment response
- Educate, reassure, eliminate caffeine, AOD, stimulants
- CBT
- Medications
  - SSRIs/SNRIs
  - short-term "rescue" BZD
  - gabapentin (Neurontin), pregabalin (Lyrica)
  - TCAs & MAOIs

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Social Anxiety Disorder

Source: MS Clip Art

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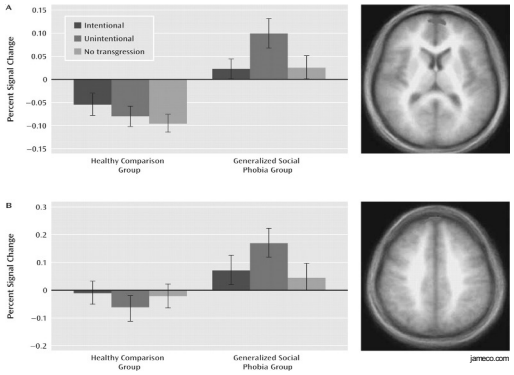
What's going on in the brain?



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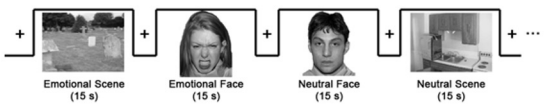
What's going on in the brain?

- Both groups ↑ medial PFC activity in response to intentional vs. unintentional transgression.
- Social Anxiety Disorder:
  - significant response to unintentional transgression
  - significant increased activity in amygdala & insula



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Treatment: Social Anxiety Disorder

- Social skills, bx therapy, CBT
- Pharmacotherapy
  - First-line BZD not generally accepted
  - Less evidence: sedating ADs & older ADs
  - β blockers (for discrete situations)
  - Naltrexone & acamprosate?

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Obsessive-Compulsive & Related Disorders

- Obsessive-Compulsive Disorder
- Body Dysmorphic Disorder
- Hoarding Disorder
- Trichotillomania
- Excoriation Disorder

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Obsessive-Compulsive Disorder

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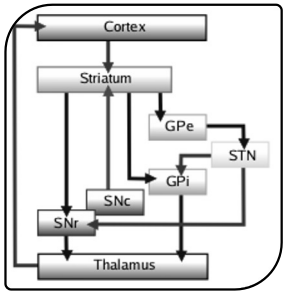
OCD Etiology



- Genetics
- Dopaminergic dysfunction
- Serotonergic dysfunction
- Cortico-striato-thalamo-cortical loop
- Autoimmune- PANDAS

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Functional Imaging & OCD

- Increased activity in right caudate
- CBT reduces resting state glucose metabolism & blood flow in right caudate (for responders)
- Similar results obtained with pharmacotherapy

MS Clip Art

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Treatment: Obsessive-Compulsive Disorder

- **40-60% treatment response**
- **Serotonergic antidepressants**
- **Behavioral therapy**
- **Adjunctive antipsychotics, DBS**
- **PANDAS**
  - **penicillin, plasmapharesis, immunotherapy**

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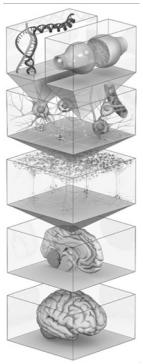
Symptom-Based Selection



innerbody.com

- Build a multi-agent “portfolio”
- Treat all residual symptoms to sustained remission
  1. **Construct** symptoms into a diagnosis
  2. **Deconstruct** into specific symptom list
  3. **Match** symptoms to *brain circuits*
  4. **Consider** known *neuropharmacology* of circuits
  5. **Match** agents to *neuropharmacology*; **fine tune**

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A few words about genetics…

- Potential for dx and tx
- Genetic complexity of psych illness
- Response isn’t “all or none”
- Predict non/response & side-effects
- CYP genotypes
- “Equipoise”

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Potential Genetic Equipoise

Gene	Protein	Biological Function	Therapeutic Implications
SLC 6A4 variation	SERT	Serotonin reuptake	Poor response, slow response, poor tolerability to SSRIs/SNRIs
$5HT_{2c}$ variation	$5HT_{2c}$ receptor	Regulates DA & NE release	Poor response, poor tolerability to atypical antipsychotics
DRD_2 variation	D_2 receptor	Mediates positive symptoms of psychosis, movements in Parkinsonism	Poor response, poor tolerability to atypical antipsychotics
COMT Val variation	COMT enzyme	Regulates DA levels in PFC; metabolizes DA & NE	Reduced executive functioning
MTHFR T variation	MTHFR enzyme	Regulates L-methylfolate levels & methylation	Reduced executive functioning, especially with Val COMT (T with Val)

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Selective Serotonin Reuptake Inhibitors: SSRIs

- Most commonly prescribed
- Mechanism: SERT inhibition?
- Somatodendritic action
- Genetic changes ➔ receptor changes

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The Usual Suspects

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- fluoxetine (Prozac®)
- sertraline (Zoloft®)
- paroxetine (Paxil®)
- fluvoxamine (Luvox®)
- citalopram (Celexa®)
- escitalopram (Lexapro®)

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SNRIs

- Wider reach
- Dose-dependent "noradrenergic boost"
  - Advantages:
    - Tx of pain syndromes
    - Tx of vasomotor symptoms
- "Two-and-a-half" actions

- **venlafaxine (Effexor®):**
  - (SERT > *dose dependent* < NET)
- **desvenlafaxine (Pristiq®):** (NET > SERT)
- **duloxetine (Cymbalta®):** "Depression Hurts"
- **levomilnacipran (Fetzima®):**
  - Good for depression characterized by:
    - Decreased concentration
    - Mental/physical slowing
    - Deficient ADLs
    - Reduced social/occupational fx

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MAOIs & Tricyclics

MAOIs

- **Should not be discounted, especially for TRD and TRA (panic and social anxiety)**

TCAs

- **Three-ring molecular structure; very effective**
- **Four (4) unwanted pharmacologic actions**
- **Good 2nd line ADs; can be good 1st line anti-anxiety medications!**

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Trauma & Stressor - Related Disorders

- Acute Stress Disorder
- Posttraumatic Stress Disorder
- Post-Severe Stress Disorder
- Chronic Stress Syndrome

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Post-Traumatic Stress Disorder

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PTSD Etiology

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- Conditioned fear
- Genetic/familial vulnerability
- Autonomic arousal immediately after trauma (predictive)
- Stress-induced hormone release

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PTSD: A Disorder of Reactivity

wikipedia.org

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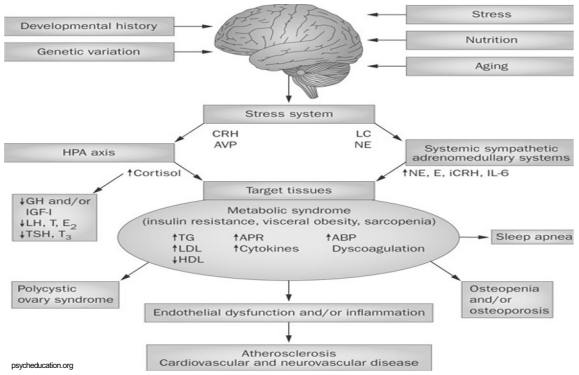
The Stress System



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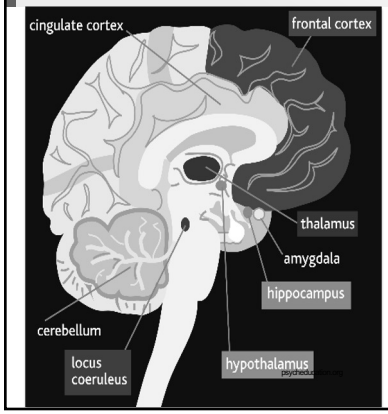
Functional Neuroimaging



- Increased amygdalar activation
- Hippocampal reactivity
- Hypoactivation of medial PFC, including OFC & anterior cingulate cortex

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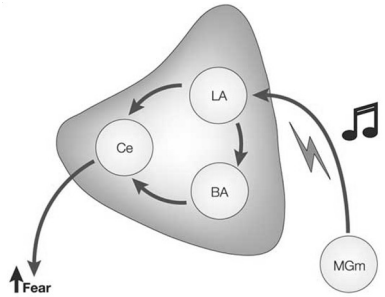
Fear Conditioning

- "Memory" and the amygdala
- Glutamate & NMDA receptors
- Synaptic restructuring
- Long-term potentiation
- Involvement of hippocampus
- Limitations of current treatment



Nature Reviews | Neuroscience

psycheducation.org

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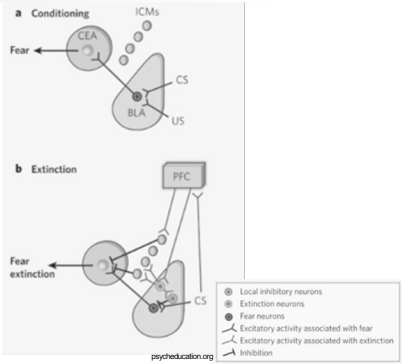
Fear Extinction

- Creates 2nd "gate" through amygdala/PFC
- Recruits GABA-ergic interneurons in amygdala
- More volatility than conditioning
- Prone to renewal
- Effect of current drug therapies < CBT
- Timed-synchronized NMDA activation
  - D-cycloserine
  - SGRIs



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Synchronized Fear Extinction

Public Domain at mashable.com

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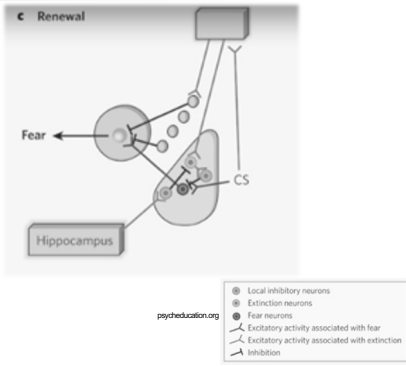
Reconsolidation

- **Molecular consolidation** less permanent than originally believed
- **Protein synthesis**
- **β blockers** disrupt reconsolidation & fear conditioning (opioids also mitigate)
- **Research**: synergy of psychotherapy & pharmacotherapy
  - Timing of application to disrupt reconsolidation



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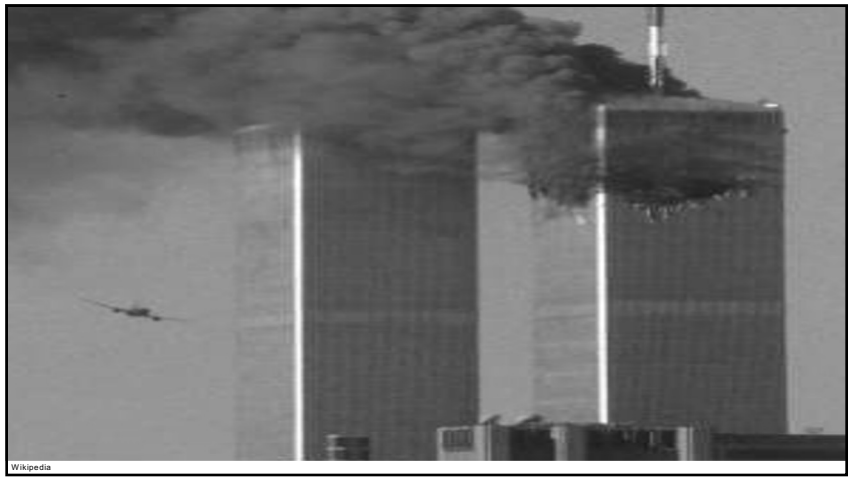

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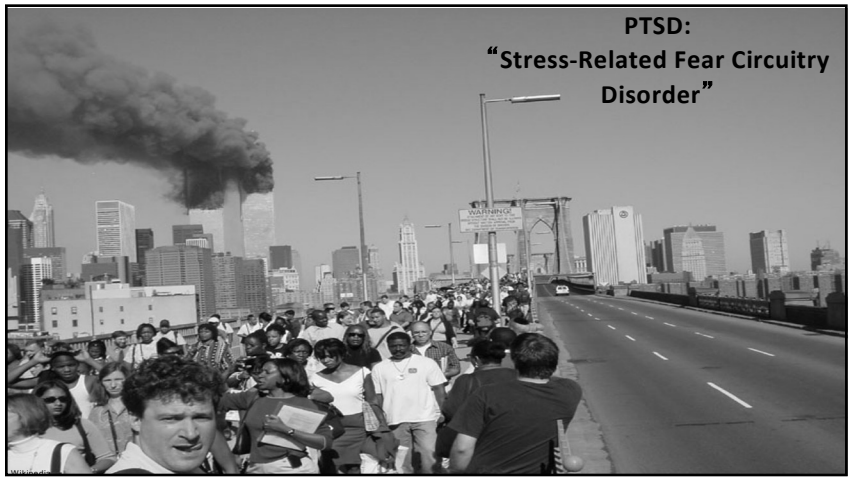

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Is PTSD a Fear Circuitry Disorder?

Cognitive-Behavioral PTSD as a model from:

- *Pavlovian Conditioning* (Kolb, 1989)
- *Activated Fear Networks* (Lang, 1977; Foa & Kozak, 1986).

Neurocircuitry

- Disrupted restraining influence of medial PFC
- Chain reaction brought about from activation of amygdala by fear stimuli[1]

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PSSD: Post-Severe Stress D/O

- "Severe" vs. "Traumatic" Stress
- Does PSSD differ from PTSD?

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Chronic Stress Syndromes

PSSD has medical consequences
PTSD also has medical consequences

Both affect HPA, cardiovascular, immunological and other systems

Should "medical" illnesses precipitated by stress be included with PSSD/PTSD as "stress disorders?"

- Chronic Fatigue Syndrome
- Fibromyalgia
- Peripheral Vascular Disease
- Endocrinopathies
- etc.

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PTSD Treatment Options

Psychosocial	Pharmacological
Exposure Therapy	TCAs/MAOIs
Cognitive Therapy	SSRIs/SNRIs
Anxiety Management	SGAs/AEDs
Desensitization	Anti-adrenergics
Hypnotherapy	Anti-anxiety Agents

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Crank Up the Serotonin!

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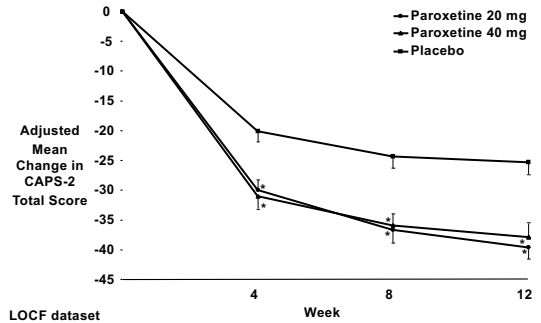
Paroxetine Fixed-Dose PTSD Study



LOCF dataset
* p < 0.001 vs placebo

Marshall RD, Beebe KL, Oldham M, et al. Am J Psychiatry 2001;158:1982-1988.

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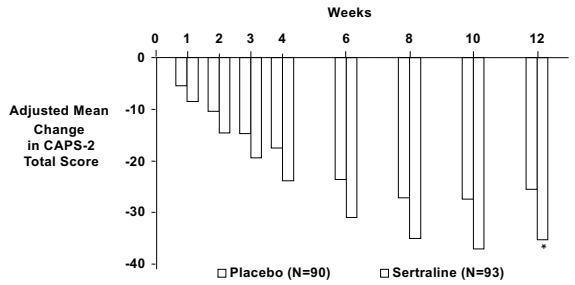
Sertraline Flexible-Dose PTSD Study



* p < 0.001 at week 12

Mean dose for completers = 151.3 mg

Brady K et al. JAMA. 2000;283:1837-1844.

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SSRI/SNRI Initiation

- Start at ½ the usual dose used for antidepressant benefit
  - i.e., citalopram at 10mg rather than the usual 20mg
- Educate!
- Judicious BZD use while initiating & titrating antidepressant

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α1 blockade

Prazosin (Minipress®)

- Start at 1mg qhs X 3 nights.
- Then increase by 1mg q3 nights until nightmares improve or patient develops postural hypotension.
- Some patients gain benefit at 1mg, and some need >10mgs!

Iloperidone (Fanapt®)

- Central alpha-1 receptors linked to reduction in nightmares when antagonized
- Dose-dependent QTc prolongation

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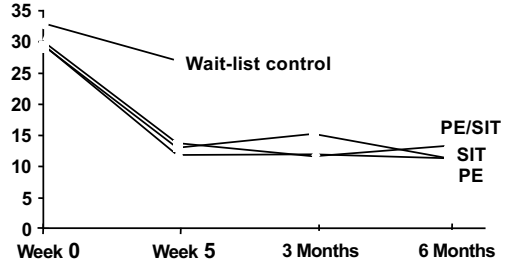
PE Therapy & SIT: Female Assault Victims with PTSD



PSS-I = Post Traumatic Stress Disorder Symptom Scale—Interview; Foa et al, 1999b

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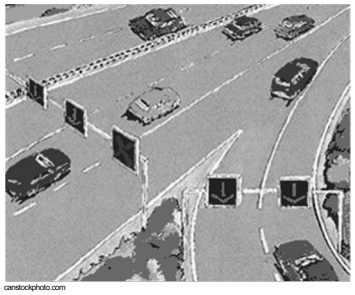
New Directions for Biological Research



- Expand focus **beyond serotonin & norepinephrine**
  - CRF, NPY, GABA, glutamate, dopamine, etc.
- PTSD as **final common pathway** (like fever or edema), caused by different patterns of psychobiological alteration
- Genetic research on **resilience and vulnerability**

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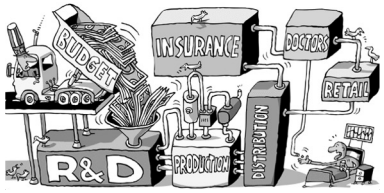
New Directions for Pharmacotherapy



- Interrupt cascade of stress-related alterations (CRF antagonists, NPY enhancers)
- Blunt fear conditioning (antiadrenergics, NMDA antagonists)
- Promote extinction of fear-conditioned reactions (cycloserine)
- Target dissociative symptoms (AEDs such as lamotrigine)

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New Directions for Pharmacotherapy

- Combined treatment with CBT
- Augmentation strategies
- Effective and safe approaches for children

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New Directions for Pharmacotherapy

- Does CBT work “top-down”?
- Do medications work “bottom-up”?
- Do different psychosocial approaches work in different ways?

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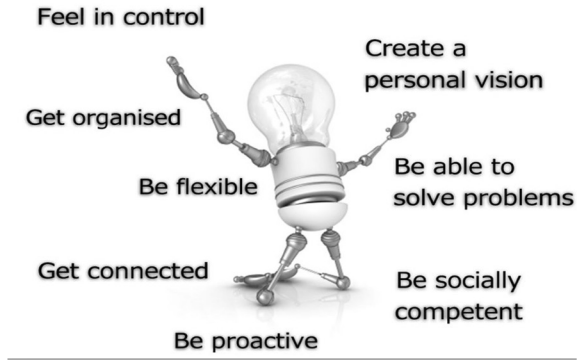
Resilience & Prevention



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“Questions?”

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End of Presentation
Thank you for your time and attention.

Josh Hamilton,
DNP, RN/PMH-BC, FNP-C, PMHNP-BC, CNE, CTMH, CLNC, FAANP

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Image Sources

All images sourced from public domain unless otherwise noted.

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Additional Reading

- ***Web clip art (public domain) is used extensively throughout this presentation.***
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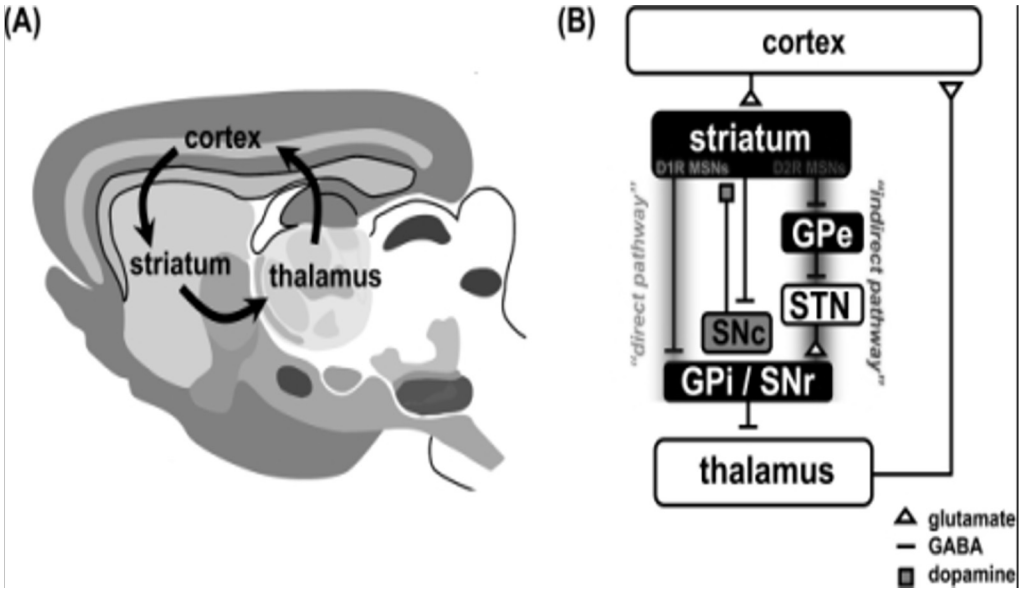
Worry

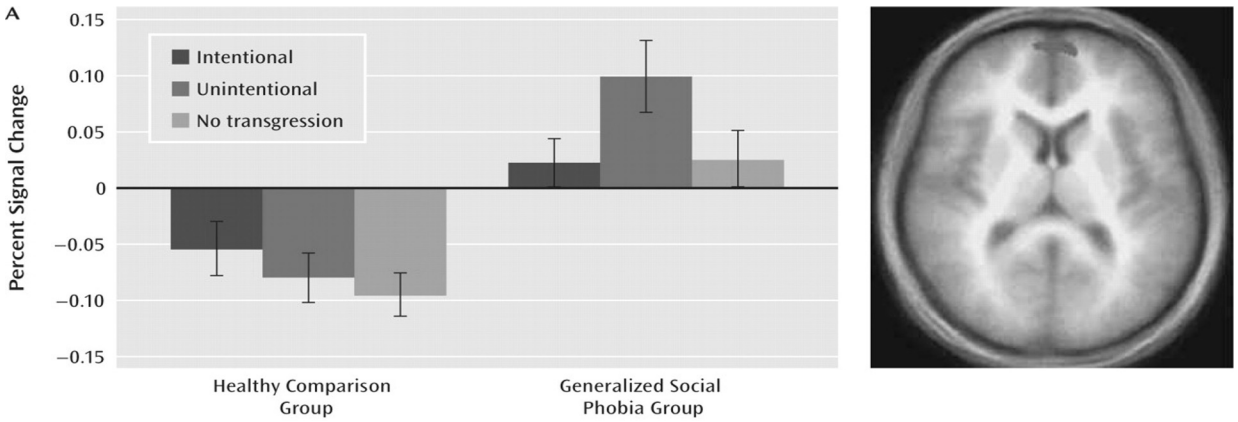
- CTSC feedback loops ("worry loops") in PFC
- Apprehension
- Obsession
- Catastrophizing
- Anxious Misery
- Ruminations and delusions?

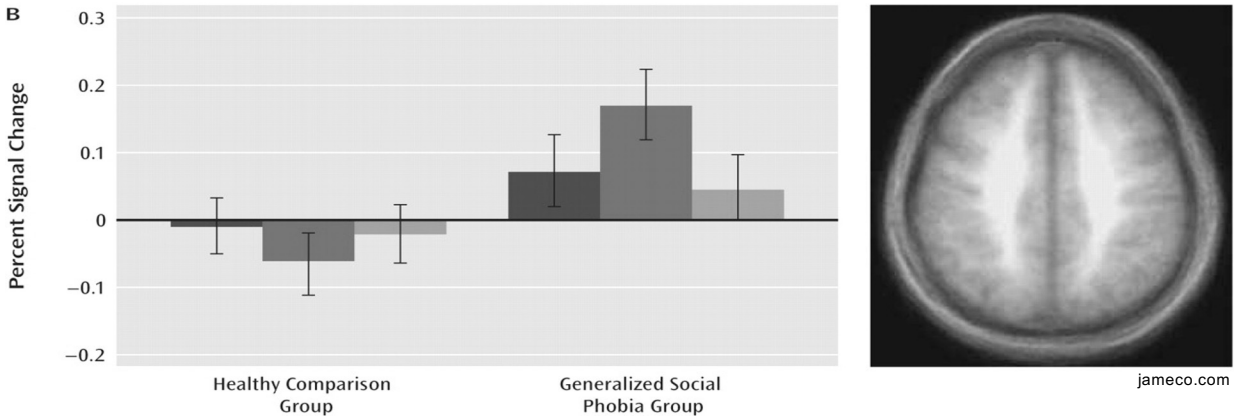


BZD Comparisons

	Action	(hrs)			Equivalent
Long-Acting					
Chlordiazepoxide (Librium)	Int	2-4	5-30 (parent) 3-100 (metab)	Oxidation	10mg
Diazepam (Valium)	Rapid	1	20-50 (parent) 3-100 (metab)	Oxidation	5mg
Flurazepam (Dalmane)	Rapid	0.5-2	47-100 (metab)	Oxidation	30mg
Intermediate Acting					
Alprazolam (Xanax)	Int	0.7-1.6	6-20 (parent)	Oxidation	0.5mg
Clonazepam (Klonopin)	Int	1-4	18-39 (parent)	Oxidation	0.25mg
Lorazepam (Ativan)	Int	1-1.5	10-20 (parent)	Conjugation	1mg
Oxazepam (Serax)	Slow	2-3	3-21 (parent)	Conjugation	15mg
Temazepam (Restoril)	Slow	0.75-1.5	10-20 (parent)	Conjugation	30mg
Short Acting					

What's going on in the brain?





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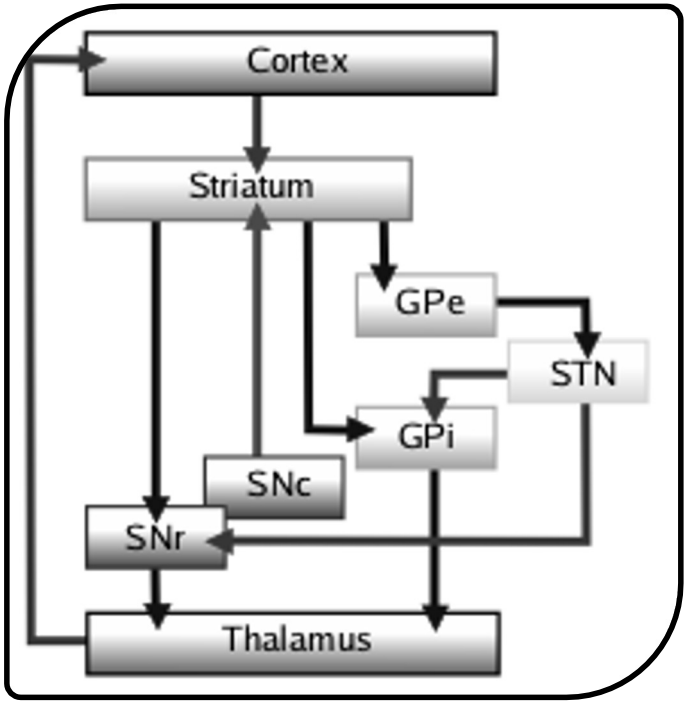
OCD Etiology



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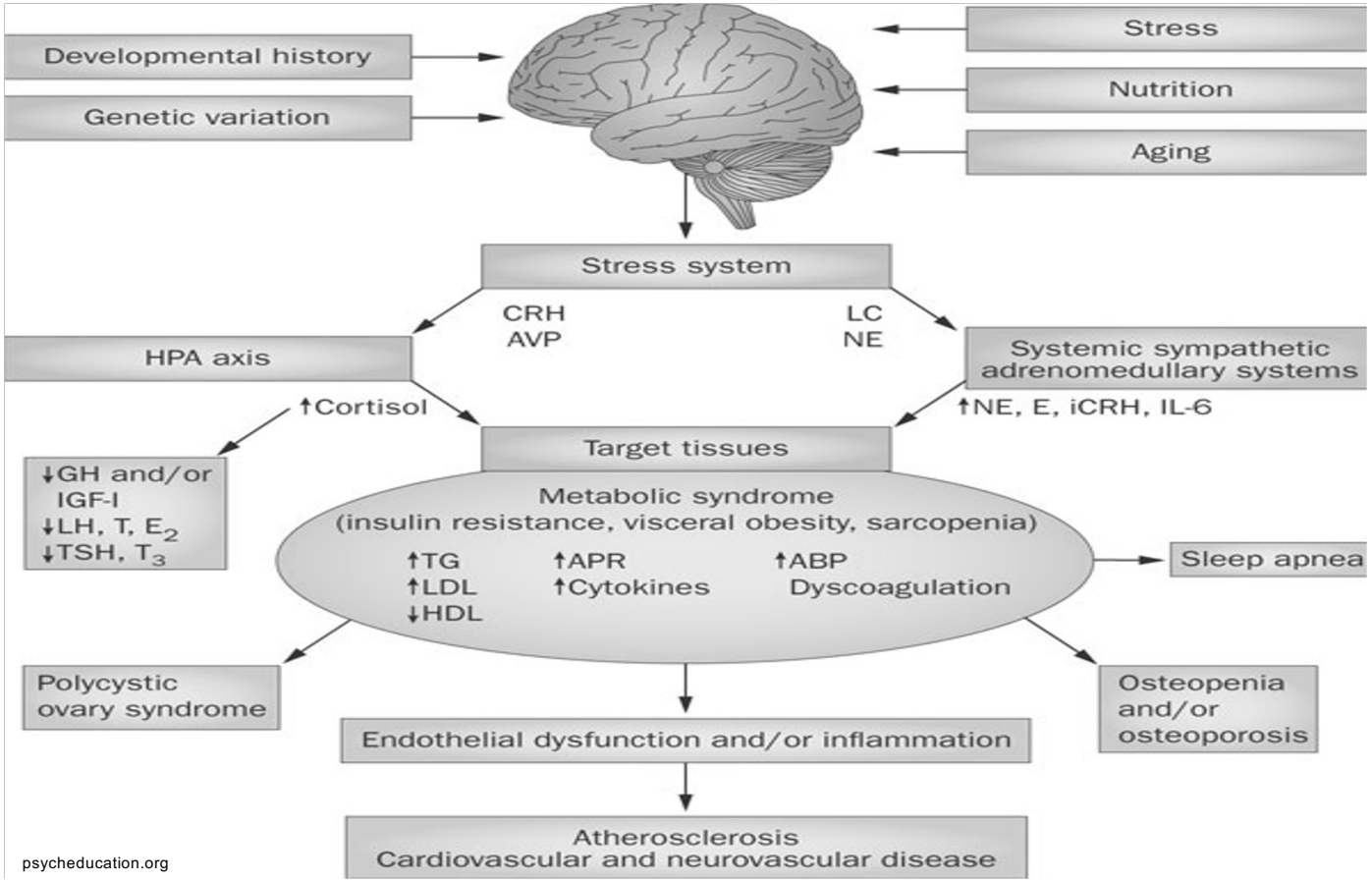
- Genetics
- Dopaminergic dysfunction
- Serotonergic dysfunction
- Cortico-striato-thalamo-cortical loop
- Autoimmune- PANDAS

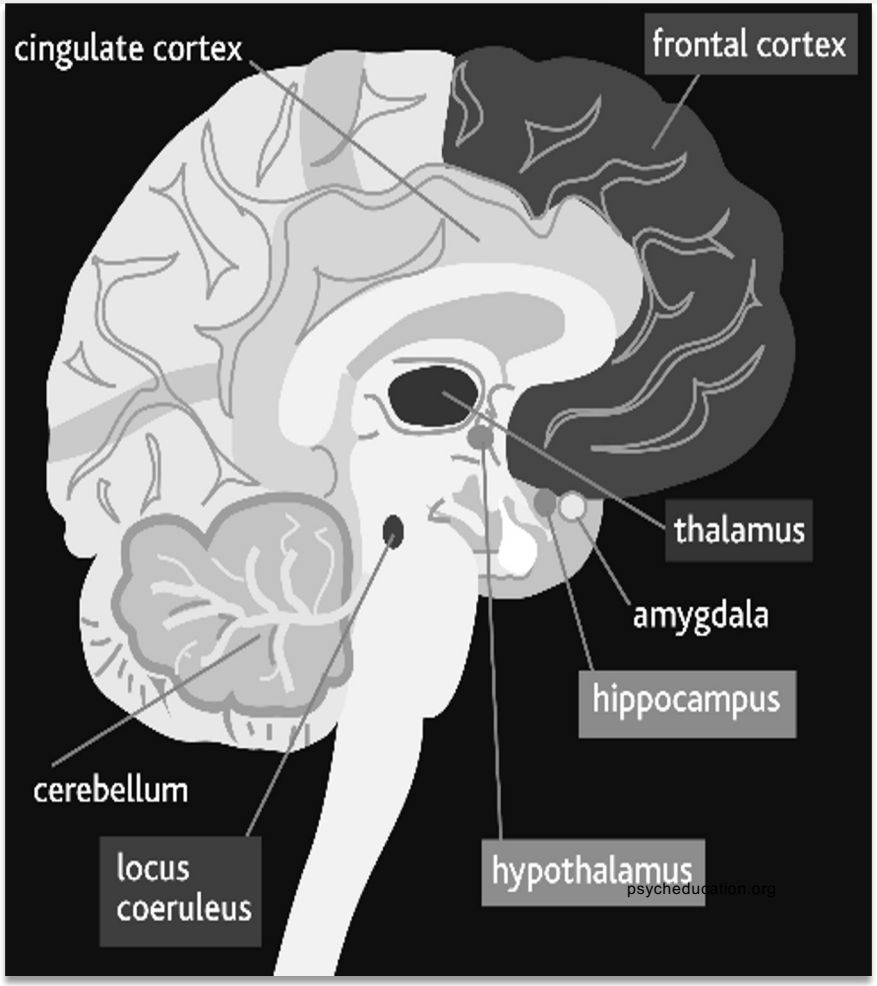
Potential Genetic Equipoise

Gene	Protein	Biological Function	Therapeutic Implications
SLC 6A4 variation	SERT	Serotonin reuptake	Poor response, slow response, poor tolerability to SSRIs/SNRIs
$5HT_{2c}$ variation	$5HT_{2c}$ receptor	Regulates DA & NE release	Poor response, poor tolerability to atypical antipsychotics
DRD_2 variation	D_2 receptor	Mediates positive symptoms of psychosis, movements in Parkinsonism	Poor response, poor tolerability to atypical antipsychotics
COMT Val variation	COMT enzyme	Regulates DA levels in PFC; metabolizes DA & NE	Reduced executive functioning
MTHFR T variation	MTHFR enzyme	Regulates L-methylfolate levels & methylation	Reduced executive functioning, especially with Val COMT (T with Val)

The Stress System



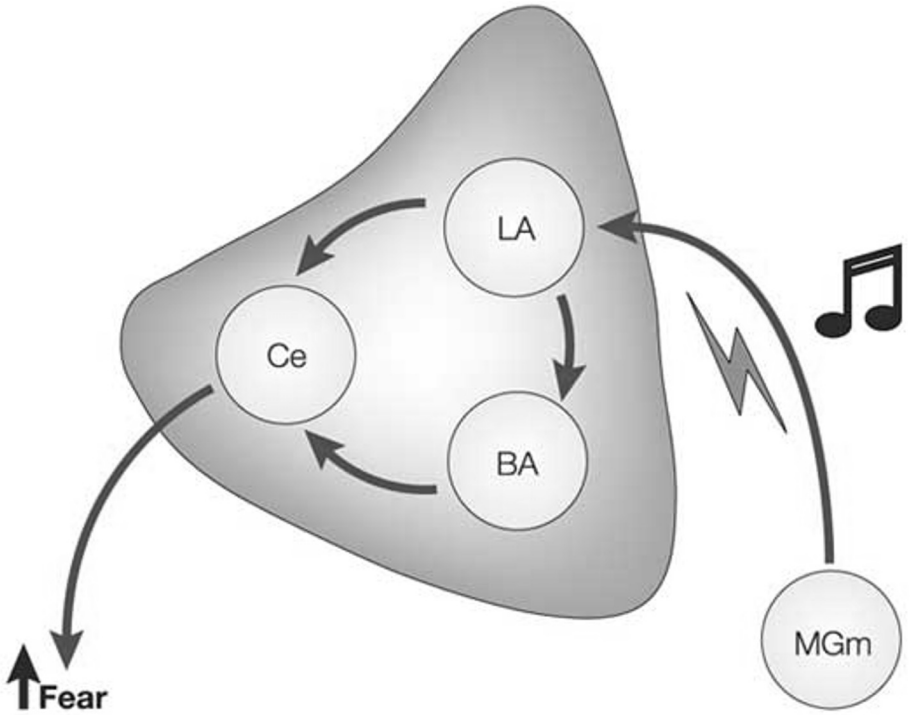
Functional Neuroimaging



- Increased amygdalar activation
- Hippocampal reactivity
- Hypoactivation of medial PFC, including OFC & anterior cingulate cortex

Fear Conditioning

- "Memory" and the amygdala
- Glutamate & NMDA receptors
- Synaptic restructuring
- Long-term potentiation
- Involvement of hippocampus
- Limitations of current treatment



Nature Reviews | Neuroscience

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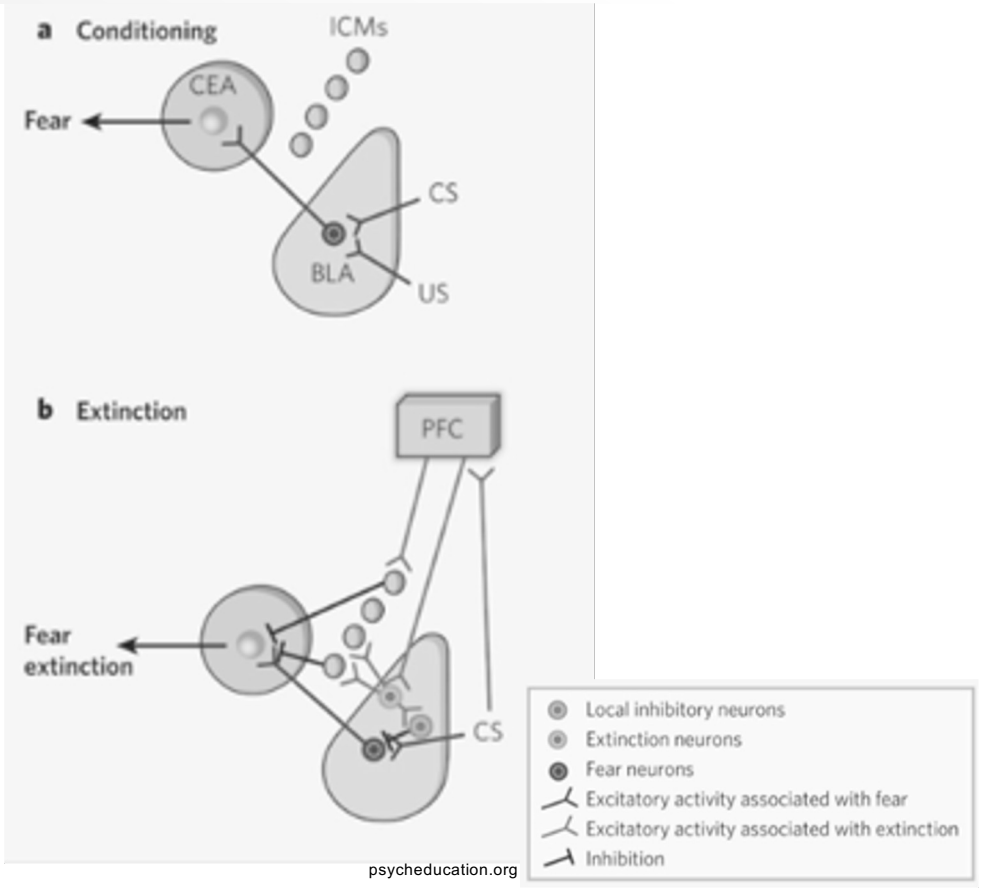
Fear Extinction

- Creates 2nd “gate” through amygdala/PFC
- Recruits GABA-ergic interneurons in amygdala
- More volatility than conditioning
- Prone to renewal
- Effect of current drug therapies < CBT
- Timed-synchronized NMDA activation
  - D-cycloserine
  - SGRIs



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Reconsolidation

- **Molecular consolidation** less permanent than originally believed
- **Protein synthesis**
- **β blockers** disrupt reconsolidation & fear conditioning (opioids also mitigate)
- **Research**: synergy of psychotherapy & pharmacotherapy
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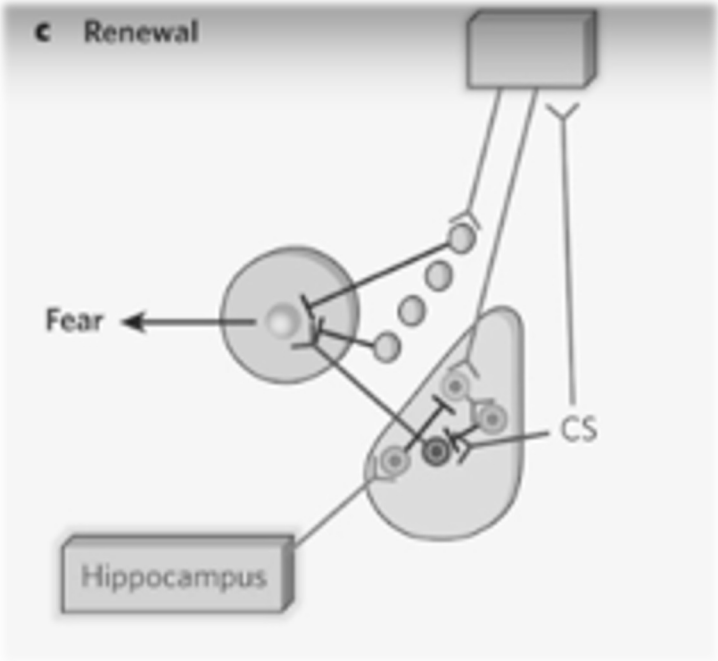

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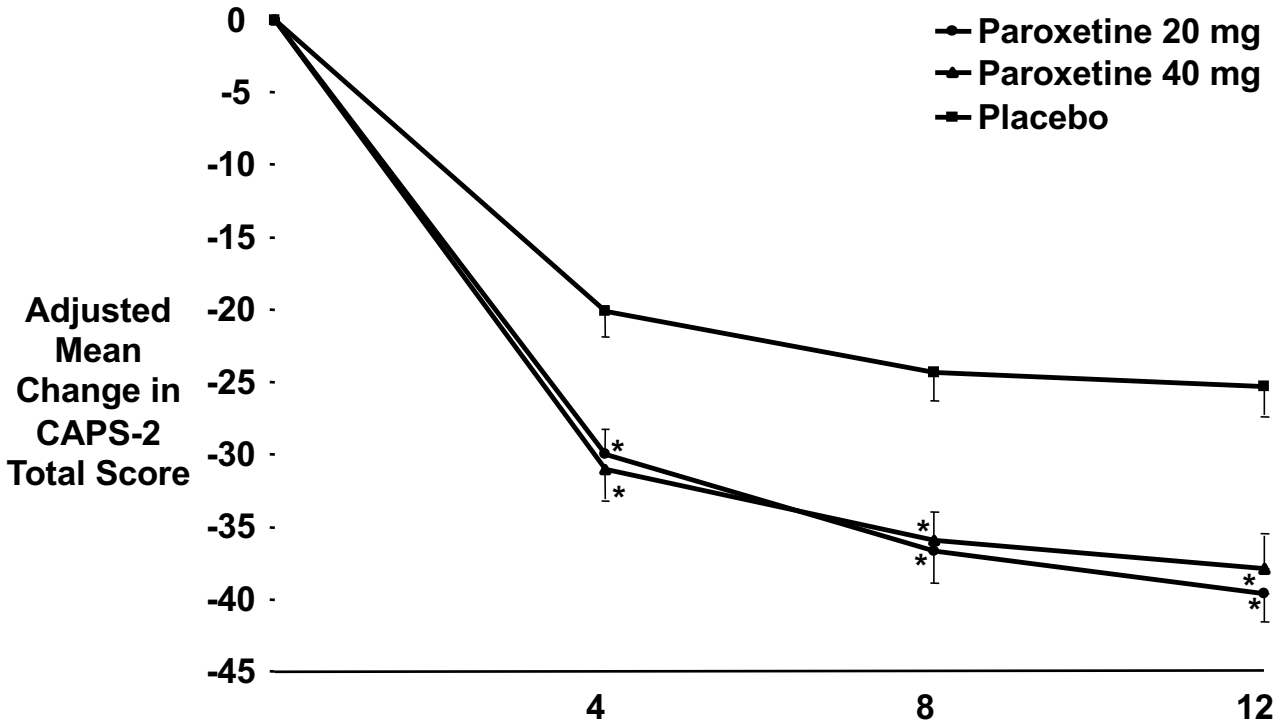
Paroxetine Fixed-Dose PTSD Study

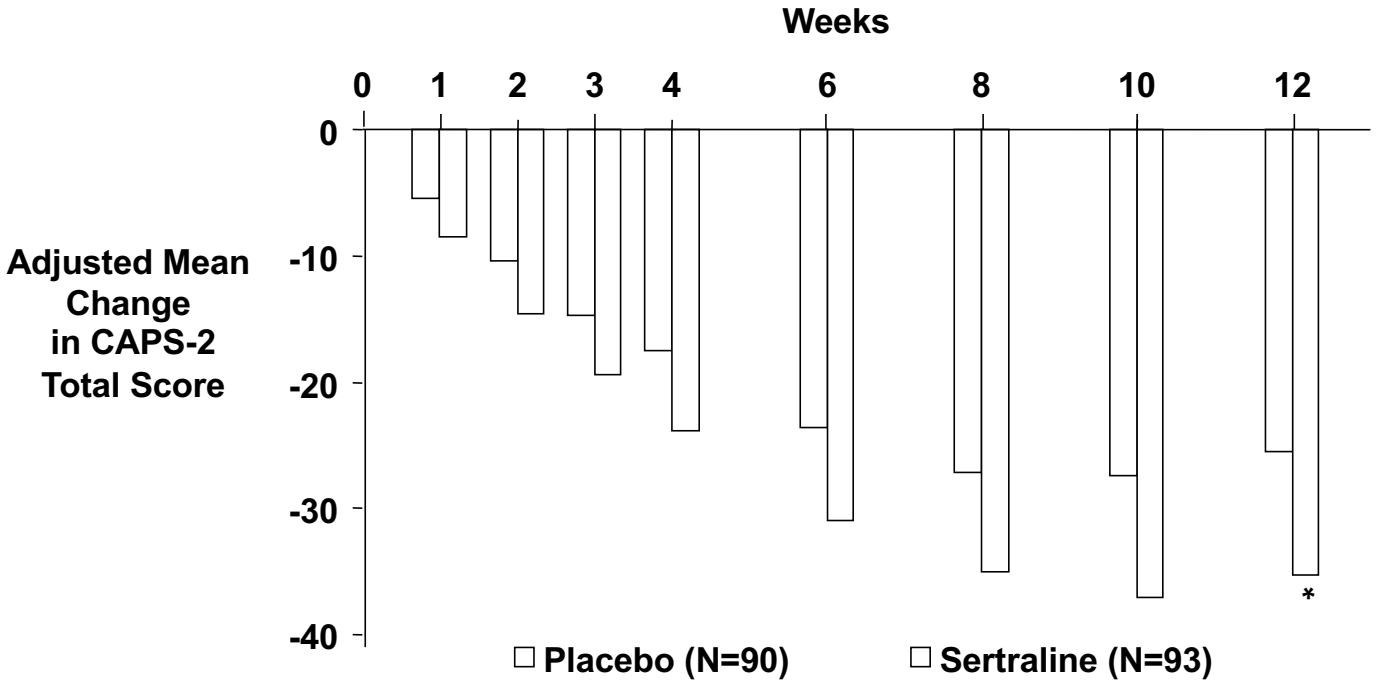


LOCF dataset

* p < 0.001 vs placebo

Marshall RD, Beebe KL, Oldham M, et al. Am J Psychiatry 2001;158:1982-1988.

Sertraline Flexible-Dose PTSD Study

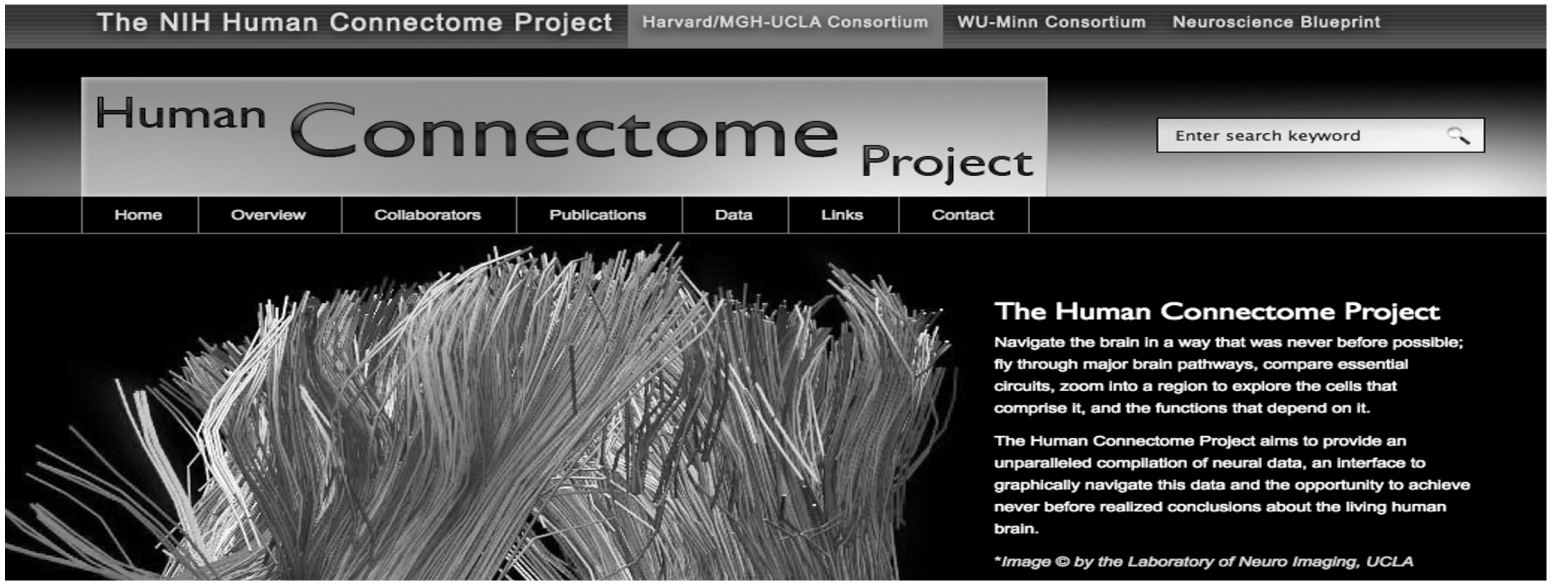


*** p < 0.001 at week 12**

Mean dose for completers = 151.3 mg

Brady K et al. JAMA. 2000;283:1837-1844.

New Directions for Pharmacotherapy



- Does CBT work “top-down”?
- Do medications work “bottom-up”?
- Do different psychosocial approaches work in different ways?

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Refocusing on ADHD: Diagnosis & Personalized Treatment for Adults

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Disclosure

Josh Hamilton, DNP, RN/PMH-BC, FNP-C, PMHNP-BC, CNE, CLNC, FAANP:

- Consultant & speaker, Myriad Neuroscience
- Paid Ambassador, Point of Care Network (POCN)

All relevant financial relationships have been mitigated.

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Objectives

At the end of this presentation, the participant will be able to:

01 **Conceptualize** mental illness in the context of epi/genetics and neurobiology, with an emphasis on attention-deficit disorders.

02 **Develop** a working knowledge of updated criteria and psychometry to improve case identification and diagnosis of attention-deficit disorders

03 **Discuss** contemporary approaches to management of attention-deficit disorders, including practical applications for nurse practitioners

04 **Apply** concepts of pharmacogenomics to the selection, prescription, and management of drug therapy for disorders of inattention and hyperactivity

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Tips

- References
  - Listed throughout and at the end of the presentation
- To facilitate your learning
  - Specific tables/images can be viewed full page at the end of your handout.

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Epidemiology

- Overall prevalence 2-18%
- School age children 8-10%
- Adults 2.8%
- More common in boys than girls
  - Male to female ratios
    - 4:1 for predominantly hyperactive type
    - 2:1 for predominantly inattentive type

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Clinical Features

Two (2) categories of <u>core symptoms</u>

1. Hyperactive and impulsive behaviors
2. Inattention

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Diagnostic Criteria

<u>DSM-5</u>

- Age <17 years: ≥6 symptoms
- Age ≥17 years: ≥5 symptoms
- Must
  - Be present > 1 setting
  - Persist > 6 months
  - Develop before age 12
  - Be developmentally inconsistent
  - Impair functioning
  - Exclude organic causes
  - Exclude another psychiatric cause

SLIDE 1
Core Symptoms of ADHD

Core Symptom	*Inattention*	*Hyperactivity-Impulsivity*
Clinical Expressions	Fails to attend to details	Fidgets with hands or feet
	Has difficulty sustaining attention	Leaves seat in classroom
	Does not seem to listen	Runs about or climbs
	Fails to finish	Difficulty playing quietly
	Has difficulty organizing tasks	Motor excess ("on the go")
	Avoids sustained efforts	Talks excessively
	Loses things	Blurts out answers
	Is distracted by extraneous stimuli	Difficulty awaiting turn
	Is forgetful	Interrupts or intrudes

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health Disorders* (DSM). 5th ed. American Psychiatric Publishing; 2013.

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DSM-IV vs DSM-5

- New overall diagnostic category
- ADHD across lifespan
- Age of onset changed from 7 to 12
- Removal of PDD/ASD exclusion

PDD = pervasive developmental disorder; ASD = autism spectrum disorder.

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Changes from Subtypes to Presentations: DSM-IV vs DSM-5

DSM-IV

- Combined subtype
  - Inattention + hyperactive-impulsivity
- Predominantly inattentive type
- Predominantly hyperactive-impulsive type

DSM-5

- Combined presentation
- Predominantly inattentive
  - 5+ inattentive and 3-5 hyperactive/impulsive symptoms
- Inattentive (restrictive)
  - 5+ inattentive and no more than 2 hyperactive/impulsive symptoms
- Predominantly hyperactive/impulsive

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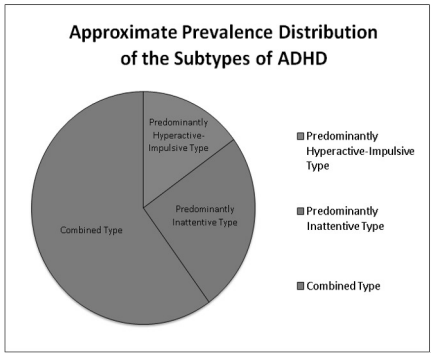
Prevalence Distribution of DSM-IV Subtypes



American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Health Disorders (DSM)*. 5th ed. American Psychiatric Publishing; 2013.

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Neurobiological Etiologies

Genetic factors (~80% of etiology)

- Twin studies – concordance
  - Up to 92% in monozygotic twins
  - 33% in dizygotic twins
- 5-6x higher risk in first-degree relatives
- Implicated genes
  - Pharmacodynamic (PD) genes
    - DA and serotonin, glutamate receptors, and transporters
    - DA beta-hydroxylase and COMT
    - ADRA2A
  - Pharmacokinetic (PK) genes

DA = dopamine.

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Environmental Etiologies

- Strong epigenetic driver
- Maternal factors
- Perinatal/early life risk factors
- Post-natal risk factors

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Adult ADHD

- Impaired academic functioning, especially for inattentive/ combined types
- Decreased rate of employment
- Lower job status
- Poor job performance
- Increased risk for un/intentional injury
- Difficulty fulfilling parental responsibilities
- Risk for developing antisocial personality disorder
- Geriatric ADHD is a “thing”

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Assessment

Behavior rating scales

- ADHD-specific (narrow-band): focus directly on core symptoms
  - Wender Utah Rating Scale
  - Conners Adult ADHD Rating Scale
  - Adult ADHD Self-Report Scale (ASRS 1.1)
- Broadband scales: assess variety of behavioral symptoms
  - Can help identify coexisting conditions
  - PHQ9, Composite International Diagnostic Interview Scale, Primary Care PTSD Screen

Neuropsychological testing

- Objective identification of executive dysfunction
- Not recommended as standard practice

PHQ = patient health questionnaire.

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Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date					
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.			Never	Rarely	Sometimes	Often	Very Often
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6. How often do you feel overly active and compelled to do things, like you were driven by a motor?							

Part A 4+ shaded boxes is positive screen

Attention Deficit Disorder Association. Accessed February 15, 2022. https://add.org/wp-content/uploads/2015/03/adhd-questionnaire-ASRS111.pdf.

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Differential Diagnosis

- Thyroid disease
- Obesity
- Sleep disorders
- Hormonal changes
- Brain injury
- Stroke
- Vascular disease
- Dementia
- Substance use (esp. cannabis)
- Medications
  - Antihistamines
  - Anticholinergics
  - Benzodiazepines
  - Sleep aids
  - Narcotics
  - Anticonvulsants
  - Muscle Relaxants

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Diagnostic "Red Flags"

- Comorbidities are *very* common – mood, anxiety, PTSD, and substance use
- Moodiness is not part of ADHD
- ADHD is not an intermittent condition
- ADHD symptoms declare early
- Multiple emerging diagnoses suggest re-evaluation
- Symptom exacerbation is not an expected effect of psychostimulant medication

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Empirical Treatment

- Psychotherapy
  - Cognitive-behavioral therapy
  - Interpersonal, supportive
  - Motivational interviewing
- Psychopharmacology
  - Stimulant medications
  - Atomoxetine, bupropion
  - Neuroprotection vs neurotoxicity
  - Abuse, misuse, and diversion
  - Controlled substance contract
  - Baseline and repeat urine drug screening

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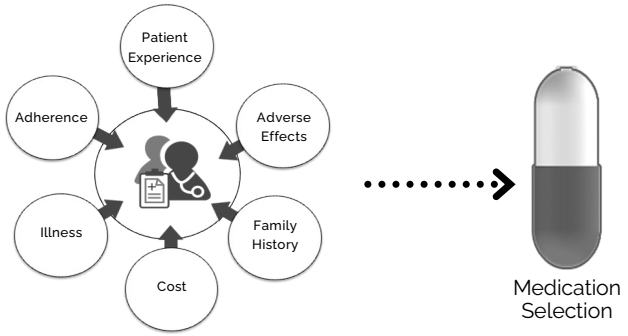
Current Medication Decision Factors



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Pharmacogenomics

- Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person
  - National Institutes of Health
  - National Human Genome Research Institute

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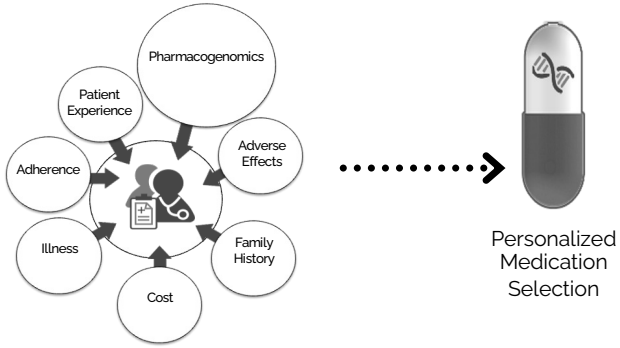
Precision Medicine



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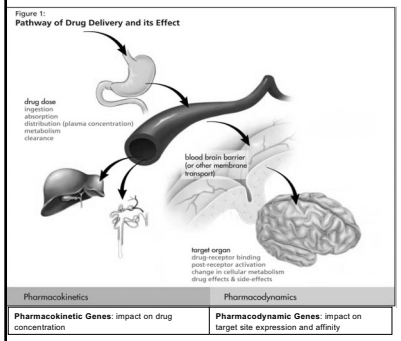
Integrative Genetics



In addition to traditional strategies, **PD genes can inform potential alternative therapy options** to which a patient is more likely to respond

Huang A. Presented at: 28th Canadian Geriatrics Society Annual Meetings; May 2021; Virtual.

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Key Pharmacogenomic Genes

ADHD

Pharmacokinetic (PK)
CYP2D6

Pharmacodynamic (PD)
ADRA2A
(α-2A adrenergic receptor)
COMT
(catechol-o-methyltransferase)

MTHFR

Pharmacokinetic (PK)
MTHFR
(methyltetrahydro-folate reductase)

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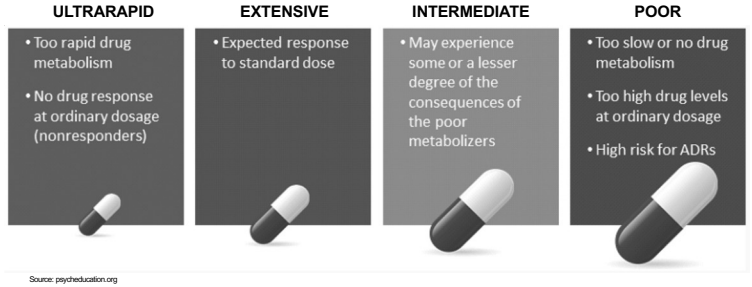
Genetics & Medication Serum Levels



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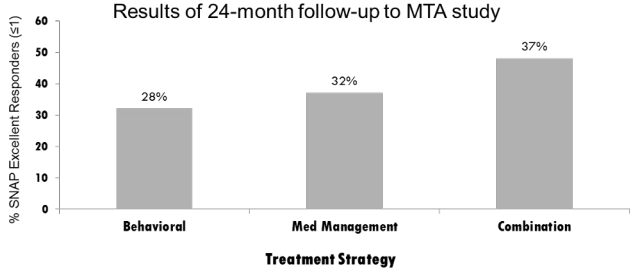
ADHD: Pharmacotherapeutic Success?

"Gold standard" response around 70% methylphenidate



MTA = multimodal treatment study; SNAP = support needs approach for patients.
MTA Cooperative Group. *Pediatrics*. 2004;113(4):754-761.

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Pharmacogenomics and ADHD

Generic Name
amphetamine salts
atomoxetine
clonidine
dexmethylphenidate
dextroamphetamine
guanfacine
lisdexamfetamine
methylphenidate

Analyzes 2 pharmacodynamic genes and 1 pharmacokinetic gene from the CYP450 family.

Gene	Significance
ADRA2A	Differing response rates to certain ADHD medications
COMT	Stimulant response rates
CYP2D6	Altered metabolism of some ADHD medications

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Dopamine Metabolism (COMT)

COMT enzyme in prefrontal cortex degrades dopamine

Variations in the COMT gene can boost or reduce the amount of dopamine that gets broken down

COMT Val/Val High Activity → ↓ Prefrontal Dopamine → Impaired Executive Function ↑ Response to **Stimulants** **TMS** may increase DA

COMT Met/Met Low Activity → ↑ Prefrontal Dopamine → Superior Executive Function ↓ Response to **Stimulants** **SAMe** is a COMT cofactor

TMS = transcranial magnetic stimulation; SAMe = S-adenosyl methionine.

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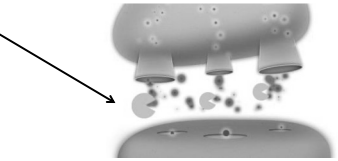
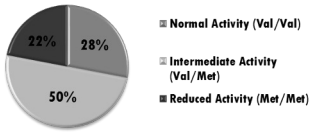
COMT Transferase

- COMT breaks down both norepinephrine and dopamine in synapse
- Val158Met polymorphism results in amino acid change – methionine (met) for valine (val) at codon 158
- Met/Met homozygotes: 4-5x less activity
- Met/Met carriers have reduced rate of response to stimulant medications





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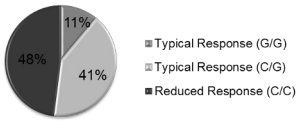
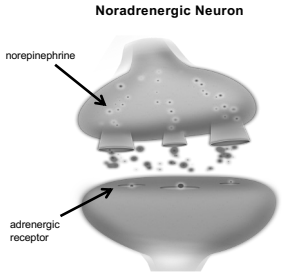
ADHD Pharmacogenomics: ADRA2A

- Alpha 2A adrenergic receptor in norepinephrine system
- SNP in promoter region (-1291G>C) shown to affect response to methylphenidate and alpha-2A agonists





SNP = single nucleotide polymorphisms.
psycheducation.org

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Atomoxetine

"Poor metabolizers of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of [atomoxetine] compared with EMs… Laboratory tests are available to identify CYP2D6 PMs… The higher blood levels in PMs lead to a higher rate of some adverse effects of [atomoxetine]."

"In …CYP2D6 PMs, [atomoxetine] should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated."

AUC = area under the curve; PM = poor metabolizers; EM = extensive metabolizers.
MedScape. Accessed March 25, 2022. https://reference.medscape.com/drug/strattera-atomoxetine-342994.

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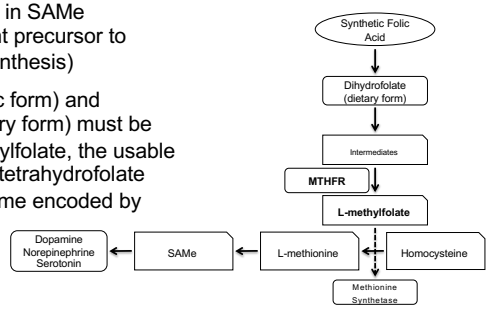
Folate Metabolism

- Folate's critical role in SAMe formation (important precursor to neurotransmitter synthesis)
- Folic acid (synthetic form) and dihydrofolate (dietary form) must be converted to l-methylfolate, the usable form, by methylenetetrahydrofolate reductase, an enzyme encoded by the MTHFR gene



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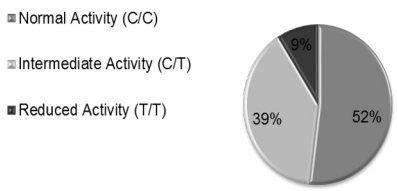
The MTHFR Gene

- C677T SNP in MTHFR gene confers reduced enzymatic activity.
- Multiple studies confirm lower serum folate levels and higher homocysteine levels in individuals with the T/T or T/C genotype relative to the C/C genotype



Nelson JC. *Am J Psychiatry.* 2012;169(12):1223-1225. Nazki F, et al. *Gene.* 2014;11-20. Molloy AM, et al. *Lancet* 1997;349:1591-1593. Anderson CAM, et al. *Mol Nutr Food Res.* 2013;67:637-644.

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MTHFR Polymorphisms

Folate Intermediates	Folate Intermediates	Folate Intermediates
MTHFR 677 C/C	MTHFR 677 T/C	MTHFR 677 T/T
NORMAL methylfolate levels	**INTERMEDIATE** methylfolate levels	**Reduced** methylfolate levels

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How Can Pharmacogenomics Help?

Pharmacogenomics could assist NPs to

- Determine if patients could benefit from supplemental folic acid or folate derivatives
- Rule out potential genetic causes of folate deficiency and refocus treatment methodology on other therapies

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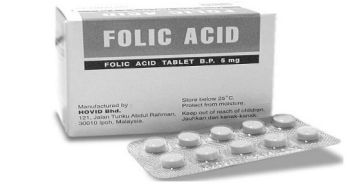
Clinical Implications of MTHFR

- Folate deficiency is treatable
- Supplementation with l-methylfolate (5-MTHF), the active form of folate
- Studies show increasing intake of folic acid can overcome effect of reduced MTHFR activity



Qin X, et al. Pharmacogenetics and Genomics. 2012;22(6):421-428. Anderson CAM, et al. Mol Nutr. Food Res. 2013;57:637-644. Ashfield-Watt PAL, et al. Am J Clin Nutr. 2002;76(1):180-186.

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Objective Imaging

- Prediction of stimulant response
- Striatal dopamine transporters
- Diagnostic stratification and categorization

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Treatment Considerations

- Monitor treatment response
  - Address appetite suppression and insomnia
- Drug holidays not routinely recommended
  - Consider if aberrant growth trajectory, excessive side effects
- Pregnancy and lactation
- Co-occurring substance use disorder

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Treatment Considerations (continued)

- Stopping medications
  - Consider if stable symptoms
  - Time appropriately
  - Stimulant medications and atomoxetine do not need taper
  - Alpha-2-adrenergic agonists should be tapered

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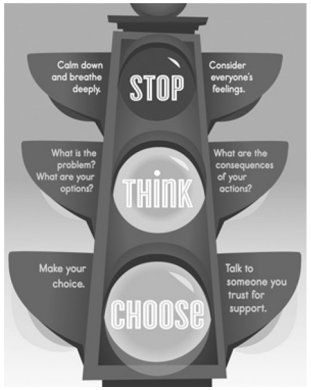
Follow Your Own Advice!



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Additional Reading

Web clip art (public domain) is used extensively throughout this presentation

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Part A
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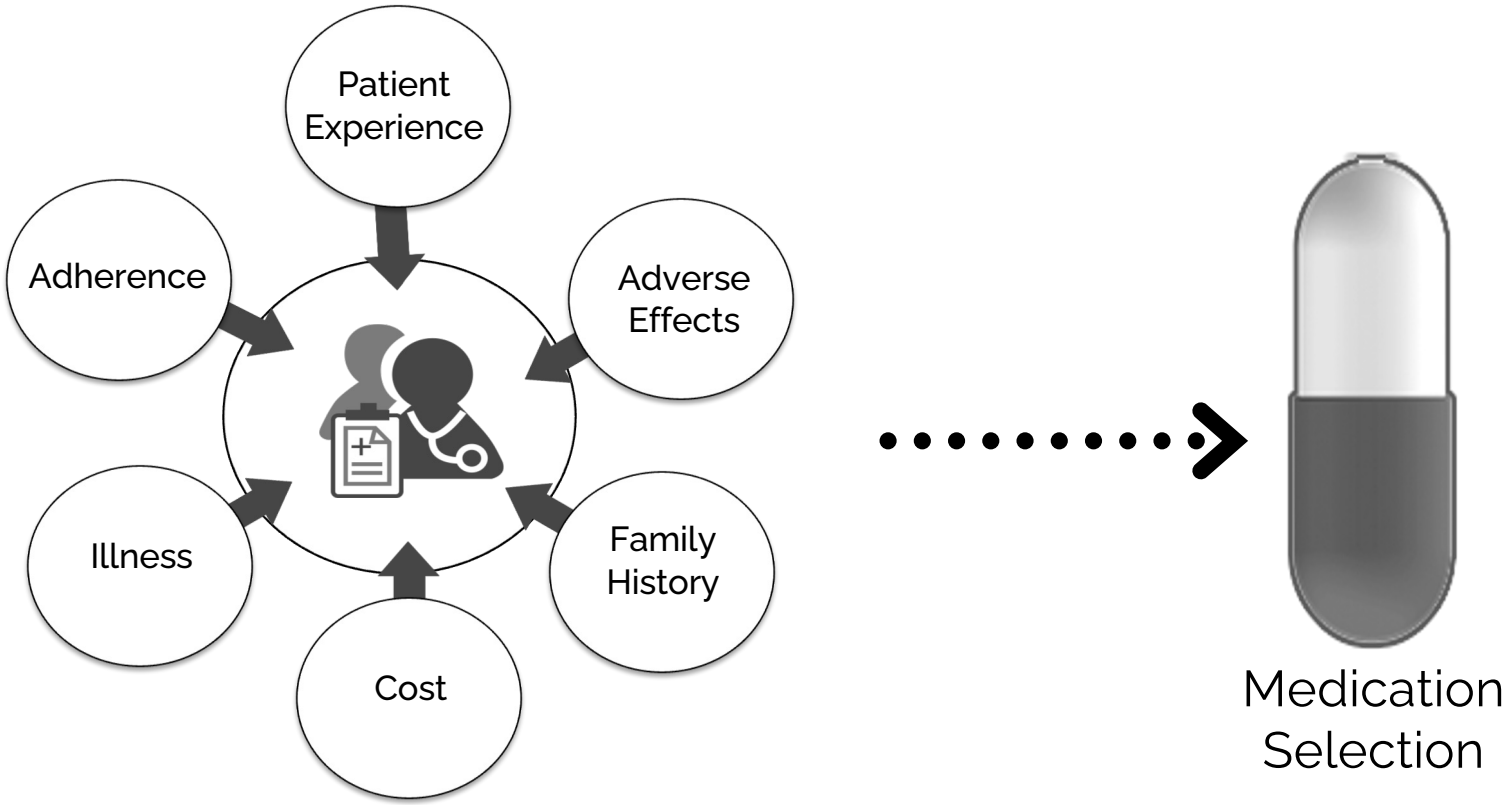
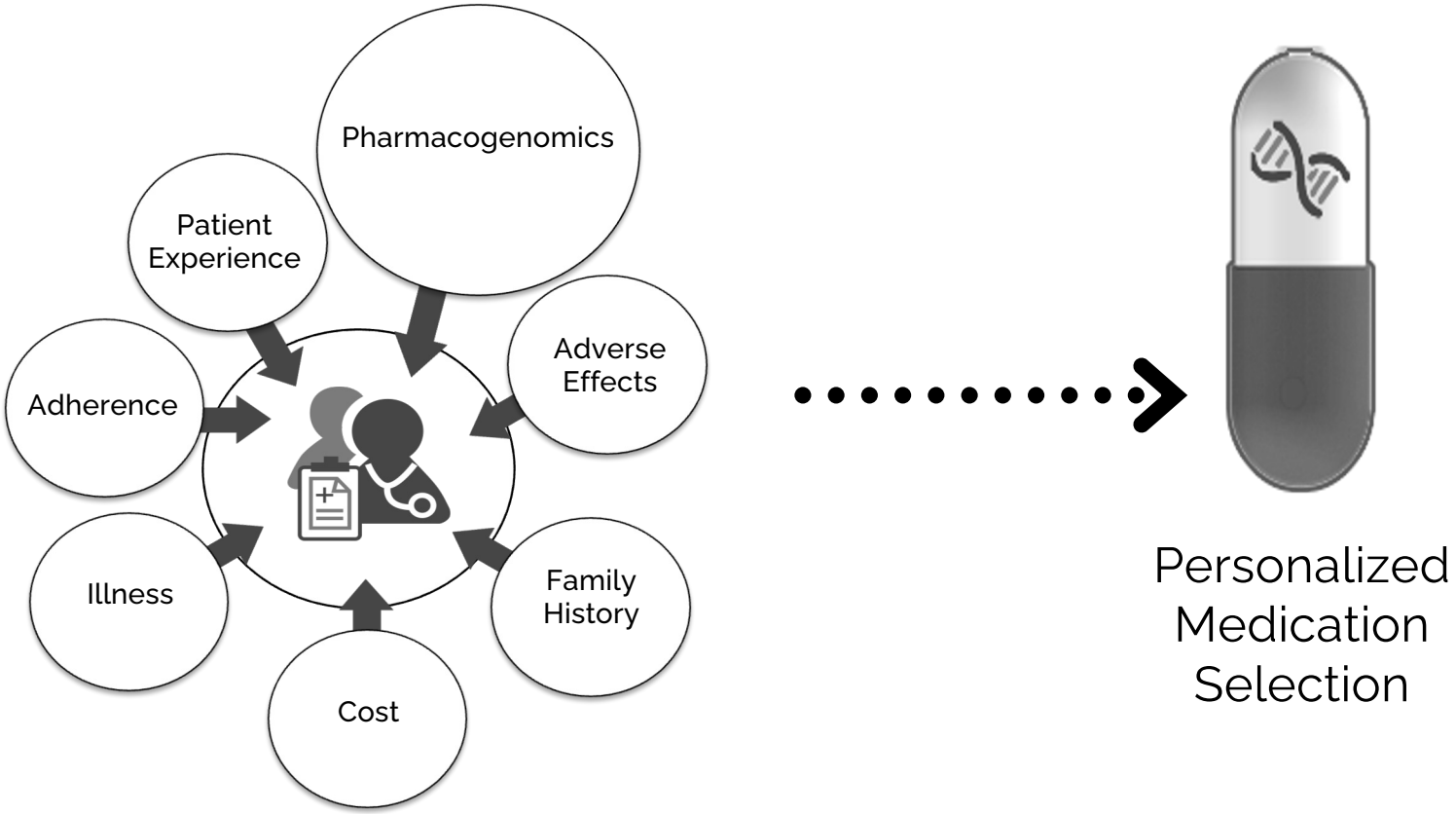
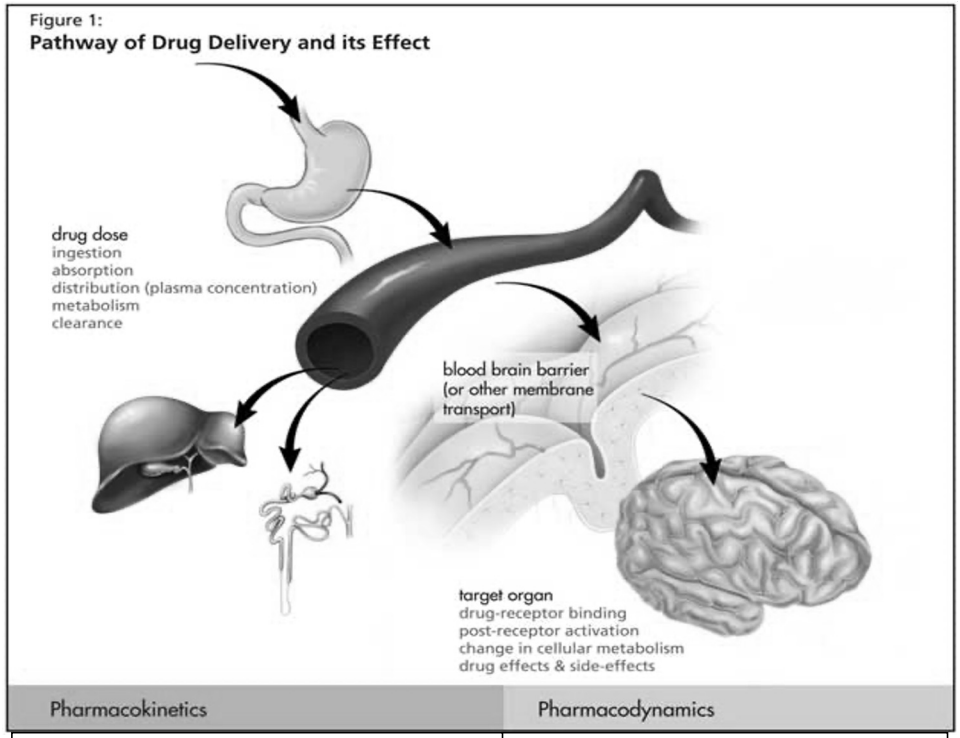
Current Medication Decision Factors



Precision Medicine



Integrative Genetics

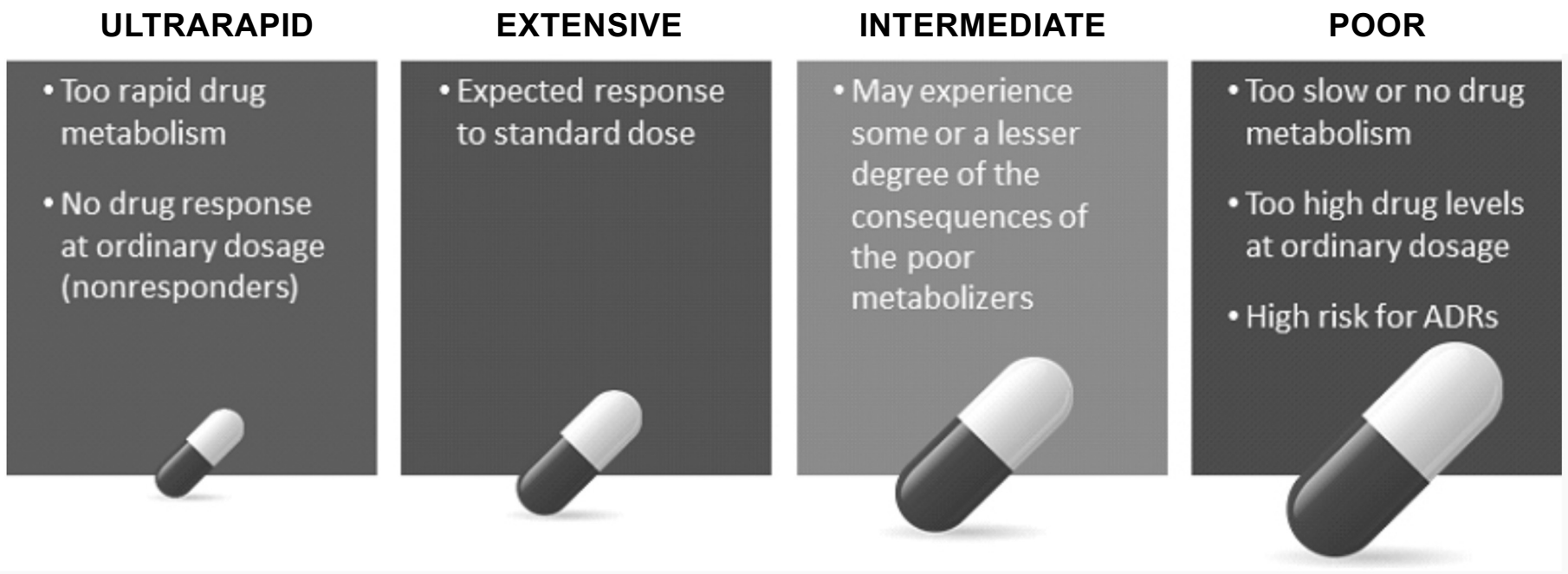


Pharmacokinetic Genes: impact on drug concentration	**Pharmacodynamic Genes**: impact on target site expression and affinity

In addition to traditional strategies, **PD genes can inform potential alternative therapy options** to which a patient is more likely to respond

Huang A. Presented at: 28th Canadian Geriatrics Society Annual Meetings; May 2021; Virtual.

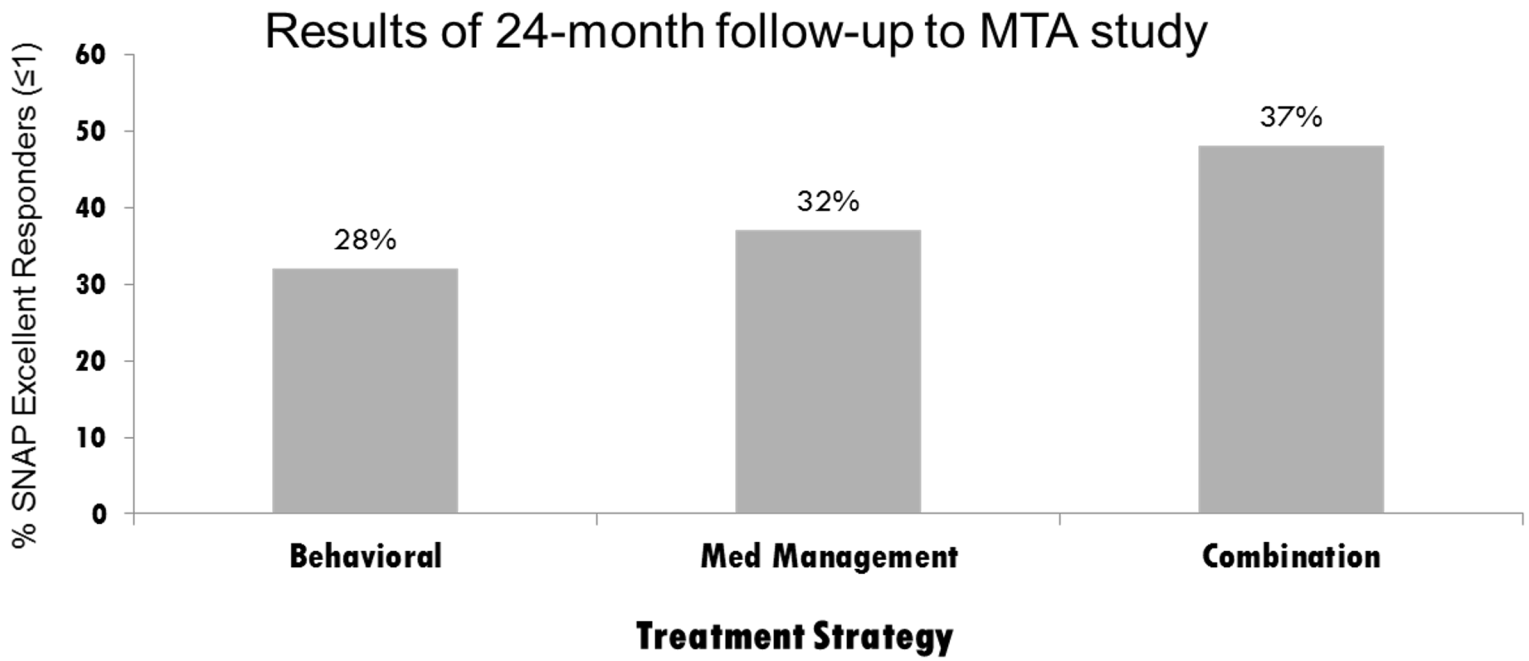
Genetics & Medication Serum Levels



Source: psycheducation.org

ADHD: Pharmacotherapeutic Success?

"Gold standard" response around 70% methylphenidate



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Dopamine Metabolism (COMT)

COMT enzyme in prefrontal cortex degrades dopamine

Variations in the COMT gene can boost or reduce the amount of dopamine that gets broken down

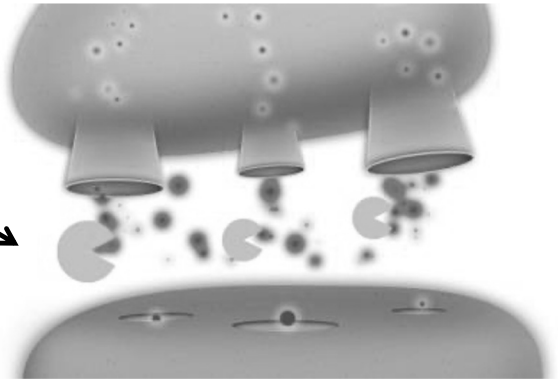
COMT Val/Val
High Activity → ↓ Prefrontal Dopamine →
Impaired Executive Function
↑ Response to **Stimulants**
TMS may increase DA

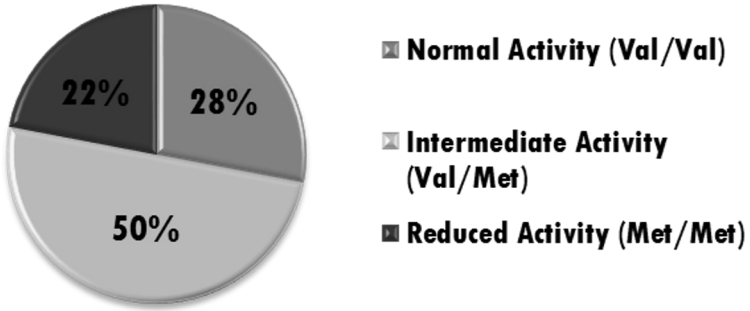
COMT Met/Met
Low Activity → ↑ Prefrontal Dopamine →
Superior Executive Function
↓ Response to **Stimulants**
SAMe is a COMT cofactor

TMS = transcranial magnetic stimulation; SAMe = S-adenosyl methionine.

COMT Transferase

- COMT breaks down both norepinephrine and dopamine in synapse
- Val158Met polymorphism results in amino acid change – methionine (met) for valine (val) at codon 158
- Met/Met homozygotes: 4-5x less activity
- Met/Met carriers have reduced rate of response to stimulant medications

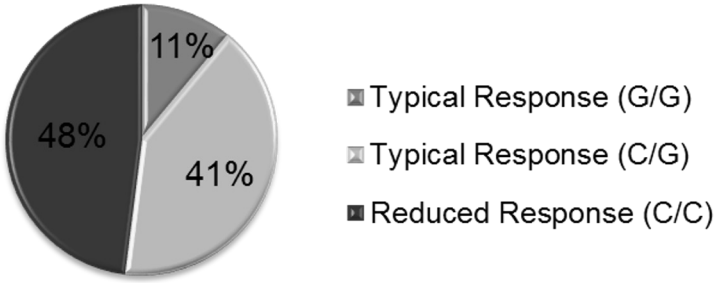


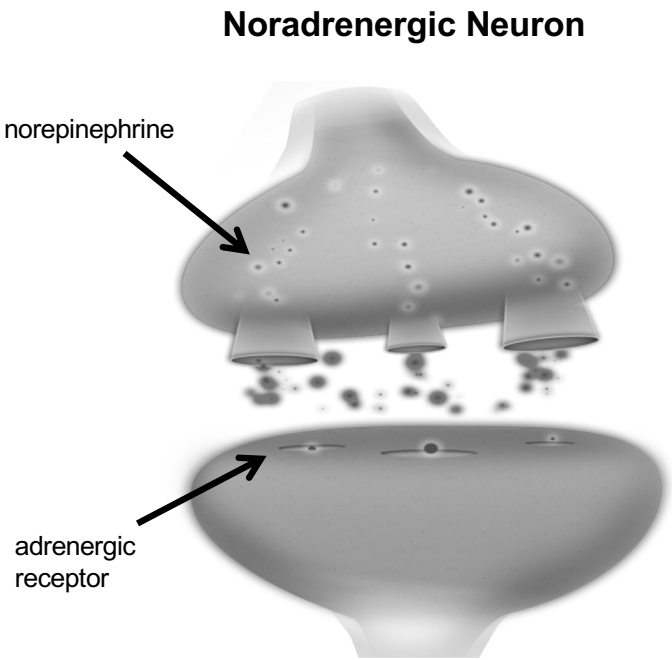


Lachman HM, et al. *Pharmacogenetics*. 1996;6(3):243-250. Cheon KA, et al. *International Clinical Psychopharmacology.* 2008;23:291-298.

ADHD Pharmacogenomics: ADRA2A

- Alpha 2A adrenergic receptor in norepinephrine system
- SNP in promoter region (-1291G>C) shown to affect response to methylphenidate and alpha-2A agonists

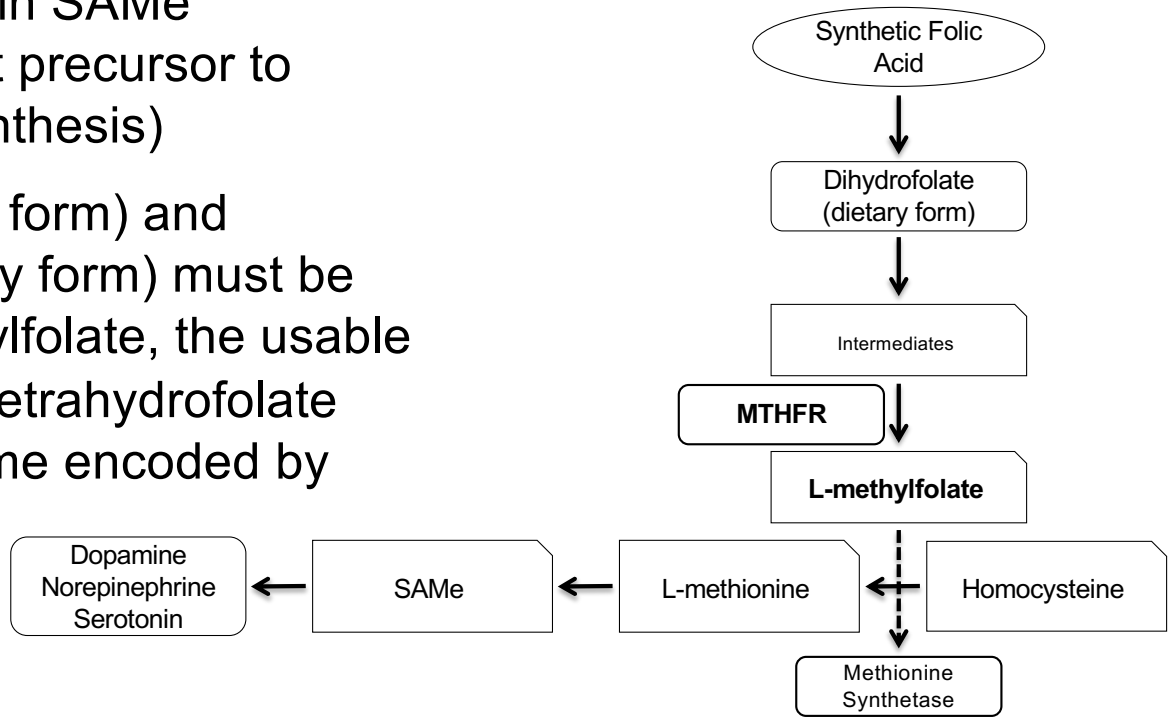




SNP = single nucleotide polymorphisms.
psycheducation.org

Folate Metabolism

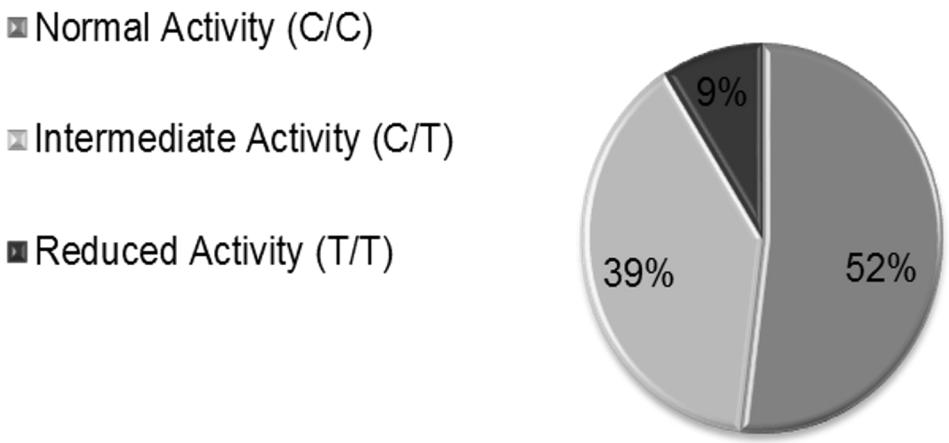
- Folate's critical role in SAMe formation (important precursor to neurotransmitter synthesis)
- Folic acid (synthetic form) and dihydrofolate (dietary form) must be converted to l-methylfolate, the usable form, by methylenetetrahydrofolate reductase, an enzyme encoded by the MTHFR gene



Nazki FH, et al. *Gene.* 2014;533:11-20. Nelson JC. *Am J Psychiatry*. 2012;169(12):1223-1225.

The MTHFR Gene

- C677T SNP in MTHFR gene confers reduced enzymatic activity.
- Multiple studies confirm lower serum folate levels and higher homocysteine levels in individuals with the T/T or T/C genotype relative to the C/C genotype



Nelson JC. *Am J Psychiatry*. 2012;169(12):1223-1225. Nazki F, et al. *Gene.* 2014;11-20. Molloy AM, et al. *Lancet* 1997;349:1591-1593. Anderson CAM, et al. *Mol Nutr Food Res.* 2013;67:637-644.

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