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The Status of Laboratory Testing to Predict Antidepressant Response: Problems and Promises

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Disclosures

- ***Research/Grants:*** National Institutes of Health (NIH)
- ***Consultant:*** ACADIA Pharmaceuticals Inc.; Bracket (Clintara); EMA Wellness; Gerson Lehrman Group, Inc. (GLG); Intra-Cellular Therapies, Inc.; Janssen Research & Development LLC; Magstim, Inc.; Navitor Pharmaceuticals, Inc.; Sunovion Pharmaceuticals Inc.; Taisho Pharmaceutical Inc.; Takeda Pharmaceuticals North America, Inc.; TC MSO, Inc.; Xhale, Inc.
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- ***Patents:*** Method and devices for transdermal delivery of lithium (US 6,375,990B1); Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2); Compounds, Compositions, Methods of Synthesis, and Methods of Treatment (CRF Receptor Binding Ligand) (US 8,511,996B2)

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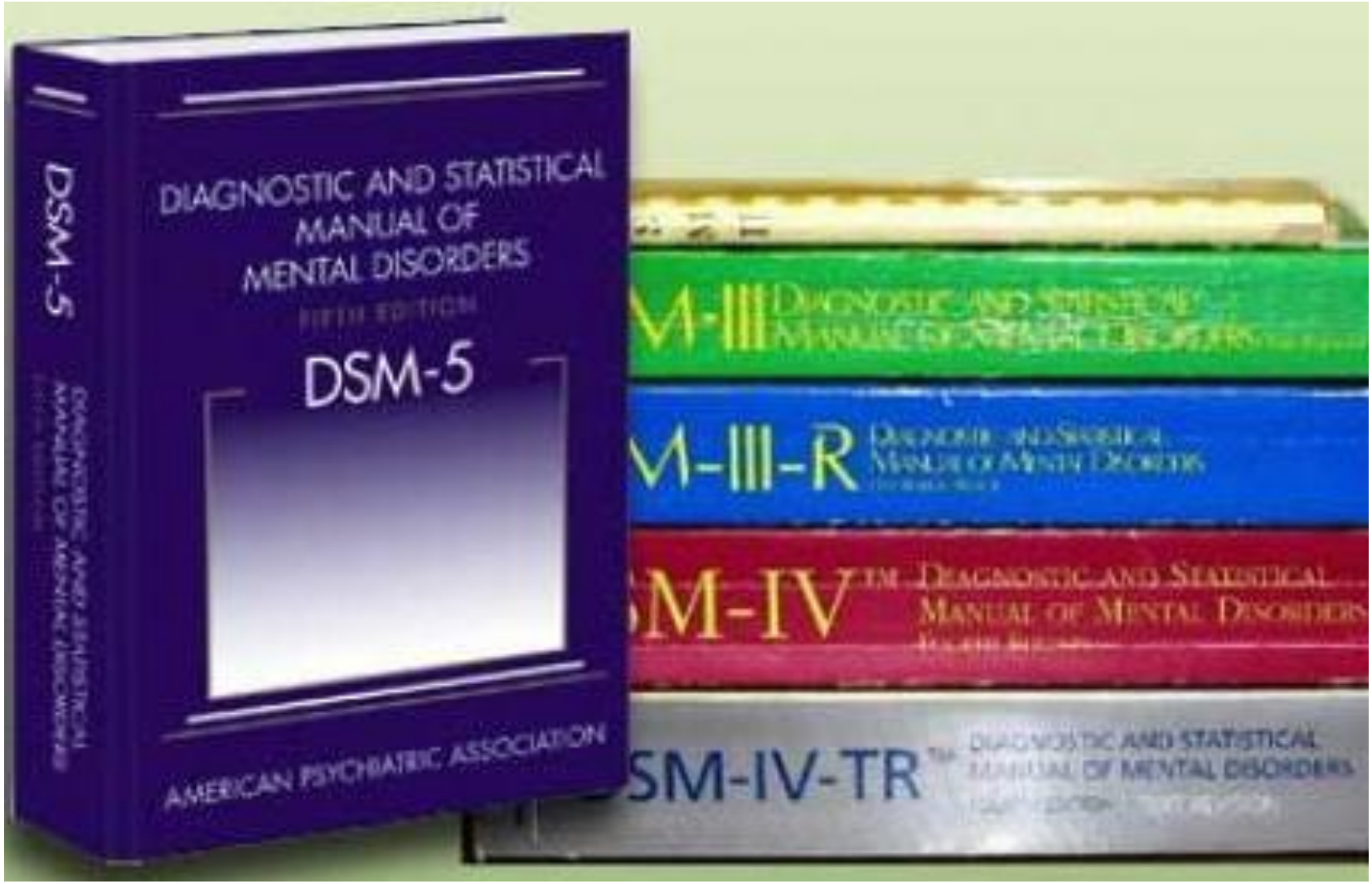
Learning Objective 1

Weigh the latest evidence for genetic testing to predict antidepressant response.


DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION
DSM-5
M-III
M-III-R
SM-IV
SM-IV-TR

Major Depressive Disorder: *DSM-5* Diagnostic Criteria

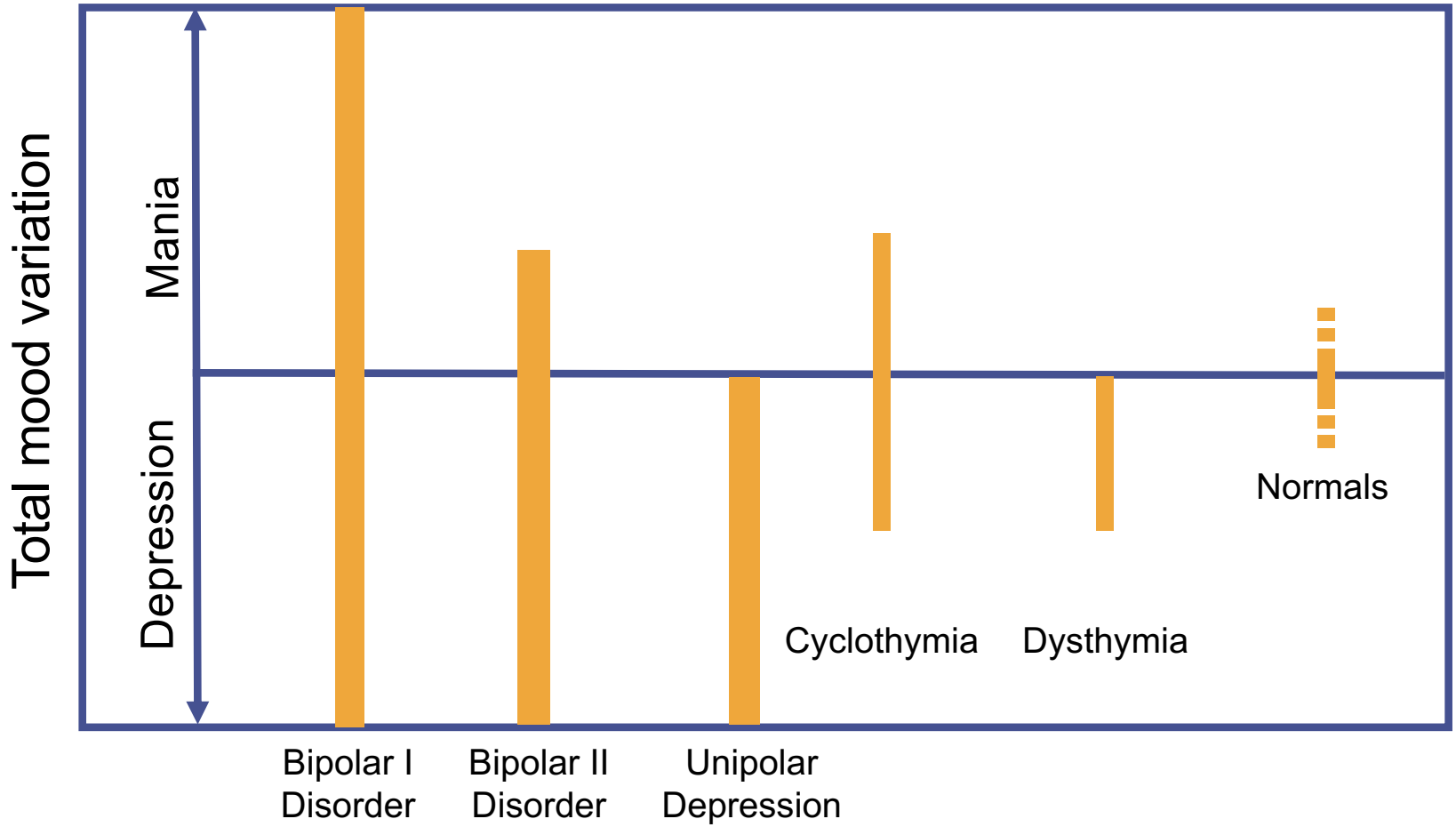
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:

Note: Do not include symptoms that are clearly attributable to another medical condition.

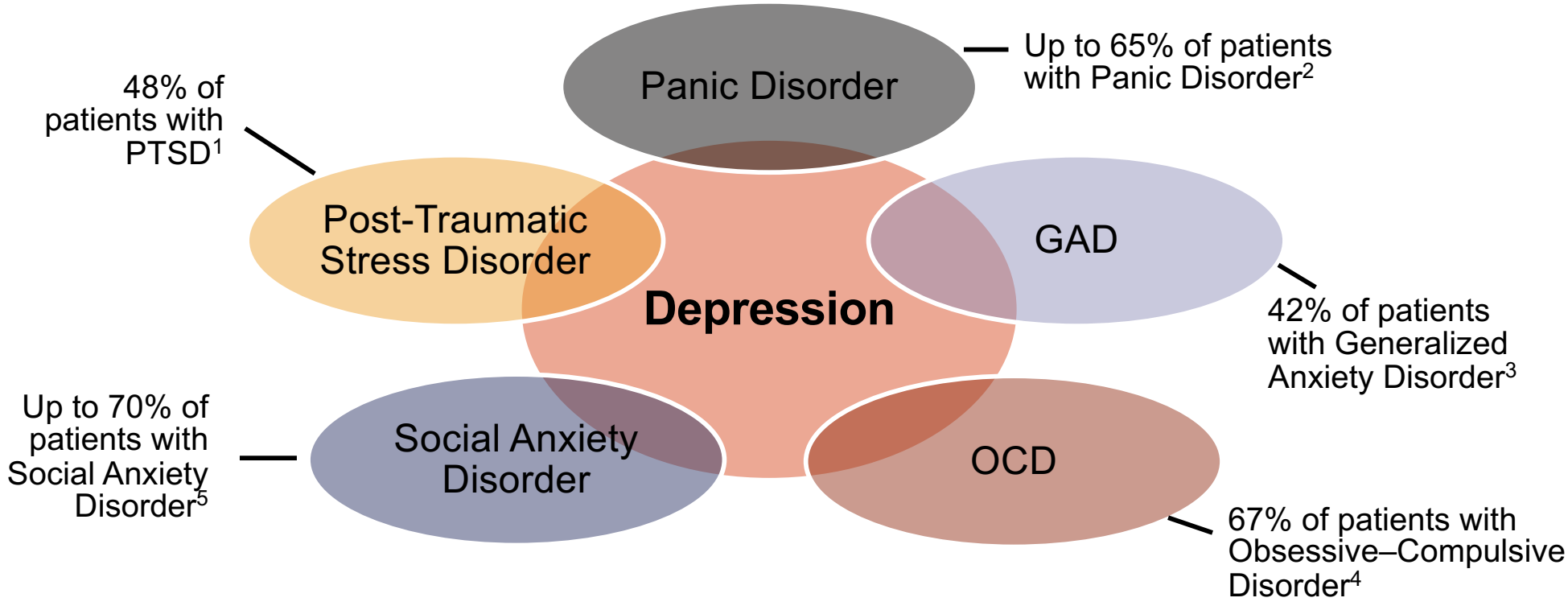
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

DSM-5, 2013.

The Mood-Disorders Spectrum

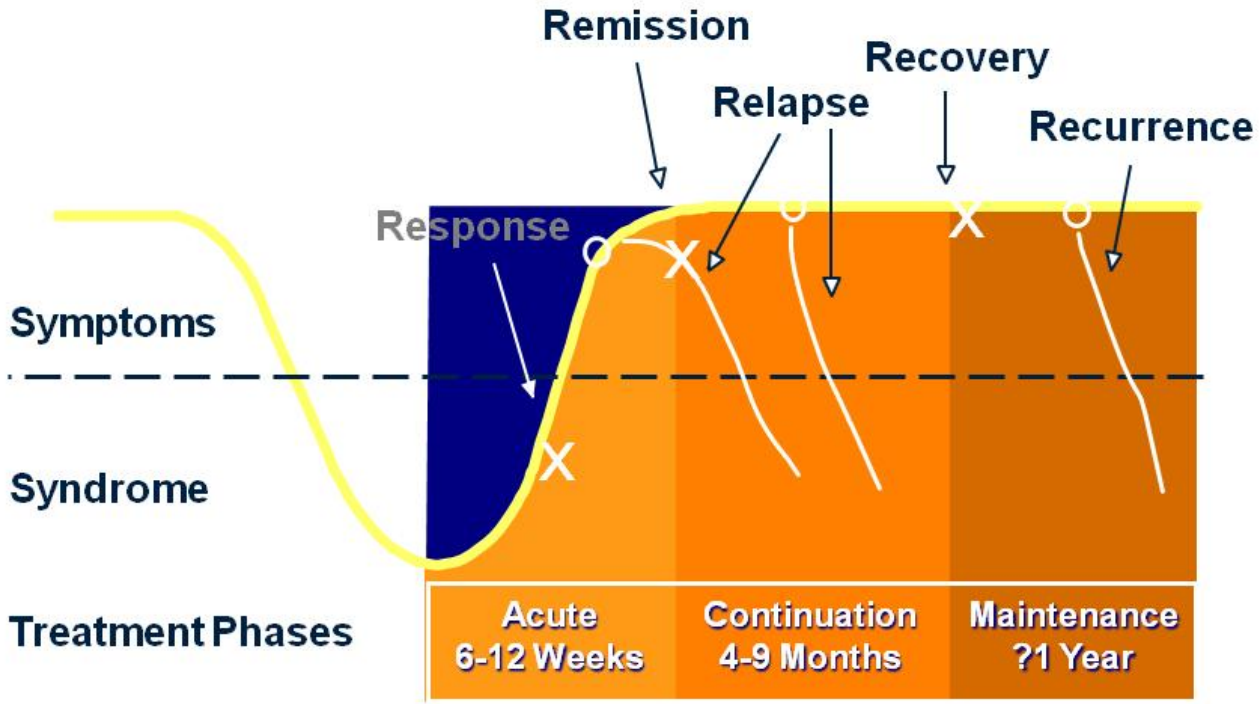


Lifetime Comorbidity of Mood and Anxiety Disorders



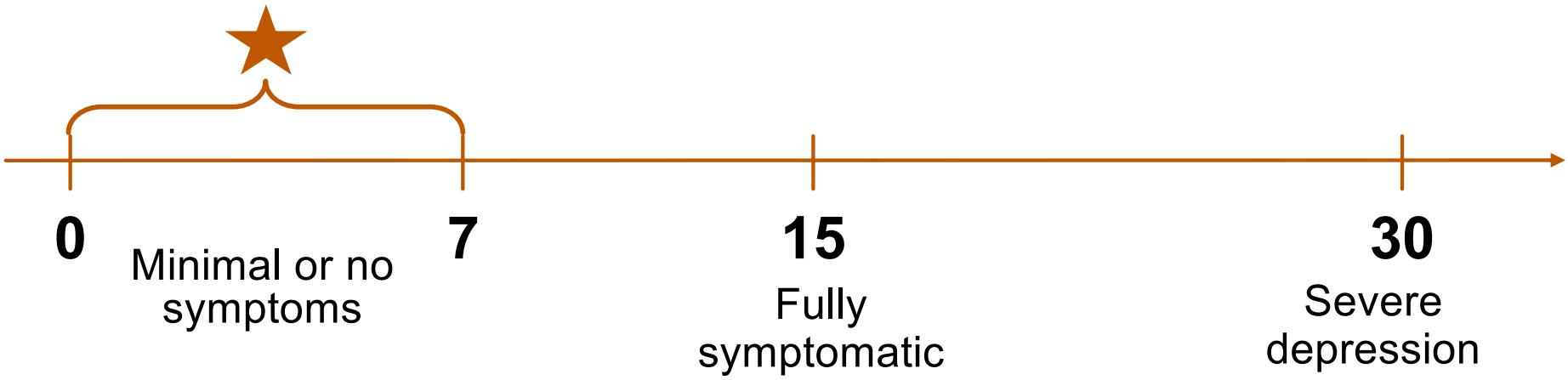
Kessler RC, et al. *Arch Gen Psychiatry*. 1995;52(12):1048-1460. DSM-IV-TR™ 2000. Rasmussen SA, Eisen JL. *J Clin Psychiatry*. 1992;53(suppl):4-10. Dunner DL. *Depression and Anxiety*. 2001;13(2):57-71. Brawman-Mintzer O, et al. *Am J Psychiatry*. 1993;150(8):1216-1218.

Outcome of Depression Treatment
The Five Rs



Operational Definition of Remission

Remission =
HAM-$D_{17} \leq 7$



Hamilton depression rating scale (HAM-D_{17})

Frank E, et al. *Arch Gen Psychiatry*. 1991;48:851-855. Rush AJ, et al. *Psychiatr Ann*. 1995;25:704. American Psychiatric Association. Practice Guidelines for the Treatment of Patients With Major Depression. 2nd ed. 2000. Anderson IM, et al. *J Psychopharmacol*. 2000;14:3-20.

Potential Consequence of Failing to Achieve Remission

- Increased risk of relapse and treatment resistance
- Continued psychosocial limitations
- Decreased ability to work and decreased workplace productivity
- Increased cost for medical treatment
- Sustained risk of suicide, substance abuse
- Sustained depression can worsen morbidity/mortality of other conditions

Paykel ES, et al. *Psychol Med*. 1995;25:1171-1180. Thase ME, et al. *Am J Psychiatry*. 1992;149:1046-1052. Judd LL, et al. *J Affect Disord*. 1998;59:97-108. Miller IW, et al. *J Clin Psychiatry*. 1998;59:608-619. Simon GE, et al. *Gen Hosp Psychiatry*. 2000;22:153-162. Druss BG, et al. *Am J Psychiatry*. 2001;158:731-734. Frasure-Smith N, et al. *JAMA*. 1993;270:1819-1825. Penninx BW, et al. *Arch Gen Psychiatry*. 2001;58:221-227. Rovner BW, et al. *JAMA*. 1991;265:993-996.

Depression Worsens Outcomes of Many General Medical Conditions

- Depression worsens morbidity and mortality after myocardial infarction[1,2]
- Depression increases risk for mortality in patients in nursing homes[3]
- Depression worsens morbidity post-stroke[4]
- Depression can worsen outcomes of cancer, diabetes, AIDS, and other disorders[5]

1. Frasure-Smith N, et al. *JAMA*. 1993;270:1819-1825. 2. Penninx BW, et al. *Arch Gen Psychiatry*. 2001;58:221-227. 3. Rovner BW, et al. *JAMA*. 1991;265:993-996. 4. Pohjasvaara T, et al. *Eur J Neurol*. 2001;8:315-319. 5. Petitto JM, Evans DL. *Depress Anxiety*. 1998;8(suppl 1):80-84.

Treatment Resistance and Depressive Sub-Types

- Atypical depression
- “Double” depression
- Psychotic depression
- Severe and melancholic depression
- Co-morbidity — psychiatric or medical

Current Treatment Options for Depression

Goal = reduce symptoms and return to full, active life

Nonpharmacologic

- Psychotherapy
  - Cognitive behavioral therapy
  - Interpersonal therapy
  - Psychodynamic therapy
- Electroconvulsive therapy
- Phototherapy
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Vagal Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)

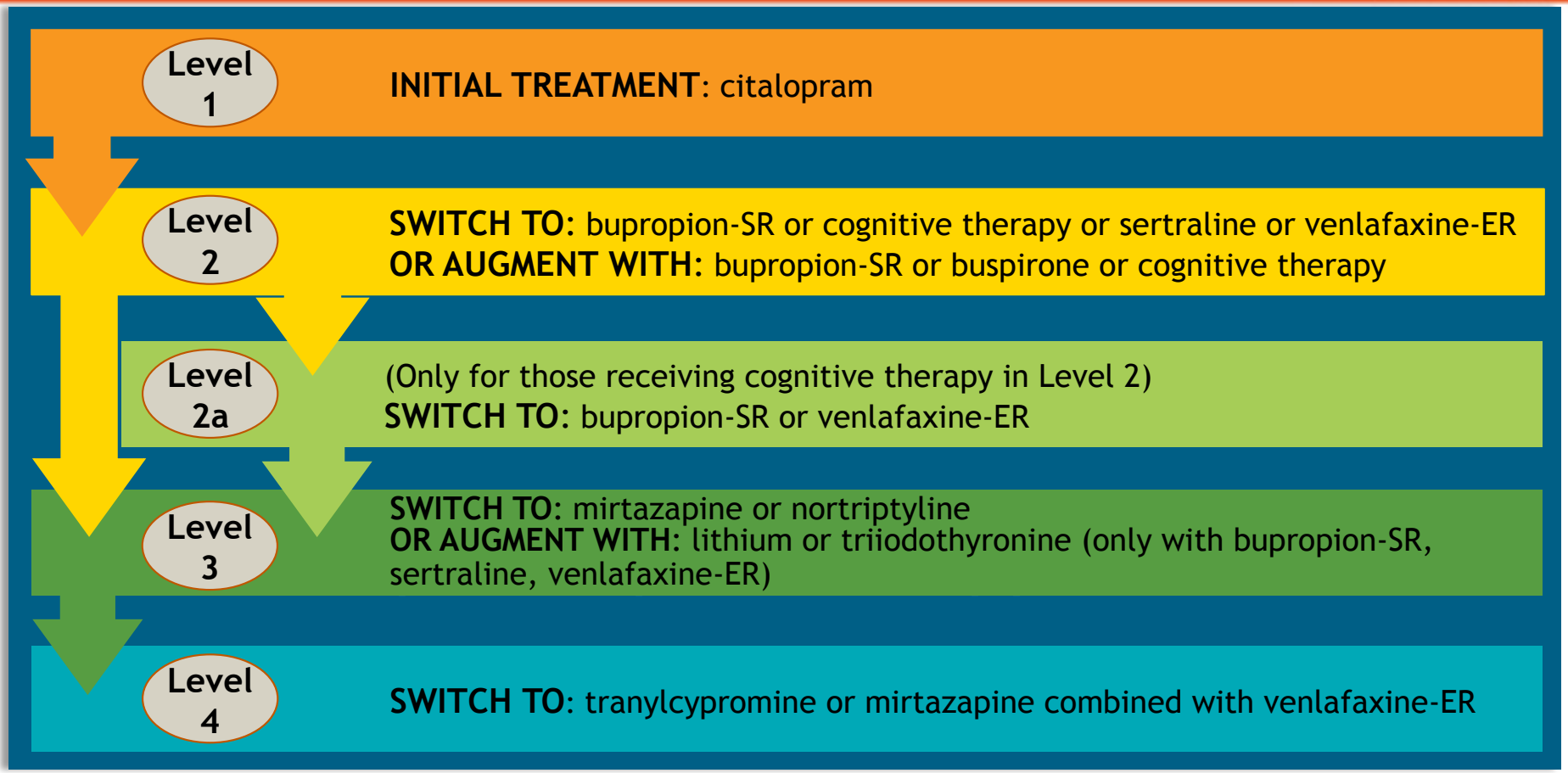
Depression Guideline Panel. Depression in Primary Care: Vol 1. Detection and Diagnosis. Clinical Practice Guideline No. 5. 1993.

Evaluation of Outcomes with Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice

Madhukar H. Trivedi, M.D., A. John Rush, M.D., Stephen R. Wisniewski, Ph.D., Andrew A. Nierenberg, M.D., Diane Warden, Ph.D., M.B.A., Louise Ritz, M.B.A., Grayson Norquist, M.D., Robert H. Howland, M.D., Barry Lebowitz, Ph.D., Patrick J. McGrath, M.D., Kathy Shores-Wilson, Ph.D., Melanie M. Biggs, Ph.D., G. K. Balasubramani, Ph.D., Maurizio Fava, M.D. and STAR*D Study Team

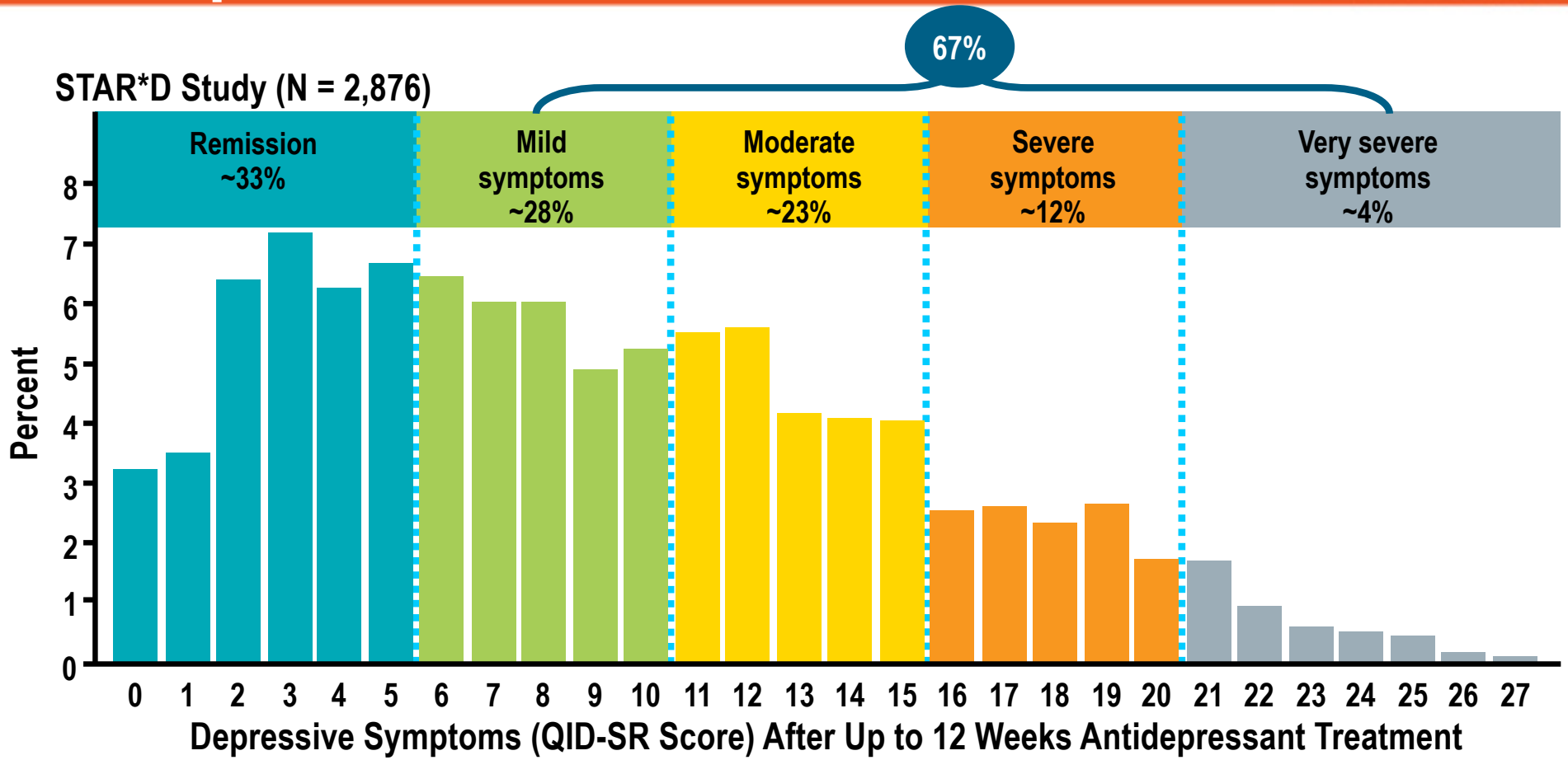
Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.

STAR*D: Treatment Algorithm Snapshot



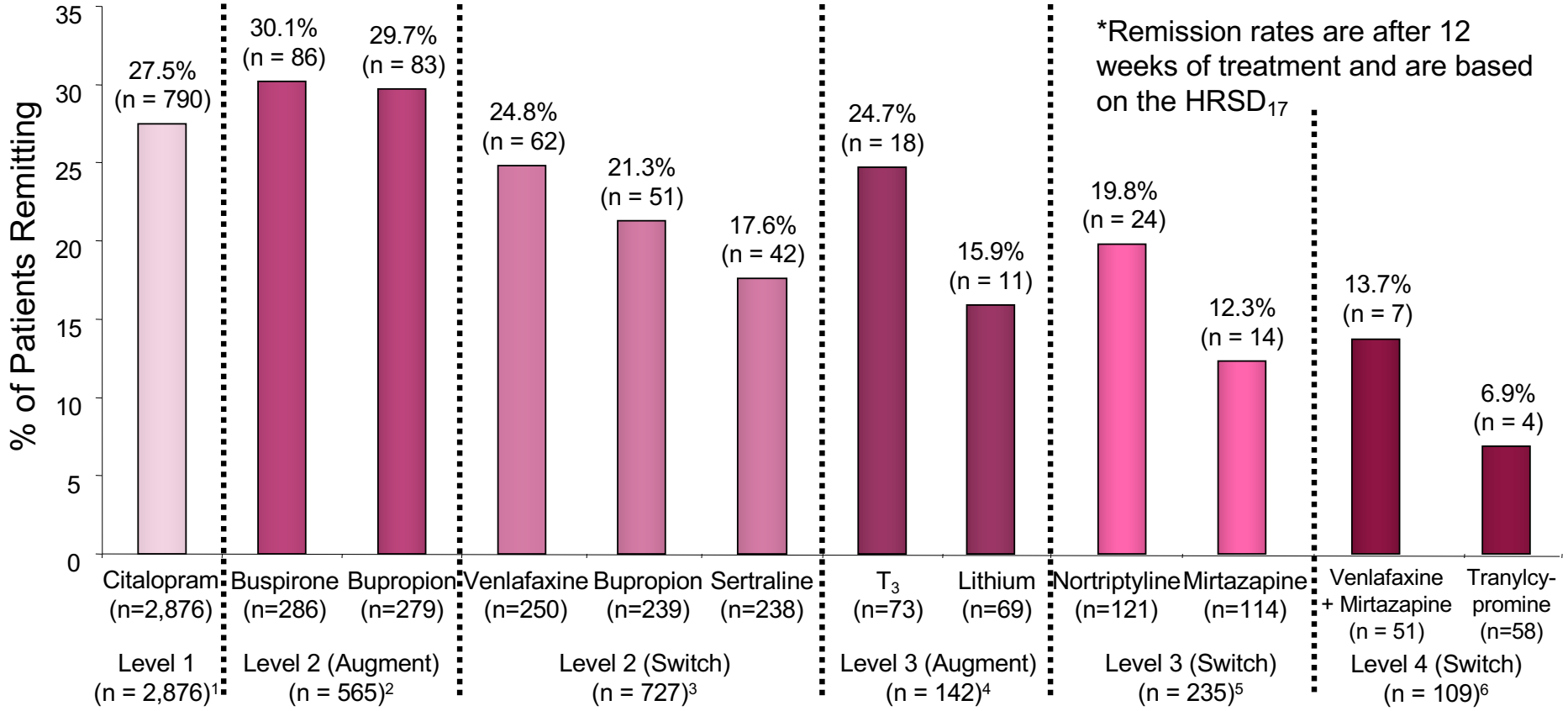
STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

STAR*D: Unresolved Symptoms Following Antidepressant Treatment



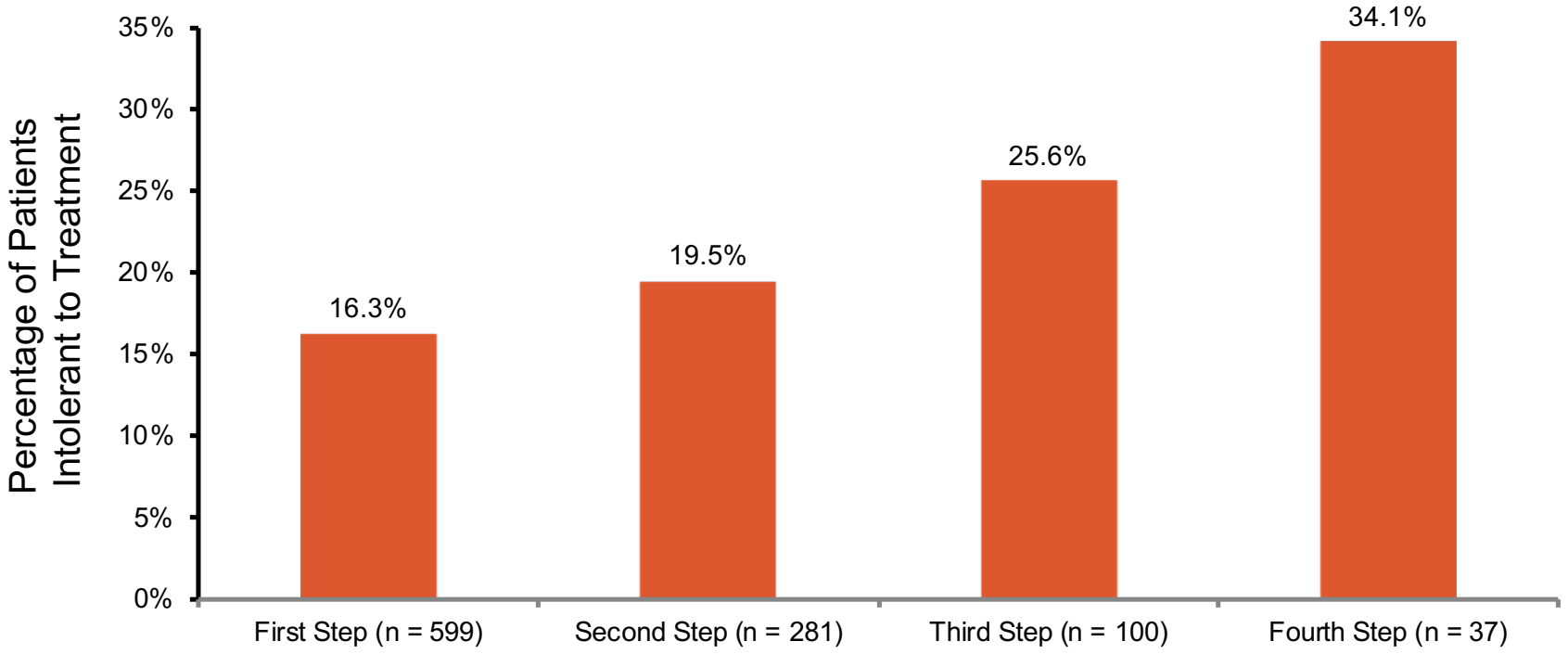
STAR*D=Sequenced Treatment Alternatives to Relieve Depression. n=2,876. Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.

STAR*D Results Demonstrate Diminishing Effectiveness of TRD Treatments



1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28. 2. Trivedi MH, et al. *N Engl J Med*. 2006;354:1243. 3. Rush AJ, et al. *N Engl J Med*. 2006;354:1231. 4. Nierenberg AA, et al. *Am J Psychiatry*. 2006;163:1519. 5. Fava M, et al. *Am J Psychiatry*. 2006;163:1161. 6. McGrath PJ, et al. *Am J Psychiatry*. 2006;163:1531.

Treatment Intolerance Increases with Each Treatment Level



*Participants were considered to have intolerable side effects if they left the treatment level prior to 4 weeks for any reason or left thereafter citing treatment intolerance as the reason.

Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917.

Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis

Valentina Nanni, M.D.

Rudolf Uher, M.U.Dr., Ph.D.

Andrea Danese, M.D., Ph.D.

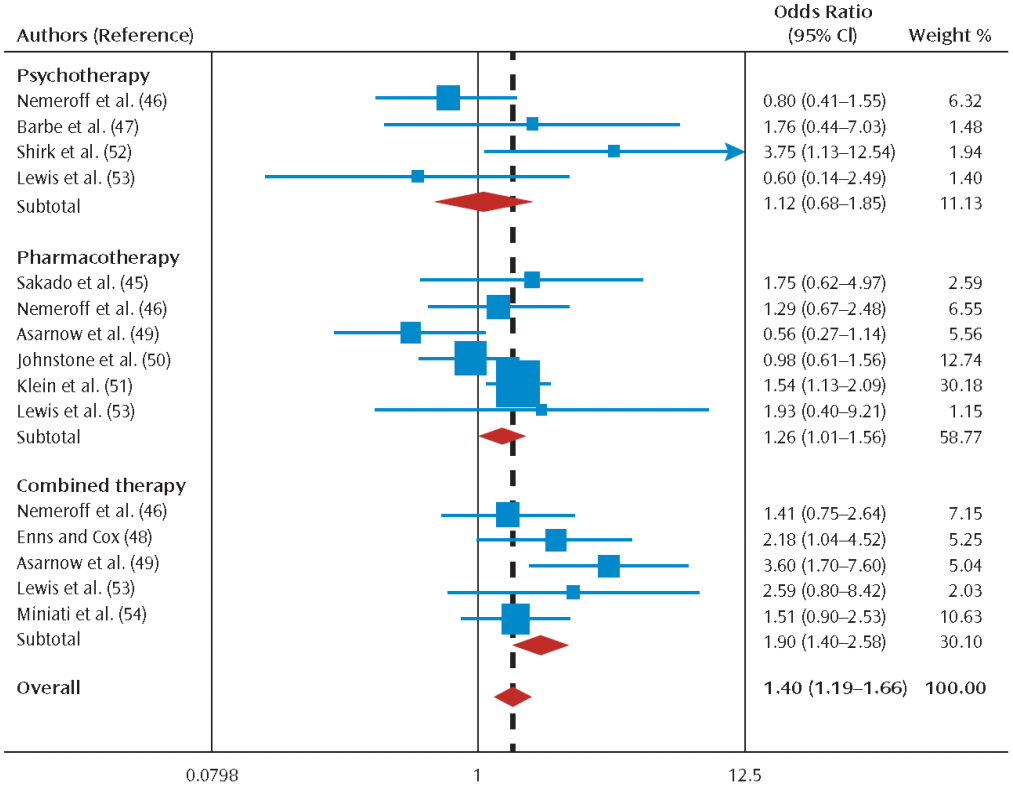
Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between childhood maltreatment and these clinically relevant measures of depression.

Results: A meta-analysis of 16 epidemiological studies (23,544 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87). A meta-analysis of 10 clinical trials (3,098 participants) revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression (odds ratio=1.43, 95% CI=1.11–1.83). Meta-regression analyses suggested that the results were not significantly affected by publication bias, choice of outcome measure, inclusion of prevalence or incidence samples, study quality, age of the sample, or lifetime prevalence of depression.

Conclusions: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression.

Nanni V, et al. *Am J Psychiatry*. 2012;169:141-151.

FIGURE 3. Meta-Analysis of Clinical Trials Investigating the Association Between Childhood Maltreatment and Treatment Outcome of Depression (Fixed Effects)[a]



[a] Based on the evidence of homogeneous distributions of effect sizes within treatment groups, we present here the results of fixed-effects model meta-analyses for different treatment groups. The overall effect size across treatment groups was estimated with a random-effects model meta-analysis with the following study weights: Nemeroff (psychotherapy): 7.88; Barbe: 2.78; Shirk: 3.49; Lewis (psychotherapy): 2.65; Sakado: 4.36; Nemeroff (pharmacotherapy): 8.03; Asarnow (pharmacotherapy): 7.32; Johnstone: 10.96; Klein: 14.09; Lewis (pharmacotherapy): 2.25; Nemeroff (combined therapy): 8.42; Enns: 7.07; Asarnow (combined therapy): 6.90; Lewis (combined therapy): 3.61; Miniati: 10.18. The red diamonds show the combined effect sizes for studies concerned with psychotherapy, pharmacotherapy, and combined therapy, as well as the overall effect size of the meta-analysis (top to bottom).

Nanni V, et al. *Am J Psychiatry*. 2012;169:141-151.


CURRENTLY ON
EXIT 58A-B
95
1
Zoloft
TP
9
Prozac
Paxil
LAST EXIT
BEFORE TOLL
Buspar
Wellbutrin
Celexa
Xanax

Personalized Medicine

From Wikipedia, the free encyclopedia

- **Personalized medicine** is a medical model emphasizing in general the customization of healthcare, with all decisions and practices being tailored to individual patients in whatever ways possible. Recently, this has mainly involved the systematic use of genetic or other information about an individual patient to select or optimize that patient's preventative and therapeutic care

TODAY....

diagnosis

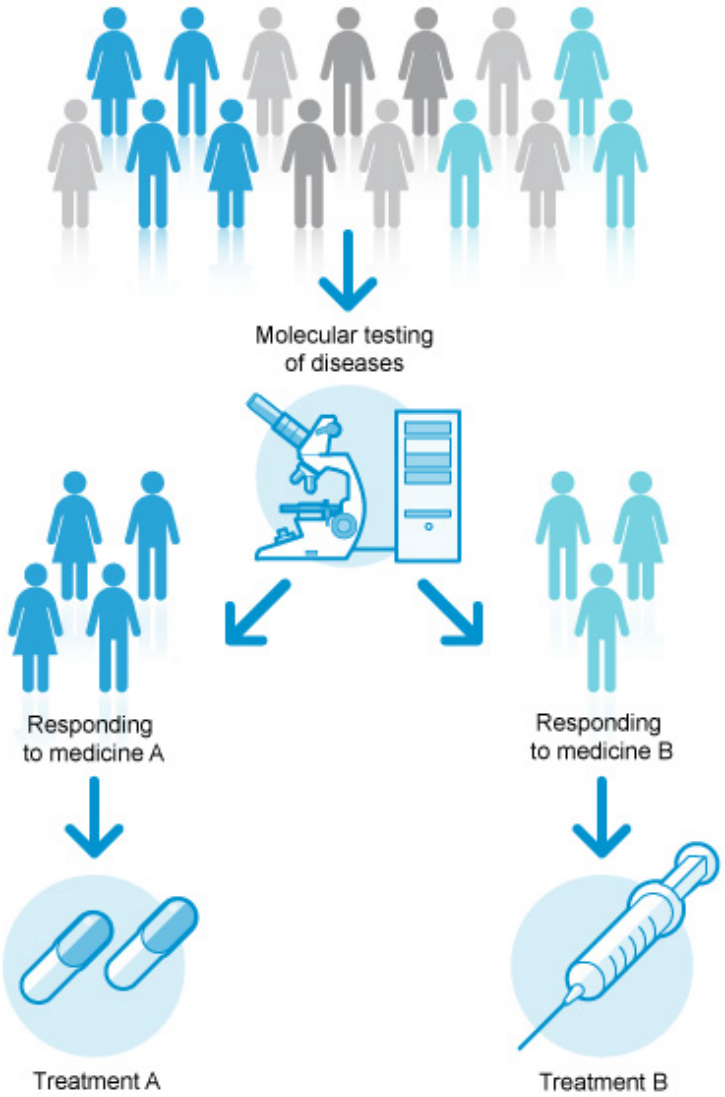
trials and errors

effective treatment

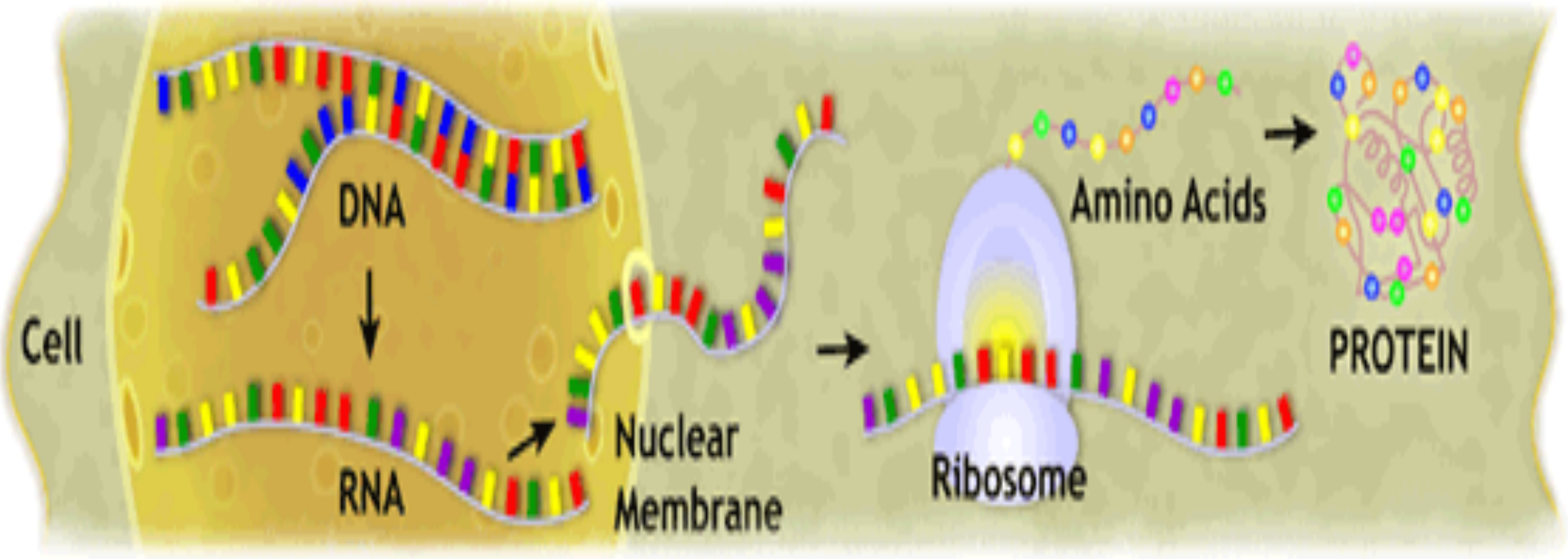
TOMORROW....

tailor made

Personalized Medicine



New molecular and diagnostic technologies can be used to match select groups of patients with treatments that may give them the best results



Our DNA is our instruction manual

We can now read the whole manual!

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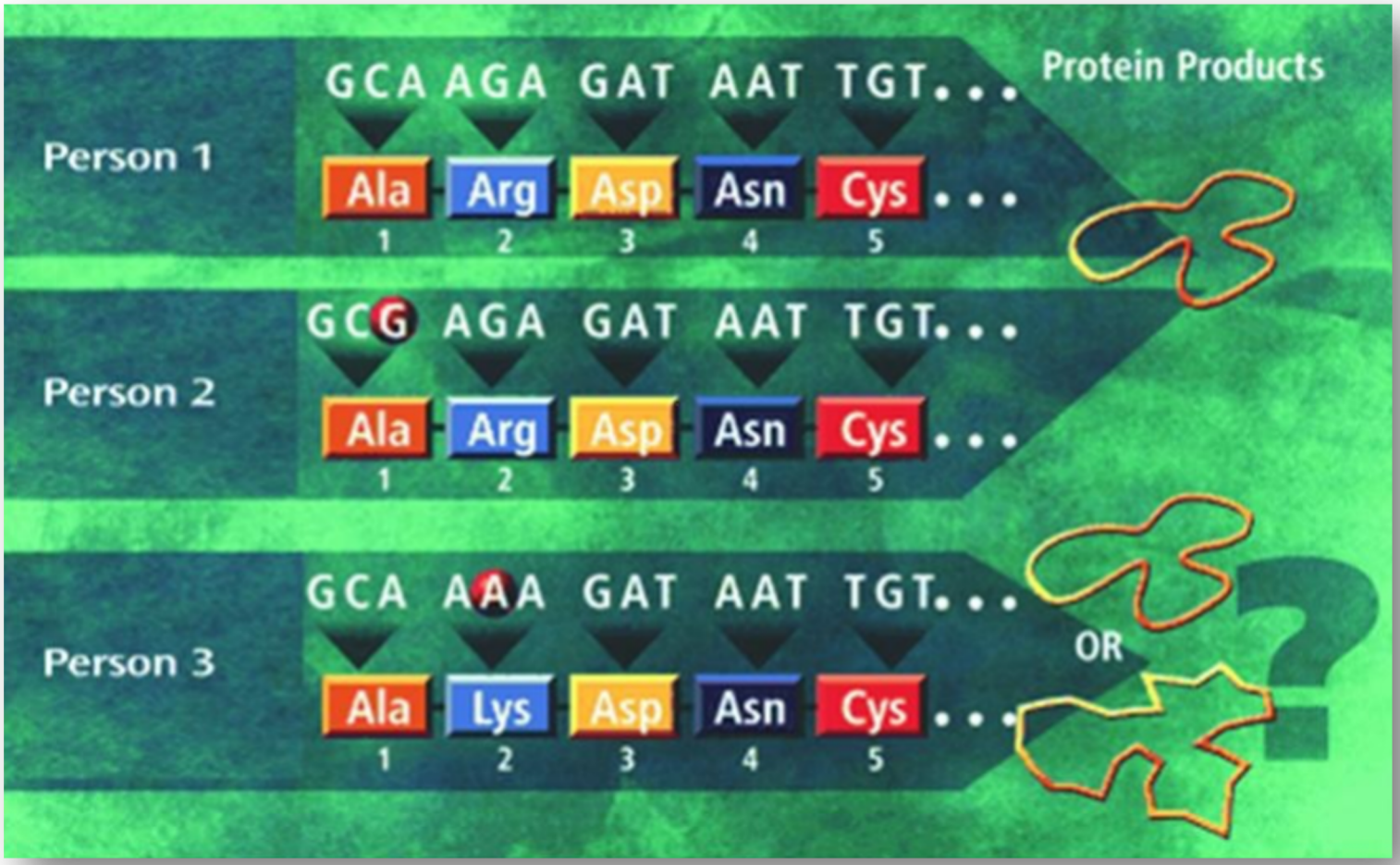


The image shows how DNA sequence variation in a gene can change the protein produced by the genetic code. The nucleotide triplet codon at position 1 in the gene depicted is different in person 1 and person 2, but the codon difference does not change the amino acid sequence. In person 3, the nucleotide triplet codon at position 2 is different from that in person 1 and person 2, and the codon change results in production of a different amino acid at position 2 in person 3.

AJP. 2001;158:791.

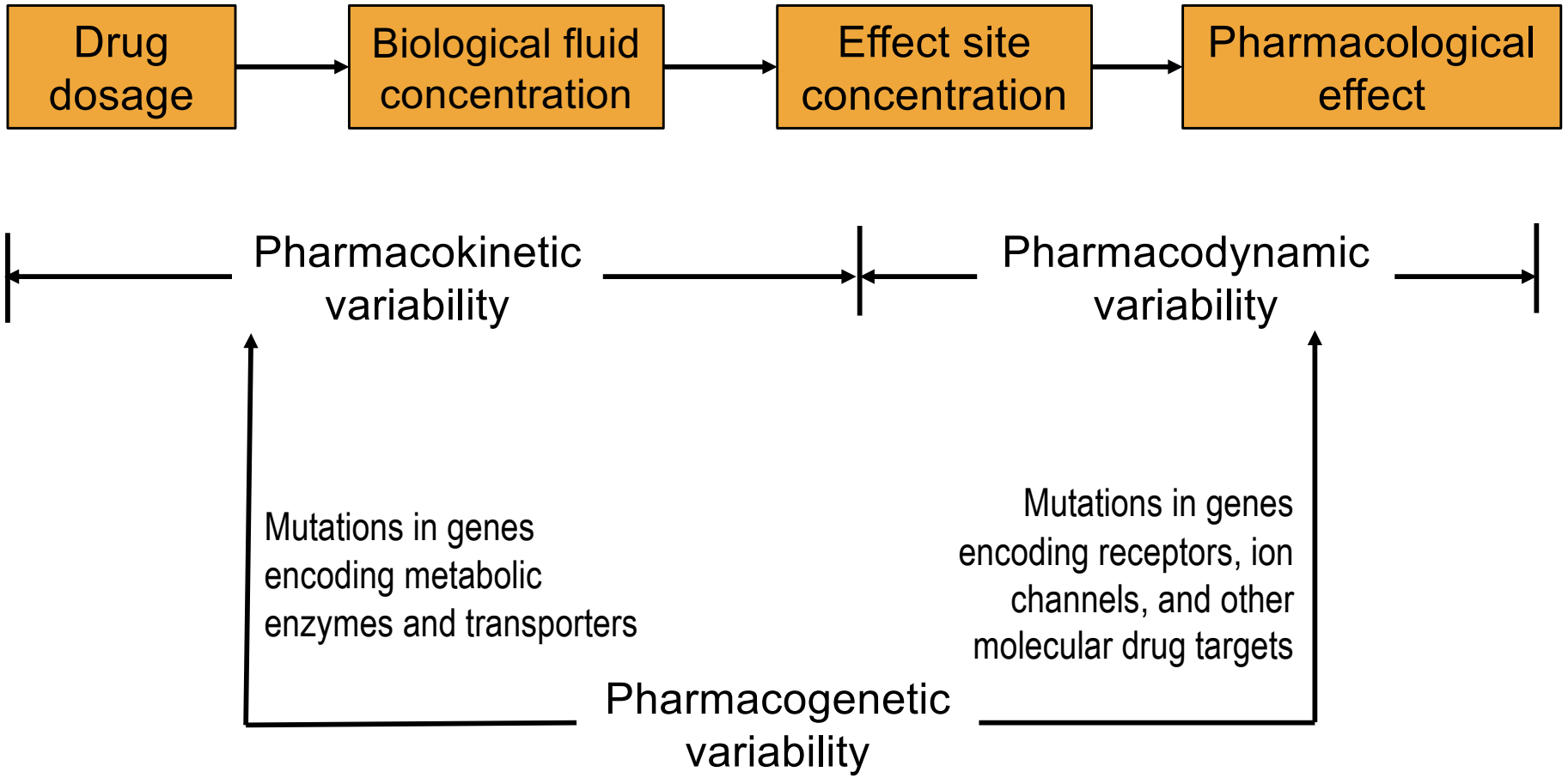
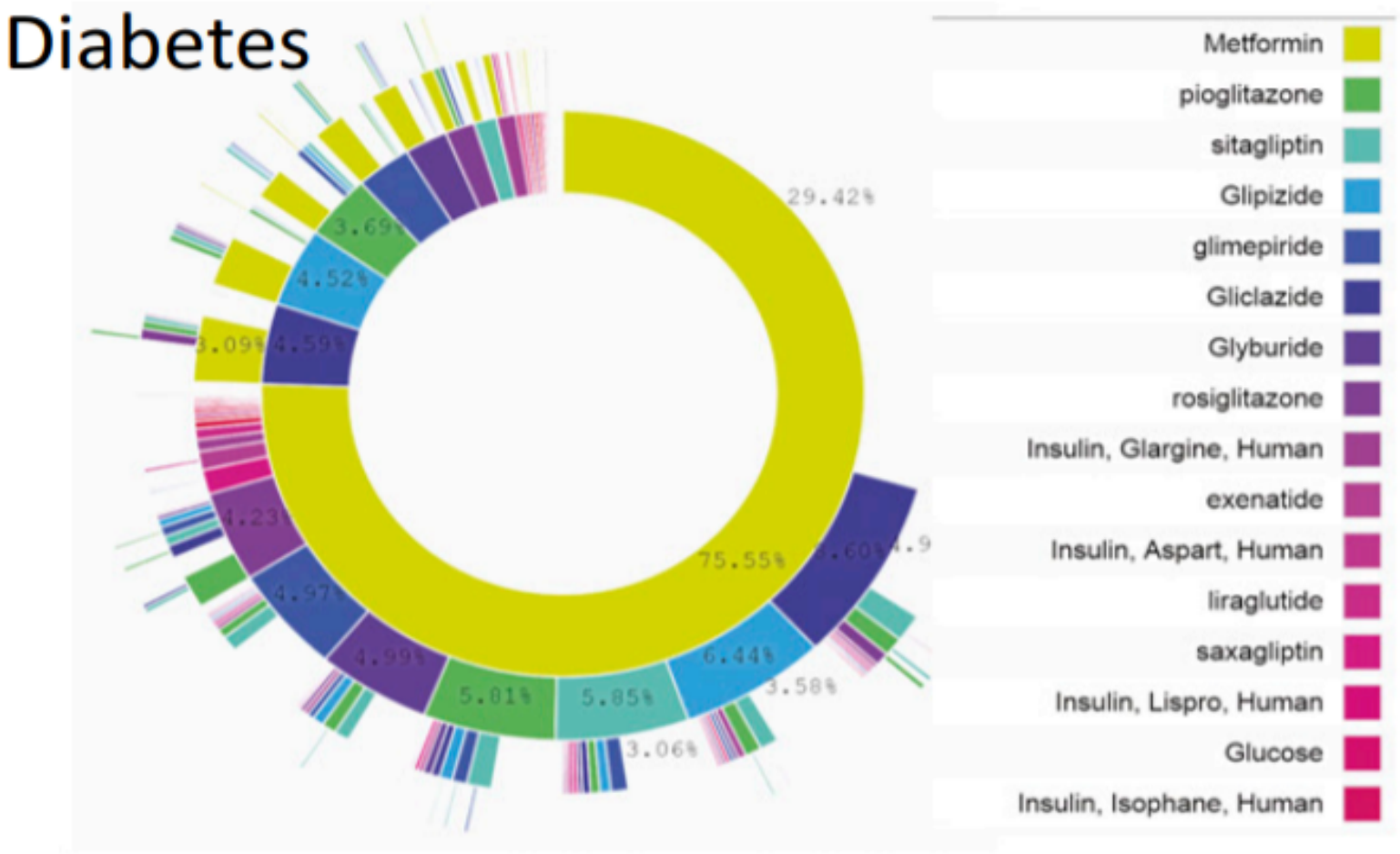
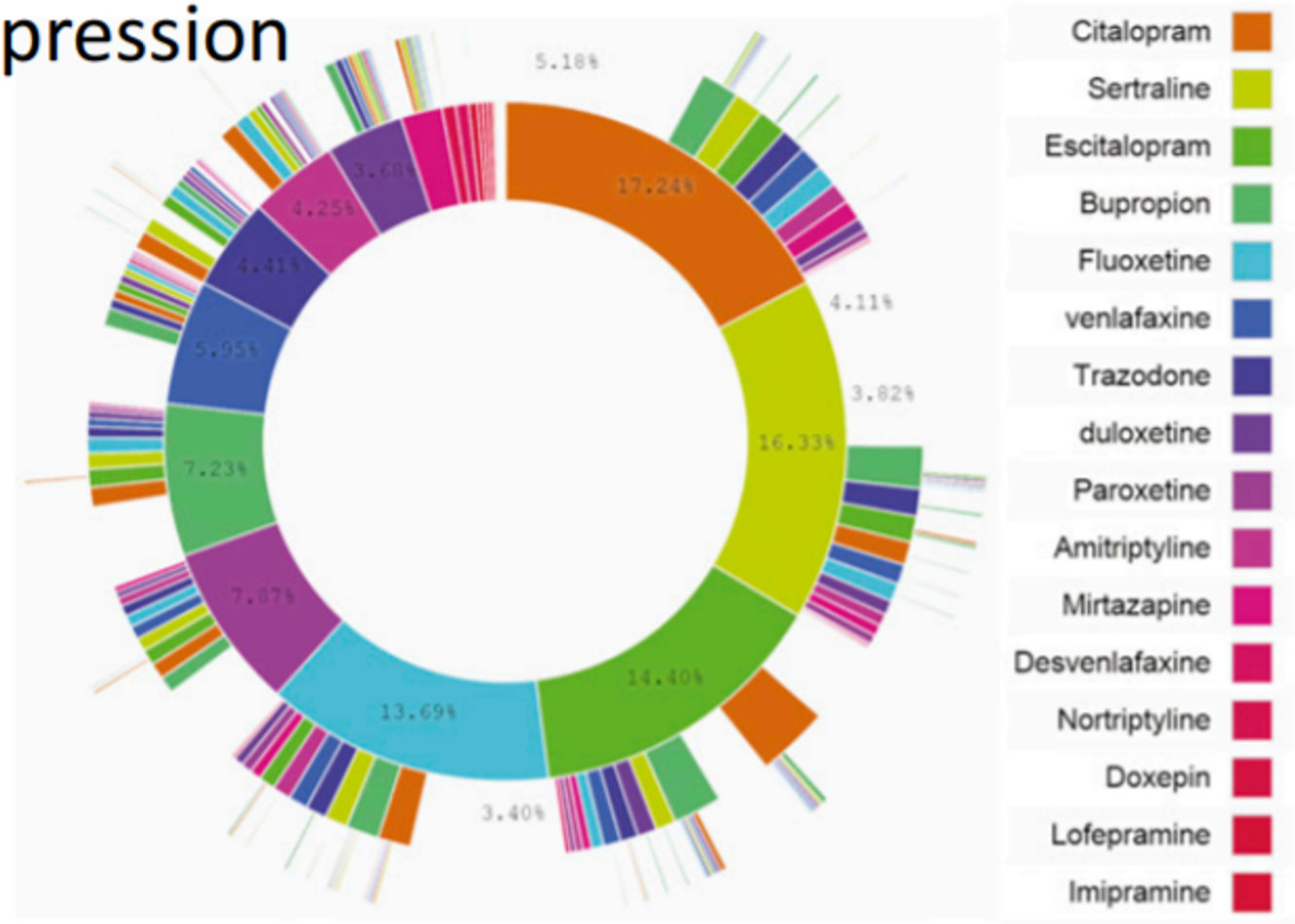


FIGURE 6-1. Pharmacokinetic, pharmacodynamics, and pharmaco-genomic variability as determinants of the dose-effect relationship



Hripcsak G, et al. *Proc Natl Acad Sci U S A*. 2016;113:7329-7336.

Depression



Hripcsak G, et al. *Proc Natl Acad Sci U S A*. 2016;113:7329-7336.

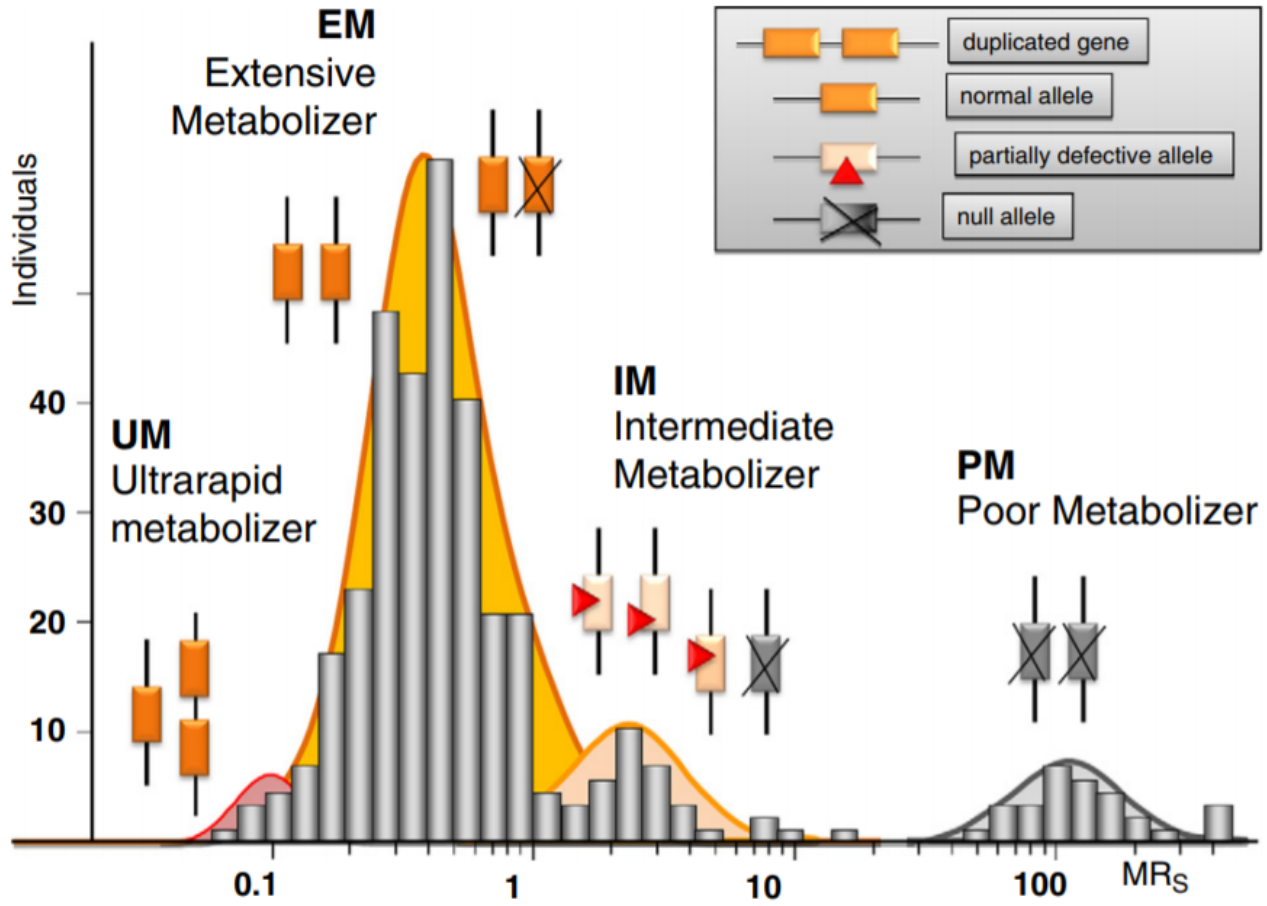


Fig. 2. Sparteine oxidation phenotype and genotype distribution in a German population (n = 308). MR_S: urinary metabolic ratio for sparteine (Raimundo et al., 2004; Zanger, 2008). Reproduced by permission of The Royal Society of Chemistry.

Pharmacokinetic

GENE	PHYSIOLOGICAL ROLE	IMPACT OF MUTATION	TREATMENT IMPACT
CYP450 (CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5)	Enzymes that metabolize medications in the liver	Large number of psychiatric medications are metabolized by CYP450s	Dose adjustment (an increase or decrease) may be required

Genes Analyzed in the Genecept Assay- *Genomind*

Cytochrome P-450 Polymorphisms and Response to Clopidogrel

Jessica L. Mega, M.D., M.P.H., Sandra L. Close, Ph.D., Stephen D. Wiviott, M.D., Lei Shen, Ph.D., Richard D. Hockett, M.D., John T. Brandt, M.D., Joseph R. Walker, Pharm.D., Elliott M. Antman, M.D., William Macias, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.

Mega JL, et al. *N Engl J Med*. 2009;360:354-362.

BACKGROUND

Clopidogrel requires transformation into an active metabolite by cytochrome P-450 (CYP) enzymes for its antiplatelet effect. The genes encoding CYP enzymes are polymorphic, with common alleles conferring reduced function.

METHODS

We tested the association between functional genetic variants in CYP genes, plasma concentrations of active drug metabolite, and platelet inhibition in response to clopidogrel in 162 healthy subjects. We then examined the association between these genetic variants and cardiovascular outcomes in a separate cohort of 1477 subjects with acute coronary syndromes who were treated with clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38.

Mega JL, et al. *N Engl J Med*. 2009;360:354-362.

RESULTS

In healthy subjects who were treated with clopidogrel, carriers of at least one *CYP2C19* reduced-function allele (approximately 30% of the study population) had a relative reduction of 32.4% in plasma exposure to the active metabolite of clopidogrel, as compared with noncarriers ($P<0.001$). Carriers also had an absolute reduction in maximal platelet aggregation in response to clopidogrel that was 9 percentage points less than that seen in noncarriers ($P<0.001$). Among clopidogrel-treated subjects in TRITON–TIMI 38, carriers had a relative increase of 53% in the composite primary efficacy outcome of the risk of death from cardiovascular causes, myocardial infarction, or stroke, as compared with noncarriers (12.1% vs. 8.0%; hazard ratio for carriers, 1.53; 95% confidence interval [CI], 1.07 to 2.19; $P=0.01$) and an increase by a factor of 3 in the risk of stent thrombosis (2.6% vs. 0.8%; hazard ratio, 3.09; 95% CI, 1.19 to 8.00; $P=0.02$).

CONCLUSIONS

Among persons treated with clopidogrel, carriers of a reduced-function *CYP2C19* allele had significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events, including stent thrombosis, than did noncarriers.

Mega JL, et al. *N Engl J Med*. 2009;360:354-362.

Table 1. Personalized medicine drugs for breast cancer as of July 2012

Biomarker	Drug		Compound	Indication
BRCA1/2				Guides surveillance and preventive treatment based on susceptibility risk for breast and ovarian cancer
Estrogen receptor (hormone receptor)	Selective estrogen receptor modulators	Nolvadex®	Tamoxifen	Tamoxifen is currently used for the treatment of estrogen receptor positive breast cancer in pre- and post-menopausal women. Additionally, it is the most common hormone treatment for male breast cancer. It is also approved by the FDA for the prevention of breast cancer in women at high risk of developing the disease
		Fareston®	Toremifen	Toremifen is an estrogen agonist/antagonist indicated for the treatment of breast cancer in postmenopausal women with estrogen-receptor positive tumors
	Aromatase inhibitors	Femara®	Letrozole	Letrozole is indicated for the treatment of postmenopausal women with hormone receptor-positive breast cancer
		Arimidex®	Anastrozole	Anastrozole is indicated for the treatment of postmenopausal women with hormone receptor-positive breast cancer
		Aromasin®	Exemestane	Exemestane is indicated for the treatment of postmenopausal women with hormone receptor-positive breast cancer
	Estrogen receptor antagonist	Faslodex®	Fulvestrant	Fulvestrant is indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy
	mTOR inhibitor	AFINITOR®	Everolimus	Everolimus is a mTOR inhibitor indicated for the treatment of postmenopausal women with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole
HER2/*neu* over-expression (HER2-positive)	Monoclonal antibody	Herceptin®	Trastuzumab	Trastuzumab is indicated for use in combination with cytotoxic chemotherapy for the treatment of breast cancer in women with HER2-positive tumor
		Perjeta®	Pertuzumab	Pertuzumab is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease
	Tyrosine kinase inhibitor	Tykerb®	Lapatinib	Lapatinib is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab

Data from National Cancer Institute. Drug information: drugs approved for different types of cancer. http://www.cancer.gov/cancertopics/druginfo/drug-page-index [36], National Cancer Institute. Drug information: drugs approved for breast cancer. http://www.cancer.gov/cancertopics/druginfo/breastcancer [37].

Sang-Hoon C, et al. *J Breast Cancer*. 2012;15:265-272.

Pharmacodynamic

GENE	PHYSIOLOGICAL ROLE	IMPACT OF MUTATION	TREATMENT IMPACT
Serotonin Transporter (SLC6A4)	Protein responsible for reuptake of serotonin from the synapse	Inhibition of this protein by SSRIs, which may lead to increased risk for non-response/side effects	Use caution with SSRIs; SNRIs or non-SSRI antidepressants may be used if clinically indicated
Calcium Channel (CACNA1C)	A subunit of the calcium channel which mediates excitatory signaling	Associated with conditions characterized by mood instability/lability	Atypical antipsychotics, mood stabilizers, and/or omega-3 fatty acids, which may help to reduce excitatory signaling, may be used if clinically indicated

Genes Analyzed in the Genecept Assay- *Genomind*

GRIK4	rs1954787 CC		Normal response Genotype predicts a normal response to citalopram in patients with major depressive disorder.
HTR2A	rs7997012 AA		Intron 2 genotype AA Genotype predicts an increased likelihood of response to citalopram.
SLC6A4	L/L (La/La)		Typical to increased expression The L/L genotype has been associated with increased likelihood and potentially quicker response to the SSRIs fluoxetine, fluvoxamine, and possibly citalopram and escitalopram.

RightMed Comprehensive Test Report

With the RightMed comprehensive test, providers receive a clinically actionable report that categorizes drugs into a simple, easy-to-read format:

MAJOR GENE-DRUG INTERACTION

MODERATE GENE-DRUG INTERACTION

MINIMAL GENE-DRUG INTERACTION

Providers may use the information from the test report to guide medication and dosage decisions based on the patient's DNA, the drug binning, and clinical annotations.

OneOme

How We Can Help

The Genecept Assay® looks at key genes in your body's DNA that affect how it responds to medication. This can help your clinician to understand if a drug may work for you before you even try it. With this information, along with your medical history, your clinician can find the right treatments so you can feel better, faster. The personalized information provided by the Genecept Assay can help your clinician to be more informed and better able to determine an optimized treatment plan – just for you.

Genecept is used to guide treatment for a range of psychiatric conditions, including:

- **depression (https://genomind.com/the-genecept-assay/genetic-testing-better-depression-treatment/)**
- **anxiety (https://genomind.com/the-genecept-assay/personalized-medicine-faster-anxiety-treatment/)**
- obsessive-compulsive disorder (OCD)
- **attention deficit hyperactivity disorder (ADHD) (https://genomind.com/the-genecept-assay/targeted-treatment-adhd/)**
- bipolar disorder
- post traumatic stress disorder (PTSD)
- autism
- schizophrenia
- chronic pain
- substance abuse

This quick and pain-free test can help your clinician work with you to build a more personalized, effective treatment plan.

Personalized medicine for Patients - *Genomind*

Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing

Zane Zeier, Ph.D., Linda L. Carpenter, M.D., Ned H. Kalin, M.D., Carolyn I. Rodriguez, M.D., Ph.D., William M. McDonald, M.D., Alik S. Widge, M.D., Ph.D., Charles B. Nemeroff, M.D., Ph.D.

The accrual and analysis of genomic sequencing data have identified specific genetic variants that are associated with major depressive disorder. Moreover, substantial investigations have been devoted to identifying gene-drug interactions that affect the response to antidepressant medications by modulating their pharmacokinetic or pharmacodynamic properties. Despite these advances, individual responses to antidepressants, as well as the unpredictability of adverse side effects, leave clinicians with an imprecise prescribing strategy that often relies on trial and error. These limitations have spawned several combinatorial pharmacogenetic testing products that are marketed to physicians. Typically, combinatorial pharmacogenetic decision support tools use algorithms to integrate multiple genetic variants and assemble the results into an easily interpretable report to guide prescribing of antidepressants and other psychotropic medications. The authors review the evidence base for several combinatorial pharmacogenetic decision support tools whose potential utility has been evaluated in clinical settings. They find that, at present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects.

Am J Psychiatry 2018; 175:873–886; doi: 10.1176/appi.ajp.2018.17111282

Zeier Z, et al. *Am J Psychiatry*. 2018;175:873-886.

Table 1. Antidepressant drug x gene associations with high/moderate level of evidence, or included in one of the CPGx tests evaluated here

Chemicals	ADRA2A	BDNF	COMT	CRHR1	FKBP5	GRIK4	HTR1A	HTR2A	SLC6A2	SLC6A4	ABCB1	CYP1A2	CYP2B6	CYP2C19	CYP2D6
	pharmacodynamic										pharmacokinetic				
amitriptyline ✔											3				1A
bupropion															
citalopram ✔		3			2B			2B		2A	3			1A	3
desipramine ✔		3													1A
doxepin ✔															1A
duloxetine ✔												1A			1A
escitalopram ✔		3			3			3		2A		3		1A	3
fluoxetine ✔		3		3	2B		3			3	3				3
fluvoxamine ✔			3				3	3			3				1A
imipramine ✔														2A	1A
maprotiline															3
mirtazapine					2B					3			3		
nefazodone ✔					3						3				
nortriptyline ✔		3									3				1A
paroxetine ✔		3	3		2B		3			3	3	3			1A
sertraline							3			3	3			1A	
trimipramine ✔															1A
venlafaxine ✔			3		2B				3		3				2A
antidepressants unspecified		3		3	2B	2B	3	2B			3				1A
SSRIs unspecified	3		2B		2B		3	2B			3				
# of variants/gene	1	6	2	2	4	2	3	5	1	3	15	9	5	8	14
interaction type *	E	E,T	E	E	E,T	E	E	E,T	E	E,T	E,T	E,T	E,O	E,M,T	E,D,M,T

NOT a comprehensive representaion of antidepressant drug x gene associations
limited to PharmGKB search terms: "Depressive Disorder, Major; Depressive Disorder; Depression; duloxetine"
excludes drug-gene interactions related to "Bipolar Disorder; Anxiety Disorder"
excludes antipsychotic and some antidepressant drugs
excludes many drug-gene associations for which low/preliminary (level 3/4) evidence exists, as defined by PharmGKB
The PharmGKB library, which was used to generate this table, is not the sole source of relevant PGx information
✔ FDA drug labeling with CYP450 PGx information
* PGx information relevant to drug efficacy (E), dosage (D), metabolism/PK (M), toxicity/ADR (T), other (O)
Values correspond to a high (1A,1B), moderate (2A,2B) or low (3) level of evidence according to the PharmGKB rating scale.

Am J Psychiatry (in press).

Myriad Announces GeneSight® Psychotropic Results from a Large Prospective Trial in Patients with Major Depressive Disorder

GeneSight Demonstrated Statistically Significant Improvement in the Gold Standard Clinical Outcomes of Remission and Response

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

John F. Greden, MD[a]; Sagar V. Parikh, MD[a]; Anthony J. Rothschild, MD[b]; Michael E. Thase, MD[c]; Boadie W. Dunlop, MD[d]; Charles DeBattista, DMH, MD[e]; Charles R. Conway, MD[f]; Brent P. Forester, MD, MSc[g]; Francis M. Mondimore, MD[h]; Richard C. Shelton, MD[i]; Matthew Macaluso, DO[j]; James Li, PhD[k]; Krystal Brown, PhD[l]; Alexa Gilbert, MSc, MBA[k]; Lindsey Burns, MBA[k]; Michael R. Jablonski, PhD[k]; Bryan Dechairo, PhD[k,l]

Greden JF, et al. *J Psychiatric Res*. 2019. 59-67.

Abstract

Outpatients (N = 1167) diagnosed with MDD and with a patient- or clinician-reported inadequate response to at least one antidepressant were enrolled in the **G**enomics **U**sed to **I**mprove **DE**pression **D**ecisions (GUIDED) trial – a rater- and patient-blind randomized controlled trial. Patients were randomized to treatment as usual (TAU) or a pharmacogenomics-guided intervention arm in which clinicians had access to a pharmacogenomic test report to inform medication selections (guided-care). Medications were considered congruent ('use as directed' or 'use with caution' test categories) or incongruent ('use with increased caution and with more frequent monitoring' test category) with test results. Unblinding occurred after week 8. Primary outcome was symptom improvement [change in 17-item Hamilton Depression Rating Scale (HAM-D17)] at week 8; secondary outcomes were response (≥50% decrease in HAM-D17) and remission (HAM-D17 ≤ 7) at week 8**. At week 8, symptom improvement for guided-care was not significantly different than TAU (27.2% versus 24.4%, p = 0.107);** however, improvements in response (26.0% versus 19.9%, p = 0.013) and remission (15.3% versus 10.1%, p = 0.007) were statistically significant. Patients taking incongruent medications prior to baseline who switched to congruent medications by week 8 experienced greater symptom improvement (33.5% versus 21.1%, p = 0.002), response (28.5% versus 16.7%, p = 0.036), and remission (21.5% versus 8.5%, p = 0.007) compared to those remaining incongruent. **Pharmacogenomic testing did not significantly improve mean symptoms** but did significantly improve response and remission rates for difficult-to-treat depression patients over standard of care (ClinicalTrials.gov NCT02109939).

Greden JF, et al. *J Psychiatric Res*. 2019. 59-67.

Major Problems with Commercial Test Data

- Over 30 pharmacogenetic testing products are available worldwide
- Most studies are:
  1. Short duration
  2. Small sample size
  3. Unblinded
  4. Usually low remission rates
  5. Comparison groups not matched for depression severity or CYP2D6 metabolic phenotype
  6. Heterogeneous diagnosis, eg MDD, bipolar disorder, schizophrenia and anxiety disorders
  7. Patient Adherence
- The tests are comprised of different genetic polymorphisms and omit several promising candidates.

VIEWPOINT

On the Marketing and Use of Pharmacogenetic Tests for Psychiatric Treatment

George S. Zubenko, MD, PhD
Distinguished Life Fellow, American Psychiatric Association, Washington, DC.

Barbara R. Sommer, MD
Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California.

Bruce M. Cohen, MD, PhD
Department of Psychiatry, Harvard Medical School, Boston, Massachusetts; and Program for Neuropsychiatric Research, McLean Hospital, Belmont, Massachusetts.

Zubenko GS, et al. *JAMA Psychiatry*. 2018;75(8):769-770.

The desire to discover biological tests to guide treatments is sincere and studies should continue, but with the usual attention to careful design and with skepticism about claims. The claims on company websites may be good marketing, but they are not balanced and the time-pressured clinician or the uniformed consumer, often in distress, may be especially vulnerable to the pitch. Medicine has a history of use of improperly evaluated treatments and some persist because consumer demand help and can find clinicians who will comply.

We may yet achieve the goal of useful biological tests to assist clinical decision making in psychiatry. That time has not come.

Zubenko GS, et al. *JAMA Psychiatry*. 2018;75(8):769-770.

FDA Statement

Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health and Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research on agency's warning to consumers about genetic tests that claim to predict patients' responses to specific medications

For Immediate Release November 1, 2018

U.S. Food and Drug Administration Website. November 1, 2018. https://www.fda.gov/news-events/press-announcements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md.

We are aware that these types of genetic tests are promoted to predict how a person will respond to specific medications used to treat conditions such as depression, heart conditions, acid reflux and others. They may claim that a specific medication may be less effective or have an increased chance of side effects due to a patient's genetic variations or indicate that the health care provider can or should change a patient's medication based on results from these tests.

For example, the FDA is aware of genetic tests that claim results can be used by physicians to identify which antidepressant medication would have increased effectiveness or side effects compared to other antidepressant medications. However, the relationship between DNA variations and the effectiveness of antidepressant medications has never been established. Moreover, the FDA is aware that health care providers have made changes to patients' medication based on genetic test results that claim to provide information on the personalized dosage or treatment regimens for some antidepressant medications, which could potentially lead to patient harm.

U.S. Food and Drug Administration Website. November 1, 2018. https://www.fda.gov/news-events/press-announcements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md.

Objective: The Predictors of Remission in Depression to Individual and Combined Treatments [PReDICT] study aimed to identify clinical and biological factors predictive of treatment outcomes in major depressive disorder among treatment-naive adults. The authors evaluated the efficacy of cognitive-behavioral therapy (CBT) and two antidepressant medications (escitalopram and duloxetine) in patients with major depression and examined the moderating effect of patients' treatment preferences on outcomes.

Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):546-556.

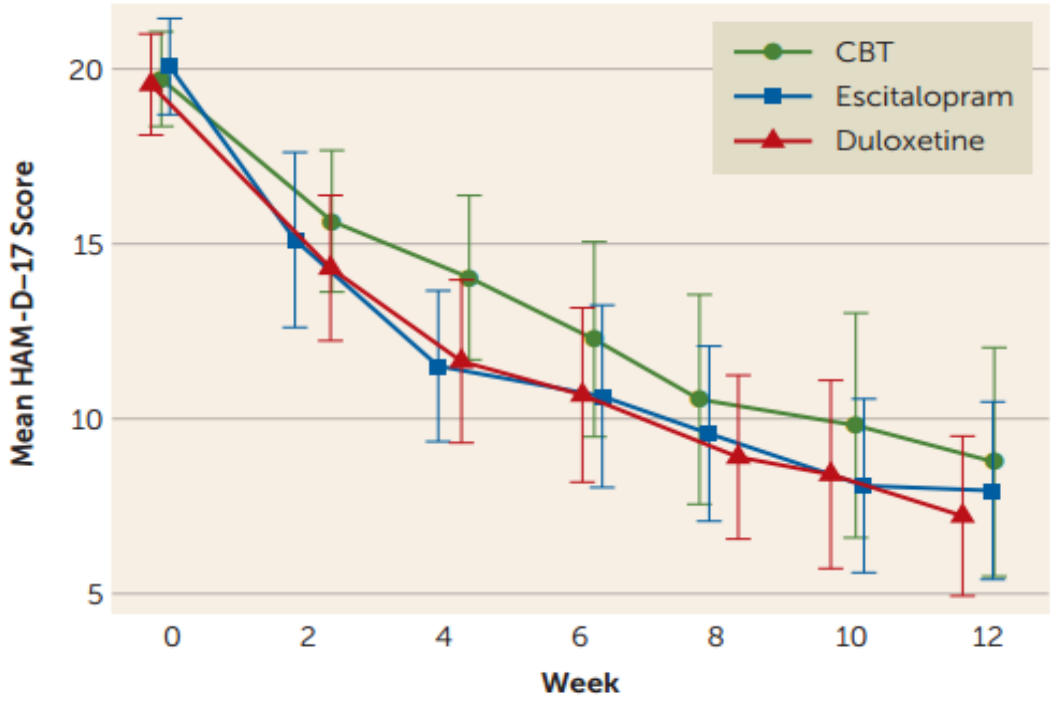
Method: Adults aged 18–65 with treatment-naive major depression were randomly assigned with equal likelihood to 12 weeks of treatment with escitalopram (10–20 mg/day), duloxetine (30–60 mg/day), or CBT (16 50-minute sessions). Prior to randomization, patients indicated whether they preferred medication or CBT or had no preference. The primary outcome was change in the 17-item Hamilton Depression Rating Scale (HAM-D), administered by raters blinded to treatment.

Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):546-556.

Results: A total of 344 patients were randomly assigned, with a mean baseline HAM-D score of 19.8 (SD=3.8). The mean estimated overall decreases in HAM-D score did not significantly differ between treatments (CBT: 10.2, escitalopram: 11.1, duloxetine: 11.2). Last observation carried forward remission rates did not significantly differ between treatments (CBT: 41.9%, escitalopram: 46.7%, duloxetine: 54.7%). Patients matched to their preferred treatment were more likely to complete the trial but not more likely to achieve remission.

Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):546-556.

Modeled Change in the Mean Hamilton Depression Rating Scale (HAM-D) Score by Week[a]



[a] CBT=cognitive-behavioral therapy; Error bars represent 95% confidence intervals.

Dunlop BW, et al. *Am J Psychiatry*. 2017;174(6):546-556.

FIGURE 6. Striatal Serotonin Transporter (5-HTT) Occupancy in Depressed Subjects After 4 Weeks of Treatment at Minimum Therapeutic Doses of Five SSRIs

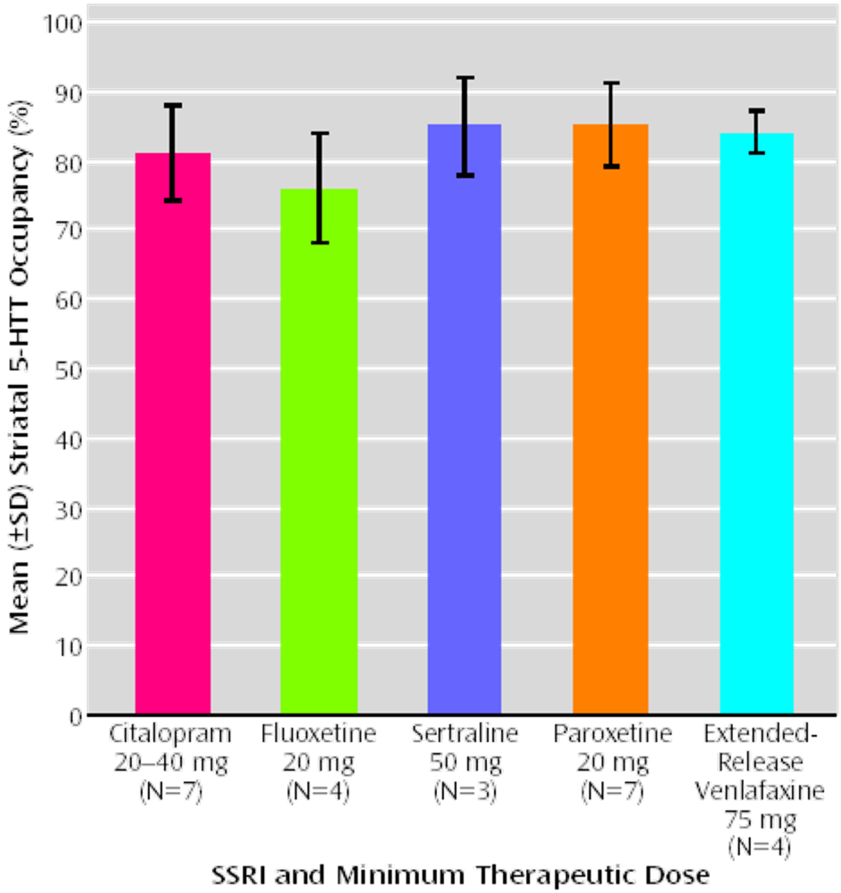
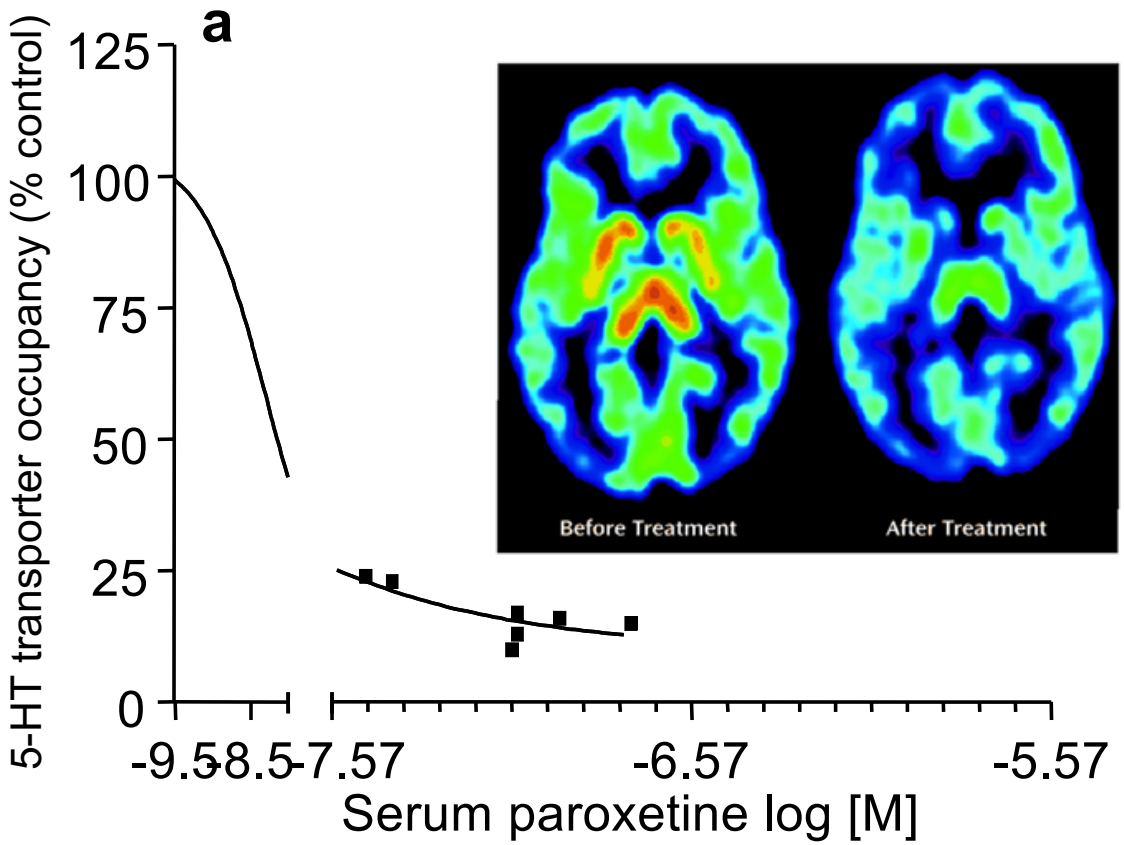


TABLE 1. Estimated Dose (ED_{50}) and Plasma Concentration (EC_{50}) Needed to Obtain 50% Serotonin Transporter Striatal Occupancy for Five SSRIs Administered to 77 Healthy and Depressed Subjects for 4 Weeks

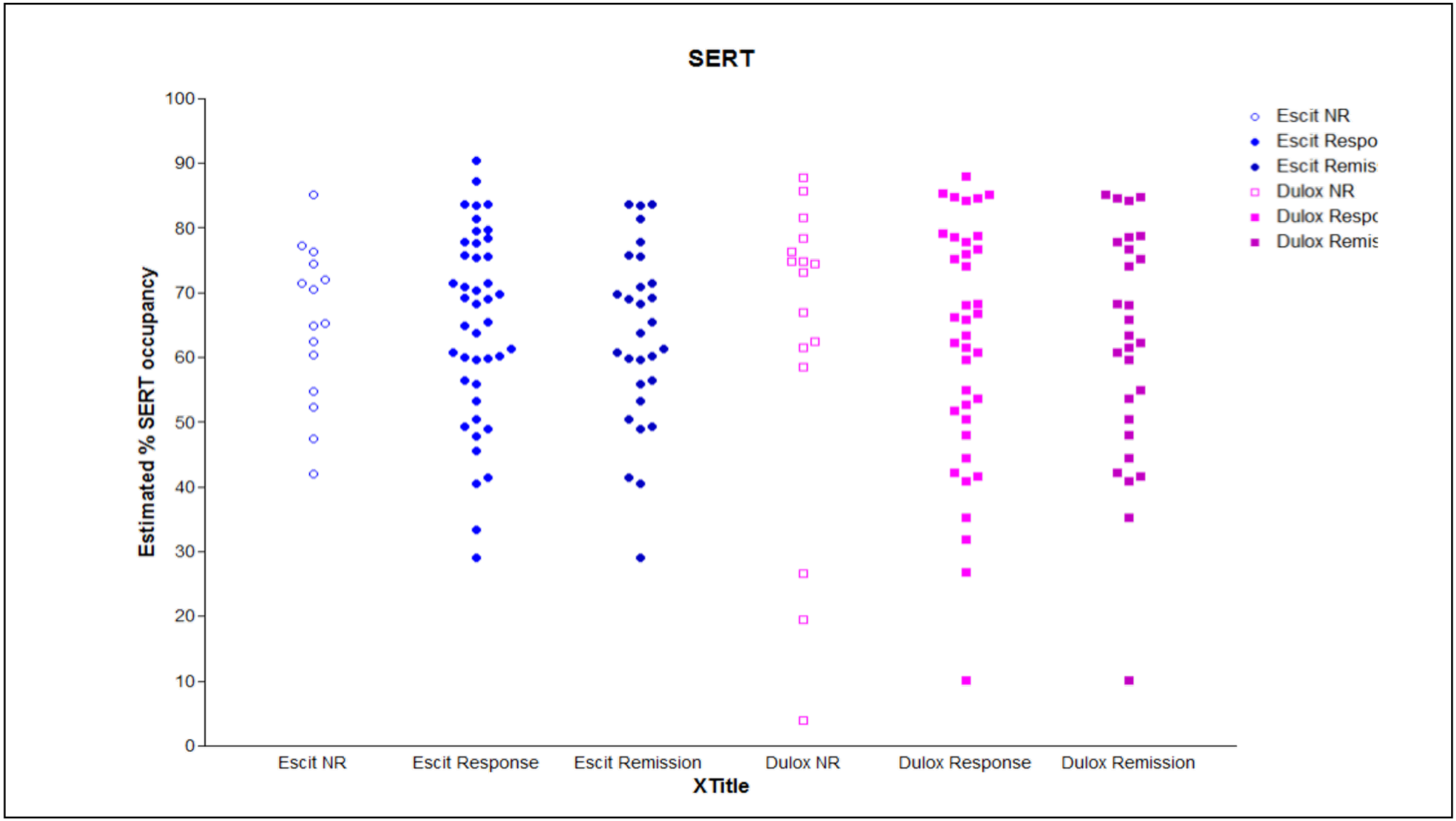
SSRI	ED_{50} (mg/day)	EC_{50} (µg/liter)
Citalopram	3.4	11.7
Fluoxetine	2.7	14.8
Sertraline	9.1	1.1
Paroxetine	5.0	2.7
Extended-release venlafaxine	5.8	3.4

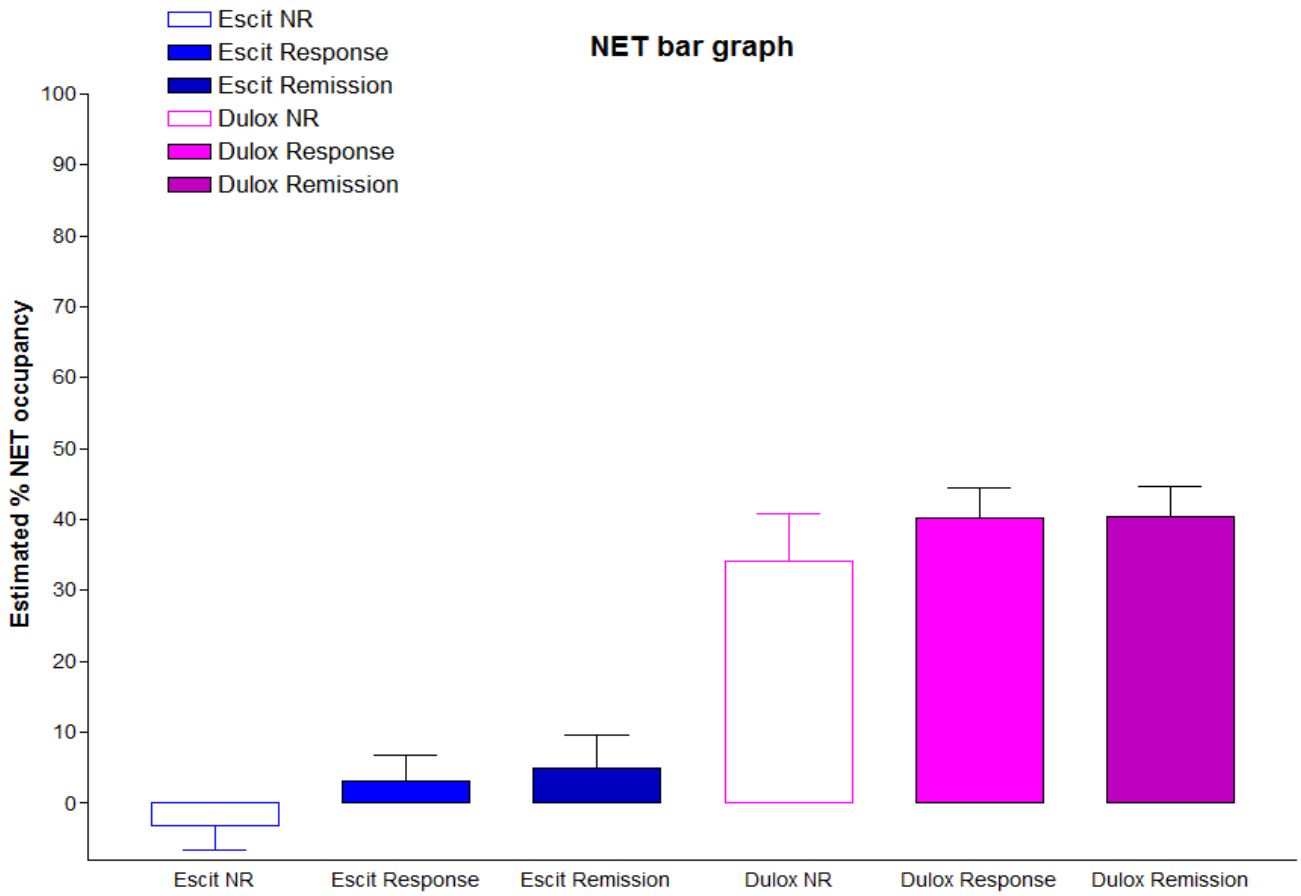
Meyer JH, et al. *Am J Psychiatry*. 2004;161:826-835.

Estimates of 5-HT transporter occupancy using PET imaging; Inset is representative PET image from a patient before and after 4-week treatment with the serotonin uptake inhibitor citalopram



Data from Meyer JH, et al. *Am J Psychiatry*. 2001;158:1843-1849.


SERT
Estimated % SERT occupancy
100
90
80
70
60
50
40
30
20
10
0
Escit NR
Escit Response
Escit Remission
Dulox NR
Dulox Response
Dulox Remission
XTitle
Escit NR
Escit Respo
Escit Remis
Dulox NR
Dulox Respc
Dulox Remis



Estimated NET occupancy (mean ± SEM) at week 12 did not predict treatment response. Escit = escitalopram; Dulox = duloxetine; NR = no response or worsening;

Article

Prediction of Antidepressant Response to Milnacipran by Norepinephrine Transporter Gene Polymorphisms

Keizo Yoshida, M.D., Ph.D.
Hitoshi Takahashi, M.D., Ph.D.
Hisashi Higuchi, M.D., Ph.D.
Mitsuhiro Kamata, M.D., Ph.D.
Ken-ichi Ito, M.D., Ph.D.
Kazuhiro Sato, M.D., Ph.D.
Shingo Naito, M.D.
Tetsuo Shimizu, M.D., Ph.D.
Kunihiko Itoh, Ph.D.
Kazuyuki Inoue, M.S.C.
Toshio Suzuki, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.

Objective: With a multitude of antidepressants available, predictors of response to different classes of antidepressants are of considerable interest. The purpose of the present study was to determine whether norepinephrine transporter gene (NET) and serotonin transporter gene (5-HTT) polymorphisms are associated with the antidepressant response to milnacipran, a dual serotonin/norepinephrine reuptake inhibitor.

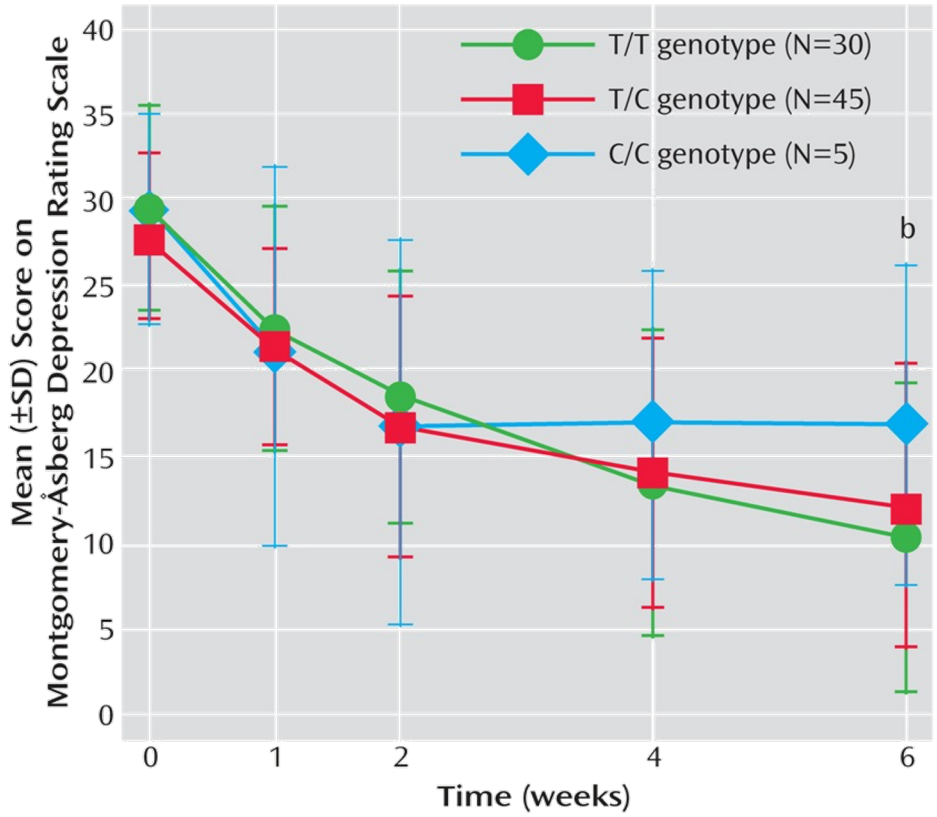
Method: Ninety-six Japanese patients with major depressive disorder were treated with milnacipran, 50–100 mg/day, for 6 weeks. Severity of depression was assessed with the Montgomery-Åsberg Depression Rating Scale. Assessments were carried out at baseline and at 1, 2, 4, and 6 weeks of treatment. The method of polymerase chain reaction was used to determine allelic variants.

Results: Eighty patients completed the study. The presence of the T allele of the NET T-182C polymorphism was associated with a superior antidepressant response, whereas the A/A genotype of the NET G1287A polymorphism was associated with a slower onset of therapeutic response. In contrast, no influence of 5-HTT polymorphisms on the antidepressant response to milnacipran was detected.

Conclusions: The results suggest that NET but not 5-HTT polymorphisms in part determine the antidepressant response to milnacipran.

(Am J Psychiatry 2004; 161:1575–1580)

Montgomery-Åsberg Depression Scores During 6-Week Treatment in Relation to the NET T-128C Polymorphism



Yoshida K, et al. *Am J Psychiatry*. 2004;161:1575-1580.

Norepinephrine Transporter Gene Variants and Remission From Depression With Venlafaxine Treatment in Older Adults

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Marshe VS, et al. *Am J Psychiatry*. 2017;174:468-475.

Objective: The primary objective of this study was to investigate five putatively functional variants of the norepinephrine transporter (*SLC6A2*, *NET*) and serotonin transporter (*SLC6A4*, *SERT*) genes and remission in depressed older adults treated with venlafaxine. A secondary objective was to analyze 17 other variants in serotonergic system genes (*HTR1A*, *HTR2A*, *HTR1B*, *HTR2C*, *TPH1*, *TPH2*) potentially involved in the mechanism of action of venlafaxine.

Method: The sample included 350 adults age 60 or older with DSM-IV-defined major depressive disorder and a score of at least 15 on the Montgomery-Åsberg Depression Rating Scale (MADRS). Participants received protocolized treatment with open-label venlafaxine, up to 300 mg/day for approximately 12 weeks, as part of a three-site clinical trial. Each individual was genotyped for 22 polymorphisms in eight genes, which were tested for association with venlafaxine remission (a MADRS score ≤10) and changes in MADRS score during treatment.

Marshe VS, et al. *Am J Psychiatry*. 2017;174:468-475.

Results: After adjusting for multiple comparisons, *NET* variant rs2242446 (T-182C) was significantly associated with remission (odds ratio=1.66, 95% CI=1.13, 2.42). Individuals with the rs2242446 C/C genotype were more likely to remit (73.1%) than those with either the C/T (51.8%) or the T/T genotype (47.3%). Individuals with the C/C genotype also had a shorter time to remission than those with the C/T or T/T genotypes and had a greater percentage change in MADRS score from baseline to end of treatment (up to week 12).

Marshe VS, et al. *Am J Psychiatry*. 2017;174:468-475.

Association of Polymorphisms in Genes Regulating the Corticotropin-Releasing Factor System With Antidepressant Treatment Response

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Binder EB, et al. *Arch Gen Psychiatry*. 2010;67(4):369-379.

Antidepressant Outcomes Predicted by Genetic Variation in Corticotropin-Releasing Hormone Binding Protein

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O'Connell CP, et al. *Am J Psychiatry*. 2018;175(3):251-261.

Objective: Genetic variation within the hypothalamic-pituitary-adrenal (HPA) axis has been linked to risk for depression and antidepressant response. However, these associations have yet to produce clinical gains that inform treatment decisions. The authors investigated whether variation within HPA axis genes predicts antidepressant outcomes within two large clinical trials.

Method: The test sample comprised 636 patients from the International Study to Predict Optimized Treatment in Depression (iSPOT-D) who completed baseline and 8-week follow-up visits and for whom complete genotyping data were available. The authors tested the relationship between genotype at 16 candidate HPA axis single-nucleotide polymorphisms (SNPs) and treatment outcomes for three commonly used antidepressants (escitalopram, sertraline, and extended-release venlafaxine), using multivariable linear and logistic regression with Bonferroni correction. Response and remission were defined using the Hamilton Depression Rating Scale. Findings were then validated using the Predictors of Remission in Depression to Individual and Combined Treatments (PReDICT) study of outcome predictors in treatment-naive patients with major depression.

O'Connell CP, et al. *Am J Psychiatry*. 2018;175(3):251-261.

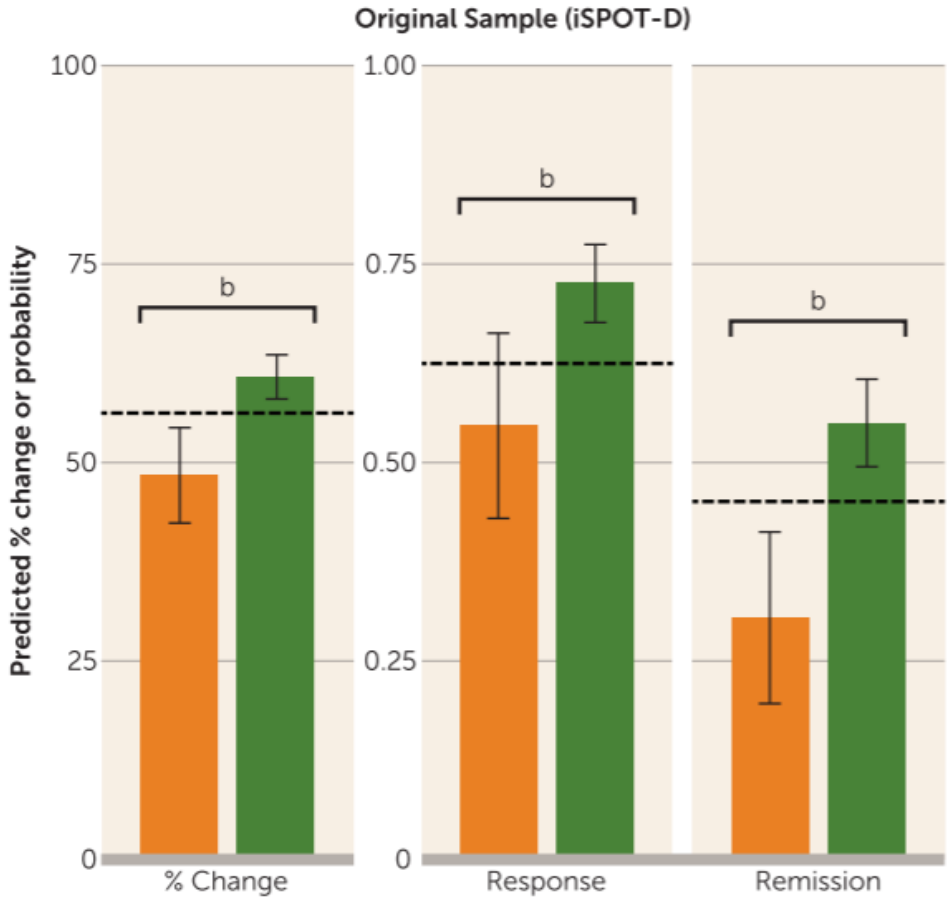
Results: The authors found that the rs28365143 variant within the corticotropin-releasing hormone binding protein (CRHBP) gene predicted antidepressant outcomes for remission, response, and symptom change. Patients homozygous for the G allele of rs28365143 had greater remission rates, response rates, and symptom reductions. These effects were specific to drug class. Patients homozygous for the G allele responded significantly better to the selective serotonin reuptake inhibitors escitalopram and sertraline than did A allele carriers. In contrast, rs28365143 genotype was not associated with treatment outcomes for the serotonin norepinephrine reuptake inhibitor venlafaxine. When patients were stratified by race, the overall effect of genotype on treatment response remained. In the validation sample, the GG genotype was again associated with favorable antidepressant outcomes, with comparable effect sizes.

O'Connell CP, et al. *Am J Psychiatry*. 2018;175(3):251-261..

Conclusions: These findings suggest that a specific CRHBP SNP, rs28365143, may have a role in predicting which patients will improve with antidepressants and which type of antidepressant may be most effective. The results add to the foundational knowledge needed to advance a precision approach to personalized antidepressant choices.

O'Connell CP, et al. *Am J Psychiatry*. 2018;175(3):251-261.

FIGURE 1. CRHBP rs28365143 Genotype and Predicted Reductions in Depressive Symptoms Based on Regression Models in Both the Original and Validation Cohorts[a]



[a] Predicted percent reduction in Hamilton Depression Rating Scale (HAM-D) score and probability of response and remission were calculated for each CRHBP rs28365143 genotype using the regression models described in the text. To calculate the expected output for an "average" participant, all other covariates (age, sex, initial HAM-D score, site) were set to the mean value for that variable in the cohort. The p values are those of the beta coefficient in the linear or logistic regression model. iSPOT-D=International Study to Predict Optimized Treatment in Depression; PReDICT=Predictors of Remission in Depression to Individual and Combined Treatments.

[b] $p<0.003938$, Bonferroni-corrected threshold for 13 hypotheses.

[c] $p<0.05$, uncorrected.

O'Connell CP, et al. *Am J Psychiatry*. 2018;175(3):251-261.

Functional Connectivity of the Subcallosal Cingulate Cortex And Differential Outcomes to Treatment With Cognitive-Behavioral Therapy or Antidepressant Medication for Major Depressive Disorder

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Dunlop BW, et al. *Am J Psychiatry*. 2017;175(6):533-545.

Objective: The purpose of this article was to inform the first-line treatment choice between cognitive-behavioral therapy (CBT) or an antidepressant medication for treatment-naive adults with major depressive disorder by defining a neuroimaging biomarker that differentially identifies the outcomes of remission and treatment failure to these interventions.

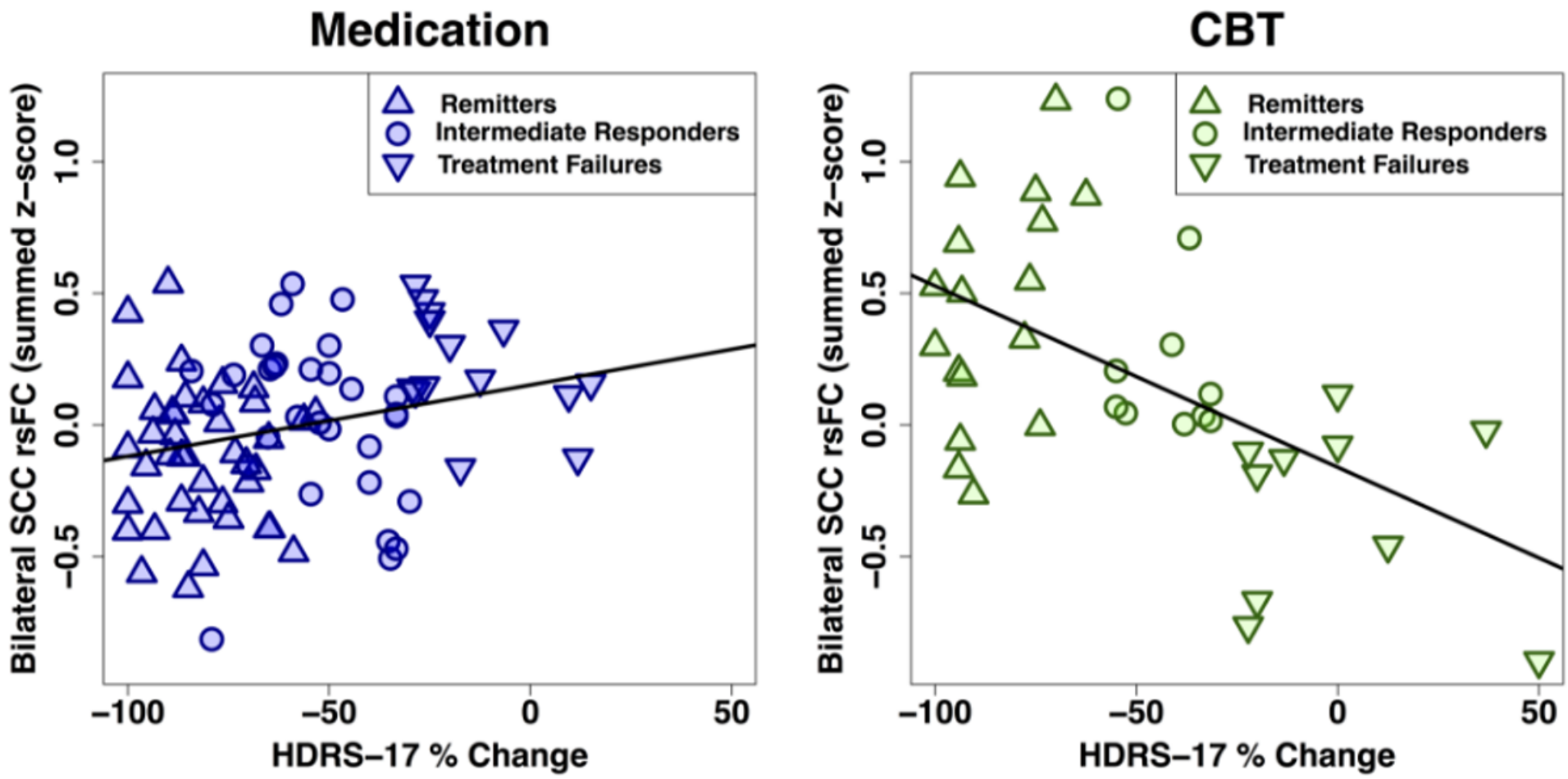
Method: Functional MRI resting-state functional connectivity analyses using a bilateral subcallosal cingulate cortex (SCC) seed was applied to 122 patients from the Prediction of Remission to Individual and Combined Treatments (PReDICT) study who completed 12 weeks of randomized treatment with CBT or antidepressant medication. Of the 122 participants, 58 achieved remission (Hamilton Depression Rating Scale [HAM-D] score ≤7 at weeks 10 and 12), and 24 had treatment failure (<30% decrease from baseline in HAM-D score). A 2×2 analysis of variance using voxel-wise subsampling permutation tests compared the interaction of treatment and outcome. Receiver operating characteristic curves constructed using brain connectivity measures were used to determine possible classification rates for differential treatment outcomes.

Dunlop BW, et al. *Am J Psychiatry*. 2017;175(6):533-545.

Results: The resting-state functional connectivity of the following three regions with the SCC was differentially associated with outcomes of remission and treatment failure to CBT and antidepressant medication and survived application of the subsample permutation tests: the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex. Using the summed SCC functional connectivity scores for these three regions, overall classification rates of 72%–78% for remission and 75%–89% for treatment failure was demonstrated. Positive summed functional connectivity was associated with remission with CBT and treatment failure with medication, whereas negative summed functional connectivity scores were associated with remission to medication and treatment failure with CBT.

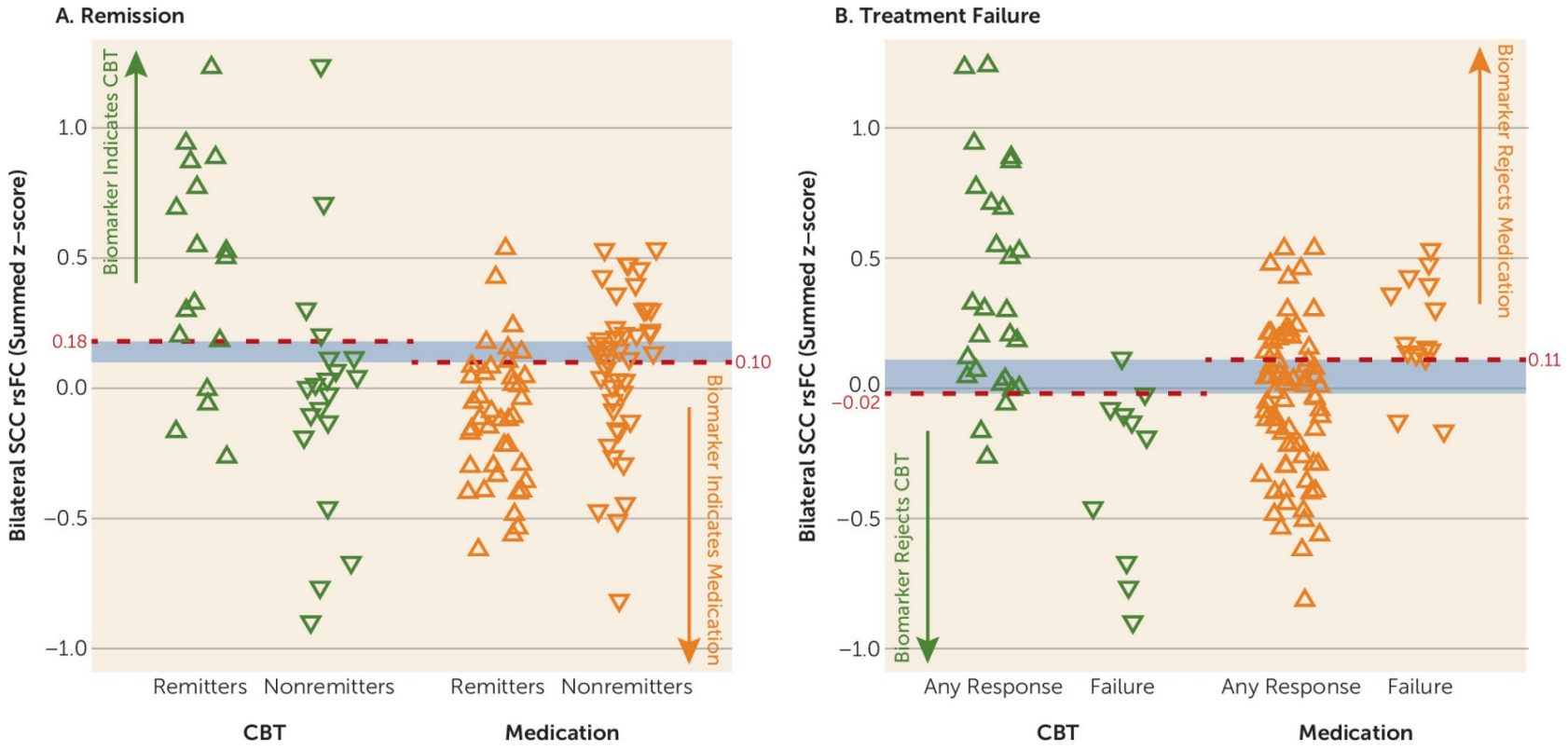
Conclusions: Imaging-based depression subtypes defined using resting-state functional connectivity differentially identified an individual's probability of remission or treatment failure with first-line treatment options for major depression. This biomarker should be explored in future research through prospective testing and as a component of multivariate treatment prediction models.

Dunlop BW, et al. *Am J Psychiatry*. 2017;175(6):533-545.



Dunlop BW, et al. *Am J Psychiatry*. 2017;175(6):533-545.

Individual Participants' Summed Functional Connectivity Scores Grouped by Treatment Outcome[a]



Dunlop BW, et al. *Am J Psychiatry*. 2017;175(6):533-545.

Electroencephalographic Biomarkers for Treatment Response Prediction in Major Depressive Illness: A Meta-Analysis.

Widge AS, et al. Am J Psychiatry. 2019.

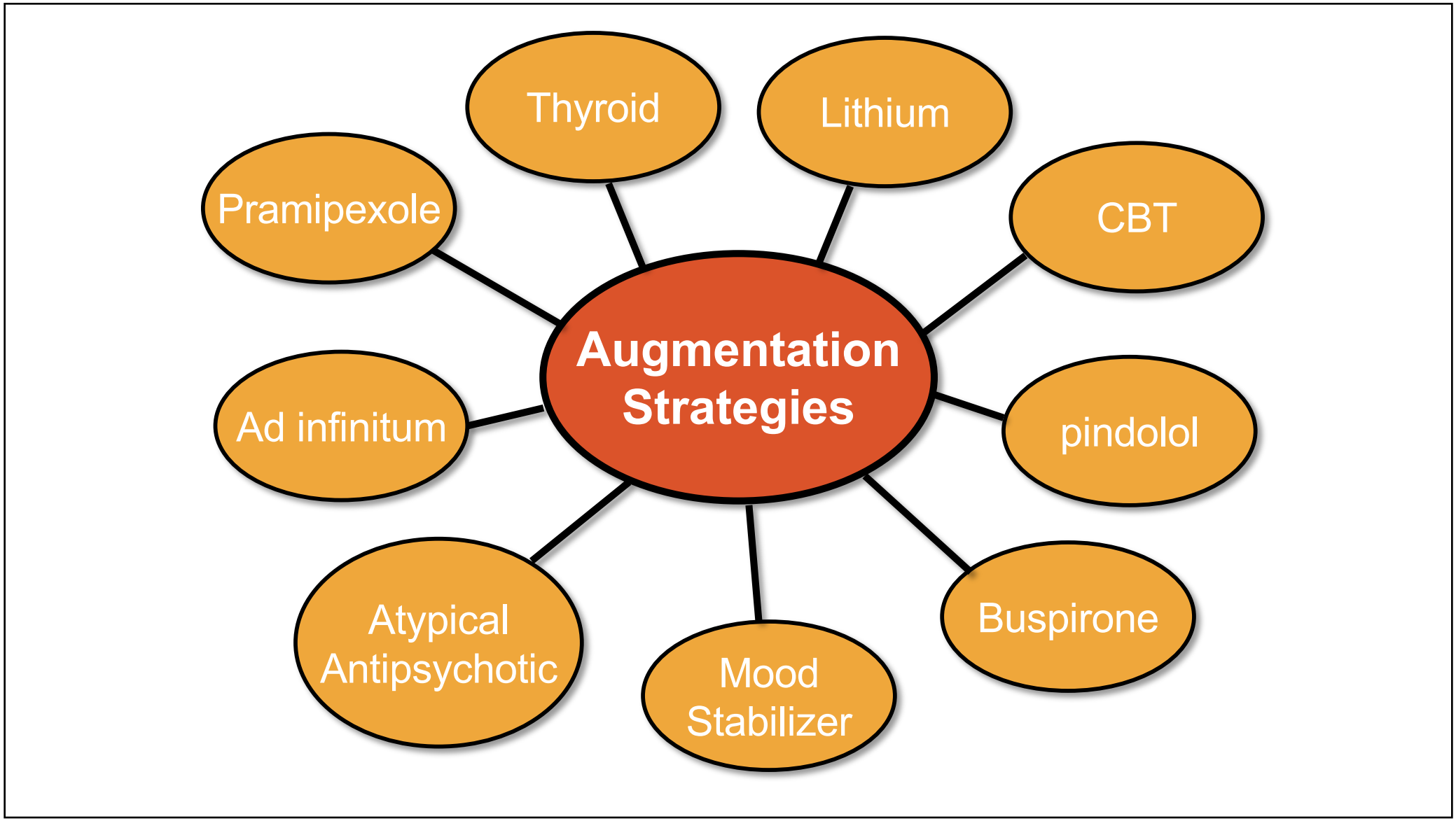
Authors

Widge AS[1], Bilge MT[1], Montana R[1], Chang W[1], Rodriguez CI[1], Deckersbach T[1], Carpenter LL[1], Kalin NH[1], Nemeroff CB[1].

Widge AS, et al. *Am J Psychiatry*. 2019;176(1):44-56.

CONCLUSIONS:: QEEG does not appear to be clinically reliable for predicting depression treatment response, as the literature is limited by underreporting of negative results, a lack of out-of-sample validation, and insufficient direct replication of previous findings. Until these limitations are remedied, QEEG is not recommended for guiding selection of psychiatric treatment.

Widge AS, et al. *Am J Psychiatry*. 2019;176(1):44-56.


Augmentation Strategies
Thyroid
Lithium
Pramipexole
CBT
Ad infinitum
pindolol
Atypical Antipsychotic
Mood Stabilizer
Buspirone

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Genetic testing to predict response to antidepressant treatment is not ready for clinical practice
- The future, however, is bright!

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.