Pharmacogenetics of Antidepressant Response in Late Life Depression

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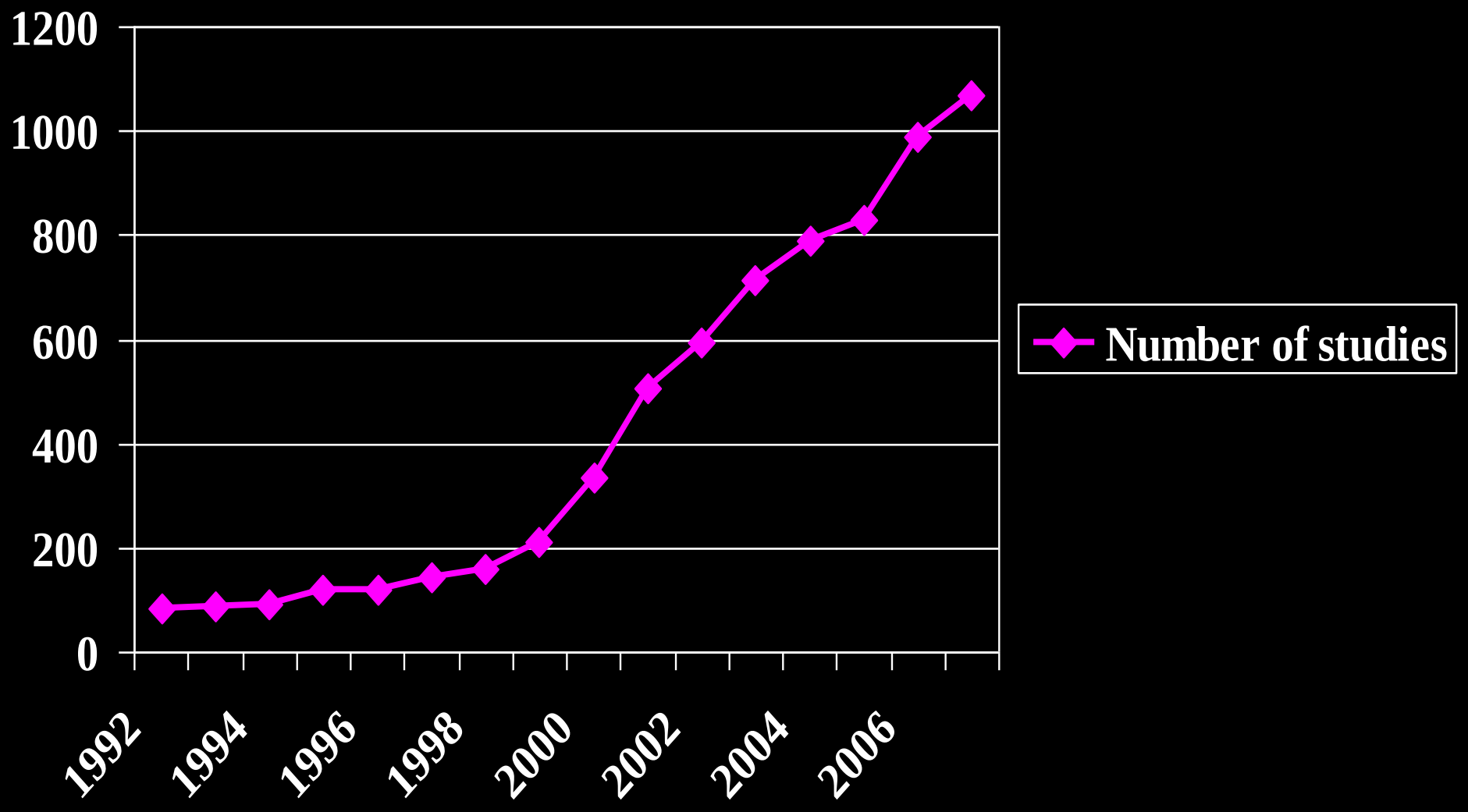
History

- 510 BC Pythagoras some people develop haemolytic anaemia after eating fava beans
- 1902 Garrod genetic factors direct chemical transformations
- 1932 Snyder phenylthiourea nontasting is inherited as an autosomal recessive trait
- 1957 Motulsky first demonstration of the relationship between adverse drug reaction and genetically determined variation
- 1959 Vogel ”pharmacogenetics”: the hereditary basis of variability in drug effects
- 1960 Evans speed of INH acetylation is under genetic control
- 1962 Kalow abnormal form of serum cholinesterase causes adverse reactions to succinylcholine
- 1977 Mahgoub polymorphism of CYP2D6 causes adverse effects to debrisoquine

Current trend of pharmacognetics in Psychiatry

Pharmacogenetic studies

(Medline 1992-2008)



Finally FDA recommend submission of pharmacogentic information on labeling

FDA News

FOR IMMEDIATE RELEASE
December 12, 2007

Media Inquiries:
Sandy Walsh, 301-827-3418
Consumer Inquiries:
888-INFO-FDA

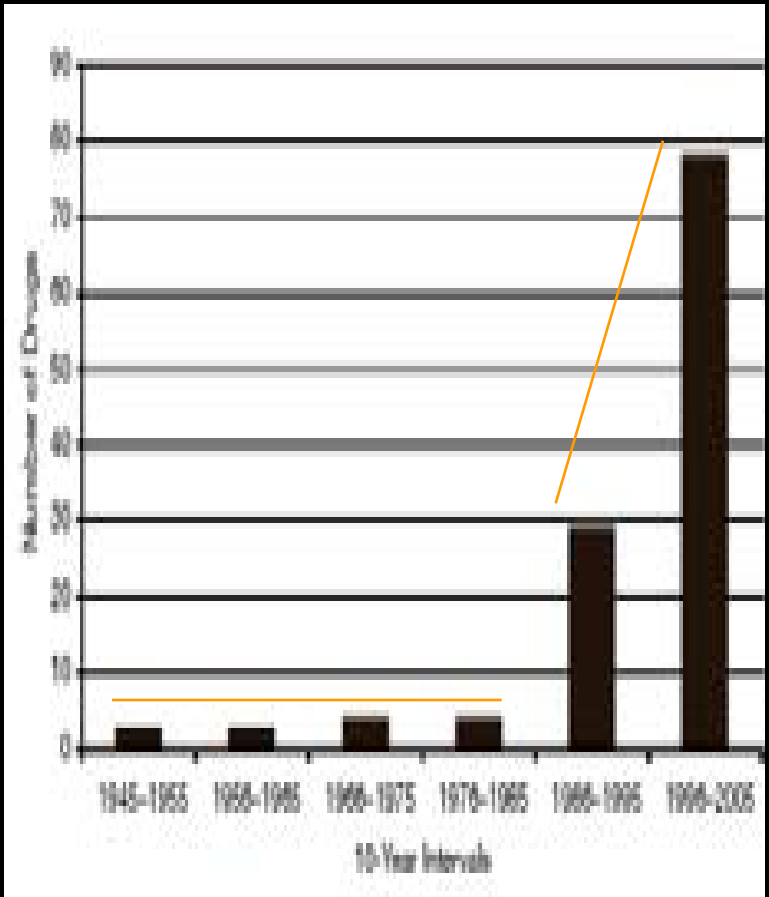
Carbamazepine Prescribing Information to Include Recommendation of Genetic Test for Patients with Asian Ancestry

Connection of genetic information with medication use can improve safe use of product

Number of drug approved with pharmacogentic information

- Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA

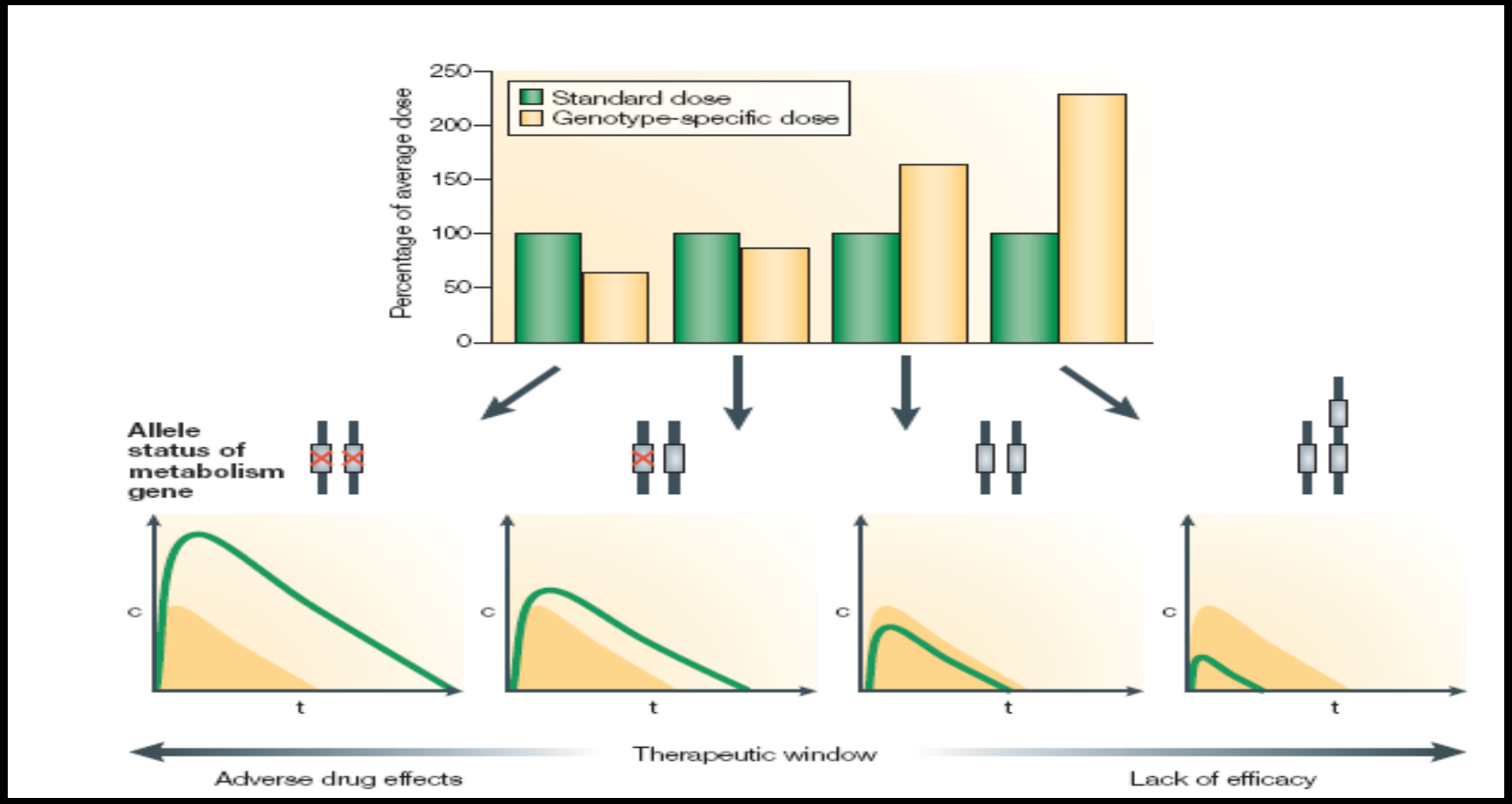
- A significant increase of labels containing such information has been observed over the last decade



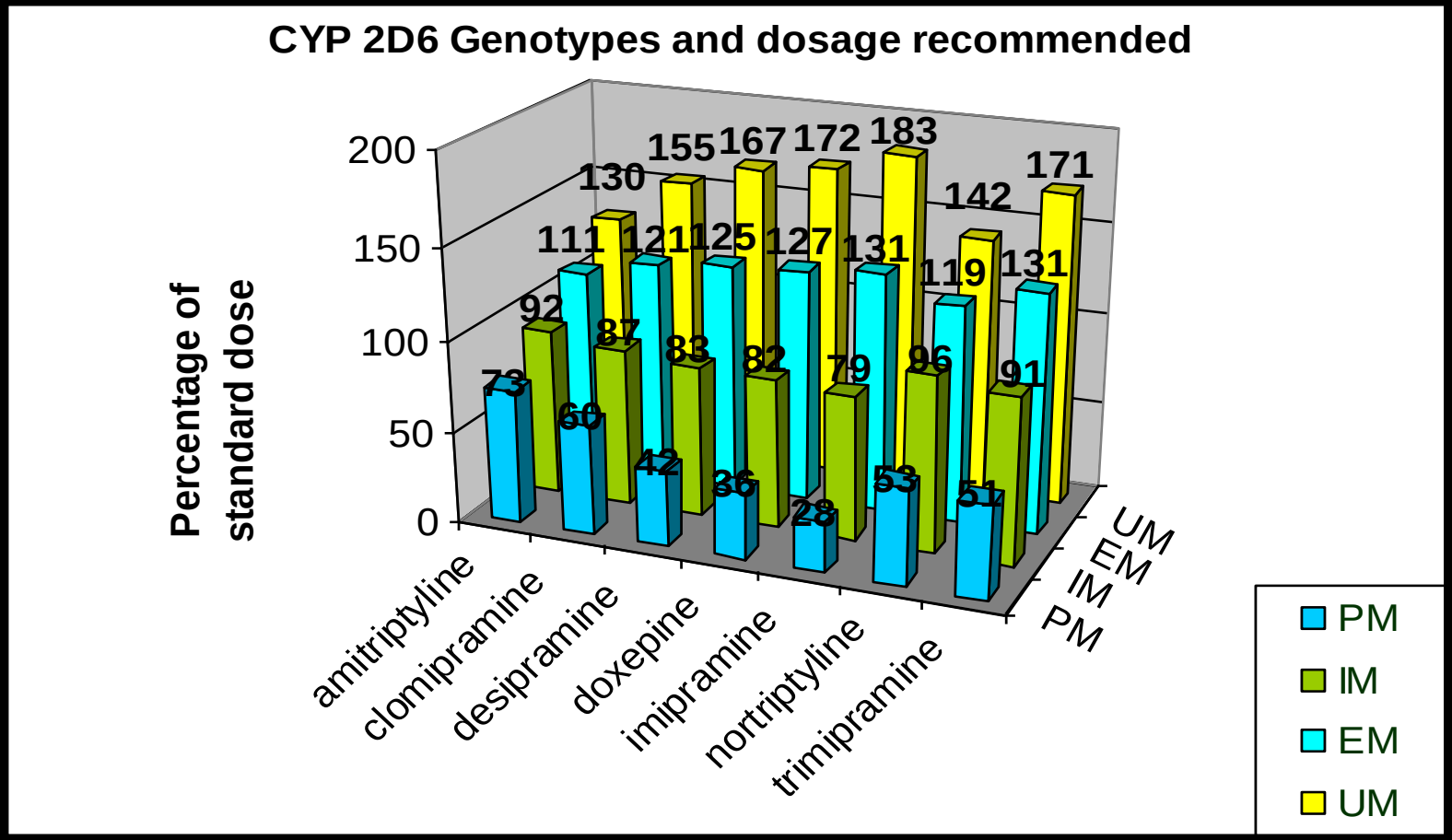
Pharmacogenetic Test Information on Drug Labels

- Test required (n=4); Test recommended (n=7) : Information only (more than 150)
- Currently, 4 drugs are required to have pharmacogenetic testing performed before they are prescribed: cetuximab, trastuzumab, maraviroc, and dasatinib
- HLA-B*1502: Carbamazepine, test recommended
- Urea cycle disorders : Valproic acid, test recommended

PGx in therapeutic decision-making: Dose adaptation



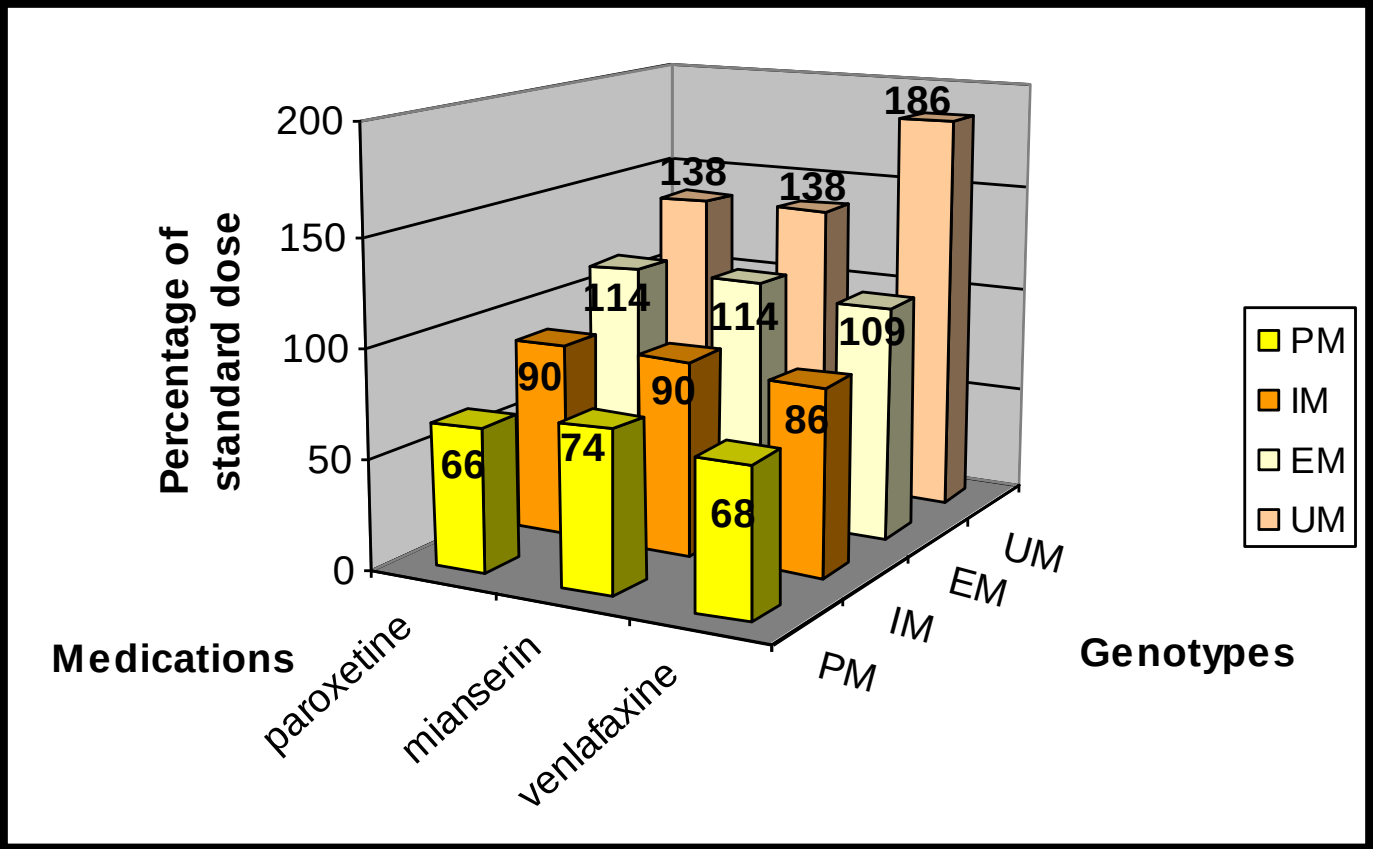
CYP 2D6 and tricyclic antidepressants



TCA dose adjustments are recommended for 2D6 PM and UM.

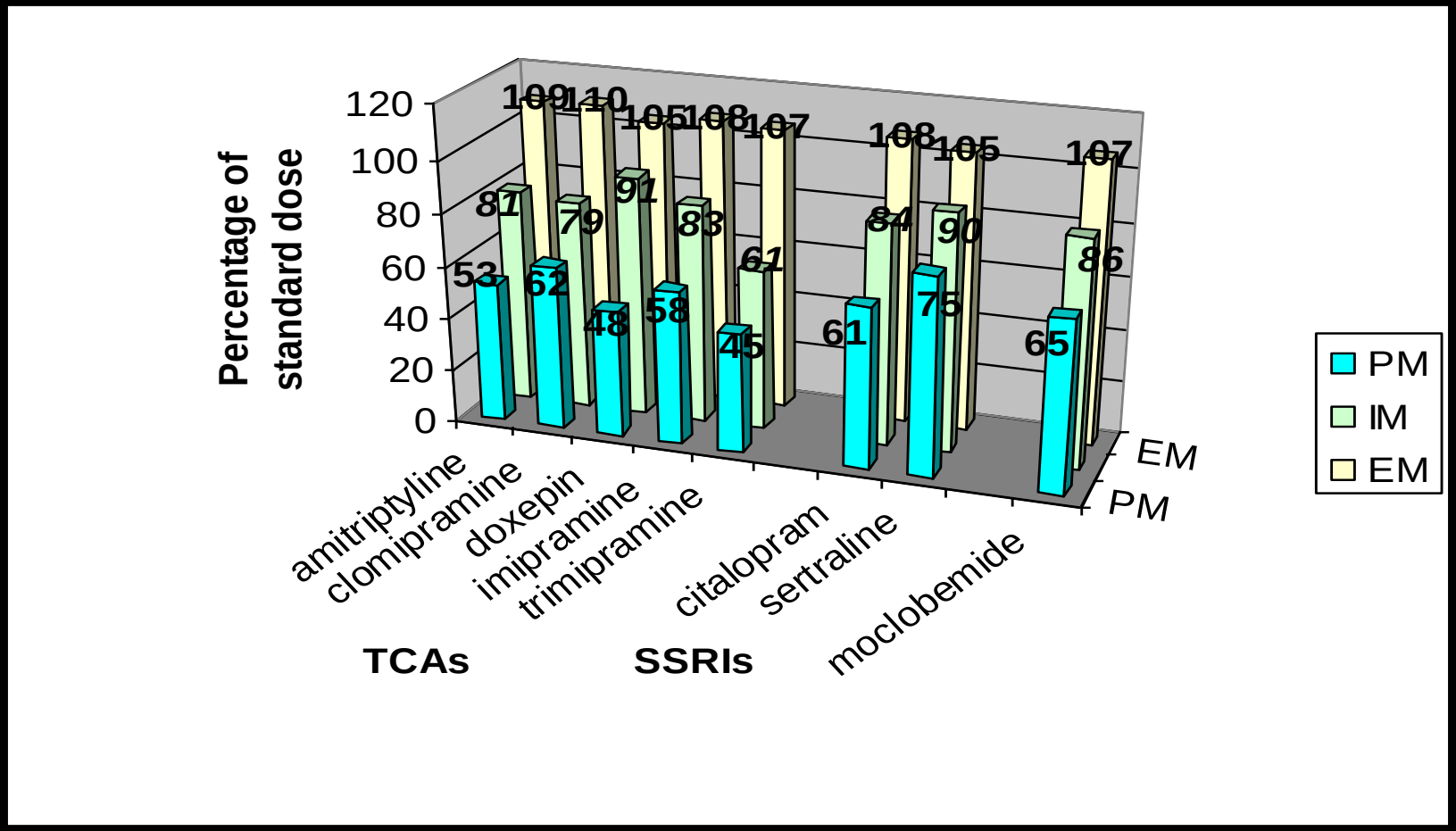
Kirchheiner et al., 2004 Mol Psychiatry

CYP 2D6 and other antidepressants



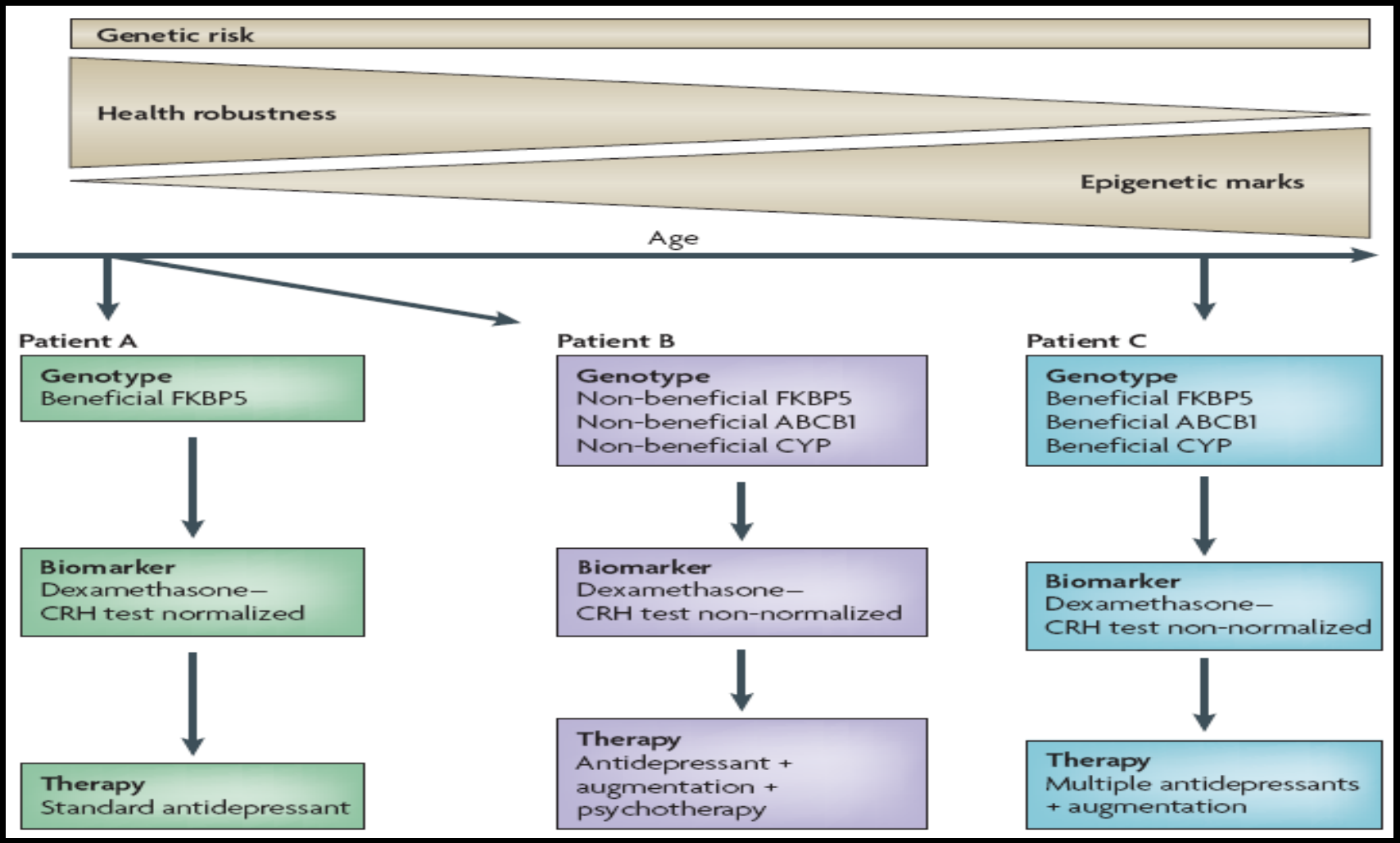
Kirchheiner et al., 2004 Mol Psychiatry

CYP 2C19 and antidepressants



Kirchheiner et al., 2004 Mol Psychiatry

Treatment strategies with biomarker and pharmacogenetics



Holsboer, 2008. Neuroscience

Potential candidate genes relating to antidepressant response

Genes investigated

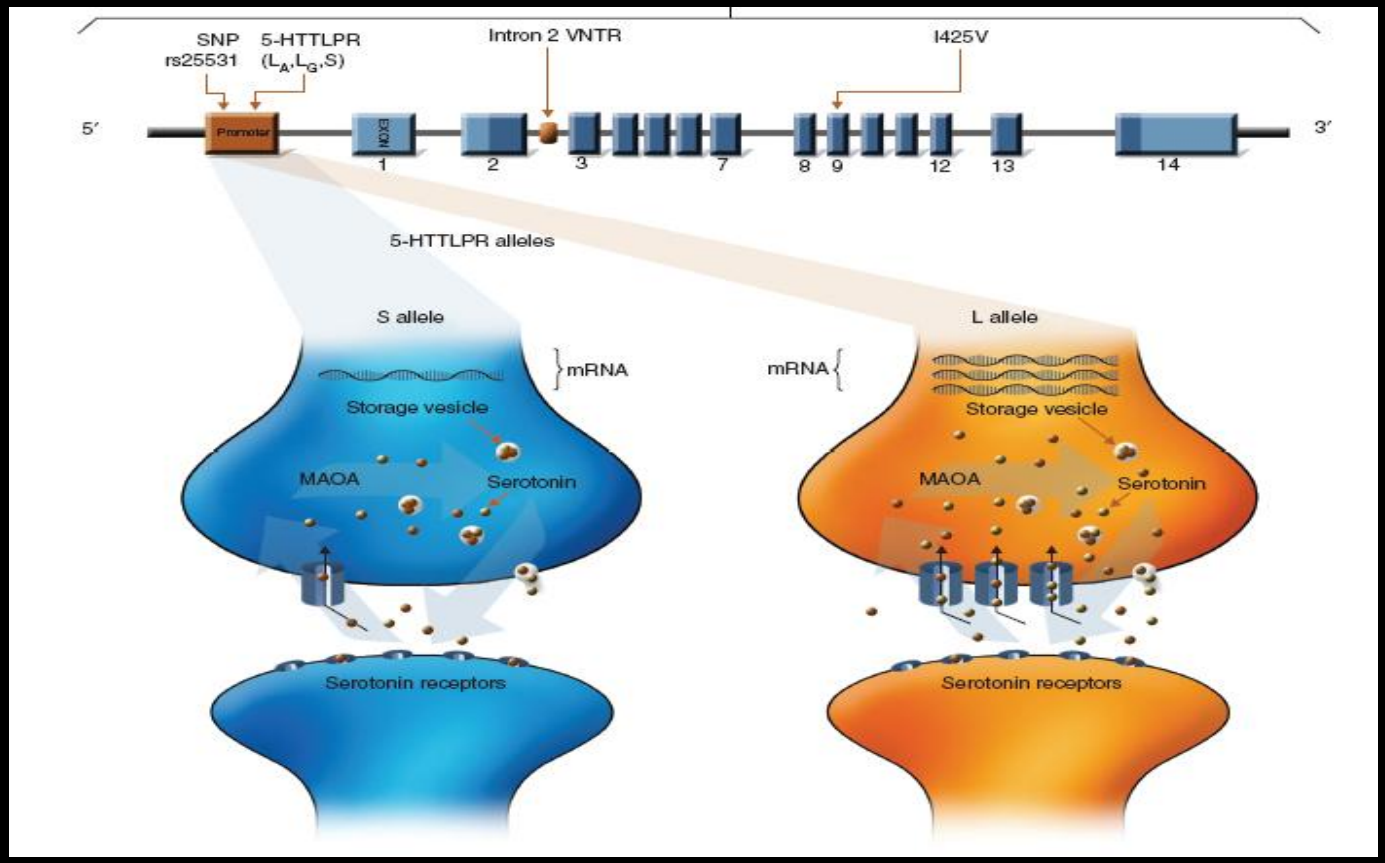
- HTTLPR
- SERT-STin2
- 5HT1A C-1019G
- 5-HT1B
- 5HT2A T102C
- 5HT2A G1438A
- 5HT2C
- 5HT6 C267T
- TPH1 A218C
- FKBP5
- NET T-182C
- NET G1287A

- COMT
- MAOA
- DRD2 S311C
- DRD4 VNTR

- ACE I/D polymorphism
- G-protein beta3 C825T
- ADRB1 G1165C
- CRHR1
- NOS C276T
- IL-1beta C511T
- CLOCK

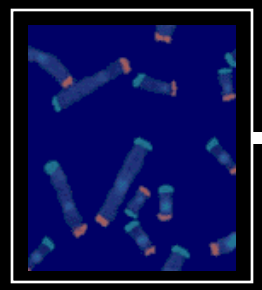
- **BDNF**
- **DTNBP1**
- **nNOS**
- **IL-1beta**
- **APOE**
- **MDR1P-gp**
- **GRIK4**

Serotonin Trasnporter gene (SLC6A4)

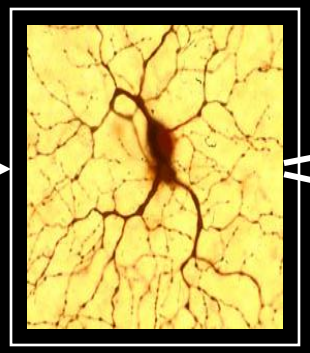


- Carriers of short allele have a poor outcome after treatment with SSRIs and a higher rate of adverse effects
- Antidepressant augmentation strategies with pindolol and lithium was beneficial to carriers of short allele

SLC6A4: How do we get there from here ?



SLC6A4:
5'HTTLPR polymor phism



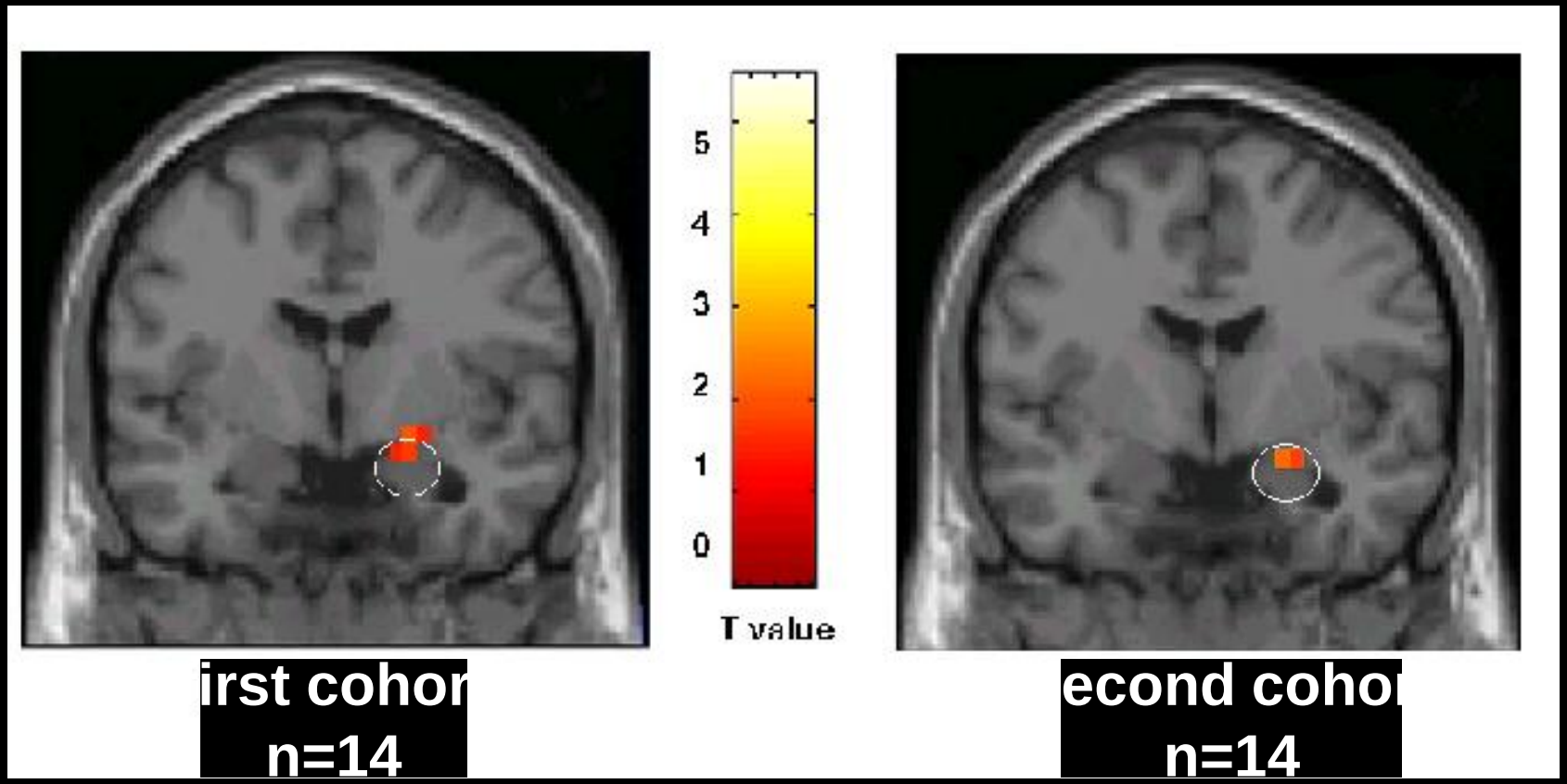
Cells:
serotonin mediated excitability

Systems:
amygdala processing of fearful stimuli

depression, anxiety disorders, neuroticism, response to SSRIs, substance abuse, hallucinations

Behavior:
complex functional interactions and emergent phenomena

5'-HTTLPR genotype and fMRI during perceptual processing of fearful faces

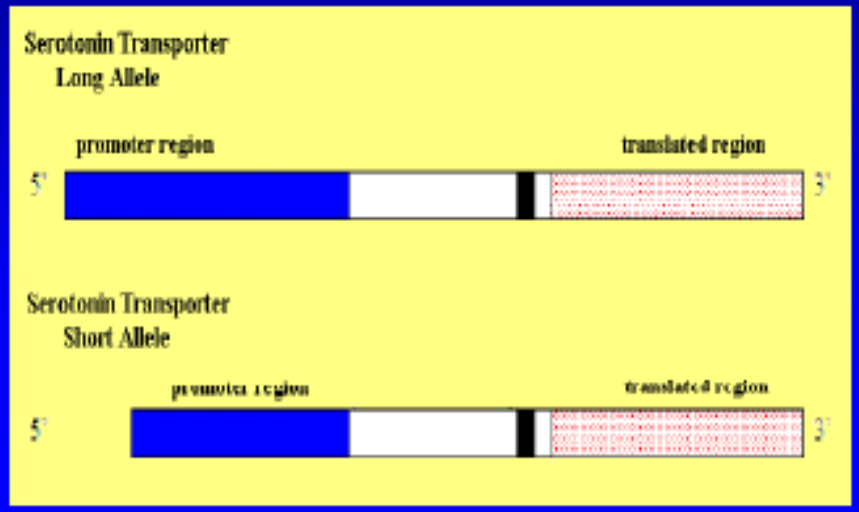


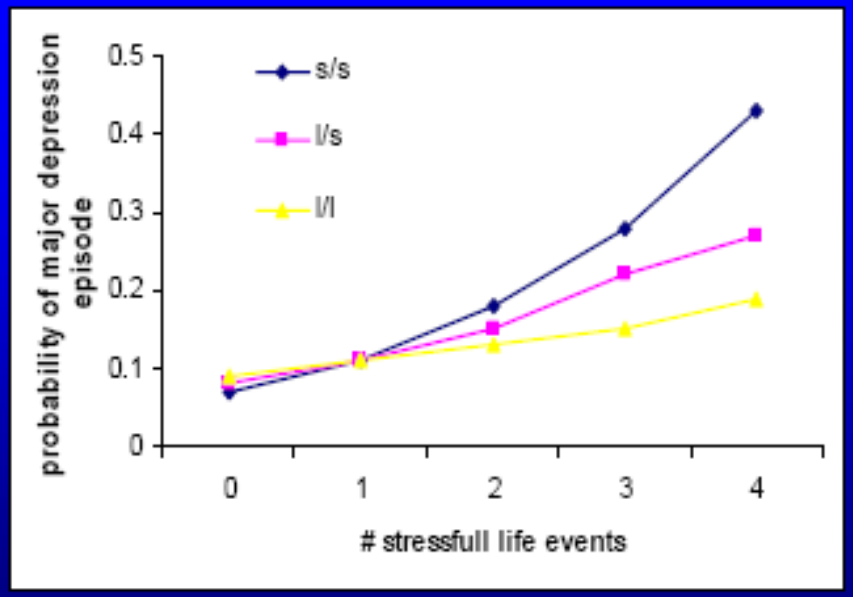
s **allele carriers show a greater amygdala response than *ll* homozygous individuals**

Genetic x environmental factors

SERT

Stressful life events and the number of short 5-HTTLPR alleles (l/l, l/s, or s/s) predicts occurrence of depression (Caspi et al, 2003)





5-HTTLPR variations……

Broad influence of a single gene on a range of aspects

Alteration of serotonin pathway plasticity

Anatomical change

Temperament

Mood disorders

Response to antidepressants

Stress reactivity

Meta-analysis for 5-HTTLPR (n=15, 1435 subjects)

Remission

Study or sub-category	l/l and l/s n/N	s/s n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Smeraldi 1998	24/38	4/15		5.73	4.71 [1.26, 17.66]
Zanardi 2000	24/42	5/16		8.41	2.93 [0.87, 9.95]
Zanardi 2001	55/68	10/14		8.59	1.69 [0.46, 6.26]
Yu 2002	3/49	2/72		4.12	2.28 [0.37, 14.19]
Arias 2003	78/104	13/27		13.98	3.23 [1.35, 7.76]
Serretti 2004	99/167	24/53		40.20	1.76 [0.94, 3.28]
Kato 2006	21/31	28/49		18.97	1.58 [0.61, 4.04]
Total (95% CI)	304 / 499	86 / 246		100.00	2.21 [1.53, 3.21]

Test for heterogeneity: $Chi^2 = 3.37$, df = 6 (P = 0.76), $I^2 = 0\%$
Test for overall effect: Z = 4.19 (P < 0.0001)

0.1 0.2 0.5 1 2 5 10

Favorable response s/s genotype | Favorable response l/l and l/s genotype

Serretti A et al. Mol Psychiatry. 2007 Mar;12(3):247-57.

Late-Life Depression Demographics

- Community sample >age 65
  - 1% Major depression
  - 2% Dysthymia
  - 4% Adjustment Disorder with depressed mood
  - 15% Sub-syndromal Depression

Clinical Features of Late-life Depression

- "Depression" without sadness
- ***Irritability***
- Prominent ***Anxiety***
- Cognitive complaints
- Prominent vague ***somatic complaints***
- Unexplained health worries
- Heightened pain complaints
- Loss of interest and pleasure
- Social withdrawal or avoidance of social interactions
- Multiple primary care visits without resolution of the problem
- Unexplained functional decline

Early-onset v. Late-onset

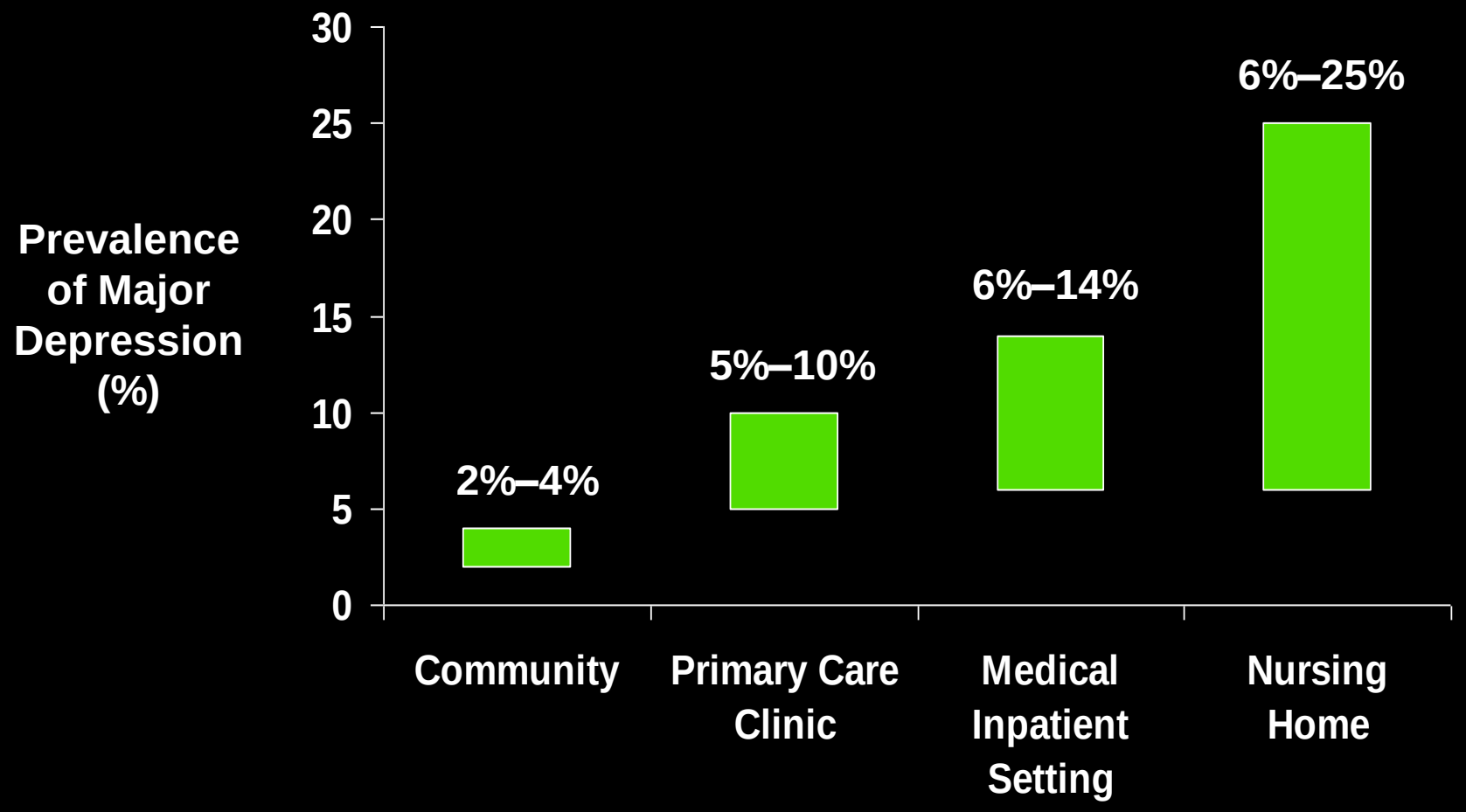
Early-onset

- Index episode in childhood or early adult life
- First degree relatives with depression
- Less physical illness
- More psychiatric comorbidity (SUD; personality disorders)
- Sad mood

Late-onset

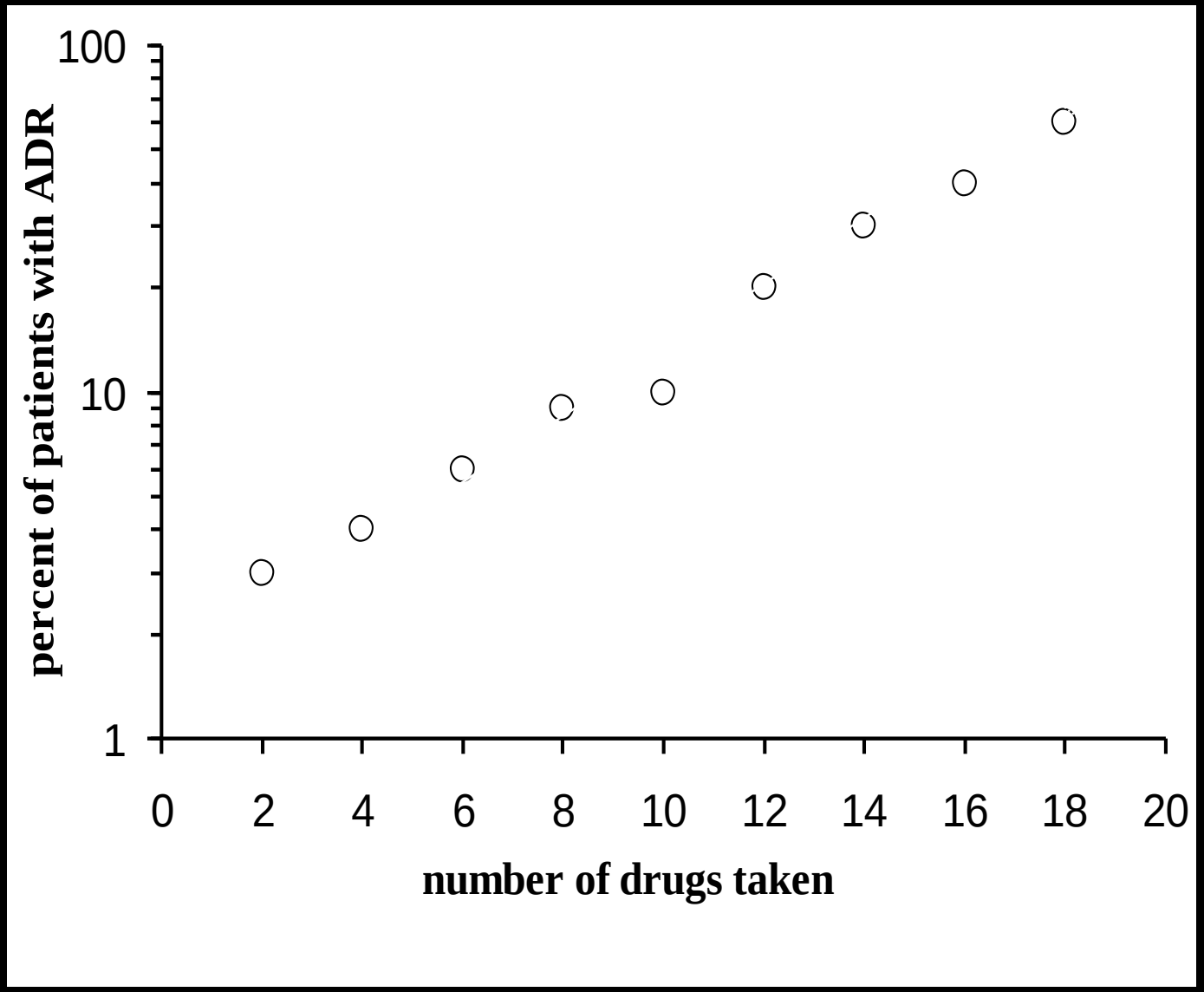
- Index episode after age 50
- Less genetic predisposition
- Chronic physical illness
- Poorer treatment response with more chronic course
- Increased mortality
- Abnormal brain imaging
- Les psych comorbidity
- Apathy and anhedonia

Major Depression Is Associated with Chronic Medical Illness



Katon W, Schulberg H. *Gen Hosp Psychiatry*. 1992;14:237-247.
Rosen J, Mulsant BH, Pollock BG. *Nursing Home Med*. 1997;5:156-165.

Medication and adverse reaction



Pharmacokinetic Changes in Aging

Parameter	Change	Effect
Absorption	Possible ↓	↓ Effectiveness
Protein binding	↓ if albumin is low	↑ free drug for protein bound
Volume of distribution	↑ for lipophilic	↑ accumulation
	↓ for hydrophilic?	↑ toxicity
Hepatic metabolism	↓ blood flow, 1st pass, demethylation and hydroxylation	↑ accumulation ↑ toxicity ↓ prodrug activation
Renal excretion	Often ↓	↓ elimination

Sheikh and Cassidy, J Anxiety Disorders 2000;14(2):173-90.

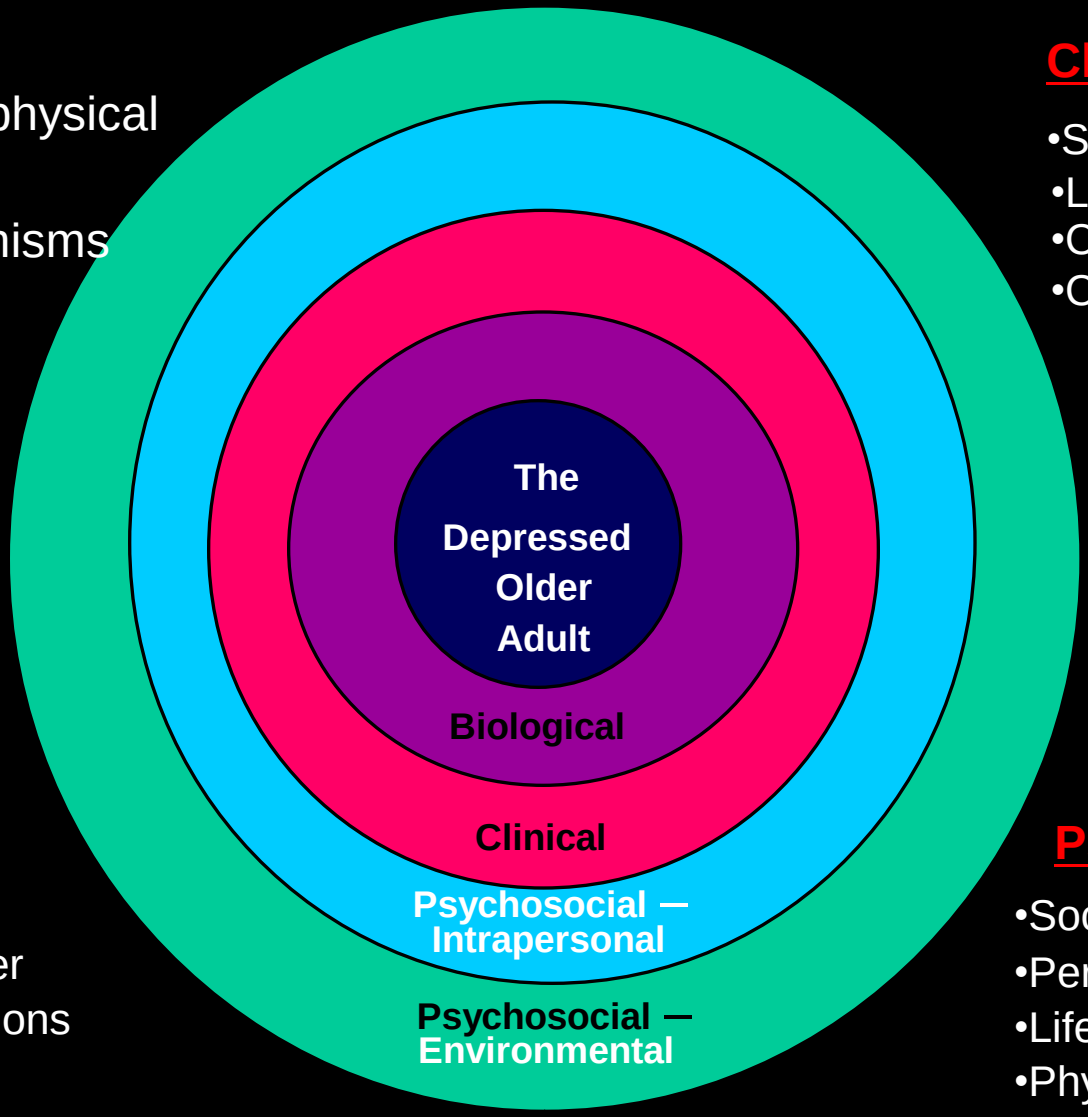
Nested Potential Predictors of Treatment Response in Late-Life Depression

Biological

- Nonpsychiatric physical illness
- Gene polymorphisms

Clinical

- Symptom severity
- Lifetime age of onset
- Comorbid anxiety
- Cognitive impairment



Psychosocial – Intrapersonal

- Demographics
- Personality disorder
- Traits and dispositions

Psychosocial

- Social supports
- Perceived chronic stress
- Life events/acute stress
- Physical environment

Individual pharmacogenetic trials

Monoamine transporter gene polymorphisms and antidepressant response in koreans with late-life depression (mean age=60)

A 6-week naturalistic treatment study with blinded outcome evaluation of 241 Korean inpatients and outpatients with major depression

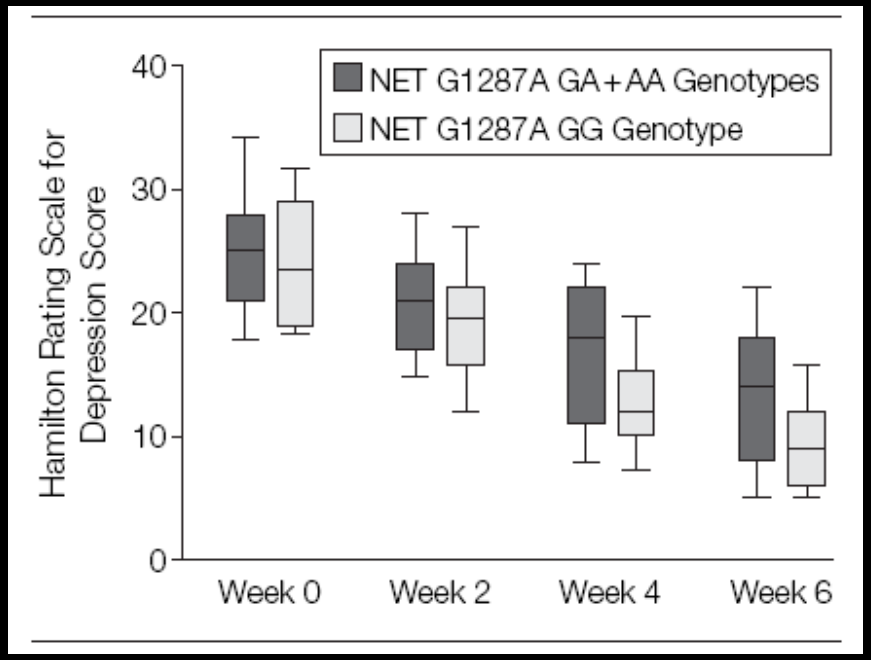
Treatment with an SSRI (fluoxetine or sertraline; n = 136) or an NRI (nortriptyline; n = 105) antidepressant. Adherence was assessed by measuring plasma concentration at 4 weeks

An SSRI and NRI response (defined as > or =50% decrease in Hamilton Rating Scale for Depression score at 6 weeks)

5-HTTLPR, 5-HTT VNTR in intron 2 and NET G1287A in exon 9

Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

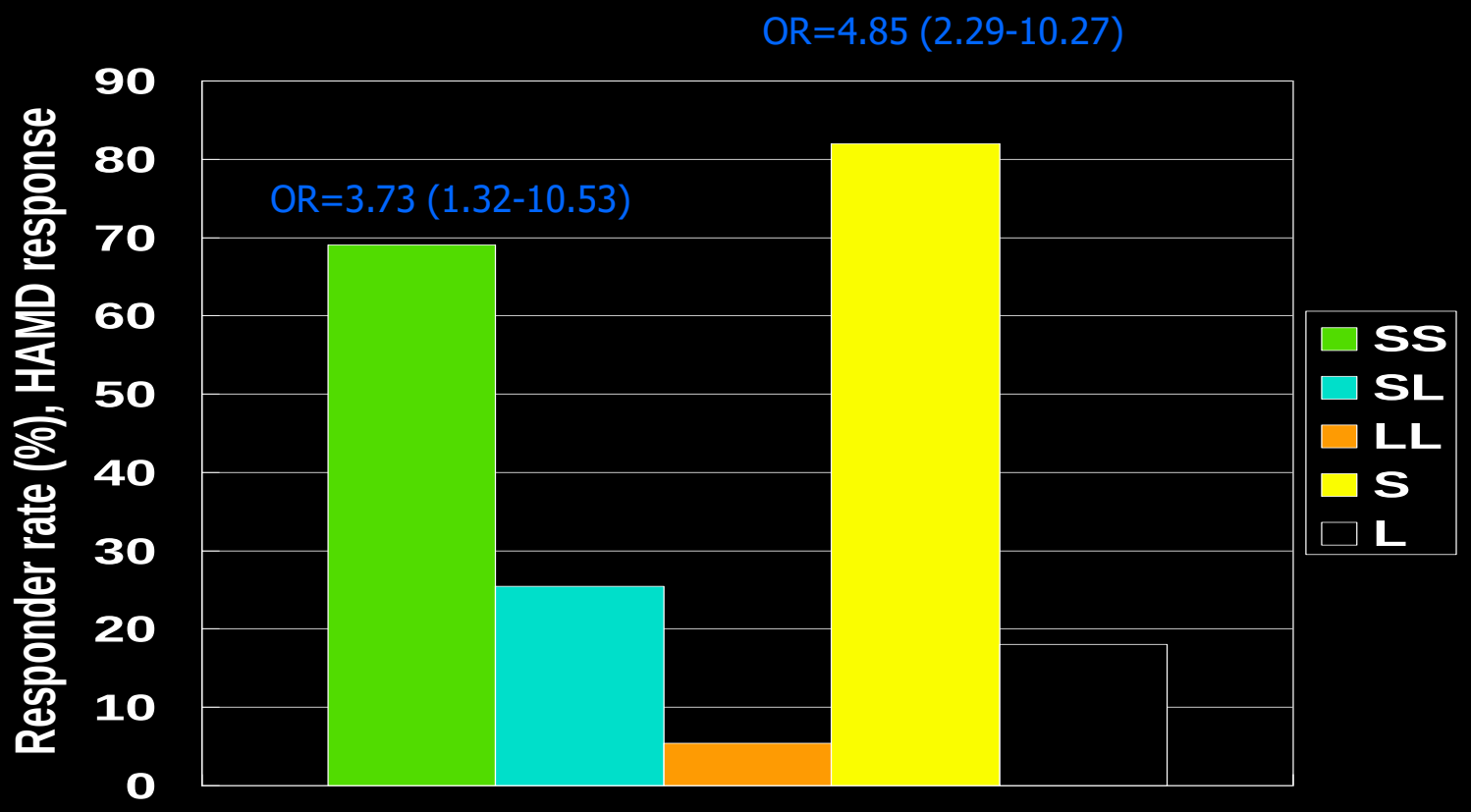
Changes in HAMD and responder rate: NET and NRI



	Responder (%)	OR and p values
GG	63.6	7.54 (2.53-22.49)
GA	29.1	
AA	7.3	
G	78	3.48 (1.67-7.30)
A	22	

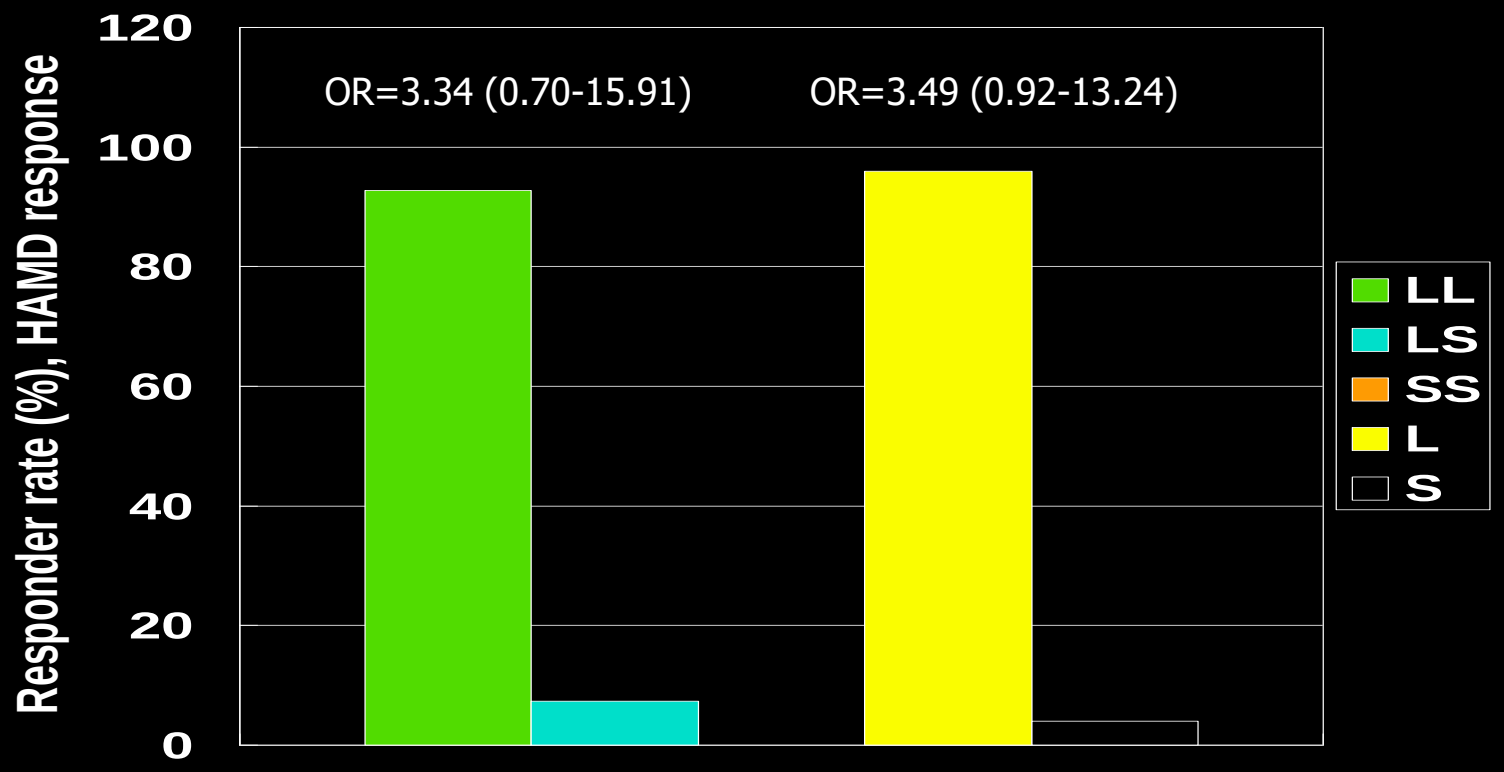
Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

Responder rate: 5-HTTLPR and NRI



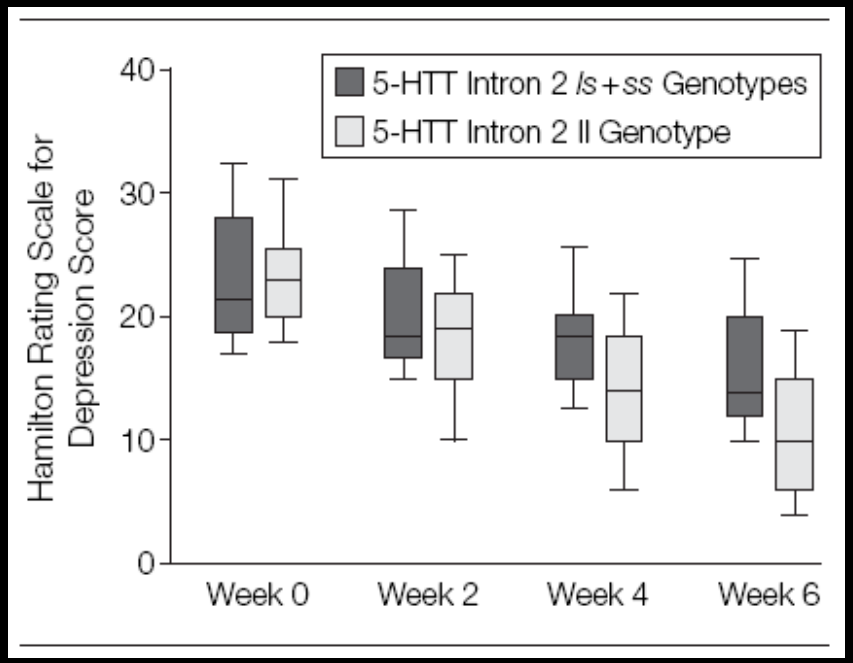
Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

Responder rate: 5-HTT intron and NRI



Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

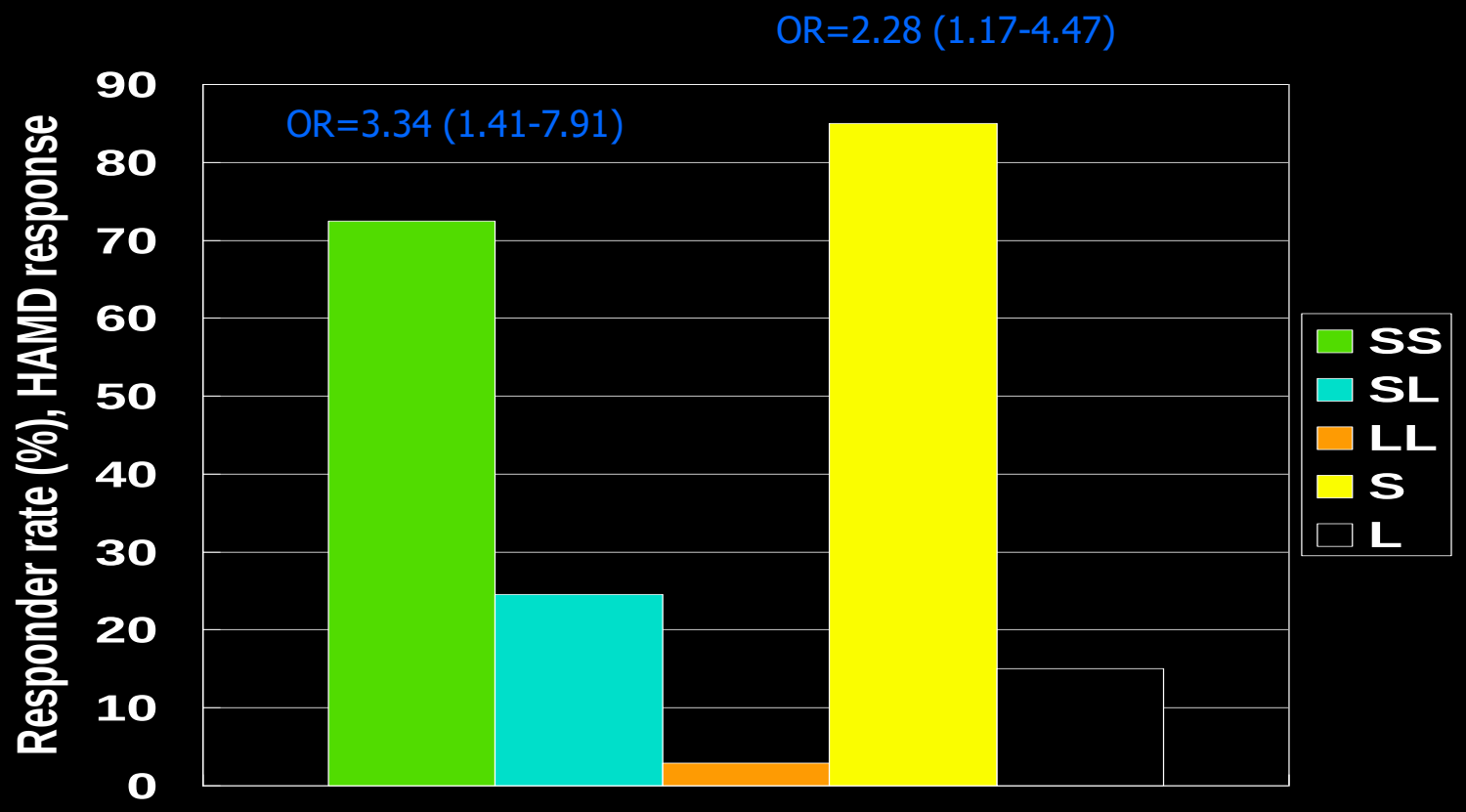
Changes in HAMD and responder rate: 5-HTT intron and SSRI



	Responder (%)	OR and p values
LL	97.1	20.11 (4.27-94.74)
LS	2.9	
SS	0	
L	99	15.87 (3.47-71.43)
S	1	

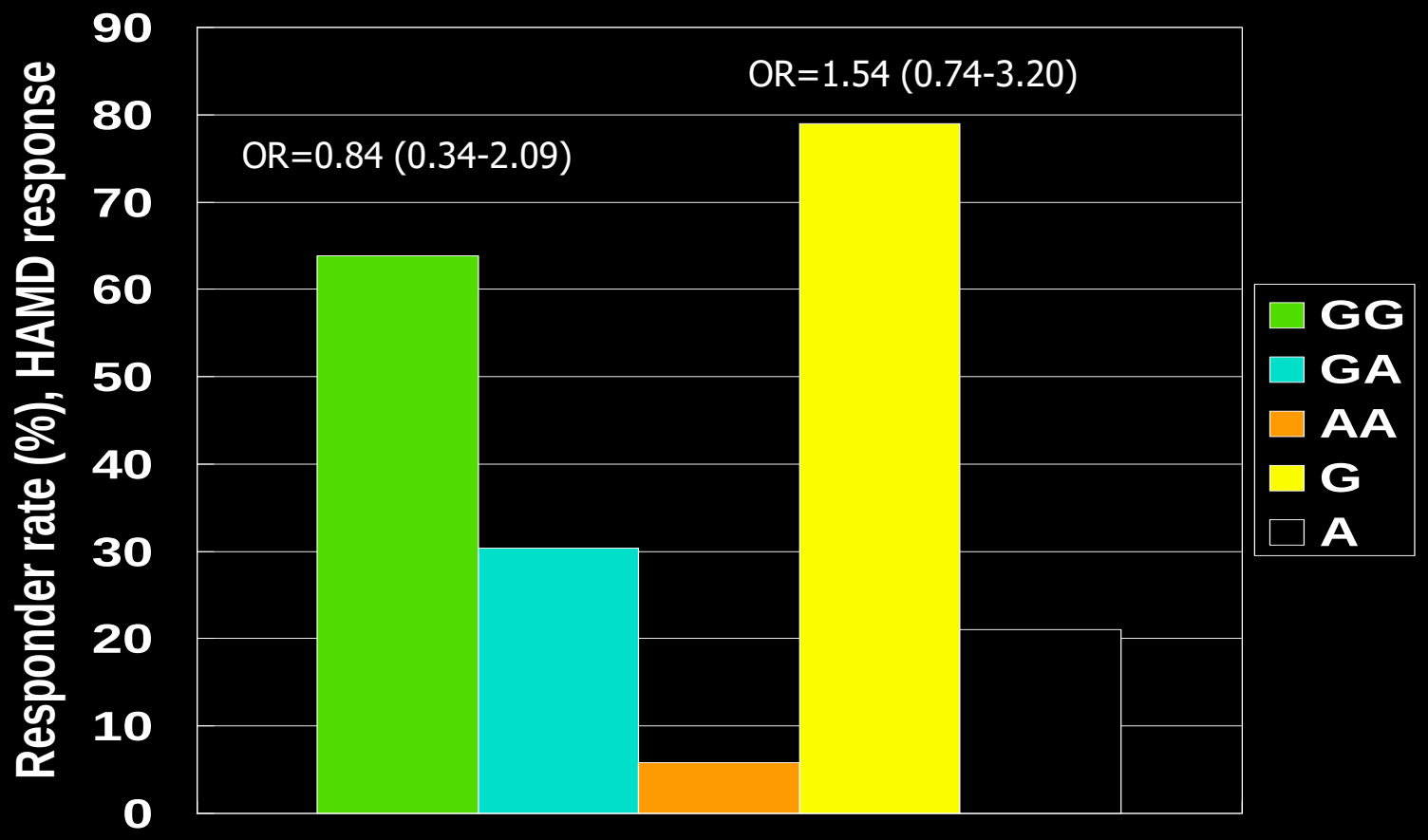
Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

Responder rate: 5-HTTLPR and SSRI



Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

Responder rate: NET and SSRI



Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

Response Rates With Combinations of Monoamine Transporter Polymorphisms

NET G1287A	5-TTLPR	5-HTT Intron 2	Response Rate, No./Total (%)	P Value*
		Norepinephrine Reuptake Inhibitor		
GG	ss	Any genotype	23/26 (88.5)	<.001
GG	l Carrier	Any genotype	12/16 (75.0)	<.008
A carrier	ss	Any genotype	15/24 (62.5)	<0.02
A carrier	l Carrier	Any genotype	5/23 (21.7)	Comparator
		Selective Serotonin Reuptake Inhibitor		
Any genotype	ss	ll	48/62 (77.4)	Comparator
Any genotype	l Carrier	ll	19/35 (54.3)	<0.06
Any genotype	ss	s Allele carriers	2/8 (25.0)	<0.01
Any genotype	l Carrier	s Allele carriers	0/14	<.001

Kim H, et al. JAMA. 2006 Oct 4;296(13):1609-18.

STAR*D, mean age=43

- **1,953 patients with major depressive disorder who were treated with the antidepressant citalopram in the Sequenced Treatment Alternatives for Depression (STAR*D) study and were prospectively assessed**
- **68 candidate genes was genotyped, with 768 single-nucleotide–polymorphism markers chosen to detect common genetic variation**
- **significant and reproducible association between treatment outcome and a marker in *HTR2A. no evidence of association among any of the four genotyped SLC6A4 markers and treatment outcome in these data***

McMahon FJ, et al. Am J Hum Genet. 2006 May;78(5):804-14

Kraft BJ, et al. Biol Psychiatry. 2007 Mar 15;61(6):734-42

Association Analysis of Genotyped *HTR2A* SNPs, Stratified by Race

	All			White			Black		
		P			P			P	
Phenotype and SNP	N	Allelewise	Genotypewise	n	Allelewise	Genotypewise	n	Allelewise	Genotypewise
Remission:									
rs7997012	1,149	.000024	.000035	911	.00107	.00183	170	NS	NS
rs1928040	1,148	.0446	.0701	910	.0626	NS	170	NS	NS
rs6313	1,183	NS	NS	942	NS	NS	172	NS	NS
rs6311	1,180	NS	NS	939	NS	NS	172	.0431	.0874
Response:									
rs7997012	1,329	.000037	.000002	1,049	.00183	.000157	199	NS	NS
rs1928040	1,327	.0709	NS	1,048	NS	NS	199	NS	NS
rs6313	1,372	NS	NS	1,086	NS	NS	202	NS	NS
rs6311	1,371	NS	NS	1,084	NS	NS	203	.0918	.0149
Change in QIDS-C_{16}:									
rs7997012	1,749	.000007	.00000146	1,380	.00123	.000516	261	NS	NS
rs1928040	1,747	.0214	.0072	1,378	.0738	.0887	261	NS	NS
rs6313	1,802	NS	.0878	1,425	NS	NS	264	NS	.0353
rs6311	1,804	.0599	.0494	1,426	NS	NS	265	.0094	.0261

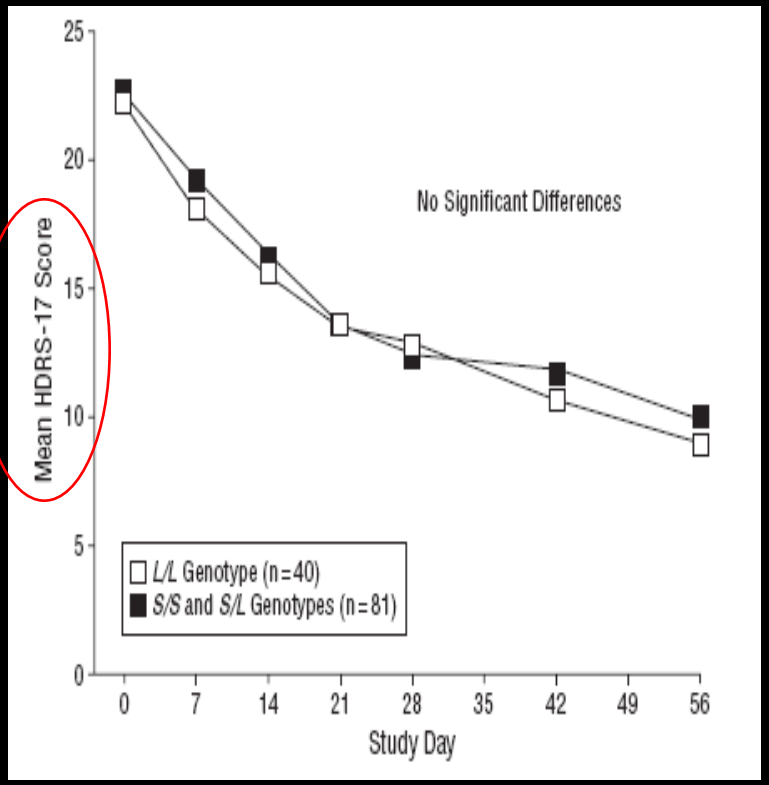
McMahon FJ, et al. Am J Hum Genet. 2006 May;78(5):804-14

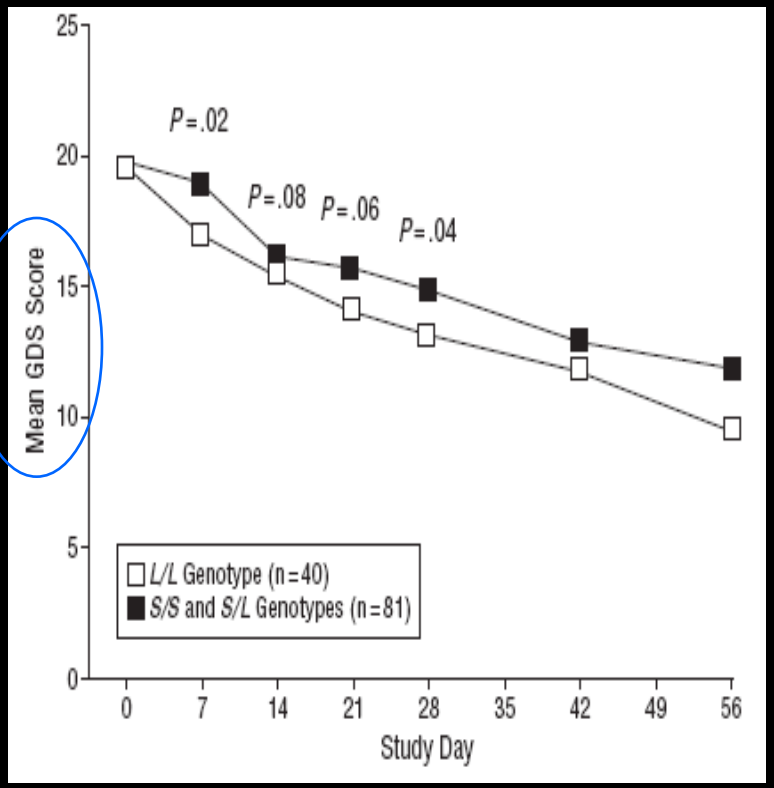
Association Results for SLC6A4 and Citalopram Response.

	White (n = 799 vs. 509)				African American (n = 130 vs. 121)			
	MAF		Additive model	Dominant OR	MAF		Additive model	Dominant OR
Marker	NonResp	Resp	p value	(95% CI)	NonResp	Resp	p value	(95% CI)
rs25531	.07	.08	.22	1.25 (.90,1.73)	.25	.27	.54	1.19 (.72,1.96)
5-HTTLPR	.44	.42	.27	.89 (.70,1.13)	.20	.22	.60	1.19 (.71,2.01)
rs25533	.06	.06	.48	1.15 (.80,1.64)	.07	.13	.05	1.81 (.92,3.56)
rs2020933	.05	.05	.83	1.06 (.71,1.58)	.32	.36	.38	1.27 (.74,2.19)
rs2020934	.46	.49	.10	1.31 (.99,1.72)	.23	.18	.28	.68 (.37,1.25)
rs16965628	.06	.07	.66	1.10 (.77,1.57)	.33	.35	.63	.96 (.56,1.65)
rs2066713	.38	.42	.09	1.29 (1.00,1.67)	.26	.29	.42	1.41 (.82,2.41)
rs6354	.20	.20	.95	1.03 (.81,1.32)	.34	.34	.99	1.07 (.62,1.82)
rs140700	.07	.10	.03	1.48 (1.04,2.10)	.04	.09	.02	2.57 (1.07,6.19)
rs140701	.44	.42	.42	1.02 (.80,1.31)	.27	.28	.95	.97 (.56,1.68)
rs1042173	.45	.43	.28	.90 (.70,1.16)	.23	.22	.82	.94 (.55,1.61)

Kraft BJ, et al. Biol Psychiatry. 2007 Mar 15;61(6):734-42

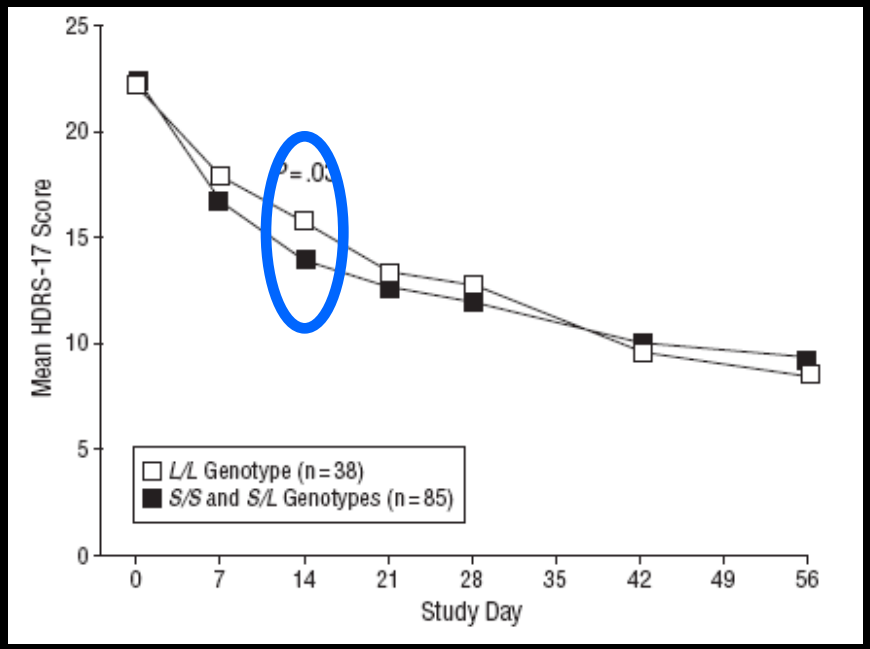
Effects of the 5HTTLPR polymorphism on the efficacy of paroxetine hydrochloride (mean age=72)

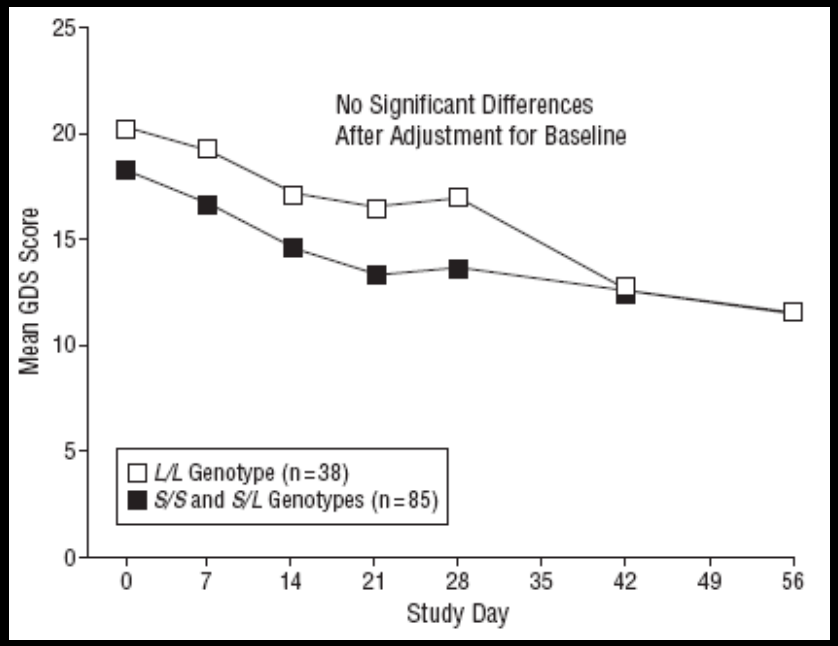




Murphy MG Jr., et al. Arch Gen Psychiatry. 2004 Nov;61(11):1163-9.

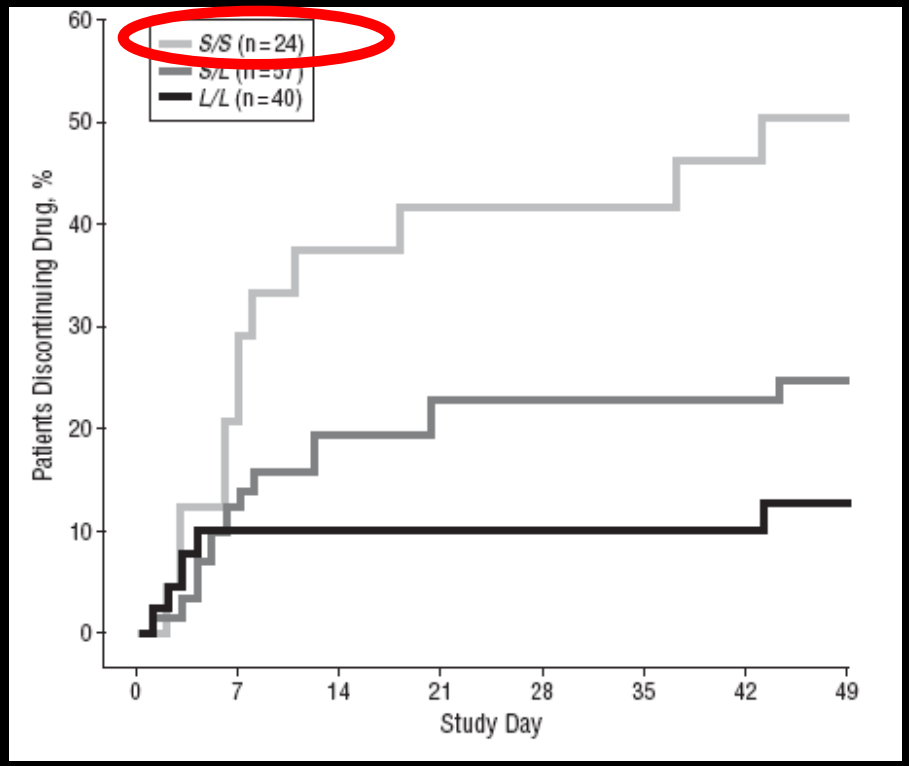
Effects of the *5HTTLPR* polymorphism on the efficacy of mirtazapine



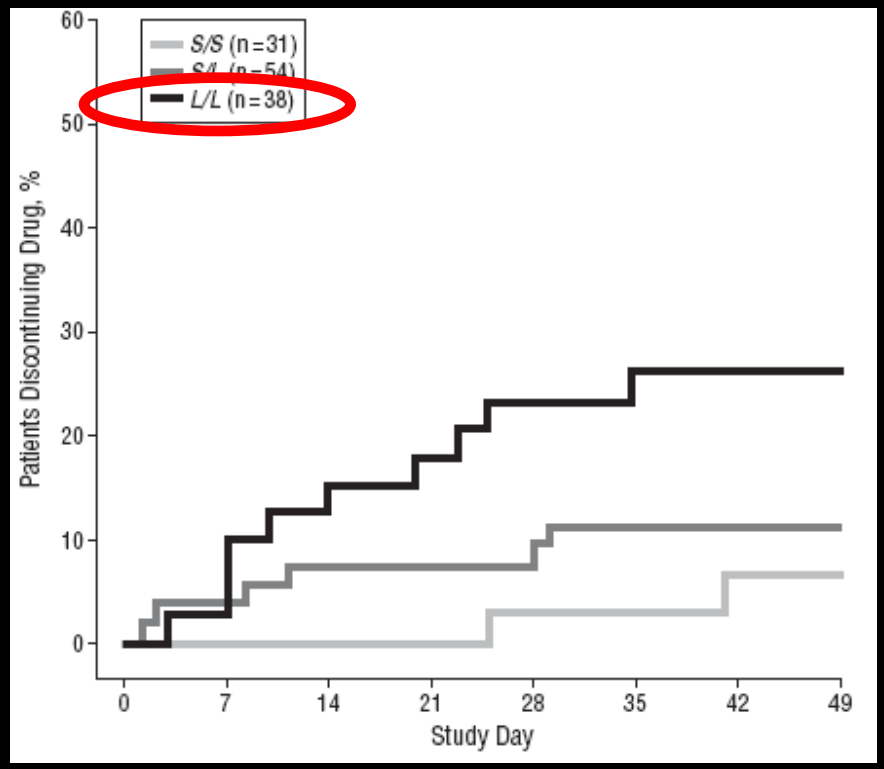


Murphy MG Jr., et al. Arch Gen Psychiatry. 2004 Nov;61(11):1163-9.

Survival curves showing discontinuations due to adverse events



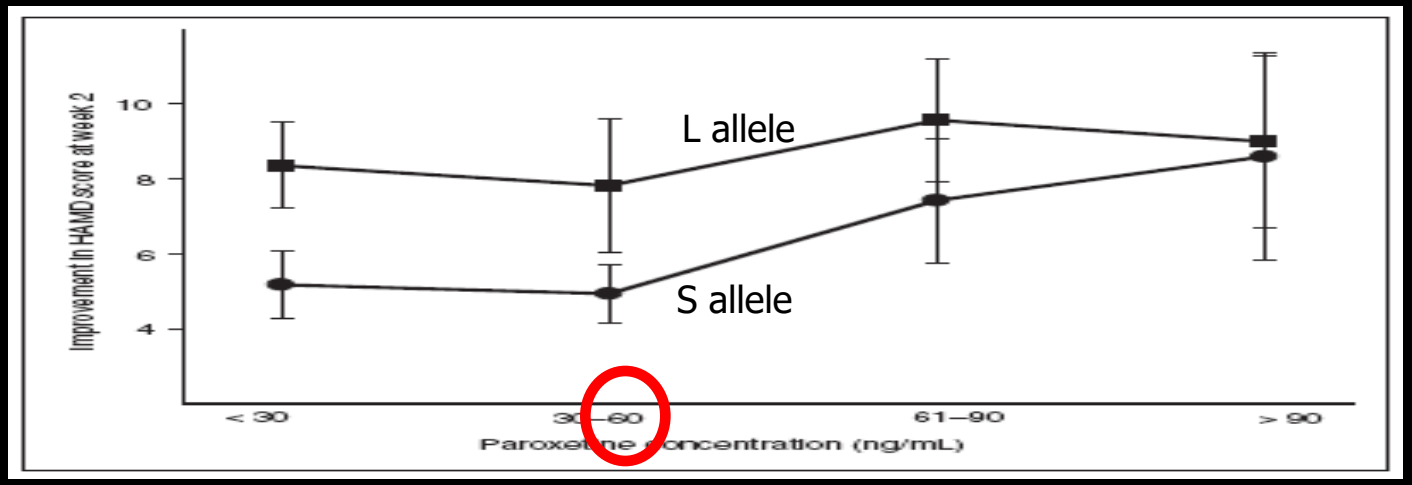
Paroxetine



Mirtazapine

Murphy MG Jr., et al. Arch Gen Psychiatry. 2004 Nov;61(11):1163-9.

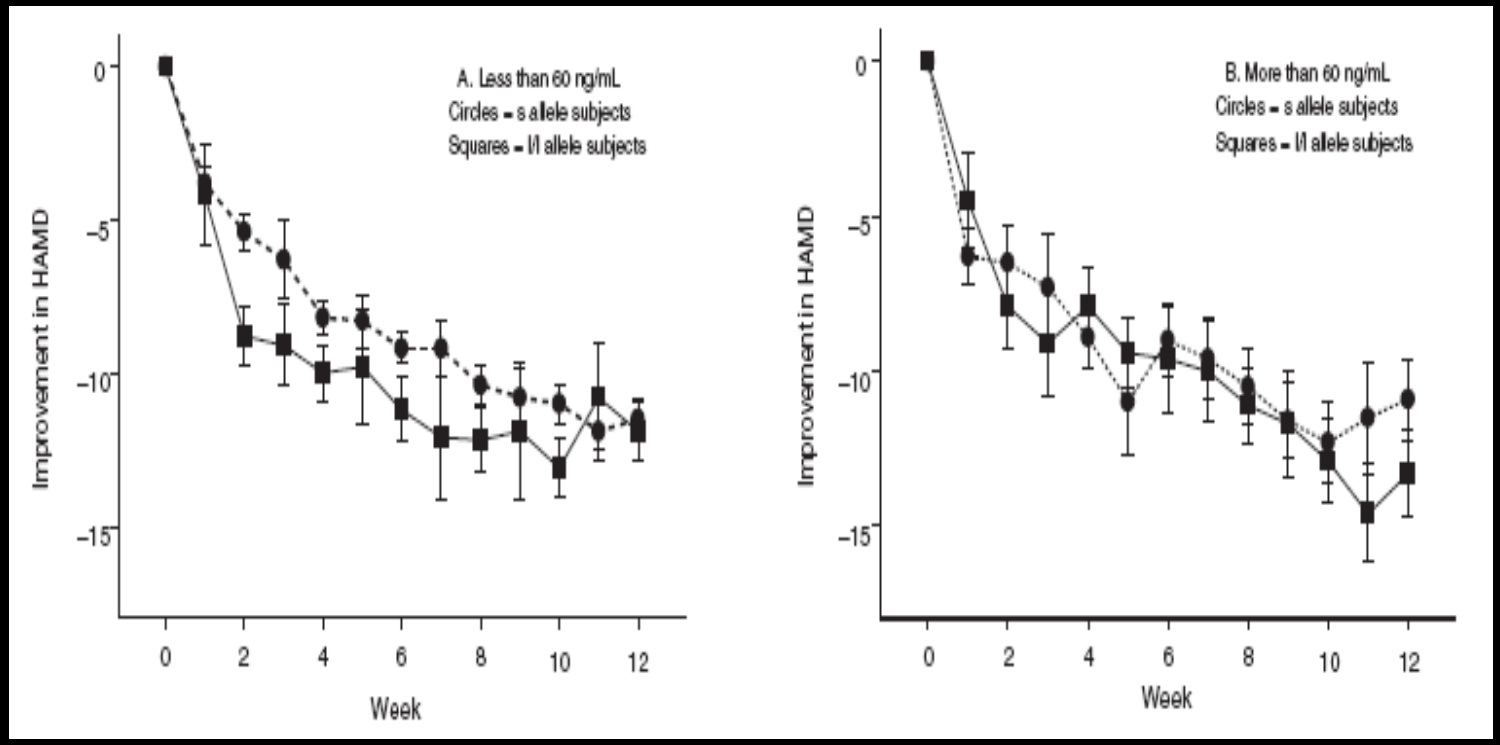
Serotonin transporter genotype interacts with paroxetine plasma levels to influence depression treatment response in geriatric patients



Subject group	Period; mean (and SEM)							
	Week 2 or 3		Week 4		Week 6		Week 10	
	Dose, mg	Level, ng/mL	Dose, mg	Level, ng/mL	Dose, mg	Level, ng/mL	Dose, mg	Level, ng/mL
l/l allele (n = 21)	16.1 (2.0)	43.9 (11.9)	21.8 (2.5)	77.9 (7.21)	24.5 (2.7)	89.7 (24.2)	30.0 (6.3)	154.6 (59.5)
s allele (n = 42)	19.2 (1.0)	55.6 (7.1)	23.5 (1.2)	100.8 (6.9)	26.4 (1.7)	110.7 (18.4)	36.7 (3.3)	185.7 (83.2)
Low exposure (n = 40)	17.7 (1.2)	28.8 (3.6)	20.9 (1.5)	46.6 (8.4)	23.5 (2.1)	62.8 (9.9)	25.0 (3.8)	92.4 (18.3)
High exposure (n = 23)	21.7 (2.1)	101.3 (10.1)	27.0 (2.1)	165.5 (20.5)	31.1 (2.6)	203.9 (21.2)	30.1 (3.7)	200.0 (29.6)

Lotrich FE et al., J Psychiatry Neurosci. 2008 Mar;33(2):123-30

The interaction between genotype and nondichotomized paroxetine levels was significant



Lotrich FE et al., J Psychiatry Neurosci. 2008 Mar;33(2):123-30

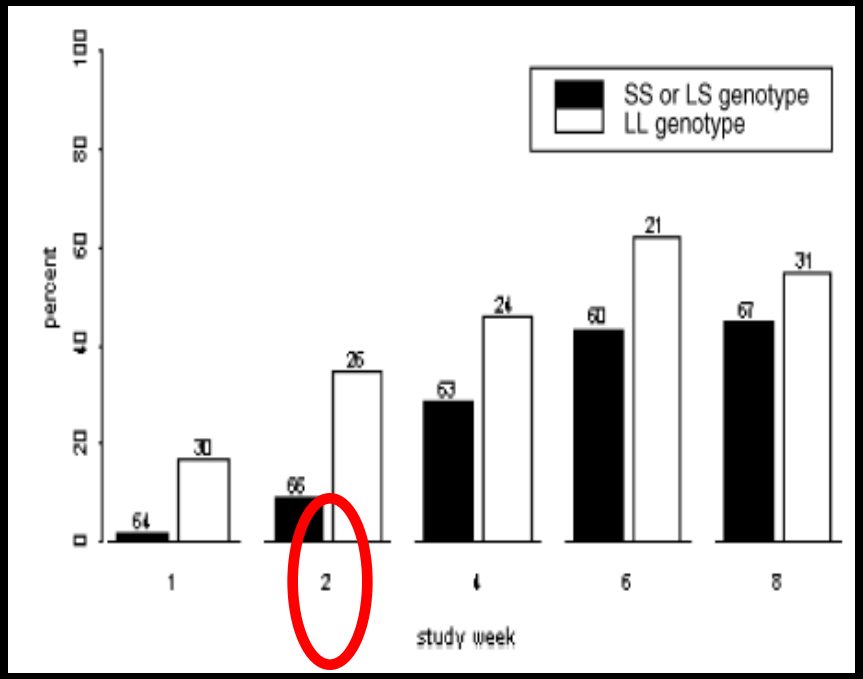
SERT and Remission: STAR*D (mean age=43)

	White non-Hispanic				White Hispanic				Black			
	Remission	N	*P*-value[a]	*P*-value[b]	Remission	N	*P*-value[a]	*P*-value[b]	Remission	N	*P*-value[a]	*P*-value[b]
Intron 2 VNTR												
9/10	52.9%	17	0.810	1.000	0%	1	1.000	1.000				
9/12	70.6%	17	0.088	0.353	100%	1	0.374	1.000				
10/10	55.7%	158	0.070	0.282	29.2%	24	0.500	1.000	35.3%	17	1.000	1.000
10/12	49.9%	469	[illegible]	1.000	38.5%	78	0.880	1.000	37.9%	95	1.000	1.000
12/12	44.1%	181	0.017	0.069	38.5%	91	0.882	1.000	37.9%	116	1.000	1.000
Global *P*-value[c]		0.041				0.670				1.000		
Indel promoter												
L/L	53.7%	69	0.012	0.024	31.7%	60	0.267	0.533	37.8%	143	0.780	1.000
L/S	45.2%	504	[illegible]	0.115	39.8%	83	0.656	1.000	41.6%	77	0.567	1.000
S/S	46.2%	195	0.527	1.000	41.5%	53	0.512	1.000	30%	10	0.744	1.000
Global *P*-value[c]		0.039				0.490				0.787		
rs25531												
A/A	47.6%	925	0.134	0.267	38.5%	174	0.644	1.000	38.9%	126	0.893	1.000
A/G	54.5%	145	0.129	0.259	35%	20	1.000	1.000	38.3%	94	1.000	1.000
G/G	50%	4	1.000	1.000	0%	2	0.528	1.000	33.3%	12	1.000	1.000
Global *P*-value[c]		0.287				0.752				0.975		

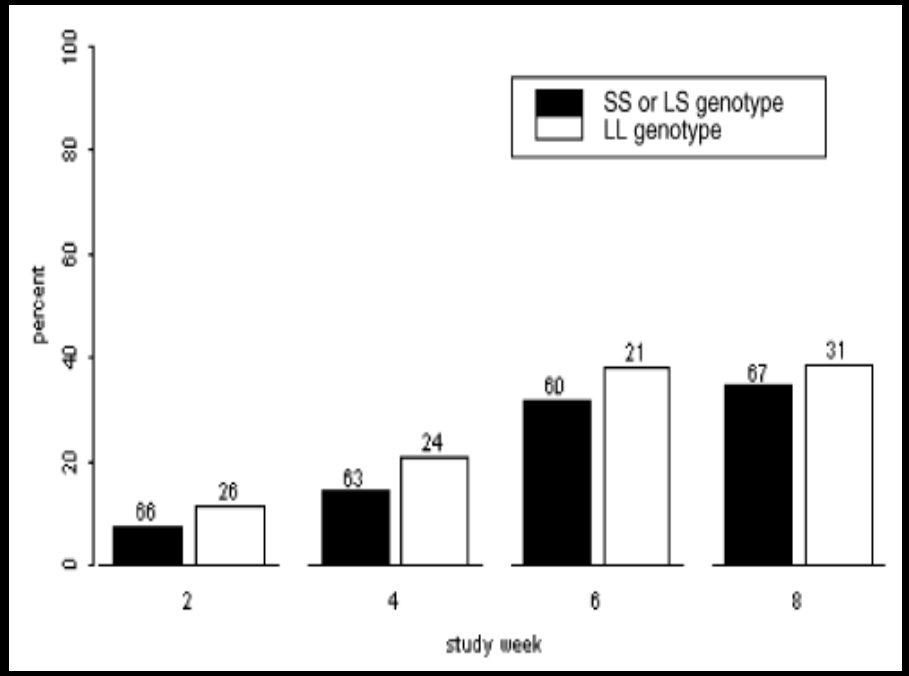
	Haplotype frequency				
Haplotype	WNH	WNH non-remitters	WNH remitters	Haplotype simulation *P*-value	Maximum statistic simulation *P*
S-a-12	0.330	0.363	0.297	0.0007	0.0031
L-a-12	0.215	0.215	0.213	0.98	
L-g-12	0.052	0.048	0.057	0.32	
S-a-10	0.085	0.074	0.097	0.23	
L-a-10	0.291	0.279	0.304	0.14	

Mrazek DA et al., Am J Med Genet B Neuropsychiatr Genet. 2009 Apr 5;150B(3):341-51.

The serotonin transporter polymorphism, 5HTTLPR, is associated with a faster response time to sertraline in an elderly population (mean age=69)



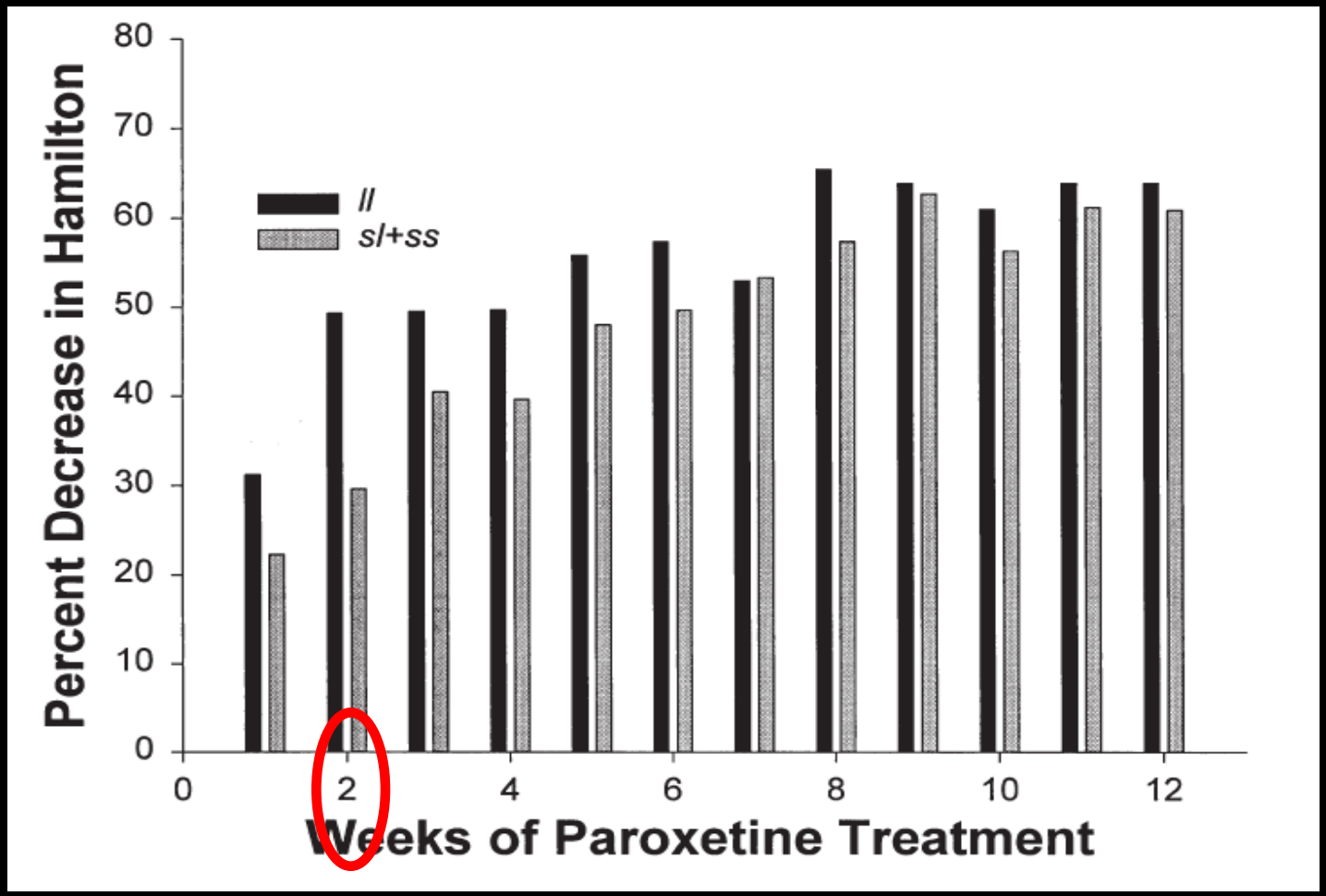
The percentage of responders (CGI-I=2 or <2)



The percentage of responders (50% or greater reduction in HAM-D)

Durham LK et al., Psychopharmacology (Berl). 2004 Aug;174(4):525-9.

Serotonin Transporter Promoter Affects Onset of Paroxetine Treatment Response in Late-Life Depression



Pollock BG et al., Neuropsychopharmacology. 2000 Nov;23(5):587-90.

Limitations to current pharmacogenetics studies

- Generally not multi-gene studies (or studies considering combinations of several genes)
- Little explanation of treatment variance by multiple small effect genes
- Statistically significant results are not necessarily clinically meaningful
- Many studies - few results replicated
- Gene-environment, gene-disease, gender, age and other hidden factors not controlled
- Candidate polymorphisms often associated with baseline disease severity
- Small samples
- Sensitivity of rating scales and response definition
- Ethnic difference in SNPs

Pharmacogenetics: problematic issues…and possible solutions

- Low variance explained by polymorphisms (HTTLPR=2.8%, TPH=2.7%, Gß3=1.2%) → Other variables influence drug response: Life events, social support, temperament, hormones…*and should be included in the model! Neural Network?*
- Epigenetic factors, CNV, Splicing, Regional expression, gene interactions…*should be controlled with multivariate or neural network models.*
- Drug response may differ across episodes…*longer follow up*

Now and Outlook

- Genotyping and SSRI plasma concentrations can be recommended clinically
- How predictive is antidepressants' efficacy and toxicity for clinical endpoints?
- Drug target: transporter, Rs, signaling pathway
- Will genetic testing to predict response and toxicity be feasible and cost-effective?

  - Maybe, but expectations are probably too high
- Large studies with many genes are needed