3-18-2009

Treatment Resistant Depression

Amresh Srivastava
University of Western Ontario, amresh.srivastava@sjhc.london.on.ca

Learning objectives

Clinical characteristics of treatment resistance

Methods to treat TRD & Evidence of their efficacy

Outcome & Treatment resistance

Causes, neurobiology & management of ‘Treatment-Resistance’

WHAT IS THE NATURE & CHARACTERISTICS OF TREATMENT RESISTANCE?

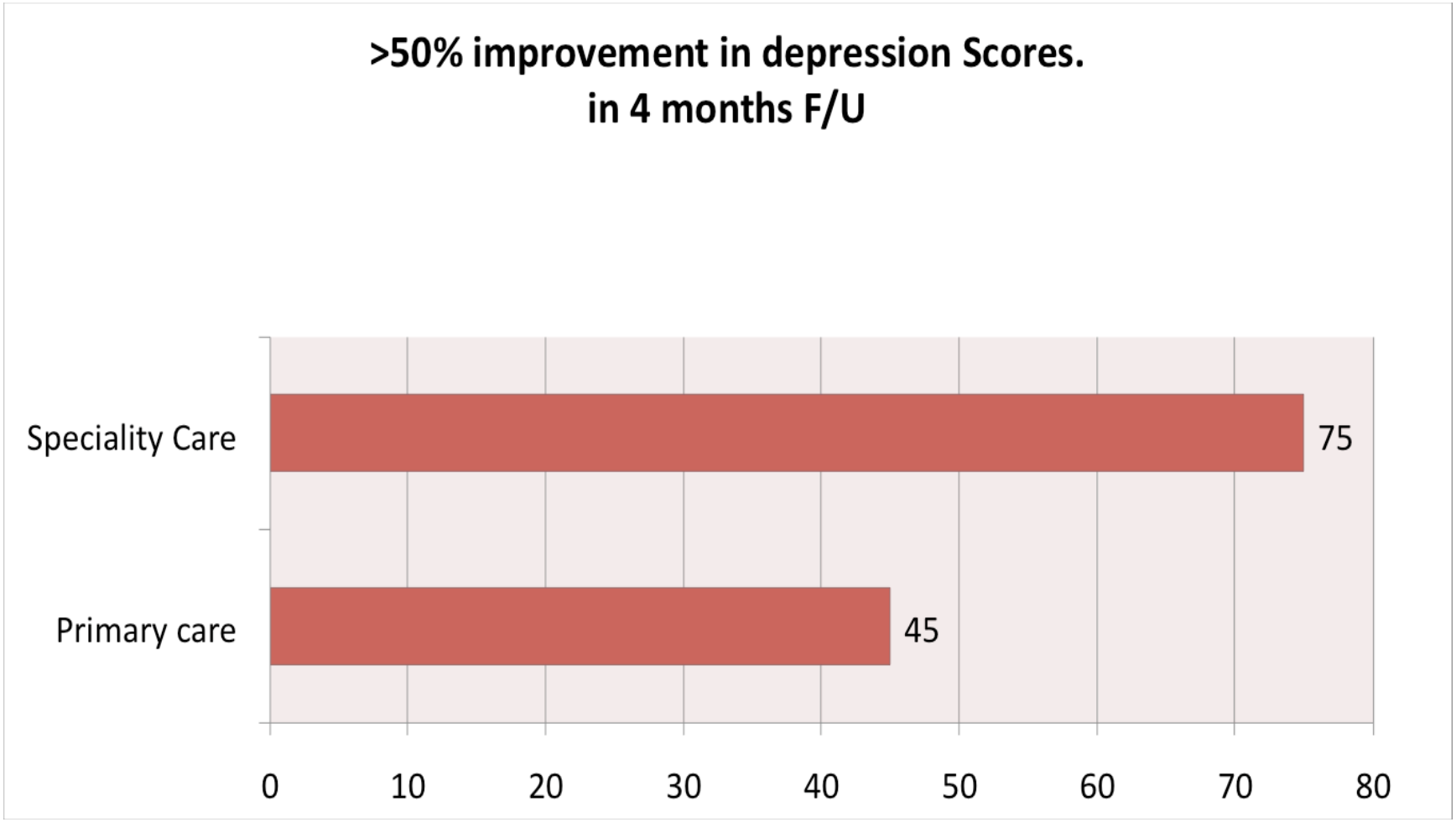
Resistance to What??

Measuring TRD: Staging Treatment Resistance

Stage I	Inadequate response to 1 monotherapy
Stage II	Inadequate response to 2 adequate monotherapy trials (different classes)
Stage III	Stage II resistance plus inadequate response to 1 augmentation trial
Stage IV	Stage III resistance plus inadequate response to a second augmentation trial
Stage V	Stage IV resistance plus inadequate response to bilateral ECT

Adapted from: Thase ME, Rush AJ. J Clin Psychiatry. 1998;59(suppl 5):5
Souery D et al. Eur Neuropsychopharmacol. 1999;9:83

TRD: chronic, recurrent, debilitating



Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression.CNS Spectr. 2007 Aug;12(8 Suppl 13):1-27

Non-response

Wijeratne C, Sachdev P.Treatment-resistant depression: critique of current approaches.Aust N Z J Psychiatry. 2008 Sep;42(9):751-62.

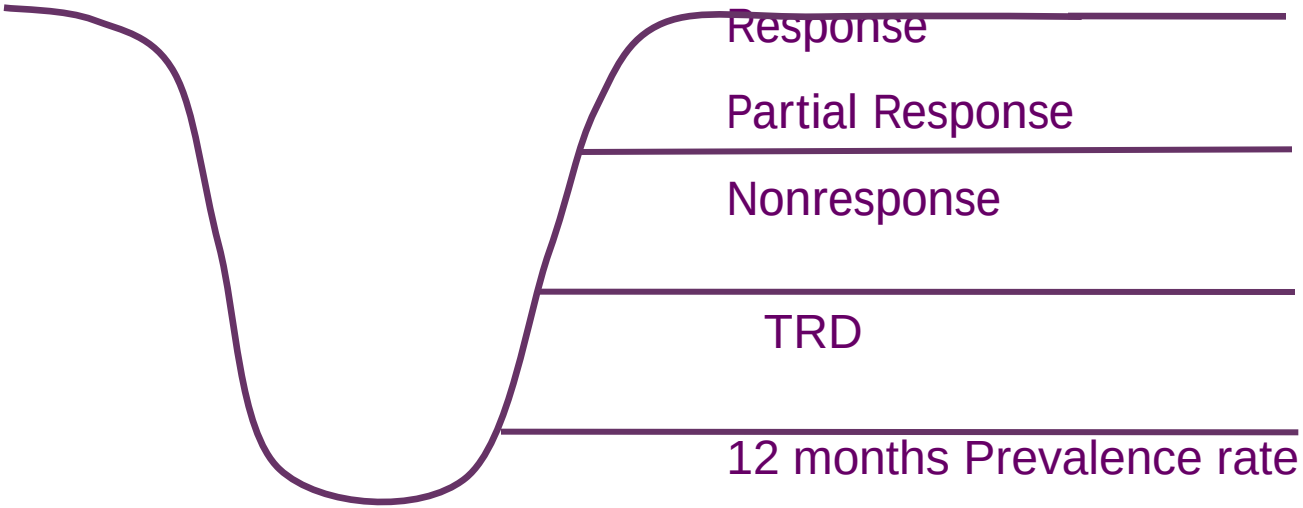
Nonremission is Common

Depression in Primary Care, Vol. 2. Treatment of Major Depression. Rockville, MD: US Dept. of Health and Human Services, AHCPR Publication No. 93-0550, 1993.

Definitions of Response and Remission

The causes of TRD are not fully understood.

	% Reduction in Score
Remission	≥75%
Response	50% - 74%
Partial Response	25% - 49%
Nonresponse	<25%
TRD	>40%[1]
12 months Prevalence rate [2]	3%- Stage 1 2% - stage 2..



1.Taylor SM: Electroconvulsive therapy, brain-derived neurotrophic factor, and possible neurorestorative benefit of the clinical application of electroconvulsive therapy. J ECT. 2008 Jun;24(2):160-5.
2. Nemeroff CB Prevalence and management of treatment-resistant depression.J Clin Psychiatry. 2007;68 Suppl 8:17-25

Paradigms Which Contribute to Faulty TRD Labeling

Parker et al 2005, J of Affect Dis Machado-Vieira R, Soares JC.Treatment-resistant mood disorders Rev Bras Psiquiatr. 2007 Oct;29 Suppl 2:S48-54

Predictors of Non-Response

Biology :

No specific neurobiology TRD.
Exploring newer brain targets

- NT: Dopamine, NMDA,
- Aminoacids : glutamate/glutamine/GABA cycling[1]
- Neuronal nitric oxide synthisase factor (NOS) via Serotonine signaling[2]
- Neuropeptides P/ Y[3]
- Endogenous modulators
- Beta 3 – adrenoreceptos (agonist: amibegrone)
- Nicotinic receptors

1.Price B, et al Biological psychiatry, 2008 Dec
2.Ulak G, Pharmacol. Biochem behav.2008.
3.Nikisch G, Eur.Psychiatry.2008.23:356-9

Biological Changes in treatment Resistant Depression

Biology[1, 2]

Reduced global cortical folding[5]

N-methyl-D-aspartate (NMDA) receptor [4]

Decreased Neurogenesis

1.Taylor SMElectroconvulsive therapy, brain-derived neurotrophic factor, and possible neurorestorative benefit of the clinical application of electroconvulsive therapy.J ECT. 2008 Jun;24(2):160-5

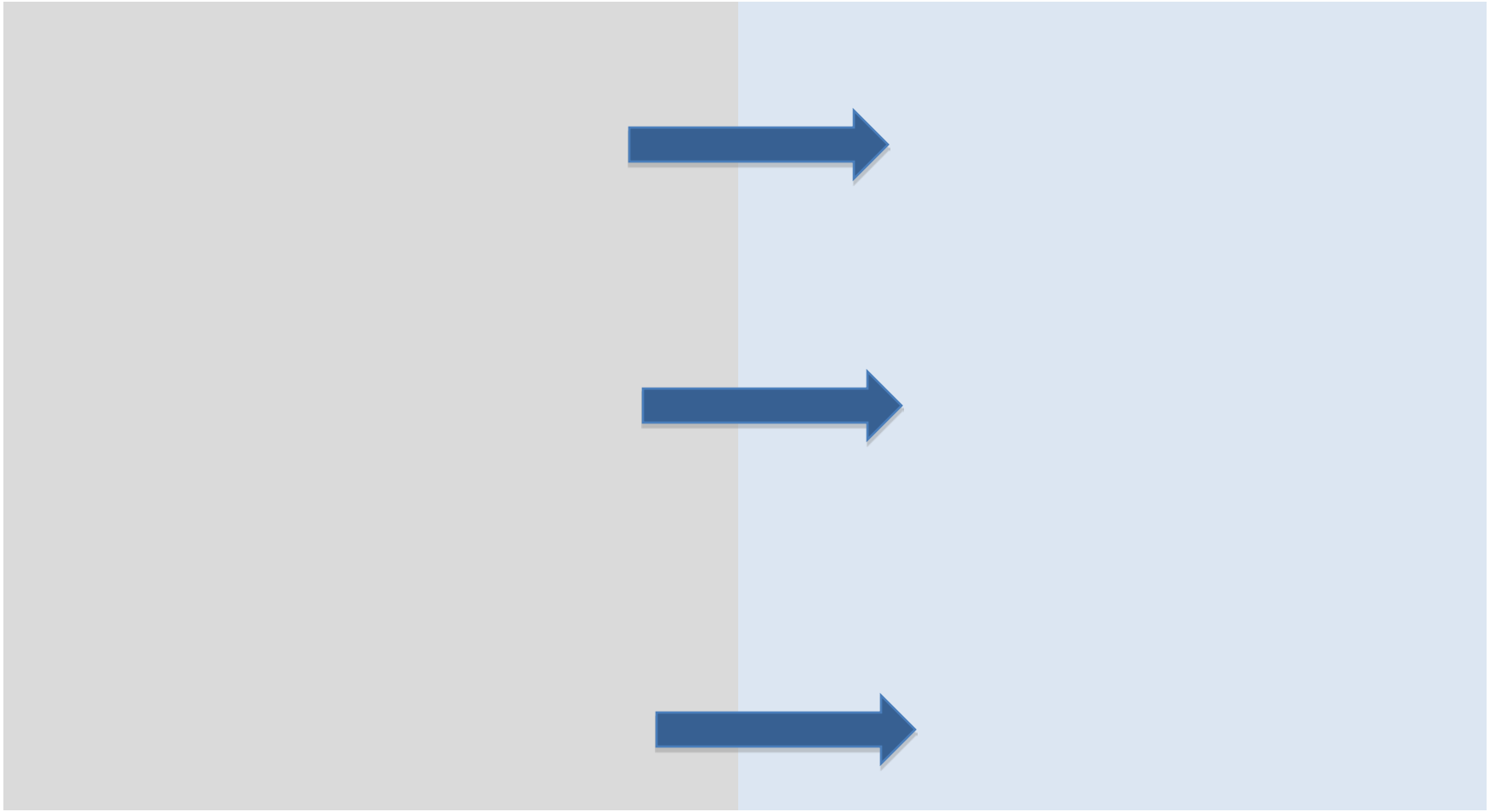
2. Kitamura Y, Gomita Y. [Development of animal models of treatment-resistant depression in rats] Nihon Shinkei Seishin Yakurigaku Zasshi. 2008 Apr;28(2):93-100

3. Wijeratne C, Sachdev P. Treatment-resistant depression: critique of current approaches. Aust N Z J Psychiatry. 2008 Sep;42(9):751-62.

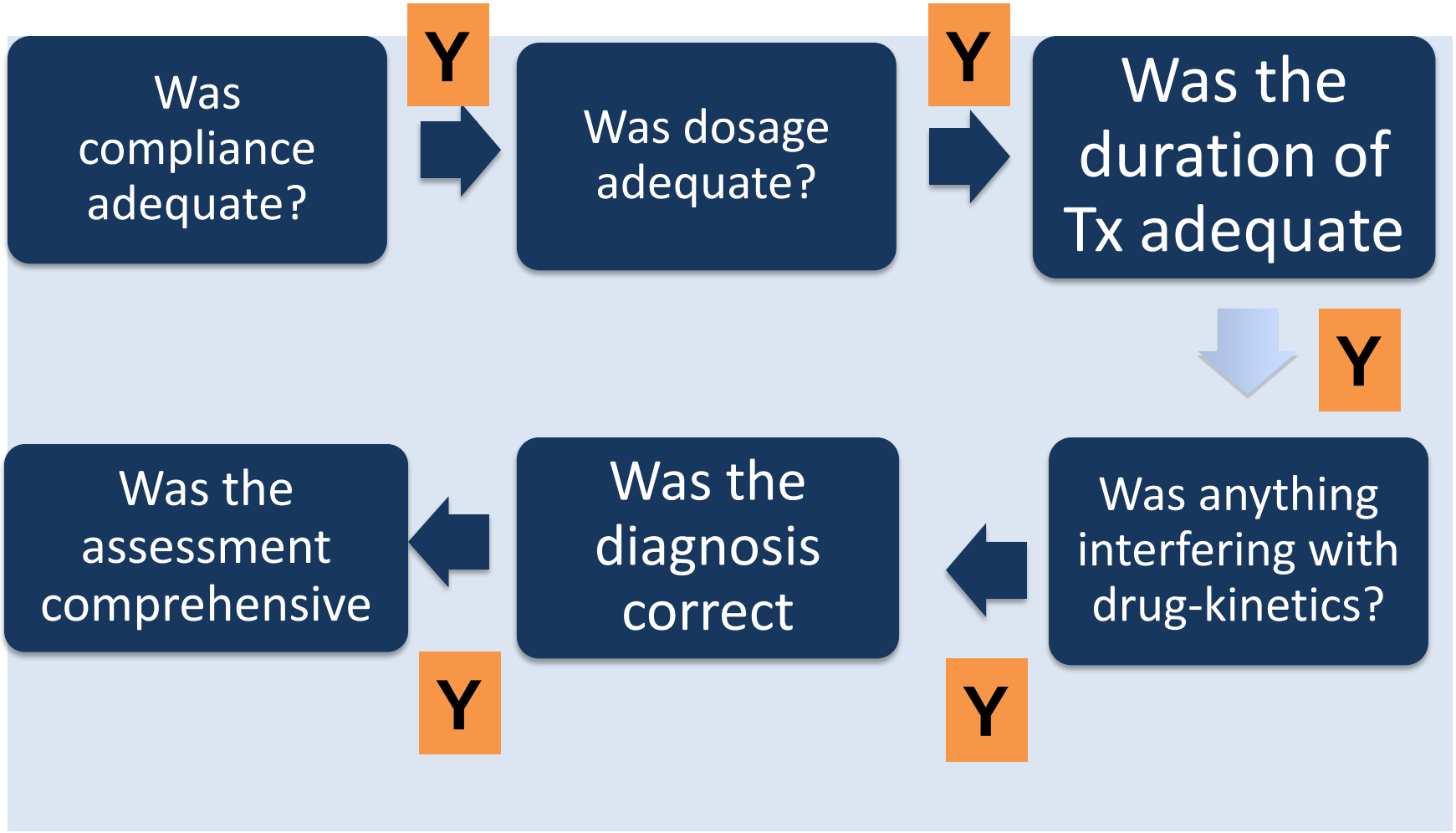
4.Maeng S, Zarate CA Jr. . The role of glutamate in mood disorders: results from the ketamine in major depression study and the presumed cellular mechanism underlying its antidepressant effects. Curr Psychiatry Rep. 2007 Dec;9(6):467-74.

5.Penttila J et al , J Psychiatry neurosci. 2009; 34(2):127-35

Decision tree for TRD

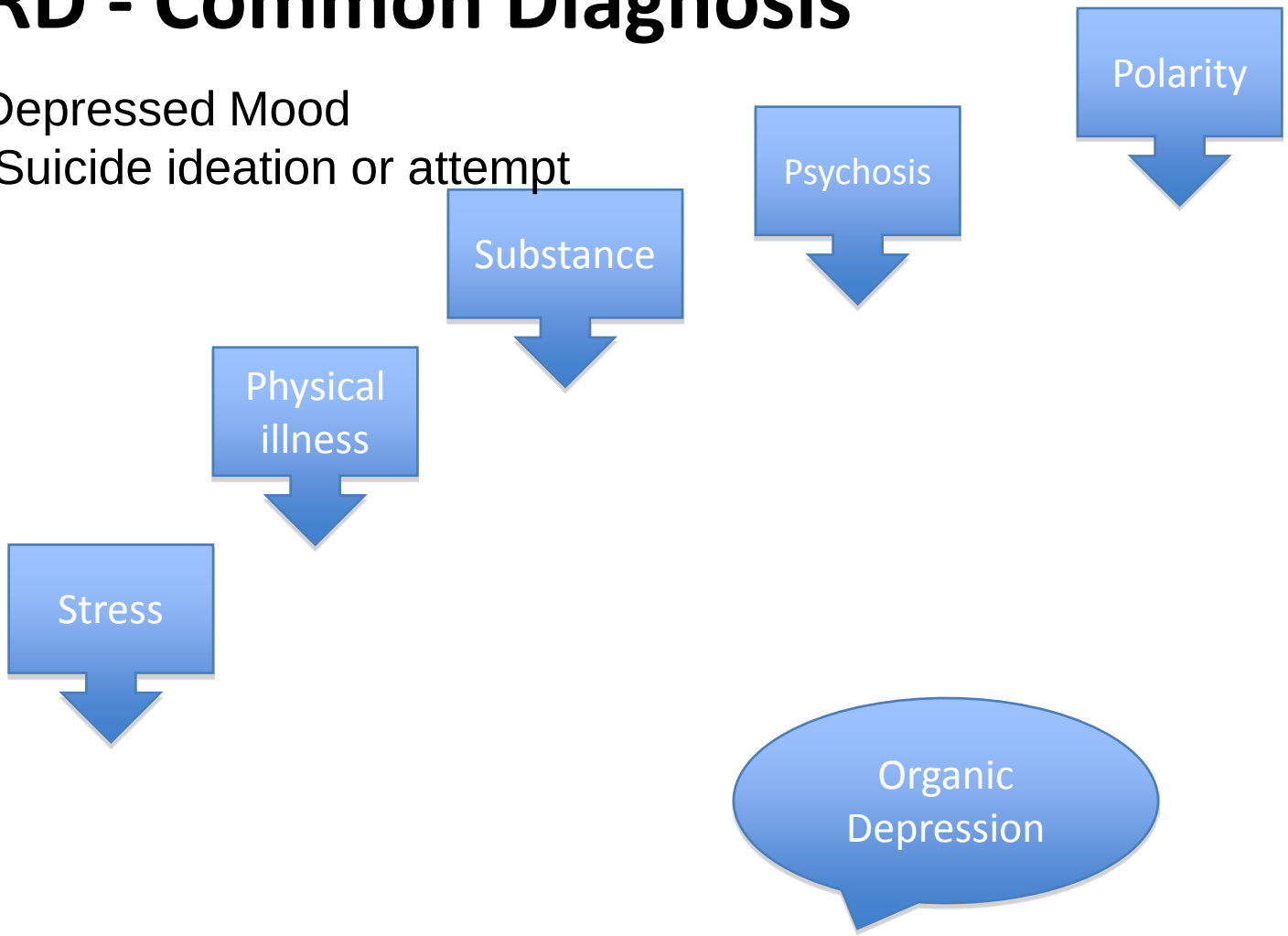


Diagnosing treatment resistance

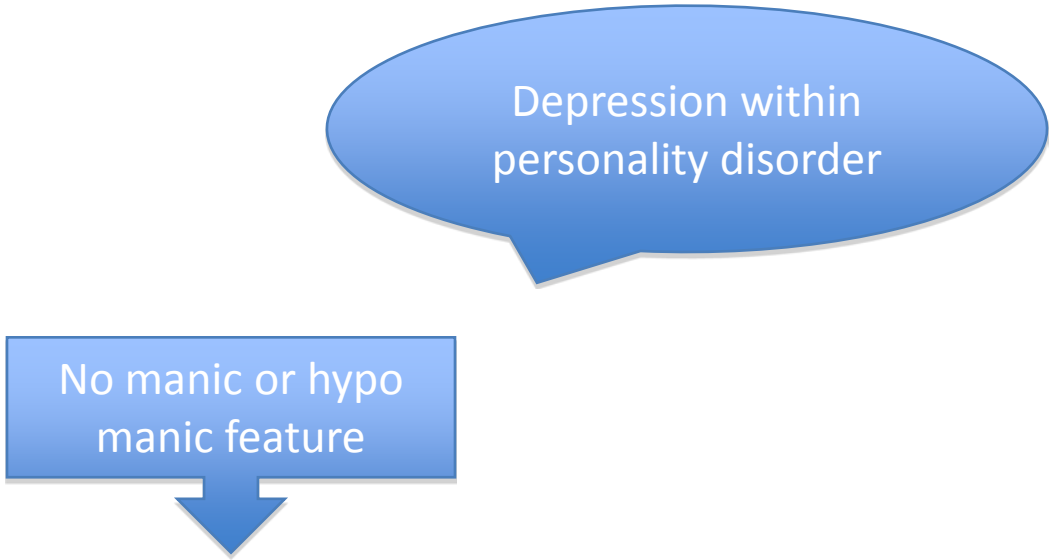


TRD - Common Diagnosis

1.Depressed Mood
2. Suicide ideation or attempt



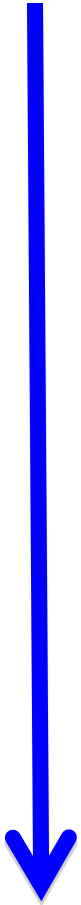
Focus on ‘symptoms constellation ’
exclusion of physical & psychiatric conditions



Differentiate treatment resistance from features of chronicity.

Towards a Comprehensive assessment of Depressive disorder.

Outcome



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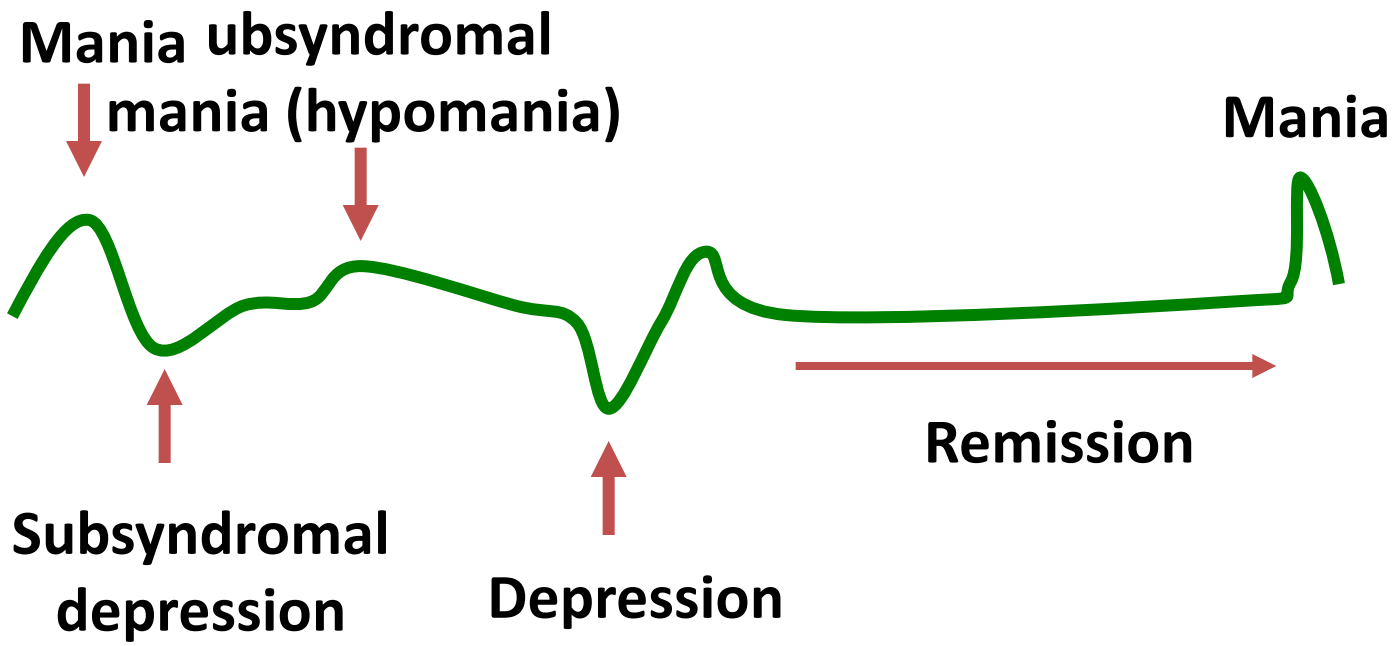
What clinical conditions may present as treatment resistant depression?

Bipolar Disorder is a Multidimensional Illness



Lifelong management of this lifelong illness involves targeting all phases of the disorder – atypical antipsychotics can play a major role

Vieta E, et al. Bipolar Disord 2005; 7 Suppl 4:21-33.

Bipolar II Depression

- Bipolar II disorder is a common disorder,
- prevalence of approximately 3-5%.
- Distinct clinical features
- The key to diagnosis - recognition of past hypomania,
- This is responsible for a significant rate of missed diagnosis,
- It is unclear if bipolar II disorder is over-represented in TRD

Bipolar II disorder: a review.
Berk M, Dodd S.
Bipolar Disord. 2005 Feb;7(1):11-21.

Bipolar diathesis for TRD

MISSED MANIA

BIPOLAR SPECTRUM DISORDER

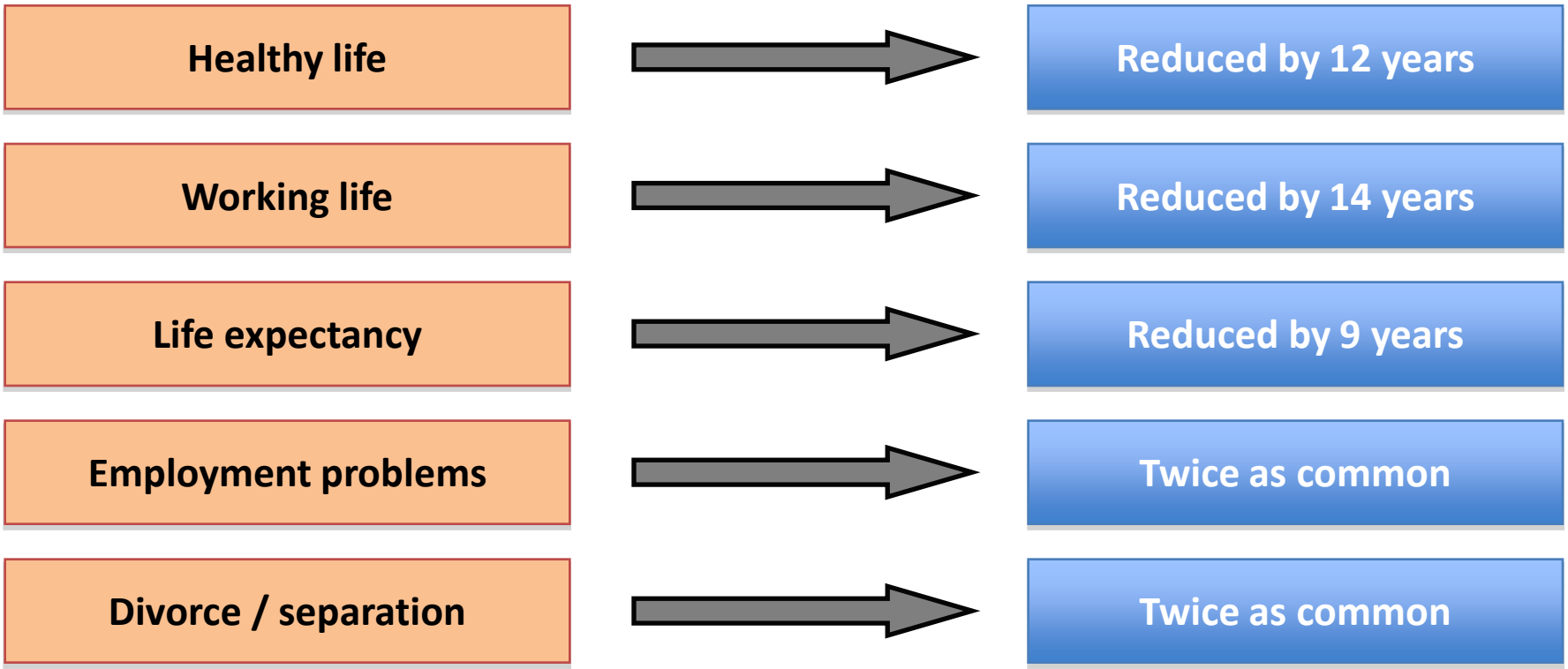
Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD.

Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, Calabrese JR, Nierenberg AA, Sachs GS.

Am J Psychiatry. 2009 Feb;166(2):173-81

Impact of Bipolar Disorder on Patients' Lives

Onset is usually during late adolescence and early adulthood, a time at which individuals are establishing their careers and building long-term relationships



Results for patients developing bipolar disorder in their mid-20s

Coryell et al 1993; Scott 1995

Atypical depression

- 70% of depression with atypical features met with DSM IV criteria for bipolar II
- 60% had antecedents cyclothymic & hyperthymic temperament
- Interpersonal sensitivity & atypical features were found to be powerful prospective predictors of bipolar II

Anxious – bipolar co morbidity

The evolving bipolar spectrum

- Prototype I,II ,III & IV
- Bipolar I – full-blown mania
- Bipolar 1 & ½ : depression with protected hippomania
- Bipolar II : depression with hippomania

Outcome status: What happens when TRD is treated?

- Not very encouraging.
- Nine outcome studies, Total N = 1279; follow-up duration - 1 to 10 years.
- In the short term, TRD was highly recurrent
- as many as 80% of those requiring multiple treatments relapsing within a year of achieving remission.
- For those with a more protracted illness, the probability of recovery within 10 years was about 40%.
- TRD was also associated with poorer quality of life and increased mortality.

Fekadu A,et al What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies Affect Disord. 2008 Nov 11.

How do we treat the Treatment resistance??
& what is the outcome?

Current (or future) Treatment Options [2,3]

Antidepressants:
SSRI, TCA
MAOI, SNRI & others

(STAR*D)[1] 50% of "real world" - MDD fail to achieve remission, even after four carefully monitored sequenced treatments.

1.Kennedy SH, Giacobbe P,Treatment resistant depression--advances in somatic therapies.Ann Clin Psychiatry. 2007 Oct-Dec;19(4):279-87.

2.Carvalho AF, Cavalcante JL, Castelo MS, Lima MC.Augmentation strategies for treatment-resistant depression: a literature review.J Clin Pharm Ther. 2007 Oct;32(5):415-28

3.. Tadić A, Lieb K. [Pharmacological therapy for therapy-resistant depression. New developments] Nervenarzt. 2007 Nov;78 Suppl 3:551-63;

.Safety & efficacy of antidepressants

1.Optimization
inadequate dose & inadequate duration

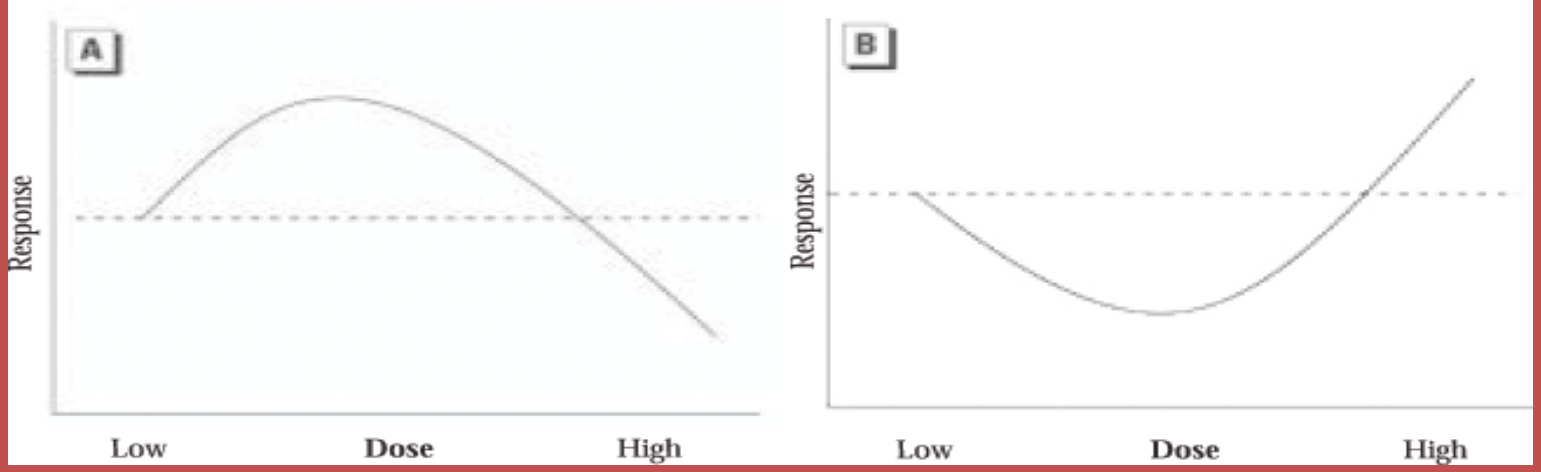
- Only 11 percent of patients receive adequate therapeutic therapy.
- Inadequate therapy - particularly prevalent in elderly patients.
- The clinician need to maximize the dosage or duration of therapy.
- Higher than recommended dosage: some patients benefit
- An adequate duration has been defined by some - four to six weeks. -- six weeks –10-12 weeks -- to elicit a full ADD response.

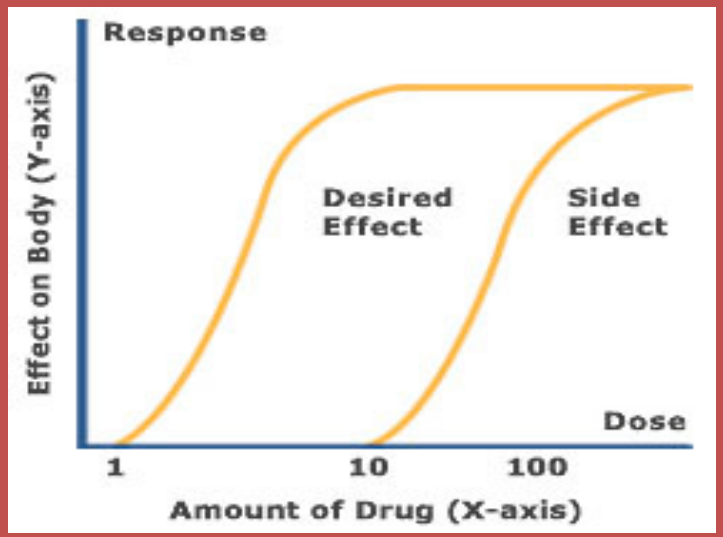
Selecting right ADD

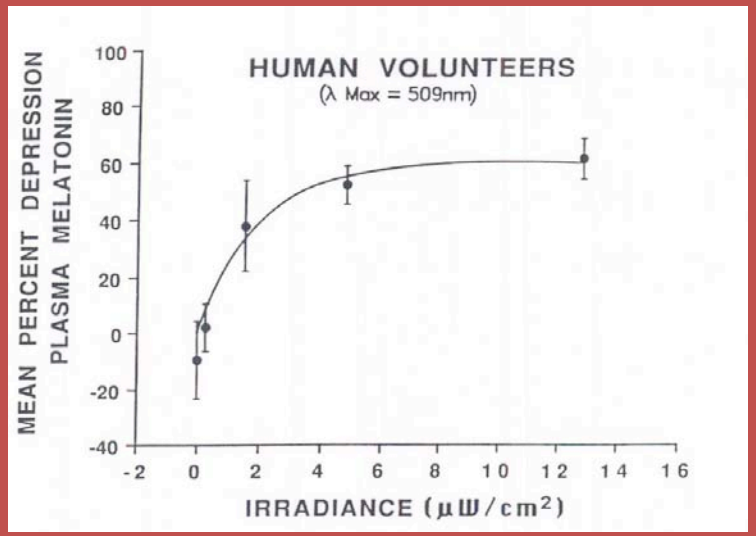
Have the cytochrome P450 (CYP450) genotyping test

Papakostas GI,et al A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor, with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. Eur Neuropsychopharmacol. 2008 Feb;18(2):122-7

Figure 1. Schematic forms of the hormetic dose response. (*A*) The most common form of the hormetic dose–response curve showing low-dose stimulatory and high-dose inhibitory responses (²- or inverted U-shaped curve). (*B*) The hormetic dose–response curve depicting low-dose reduction and high-dose enhancement of adverse effects (J- or U-shaped curve).

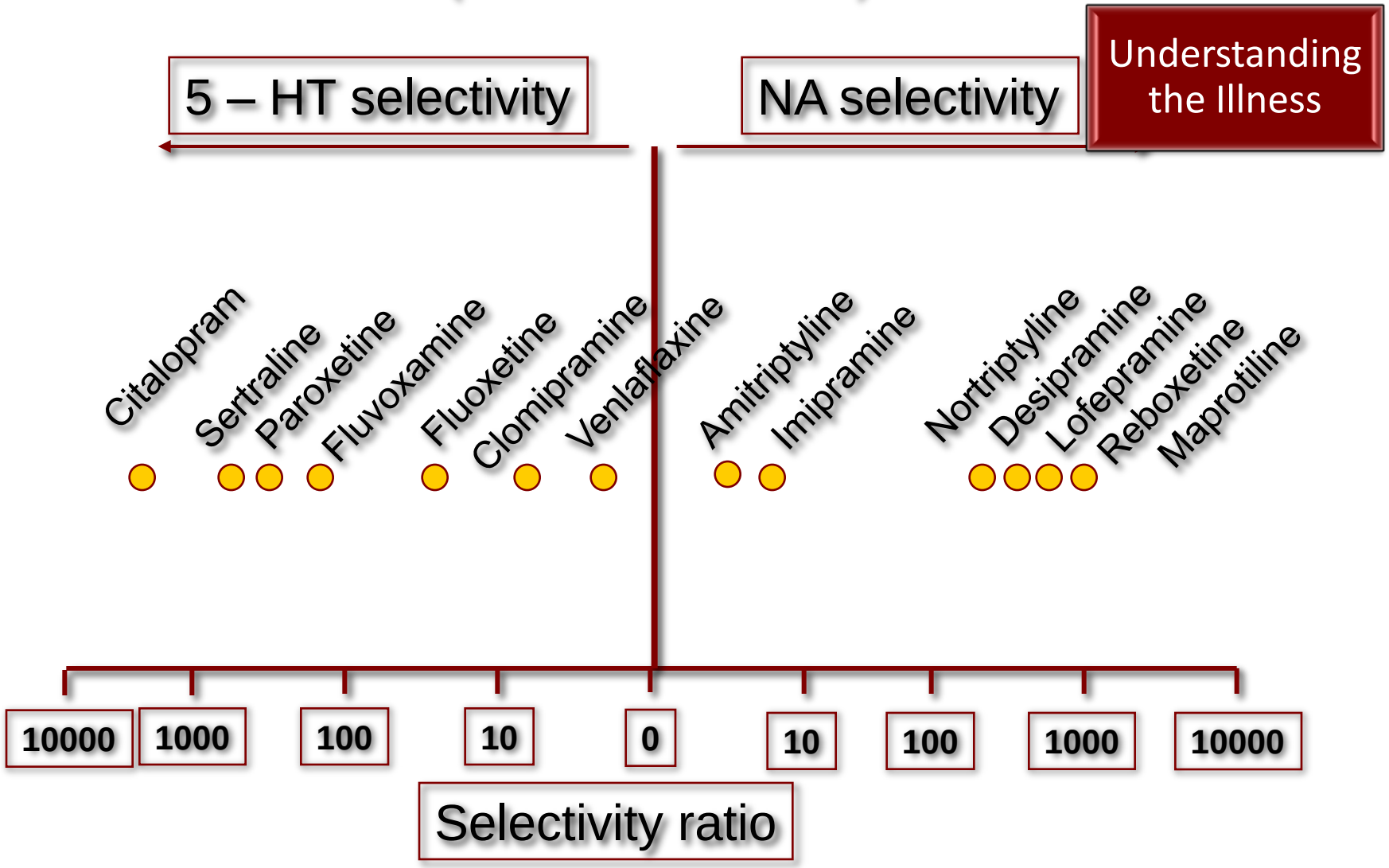






Selectivity Ratios for Uptake Inhibitor Antidepressants

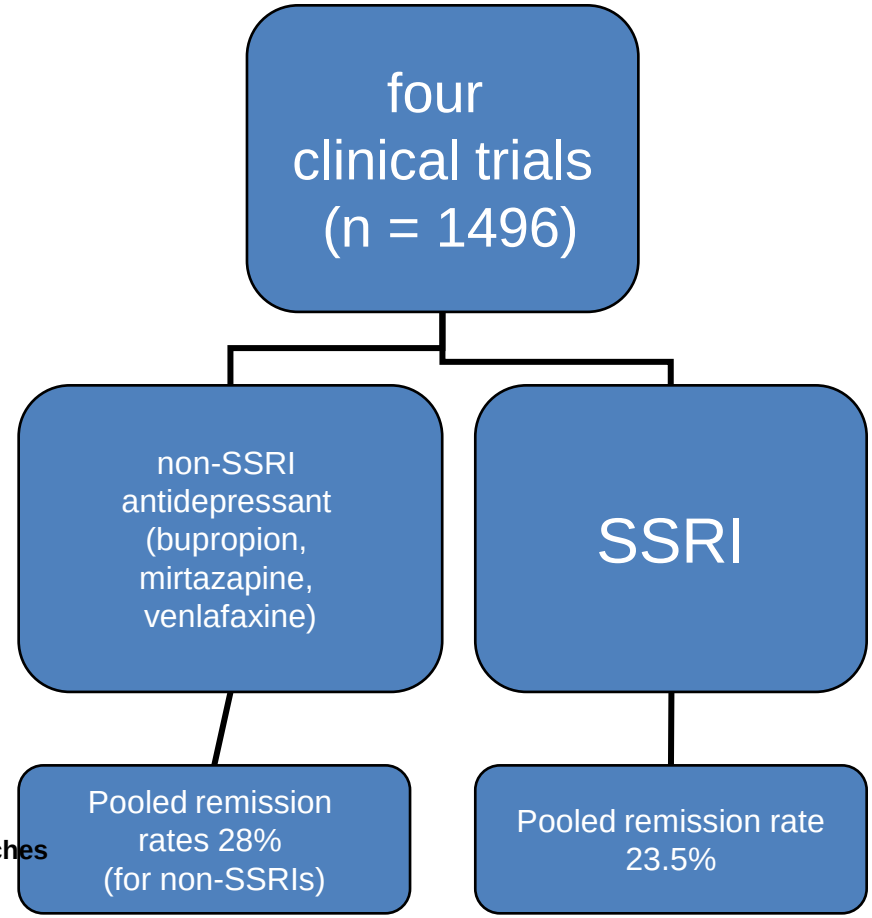
(measured in vitro)



The way Forward

Switch to another ADD? Which…??

- 1 in 4 patients on SSRI's have a response on 2nd drug:
  - Bupropion-SR
  - Sertraline
  - Venlafaxine-XR
- Within class
- 1st SSRI may be ineffective/ intolerable
- 2nd SSRI may be effective/ tolerable
- Out-of-class
- SSRI ----> TCA = 30 to 50%



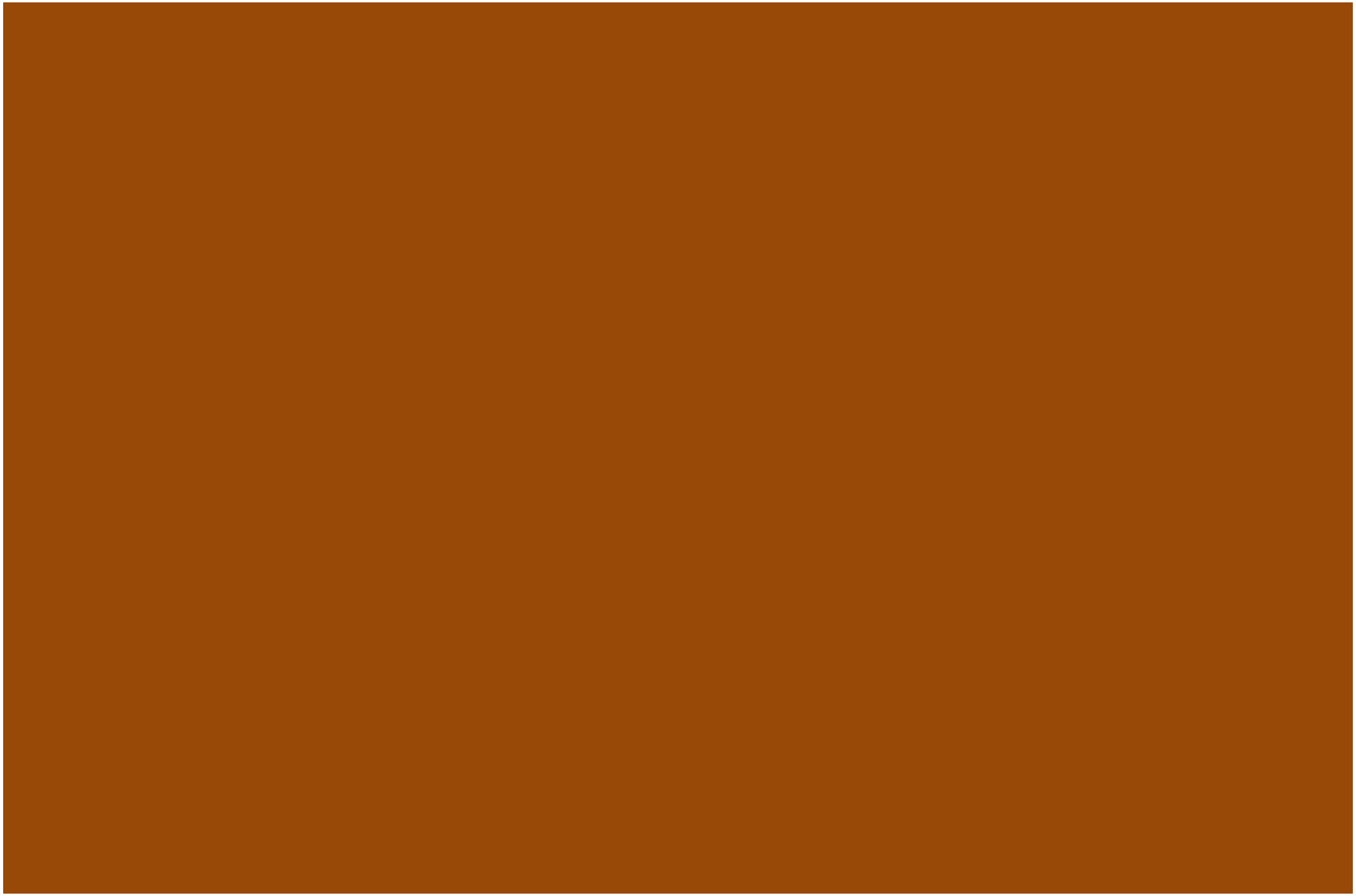
Papakostas GI et al **Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches Biol Psychiatry. 2008 Apr 1;63(7):699-704.**

3/18/09

3. Combination Therapy [1]

- Combination therapy involves the addition of a second antidepressant agent to the therapeutic regimen.
- Concurrent administration of two or more antidepressant agents (e.g., adding trazodone [Desyrel], desipramine [Norpramine] or bupropion [Wellbutrin] to fluoxetine) may result in a different therapeutic response than that produced by use of either drug alone.
- However, no double-blind, placebo-controlled studies recommend the usefulness of this practice.
- In addition, this approach does not allow for adequate evaluation of monotherapy and may lead to significant adverse effects or drug-drug interactions

1.Berlim MT, Fleck MP, Turecki G.Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview.Ann Med. 2008;40(2):149-59



4.Augmentation Therapy[1]

- Involves adding a second agent, but one that is not routinely regarded as an antidepressant.[2]

  - Dopaminergic agents, [7]
  - atypical antipsychotics, [7]
  - Psychostimulants, benzodiaze pines/hypnotics, hormones and
  - Anticonvulsants. [7]

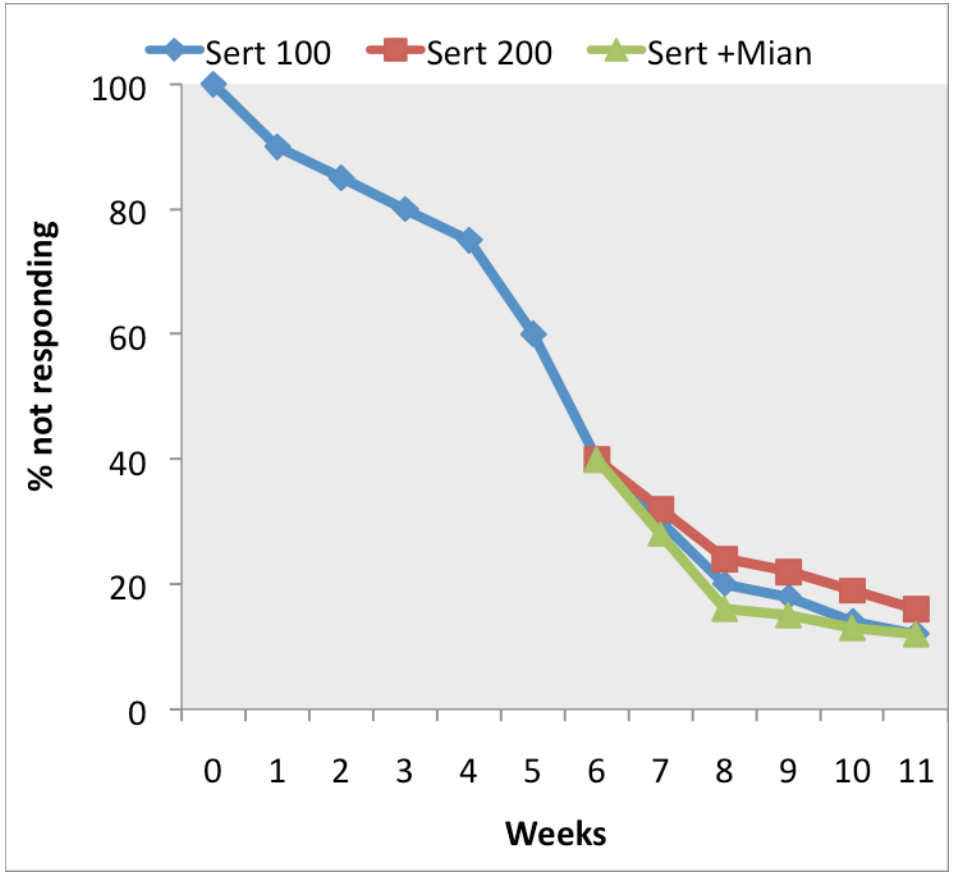
  - Testosterone [1]
  - Foliate [3]
  - Omega 3[4]
  - Lamotregene[5]
  - Olanzapine/fluoxetine[6]

1.Amiaz R, Seidman SN.Testosterone and depression in meCurr Opin Endocrinol Diabetes Obes. 2008 Jun;15(3):278-83.
2. Wijeratne C, Sachdev P. Treatment-resistant depression: critique of current approaches. Aust N Z J Psychiatry. 2008 Sep;42(9):751-62
3. Morris DW, Trivedi MH, Rush AJ. Folate and unipolar depression. J Altern Complement Med. 2008 Apr;14(3):277-85.
4.Owen C, Rees AM, Parker G The role of fatty acids in the development and treatment of mood disorders. Curr Opin Psychiatry. 2008 Jan;21(1):19-24.
5.McIntyre J, Moral MA. Spotlight on lamotrigine for depression.Drug News Perspect. 2006 Sep;19(7):427-30
6. Dodd S, Berk M. Olanzapine/fluoxetine combination for treatment-resistant depression: efficacy and clinical utility. Expert Rev Neurother. 2008 Sep;8(9):1299-306
7. Carvalho AF, et al Augmentation strategies for treatment-resistant depression: a literature review . J Clin Pharm Ther. 2007 Oct;32(5):415-28

Crucial questions

Progress

Shall I persist, increase or add?



Amitriptyline and clomipramine are more effective than SSRIs (but more side effects and more toxic in overdose)

The difference is that these drugs affect both serotonin (5HT) and noradrenaline

Other drugs that have a similar effect are:
Venlafaxine
Mirtazepine
Duloxetine

Licht & Qvitzau 2002

Are these also more effective?

Combining and Switching

Crucial questions

4b.Thyroid hormone: Low dose, short- term

- The thyroid hormone triiodothyronine (T3) appears to be a more effective than tetraiodothyronine (T4)
- Effective in small dosages; for example, 25 to 50 µg per day.
- T3 may be used to augment response to TCA, MAOI, and SSRIs.
- effective in 50 to 6%0 patients.
- Monitoring thyroid function
- T3 potentiates noradrenergic activity,
- Its mechanism of action is not clearly understood.
- Relatively safe, few AE – allergic x 2-3 weeks

4d.Buspirone.

- Anxiolytic.
- No specific/intrinsic antidepressant effects.
- Dosages of 15 to 30 mg /D x 3 Months : improved response – 2/3rd of patients.
- Full agonist at the presynaptic autoreceptor and partial agonist at the postsynaptic autoreceptor.
- Decreases extracellular serotonin concentrations over the short term.

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4e.Pramipexole

- Large effect size (0.6-1.1):
- With a low switching in bipolar patients (1% mania, 5% hypomania).
- The pooled discontinuation rate - 9%.
- Neuroprotective
- Effects on sleep architecture.
- SE in Parkinson's disease
- Sleep attacks,
- Compulsive behaviors
- Pathologic gambling,
- Restless legs syndrome;
- Psychosis
- Aiken CB.Pramipexole in psychiatry: a systematic review of the literature.J Clin Psychiatry. 2007 Aug;68(8):1230-6.

4f.Anticonvulsants

- Lamotregene
- Carbamezapine

- Triple Reuptake Inhibitors (TRI)
  - Target all three of brain's monoamines (serotonin, norepinephrine, dopamine)
  - Expected on the market by 2010
  - Better efficacy and tolerability, faster acting, less side effects, treats broader range of symptoms

4g.Novel Antipsychotics

1- combination (OFC) 2- Switch to AATPD

- SDA, beneficial
- 50% Response
- 25% Remission
- Olanzapine [1]
- According to results, Aripiprazole, Olanzapine, and Risperidone are reasonable choices as augmentation agents
- With only aripiprazole currently having an FDA(USA) indication for this use.[2]

Clozapine in medication- and electroconvulsive therapy-resistant, depressed inpatients: a case series

- **Quante A**, J Clin Psychopharmacol. 2007 Dec;27(6):715-7.

1. Selis MA, Peeters FP. Augmentation with atypical antipsychotics for the treatment of patients with a therapy-resistant depression: a review] Tijdschr Psychiatr. 2008;50(4):213-22
2. Philip NS, Carpenter LL, Tyrka AR, Price LH. Augmentation of antidepressants with atypical antipsychotics: a review of the current literature. J Psychiatr Pract. 2008 Jan;14(1):34-44

Summary of the Evidence Base for the Efficacy of Atypical Antipsychotics in Bipolar Disorder

	Acute Treatment		Maintenance / Continuation Treatment	
	Mania	**Depression**	**Mania**	**Depression**
Quetiapine	++	++	++	++
Olanzapine	++	+	++	+
Risperidone	++	?	++	+?
Aripiprazole	++	–	++	–
Ziprasidone	++	?	?	?
Asenapine	++	?	?	?
Paliperidone	++	?	?	?

++ = at least one good RCT showing clinically significant effects
+ = at least one RCT showing some effect
- = RCT evidence of a lack of clinically significant effects
? = uncertain or no controlled data available

Health Canada Approved Indications for Agents Used in the Treatment of Bipolar Disorder

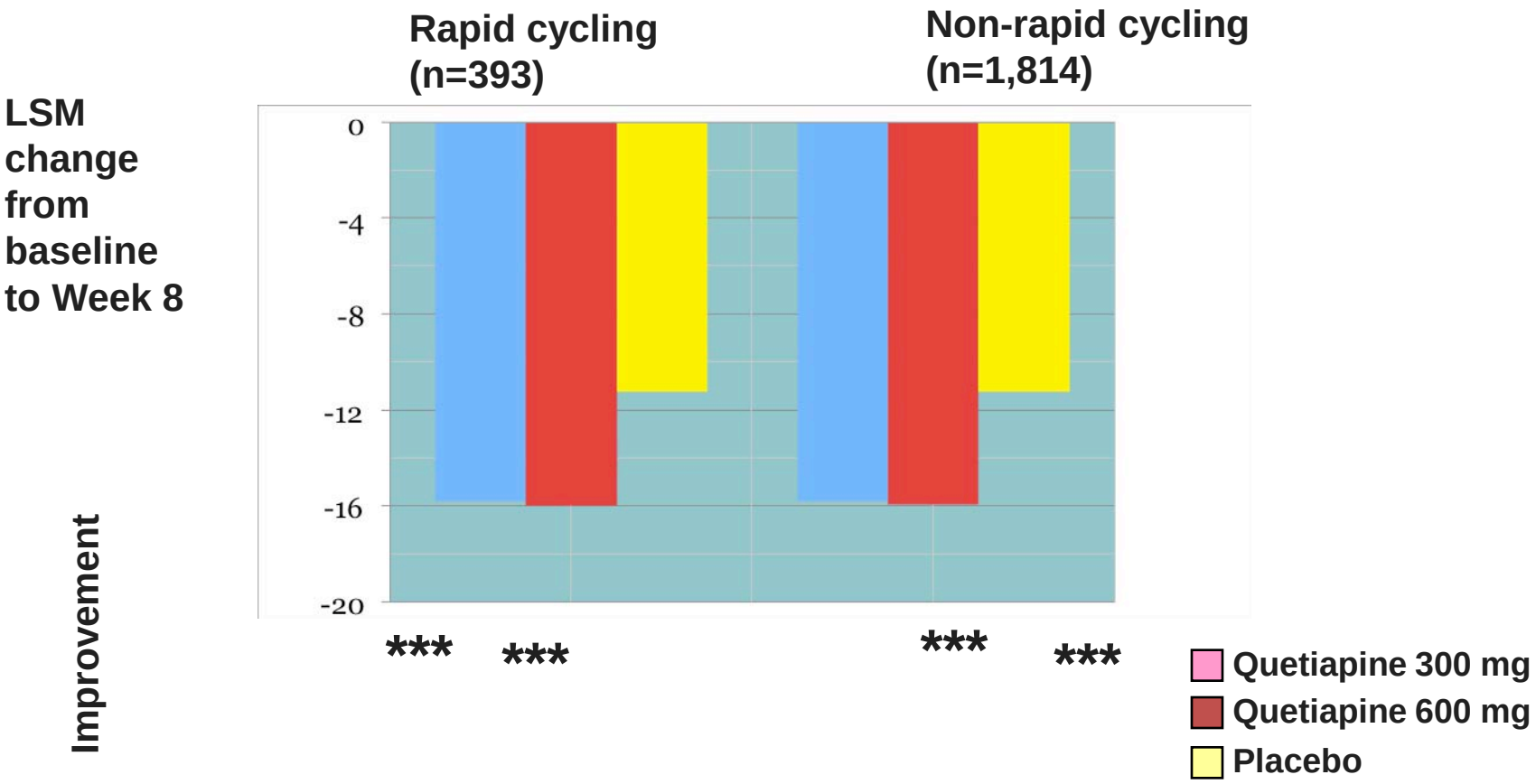
	Acute Bipolar Depression	Acute Mania	Maintenance Treatment
Agents			
ATYPICALS			
Clozapine			
Olanzapine		√	√*
Quetiapine (SEROQUEL XR)	√	√	
Risperidone		√	
Paliperidone			
Ziprasidone			
OTHER			
Carbamazepine		√	√+
Divalproex		√	
Lamotrigine			
Lithium		√	√

+ for use after treatment failure on traditional mood stabilizer

*See PM. Evaluation from 2 “time to relapse” trials with manic or mixed index episode

This chart does not imply comparable efficacy or safety profiles.

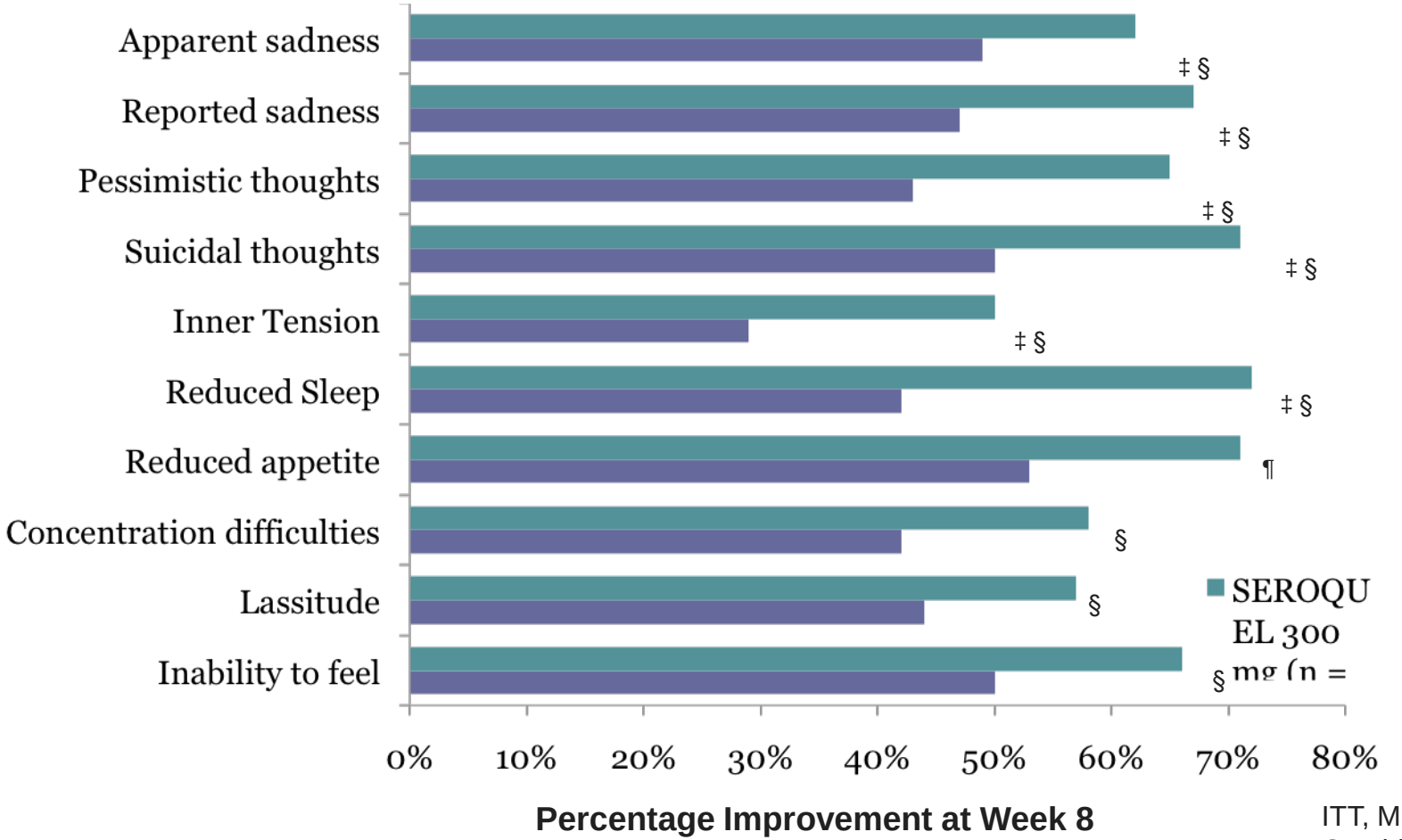
BOLDER & EMBOLDEN (acute phase): Change in MADRS Total Score



*** p<0.001 vs placebo ITT, LOCF
Baseline values: Rapid cycling - quetiapine 300 mg, 29.4; 600 mg, 29.5; placebo, 29.9
Non-rapid-cycling - quetiapine 300 mg, 28.7; 600 mg, 28.3; placebo, 28.9

BOLDER I & BOLDER II:MADRS Items at Week 8

At **Week 1**, significant improvement was seen in 6 out of 10 items‡



ITT, MMRM** Combined Studies

* Montgomery-Asberg Depression Rating Scale.

† Data combined from two 8-week, multicenter, randomized, double–blind, placebo-controlled, monotherapy bipolar depression trials.

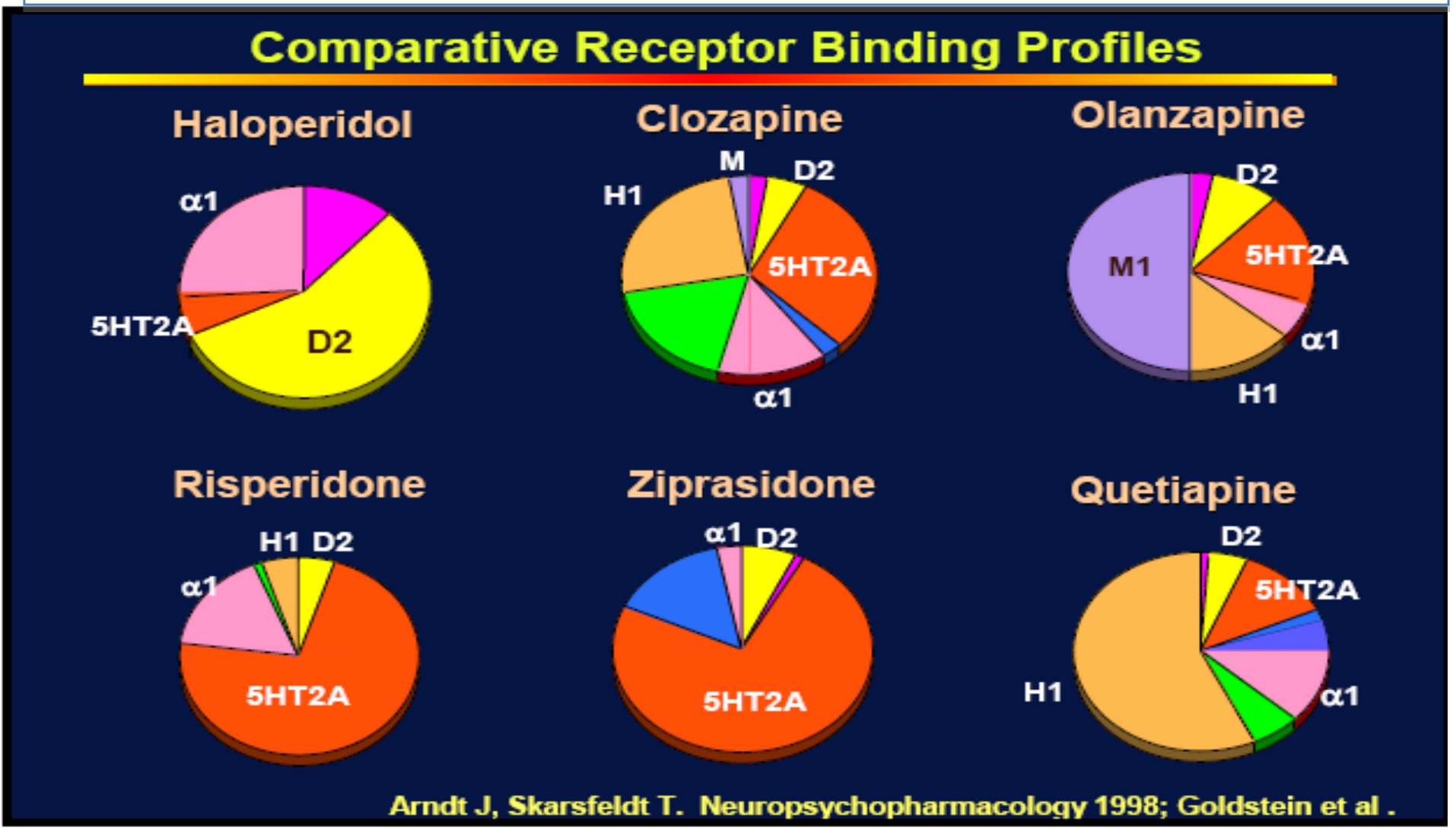
‡ $P < 0.05$ vs placebo at Week 1 § $P < 0.001$ vs placebo at Week 8 ¶ $P < 0.05$ vs placebo at Week 8.

Data on File, DA-SER-45.

How do we explain?

Why do Atypical antipsychotics have Antidepressant action?

A: Regional distribution of 5-HT System in the Brain??



Depression in schizophrenia : perspective in era of 'atypical antipsychotics'. Siris ,S.G.AJP 2000 ;157

ECT

- ECT in TRD
- average 14.6 months in their current episodes
- 6.2 years of their lifetime in depression.
- Failed to respond to an average of 5.4 different ADD
- (65.8%) responded
- (53.3%) achieved remission

.

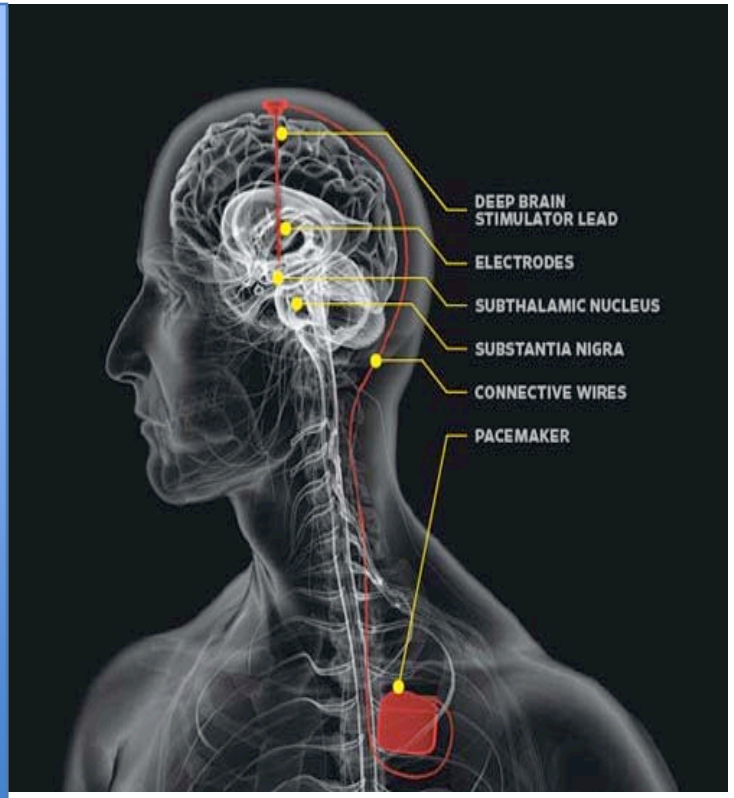
  - **Khalid N The effectiveness of electroconvulsive therapy in treatment-resistant depression: a naturalistic study. J ECT. 2008 Jun;24(2):141-5.**

- The acute effect is well established
  - Continuation Tx is required
  - In 1 study, within 24 weeks of achieving remission, 64% relapsed.[1]
  - TRD is predictive of post-ECT relapse
    - TRD patients at high risk for relapse: only 32% maintained response in next 12 months[2]

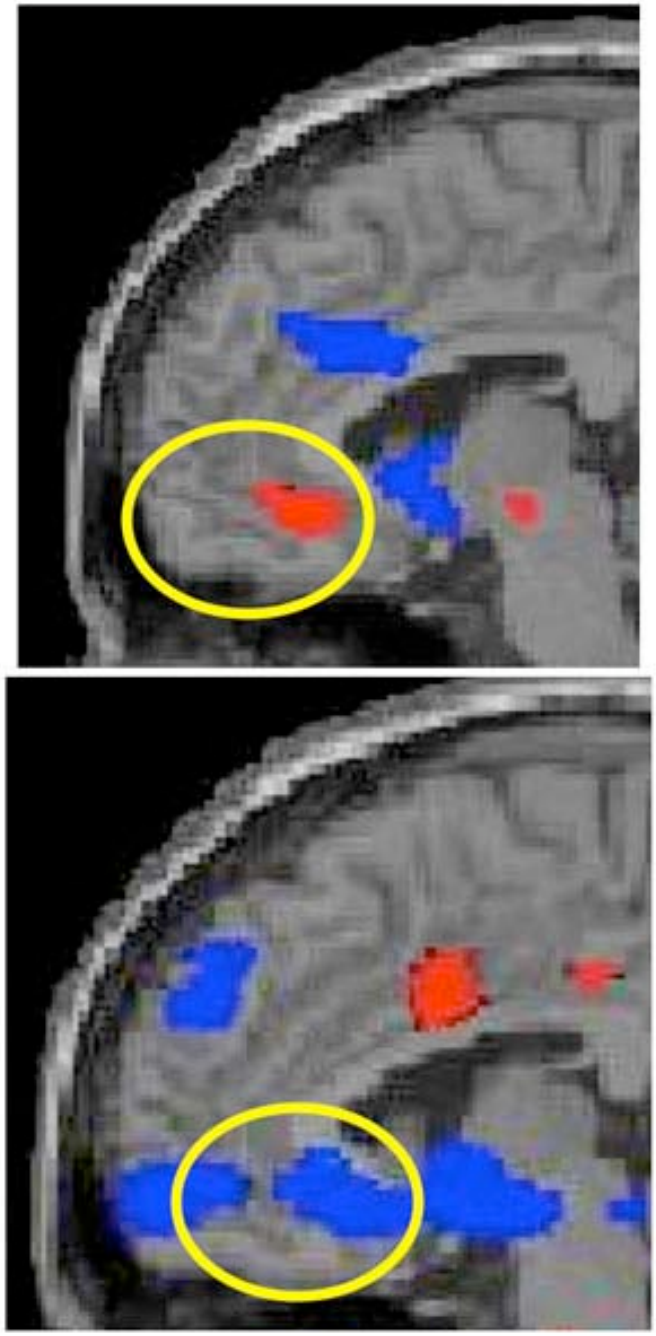
1. Sackeim et al, JAMA,2001;285:1299-1307.
2. Prudic J, et al Biol.Psychiatry,2004;55:301-312.

Deep Brain Stimulation (DBS): The Surgical option

- Five potential targets – identified :
- Ventral striatum/nucleus accumbens,
- Subgenual cingulate cortex (area 25),
- Inferior thalamic peduncle,
- Rostral cingulate cortex (area 24a), and
- Lateral habenula.



Hauptman JS, DeSalles AA, Espinoza R, Sedrak M, Ishida W.Potential surgical targets for deep brain stimulation in treatment-resistant depression.Neurosurg Focus. 2008;25(1):E3



Deep Brain stimulation

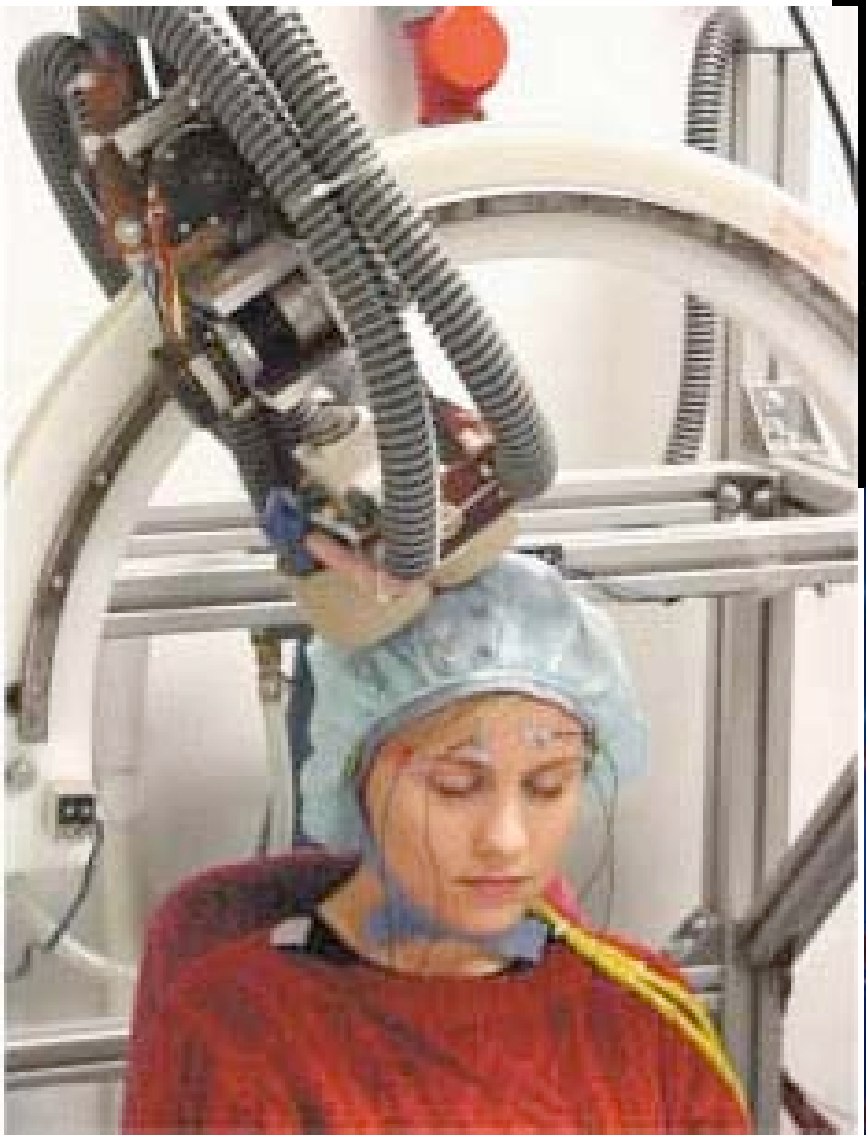
Efficacy: [Subcallosal cingulate gyrus] for treatment-resistant depression

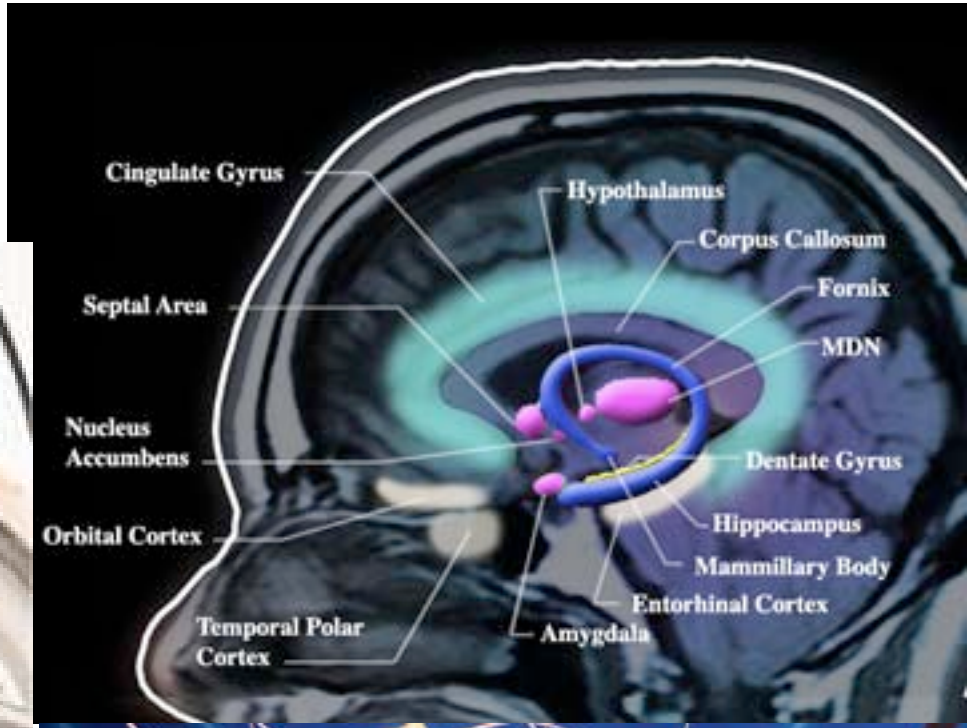
- There were both early and progressive benefits to DBS. One month after surgery,
- 35% - response
- 10%- remission.
- Six months after surgery,
- 60% -responders
- 35% -remission,
- Benefits maintained at 12 months.

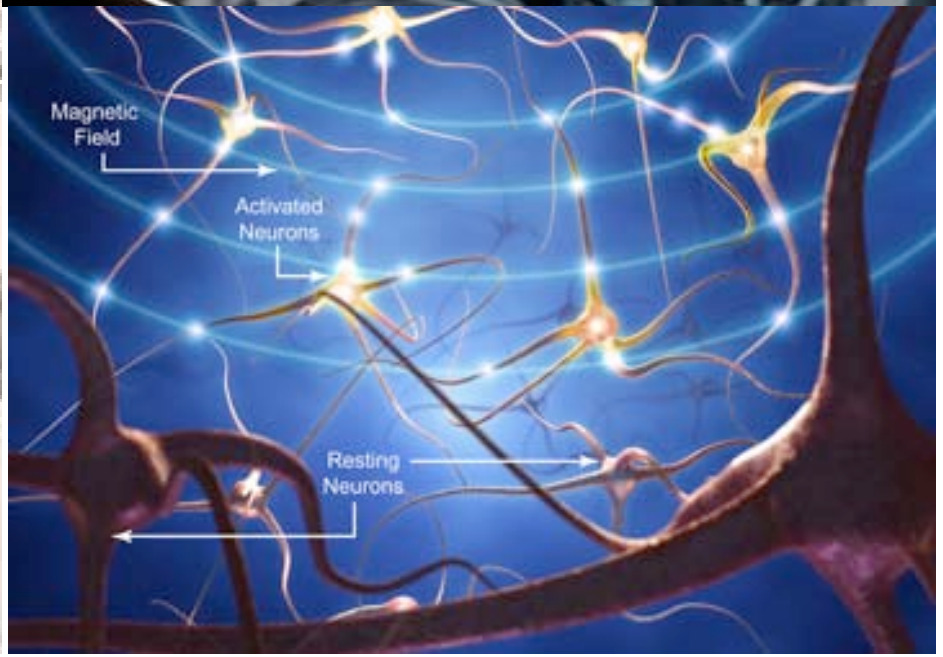
- Reduced activity in this region (shown in blue at bottom) is seen with six months of chronic deep brain stimulation.
- This reduction correlates with the antidepressant effect of the treatment.
- (Images courtesy of Helen Mayberg)

- www.dana.org/uploadedImages/Images/Spotlight_Images/Cerebrum_DBS_2008-03_spot.jpg

rTMS




Cingulate Gyrus
Hypothalamus
Corpus Callosum
Fornix
Septal Area
MDN
Nucleus Accumbens
Dentate Gyrus
Orbital Cortex
Hippocampus
Mammillary Body
Entorhinal Cortex
Temporal Polar Cortex
Amygdala


Magnetic Field
Activated Neurons
Resting Neurons

Review Paper

Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Metaanalysis

Raymond W Lam, MD, FRCPC[1]; Peter Chan, MD, FRCPC[2];
Michael Wilkins-Ho, MD, FRCPC[3]; Lakshmi N Yatham, MBBS, MRCPsych (UK), FRCPC[4]

Vegus Nerve stimulation (VNS)

- Well tolerated
- A safe and feasible procedure, despite its limitations
- Acts via innervation of the nucleus tractus solitarius, with secondary projections to limbic and cortical structures that are involved in mood regulation
- Efficacy data not randomized
- Surgical procedure
- Non-acute antidepressant effect
- MRI contraindication
- Battery

1.Daban C, et al Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. J Affect Disord. 2008 Sep;110(1-2):1-15
2.Nemeroff CBVNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology. 2006 Jul;31(7):1345-55.

Preventing treatment resistance

Treating treatment resistance