




# The Assessment of Treatment Resistance in Depressive Disorders: Reliability and Validity

Center for Medicare and Medicaid Services,  
MEDCAC on Treatment Resistant Depression

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Harold A. Sackeim, PhD

Professor, Departments of Psychiatry and Radiology,  
College of Physicians and Surgeons of Columbia University



Emeritus Chief, Department of Biological Psychiatry,  
New York State Psychiatric Institute

Founding Editor,  
Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation

# Disclosures

- Brain Stimulation Industry: Consultant (Mild) Brainsway, Cervei Neurotech, Magstim, NeoSync, Neuronetics (Advisory Board), NeuroPace ; Consultant and Research Support (Major) Cyberonics, Inc. and MECTA
- Pharmaceutical Industry: Consultant (Mild) Novartis and Wyeth; Speaker's Bureau and Consultant (Major) Eli Lilly, Consultant and Research Support (Major) Pfizer
- Inventor: Focal Electrically Administered Seizure Therapy (FEAST) (Patent as Inventor) (Mild)
- Inventor: Magnetic Seizure Therapy (Mild)

# Antidepressant Treatment History Form (ATHF)

## The Definition and Meaning of Treatment-Resistant Depression

Sackeim, H.A. The definition and meaning of treatment-resistant depression. J Clin Psychiatry 2001, 62 (Suppl 16):10-17.

- ATHF most commonly used instrument to assess TRD in studies of both pharmacological and brain stimulation interventions
- Retrospective evaluation of adequacy of each treatment trial in current or previous episodes
- Multiple sources of information (patient, provider, pharmacy)
- Explicit criteria for dose and duration of interventions
- Accounts for adherence and outcome
- Each trial rated on 1-5 potency scale, with threshold of 3 for adequacy
- Established augmentation strategies increase potency score
- Combination antidepressant & antipsychotic required for psychotic depression; different criteria for lithium and convulsants in bipolar vs. unipolar depression

**TCA/Tetracyclic**

I. Amitriptyline (Elavil, Endep), imipramine (Tofranil), desipramine (Norpramin, Pertofrane), trimipramine (Surmontil), clomipramine (Anafranil), maprotiline (Ludiomil), doxepin (Sinequan, Adapin), nortriptyline.

By blood level: imipramine and desipramine only; levels take precedence

4 = 4 wk or more and desipramine level  $\geq$  125 ng/mL

4 = 4 wk or more and imipramine + desipramine level  $\geq$  225 ng/mL

By dosage:

1 = any drug < 4 wk or any drug < 100 mg/d

2 = 4 wk or more and 100–199 mg/d

3 = 4 wk or more and 200–299 mg/d

4 = 4 wk or more and  $\geq$  300 mg/d

II. Nortriptyline (Pamelor, Aventyl)

By blood level: levels take precedence

1 = nortriptyline < 4 wk

2 = 4 wk or more and level < 50 ng/mL

3 = 4 wk or more and level 50–99 ng/mL

4 = 4 wk or more and level  $>$  100 ng/mL

By dosage:

1 = nortriptyline < 4 wk or 4 wk or more and nortriptyline < 50 mg/d

2 = 4 wk or more and nortriptyline 50–75 mg/d

3 = 4 wk or more and nortriptyline 76–100 mg/d

4 = 4 wk or more and nortriptyline  $>$  100

III. Protriptyline (Vivactil)

1 = drug < 4 wk or 4 wk or more and dosage  $\leq$  30 mg/d

2 = 4 wk or more and dosage 31–40 mg/d

3 = 4 wk or more and dosage 41–60 mg/d

4 = 4 wk or more and dosage  $>$  60 mg/d

Notes:

For TCA-MAOI combinations: score each agent alone, as a separate trial.

For TCA-paroxetine/fluoxetine combination trials: after 1 week on 20 mg of paroxetine or fluoxetine, the dosage equivalent of the TCA should be doubled to determine resistance rating.

**SSRIs**

I. Fluoxetine (Prozac), citalopram (Celexa)

1 = drug < 4 wk or 4 wk or more and dosage 1–9 mg/d

2 = 4 wk or more and dosage 10–19 mg/d

3 = 4 wk or more and dosage 20–39 mg/d

4 = 4 wk or more and dosage  $\geq$  40 mg/d

II. Fluvoxamine (Luvox)

1 = drug < 4 wk or drug < 100 mg/d

2 = 4 wk or more and 100–199 mg/d

3 = 4 wk or more and 200–299 mg/d

4 = 4 wk or more and  $\geq$  300 mg/d

III. Paroxetine (Paxil)

1 = less than 4 wk or 4 wk or more and dosage 1–9 mg/d

2 = 4 wk or more and dosage 10–19 mg/d

3 = 4 wk or more and dosage 20–29 mg/d

4 = 4 wk or more and dosage  $\geq$  30 mg/d

IV. Sertraline (Zoloft)

1 = drug < 4 wk or 4 wk or more and dosage < 50 mg/d

2 = 4 wk or more and dosage 50–99 mg/d

3 = 4 wk or more and dosage 100–199 mg/d

4 = 4 wk or more and dosage  $\geq$  200 mg/d

**Other Antidepressants**

I. Bupropion (Wellbutrin)

1 = drug < 4 wk or 4 wk or more and dosage < 150 mg/d

2 = 4 wk or more and dosage 150–299 mg/d

3 = 4 wk or more and dosage 300–449 mg/d

4 = 4 wk or more and dosage  $\geq$  450 mg/d

II. Mirtazapine (Remeron)

1 = less than 4 wk or 4 wk or more and dosage < 15 mg/d

2 = 4 wk or more and dosage 15–29 mg/d

3 = 4 wk or more and dosage 30–44 mg/d

4 = 4 wk or more and dosage  $\geq$  45 mg/d

III. Nefazodone (Serzone)

1 = drug < 4 wk or 4 wk or more and dosage < 150 mg/d

2 = 4 wk or more and dosage 150–299 mg/d

3 = 4 wk or more and dosage 300–599 mg/d

4 = 4 wk or more and dosage  $\geq$  600 mg/d

IV. Trazodone (Desyrel), amoxapine (Asendin)

1 = drug < 4 wk or 4 wk or more and dosage < 200 mg/d

2 = 4 wk or more and dosage 200–399 mg/d

3 = 4 wk or more and dosage 400–599 mg/d

4 = 4 wk or more and dosage  $\geq$  600 mg/d

Note: Amoxapine will also receive an antipsychotic rating.

V. Venlafaxine (Effexor and Effexor XR)

1 = less than 4 wk or 4 wk or more and dosage < 75 mg/d

2 = 4 wk or more and dosage 75–224 mg/d

3 = 4 wk or more and dosage 225–374 mg/d

4 = 4 wk or more and dosage  $\geq$  375 mg/d



**MAOIs****I. Phenelzine (Nardil)**

- 1 = drug < 4 wk or 4 wk or more and dosage  $\leq$  30 mg/d
- 2 = 4 wk or more and dosage 31–60 mg/d
- 3 = 4 wk or more and dosage 61–90 mg/d
- 4 = 4 wk or more and dosage 91 mg/d or greater

**II. Moclobemide**

- 1 = less than 4 wk or 4 wk or more and dosage < 150 mg/d
- 2 = 4 wk or more and dosage 150–299 mg/d  
(100 mg–200 mg = 30 mg phenelzine)
- 3 = 4 wk or more and dosage 300–599 mg/d  
(300 mg = 60 mg phenelzine)
- 4 = 4 wk or more and dosage  $\geq$  600 mg/d  
(600 mg = 90 mg phenelzine)

**III. Selegiline (Eldepryl)**

- 1 = drug < 4 wk or 4 wk or more and dosage  $\leq$  20 mg/d
- 2 = 4 wk or more and dosage 21–40 mg/d
- 3 = 4 wk or more and dosage 41–59 mg/d
- 4 = 4 wk or more and dosage  $\geq$  60 mg/d

**IV. Tranylcypromine (Parnate), isocarboxazid**

- 1 = drug < 4 wk or 4 wk or more and dosage  $\leq$  20 mg/d
- 2 = 4 wk or more and dosage 21–40 mg/d
- 3 = 4 wk or more and dosage 41–60 mg/d
- 4 = 4 wk or more and dosage  $\geq$  61 mg/d

**Notes:**

MAOI inhibition: 80% inhibition will rate 4.  
For TCA-MAOI combinations, score each agent considered alone.  
TCA/SSRI and any other combinations, e.g., SSRI/bupropion, should be treated as TCA/MAOI combinations; rate each medication separately.

**Lithium****I. Lithium alone**

- For bipolar patients: levels take precedence over dosage
- 1 = drug < 4 wk or 4 wk or more and level  $\leq$  0.4 mEq/L or 4 wk or more and dosage < 600 mg/d for any duration
- 2 = 4 wk or more and level 0.41–0.6 mEq/L or 4 wk or more and dosage 600–899 mg/d
- 3 = 4 wk or more and level > 0.6 mEq/L or 4 wk or more and dosage  $\geq$  900 mg/d

Unipolar patients can receive a maximum rating of 2 for lithium alone.

**II. Lithium as an augmenting agent**

- 4 = antidepressant drugs (TCAs, SSRIs, others, MAOIs) rated level 3 and lithium for at least 2 wk
- Carbamazepine rated level 3 and lithium for at least 2 wk
- 5 = antidepressant drugs (TCAs, SSRIs, other antidepressants, MAOIs) rated level 4 and lithium for at least 2 wk

**ECT****I. Unilateral or unknown ECT**

- 1 = 1–3 unilateral ECT
- 2 = 4–6 unilateral ECT
- 3 = 7–9 unilateral ECT
- 4 = 10–12 unilateral ECT
- 5 = 13 or more unilateral ECT

**II. Bilateral ECT**

- 1 = 1–3 bilateral ECT
- 2 = 4–6 bilateral ECT
- 3 = 7–9 bilateral ECT
- 5 = 10 or more bilateral ECT

**Notes:**

A point is added to an ECT trial if the patient has had  $\geq$  7 adequate bilateral treatments. The highest rating is a 5.

If ECT and antidepressant medication are given simultaneously, this does not constitute a combination/augmentation trial. Each should be rated separately.

**Anticonvulsants****I. Carbamazepine (Tegretol)****For bipolar patients:**

- 1 = Carbamazepine < 4 wk or 4 wk or more and level < 6 mEq/L
- 2 = 4 wk or more and level 6–7.9 mEq/L
- 3 = 4 wk or more and level  $\geq$  8 mEq/L

Note: Unipolar patients can receive a maximum rating of 2 for carbamazepine alone.

**II. Lamotrigine (Lamictal)****For bipolar patients:**

- 1 = drug < 4 wk or 4 wk or more and dosage < 50 mg/d
- 2 = 4 wk or more and dosage 50–199 mg/d
- 3 = 4 wk or more and dosage  $\geq$  200 mg/d

Note: Unipolar patients can receive a maximum rating of 2 for lamotrigine alone.

**III. Gabapentin (Neurontin)****For bipolar patients:**

- 1 = drug < 4 wk or 4 wk or more and dosage  $\leq$  800 mg/d
- 2 = 4 wk or more and dosage  $\geq$  1600 mg/d

Note: Unipolar patients can receive a maximum score of 1 for gabapentin alone.

**IV. Clonazepam (Klonopin), valproic acid (Depakene), and topiramate (Topamax) can be rated 1 if used alone; they are not considered augmenting agents****Benzodiazepines****I. Alprazolam (Xanax)**

- 1 = alprazolam < 4 wk or 4 wk or more and dosage < 4 mg/d
- 2 = 4 wk or more and dosage  $\geq$  4 mg/d

**II. Other benzodiazepines**

- 1 = any dosage for any duration
- Note: These drugs are not considered augmenting agents.

**Miscellaneous****I. Stimulants, e.g., dextroamphetamine (Dexedrine), methylphenidate (Ritalin), pemoline (Cylert)**

- 1 = any dosage for any duration
- Note: These drugs are not considered augmenting agents.

**II. Antipsychotics**

- 1 = any dosage for any duration
- Note: These drugs are not considered augmenting agents.

**III. Antipsychotics**

- 1 = when used in nonpsychotic patients and should be rated together into one continuous trial, no matter how many different neuroleptics were given

**IV. Clonidine (Catapres), L-tryptophan, thyroid hormones (e.g., liothyronine [Cytomel, Triostat], L-thyroxine [Levothyroid, Synthroid]), estrogen, fenfluramine**

- 0 = any dosage for any duration
- Note: These drugs are not considered augmenting agents.

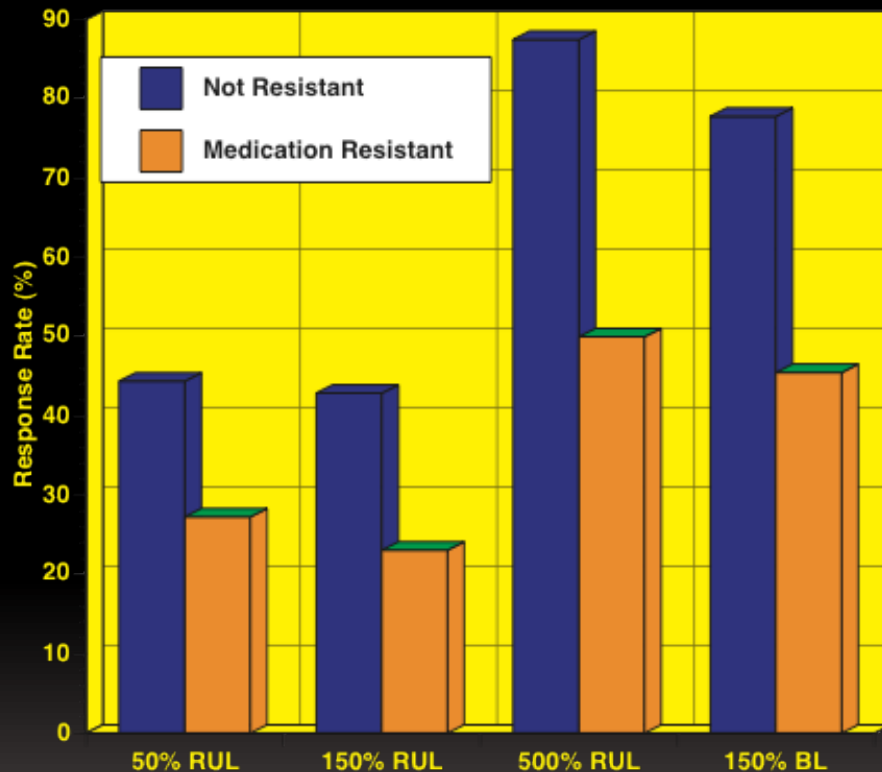
**V. Sedatives (buspirone [BuSpar], zolpidem [Ambien], lorazepam**

- [Ativan], clonazepam [Klonopin], and diphenhydramine [Benadryl])
- 1 = any dosage for any duration when used as a psychotropic

Note: If the patient uses different sedatives, with the exception of alprazolam, it should be rated as one continuous trial.

**VI. Phototherapy in any form: 1****VII. Herbal agents and uncertain somatic therapies (e.g., St. John's Wort, repetitive transcranial magnetic stimulation, vagus nerve stimulation) all receive a score of 1.**

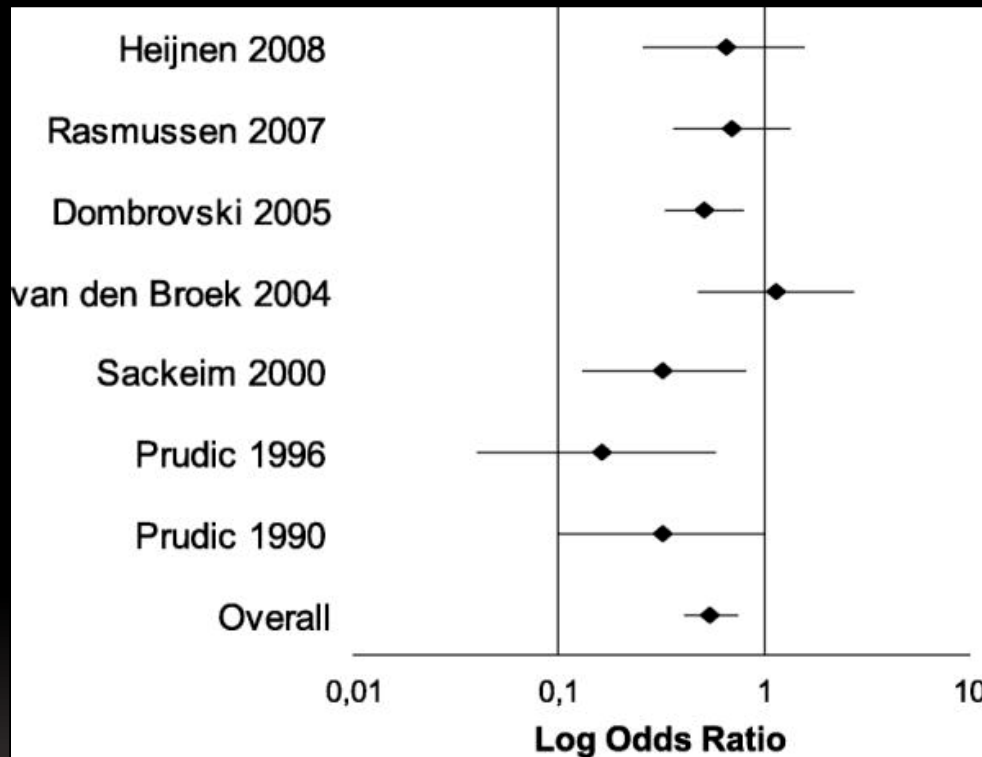
# Treatment Resistance and Prediction of Acute ECT Outcome



- Efficacy highly dependent of electrode placement and electrical dosage
- Across all types of ECT, treatment resistance exerts profound effect
- Remission rates among medication resistant still higher than with alternative interventions

Sackeim et al.: A prospective, randomized, double-blind comparison of bilateral and right unilateral ECT at different stimulus intensities. *Arch Gen Psychiatry*, 2000, 57:425-437.

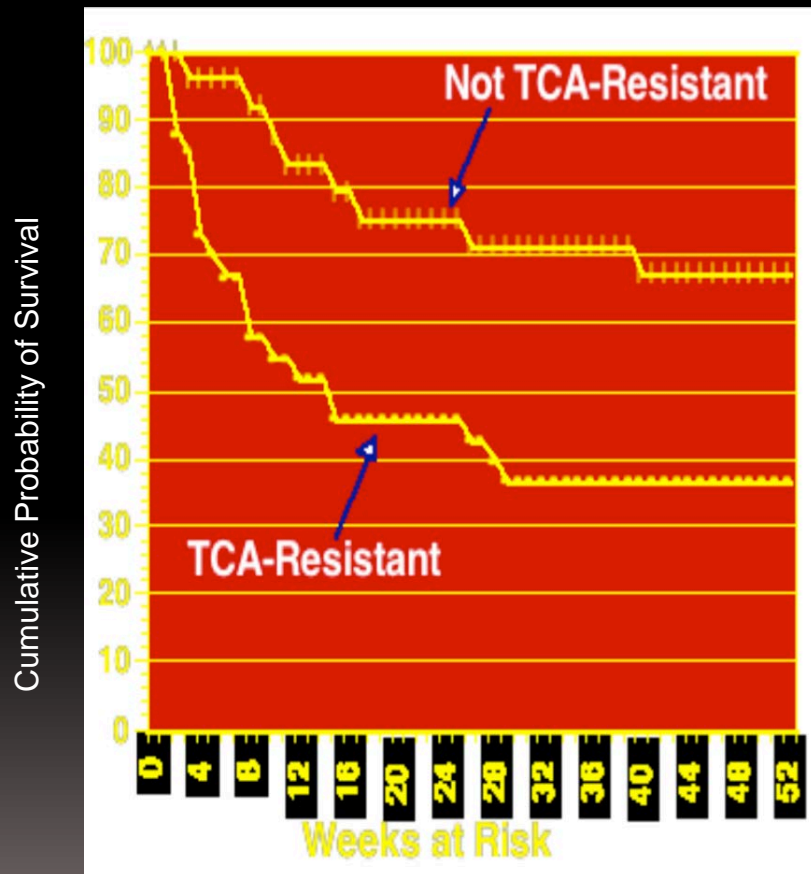
# Treatment Resistance and ECT Outcome



Heijnen et al. J Clin Psychopharm, 2010

- Medication resistance consistently tied to poorer antidepressant outcome
- In meta-analysis, response rates for resistant and non-resistant patients was 48% and 65%, respectively. OR = 0.52
- Little information on predictive power of specific regimens; does a SSRI trial convey same information as a TCA-Li trial?

# Relapse PostECT: Impact of PreECT Medication Resistance

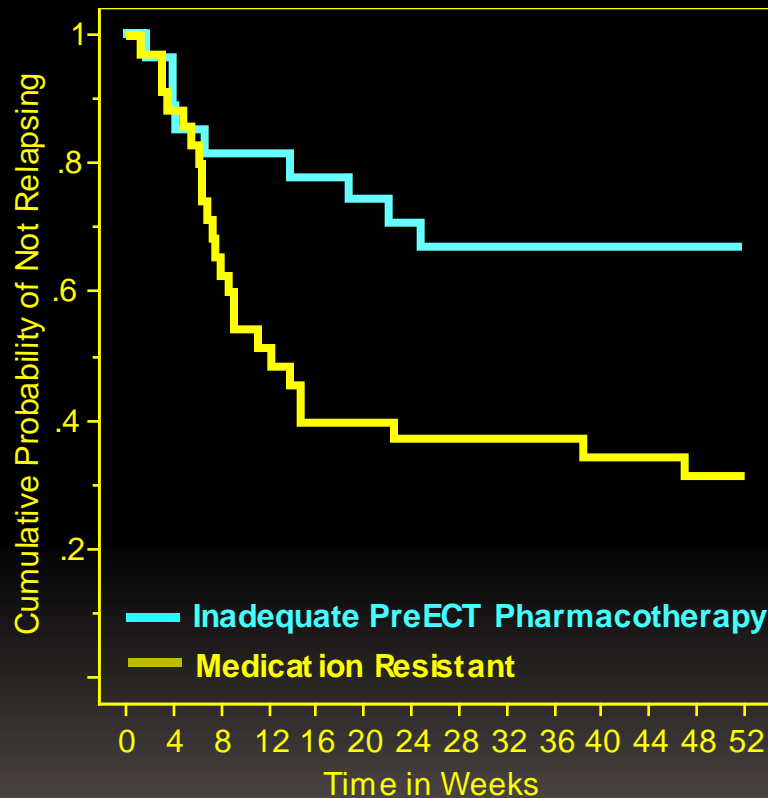


- Medication resistant patients relapse at twice the rate of patients who did not receive an adequate TCA trial before ECT (64% vs. 32%)

Sackeim et al. J Clin Psychopharm (1990)



# Independent Replication: PreECT Medication Resistance Predicts PostECT Relapse

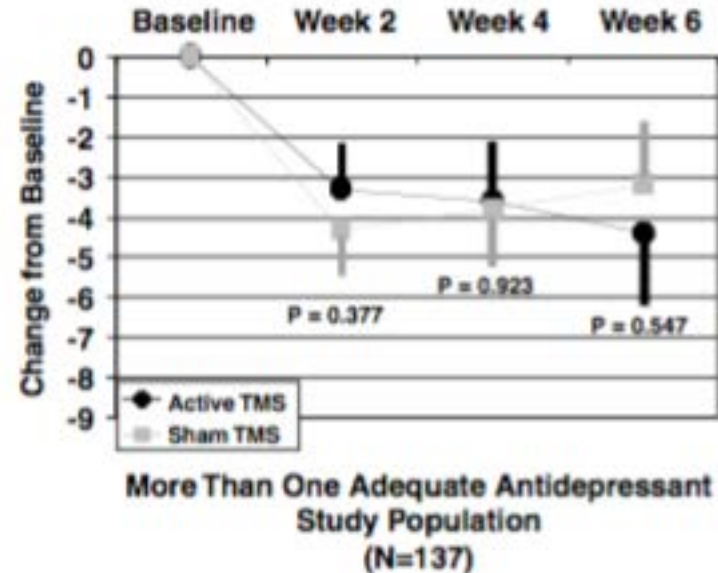
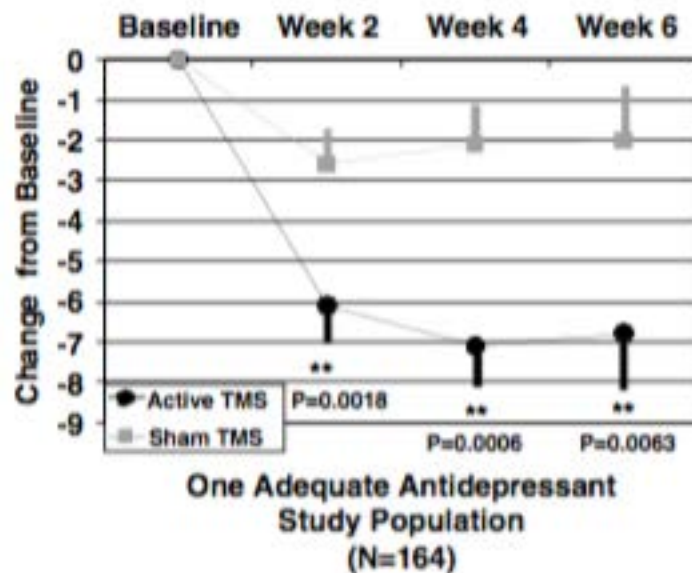


- Relapse was more than twice as likely among medication-resistant patients (68.6%) compared to patients who had not received an adequate medication trial prior to ECT (33.3%), likelihood ratio = 5.96,  $P=0.01$ .

# General Observations on Assessment of TRD

- Patients typically undergo twice as many treatment trials compared to the number of adequate trials (“Clinical Trials vs. Research Quality Trials”)
- Various studies examined the predictive power of total potency score, total number of trials, and total number of adequate trials. The latter is strongest predictor of efficacy of future interventions
- Assessment of TRD predictive of both immediate outcome of future intervention, as well as relapse given acute remission following that intervention
- Relevance for Medicare population: Approximately 2/3s of the ECT samples were 65 years or older. Medicare beneficiaries due to disability also represented

# Treatment Resistance Predicts Antidepressant Efficacy of rTMS



Lisanby et al.: Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*, 2009, 34:522-534.

- Post hoc findings using a modified version of ATHF were instrumental in obtaining FDA approval for rTMS in MDD and influencing labeling
- The other large, multi-site, active sham controlled study (sponsored by NIMH) replicated this finding (George et al., *Arch Gen Psychiatry*, 2010, 67:507-516)

# STAR\*D Algorithm: Prospective Determination of Treatment Resistance and Predictive Power for Future Interventions



Source: Rush AJ, et al. Am J Psychiatry. 2006 Nov;163(11):1905-17;  
Illustration adapted from <http://www.dialogues-cns.com/>

# Remission and Relapse Rates at Each Level of STAR\*D

	Acute Remission Rate	Probability of Remaining Well for 12 Months After Acute Remission	Probability of Sustained Benefit
Level 1	36.80%	69.90%	25.72%
Level 2	30.60%	44.70%	13.68%
Level 3	13.70%	35.40%	4.85%
Level 4	13.00%	28.90%	3.76%
Rush AJ, et al. Am J Psychiatry. 2006;163(11):1905-17			

- Increasing treatment resistance associated with decreased acute remission rate and increased relapse rate
- By Level 3, <5% of patients achieved sustained remission
- Other TRD treatments (e.g., ECT, VNS) have superior rates of sustained remission at comparable or higher levels of treatment resistance



# Conclusions

- Treatment resistance can be reliably assessed, either prospectively or retrospectively
- These assessments have strong predictive validity
- In general, higher levels of treatment resistance are associated with poorer acute response to new interventions and higher rates of relapse if the new interventions produce remission
- These patterns hold for brain stimulation treatments and for psychopharmacological treatments of major depressive episodes
- Substantial percentage of patients in these studies were Medicare eligible
- Almost all approaches focus on treatment resistance in the current episode
- There is a very high rate of “pseudo-resistance”; treatment trials that do not meet dose-duration adequacy criteria, or were characterized by non-adherence