

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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Disclosures

- Brain Stimulation Industry: Consultant (Mild) Brainsway, Cervel 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

Appendix 2. ATHF Rating Scales: Rating Medication Trials for Antidepressant Potency (cont.)*

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
 4 = 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.

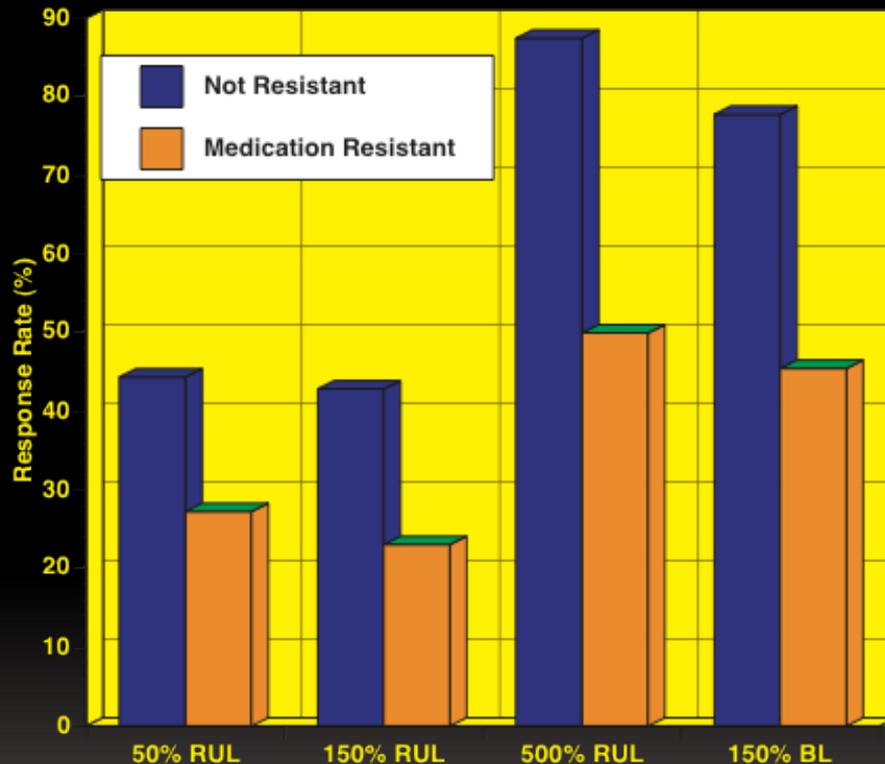
V. Sedatives (buspirone [BuSpar], zolpidem [Ambien], lorazepam

- [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.

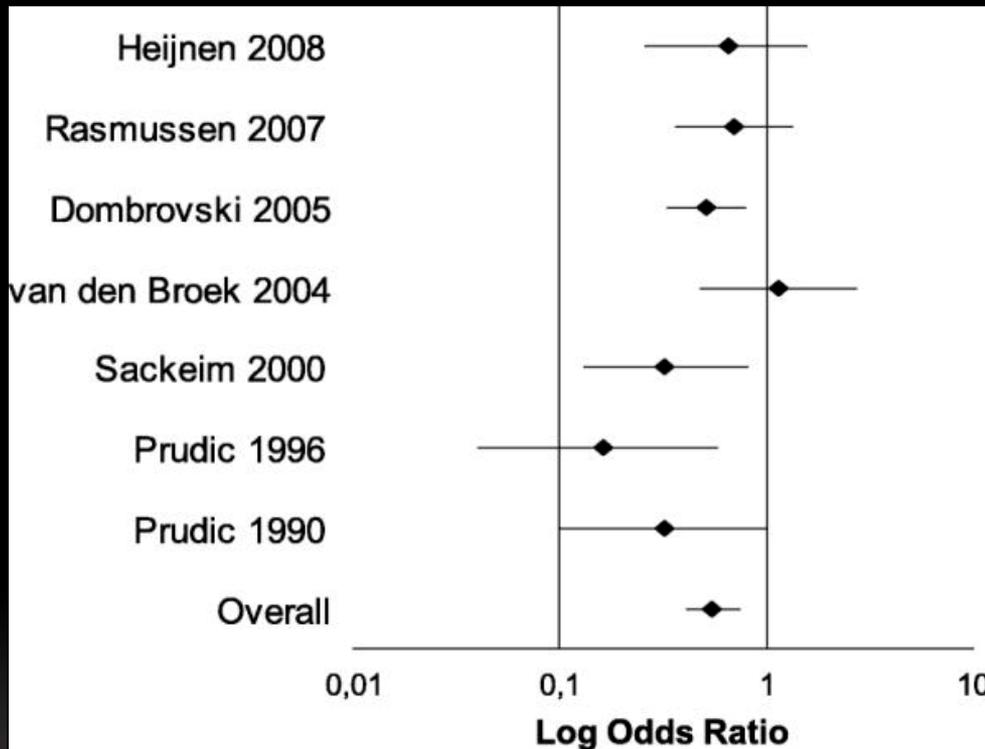
Treatment Resistance and Prediction of Acute ECT Outcome



- 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.

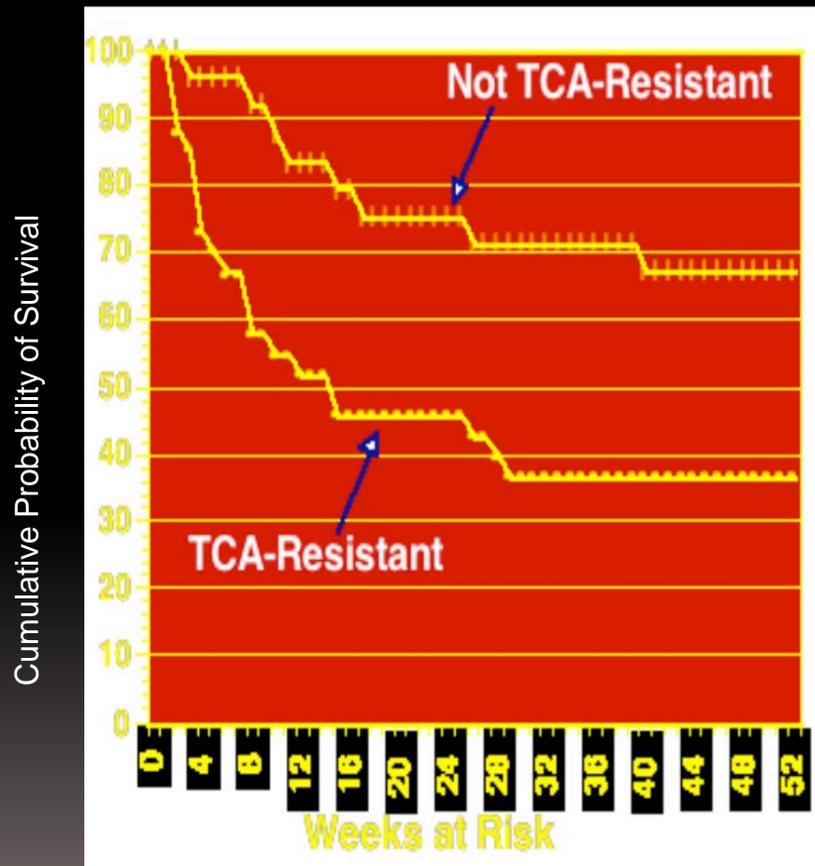
Treatment Resistance and ECT Outcome



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?

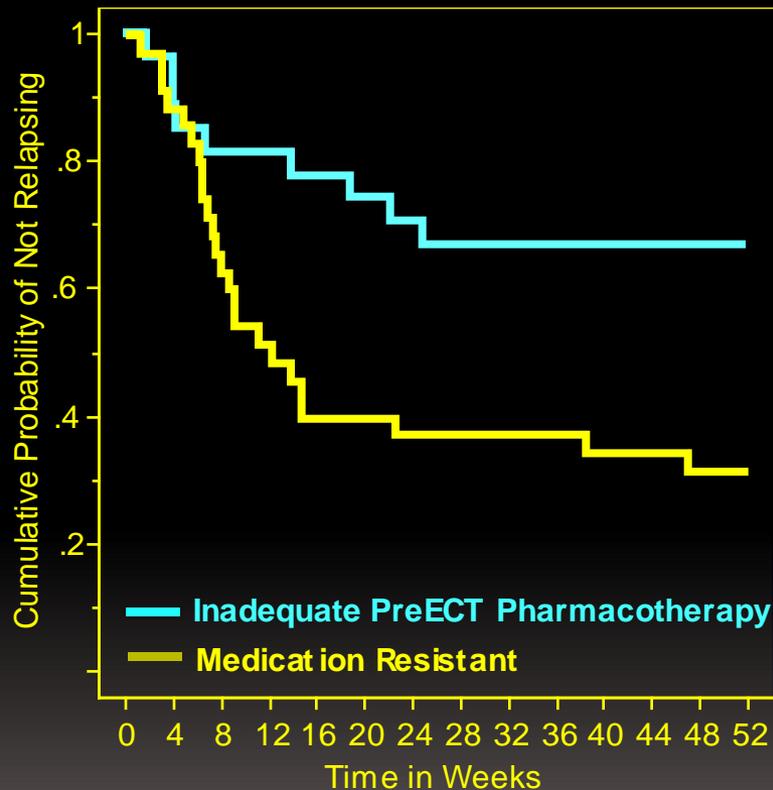
Relapse PostECT: Impact of PreECT Medication Resistance



- 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

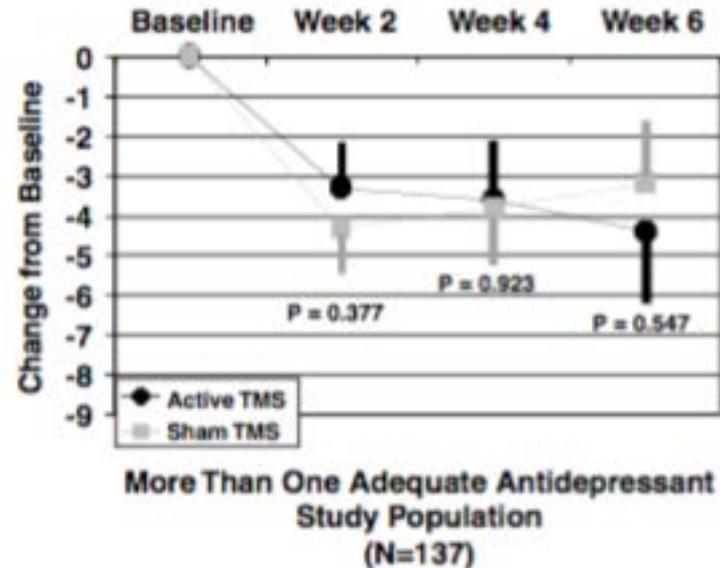
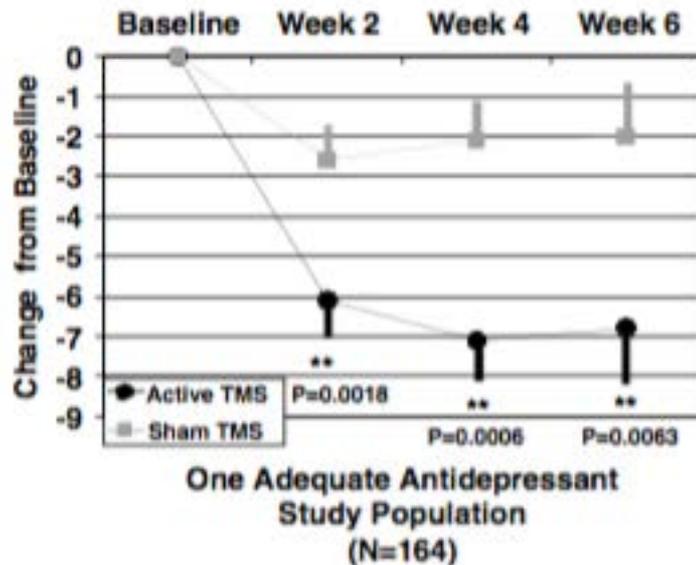


- Relapse was more than twice as likely among medication-resistant patients (68.6%) compared to patients who had not received an adequate medication trial prior to ECT (33.3%), likelihood ratio = 5.96, $P=0.01$.

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