

# Treatment Resistant Depression: *Clinical Trials and Tribulations*



**Matthew V. Rudorfer, M.D.**

*Division of Services & Intervention Research  
National Institute of Mental Health*

CMS MEDCAC Meeting  
April 27, 2016



National Institute  
of Mental Health

# Disclaimer

- ▣ I have no conflicts of interest, financial or otherwise, to disclose.
- ▣ The opinions expressed during this presentation are solely my own and do not necessarily reflect the views of NIH / NIMH, the Department of Health and Human Services, or the Federal Government.



Driscoll HC, Karp JF, Dew MA, Reynolds CF III. Getting better, getting well: Understanding and managing partial and non-response to pharmacological treatment of non-psychotic major depression in old age. *Drugs & Aging* 2007; 24:801-814.

*“In general, the pharmacological treatment of non-psychotic major depressive disorder in old age is only partially successful, with only approximately 50% of older depressed adults improving with initial antidepressant monotherapy. If an initial antidepressant trial fails, the clinician has two pharmacological options: switch or augment / combine antidepressant therapies. About 50% of patients who do not improve after initial antidepressant therapy will respond to either strategy. ..*

*“If the clinician treats vigorously and if the patient and clinician persevere, up to 90% of older depressed patients will respond to pharmacological treatment. Furthermore, electroconvulsive therapy is a safe and effective non-pharmacological strategy for non-psychotic major depression that fails to respond to pharmacotherapy.*

*“Getting well and staying well is the goal; thus, clinicians should treat to remission, not merely to response.”*





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## *Papers and Originals*

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### **Clinical Trial of the Treatment of Depressive Illness**

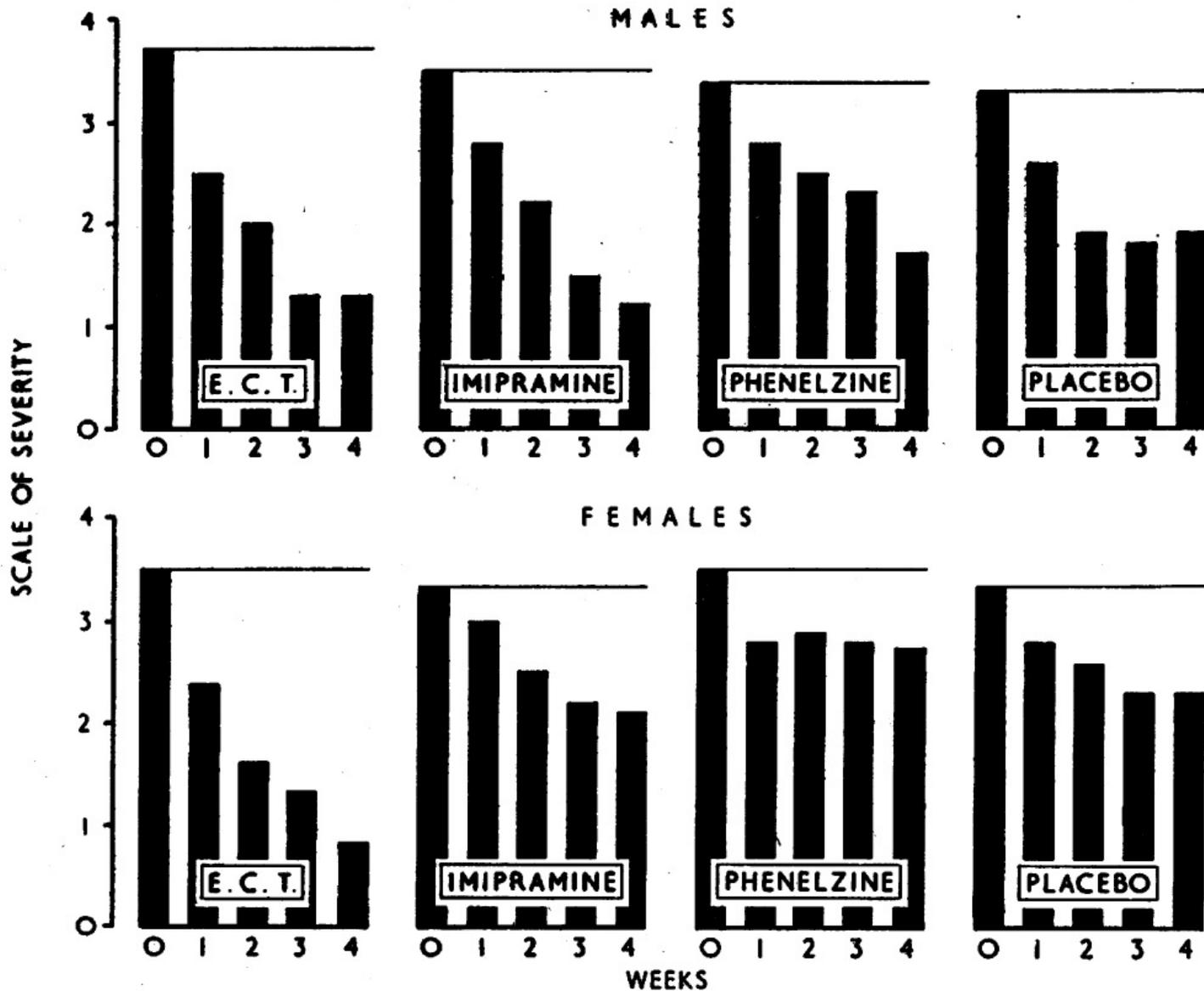
**Report to the Medical Research Council by its Clinical Psychiatry Committee\***

*Brit. med. J.*, 1965, 1, 881-886

N = 250 hospitalized patients (aged 40 – 69) with primary depression, randomly assigned to 4 weeks of inpatient treatment (double-blind except open in the case of ECT):

- **Imipramine** (*tricyclic antidepressant*)
- **Phenelzine** (*monoamine oxidase inhibitor*)
- **Placebo**
- **Electroconvulsive therapy (ECT)**





Severity of illness on admission to the trial and at weekly intervals (mean values).

# Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Protocol

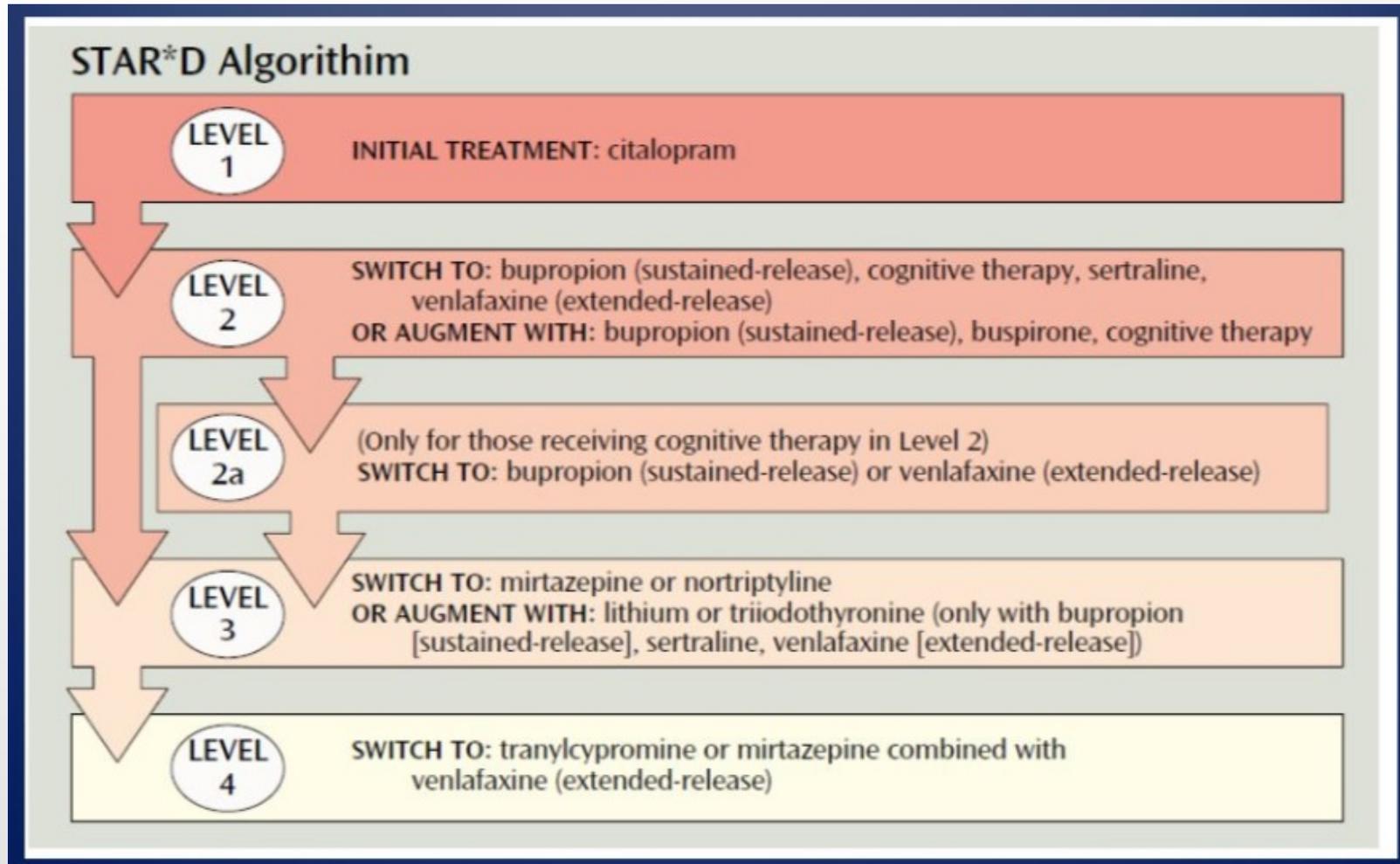


Table 1

Treatment algorithm and outcomes in 2 randomized studies comparing a stepped-care approach with treatment as usual for the treatment of late-life depression

Study (Authors, <sup>Ref.</sup> Year)	No. of Patients	Treatment Algorithm	Outcomes
IMPACT (Unutzer et al, <sup>20,21</sup> 2001, 2002)	1801	Step 1: AD (typically an SSRI) or PST (8–12 wk) Step 2: Nonresponse: switch to other AD or PST Partial response: combine with other AD or PST Step 3: Combine AD and PST Consider ECT or other specialty services	Rate of response (50% reduction in depression score) after 12 mo: Intervention: 45% Usual care: 19%
PROSPECT (Mulsant et al, <sup>22</sup> 2001; Bruce et al, <sup>23</sup> 2004; Alexopoulos et al, <sup>24,25</sup> 2005, 2009)	599	Step 1: Optimize current AD (if applicable) Nonresponse: Switch to: Step 2: citalopram 30 mg once daily Step 3: bupropion SR 100–200 mg twice daily Step 4: venlafaxine XR 150–300 mg once in AM Step 5: nortriptyline (target 80–120 ng/mL) Step 6: mirtazapine 30–45 mg in the evening Partial response: Add: Step 2: bupropion SR 100–200 mg twice daily Step 3: nortriptyline (target 80–120 ng/mL) Step 4: lithium (target 0.60–0.80 mEq/L) Then steps 2, 4, 6 for nonresponders Also, IPT can be used as an alternative to AD or as an augmentation to AD	Rate of response (HDRS score of $\leq 10$ ) After 4 mo: Intervention: 33% Usual care: 16% After 12 mo: Intervention: 54% Usual care: 45%

Abbreviations: AD, antidepressant; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; IPT, interpersonal therapy; PST, problem-solving therapy; SSRI, selective serotonin reuptake inhibitor; SR, sustained release; XR, extended release.

Table 3 Recommendations for pharmacotherapy for major depression from the 2001 United States expert consensus guidelines and the 2006 Canadian guidelines		
	2001 US Expert Consensus Guidelines	2006 Canadian Guidelines
Preferred treatment	An antidepressant (SSRI or venlafaxine XR preferred) plus psychotherapy	An antidepressant, psychotherapy, or a combination of both if the depression is of mild or moderate severity; a combination of an antidepressant and psychotherapy for severe depressions
Specific antidepressant	Citalopram and sertraline are preferred with paroxetine as another first-line option	Citalopram, sertraline, venlafaxine, bupropion, or mirtazapine
Starting dose	Begin with "somewhat lower doses" than in younger adults	Half of the recommended dose for younger adults
Increases in dose	Wait 2–4 wk before increasing a low dose if there is little or no response and 3–5 wk if there is a partial response	Aim for "an average dose" within 1 mo if the medication is well tolerated. In the absence of improvement after at least 2 wk on "an average dose," increase dose gradually (up to maximum recommended dose) until clinical improvement or limiting side effects are observed
When to change treatment	After 3–6 wk at a "therapeutic" or the maximum tolerated dose if there is little or no response and 4–7 wk if there is a partial response	After at least 4 wk at the maximum tolerated or recommended dose if there is no or minimal response after 4–8 wk if there is some partial response
What to do in case of minimal or no response to initial antidepressant	Preferred option: switch to venlafaxine or bupropion. Alternative option: switch to nortriptyline, mirtazapine, or another SSRI	Consider "all reasonable treatment options" including ECT, combination of antidepressants or mood stabilizers, addition of psychotherapy
What to do in case of partial response to initial antidepressant	Combine or augment initial antidepressant with another agent	Switch to another antidepressant of the same or another class while considering the risk of losing the improvements made with the first treatment
Agents to consider for combination or augmentation	Bupropion, lithium, or nortriptyline	Mirtazapine, bupropion, or lithium

Abbreviations: ECT, electroconvulsive therapy; SSRI, selective serotonin reuptake inhibitor; XR, extended release.

**Table 4****Updated pharmacotherapy algorithm for the treatment of late-life depression**

	<b>Majority Consensus and Minority Alternative</b>
Step 1	Escitalopram Alternatives: sertraline, duloxetine
Step 2 for minimal or no response	Switch to duloxetine Alternatives: venlafaxine, desvenlafaxine
Step 3 for minimal or no response	Switch to nortriptyline Alternative: bupropion
Step 2–3 for partial response	Augment antidepressant with lithium or an atypical antipsychotic Alternatives: combine SSRI or SNRI with mirtazapine or bupropion
Duration of each step	6 wk Alternatives: 4 wk; 8 wk

*Abbreviation:* SNRI, serotonin-norepinephrine reuptake inhibitor.

Mulsant et al. *Clin Geriatr Med*, 2014



# TYPES OF CLINICAL TRIALS

- *Yesterday*: Efficacy
- *Today*: Effectiveness
- *Tomorrow*: Experimental Therapeutics; RDoC
- *Future*: Biomarker-guided

\*\*\*\*\*

- *Ultimate goal*: Personalized treatment



# My BLOG

Tom Insel, M.D.  
NIMH Director

Home > About NIMH > Director's Blog

## Director's Blog: A New Approach to Clinical Trials

*"... future trials will follow an experimental medicine approach in which interventions serve not only as potential treatments, but as probes to generate information about the mechanisms underlying a disorder. Trial proposals will need to **identify a target** or mediator; a positive result will require not only that an intervention ameliorated a symptom, but that it had a **demonstrable effect on a target**, such as a neural pathway implicated in the disorder or a key cognitive operation."*



# SUBJECTS IN CLINICAL TRIALS

- **Patients** with unipolar and/or bipolar depression or other specific subtypes, chronic vs episodic; defined treatment history (*e.g. failure to respond to X adequate treatment trials in current episode*)
- **Recruited** either thru clinical path or marketing/advertising
- **Comorbid conditions** excluded in Efficacy trials; OK in Effectiveness trials
- **Control group:**
  - Healthy volunteers (*typically baseline only; no treatment*)
  - No separate control group (*e.g. Pre- vs post in experimental subjects only*)
  - “ “ “ “ (*experimental subjects randomized to different augmentation or alternative treatments, or to placebo, or to continuation of existing treatment*)
  - Similar patients (*e.g. alternative protocol treatment or TAU*)
  - Similar patients of different age range on same protocol (*e.g. geriatric vs middle-aged*)
  - Patients with different diagnosis, similar treatment (*e.g. mechanistic studies*)

# CLINICAL TRIALS: TYPES OF TREATMENT CONTROLS

- **Treatment assignment:** Randomized (ideal), stratified, clinician's / patient's choice, TAU; acute / continuation / maintenance phase treatment.
- **Pharmacotherapy trials** (*baseline treatment and/or augmentation agent*): Range from open-label, to single-blind, to double-blind; parallel / crossover designs
- **Nature of placebo:** inert versus active
- **Device-based interventions:** Sham control; staggered start
- **Psychotherapy:** Wait list; psychoeducation; therapy of limited scope; combined with active medication or placebo

***Also in the literature:*** Case reports, case series, comparative effectiveness studies, meta-analyses



# OUTCOME MEASURES

- **Depression rating** (*e.g. Hamilton Depression Rating Scale, HDRS*) = classical outcome measure (*alternative: Clinical Global Impression*)
- **Suicidal ideation / behavior**
- **Functioning**
- **Quality of Life**
- **Physical health, e.g. cardiac function**

# CHALLENGES IN DEPRESSION CLINICAL TRIALS

- **Diagnostic Issues**
  - **Subtypes** that can influence treatment response: e.g. Bipolar, Psychotic, Dysthymic, Chronic Major, Schizoaffective, Seasonal, Postpartum, Complicated Grief, Medication/Substance-Induced
  - **Comorbid conditions:** e.g. Psychiatric (*anxiety disorder, personality disorder, eating disorder, substance use disorder*); Medical (*e.g. thyroid disorder*)
- **Screening tools** (e.g. PHQ-9) and **rating instruments** (e.g. Hamilton depression rating scale) are not substitutes for complete history and diagnostic assessment; appropriate **outcome measures**
- **History:** Family history of mood disorder; early trauma
- **Choice of Treatment:** e.g. Medication, Psychotherapy, Combination; ECT/TMS
- **Adequate dose and duration** of treatment
- **Residual symptoms**
- **Benefit:Risk Ratio** – Guides selection and sequence of treatments; May differ among individuals for a given treatment, and for the same individual at different times in the treatment course

# A Double-blind Randomized Controlled Trial of Olanzapine Plus Sertraline vs Olanzapine Plus Placebo for Psychotic Depression

*The Study of Pharmacotherapy of Psychotic Depression (STOP-PD)*

Barnett S. Meyers, MD; Alastair J. Flint, MD; Anthony J. Rothschild, MD; Benoit H. Mulsant, MD; Ellen M. Whyte, MD; Catherine Peasley-Miklus, PhD; Eros Papademetriou, MA; Andrew C. Leon, PhD; Moonseong Heo, PhD; for the STOP-PD Group

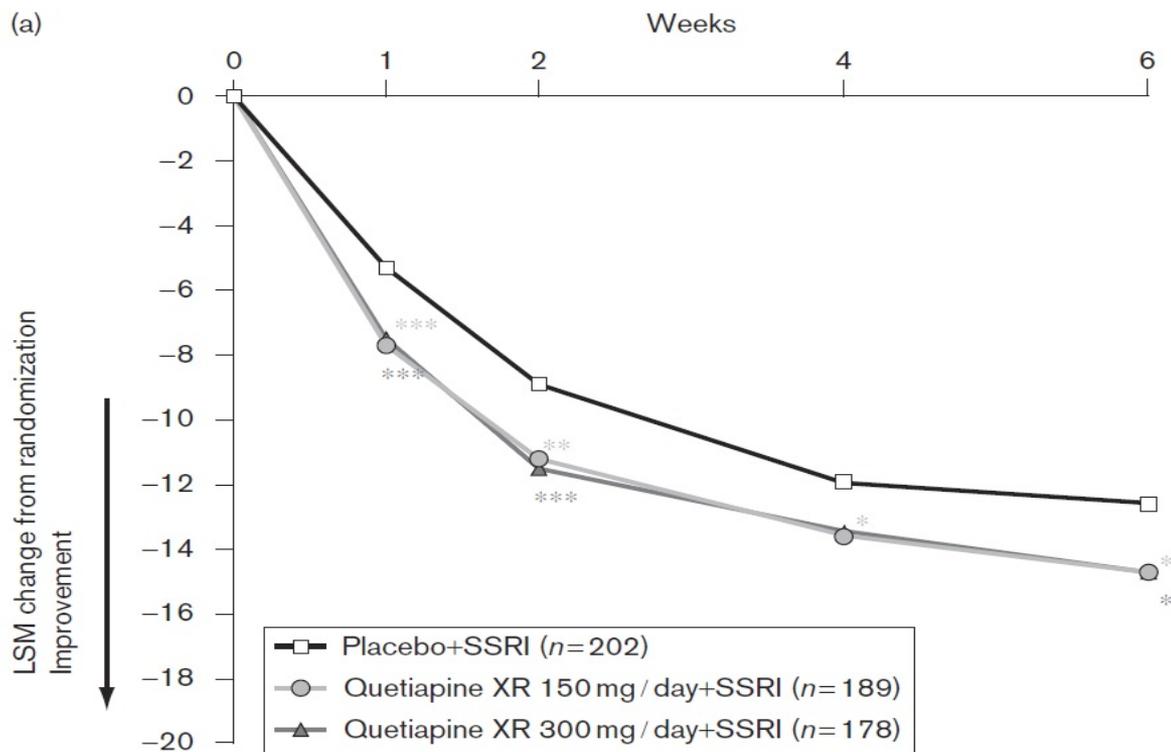
*Arch Gen Psychiatry, 2009*

# Atypical Antipsychotic Potentiation of Inadequate Antidepressant Response

■ Bauer et al.

20 International Clinical Psychopharmacology 2014, Vol 29 No 1

Fig. 1



# Atypical Antipsychotic Potentiation: TRD in Late Life

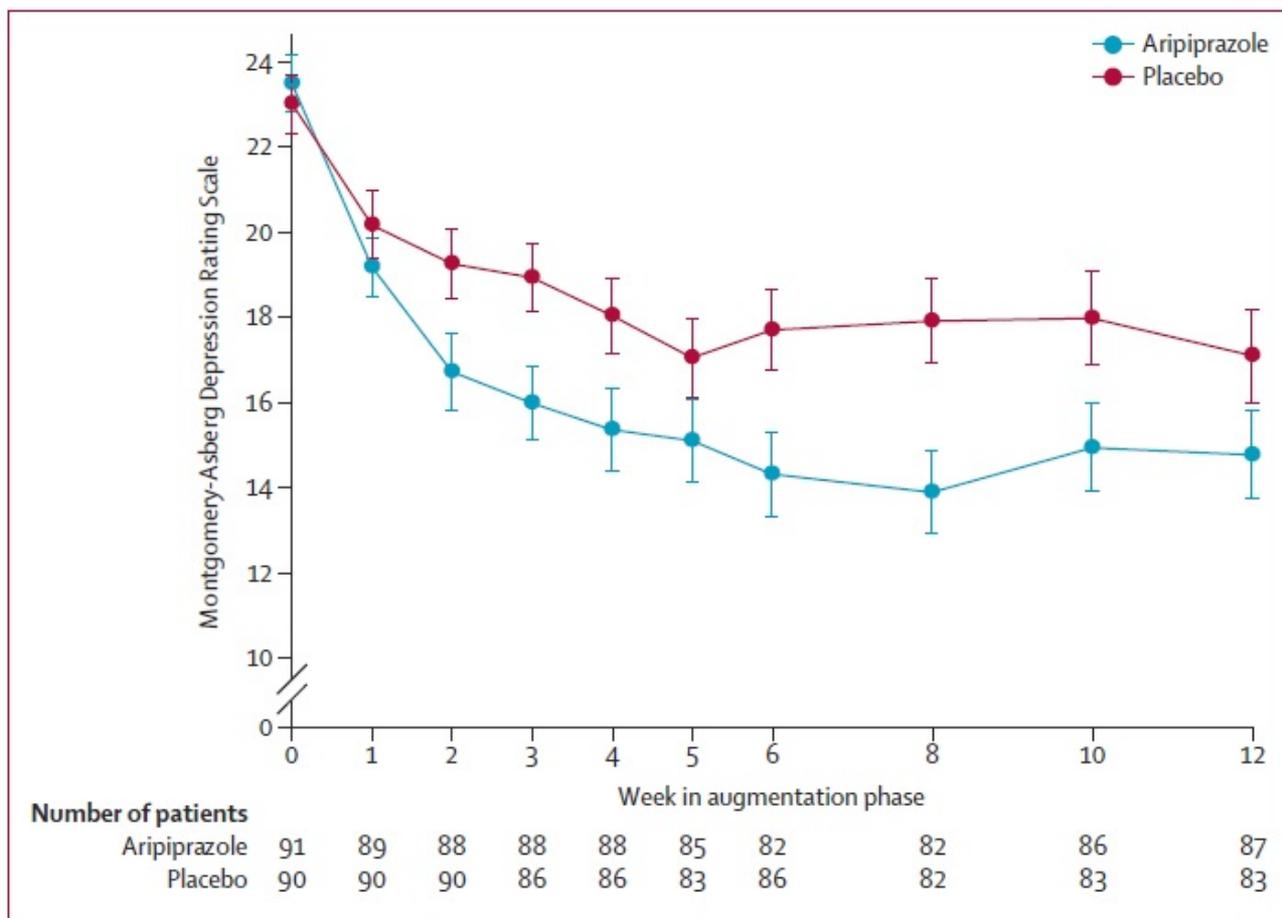


Figure 2: Reduction in depressive symptoms during augmentation with aripiprazole or placebo

Lenze et al. *Lancet*, 2015



## RESEARCH ARTICLE

# Atypical Antipsychotic Augmentation for Treatment-Resistant Depression: A Systematic Review and Network Meta-Analysis

Xinyu Zhou, PhD\*; Gabor I Keitner, PhD\*; Bin Qin, MD\*;

## Abstract

**Background:** Previous meta-analyses of atypical antipsychotics for depression were limited by few trials with direct comparisons between two treatments. We performed a network meta-analysis, which integrates direct and indirect evidence from randomized controlled trials (RCTs), to investigate the comparative efficacy and tolerability of adjunctive atypical antipsychotics for treatment-resistant depression (TRD).

**Methods:** Systematic searches resulted in 18 RCTs (total  $n = 4422$ ) of seven different types and different dosages of atypical antipsychotics and a placebo that were included in the review.

**Results:** All standard-dose atypical antipsychotics were significantly more efficacious than placebo in the efficacy (standardized mean differences [SMDs] ranged from  $-0.27$  to  $-0.43$ ). There were no significant differences between these drugs. Low-dose atypical antipsychotics were not significantly more efficacious than the placebo. In terms of tolerability, all standard-dose atypical antipsychotics, apart from risperidone, had significantly more side-effect discontinuations than placebo (odds ratios [ORs] ranged from  $2.72$  to  $6.40$ ). In terms of acceptability, only quetiapine (mean  $250$ – $350$  mg daily) had significantly more all-cause discontinuation than placebo (OR =  $1.89$ ). In terms of quality of life/functioning, standard-dose risperidone and standard-dose aripiprazole were more beneficial than placebo (SMD =  $-0.38$ ; SMD =  $-0.26$ , respectively), and standard-dose risperidone was superior to quetiapine (mean  $250$ – $350$  mg daily).

**Conclusions:** All standard-dose atypical antipsychotics for the adjunctive treatment of TRD are efficacious in reducing depressive symptoms. Risperidone and aripiprazole also showed benefits in improving the quality of life of patients. Atypical antipsychotics should be prescribed with caution due to abundant evidence of side effects.



Contents lists available at ScienceDirect

## Journal of Affective Disorders

journal homepage: [www.elsevier.com/locate/jad](http://www.elsevier.com/locate/jad)

Preliminary communication

## Psychostimulants for managing unipolar and bipolar treatment-resistant melancholic depression: A medium-term evaluation of cost benefits

Gordon Parker<sup>a,b,\*</sup>, Heather Brotchie<sup>a,b</sup>, Georgia McClure<sup>a,b</sup>, Kathryn Fletcher<sup>a,b</sup><sup>a</sup> School of Psychiatry, University of New South Wales, NSW, Australia<sup>b</sup> Black Dog Institute, Hospital Road, Randwick, NSW 2031, Australia

## ARTICLE INFO

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Melancholic depression

Bipolar disorder

Psychostimulant

Treatment

## ABSTRACT

**Background:** We earlier reported an open study of 50 unipolar and bipolar treatment resistant depressed patients indicating that psychostimulants may have differential superiority for the melancholic depressive sub-type. We designed an extension study to examine cost benefits of psychostimulants more closely for those only with melancholic depression.

**Method:** The sample comprised patients clinically diagnosed with melancholic depression who had failed to respond to and/or experienced significant side-effects with at least two antidepressants. Data were collected for 61 unipolar and 51 bipolar II patients receiving a psychostimulant for a mean interval of 69 weeks. Benefits and side-effects were assessed.

**Results:** Effectiveness ratings were similar across unipolar and bipolar sub-sets. Psychostimulants were judged as 'very' effective for 20% of patients and 'somewhat' effective for 50%. Forty percent judged the psychostimulant as being 'as effective' or as 'superior' to previously prescribed antidepressants, and worthy of being maintained. Significant side-effects were experienced by 40% of patients, requiring medication to be ceased in 12%. Twenty percent of the bipolar patients experienced a worsening of highs.

**Limitations:** The study was uncontrolled and retrospective, no formal rater-completed or patient-completed interval measures of severity were completed, while diagnostic judgments about melancholic depression and bipolar disorder were clinically judged.

**Conclusions:** This open study suggests that psychostimulants may be efficacious antidepressant options for managing unipolar and bipolar melancholia, often seemingly having very rapid onset and generally requiring only low doses, and arguing the need for controlled studies in melancholic patients.

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# Clinical Experience With High-Dosage Pramipexole in Patients With Treatment-Resistant Depressive Episodes in Unipolar and Bipolar Depression

Jan Fawcett, M.D., A. John Rush, M.D., John Vukelich, M.D., Shanna H. Diaz, D.O., Lucas Dunklee, M.D., Paul Romo, M.D., Brandon C. Yarns, M.D., Rodrigo Escalona, M.D.

**TABLE 2. Outcomes by Mood Disorder Group in 42 Patients With Treatment-Resistant Depressive Episodes Treated With Pramipexole**

Group	Remission	Response	Nonresponse	Intolerant
Bipolar disorder (N=18)	9	5	1	3
Unipolar depression (N=24)	11	7	1	5
Total	20	12	2	8

## TABLE 1. Practical Guidance in the Use of Pramipexole in Treatment-Resistant Depressive Episodes

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Slower titration rate in younger patients

Starting dose not more than 0.125–0.50 mg/day h.s.

Dose only once a day at bedtime, unless patient has trouble with sleep (rare)

Therapeutic dose range, 1.0–5.0 mg/day

Common adverse events: nausea, sleepiness, dizziness, tremors, compulsive behaviors, sleep attacks

Depressive episodes that are associated with severe anhedonia, lack of motivation, inability to initiate behaviors, and unreactive mood are likely good candidates

Expected benefit, if it occurs, by 4 weeks at maximally tolerated dose

Avoid abrupt discontinuation because the risk of dopamine agonist withdrawal syndrome<sup>a</sup> may be as high as 1 in 7

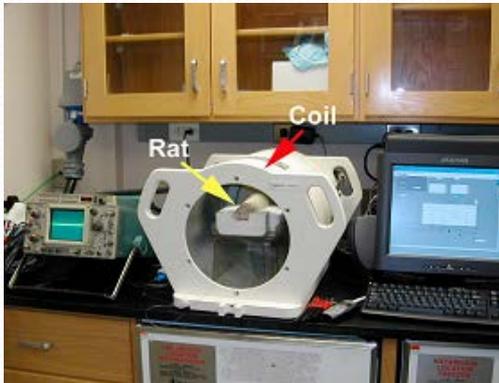
When nausea is encountered, reduce the dosage, then try raising it again after 1–2 weeks

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<sup>a</sup> Dopamine agonist withdrawal syndrome is characterized by autonomic instability, anxiety, insomnia, fatigue, and motor symptoms that can persist.

Fawcett et al. *Am J Psychiatry*, Feb 2016

# Devices for Depression



**LFMS** – Low Field Magnetic Stimulation (Class I?)



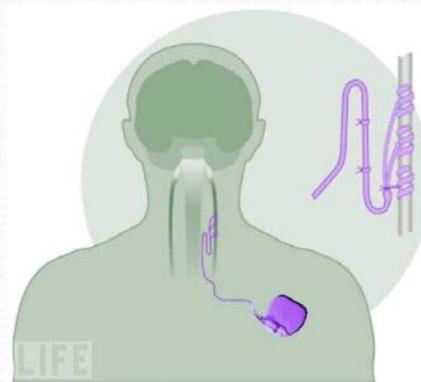
**rTMS** – Repetitive Transcranial Magnetic Stimulation (Class II)



**ECT** – Electroconvulsive Therapy (Class III – Reclassification to Class II under consideration)



**DBS** – Deep Brain Stimulation (Class III – Parkinson's; under study for depression and OCD)



**VNS** – Vagus Nerve Stimulation (Class III)



**CES** – Cranial Electrotherapy Stimulation (Class III)

KITTY DUKAKIS *and* LARRY TYE

# SHOCK

*The Healing Power  
of Electroconvulsive Therapy*

A Journalist's Account of  
Psychiatry's Most Controversial Treatment,  
and a Moving Portrait of One Woman's  
Life-Changing Experience



National Institute  
of Mental Health

## OLDER ADULTS AND MENTAL HEALTH

### Mental Health: A Report of the Surgeon General



Department of Health and Human Services

1999



NIH

National Institute  
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### *Electroconvulsive Therapy*

Electroconvulsive therapy (ECT) is regarded as an effective intervention for some forms of treatment-resistant depression across the life cycle (NIH & NIMH Consensus Conference, 1985; Depression Guideline Panel, 1993). It may offer a particularly attractive benefit:risk ratio in older persons with depression (NIH Consensus Development Panel on Depression in Late Life, 1992; Sackeim, 1994). Chapter 4 reviews research . . . earlier, older adults respond more slowly than younger ones to antidepressant medications, rendering the faster onset of action of ECT another advantage in the older patient (Markowitz et al., 1987). Immobility and reduced food and fluid intake in the older person with depression may pose a greater imminent physical health risk than would typically be the case in a younger patient, again strengthening the case for considering ECT early in the treatment hierarchy (Sackeim, 1994).

CLINICAL THERAPEUTICS

# Electroconvulsive Therapy for Depression

Sarah H. Lisanby, M.D.

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CLINICAL EVIDENCE

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ECT has been reported to result in a prompt improvement in symptoms of depression in the majority of patients treated. The Consortium for Research in ECT (CORE) reported a 75% remission rate among 217 patients who completed a short course of ECT during an acute episode of depression, with 65% of patients having remission by the fourth week of therapy.<sup>29</sup> A systematic review of six trials involving 256 patients by the UK [United Kingdom] ECT Review Group, reported in 2003, showed that the effect size for ECT was 0.91 (significantly more effective than sham ECT), and a review of 18 trials involving 1144 patients showed that the effect size for ECT was 0.80 (more effective than pharmacotherapy).<sup>30</sup> These



# Continuation Pharmacotherapy in the Prevention of Relapse Following Electroconvulsive Therapy

## A Randomized Controlled Trial

JAMA 2000

Harold A. Sackeim, PhD

Roger F. Haskett, MD

Benoit H. Mulsant, MD

Michael E. Thase, MD

J. John Mann, MD

Helen M. Pettinati, PhD

Robert M. Greenberg, MD

Raymond R. Crowe, MD

Thomas B. Cooper, MA

Joan Prudic, MD

**Context** Electroconvulsive therapy (ECT) is highly effective for treatment of major depression, but naturalistic studies show a high rate of relapse after discontinuation of ECT.

**Objective** To determine the efficacy of continuation pharmacotherapy with nortriptyline hydrochloride or combination nortriptyline and lithium carbonate in preventing post-ECT relapse.

**Design** Randomized, double-blind, placebo-controlled trial conducted from 1993 to 1998, stratified by medication resistance or presence of psychotic depression in the index episode.

**Setting** Two university-based hospitals and 1 private psychiatric hospital.

**Patients** Of 290 patients with unipolar major depression recruited through clinical referral who completed an open ECT treatment phase, 159 patients met remitter criteria; 94 remitting patients were eligible and agreed to participate in the continuation

ORIGINAL ARTICLE

# Continuation Electroconvulsive Therapy vs Pharmacotherapy for Relapse Prevention in Major Depression

*A Multisite Study From the Consortium for Research  
in Electroconvulsive Therapy (CORE)*

Arch Gen Psychiatry 2006

Charles H. Kellner, MD; Rebecca G. Knapp, PhD; Georgios Petrides, MD; Teresa A. Rummans, MD;  
Mustafa M. Husain, MD; Keith Rasmussen, MD; Martina Mueller, PhD; Hilary J. Bernstein, DHA;  
Kevin O'Connor, MD; Glenn Smith, PhD; Melanie Biggs, PhD; Samuel H. Bailine, MD;  
Chitra Mahur, MD; Eunsil Yim, MS; Shawn McClintock, MS;  
Shirlene Sampson, MD; Max Fink, MD



NIH National Institute  
of Mental Health

# Speed of remission in elderly patients with depression: electroconvulsive therapy v. medication

Harm-Pieter Spaans, Pascal Sienaert, Filip Bouckaert, Julia F. van den Berg, Esmée Verwijk, King H. Kho, Max L. Stek and Rob M. Kok

## Background

Severe depression can be a life-threatening disorder, especially in elderly patients. A fast-acting treatment is crucial for this group. Electroconvulsive therapy (ECT) may work faster than medication.

## Aims

To compare the speed of remission using ECT v. medication in elderly in-patients.

## Method

The speed of remission in in-patients with a DSM-IV diagnosis of major depression (baseline MADRS score  $\geq 20$ ) was compared between 47 participants (mean age 74.0 years, s.d. = 7.4) from an ECT randomised controlled trial (RCT) and 81 participants (mean age 72.2

years, s.d. = 7.6) from a medication RCT (nortriptyline v. venlafaxine).

## Results

Mean time to remission was 3.1 weeks (s.d. = 1.1) for the ECT group and 4.0 weeks (s.d. = 1.0) for the medication group; the adjusted hazard ratio for remission within 5 weeks (ECT v. medication) was 3.4 (95% CI 1.9–6.2).

## Conclusions

Considering the substantially higher speed of remission, ECT deserves a more prominent position in the treatment of elderly patients with severe depression.

## Declaration of interest

None.



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## Prolonging Remission in Depressed Elderly (PRIDE) (PRIDE)

**This study has been completed.**

**Sponsor:**

Icahn School of Medicine at Mount Sinai

**Collaborator:**

National Institute of Mental Health (NIMH)

**Information provided by (Responsible Party):**

Icahn School of Medicine at Mount Sinai

**ClinicalTrials.gov Identifier:**

NCT01028508

First received: December 7, 2009

Last updated: September 29, 2015

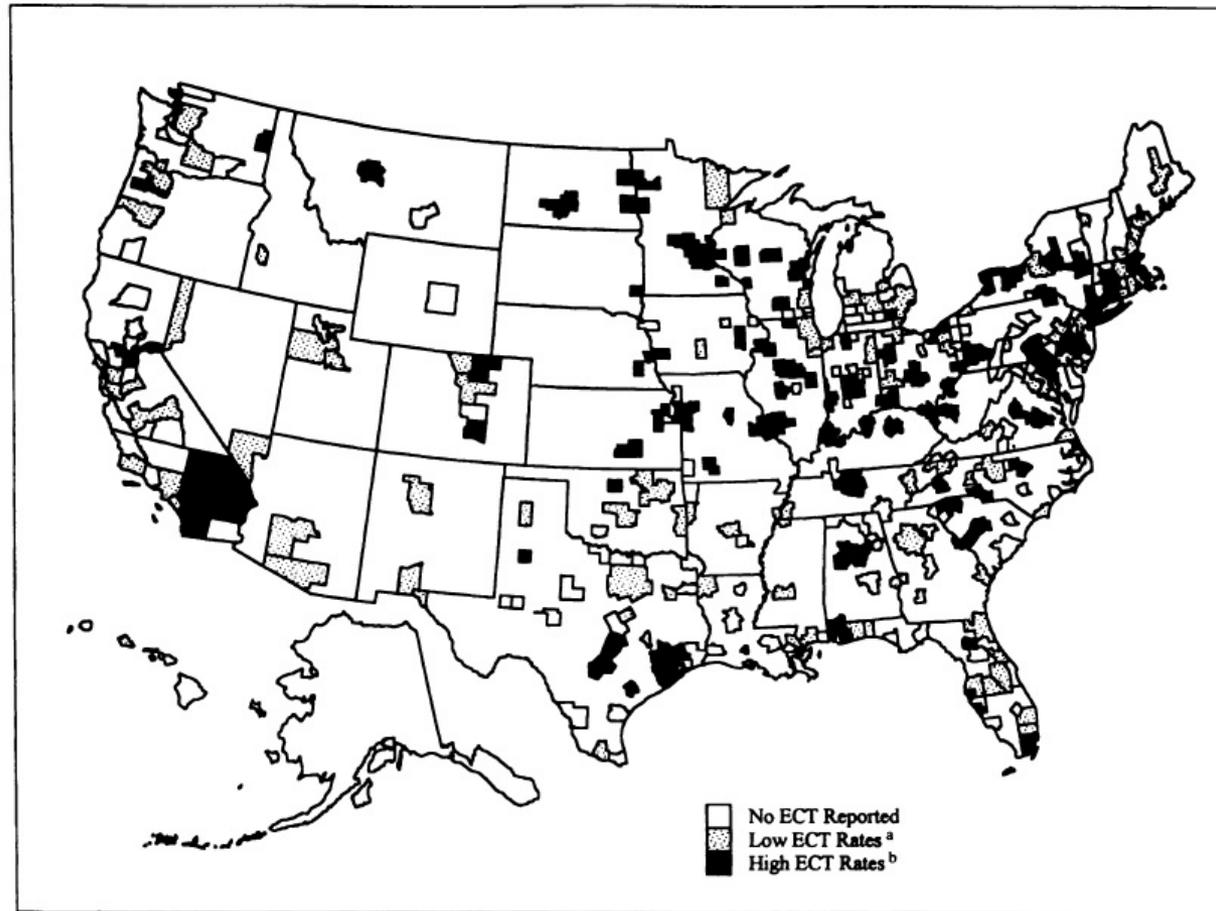
Last verified: September 2015

[History of Changes](#)



# Wide variability in ECT availability in the U.S. (1995)

FIGURE 1. Annual ECT Use in 317 U.S. Metropolitan Statistical Areas



<sup>a</sup>ECT use per capita greater than zero and less than the median rate for all metropolitan statistical areas.

<sup>b</sup>ECT use per capita equal to or greater than the median rate for all metropolitan statistical areas.

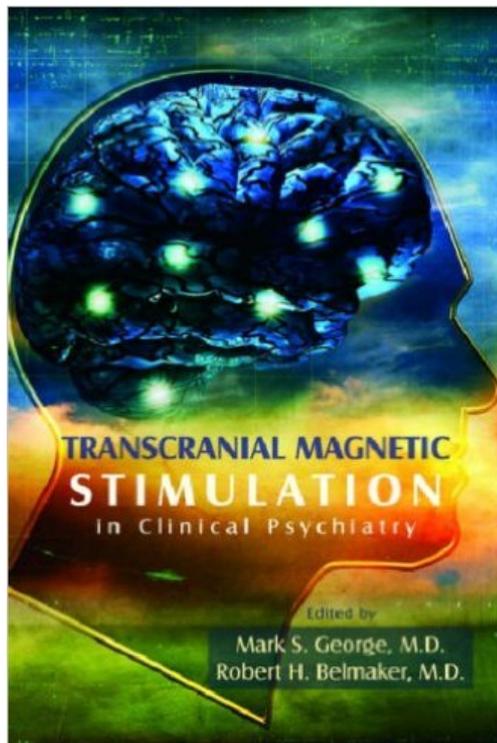
Hermann et al,  
*Am J Psychiatry* 1995



# Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder

## *A Sham-Controlled Randomized Trial*

Mark S. George, MD; Sarah H. Lisanby, MD; David Avery, MD; William M. McDonald, MD; Valerie Durkalski, PhD; Martina Pavlicova, PhD; Berry Anderson, PhD, RN; Ziad Nahas, MD; Peter Bulow, MD; Paul Zarkowski, MD; Paul E. Holtzheimer III, MD; Theresa Schwartz, MS; Harold A. Sackeim, PhD



*Arch Gen Psychiatry*, 2010

**Context:** Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) has been studied as a potential treatment for depression, but previous work had mixed outcomes and did not adequately mask sham conditions.

**Objective:** To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder.

**Design:** Prospective, multisite, randomized, active sham-controlled (1:1 randomization), duration-adaptive design with 3 weeks of daily weekday treatment (fixed-dose phase) followed by continued blinded treatment for up to another 3 weeks in improvers.

**Setting:** Four US university hospital clinics.

**Patients:** Approximately 860 outpatients were screened, yielding 199 antidepressant drug-free patients with unipolar nonpsychotic major depressive disorder.

**Intervention:** We delivered rTMS to the left prefrontal cortex at 120% motor threshold (10 Hz, 4-second train duration, and 26-second intertrain interval) for 37.5 minutes (3000 pulses per session) using a figure-eight solid-core coil. Sham rTMS used a similar coil with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.

**Main Outcome Measure:** In the intention-to-treat sample (n=190), remission rates were compared for the 2 treatment arms using logistic regression and controlling for site, treatment resistance, age, and duration of the current depressive episode.

**Results:** Patients, treaters, and raters were effectively masked. Minimal adverse effects did not differ by treatment arm, with an 88% retention rate (90% sham and 86% active). Primary efficacy analysis revealed a significant effect of treatment on the proportion of remitters (14.1% active rTMS and 5.1% sham) ( $P=.02$ ). The odds of attaining remission were 4.2 times greater with active rTMS than with sham (95% confidence interval, 1.32-13.24). The number needed to treat was 12. Most remitters had low antidepressant treatment resistance. Almost 30% of patients remitted in the open-label follow-up (30.2% originally active and 29.6% sham).

**Conclusion:** Daily left prefrontal rTMS as monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects greater than sham.

**Trial Registration:** [clinicaltrials.gov](https://clinicaltrials.gov) Identifier: NCT00149838

*Arch Gen Psychiatry.* 2010;67(5):507-516



# Treatment of Complicated Grief in Elderly Persons

## A Randomized Clinical Trial

M. Katherine Shear, MD; Yuanjia Wang, PhD; Natalia Skritskaya, PhD; Naihua Duan, PhD;  
Christine Mauro, MS; Angela Ghesquiere, PhD

**IMPORTANCE** Complicated grief (CG) is a debilitating condition, most prevalent in elderly persons. However, to our knowledge, no full-scale randomized clinical trial has studied CG in this population.

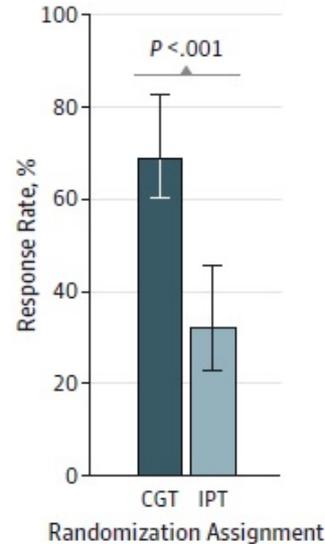
**OBJECTIVE** To determine whether complicated grief treatment (CGT) produces greater improvement in CG and depressive symptoms than grief-focused interpersonal psychotherapy (IPT).

**DESIGN, SETTING, AND PARTICIPANTS** Randomized clinical trial enrolling 151 individuals 50 years or older (mean [SD] age, 66.1 [8.9] years) scoring at least 30 on the Inventory of Complicated Grief (ICG). Participants were recruited from the New York metropolitan area from August 20, 2008, through January 7, 2013, and randomized to receive CGT or IPT. The main outcome was assessed at 20 weeks after baseline, with interim measures collected at 8, 12, and 16 weeks after baseline.

**INTERVENTIONS** Sixteen sessions of CGT (n = 74) or IPT (n = 77) delivered approximately weekly.

**MAIN OUTCOMES AND MEASURES** Rate of treatment response, defined as a rating from an independent evaluator of much or very much improved on the Improvement subscale of the Clinical Global Impression Scale.

Figure 2. Response Rates at Week 20 Adjusted for Missing Data by Inverse Probability Weighting

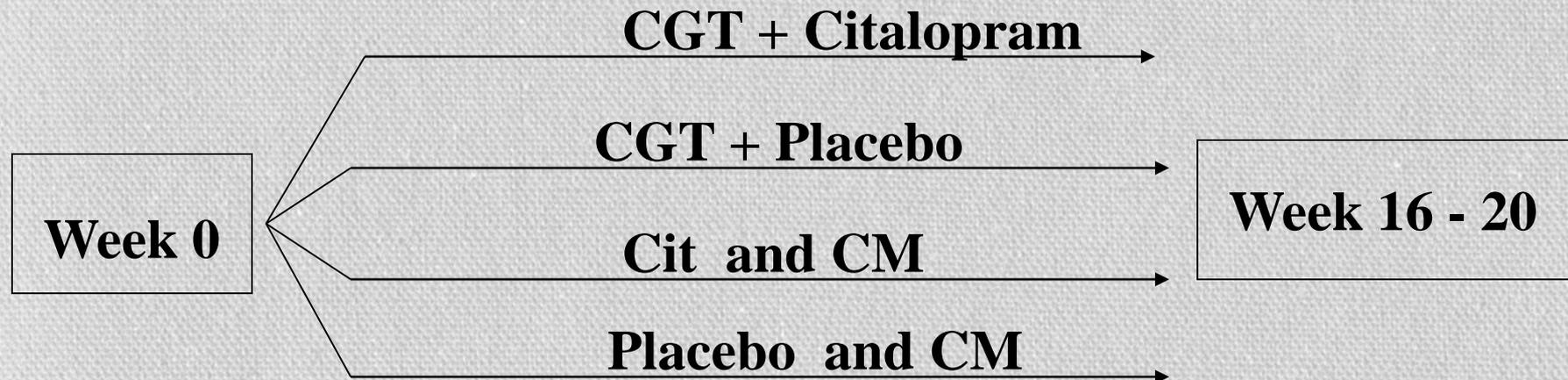


Among those receiving complicated grief treatment (CGT), 52 individuals (70.5%; 95% CI, 60.3%-82.6%) responded compared with 24 (32.0%; 95% CI, 22.7%-45.2%) among those receiving interpersonal psychotherapy (IPT). Whiskers indicate 95% confidence intervals.

**CONCLUSIONS AND RELEVANCE** Complicated grief treatment produced clinically and statistically significantly greater response rates for CG symptoms than a proven efficacious treatment for depression (IPT). Results strongly support the need for physicians and other health care providers to distinguish CG from depression. Given the growing elderly population, the high prevalence of bereavement in aging individuals, and the marked physical and psychological impact of CG, clinicians need to know how to treat CG in older adults.

# OPTIMIZING TREATMENT FOR COMPLICATED GRIEF

*4-Site NIMH Collaborative-R01 Clinical Trial:  
Columbia Univ, with MGH, UCSD, UPMC*



**CGT = Complicated Grief Therapy**

**Cit = Citalopram**

**CM = Clinical Management**



**NIH** National Institute  
of Mental Health

# Examination of the Utility of Psychotherapy for Patients with Treatment Resistant Depression: A Systematic Review

Ranak B. Trivedi, PhD<sup>1</sup>, Jason A. Nieuwsma, PhD<sup>2</sup>, and John W. Williams, Jr. MD, MHS<sup>3</sup>

<sup>1</sup>VA Puget Sound Health Care System, University of Washington School of Public Health, Seattle, WA, USA; <sup>2</sup>Durham VA MIRECC, Duke University Medical Center, Durham, NC, USA; <sup>3</sup>Durham VA Medical Center, Duke University Medical Center, Evidence-Based Practice Center, Durham, NC, USA.

**RESULTS:** Of 941 original titles, 13 articles evaluating 7 unique treatment comparisons were included. Psychotherapy was examined as an augmentation to antidepressants in five studies and as substitution treatment in two studies. A total of 592 patients were evaluated (Mean age ~40 y; Females=50-85%; Caucasians ≥75%). The STAR\*D trial used an equipoise stratified randomization design; the remaining studies were RCTs. Compared to active management, two good quality trials showed similar benefit from augmenting antidepressants with psychotherapy; one fair quality and one poor quality trial showed benefit from psychotherapy augmentation; and one good and one poor trial found similar benefit from substituting psychotherapy for antidepressants. One fair quality trial showed lithium augmentation to be more beneficial than psychotherapy.

**CONCLUSIONS:** Review demonstrates the utility of psychotherapy in managing treatment resistant depression. However, evidence is sparse and results are mixed. Given that quality trials are lacking, rigorous clinical trials are recommended to guide practice.

*...includes positive results from STAR\*D augmentation and switch arms: no sig difference between CT and meds.*

*...does not include negative results from REVAMP study using CBASP augmentation.*



# Cognitive Behavioral Analysis System of Psychotherapy and Brief Supportive Psychotherapy for Augmentation of Antidepressant Nonresponse in Chronic Depression

## *The REVAMP Trial*

James H. Kocsis, MD; Alan J. Gelenberg, MD; Barbara O. Rothbaum, PhD; Daniel Madhukar H. Trivedi, MD; Rachel Manber, PhD; Martin B. Keller, MD; Andrew C. Steven R. Wisniewski, PhD; Bruce A. Arnow, PhD; John C. Markowitz, MD; Micho for the REVAMP Investigators

*Arch Gen Psychiatry*, 2009

**Context:** Previous studies have found that few chronically depressed patients remit with antidepressant medications alone.

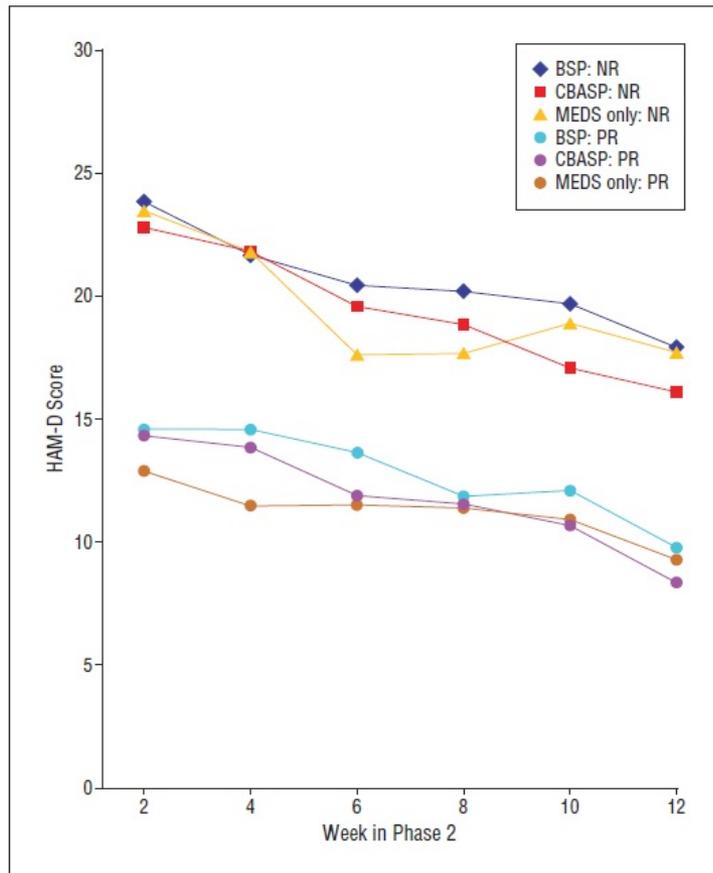
**Objective:** To determine the role of adjunctive psychotherapy in the treatment of chronically depressed patients with less than complete response to an initial medication trial.

**Design:** This trial compared 12 weeks of (1) continued pharmacotherapy and augmentation with cognitive behavioral analysis system of psychotherapy (CBASP), (2) continued pharmacotherapy and augmentation with brief supportive psychotherapy (BSP), and (3) continued optimized pharmacotherapy (MEDS) alone. We hypothesized that adding CBASP would produce higher rates of response and remission than adding BSP or continuing MEDS alone.

**Setting:** Eight academic sites.

**Participants:** Chronically depressed patients with a current DSM-IV–defined major depressive episode and persistent depressive symptoms for more than 2 years.

# Kocsis et al. – REVAMP Study, *cont'd*



**Figure 3.** Phase 2 Hamilton Scale for Depression (HAM-D) scores according to phase 1 response status. BSP indicates brief supportive psychotherapy; CBASP, cognitive behavioral analysis system of psychotherapy; MEDS, optimized pharmacotherapy; NR, nonresponder; and PR, partial responder.

**Conclusions:** Although 37.5% of the participants experienced partial response or remitted in phase 2, neither form of adjunctive psychotherapy significantly improved outcomes over that of a flexible, individualized pharmacotherapy regimen alone.

*Arch Gen Psychiatry*, 2009



**CoBaIT: Cognitive Behavioural Therapy as an adjunct to pharmacotherapy for treatment resistant depression in primary care: a randomised controlled trial.**

Each year many people visit their doctor with depression. Currently, antidepressants are the most widely available treatment. However, two-thirds of people with depression don't respond fully to antidepressants, even after an adequate dose and duration of treatment. At the moment doctors are not certain about the best way to treat these people.

There is some evidence that a talking treatment called Cognitive Behaviour Therapy (CBT) is helpful for depression, so it may be that a combination of treatments is effective. *In CoBaIT we want to find out whether giving CBT in addition to antidepressants can improve outcomes for people with treatment resistant depression, compared to antidepressant treatment alone.* In order to do this we need to compare the two approaches in a randomised controlled trial.

**Patients aged between 18 and 75 who have taken antidepressants for at least 6 weeks at an adequate dose, but who continue to have significant symptoms of depression may take part.** Those who agree to take part will be randomly assigned to one of the two treatment groups. Both groups will be followed up by the research team for one year, with 3 – 5 years' follow-up.

# Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaT randomised controlled trial



*Lancet Psychiatry*, Feb 2016

Nicola J Wiles, Laura Thomas, Nicholas Turner, Kirsty Garfield, Daphne Kounali, John Campbell, David Kessler, Willem Kuyken, Glyn Lewis, Jill Morrison, Chris Williams, Tim J Peters, Sandra Hollinghurst



**Methods** CoBaT was a randomised controlled trial done across 73 general practices in three UK centres. CoBaT recruited patients aged 18–75 years who had adhered to antidepressants for at least 6 weeks and had substantial depressive symptoms (Beck Depression Inventory [BDI-II] score  $\geq 14$  and met ICD-10 depression criteria). Participants were randomly assigned using a computer generated code, to receive either usual care or CBT in addition to usual care.

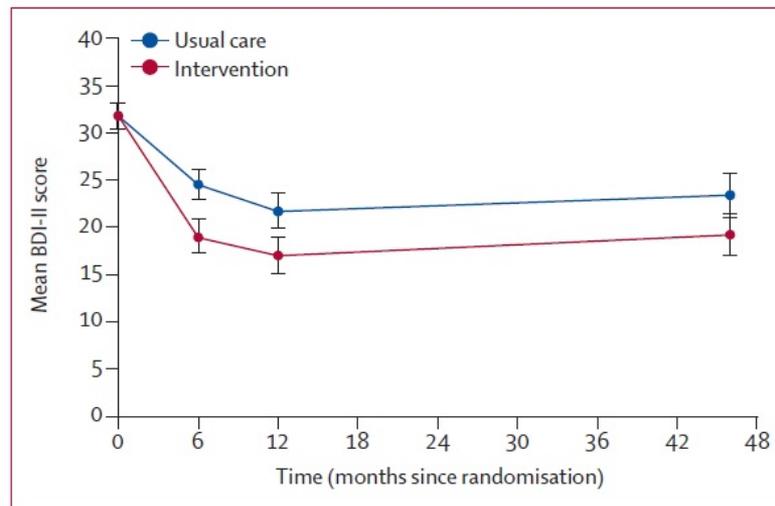


Figure 2: Mean BDI-II scores for the intervention and usual care groups at 6, 12, and 46 months  
Error bars represent SD. BDI-II=Beck Depression Inventory score.

# Wiles et al. – CoBaIT Study, 2016, *cont'd*

**Interpretation** CBT as an adjunct to usual care that includes antidepressants is clinically effective and cost effective over the long-term for individuals whose depression has not responded to pharmacotherapy. In view of this robust evidence of long-term effectiveness and the fact that the intervention represented good value-for-money, clinicians should discuss referral for CBT with all those for whom antidepressants are not effective.

## Added value of this study

To our knowledge, this study has provided the first evidence of the long-term effectiveness (3-5 years) and cost-effectiveness of CBT as an adjunct to pharmacotherapy for primary care patients with treatment-resistant depression.

## Implications of all the available evidence

In view of this robust evidence of long-term effectiveness and the fact that the intervention represented good value for money, clinicians should discuss referral for CBT with all those for whom antidepressants are not effective.

Original Investigation

# Effect of Cognitive Therapy With Antidepressant Medications vs Antidepressants Alone on the Rate of Recovery in Major Depressive Disorder

## A Randomized Clinical Trial

Steven D. Hollon, PhD; Robert J. DeRubeis, PhD; Jan Fawcett, MD; Jay D. Amsterdam, MD; Richard C. Shelton, MD; John Zajecka, MD; Paula R. Young, PhD; Robert Gallop, PhD

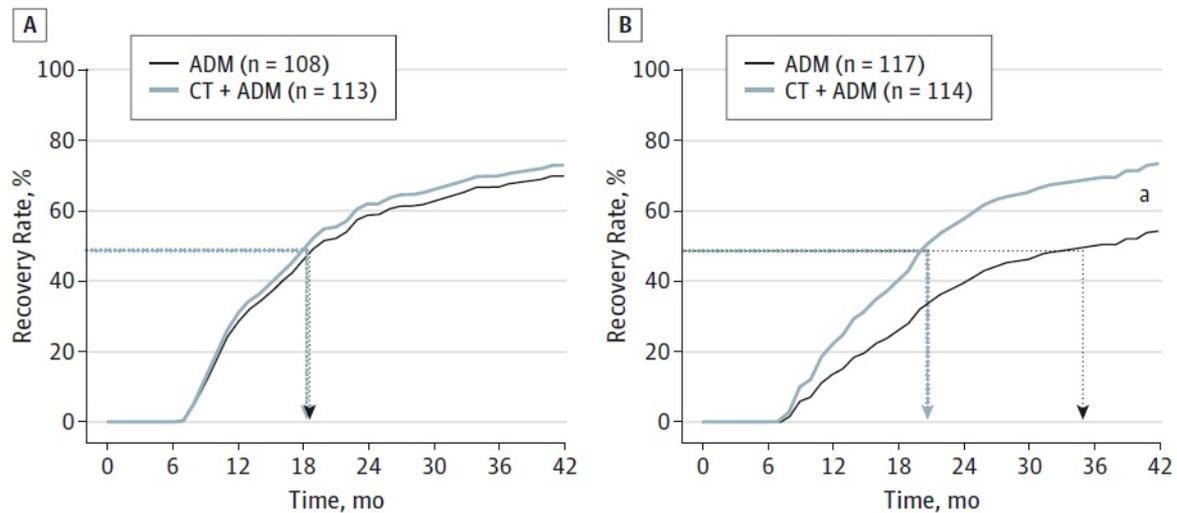
**IMPORTANCE** Antidepressant medication (ADM) is efficacious in the treatment of depression, but not all patients achieve remission and fewer still achieve recovery with ADM alone.

**OBJECTIVE** To determine the effects of combining cognitive therapy (CT) with ADM vs ADM alone on remission and recovery in major depressive disorder (MDD).

**DESIGN, SETTING, AND PARTICIPANTS** A total of 452 adult outpatients with chronic or recurrent MDD participated in a trial conducted in research clinics at 3 university medical centers in the United States. The patients were randomly assigned to ADM treatment alone or CT combined with ADM treatment. Treatment was continued for up to 42 months until recovery was achieved.

# Hollon et al. 2014, cont'd

Figure 2. Time to Recovery as a Function of Severity by Condition

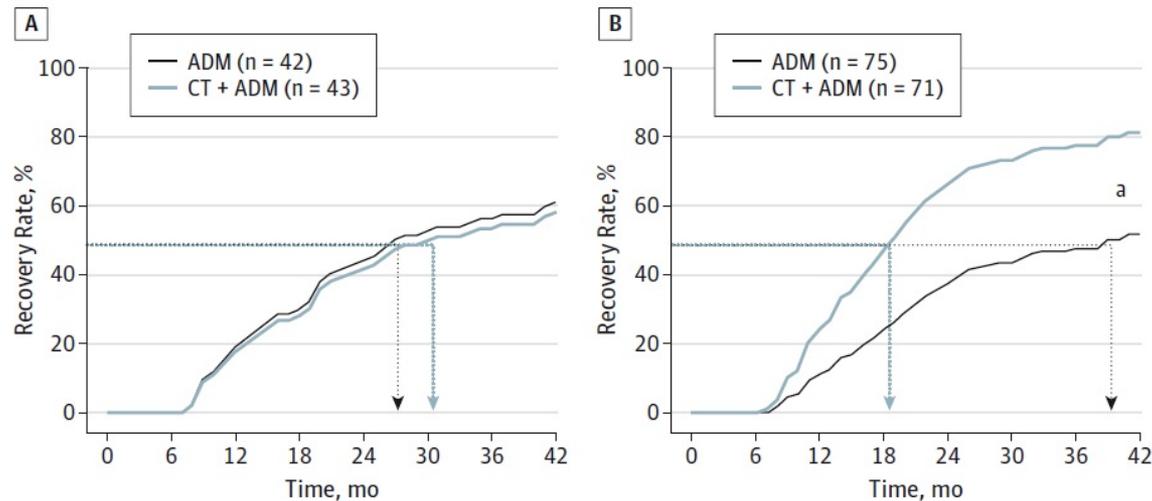


Recovery was defined as 6 months without relapse following remission. A, Low-severity major depressive disorder (MDD), defined as an HRSD score of less than 22 at intake. B, High-severity MDD, defined as an HRSD score of 22 or greater at intake. ADM indicates antidepressant medication; CT+ ADM, cognitive therapy combined with ADM; HRSD, Hamilton Rating Scale for Depression; and dashed lines, median time to recovery (50th percentile).

<sup>a</sup>  $P < .001$ .

# Hollon et al. 2014, cont'd

Figure 3. Time to Recovery as a Function of Chronicity by Condition Within High Severity



Recovery was defined as 6 months without relapse following remission. A, High-severity chronic major depressive disorder (MDD), defined as an HRSD score of greater than 22 at intake and episode duration of 2 years or more. B, High-severity nonchronic MDD, defined as an HRSD score of 22 or greater at intake and episode duration of less than 2 years. ADM indicates antidepressant

medication; CT+ADM, cognitive therapy combined with ADM; HRSD, Hamilton Rating Scale for Depression; and dashed lines, median time to recovery (50th percentile).

<sup>a</sup>  $p < .001$ .

## Conclusions

Cognitive therapy combined with medication treatment enhanced rates of recovery relative to medications alone, with the effect limited to patients with severe nonchronic depressions. Combined treatment also reduced the frequency of severe adverse events, but largely because it reduced time in episode.

# Large-Scale Study Suggests Specific Indicators for Combined Cognitive Therapy and Pharmacotherapy in Major Depressive Disorder

Michael E. Thase, MD

**The article by Hollon and colleagues** <sup>1</sup> in this issue of *JAMA Psychiatry* describes the main findings of one of the most important studies ever undertaken to evaluate the merits of combining psychotherapy and pharmacotherapy for treatment of major depressive disorder (MDD).



Although much attention has been given to pharmacotherapy, comparable efforts are needed to develop and test alternate models of psychotherapy. The Beck model of CT is conventionally a time-limited treatment and may not have offered sufficient flexibility to enable therapists to keep working productively with patients who did not benefit from the first few months of psychotherapy. Whereas reasonable al-

*JAMA Psychiatry*, Oct 2014

gorithms have been developed for switching, augmenting, and combining antidepressant medications, little clinical and no empirical guidance exists for comparable decisions about psychotherapy. There is no debate about whether CT should be thought of as a first-line option, but what should a psychotherapist do when it does not work?

# Ketamine / Rapidly-Acting Antidepressants

Ann. N.Y. Acad. Sci. ISSN 0077-8923

2015

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *Qatar Clinical Neuroscience Conference*

## The promise of ketamine for treatment-resistant depression: current evidence and future directions

Kaitlin E. DeWilde,<sup>1</sup> Cara F. Levitch,<sup>1</sup> James W. Murrough,<sup>1</sup> Sanjay J. Mathew,<sup>2</sup>  
and Dan V. Iosifescu<sup>1</sup>

<sup>1</sup>Mood and Anxiety Disorders Program, Icahn School of Medicine at Mount Sinai, New York, New York. <sup>2</sup>Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas



# Ketamine, cont'd

DeWilde *et al.*

Ketamine for treatment-resistant depression

**Table 2.** Studies of repeated dose IV ketamine administration in patients with MDD

Study	Method	No. of patients ( <i>n</i> )	Design	Treatment response <sup>a</sup> (%)
aan het Rot <i>et al.</i> <sup>49</sup>	IV	10	Open label	65%
Murrough <i>et al.</i> <sup>16</sup>	IV	24	Open label	70.8%
Diamond <i>et al.</i> <sup>12</sup>	IV	28	Open label	29%
Rasmussen <i>et al.</i> <sup>50</sup>	IV	10	Open label	80%
Segmiller <i>et al.</i> <sup>51</sup>	IV	6	Open label (esketamine)	50%

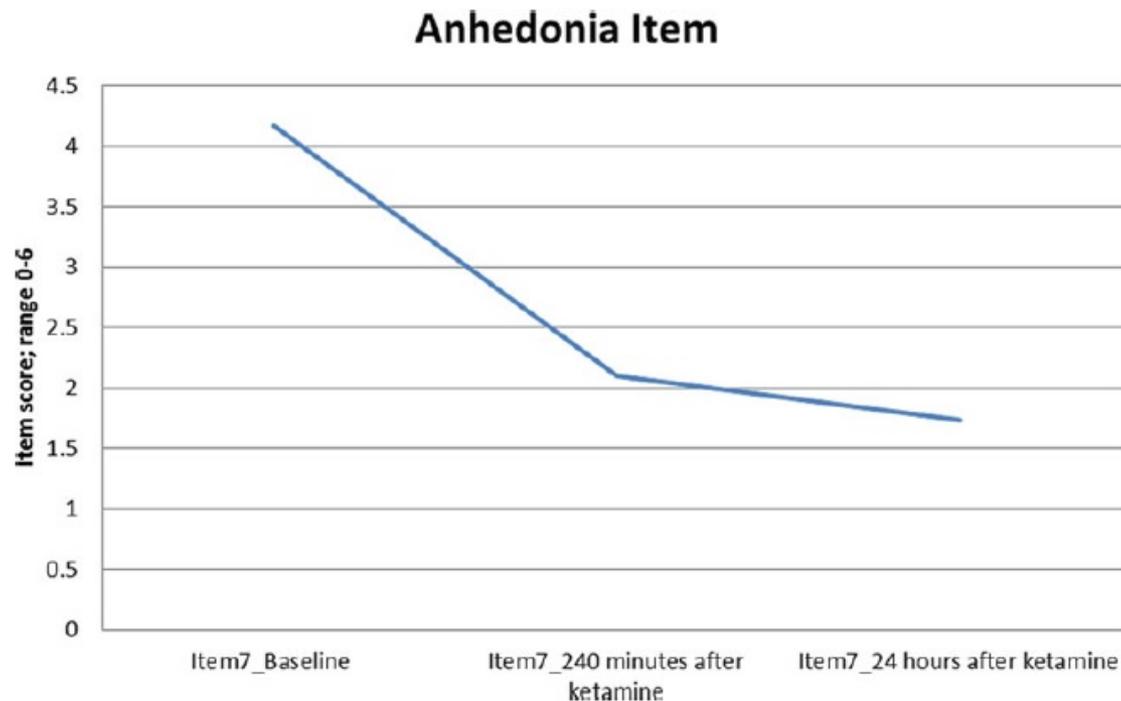
<sup>a</sup>Response is defined as  $\geq 50\%$  reduction in depressive symptoms (e.g., HAM-D or MADRS score) 24 h following IV ketamine.

*Ann NY Acad Sci, 2015*

# Ketamine, *cont'd*

Ketamine for treatment-resistant depression

DeWilde *et al.*



**Figure 1.** Changes in anhedonia. MADRS item score #7 showing improvements in anhedonia during ketamine infusion (percentage change from baseline to 24 h =  $-0.63$ ). A lower score on the MADRS #7 signifies improved anhedonia. Data from an RCT of 72 patients with TRD.<sup>16</sup>



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## Improvement in suicidal ideation after ketamine infusion: Relationship to reductions in depression and anxiety<sup>☆</sup>

Elizabeth D. Ballard<sup>\*</sup>, Dawn F. Ionescu, Jennifer L. Vande Voort, Mark J. Niciu, Erica M. Richards, David A. Luckenbaugh, Nancy E. Brutsché, Rezvan Ameli, Maura L. Furey, Carlos A. Zarate Jr.

Experimental Therapeutics & Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institute of Mental Health, Bethesda, MD 20892, USA

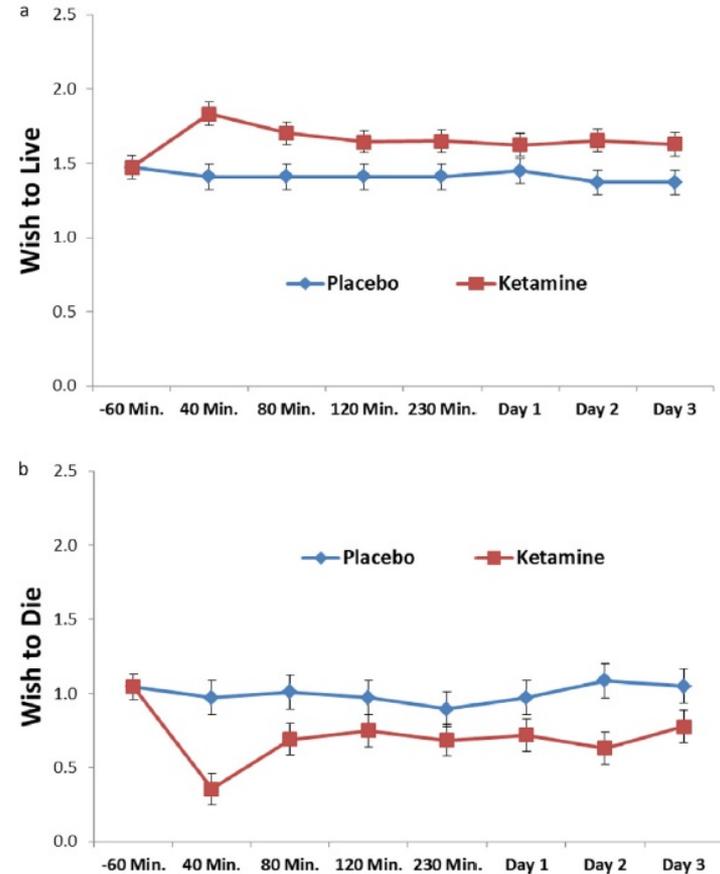


Fig. 2. 2a and 2b. Reductions in cognitions related to suicidal ideation as measured by the SSI in placebo-controlled trials of ketamine, limited to patients any suicidal thoughts at baseline. 2a. Wish to Live. 2b. Wish to Die.

Original Investigation

# Indicators for Remission of Suicidal Ideation Following Magnetic Seizure Therapy in Patients With Treatment-Resistant Depression

Yinming Sun, MSc; Faranak Farzan, PhD; Benoit H. Mulsant, MD, MS, FRCPC; Tarek K. Rajji, MD, FRCPC; Paul B. Fitzgerald, MBBS, MPM, PhD, FRANZCP; Mera S. Barr, PhD; Jonathan Downar, MD, PhD; Willy Wong, PhD; Daniel M. Blumberger, MD, MS, FRCPC; Zafiris J. Daskalakis, MD, PhD, FRCPC

**OBJECTIVE** To identify a biomarker that may serve as an indicator of remission of suicidal ideation following a course of MST by using cortical inhibition measures from interleaved transcranial magnetic stimulation and electroencephalography (TMS-EEG).

**CONCLUSIONS AND RELEVANCE** These results suggest that cortical inhibition may be used to identify patients with TRD who are most likely to experience remission of suicidal ideation following a course of MST. Stronger inhibitory neurotransmission at baseline may reflect the integrity of transsynaptic networks that are targeted by MST for optimal therapeutic response.

REVIEW ARTICLE

# The Prevalence, Measurement, and Treatment of the Cognitive Dimension/Domain in Major Depressive Disorder

Roger S. McIntyre<sup>1,2,3</sup> · Holly X. Xiao<sup>3</sup> · Kahlood Syeda<sup>3</sup> · Maj Vinberg<sup>4</sup> ·  
Andre F. Carvalho<sup>5</sup> · Rodrigo B. Mansur<sup>3</sup> · Nadia Maruschak<sup>3</sup> · Danielle S. Cha<sup>2,6</sup>

## Key Points

Cognitive dysfunction is a core domain disturbance in adults with major depressive disorder (MDD) that is correlated with, yet independent of, mood domain symptoms.

Disparate antidepressant modalities (e.g. pharmacotherapy, neuromodulation) would be expected to improve measures of cognitive function; notwithstanding, pseudospecificity can only be ruled out if studies employ methods to adjust for the contribution of mood symptoms (e.g. path analysis, subgroup analysis).

Vortioxetine is the only approved/proven treatment for MDD with replicated evidence demonstrating direct and independent effects on cognitive function in adults with MDD across multiple subdomains of cognitive function.



# NIMH Research Domain Criteria (RDoC)

## Research Domain Criteria (RDoC)

RDoC is a research framework for new ways of studying mental disorders. It integrates many levels of information (from genomics to self-report) to better understand basic dimensions of functioning underlying the full range of human behavior from normal to abnormal.



### Construct: Loss

#### RDoC Classification

Domain: **Negative Valence Systems**

#### Description

A state of deprivation of a motivationally significant con-specific, object, or situation. Loss may be social or non-social and may include permanent or sustained loss of shelter, behavioral control, status, loved ones, or relationships. The response to loss may be episodic (e.g., grief) or sustained.

#### Genes

5-HTTLPR 5HTRs COMT DAT1 MAOA

### Behavior

Amotivation Anhedonia Attentional bias to negative valenced information Crying  
Executive function Guilt Increased self-focus Loss of drive Loss-relevant recall bias  
Morbid Thoughts Psychomotor retardation Rumination Sadness Shame Withdrawal  
Worry

### Self-Report

Change in attributional style Hopelessness

*Thank you !*



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