Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

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Advances in the Management of Treatment-Resistant Depression

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CME Outfitters

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Disclosures

- ***Research/Grants:*** Pritzker Foundation, Janssen Research and Development, LLC
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- ***Stockholder:*** Amnestix, Inc.; Corcept Therapeutics; Gilead; Incyte Corporation; Merck & Co., Inc.; Seattle Genetics, Inc.; Synosia; Titan Pharmaceuticals, Inc.; Xhale, Inc.
- ***Other Financial Interest:*** American Psychiatric Assoc. - Royalties; Pfizer - Speaking; Patent License - Corcept Therapeutics/Stanford University

Learning Objectives

- Evaluate patients at frequent intervals for the presence of residual symptoms or treatment resistance.
- Initiate a treatment plan that includes the latest pharmacotherapeutic options for the management of treatment resistant depression.

Audience Response

How many weeks constitutes an adequate trial of an antidepressant?

A. 2 weeks
B. > 4 weeks
C. < 6 weeks
D. 8 weeks

Audience Response

Remission is defined as what percent reduction in symptomatology?

A. 60%
B. 70%
C. 80%
D. 90%

Understanding Antidepressant Nonresponse

- Diagnosis
- Drug selection
- Dosage/adherence
- Duration of therapy
- Disabilities/complexity/comorbidities

Antidepressant Nonresponse is Often Explained By…

- Nonadherence
- Unrecognized bipolarity
- Unrecognized psychosis
- Unrecognized comorbidities

Response and Remission

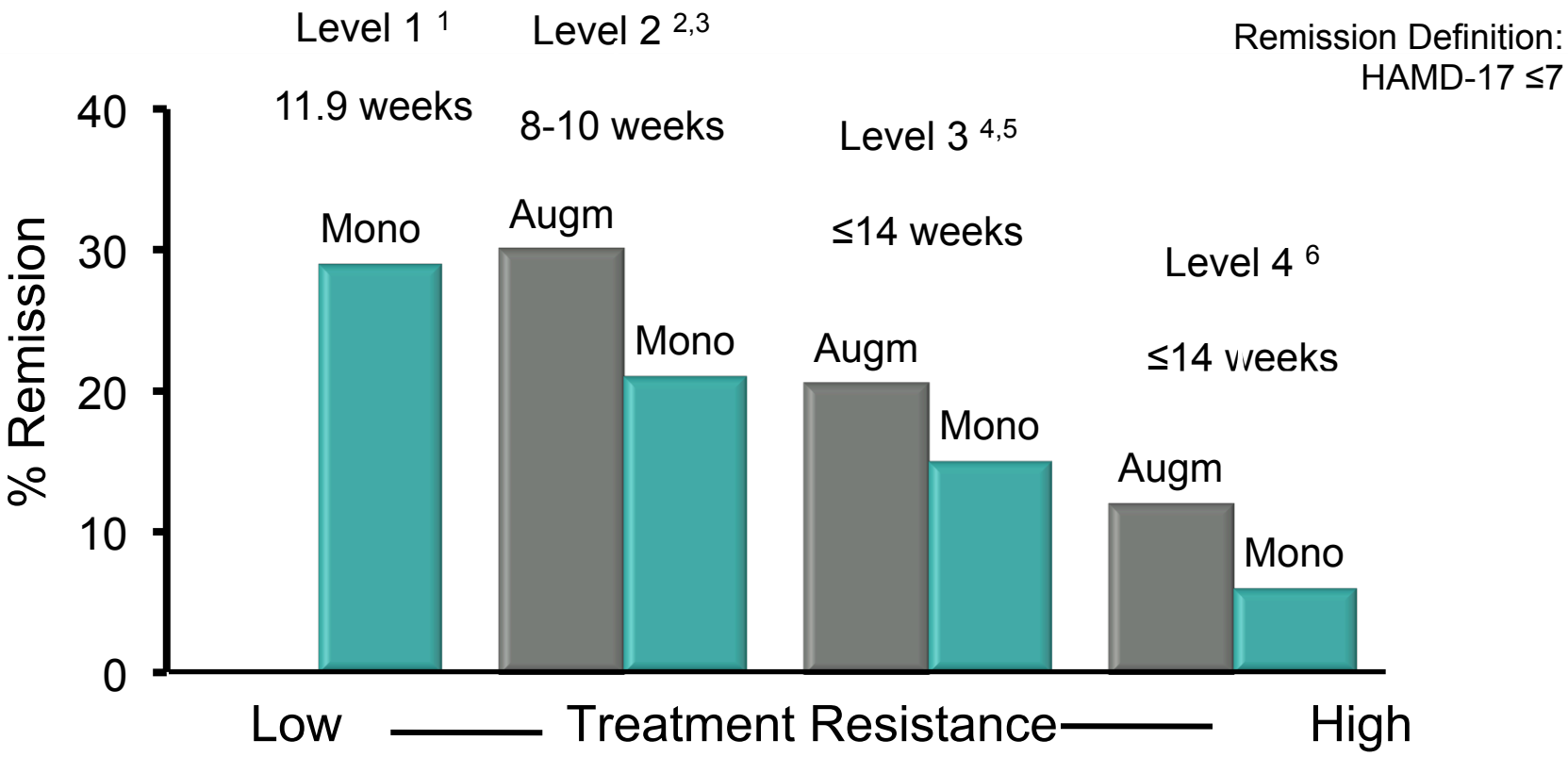
- Response – usually defined as 50% improvement in symptoms
  - Allows for the presence of significant residual symptoms, which may predispose patients to recurrence, chronicity, and suicidality
- Remission – often defined as 80% reduction in symptomatology using one of the accepted rating scales, or as an absolute cutoff score, such as <7 on the 17-item Hamilton Rating Scale for Depression (HAM-D) or <5 on the PHQ-9

Culpepper L, et al. *Am J Med*. 2015;128(9 Suppl):S1-S15.

What Constitutes an Adequate Trial of an Antidepressant?

- Longer (duration) is generally better (>4 weeks at a full therapeutic dose)
- Whenever possible, the dose should be increased above the minimum
- Intolerance does not equal nonresponse
- Residual symptoms (nonremission) do not equal nonresponse

STAR-D Remission Rates Across All 4 Levels



Mono, single medication regimen; Augm, combination medication treatment.

[1]Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40; [2]Trivedi MH et al. *N Engl J Med*. 2006;354(12):1243-1252; [3]Rush AJ et al. *N Engl J Med*. 2006;354(12):1231-1242; [4]Nierenberg AA et al. *Am J Psychiatry*. 2006;163(9):1519-1530; [5]Fava M et al. *Am J Psychiatry*. 2006;163(7):1161-1172; [6]McGrath PJ et al. *Am J Psychiatry*. 2006;163(9):1531-1541.

Should We Switch or Use Adjunctive Strategies?

- Parsimony favors switching
- Adjunctive therapies often easier to implement (i.e., avoids washout and cross-titration)
- STAR*D disappointingly did not answer this question aside from demonstrating that adjunctive strategies preferred for partial responders and switching preferred for nonresponders

New and Emerging Antidepressant Strategies in MDD

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Mechanisms of Action of Known or Putative Antidepressants

- Enchanced NE and 5-HT Monoaminergic Synaptic Activity
- Second Generation Antipsychotics
- Glutamatergic Transmission
- Hormone/Peptide Regulators
- Opioid Modulators
- Onabotulinumtoxin-A (OBA)
- Deep Brain Stimulation (DBS)

Vortioxetine

- 5HT1A agonist; 5HT reuptake blocker; 5HT1b partial agonist; 5HT3 and 5HT7 antagonist
- Positive trials reported in severe and nonsevere MDD; dose is 10-20 mg per day
- Improves cognition in MDD

McIntyre R, et al., *Int J Neuropsychopharmacol*. 2014; 17(10): 1557–1567.

Vilazodone

- SSRI and 5-HT1A Receptor Partial Agonist
- Positive trials reported in severe and nonsevere MDD; dose is 10-20 mg per day
- Improves sexual function in MDD

Khan A, et al. *Int Clin Psychopharmacol.* 2014;29(2):86-92. PMID: 24247740.

Levomilnacipran

- Serotonin and norepinephrine reuptake inhibitor (SNRI)
- Extended release
- Improves functional impairment in MDD

Montgomery SA, et al. *J Clin Psychiatry*. 2013;74(4):363-369.

Second Generation Antipsychotics

- D_2 and 5-HT_2 antagonists (e.g., quetiapine, olanzapine, etc.)
- D_2 partial agonists with serotonin receptor properties (aripripralzole and brexpiprazole)
- D_2 antagonism and mixed 5HT receptor effects (lurasidone)
- Efficacy primarily in bipolar mania, bipolar depression, and MDD augmentation

Lurasidone in MDD with Mixed Features*

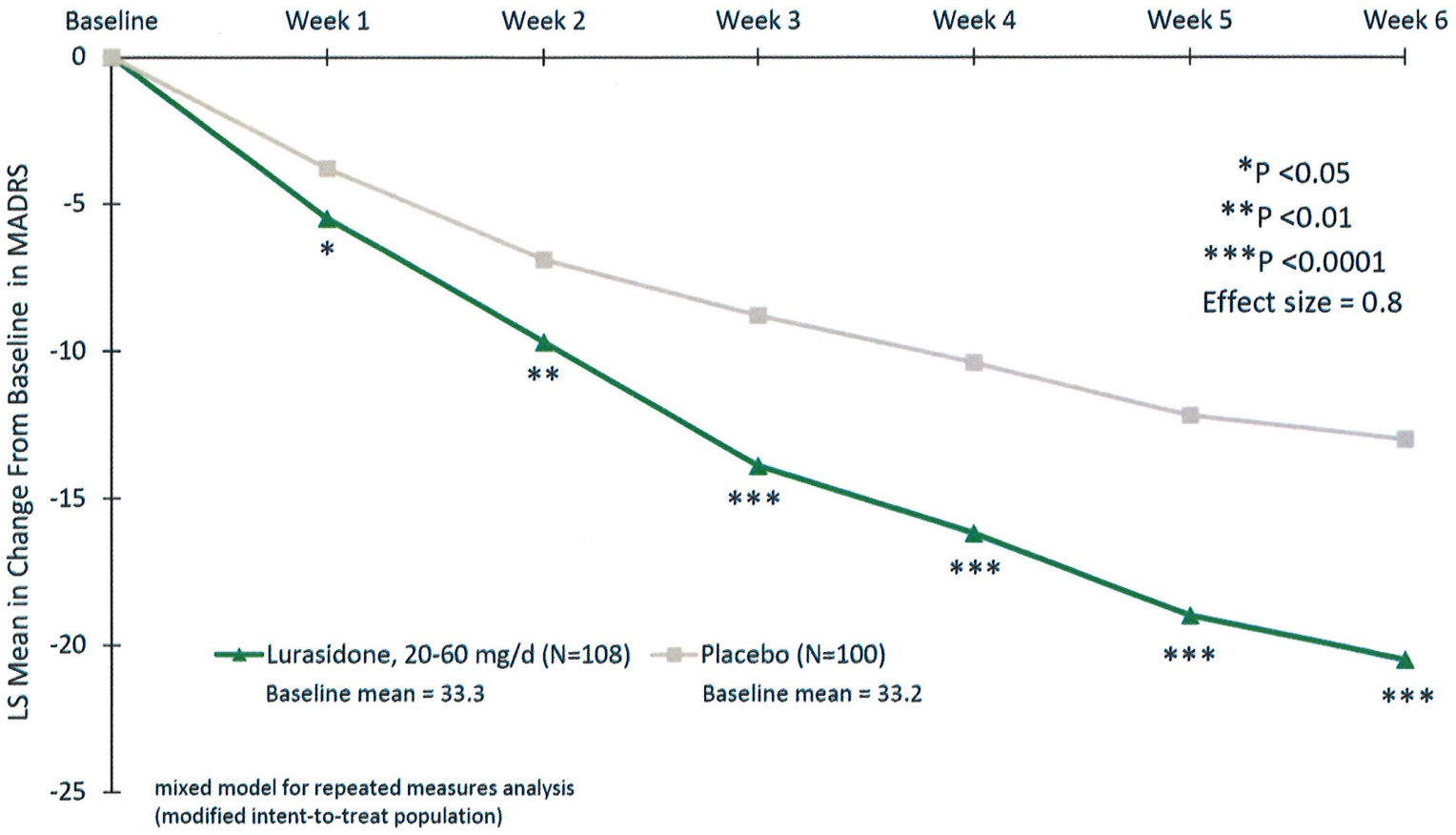
- *DSM-5* MDD "Mixed" requires 3 manic features
- Two or three mixed features in trial
- Lurasidone 20-60 mg/day vs. placebo x 6 weeks
- NNT = 3; highly effective
- Lurasidone was well tolerated; nausea 6.4% vs. 2% for placebo

*Not FDA approved for the treatment of MDD

Suppes T, et al. *Am J Psychiatry.* 2016 Apr 1;173(4):400-407.

Lurasidone in MDD with Mixed Features

Figure 2. LS Mean Change From Baseline in Efficacy Measures (MMRM analysis; ITT Population)
(A) MADRS total score



Suppes T, et al. *Am J Psychiatry*. 2016;173(4):400-407.

*Not FDA approved for the treatment of MDD

Brexpiprazole: Adjunctive Treatment in MDD

- 5HT1A and D_2 partial agonist
- 5HT2a antagonist
- Antagonist at various NE sites
- Dose related akathisia; have lower incidence than with aripriprazole
- Long-term trial 24% had weight gain (3.1 kg mean)

McKeage K. *CNS Drugs,* 2016;30(2):91-99.

Cariprazine*

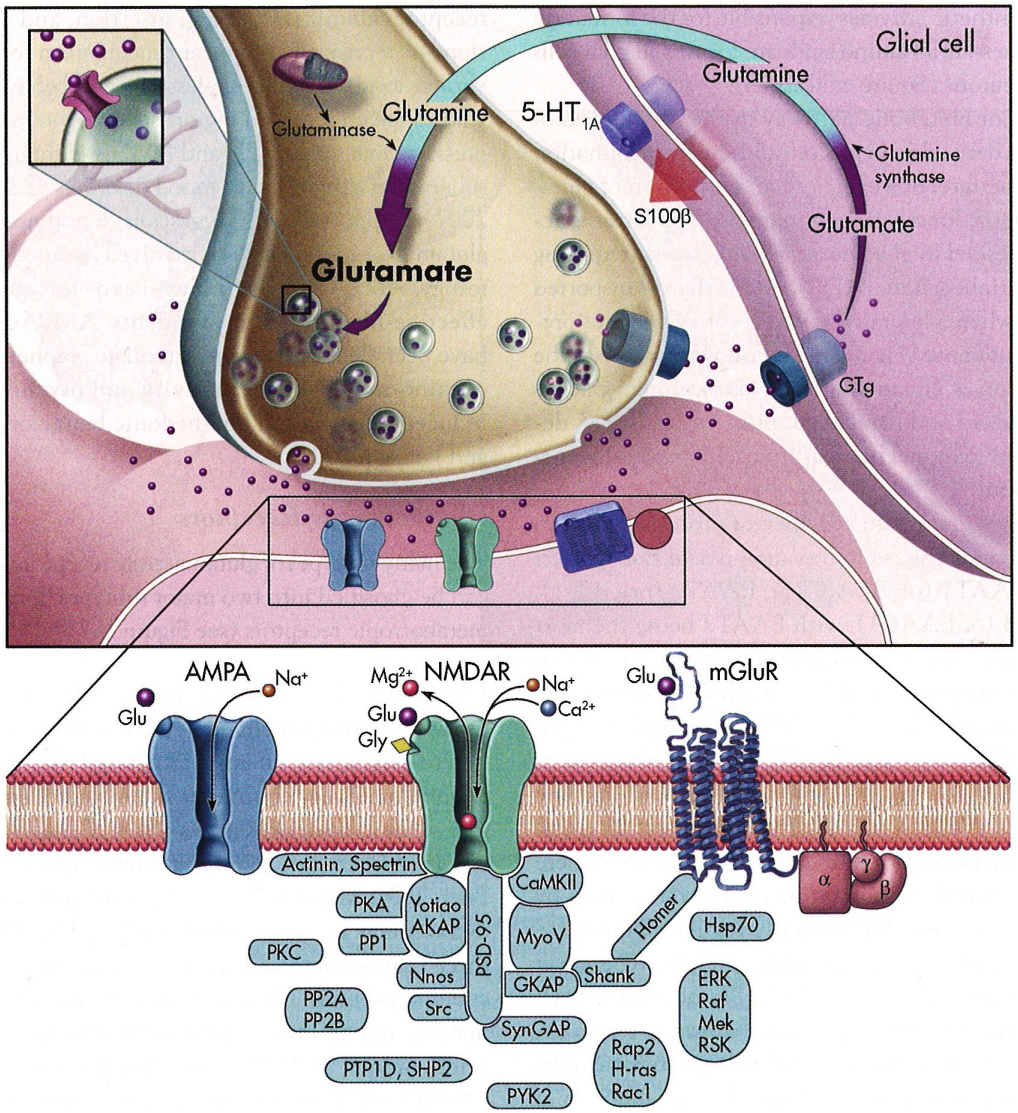
- D3 and D2 partial agonist
- Less effect as 5H2a antagonist
- Superior to placebo in MDD augmentation (NNT= 9; NNH = 10)
- Dose related akathisia
- Low weight gain

*Not FDA approved for the treatment of MDD

Durgam S et al. *Am J Psychiatry*. 2016;173(3):271-281.

Mechanisms of Action Glutamatergic Agents

- NMDA antagonism – e.g., ketamine
- Other glutamate effects – e.g, GLYX-13; D-cycloserine, etc.



Receptor Subunit Types

Ionotropic			Metabotropic		
NMDA	AMPA	Kainate	Group I	Group II	Group III
NR1	GluR1	GluR5	mGluR2 a-b-c-d	mGluR2	mGluR4 a-b
NR2 A-B-C-D	GluR2	GluR6	mGluR5 a-b	mGluR5	mGluR6
NR3 A-B	GluR3	GluR7			mGluR7 a-b
	GluR4	KA1			mGluR8 a-b
		KA2			

Ketamine*

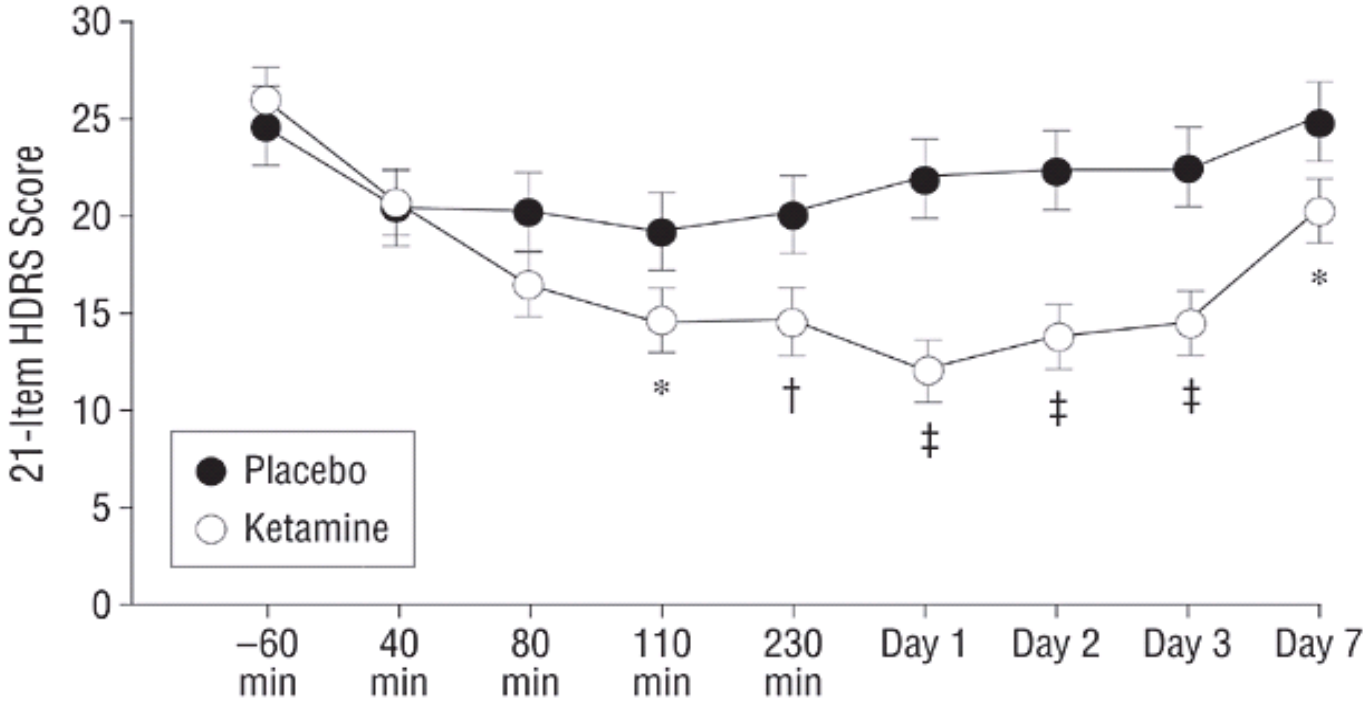
- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist;
- Mu opiod agonist; stimulant (?)
- Psychotomimetic; dissociation
- Acute antidepressant efficacy not sustained

*Not approved by the US FDA for MDD

Zarate CA, et al. *Arch Gen Psychiatry* 2006;63:856-864.

Ketamine: Change in the Hamilton Depression Rating Scale

The 21-item Hamilton Depression Rating Scale (HDRS) over 1 week (n = 18)



Zarate CA, et al. *Arch Gen Psychiatry* 2006;63:856-864.

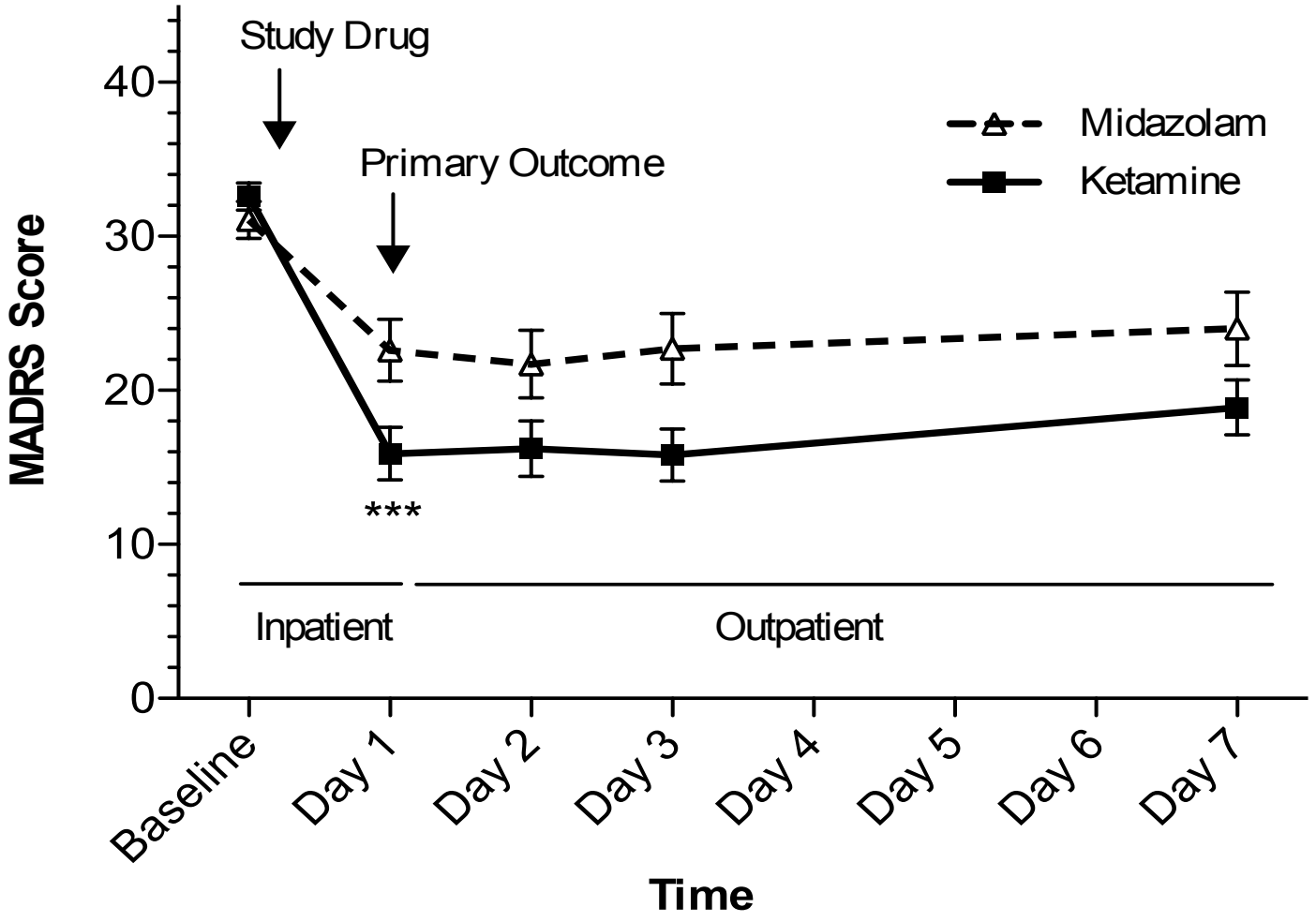
Rationale for OPT KET NIMH Trial in Treatment-Resistant Depression

- Several single-site studies supported the rapid antidepressant efficacy of ketamine in TRD; however, uncertainties remained
  - Small sample size
  - Crossover design
  - Saline as control condition
  - Response persistence
  - Safety and tolerability
- Would a single infusion of ketamine prove superior to an "active" placebo in a parallel-arm randomized controlled trial?
- Ketamine (N = 47); midazolam (N = 25)

*Not approved by the US FDA for MDD

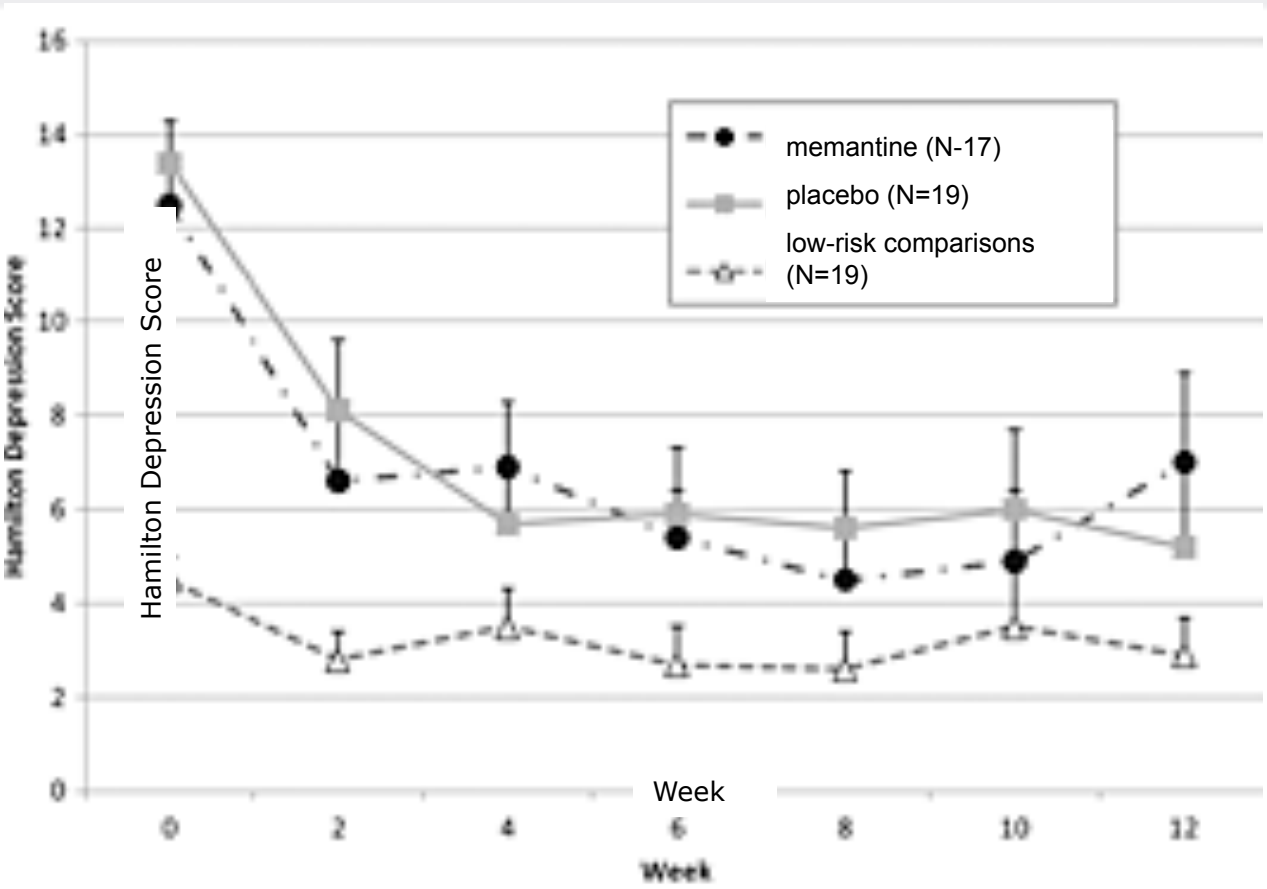
Zurate C. ClinicalTrials.gov Website. https://www.clinicaltrials.gov/ct/show/NCT00088699.

Ketamine Primary Efficacy Outcome



Murrough JW et al. *Am J Psychiatry*. 2013;170(10):1134-1142.

Memantine for Late-Life Depression and Apathy After Disabling Medical Event: HDRS Effect



*Not approved by the US FDA for MDD

Lenze EJ, et al. *Int J Geriatr Psychiatry*. 2012;27(9):974-980.

AZD 6765

- Synaptic glutamate binder
- Recent multicenter trials failed to demonstrate efficacy in multiple doses per week protocols over several weeks
- Program reportedly canceled

Zarate CA Jr, et al. *Biol Psychiatry*. 2013;74(4):257-264.

GLYX-13 in Major Depression

- U shaped dose response in rat models and in Phase 2A study
- No ketamine-like side effects
- Phase 2A study – 1,5,10 or 30 mg or placebo; i.v.
- 5 mg. and 10 mg. separated from placebo at day 7 but not at day 14; other doses did not
- Effect size for single dose 0.58

Burch RM: Presented at the ACNP Annual Meeting, December 2-6, 2012.

A Randomized Add-On Trial of High-Dose D-cyloserine for Treatment-Resistant Depression

Abstract

Antagonism of N-methyl-d-aspartate glutamatergic receptors (NMDAR) may represent an effective antidepressant mechanism. d-cycloserine (DCS) is a partial agonist at the NMDAR-associated glycine modulatory site that at high doses acts as a functional NMDAR antagonist. Twenty-six treatment-resistant major depressive disorder patients participated in a double blind, placebo-controlled, 6-wk parallel group trial with a gradually titrated high dose (1000 mg/d) of DCS added to their antidepressant medication. DCS treatment was well tolerated, had no psychotomimetic effects and led to improvement in depression symptoms as measured by Hamilton Depression Rating Scale (HAMD; $p = 0.005$) and Beck Depression Inventory ($p = 0.046$). Of the 13 subjects treated with DCS, 54% had a ⩾50% HAMD score reduction vs. 15% of the 13 patients randomized to placebo ($p = 0.039$). A significant ($p = 0.043$) treatment× pre-treatment glycine serum levels interaction was registered. These findings indicate that NMDAR glycine site antagonism may be a cost-effective target for development of mechanistically novel antidepressants. Larger-sized DCS trials are warranted.

Heresco-Levy U et al. *Int J Neuropsychopharmacol 2013;*16(3):501-506.

Mechanisms of Action
Opioid Modulators

- Mu partial or full agonists – buprenorphine; ketamine
- Mixed mu agonist – antagonist – buprenorphine/SAM
- Kappa antagonists

Buprenorphine*

- Partial mu opioid agonist
- Kappa antagonist
- Used in addiction treatment
- Open label, positive data in refractory depression
- Being developed (in combination with samidorphan, a mu antagonist) for treatment of refractory major depression[1]

*Not approved by the US FDA for MDD

Fava M, et al. *Am J Psychiatry*. 2016;173(5):499-508.

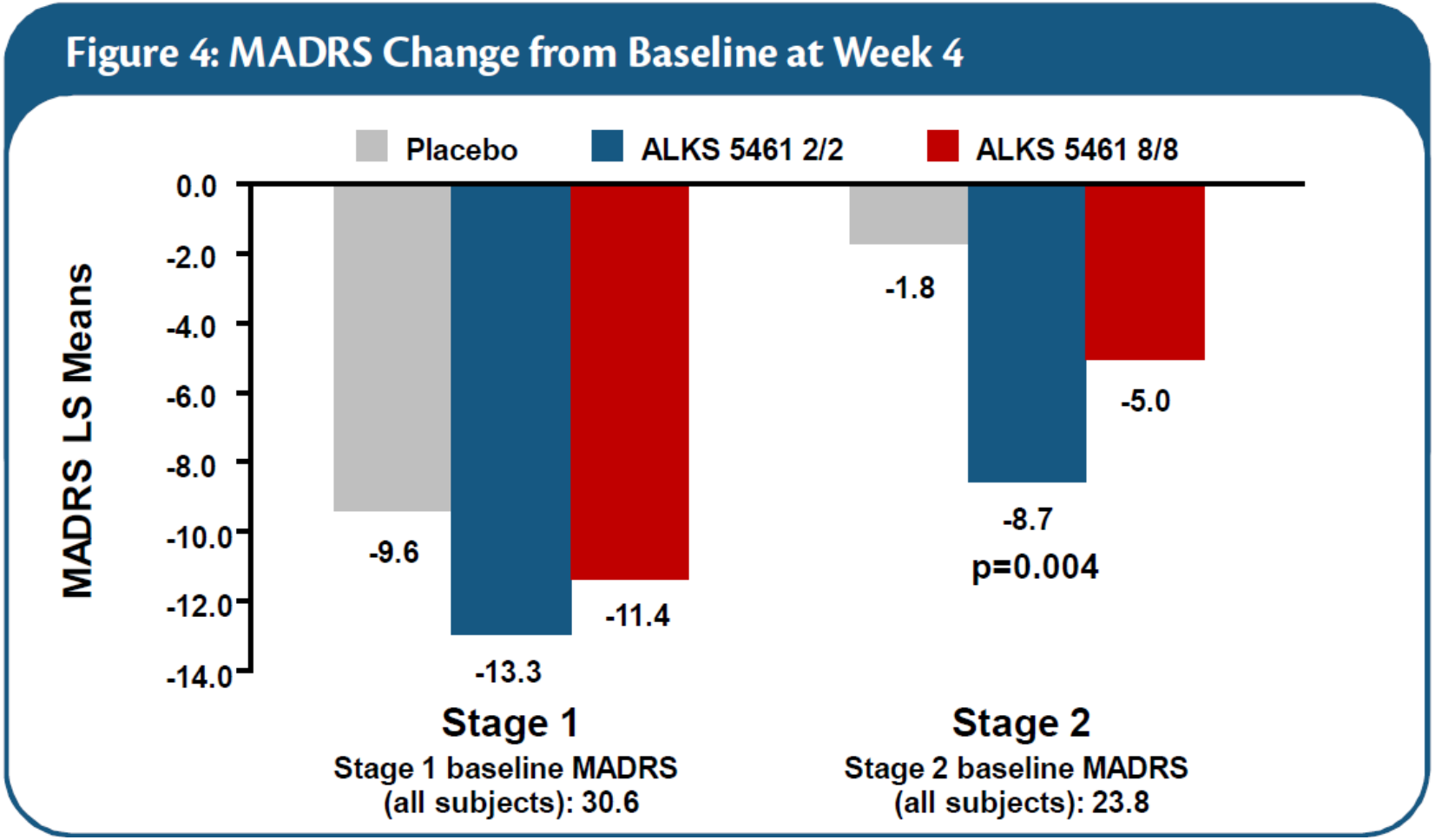
Low Dose Buprenorphine Reduces Suicidal Ideation

- 88 patients with clinically significant suicidal ideation
- Buprenorphine 0.1-0.8 mg/day (mean dose 0.44 mg/day)

  or placebo for 4 weeks
- Buprenorphine superior to PBO for reducing suicidal ideation at 2 and 4 weeks
- No withdrawal symptoms after treatment discontinuation

Psychiatric News. Low-Dose Buprenorphine Found to Decrease Suicidal Ideation, but Experts Remain Cautious. Website:http://alert.psychnews.org/2015/12/low-dose-buprenorphine-found-to.html. Published December 2015. Accessed May 20, 2016.

RCT of ALKS 5461 (buprenorphine plus the mu antagonist ALKS 33) in SSRI non-responders



Fava M, et al. *Am J Psychiatry*. 2016;173(5):499-508.

ALKS-5461 As Adjunct in MDD

- FORWARD-3 and FORWARD-4
- 814 patients in DB, PBO controlled 11 week trials in antidepressant non-responders
- Doses of buprenorphine/samidorphan (0.5/0.5 mg and 2/2 mg)
- Both doses not superior to PBO
- FORWARD-5 (1/1 mg and 2/2 mg) continues

Fava M, et al. *Am J Psychiatry*. 2016;173(5):499-508.

Mechanisms of Action Hormone/Peptide Regulators

- Glucocorticoid receptor antagonists
  - e.g., mifepristone
- CRH-R1 antagonists
- Melatonin type 1 and 2 receptor agonist
  - e.g., agomelatine

Agomelatine*

- M1 and M2 agonist
- 5HT2c antagonist
- Several positive European studies led to European licensure
- Phase III US program – 2 positive trials published
- Elevated LFTs are a potential limiting factor for FDA approval

*Not approved by the US FDA for MDD

Zarecka, et al. *J Clin Psychopharmacol.* 2010 Apr;30(2):135-144.
Stahl, S, et al. *CNS Spectr*. 2014;19(3):207-212.

Agomelatine Efficacy and Acceptability Revisited: Systematic Review and Meta-Analysis of Published and Unpublished Randomized Trials*

METHOD:

- Randomised controlled trials comparing agomelatine with placebo in the treatment of unipolar major depression were systematically reviewed. Primary outcomes were (a) Hamilton Rating Scale for Depression (HRSD) score at the end of treatment (short-term studies) and (b) number of relapses (long-term studies).

RESULTS:

- Meta-analyses included 10 acute-phase and 3 relapse prevention studies. Seven of the included studies were unpublished. Acute treatment with agomelatine was associated with a statistically significant superiority over placebo of -1.51 HRSD points (99% CI -2.29 to -0.73, nine studies). Data extracted from three relapse prevention studies failed to show significant effects of agomelatine over placebo (relative risk 0.78, 99% CI 0.41-1.48). Secondary efficacy analyses showed a significant advantage of agomelatine over placebo in terms of response (with no effect for remission). None of the negative trials were published and conflicting results between published and unpublished studies were observed.

Koesters M, et al. *Br J Psychiatry*. 203:179-87, 2013.

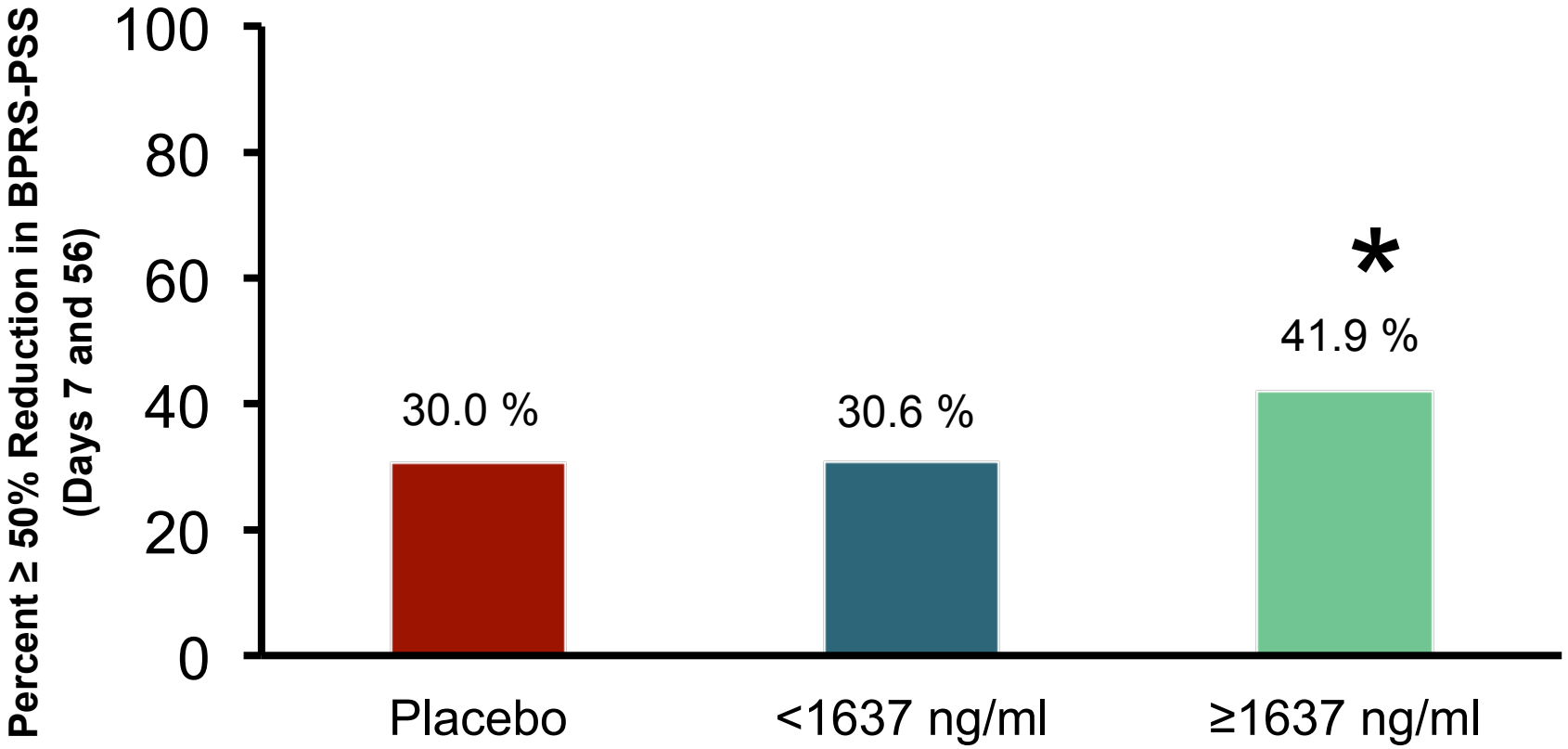
*Not approved by the US FDA for MDD

Psychotic Major Depression

- 15-19% of community-based subjects with major depression[1]
- Marked neuropsychological impairments [2,3]
- Excessive HPA axis activity[4] proposed as a cause of psychosis and/or cognitive impairment and target for treatment[5]
- Mifepristone – GR antagonist 7 day treatment with longer term relief out to 8 weeks[6]

1.Ohayon MM and Schatzberg AF. *Am J Psychiatry*. 2002;159(11):1855-1861;2. 3.Schatzberg et al., Am J Psychiatry. 2000l;157(7):1095-1100; 3.Jeste D, et al, *Am J Psychiatry.* 1996;153(4):490-496;4. Nelson JC,, et al. *Am J Psychiatry.* 1997;154(11):1497-1503;5.Schatzberg AF. *J Psychiatr Res.* 1985;19(1):57-64;6. Belanoff JK, et al. *Biol Psychiatry*. 2002;52(5):386-392

Mifepristone** Plasma Level: Clinical Response
(Placebo N = 626; Drug N = 824)

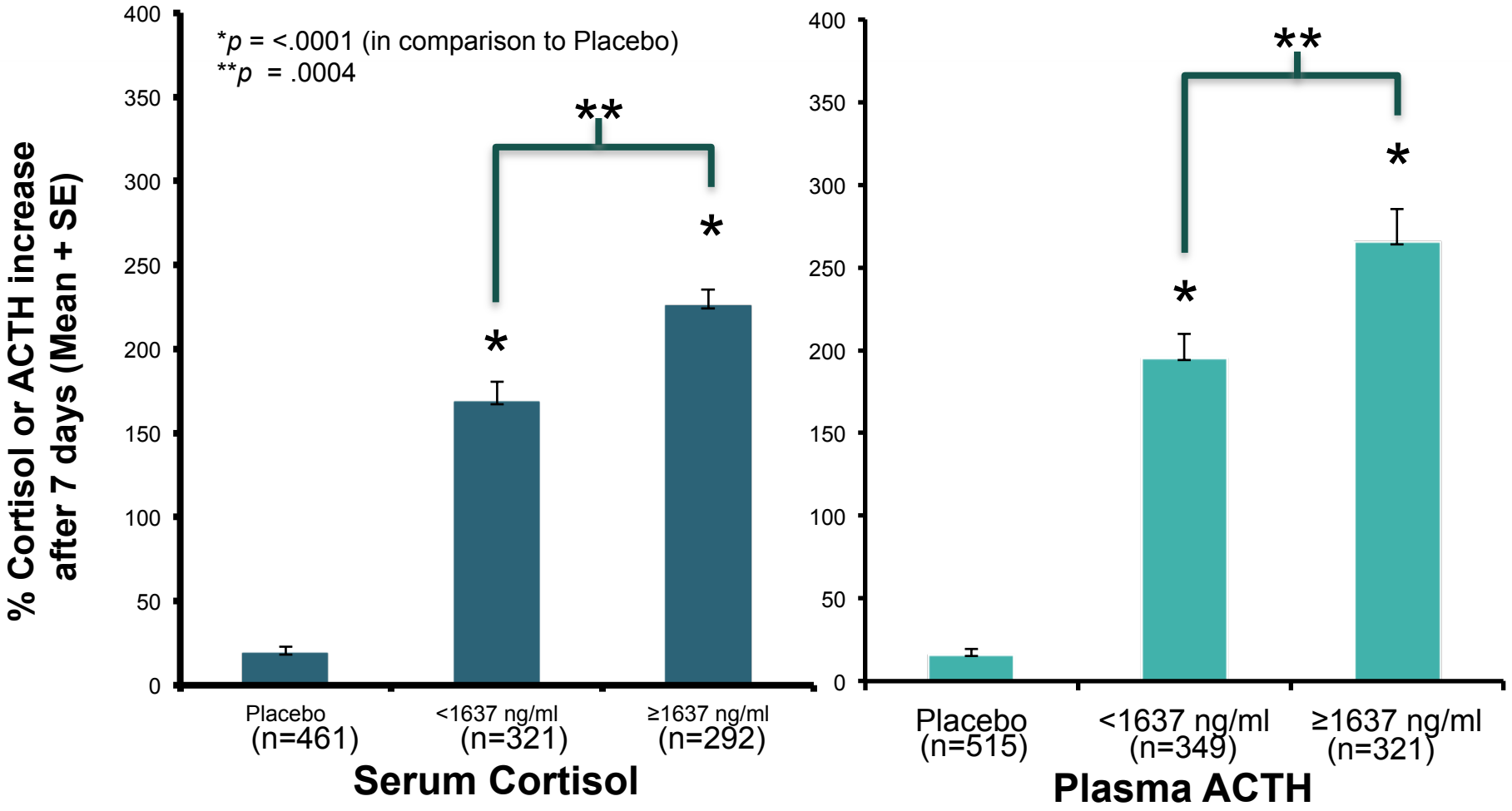


* *p* = .0004 (in comparison to Placebo)

**Not approved by the US FDA for MDD

Schatzberg AF. *Biol Psychiatry* 2015;77(9S): Abs403.

Mifepristone Plasma Level:
Serum Cortisol and ACTH, at Day 7



Schatzberg AF. *Biol Psychiatry* 2015;77(9S): Abs403

*p = <.0001 (in comparison to Placebo)
**p = .0040

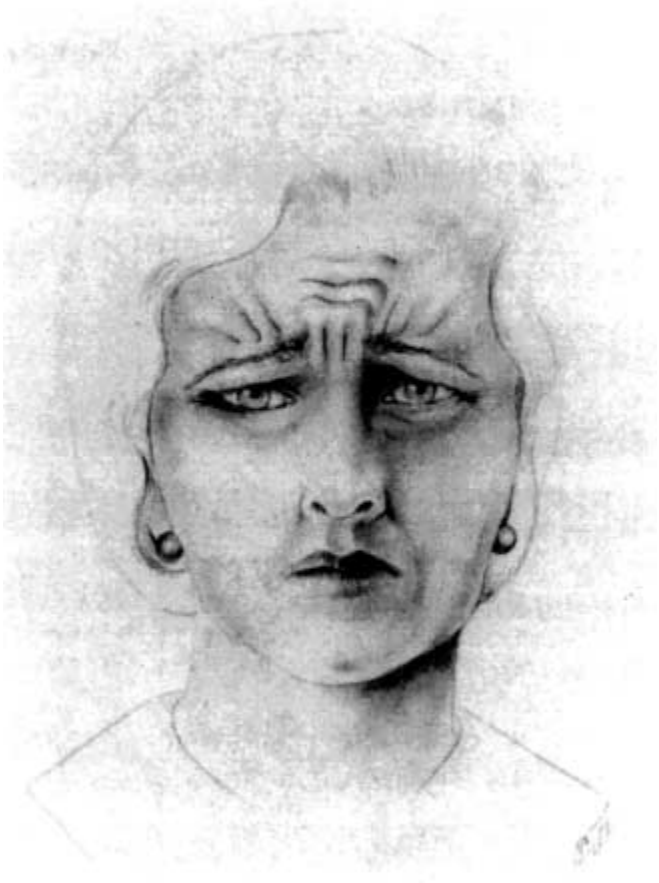
Onabotuliniumtoxin A*

- ACh release inhibitor and neuromuscular blocking agent
- Pain indications – chronic migraine and cervical dystonia
- 2 positive RCT's in major depression
- Effects of one injection last up to 16 weeks

*Not approved by the US FDA for MDD

Greden J, et al, *Am J Psychiatry*. 1985;42(3):348-351.

Drawing of Patient Showing Omega Sign and Veraguth's Fold

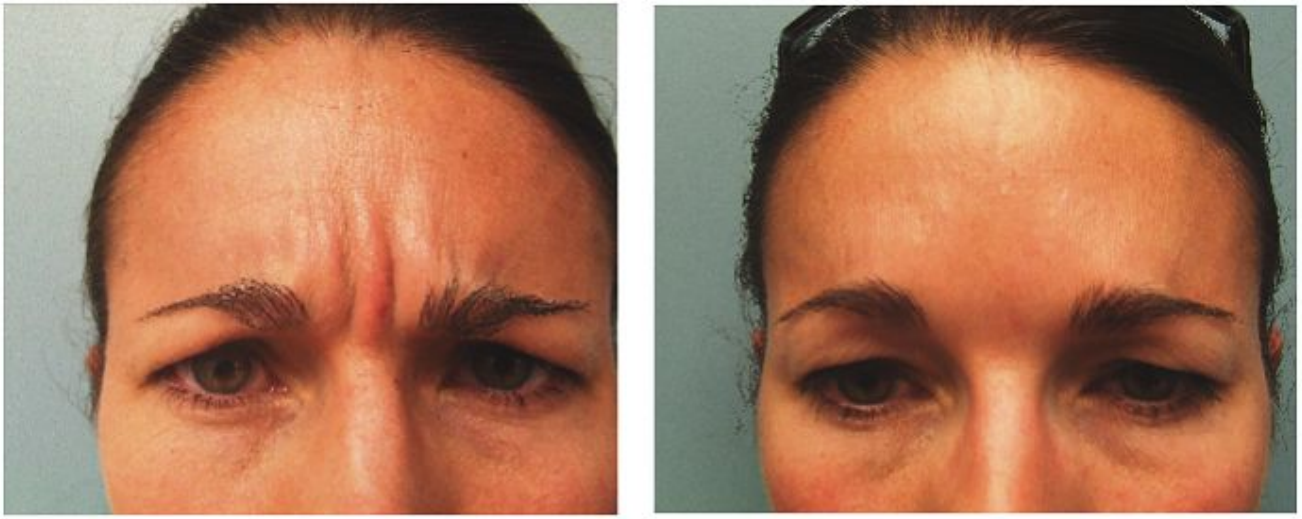


Greden et al, *Am J Psychiatry*. 1985;42(3):348-351.

OnabotulinumtoxinA* (OBA) and Frown Expression

Frown Expression before and after OBA treatment

(N = 30)



before after

(patient went into remission)

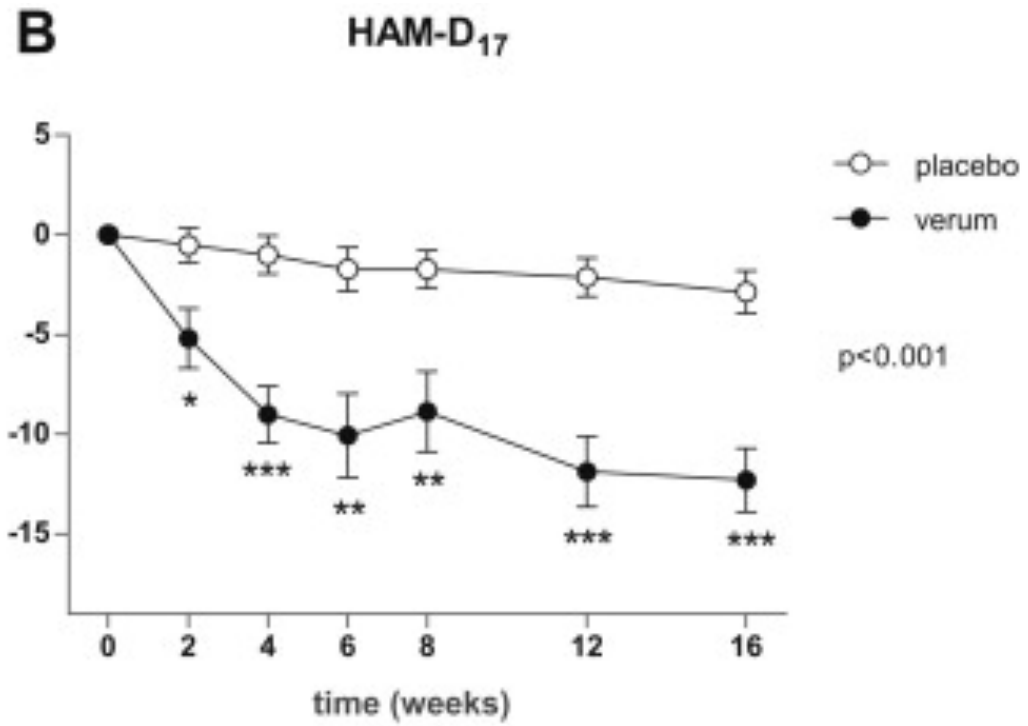
Dose – Women 29U
Men 40U

*Not approved by the US FDA for MDD

Wollmer MA, et al. *J Psych Res*. 2012;46:574-581.
Finzi, Rosenthal: ACNP Annual Meeting, 2012.

OnabotulinumtoxinA* (OBA) vs. Placebo in Major Depression: HDRS-17

(N = 30)



Dose – Women 29U
Men 39U

*Not approved by the US FDA for MDD

Wollmer MA, et al. *J Psych Res*. 2012;46:574-581, PMID: 22364892.

Amygdala-prefrontal Coupling Underlies Individual Differences in Emotion Regulation

Abstract

Despite growing evidence on the neural bases of emotion regulation, little is known about the mechanisms underlying individual differences in cognitive regulation of negative emotion, and few studies have used objective measures to quantify regulatory success. Using a trait-like psychophysiological measure of emotion regulation, corrugator electromyography, we obtained an objective index of the ability to cognitively reappraise negative emotion in 56 healthy men (Session 1), who returned 1.3 years later to perform the same regulation task using fMRI (Session 2). Results indicated that the corrugator measure of regulatory skill predicted amygdala-prefrontal functional connectivity. Individuals with greater ability to down-regulate negative emotion as indexed by corrugator at Session 1 showed not only greater amygdala attenuation but also greater inverse connectivity between the amygdala and several sectors of the prefrontal cortex while down-regulating negative emotion at Session 2. Our results demonstrate that individual differences in emotion regulation are stable over time and underscore the important role of amygdala-prefrontal coupling for successful regulation of negative emotion.

Lee H, et al. *Neuroimage*, 2012;62(3):1575-81.

Neuron, Vol. 45, 1–10, March 3, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.02.014

Deep Brain Stimulation for Treatment-Resistant Depression

Helen S. Mayberg,[1,2,*] Andres M. Lozano,[3,*]
Valerie Voon,[4] Heather E. McNeely,[5]
David Seminowicz,[6] Clement Hamani,[3]
Jason M. Schwalb,[3] and Sidney H. Kennedy[4]

First published study of DBS for TRD
Hypothesis driven, safety/proof-of-concept study
Open trial of subcallosal cingulate white matter DBS in 6 pts
4/6 Responders at 6 months (HRDS=8±3)
All 4 still well at 5+ years with continued Stimulation

Recent DBS Results

- Trial using the anterior capsule canceled after interim analysis
- Trial on subgenual capsule canceled after interim analysis
- Pilot trial suggested medial forebrain bundle may be a preferred site for implantation; further study resulted in failed trial

Schlaepfer TE, et al. *Biol Psychiatry* 201315;73(12):1204-1212.

Psychotherapy for MDD

- Cognitive Behavioral therapy (CBT)
  - How thoughts effect feelings
  - “Automatic thoughts”
  - Homework
- Interpersonal Therapy (IPT)
  - Form of CBT, emphasis on interactions
- Problem-Solving Therapy (PST)
  - Form of CBT, emphasis on identifying and solving a particular problem related to depression

Mulsant BH, et al. *Psychopharmacology*. In: The American Psychiatric Publishing Textbook of Geriatric Psychiatry. 4th ed. 2009

Audience Response

How many weeks constitutes an adequate trial of an antidepressant?

A. 2 weeks
B. > 4 weeks
C. < 6 weeks
D. 8 weeks

Audience Response

Remission is defined as what percent reduction in symptomatology?

A. 60%
B. 70%
C. 80%
D. 90%

Questions & Answers

CME Outfitters