A SHORT TRIP ACROSS 50 YEARS (NEARLY) OF PROGRESS IN CLINICAL PSYCHOPHARMACOLOGY

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Michael E Thase Disclosure: Past Three Years

- ***Consultant:*** Abbvie; Axsome Therapeutics, Inc.; Bristol-Myers Squibb; Boehringer Ingelheim; Eli Lilly, Gerson Lehrman Group; GH Research; Johnson & Johnson (Intracellular, Inc; Janssen Pharmaceuticals); H. Lundbeck; Merck & Company, Inc.; Otsuka Pharmaceutical Co., Ltd.; Sage Pharmaceuticals; Takeda Pharmaceutical Company, Ltd.
- ***Grant Support:*** Atai Life Sciences; Axsome Therapeutics Inc.; Johnson & Johnson (Intracellular, Inc.; Janssen Pharmaceuticals, Inc.); National Institute of Mental Health; Otsuka Pharmaceuticals; Patient-Centered Outcomes Research Institute (PCORI); Reunion Inc; Takeda Pharmaceutical Company, Ltd.
- ***Royalties:*** American Psychiatric Press., Inc.; Guilford Publications; Herald House; Kluwer-Wolters; W.W. Norton & Company, Inc.
- ***Spouse's Employment:*** Dr. Diane Sloan is an Executive Vice President of Open Health, which does business with many pharmaceutical companies.

Relevant Historical Disclosures (1983-2010)

- ***Consultant and Grant Support***
  - AstraZeneca
  - Burroughs Wellcome
  - Glaxo Smith Klein
  - Mead Johnson
  - Organon Akzo Nobel
  - Pfizer Pharmaceuticals
  - The Upjohn Company
  - Wyeth-Ayerst Pharmaceuticals

Special Thanks to….

- **Susan Kornstein, MD.** Professor of Psychiatry and Obstetrics & Gynecology, Virginia Commonwealth University School of Medicine, Executive Director, VCU Institute for Women's Health
- **Maurizio Fava, MD**. Professor of Psychiatry, Harvard Medical School and Chair of Psychiatry, Mass General Brigham AMC
- **Madhukar Trivedi, MD**. Professor of Psychiatry, Betty Jo Hay Distinguished Chair in Mental Health and Julie K. Hersh Chair for Depression Research at the UT Southwestern Medical Center.
- **ASCP Award Committee**

In the Beginning: Before I was a Physician (1952-1979)

- Family history and early life on the farm: code of the midwest
- Importance of baseball and lessons learned
- Tumult of 1968-1970
- Finding my 2nd groove: critical life decisions #1, 2 & 3
    - transferring from OSU to Wright State University in 1973
    - first meaningful academic mentors (Moss & Page)
    - wise advice from my brother-in-law and the post-bac year
    - good luck not to be accepted into an MD/PhD program

Pharmacotherapy of Depressive Disorders: 1970s-1983

Intertwined Developments with Career Developmental Milestones

- 1976: Began medical school in an era of TCA hegemony. MAOIs and ECT primary alternatives for TCA nonresponders. Wrote first prescription (amitriptyline) in January ’78 – caused first delirium. Chose Pitt/WPIC for internship/residency
- 1980: Began residency in general psychiatry at Pitt/WPIC; purchased and devoured Klein et al textbook. Began 1 year of inpatient experience (Chip Reynolds & Mike Shostak, attendings) and permitted to have a 1 year elective in Jon Himmelhoch’s Affective Disorders Clinic ultimately lasting 3 years
- 1981: FDA approves trazodone – first novel nonTCA/nonMAOI antidepressant
- 1982: Began 2 year NIMH-funded post-doc in clinical research. David J Kupfer(DJK) primary mentor. Began work as a study doctor on two NIMH funded RCTs. Met Donald F Klein (DFK) and collaborated “remotely” on extracting a HAMD subscale that better captured his endogenomorphic depression construct
- 1983: Joined Pitt faculty and became a member of DJK’s CRC investigator group

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Pharmacotherapy of Depressive Disorders: 1983-1989

Intertwined Developments with Career Developmental Milestones

- 1983-1985: David Kupfer becomes Chair. Approved my “design”of standardized case series for management of imipramine nonresponders (sequential trials of lithium, thyroid and/or perphenazine “augmentation” and switching to MAOIs). Joined Mead Johnson and Upjohn speaker’s bureaus. CRC supported papers and chapters. Began collaborations with other senior colleagues, including Ellen Frank and Chip Reynolds.
- 1986-1989: Wrote first NIMH grant (funded on 2nd review). Obtained first industry grant (clomipramine treatment for OCD). Began to collaborate with John Rush on developing standardized algorithms for TCA nonresponders. Fluoxetine approved by FDA: dawn of the SSRI era. Joined Lilly Speaker’s bureau. Obtained 2nd industry funded grant (Lilly). Promoted to Associate Professor. Attended first NCEU meeting and presented paper on MAOI treatment of imipramine nonresponders. Got to hobnob with DFK.

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Pharmacotherapy of Depressive Disorders: 1990-2000

Intertwined Developments with Career Developmental Milestones

- 1990: Began 20+ year collaboration with Keller, Hirschfeld, Gelenberg et al studying chronic forms of depression (Pfizer, BMS, NIMH)
- 1992-2000: Phase 3 and 4 studies of all newer generation antidepressants
- Pitt/WPIC original patient data meta-analysis (first presented at NCDEU)
- Fluoxetine approved by FDA: dawn of the SSRI era. Joined Lilly Speaker's bureau. Obtained 2nd industry funded grant (Lilly). Promoted to Associate Professor. Attended first NCEU meeting and presented paper on MAOI treatment of imipramine nonresponders. Got to hobnob with DFK.

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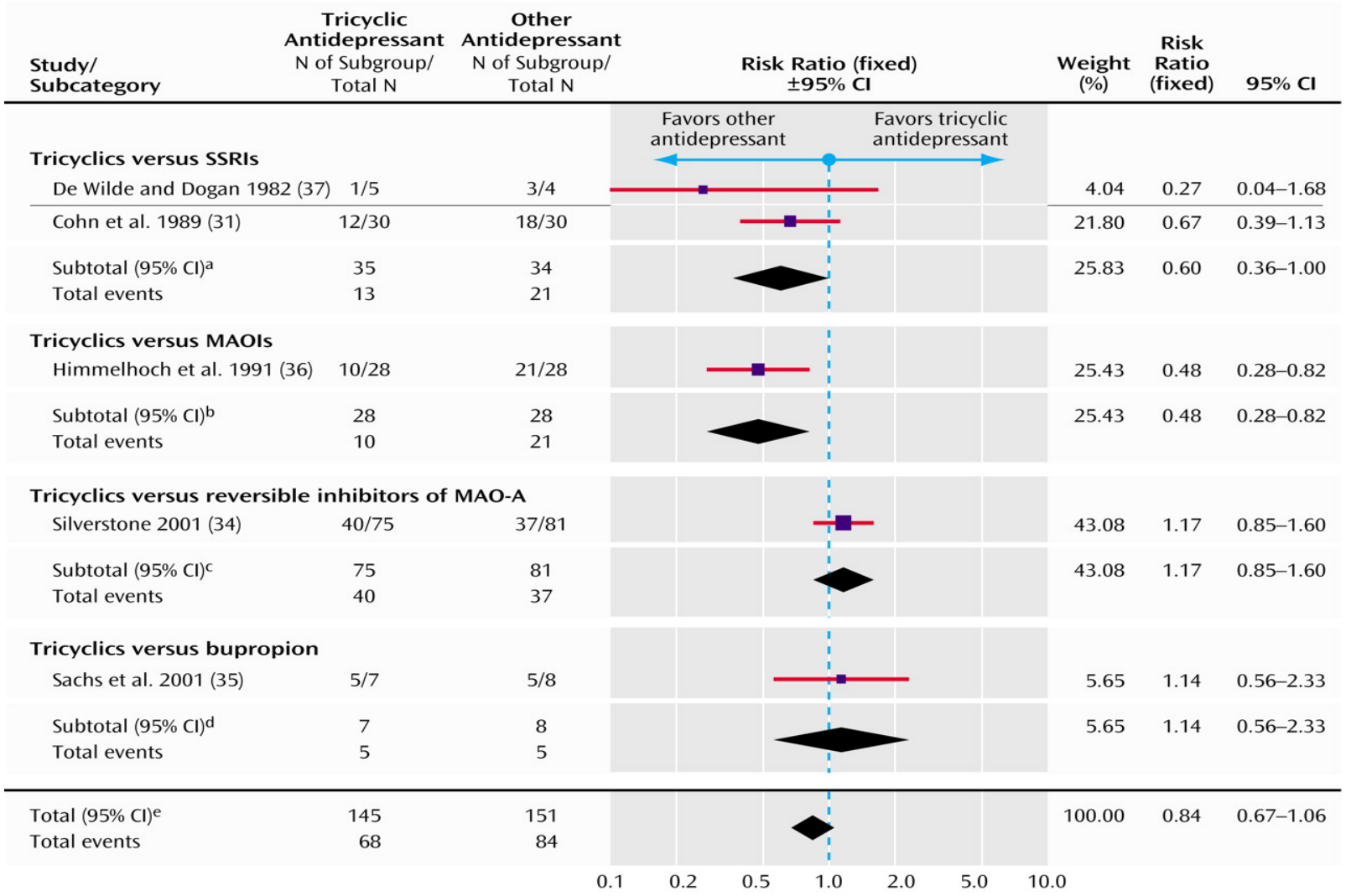
Antidepressants in Bipolar Depression: Tricyclic Antidepressants vs. Other Antidepressants



Study/ Subcategory	Tricyclic Antidepressant N of Subgroup/ Total N	Other Antidepressant N of Subgroup/ Total N	Weight (%)	Risk Ratio (fixed)	95% CI
Tricyclics versus SSRIs					
De Wilde and Dogan 1982 (37)	1/5	3/4	4.04	0.27	0.04–1.68
Cohn et al. 1989 (31)	12/30	18/30	21.80	0.67	0.39–1.13
Subtotal (95% CI)[a]	35	34	25.83	0.60	0.36–1.00
Total events	13	21			
Tricyclics versus MAOIs					
Himmelhoch et al. 1991 (36)	10/28	21/28	25.43	0.48	0.28–0.82
Subtotal (95% CI)[b]	28	28	25.43	0.48	0.28–0.82
Total events	10	21			
Tricyclics versus reversible inhibitors of MAO-A					
Silverstone 2001 (34)	40/75	37/81	43.08	1.17	0.85–1.60
Subtotal (95% CI)[c]	75	81	43.08	1.17	0.85–1.60
Total events	40	37			
Tricyclics versus bupropion					
Sachs et al. 2001 (35)	5/7	5/8	5.65	1.14	0.56–2.33
Subtotal (95% CI)[d]	7	8	5.65	1.14	0.56–2.33
Total events	5	5			
Total (95% CI)[e]	145	151	100.00	0.84	0.67–1.06
Total events	68	84			

Gijsman HJ, et al. *Am J Psychiatry*. 2004;161:1537-1547.

Pharmacotherapy of Depressive Disorders: 1990-2000

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- Pitt/WPIC original patient data meta-analysis (first presented at NCDEU)
- First and second RO1 data published
- Promoted to Professor (1994)

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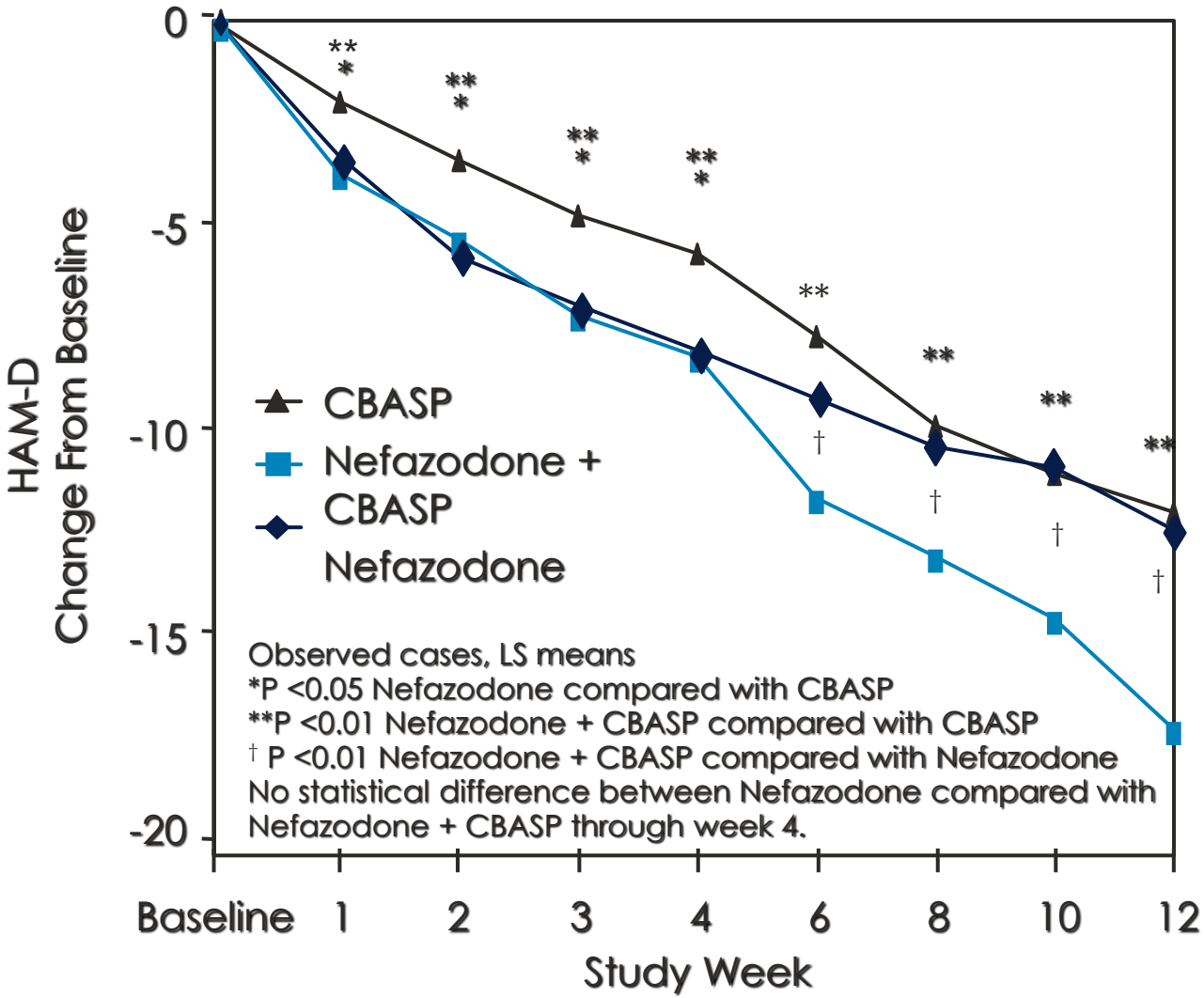
CBASP, Nefazodone, and Their Combination for Treatment of Chronic Depression



Keller MB, et al. *New Eng J Med.* 2000;342(20):1462-1470

Pharmacotherapy of Depressive Disorders: 1990-2000

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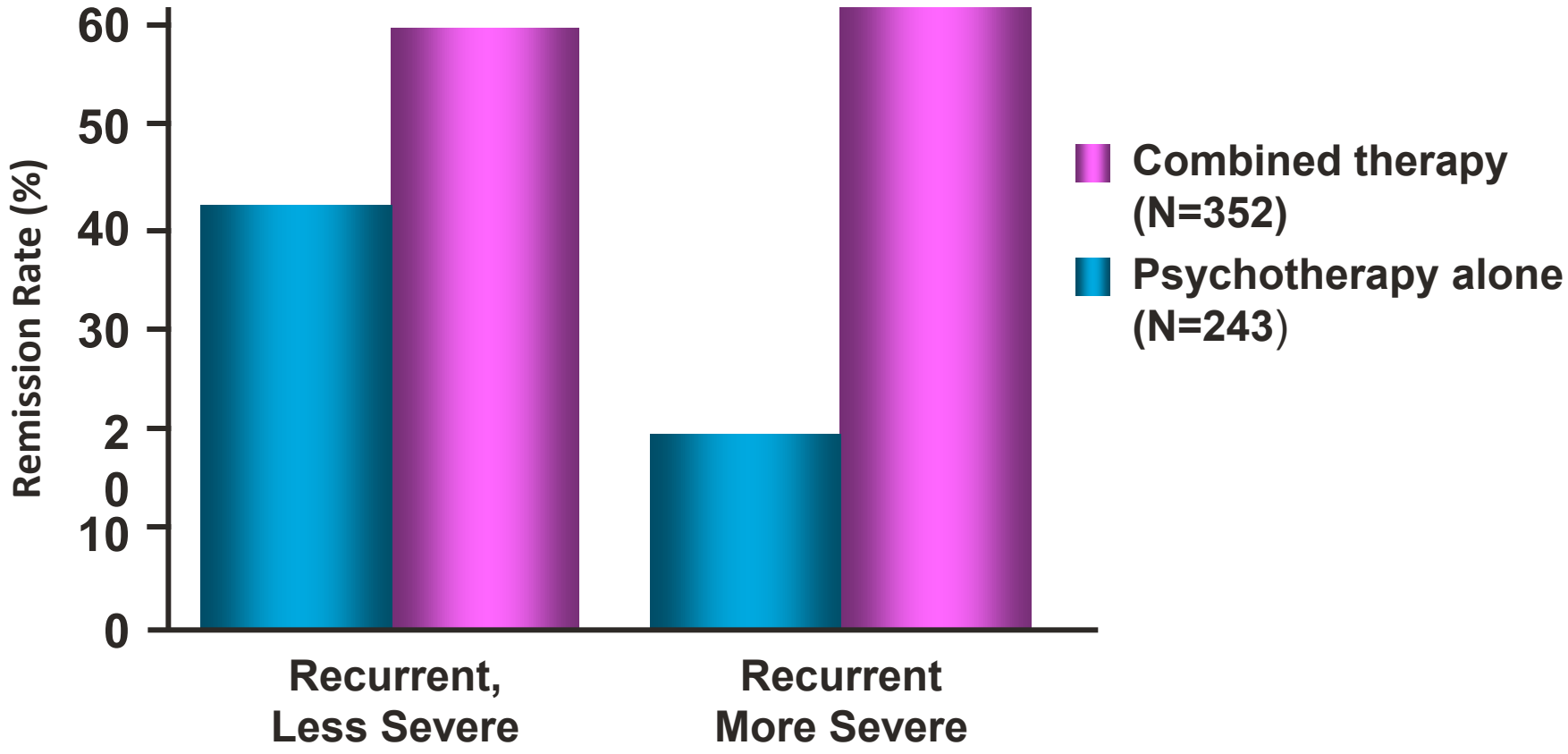
Combined Treatment Superior to Psychotherapy Alone for Patients with More Severe, Recurrent Depressions



Thase ME, et al. *Arch Gen Psychiatry.* 1997;54:1009-1015

Pharmacotherapy of Depressive Disorders: 2000-2010

Intertwined Developments with Career Developmental Milestones

- **2000 Large Scale Collaborations with NIMH**

  - **STEP-D (co-led with Gary Sachs)**

    - STAR*D (led by Rush, Fava & Trivedi)

  - REVAMP (co-led with James Kocsis & Trivedi)

Critical life decision # 4: moving to Philadelphia (2007)

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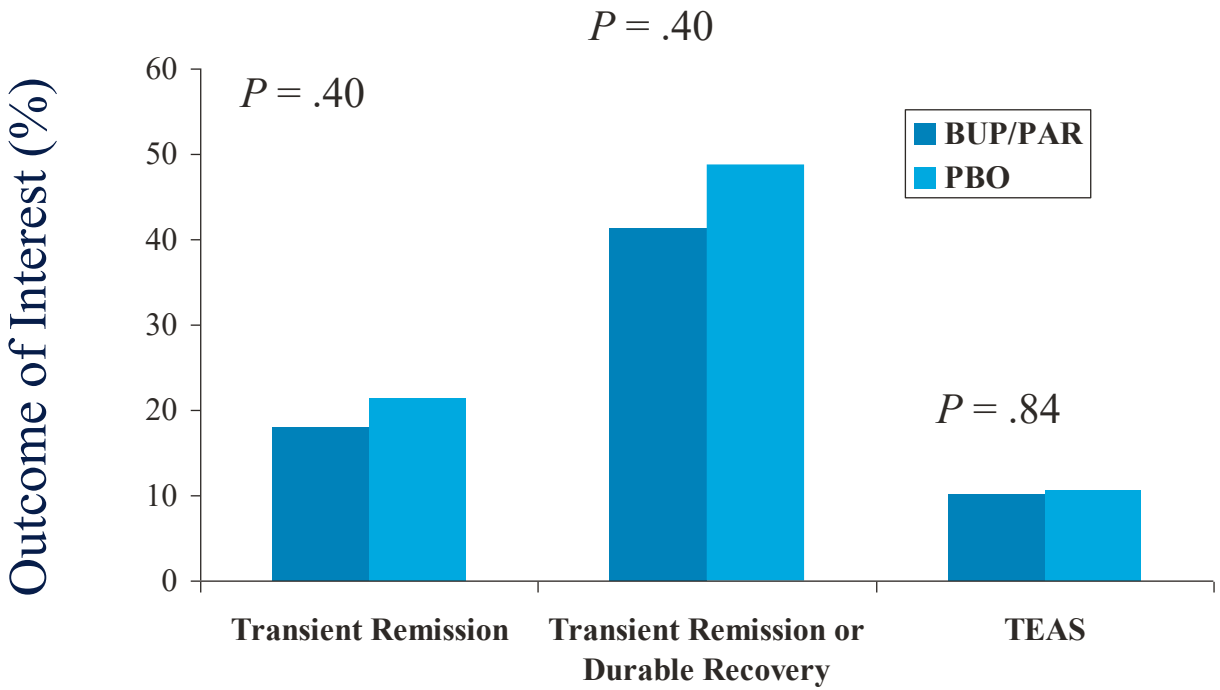
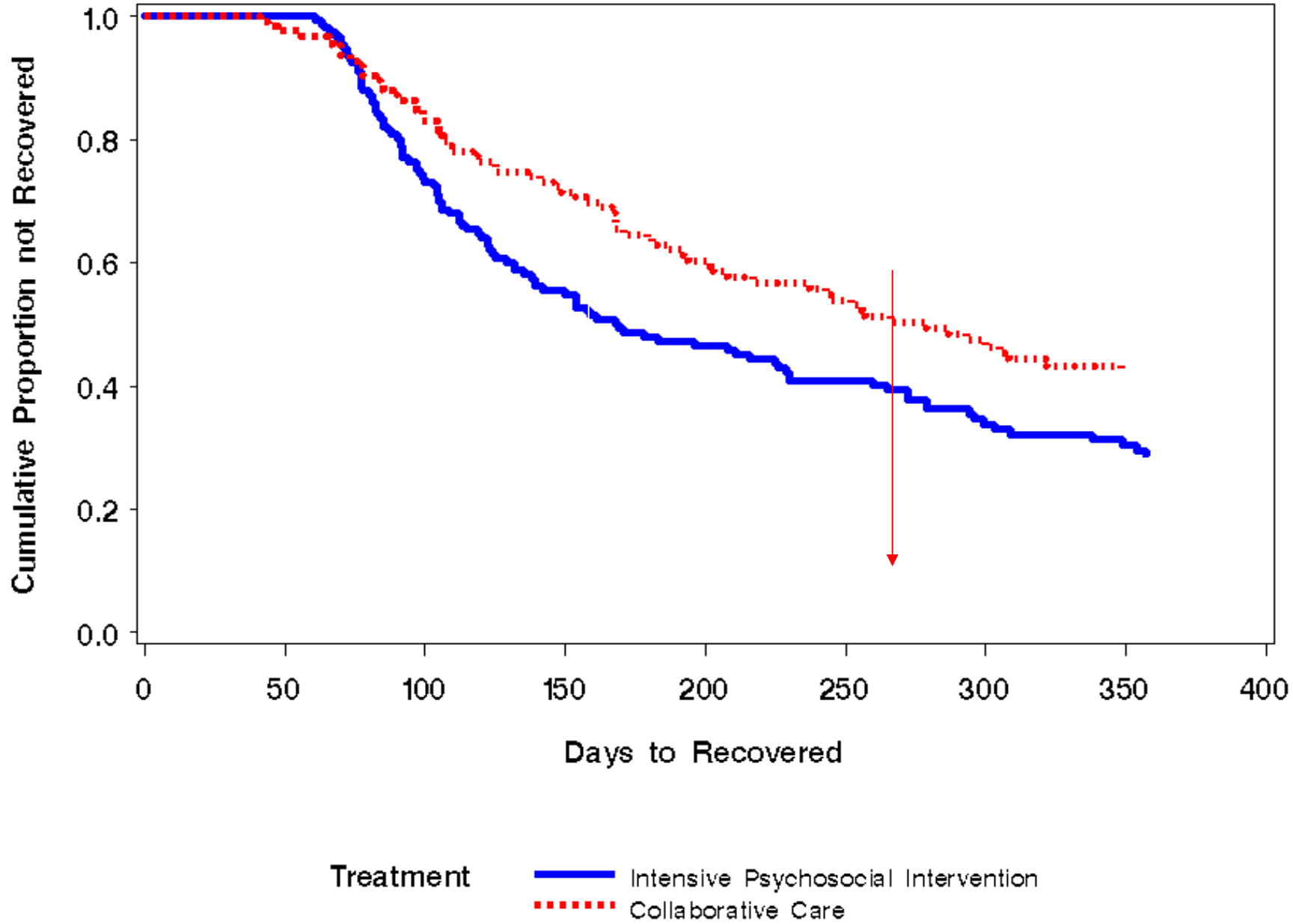
STEP-BD: Response to Adjunctive ADs



Sachs GS et al. *New Engl J Med.* 2007;356(17):1711-1722.

STEP-BD: Adjunctive Intensive Psychotherapy



Pharmacotherapy of Depressive Disorders: 2000-2010

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- **2000 Large Scale Collaborations with NIMH**
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  - REVAMP (co-led with James Kocsis & Trivedi)

Critical life decision # 4: moving to Philadelphia (2007)

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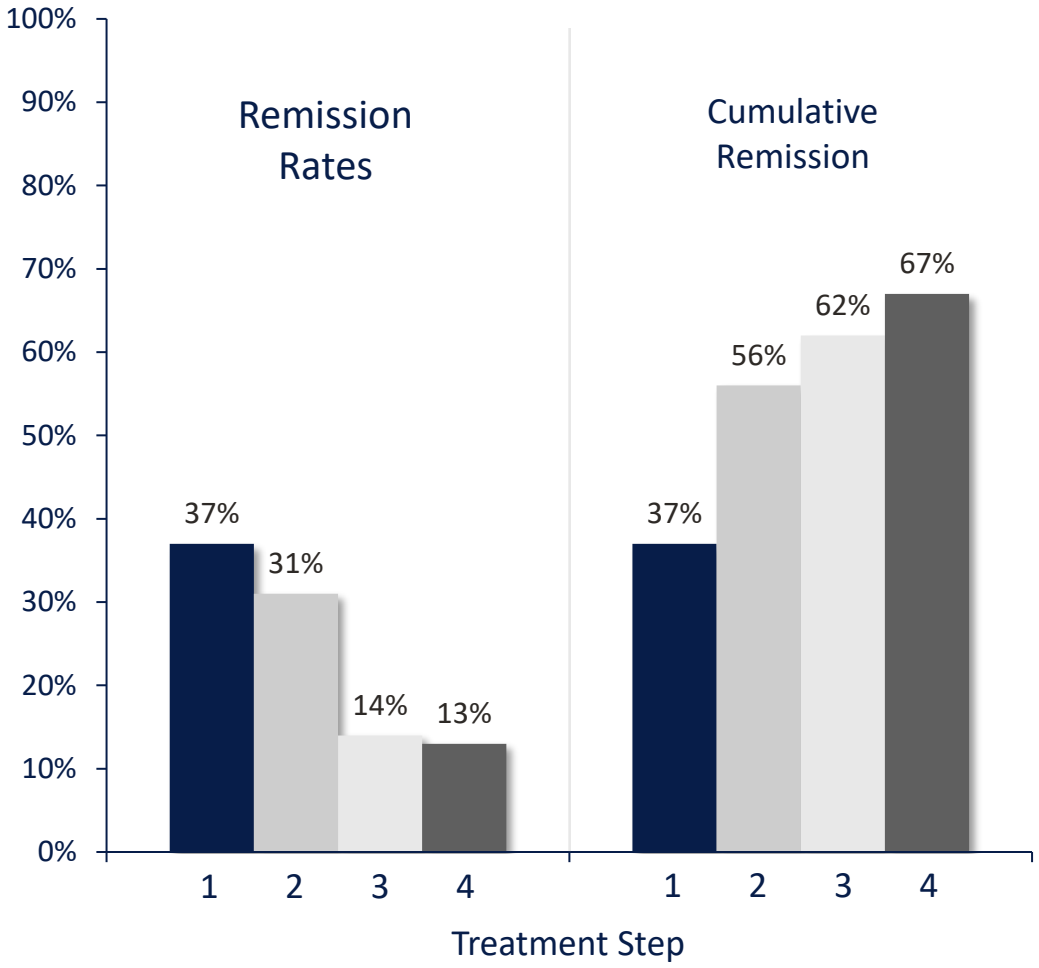
The Therapeutic Decrement in STAR*D: Declining Likelihood of Benefit Across Stages Blunts Cumulative Remission Rate



Legend	Steps	Drug
	Step 1 N=3,671	• Citalopram
	Step 2 N=1,439	• Switch: VEN/BUP/SER • Combine: BUP/BUS • Switch/Combine: CT
	Step 3 N=390	• Switch: NOR/MIR • Augment: LI/T3
	Step 4 N=123	• Switch: TCP/MIR+VEN

QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Rated; VEN, venlafaxine; BUP, bupropion; SER, sertraline; BUS, buspirone; CT, cognitive therapy; NOR, nortriptyline; MIR, mirtazapine; LI, lithium; T3, triiodothyronine; TCP, tranylcypromine.

Rush AJ et al. *Am J Psychiatry* 2006;163:1905-17.

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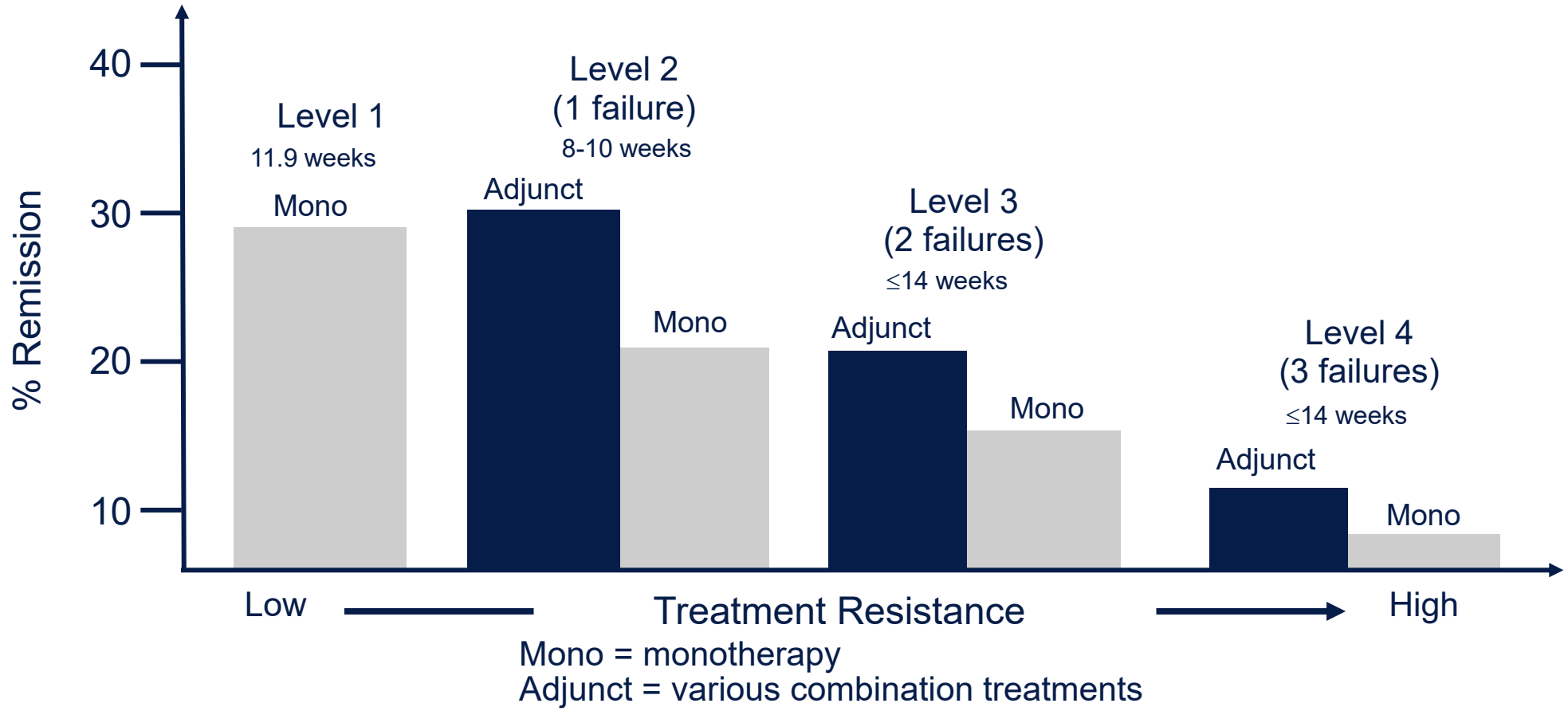
Optical Advantage of Adjunctive Therapies in STAR*D



STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

McGrath PJ et al. *Am J Psychiatry.* 2006;163:1531-1541; Rush AJ et al. *Am J Psychiatry.* 2006;163:1905-1917; Nierenberg AA et al. *Am J Psych*iatry. 2006;163:1519-1530; Trivedi MH et al. *J Clin Psychiatry.* 2006;67:1458-1465. Trivedi MH et al. *N Engl J Med.* 2006;354(:1243-1252.

Pharmacotherapy of Depressive Disorders: 2000-2010

Intertwined Developments with Career Developmental Milestones

- **2000 Large Scale Collaborations with NIMH**
  - STEP-D (co-led with Gary Sachs)
  - STAR*D (led by Rush, Fava & Trivedi)
  - **REVAMP (co-led with James Kocsis & Trivedi)**

Began a 15 year run of comprehensive original data meta-analyses with almost all newer generation antidepressants

Critical life decision # 4: moving to Philadelphia (2007)

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Pharmacotherapy of Depressive Disorders: 2000-2010

Intertwined Developments with Career Developmental Milestones

- **2000 Large Scale Collaborations with NIMH**
  - STEP-D (co-led with Gary Sachs)
  - STAR*D (led by Rush, Fava & Trivedi)
  - REVAMP (co-led with James Kocsis & Trivedi)

Critical life decision # 4: moving to Philadelphia (2007) and the importance of work-life balance

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Pharmacotherapy of Depressive Disorders: 2007-2020

Intertwined Developments with Career Developmental Milestones

- 2007-2020: Studies of adjunctive therapy with second generation antipsychotics (all 6 approved drug)
- 2007-2016: Bipolar Network Studies (NIMH, PCORI)
- 2010-2015: Computer Facilitated CBT (NIMH)
- 2009-2017: VA Cooperative Studies (TMS & VAST-D)
- 2014-2020: Helped to design and conduct Phase 2, 3 and 4 studies of esketamine (Janssen/Johnson & Johnson)

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Pharmacotherapy of Depressive Disorders: 2020-Present

Intertwined Developments with Career Developmental Milestones

Addressing unmet needs through studies of treatments with novel mechanisms of action

- **2020-present: Designing and collaborating on the initial EU-based study of Mebufotenin**
- 2020-present: studies of novel therapies within the VHA
  - - PRIME D (led by Dave Olsin)

    - VAST-D II (Co-led with Somaia Mohamed and James Murrough)

    - PIVOT (led by Lori Davis)

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Pharmacotherapy of Depressive Disorders: 2020-Present

Intertwined Developments with Career Developmental Milestones

Addressing unmet needs through studies of treatments with novel mechanisms of action

- 2020-present: Designing and collaborating on the initial EU-based study of Mebufotenin
- 2020-present: studies of novel therapies within the VHA

  - VAST-D II (Co-led with Somaia Mohamed and James Murrough)

  - PIVOT (led by Lori Davis): 5 center trial of psilocybin (25 mg vs 1 mg) in Veterans with TRD (1/2 with PTSD)

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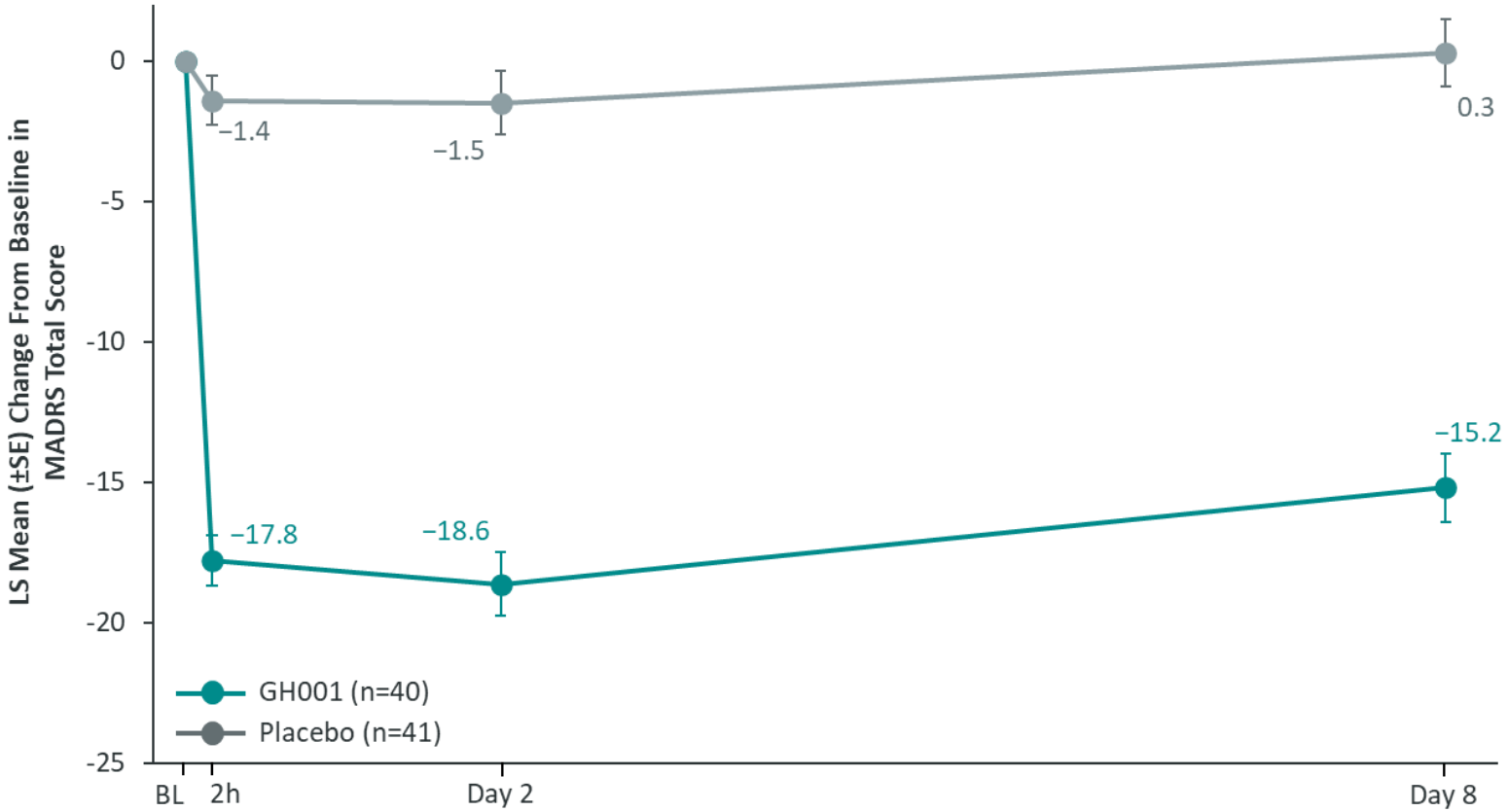
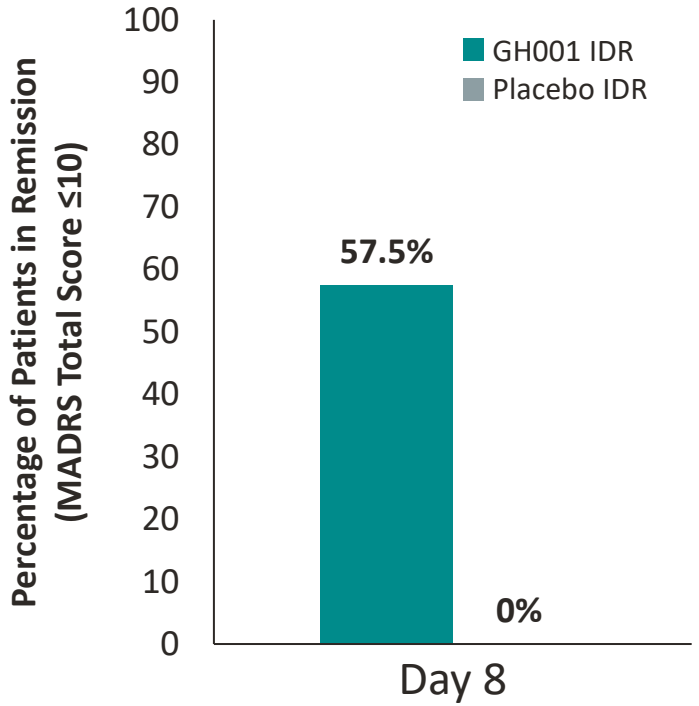
Clinical Pharmacology of GH001 (Mebufotenin)

- **5-methoxy-N,N-dimethyltryptamine** (5-MeO-DMT).
- Extremely short half-life and onset of action
  - experience begins in seconds if inhaled, minutes if snorted
  - total “trip” lasts 5-15 minutes
- Inhaled dose typically 6-18 mg, titrated to an intense experience
- Individual dose determined by an up to 3-hour protocol (IDR)
- With monthly dosing no attenuation of effect, no change in dose

Cubala et al. GH001 vs Placebo in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2026 Mar 25:e260096. doi: 10.1001/jamapsychiatry.2026.0096. Epub ahead of print.

GH001-TRD-201 Primary Endpoint[a]: Single Day Dosing (IDR) of Mebufotenin Led to Mean MADRS Reduction From Baseline of −15.5 on Day 8 vs Placebo[1]





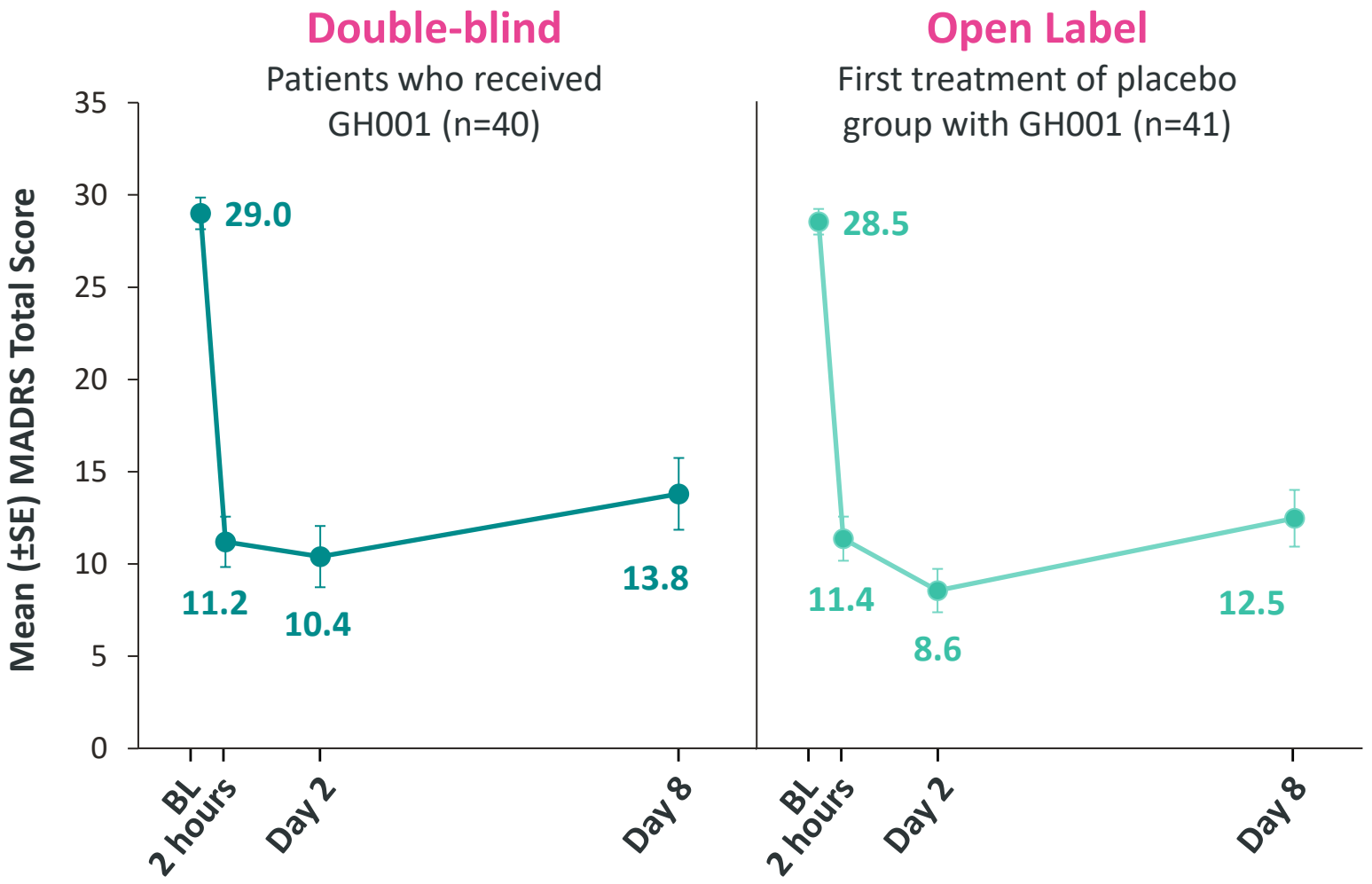
The LS mean difference between GH001 and placebo at Day 8 was −15.5 (SE=1.71; 95% CI, −18.89 to −12.03; *P*<0.0001)
The effect size (Cohen's *d*) for change in MADRS score from baseline to Day 8 was −2.0

[a]FDA Guidance notes that efficacy with rapid-acting antidepressants generally should be demonstrated within 1 week, supporting a primary efficacy endpoint within this timeframe. EMA guidelines also specifies that an earlier efficacy endpoint can be used depending on the study drugs mechanism of action.[2,3]

Abbreviations: BL = Baseline; CI = Confidence interval; FDA = Food and Drug Administration; h = Hour; IDR = Individualised dosing regimen; LS = Least square; MADRS = Montgomery-Åsberg Depression Rating Scale; SE = Standard error.

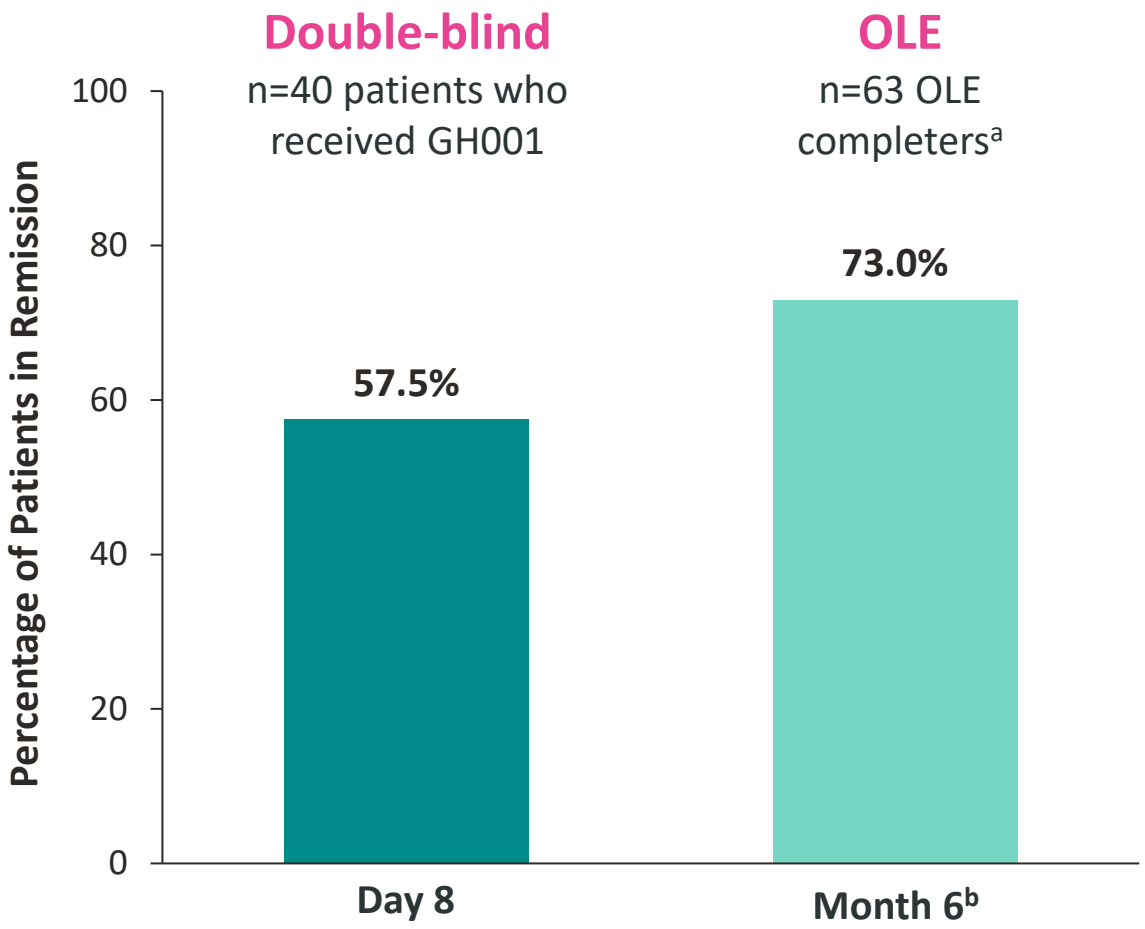
1. Thase ME et al. Presented at the American Society of Clinical Psychopharmacology Annual Meeting, Scottsdale, AZ, USA, May 27–30, 2025. 2.U.S. Food and Drug Administration. Psychedelic Drugs: Considerations for Clinical Investigations. FDA. Published June 26, 2023. Accessed September 18, 2025. 3. European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression (Revision 3). EMA/CHMP/185423/2010 Rev.3. Published January 20, 2025. Accessed September 18, 2025.

Reduction in MADRS with Double Blind Mebufotenin Replicated by Open-label Treatment of Placebo Nonrespnders



BL = Baseline; MADRS = Montgomery-Åsberg Depression Rating Scale; OLE = Open-label extension; SE = Standard error.

Remission Rates for Repeated Doses of Mebufotenin Six Months After Beginning Treatment



The OLE was completed in Q1 2025

- 63 completed, 18 early terminations (n=1 due to TEAE)

For patients who completed the OLE:

- **73.0%** (n=46) of patients were in remission[c] at 6 months (79.4% with clinical response)[d]
  - Of the 46 patients in remission, 23 were randomized to GH001 and 23 were randomized to placebo in the double-blind part
- Completers (n=63) had a mean MADRS total score of **9.4 at 6 months**
- **63.5%** (n=40) received **1–4 treatments** with GH001
- **No drug-related serious TEAEs were reported in the OLE**; one non-drug-related serious TEAE was reported during the OLE[e]

Note: data collection for the OLE has completed but data cleaning is ongoing. All analyses of OLE data are subject to change following database lock.

[a]63 patients who received active drug and completed the 6-month OLE per protocol (patients who terminated early are excluded). [b]Approximately 6 months post-study start (mean 168 days from Day 1 of double-blind period). [c]MADRS total score ≤10. [d]≥50% reduction from baseline in total MADRS score. [e]The non-drug-related serious TEAE reported was preferred term status migrainosus. Onset was 73 days after the patients most recent administration of the GH001 IDR. 29

MADRS = Montgomery-Åsberg Depression Rating Scale; OLE = Open-label extension; TEAE = Treatment-emergent adverse event.

Some Additional Thank Yous!

- The late Carl and Evelyn Thase
- Diane M. Sloan, PharmD and Linda, John, Austin, Sarah, Charlotte and Carly Thase
- Ms. Lisa Stupar, Ms. Christine Johnson and Dr. Judith Lis
- Drs. Ed Friedman, Bob Howland, Claudia Baldassano and Golkoo Hosseini
- The late Dr. Dwight Evans and Dr. Maria Oquendo

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Conclusions and Final Words of Advice

- Some aspects of the Code of Midwest really do pay off if you work hard, persist through setbacks and have good fortune
- This is particularly true if you do work that is meaningful and even more so if you enjoy what you do
- Pick your spouse(s), mentors, colleagues and employees as well as humanly possible
- Remember work-life balance and always be open to feedback when things may have become transiently imbalanced

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