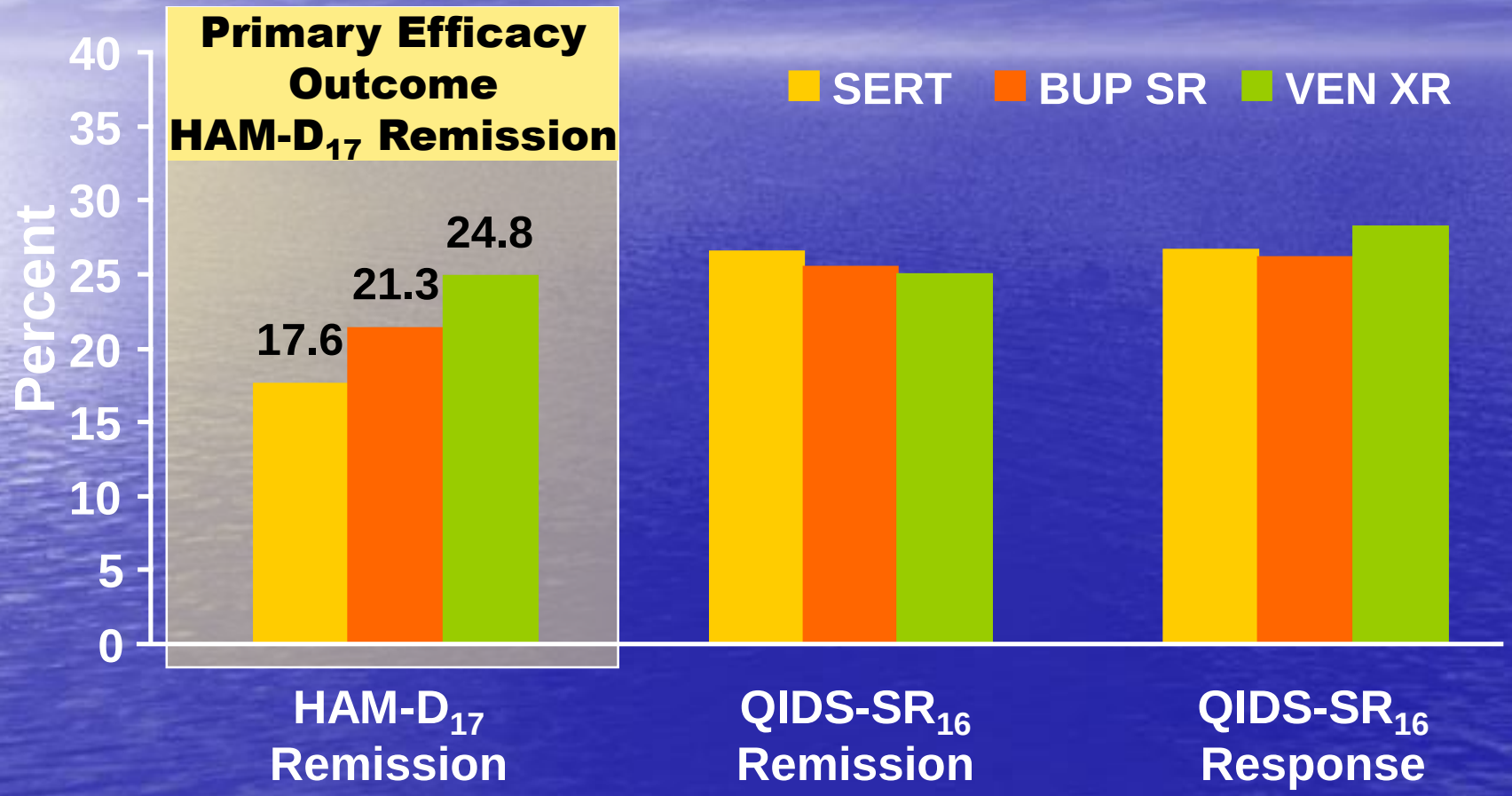
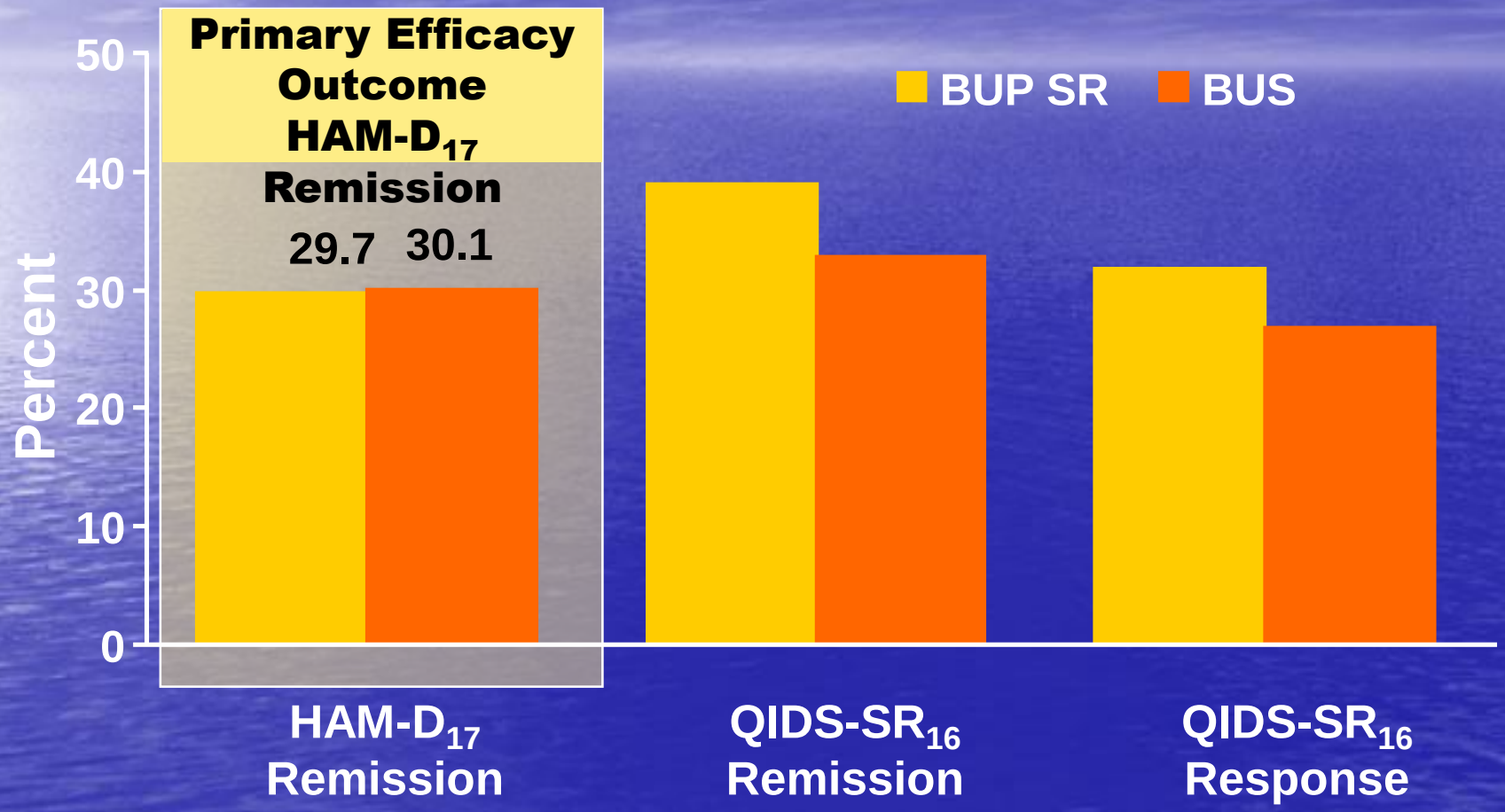
Level 2 Switch: Primary and Secondary Efficacy Outcomes



N=727; QIDS-SR = Quick Inventory of Depressive Symptomatology—Self-Rated; No significant differences among treatment groups; Rush AJ et al. (2006), N Engl J Med 354(12):1231-1242

Level 2 Medication Augmentation

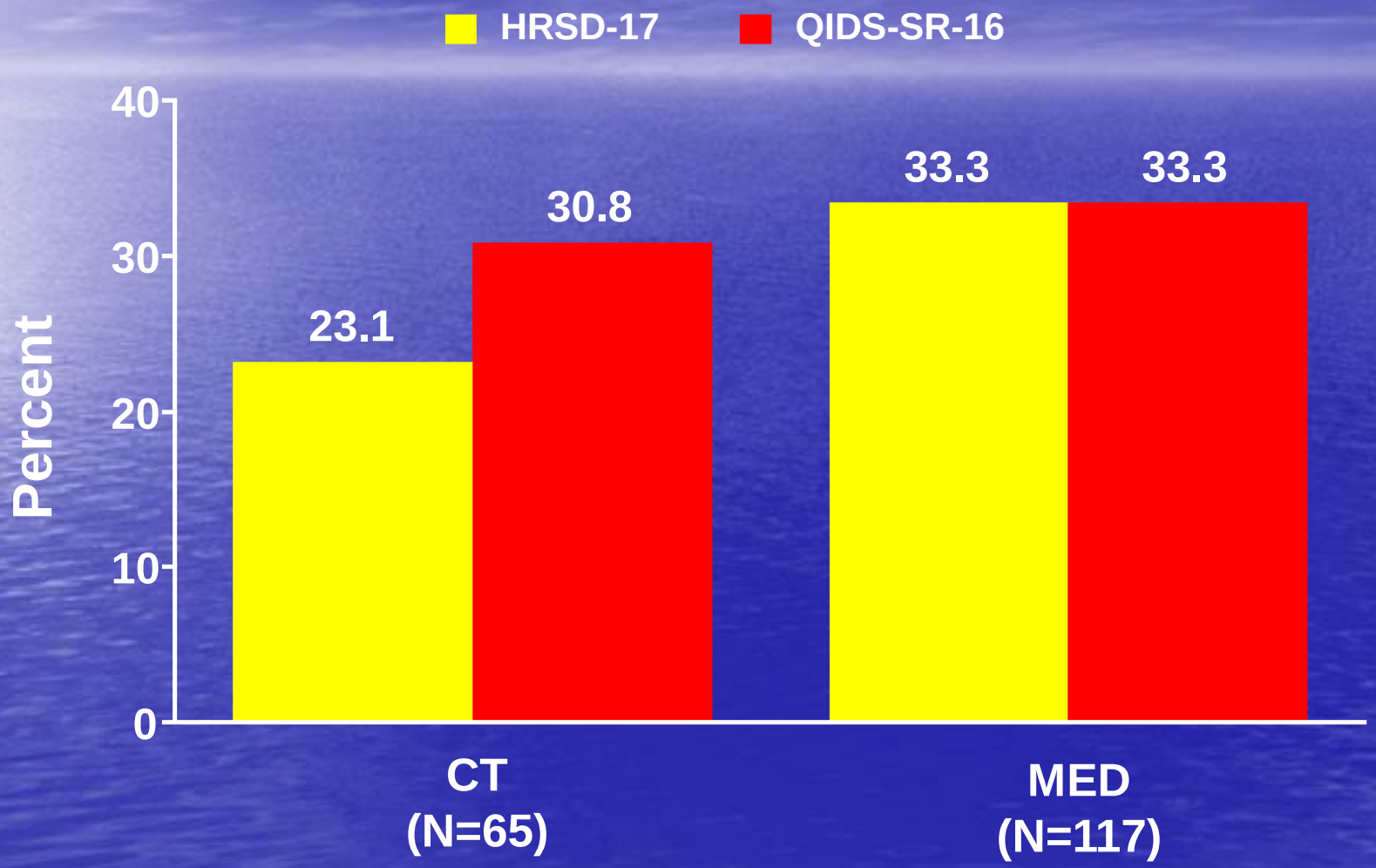
Level 2 Augment: Primary and Secondary Efficacy Outcomes



N=565; No significant differences among treatment groups; Trivedi MH et al. (2006), N Engl J Med 354(12):1243-1252

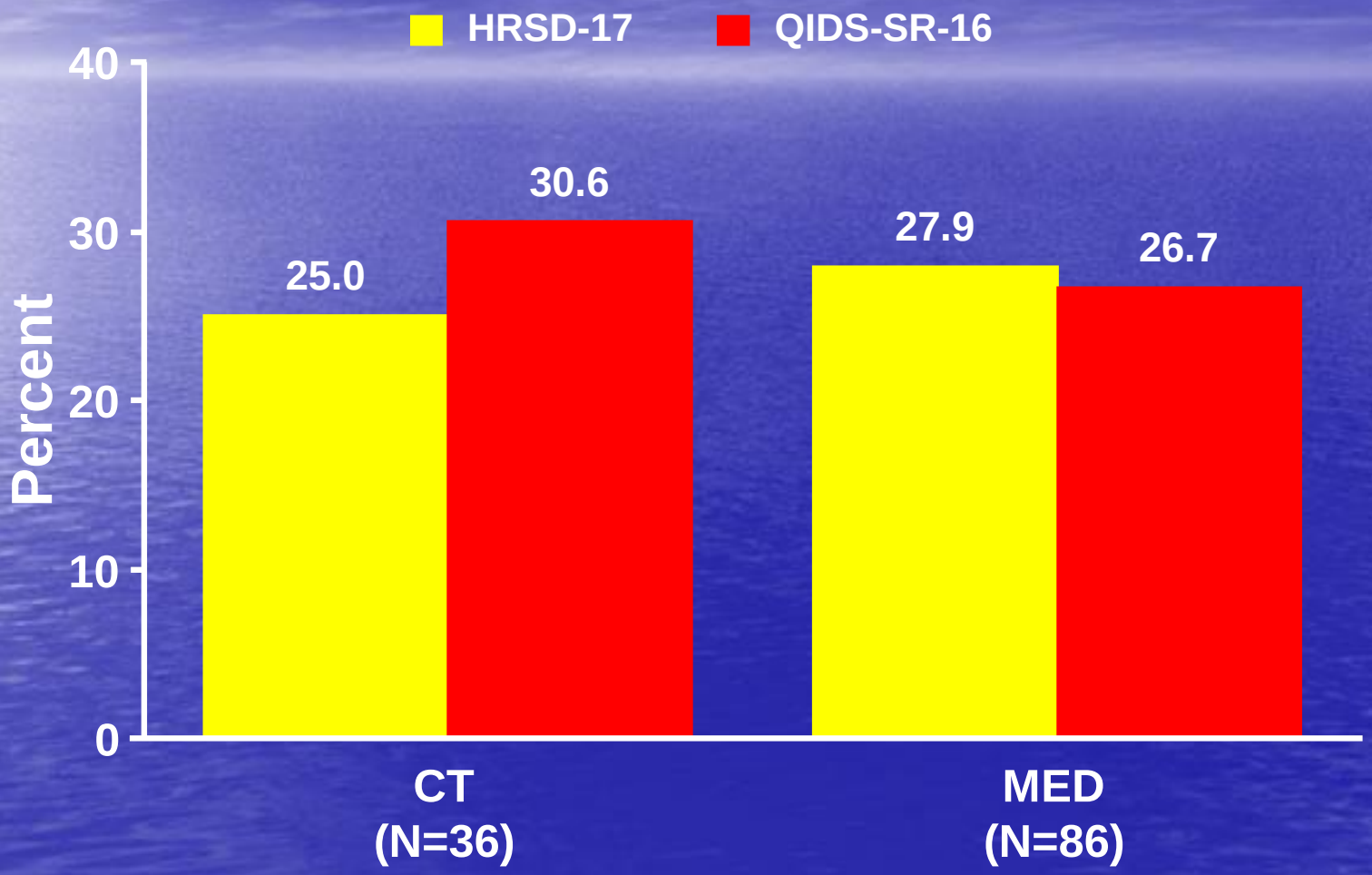
Level 2 Cognitive Therapy Studies

STAR*D Treatment Outcomes: Remission Rates CT vs. Medication Augment



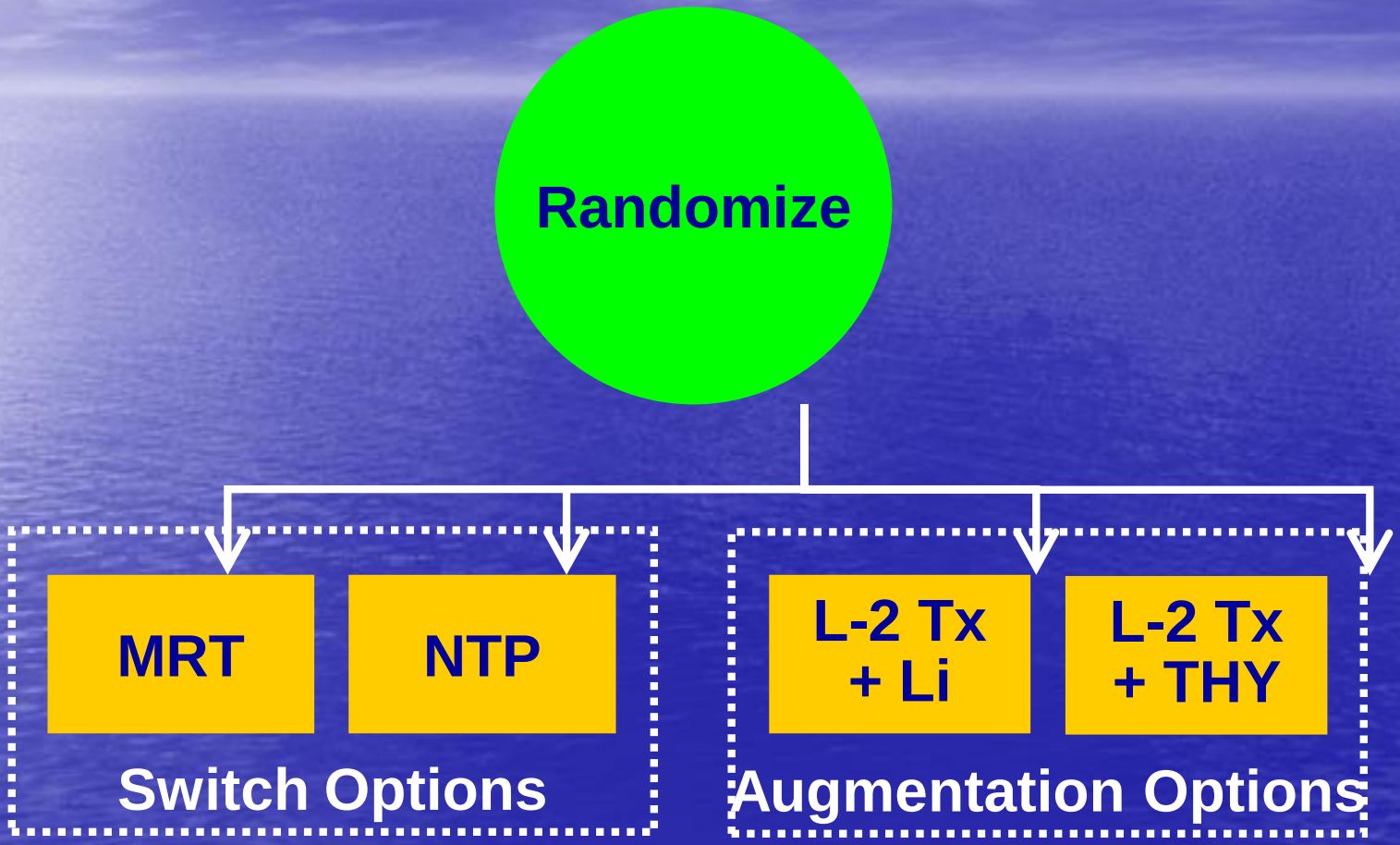
MED = medication augmentation; Thase ME et al. (2007), Am J Psychiatry 164(5):739-752

STAR*D Level 2 Treatment Outcomes: Remission Rates CT vs. Medication Switch



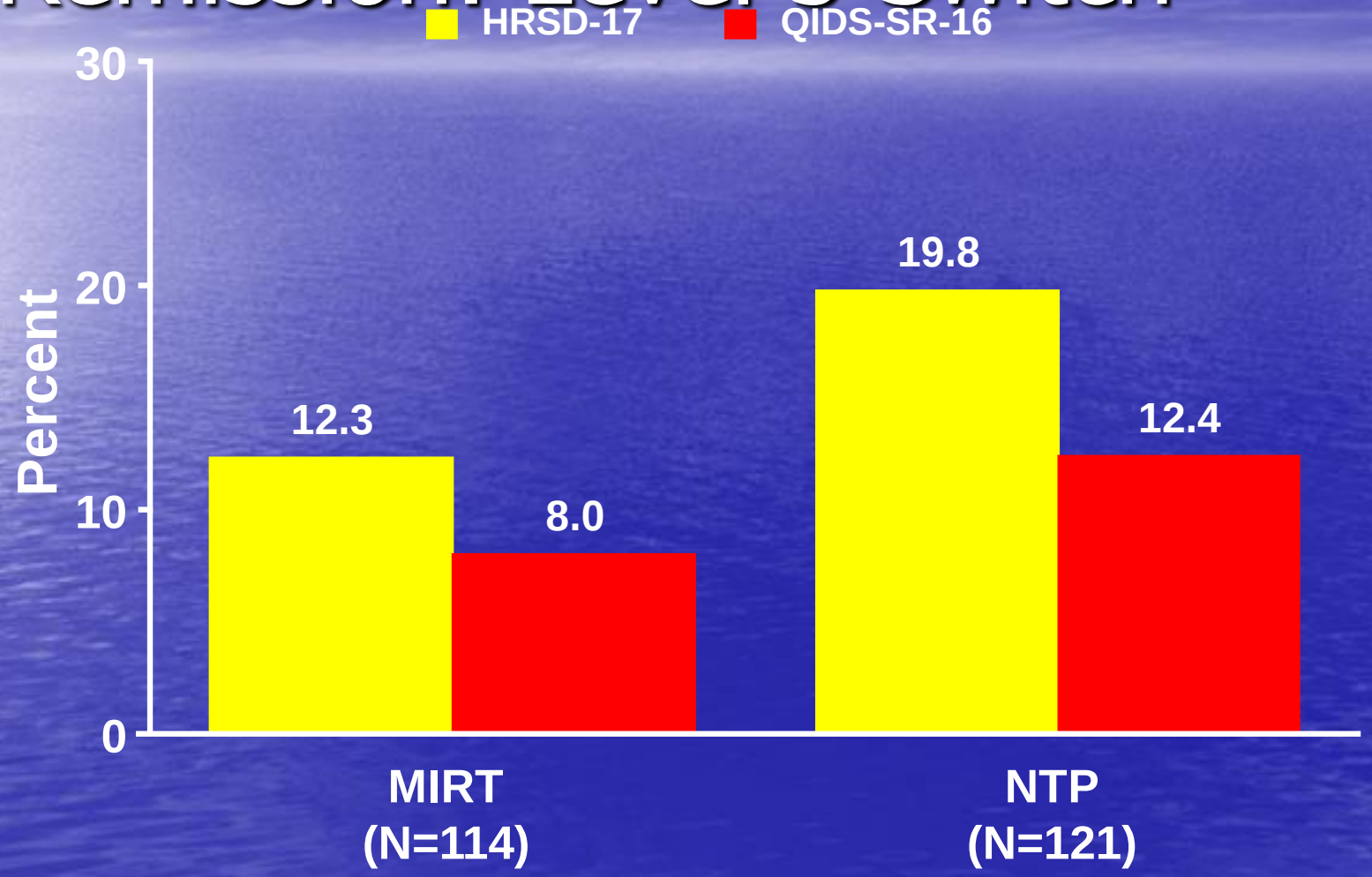
Thase ME et al. In preparation

Level 3



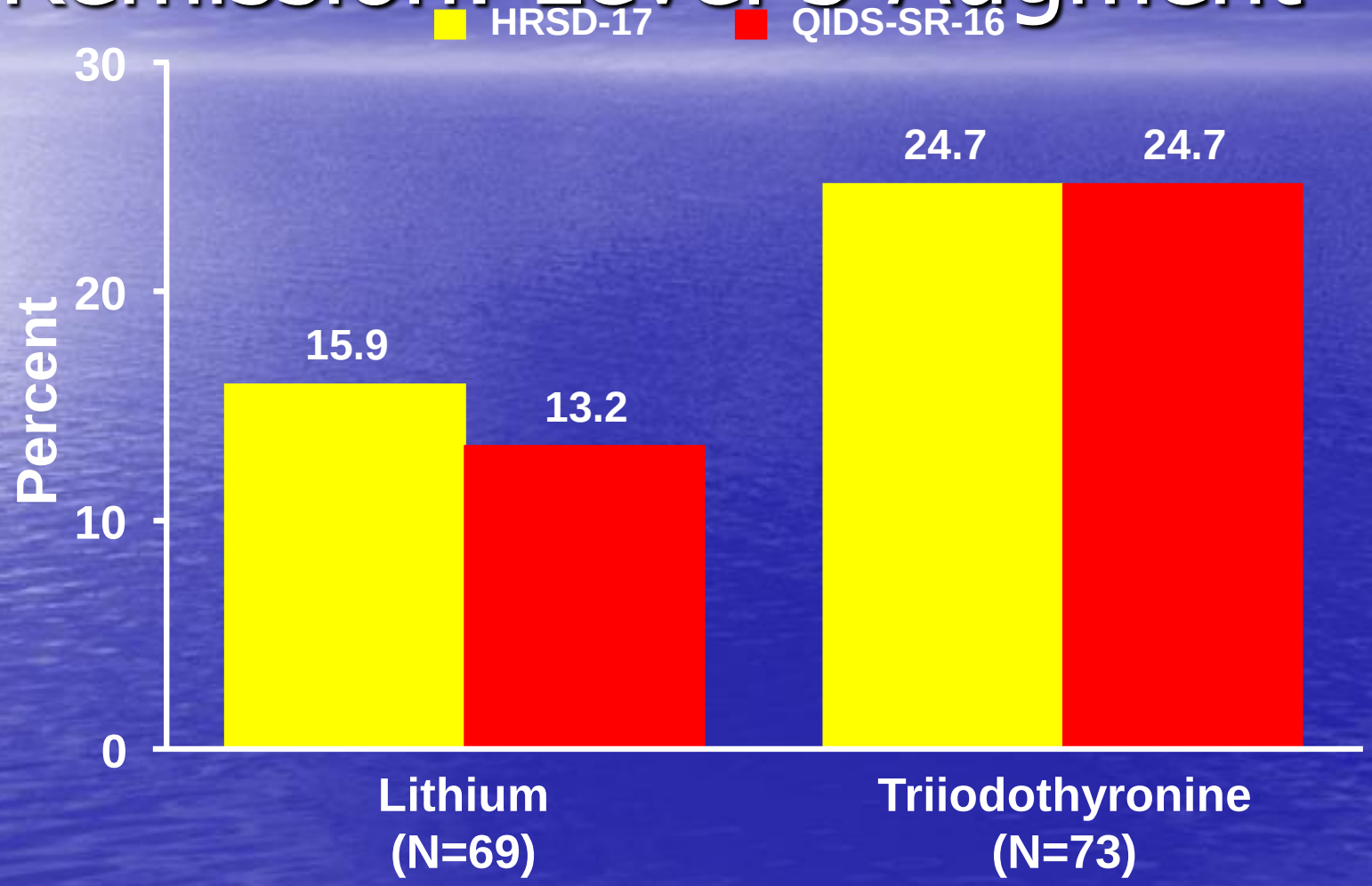
MIRT = mirtazapine; NTP = nortriptyline; Rush AJ et al. (2004), Control Clin Trials 25(1):119-142

Treatment Outcomes Remission: Level 3 Switch



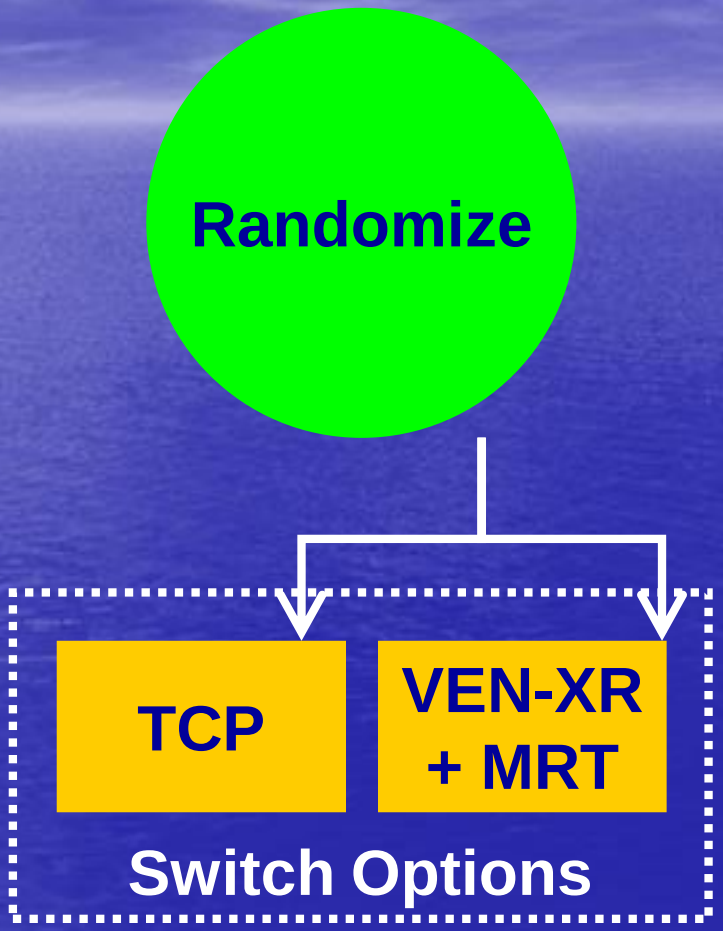
Fava M et al. (2006), Am J Psychiatry 163(7):1161-1172

Treatment Outcomes Remission: Level 3 Augment



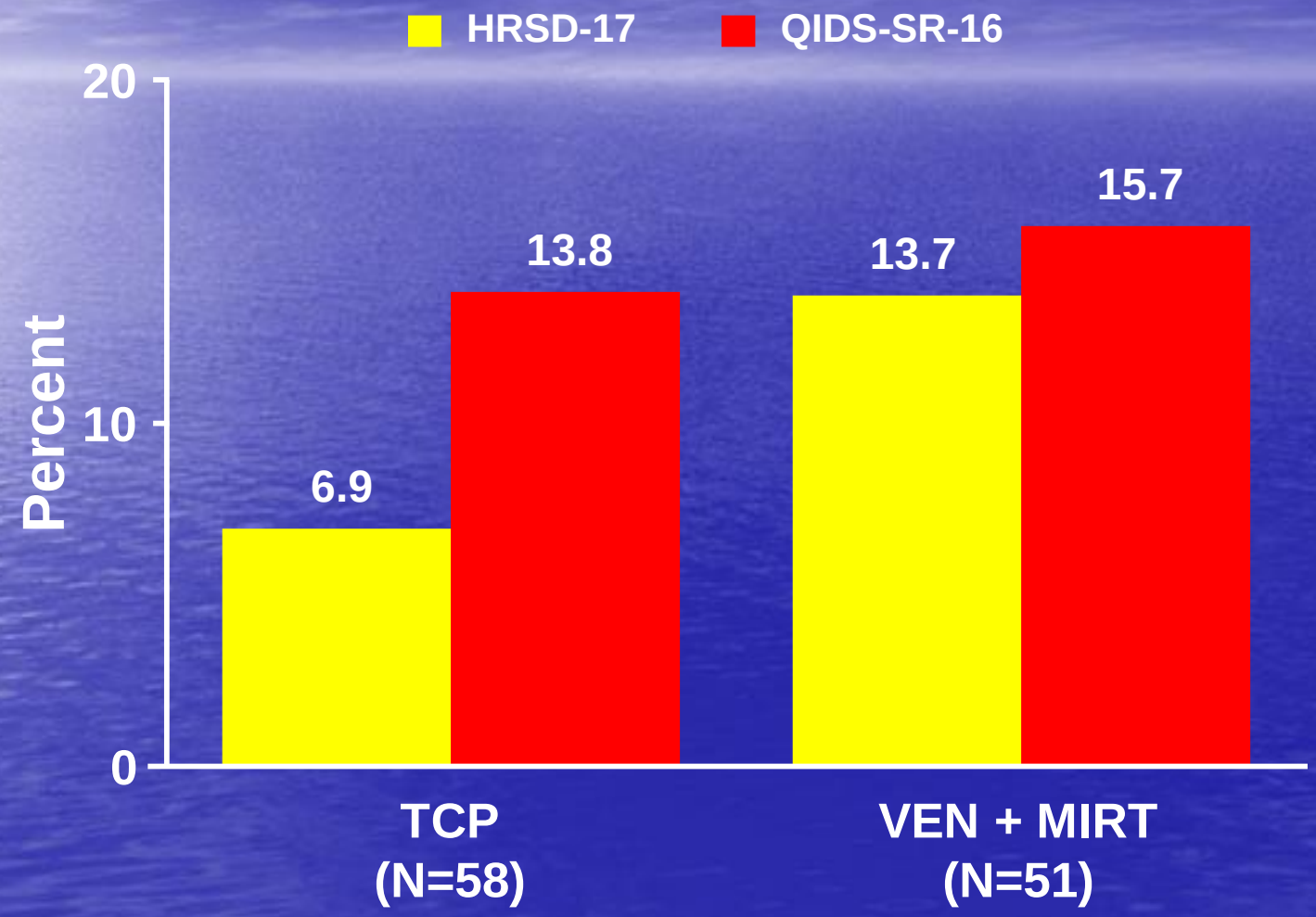
Nierenberg AA et al. (2006), Am J Psychiatry 163(9):1519-1530

Level 4



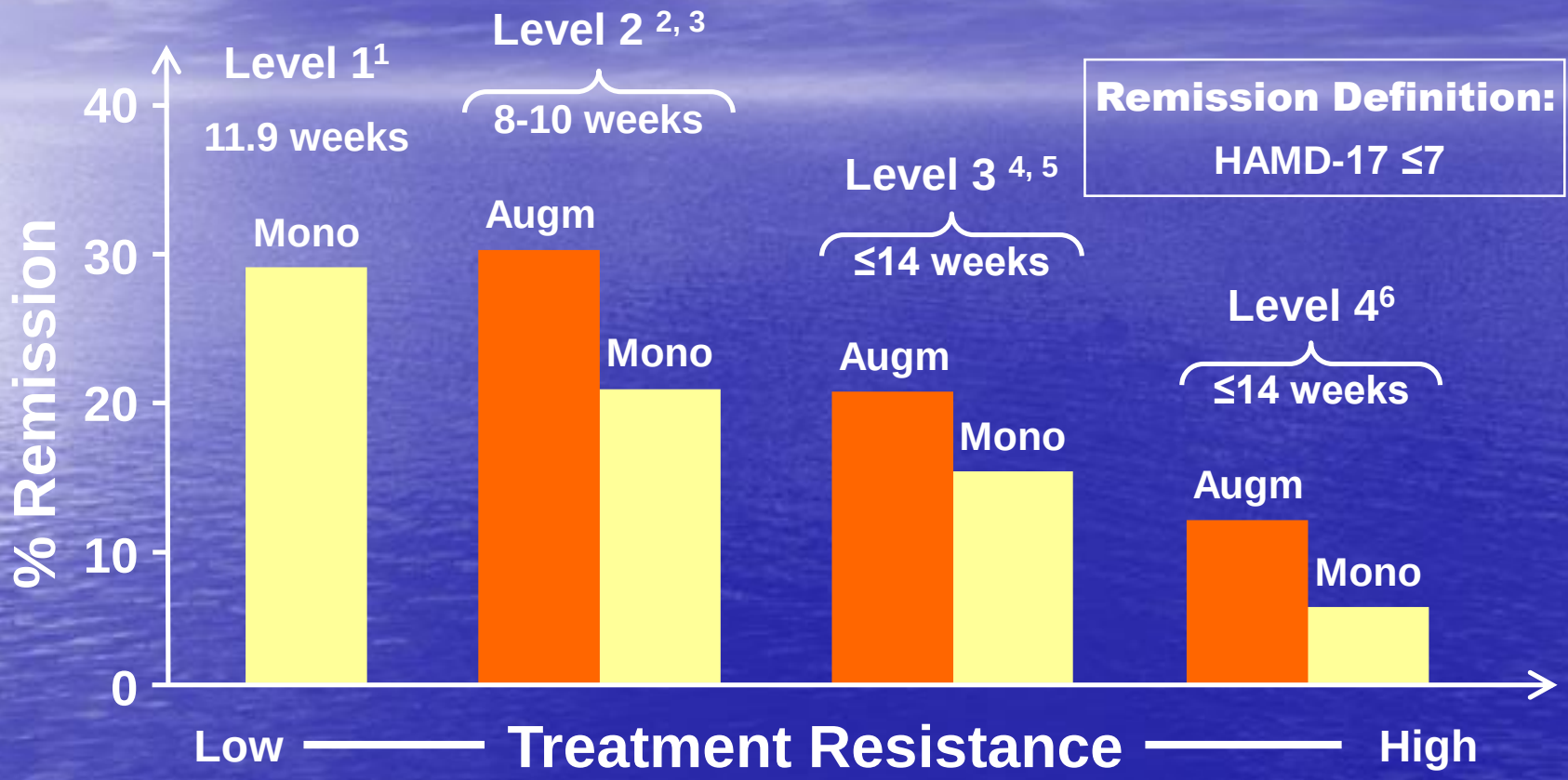
TCP = tranylcypromine; Rush AJ et al. (2004), Contol Clin Trials 25(1):119-142

Treatment Outcomes Remission: Level 4



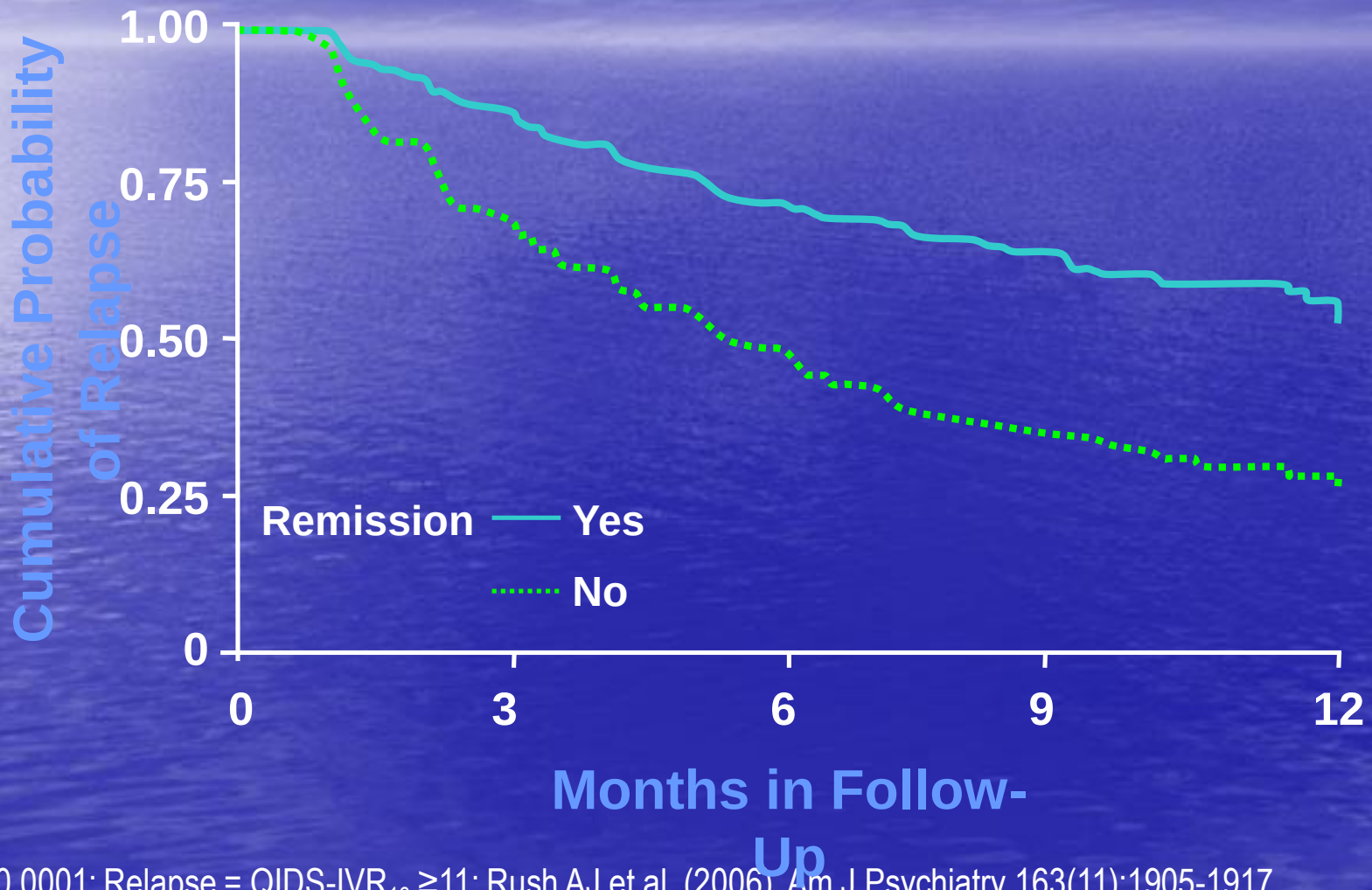
McGrath PJ et al. (2006), Am J Psychiatry 163(9):1531-1541

STAR-D Remission Rates Across All 4 Levels



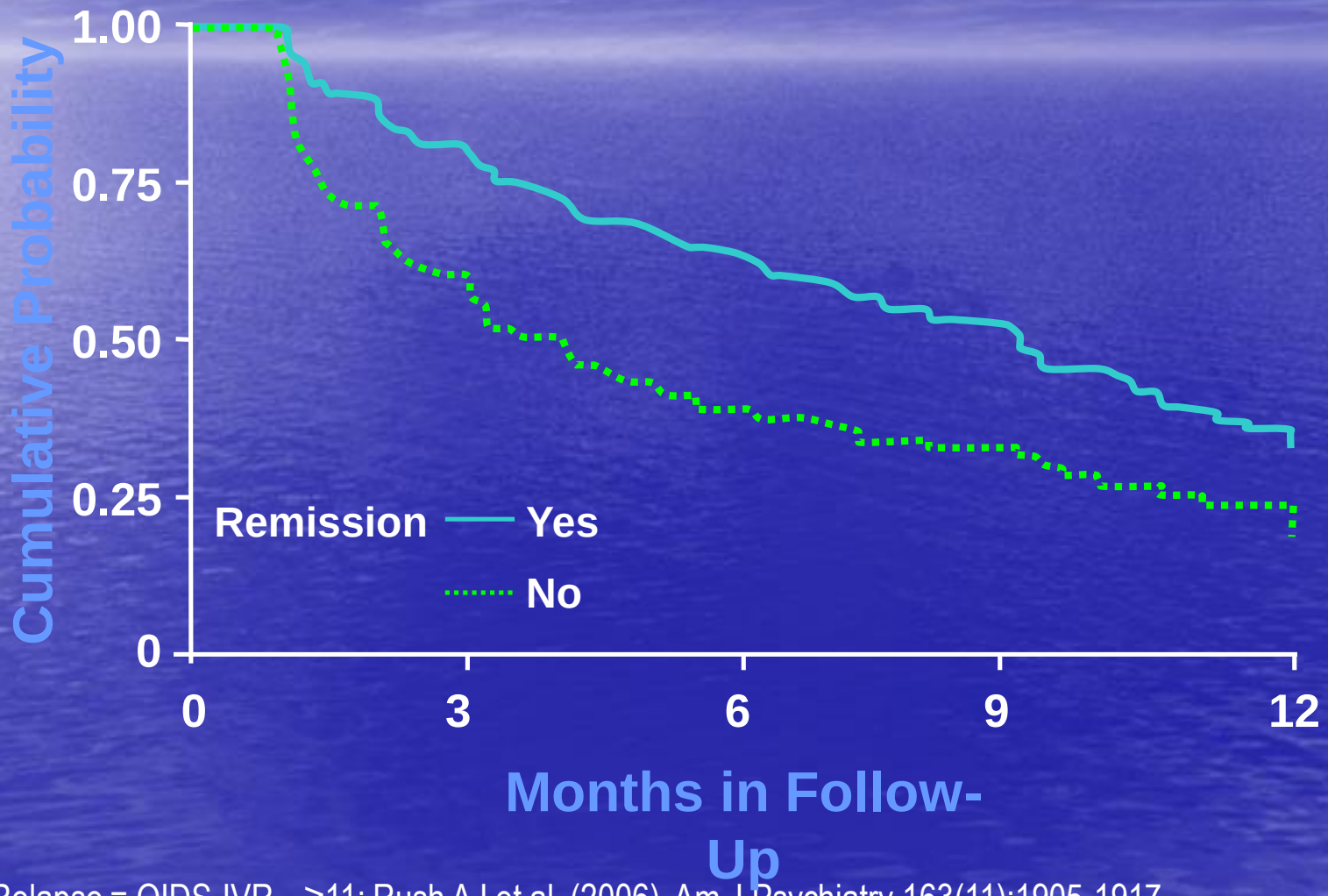
Mono = single medication regimen; Augm = combination medication treatment; [1]Trivedi MH et al. (2006), Am J Psychiatry 163:28-40; [2]Trivedi MH et al. (2006), N Engl J Med 354:1243-1252; [3]Rush AJ et al. (2006), N Engl J Med 354:1231-1242; [4]Nierenberg AA et al. (2006), Am J Psychiatry 163:1519-1530;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

Level 1 Follow-Up: Relapse Rates



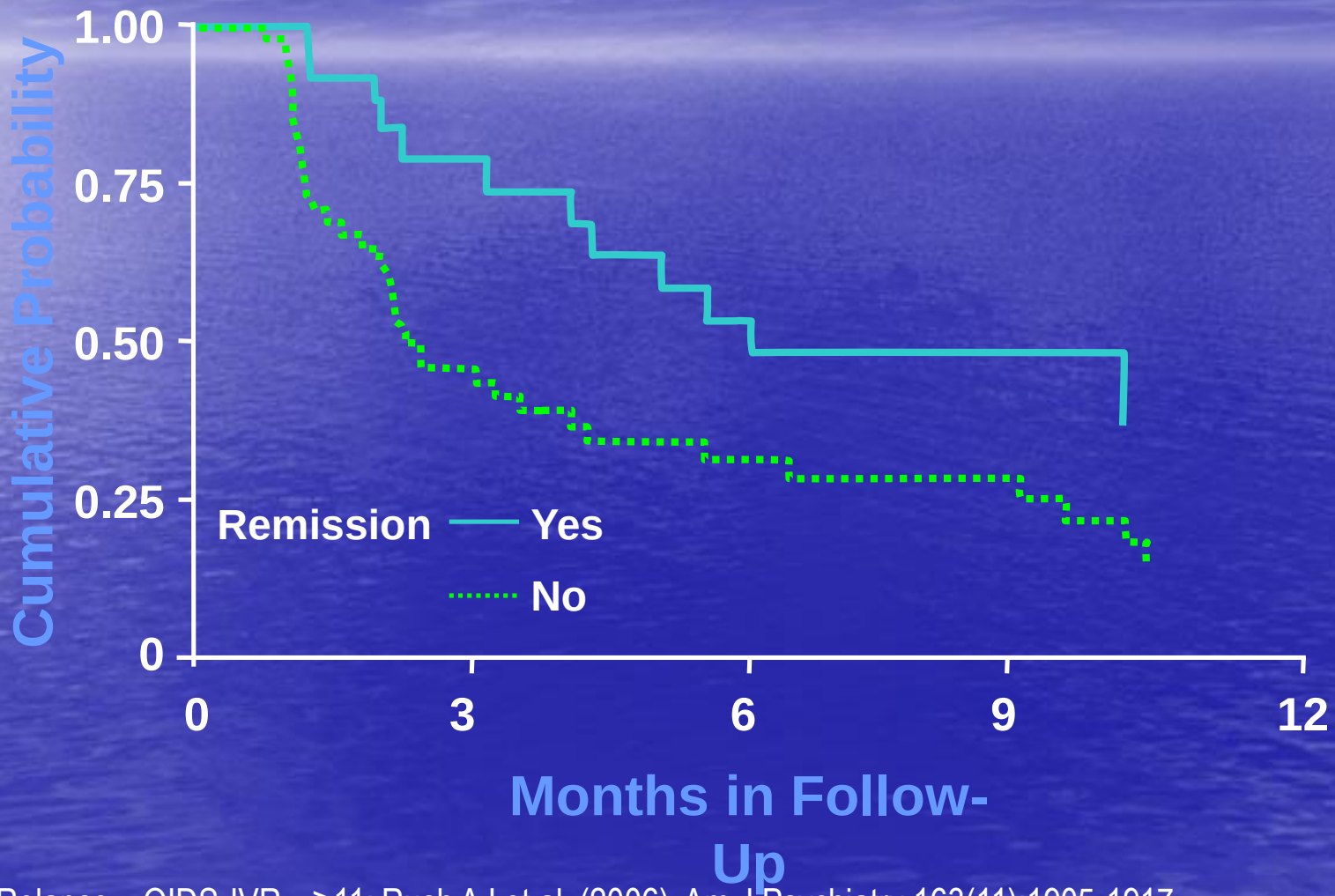
p<0.0001; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Level 2 Follow-Up



p<0.0001; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Level 3 Follow-Up



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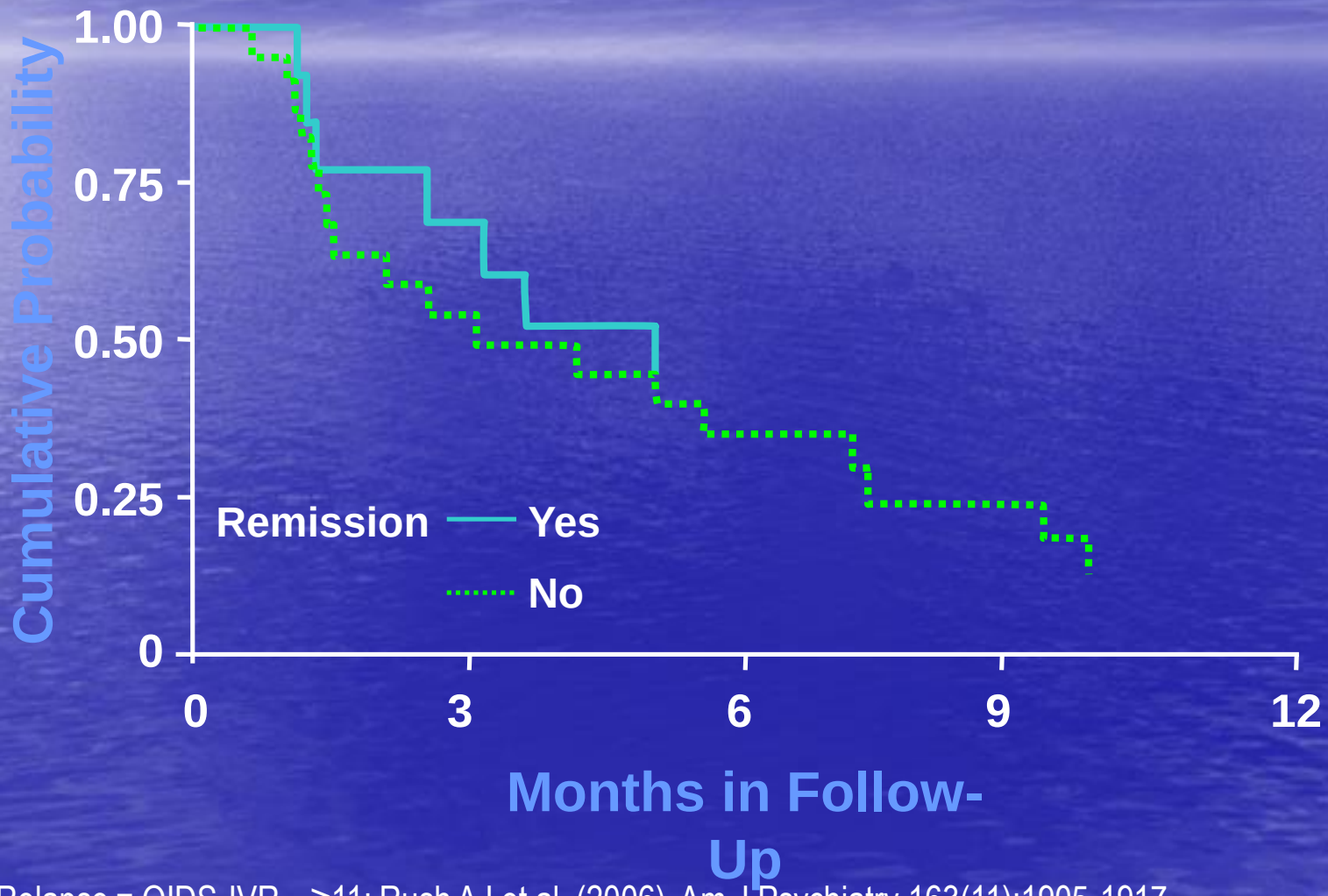
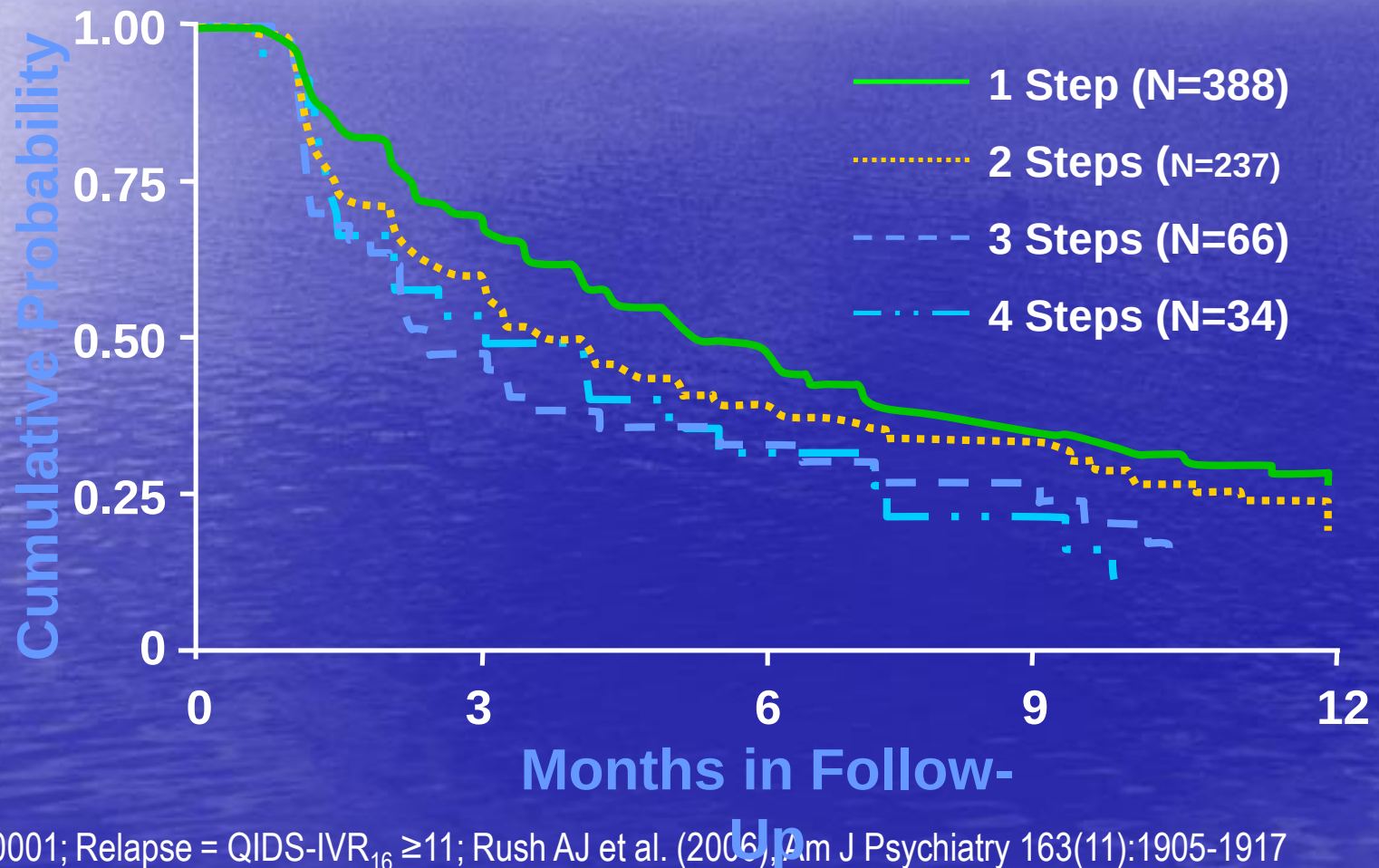
Level 4 Follow-Up



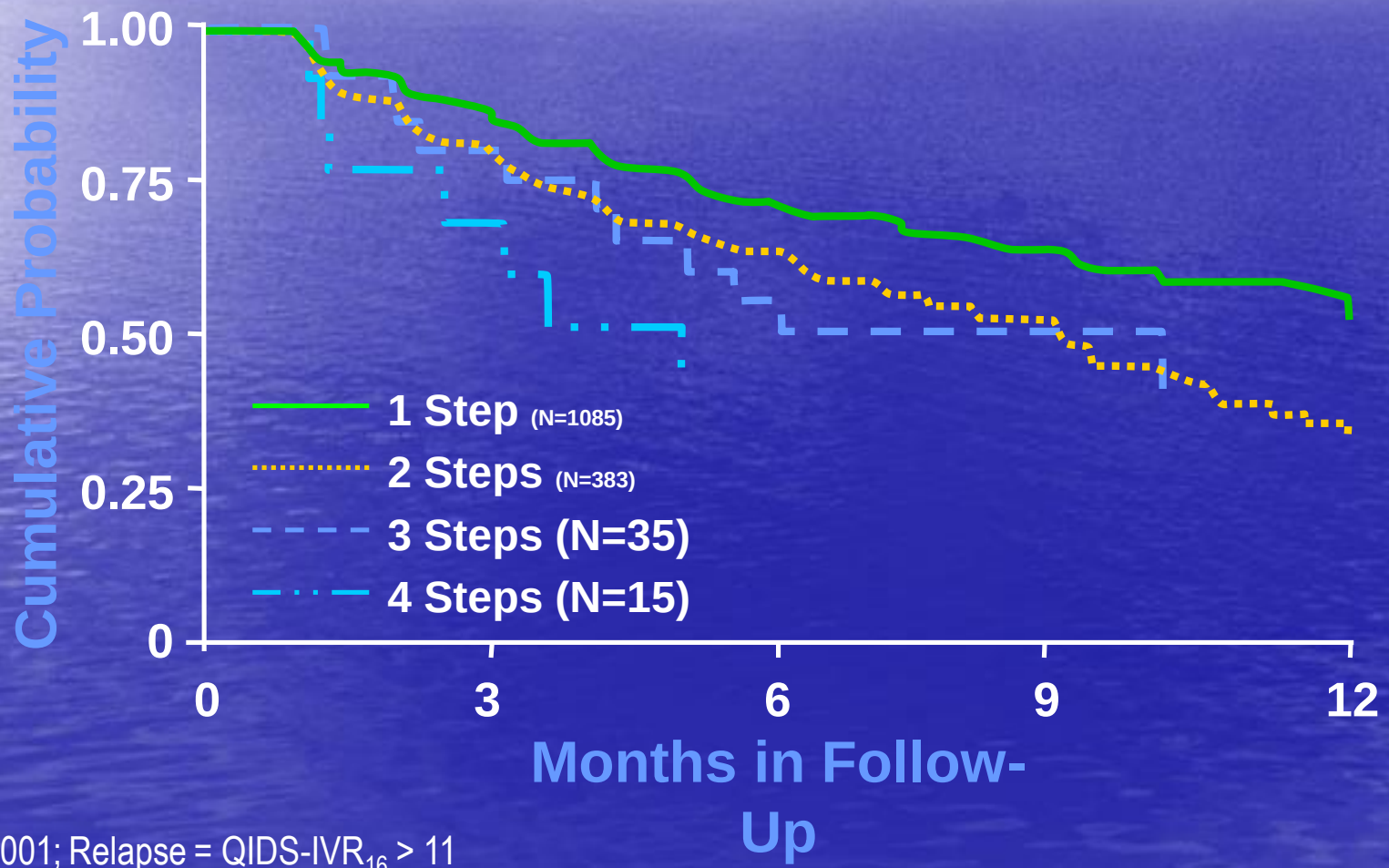
P<0.1387; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Relapse in Follow-Up for Patients Not Remitting to Different Numbers of Acute Treatment Steps



p<0.0001; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Relapse in Follow-Up for Patients Remitting With Different Numbers of Acute Treatment Steps



p<0.0001; Relapse = QIDS-IVR$_{16}$ ≥ 11

Use of ECT in Patients With MDD

- Patients with MDD most likely to benefit from ECT
  - Patients with delusions[1]
  - Elderly patients[1]
  - Patients presenting with high suicide risk[1]
  - Patients with history of poor response to pharmacotherapy[2]
  - Patients with history of responsiveness to ECT[2]
  - Patients who choose it[2]
  - Patients with bipolar disorder[3]
- ECT is a treatment used for MDD only after multiple treatments have been poorly tolerated or do not yield a therapeutic response

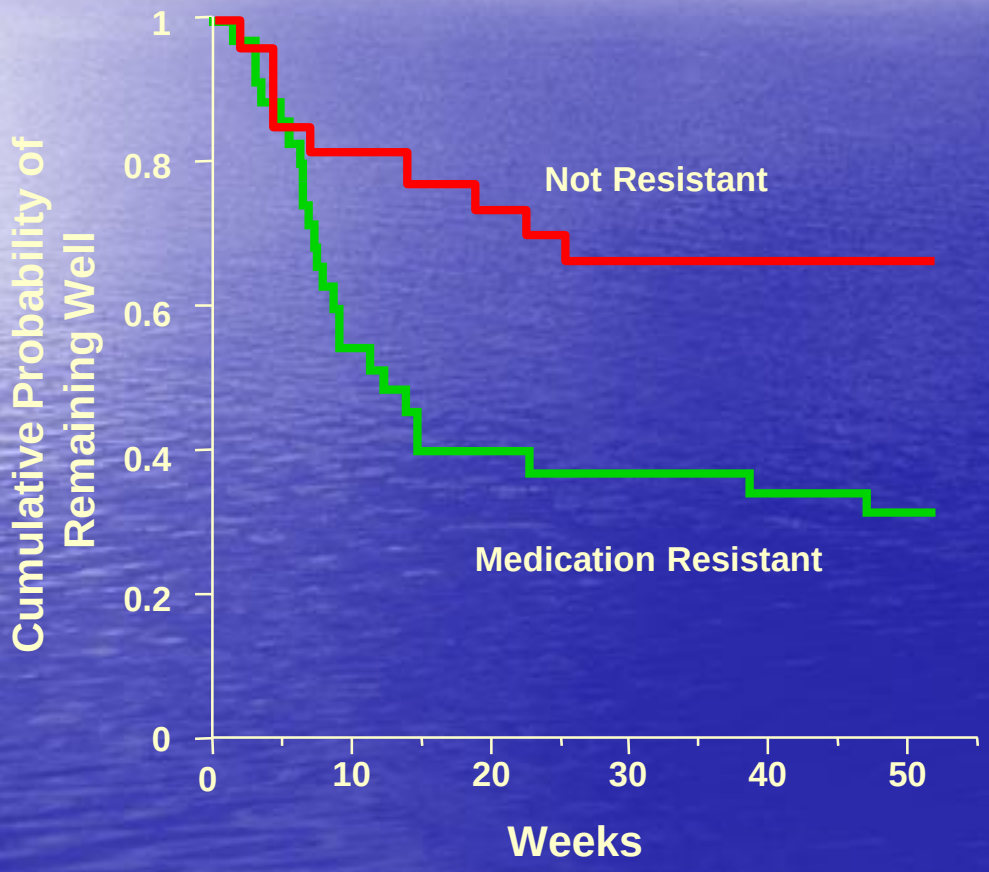
1. Fink M, Bailine S. *Am J Managed Care.* 1998;4:107-112. 2. Weiner RD, Krystal AD. In: Gabbard GO, ed. *Treatments of Psychiatric Disorders.* Washington, DC: American Psychiatric Press; 2001:1267-1293. 3. Kahn DA, et al. *J Psychiatr Pract.* 2000;6:197-211.

Efficacy of ECT in MDD and TRD

- The acute effect of ECT in MDD is well established
  - Continuation therapy is required to prevent relapses[1]
  - In 1 recent study, within 24 weeks of achieving remission (HAMD reduced by 60% and ≤10), 64% of patients had relapsed[2]
- TRD is predictive of post-ECT relapse
  - Patients with TRD are at high risk for relapse within 1 year following ECT response[3]
    - Only 32% of patients with TRD maintained their response during the year after ECT treatment[4]

1. Sackeim HA, et al. *JAMA.* 2001;285:1299-1307. 2. Prudic J, et al. *Biol Psychiatry*. 2004;55: 301-312. 3. Sackeim HA, et al. *J Clin Psychopharmacol.* 1990;10:96-104. 4. Sackeim HA, et al. *Arch Gen Psychiatry*. 2000;57:425-434.

Medication Resistance Predicts Relapse Following Successful ECT



- 94% of relapses occurred in the first 6 months
- Patients with TRD were twice as likely to relapse
- Significantly greater relapse in TRD (p=0.01)
  - TRD=68% relapse
  - Non-TRD=36% relapse
- Higher HAMD at end of ECT predicted relapse

Sackeim HA, et al. *Arch Gen Psychiatry*. 2000;57:425-434.

Transcranial Magnetic Stimulation

Time-varying electrical current in a coil produces

↓

focal 2 tesla magnetic field that passes unimpeded through skull and

↓

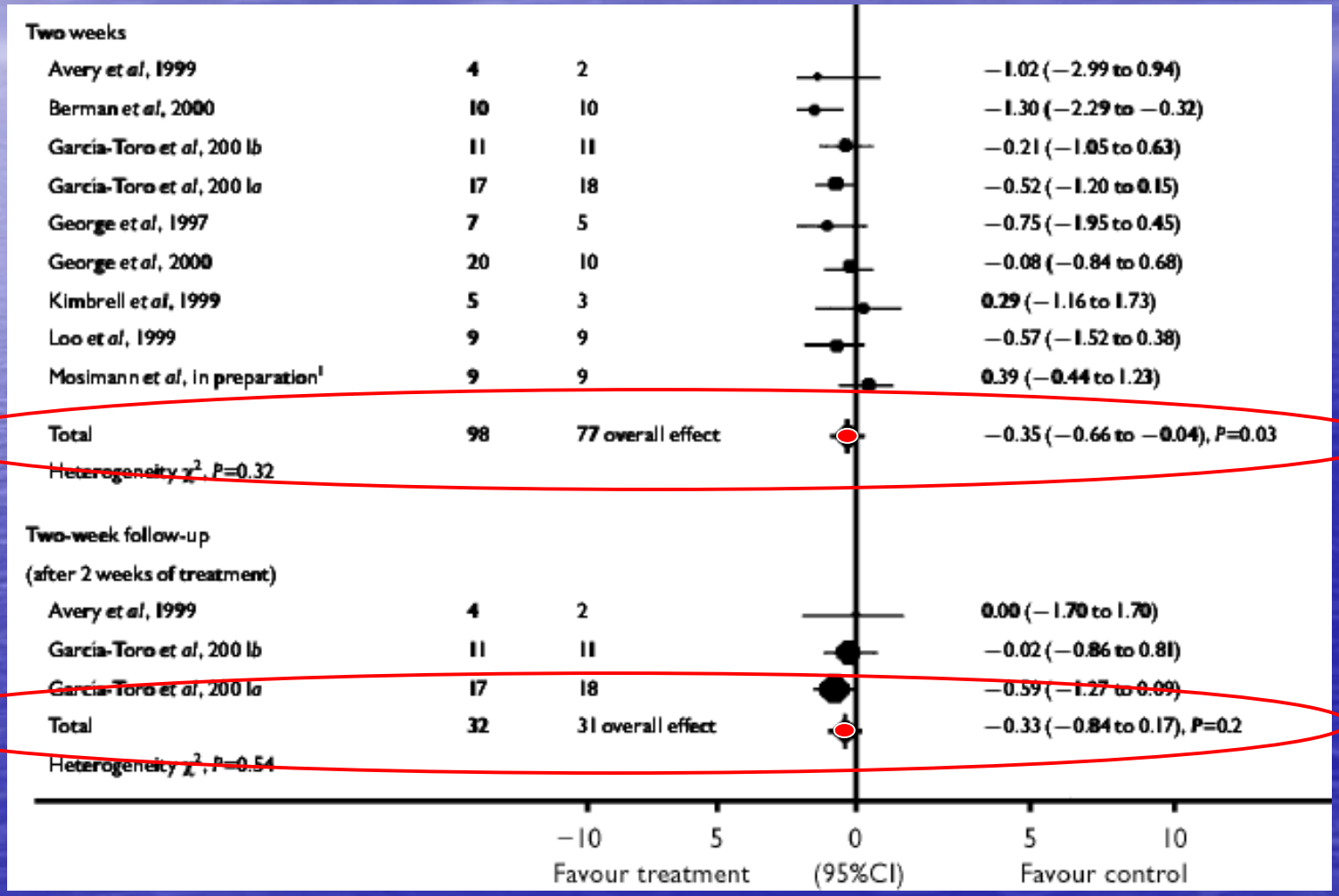
induces current in neurons and

↓

behavioral change

Modest to moderate effects in Sham Controlled studies

TMS Efficacy Yet to Be Established: Meta-analysis of 14 Controlled Trials

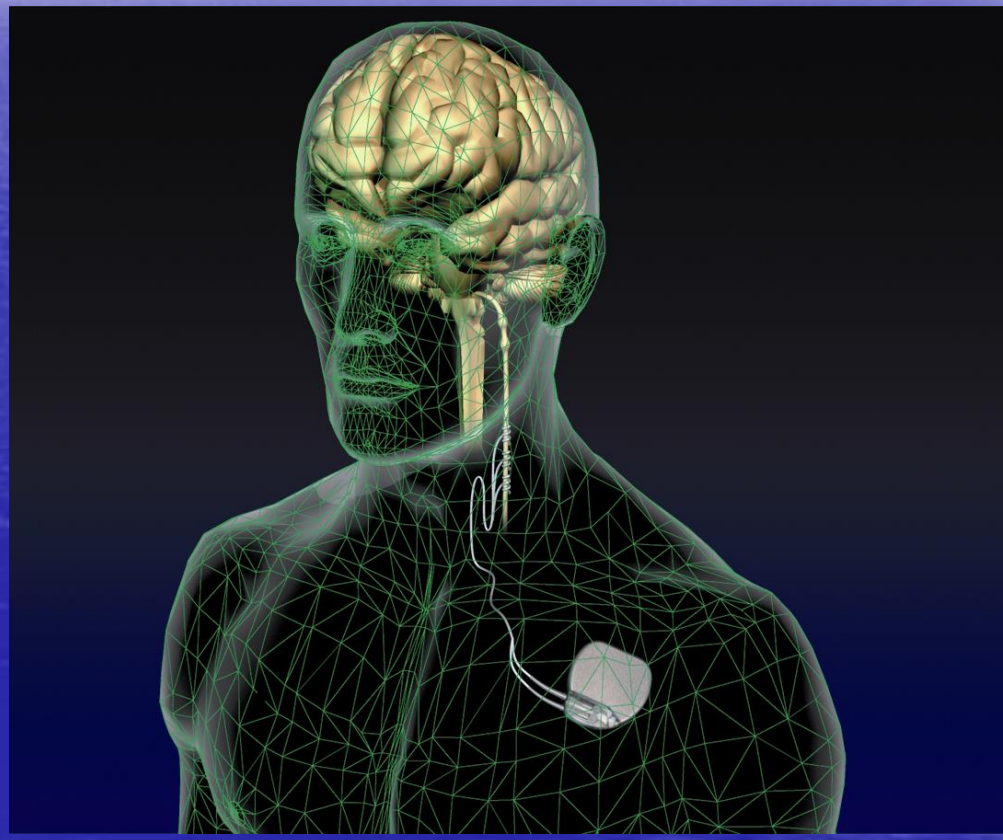


Martin JLR et al, Br J Psychiatry (2003), 182, 480-491.

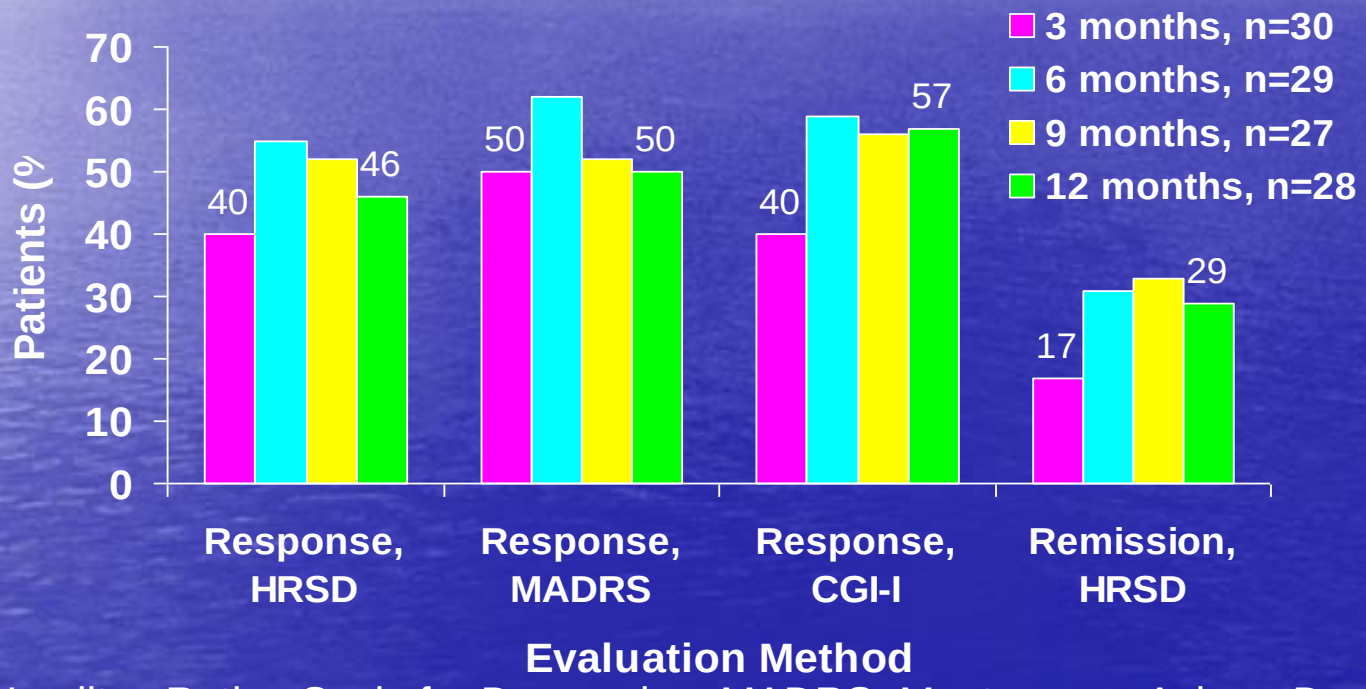
Vagus Nerve Stimulation (VNS)

Limitations

- Efficacy data from nonrandomized study
- Surgical procedure
- Cosmesis
- Nonacute antidepressant effect
- MRI contraindication
- Battery Life



VNS Clinical Outcomes: One Year Post-Implantation

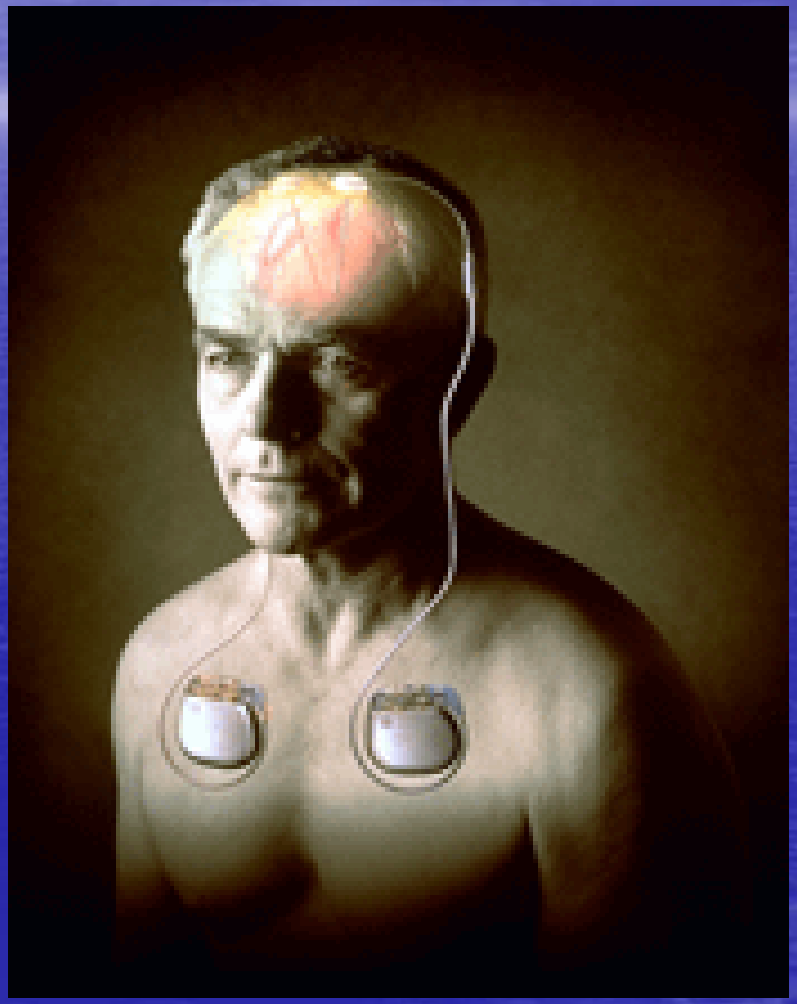


HRSD=Hamilton Rating Scale for Depression, MADRS=Montgomery Asberg Depression Rating Scale, CGI-I=Clinical Global Impression-Improvement. HRSD≤10, for remission. Patients received an additional 9 months of VNS after exiting a 3-month acute study.

Marangell LB et al. Biol Psychiatry 2002.

Deep Brain Stimulation (DBS)

- FDA Approved for Parkinson's and Tremor
- Investigational for OCD, TRD
- Stereotactic Target from MRI
- Two chest-wall Internal Pulse Generators
- Burr holes in skull for electrode placement
- Stimulation parameters programmed by computer, through "wand"



DBS: Subgenual Cingulate (Cg25) Region

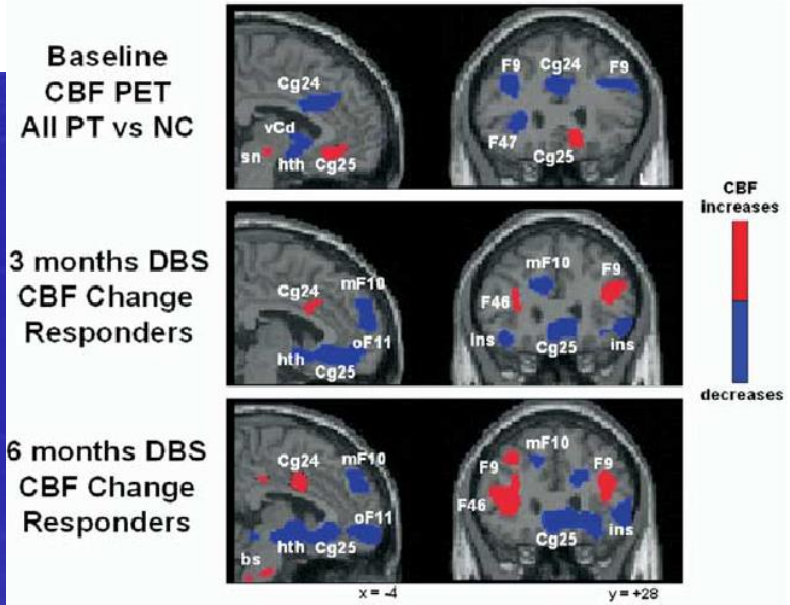
Table 2. Hamilton Depression Rating Scale, HDRS-17, Scores over Time for Each Subject

Time	Hamilton Score[a]					
	Pt 1[b]	Pt 2[c]	Pt 3[b]	Pt 4[c]	Pt 5[b]	Pt 6[b]
Preop baseline	29	22	29	24	26	25
1 week postop (acute stimulation)	5	10	12	18	17	12
2 weeks postop (DBS off)	9	13	23	18	22	n/a
1 month	10	14	17	20	22	12
2 months	13	11	12	18	10	12
3 months	2	15	14	25	7	14
4 months	4	9	12	24	6	12
5 months	5	18	7	23	8	n/a
6 months	5	15	9	23	6	12

[a] Clinical response: decrease HDRS score >50%. Clinical remission: absolute HDRS score <8.
[b] Clinical responders.
[c] Clinical nonresponders.

Response in 4 of 6 patients
Response associated with reduction in local and downstream limbic CBF on PET

Mayberg HS et al, Neuron, 2005



Conclusions

- TRD is common and associated with significant morbidity and mortality
- STAR*D highlights the difficulties of achieving and sustaining remission
- Combinations of medications are often needed
- Devices may play an increasing role in highly resistant depression

1. American Pharmaceutical Association Web site. Accessed December 18, 2004. 2. Russell JM, et al. *J Clin Psychiatry*. 2004;65:341-347. 3. Crown WH, et al. *J Clin Psychiatry*. 2002;63:963-971. 4. Lépine J-P, et al, on behalf of the DEPRES Steering Committee. *Int Clin Psychopharmacol*. 1997;12:19-29.

Post-Lecture Exam Question 1

Limitations of the STAR*D trial include

1. Lack of a placebo group
2. Patients had the option of not participating in a randomization
3. Lack of inclusion of common augmenting agents such as antipsychotics
4. All of the above

Question 2

The chance of achieving acute remission by one or more trials in STAR*D was

1. 20%
2. 50%
3. 80%
4. 100%

Question 3

Compared to medication augmentation in the STAR*D trial, the addition of cognitive therapy was

a. significantly less effective
b. significantly more effective
c. about equally effective
d. not studied

Question 4

Transcranial magnetic stimulation has an effect size in clinical trials that is

1. About that of unilateral ECT
2. About that of bilateral ECT
3. Less than that of ECT
4. Greater than that of ECT

Question 5

The typical time to see effects from vagus nerve stimulation are

1. 4-8 weeks
2. 12 weeks
3. 16-24 weeks
4. Greater than 24 weeks

Answers to Pre and Post Lecture Exams

1. D
2. C
3. C
4. C
5. D