Overview of Treatment-Resistant Depression

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Teaching Points

- Most depression does not respond adequately to single monotherapy trials
- STAR*D provides some insights on the utility of combination treatment
- Devices may play an increasing role in TRD

Outline

- Definition of treatment resistance
- Implications of failure to treat to remission
- Biological factors in treatment resistance

STAR*D Acute findings

- Level 1
- Level II
- Level III
- Level IV

STAR*D relapse findings

Role of Devices in treatment resistant depression

- ECT
- TMS
- VNS
- DBS

Pre-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

Major Depressive Disorder (MDD)

- Affects 18 million US residents and 340 million worldwide[1] (16.2% lifetime risk)[2]; 2/3 are female
- Depression is chronic or recurrent
  - 25% to 40% experience a recurrence within 2 years of the index episode[3]
  - 85% experience recurrence after 15 years[3]
  - 20% to 35% of patients who experience one episode of depression have chronic depression[4-6]

1. Greden JF. *J Clin Psychiatry.* 2001;62(suppl 22):5-9. 2. Kessler RC, et al. *JAMA.* 2003;289:3095-3105. 3. Keller MB, et al. *Biol Psychiatry.* 1998;44:348-360. 4. Keller MB, et al. *Am J Psychiatry.* 1982;139:438-442. 5. Mueller TI, et al. *Psychiatr Clin North Am.* 1996;19:85-102. 6. Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am.* 2003;26:457-494.

The Need for Long-Term Treatment Options in Depression

- Fourth most disabling condition worldwide[1]; most disabling condition for females (US)
- Increased morbidity of comorbid general medical conditions[2] and increased rate of suicide as percent of total mortality[3]
- Loss of productivity in workplace[2]
- Patients with depression use substantially more healthcare services than do patients without depression[4-6]
- Depression is life shortening
  - Increased risk of CV events, stroke, etc.

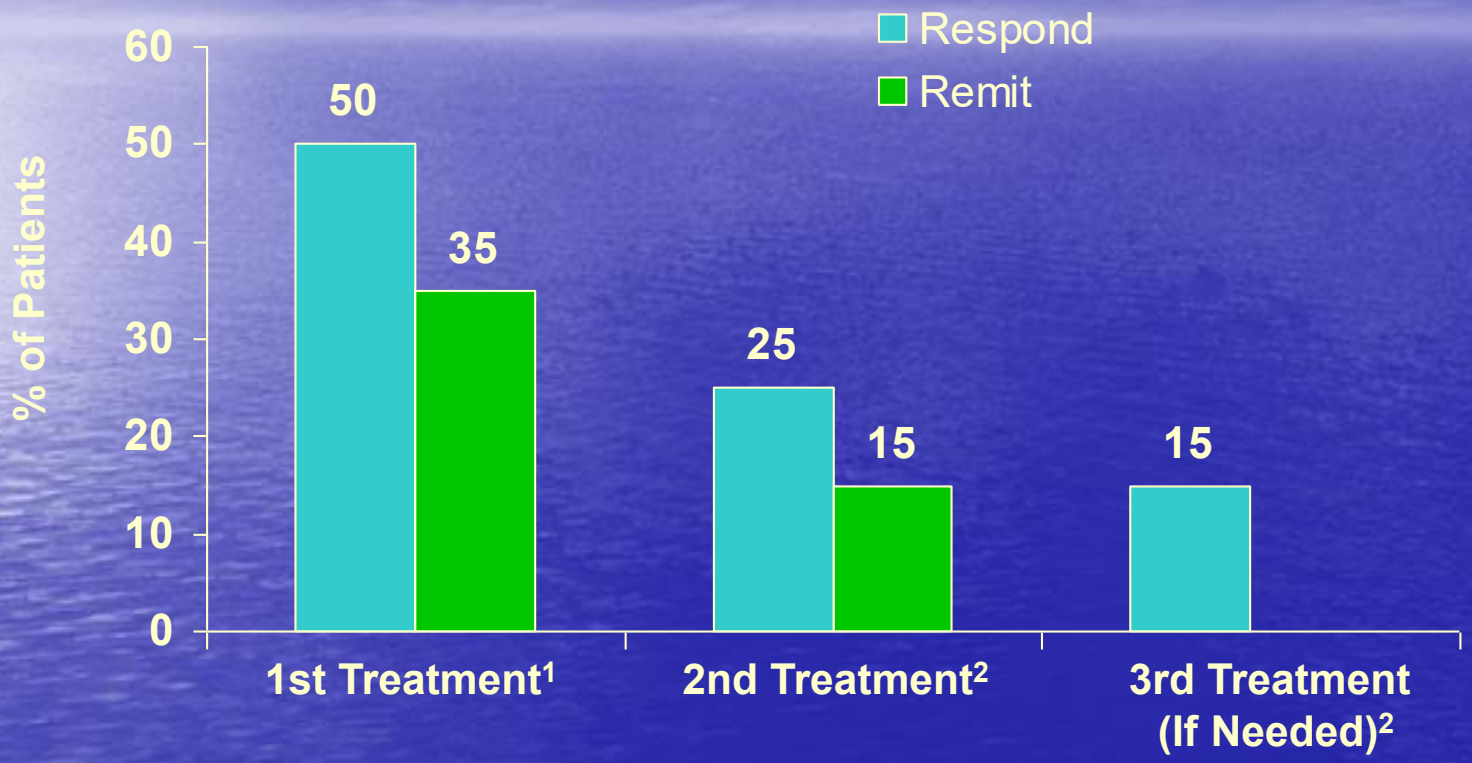
1. World Health Organization Web Site. Accessed July 7, 2005. 2. Greden JF. *J Clin Psychiatry.* 2001;62(suppl 22):5-9. 3. Fawcett J. *Int Clin Psychopharmacol.* 1993;8:217-220. 4. Rowan PJ, et al. *Psychol Med.* 2002;32:903-908. 5. Druss BG, et al. *Am J Psychiatry.* 2000;157:1274-1278. 6. Simon GE. *Biol Psychiatry.* 2003;54:208-215.

TRD Overview: Levels of Resistance

Stage	Treatment Response
0	No single adequate trial of medication
1	Failure to respond to an adequate trial of 1 medication
2	Failure to respond to 2 different monotherapy trials of medications with different pharmacologic profiles
3	Stage 2 plus failure to respond to augmentation of 1 of the monotherapies
4	Stage 3 plus failure of a second augmentation strategy
5	Stage 4 plus failure to respond to ECT

Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: The Fourth Generation of Progress.* New York, NY: Raven Press, Ltd.; 1995:1082-1097.

TRD Outcome



Thus, over 20% of patients with MDD have TRD

1. *Depression in Primary Care, Vol 2. Treatment of Major Depression.* Rockville, Md: Agency for Healthcare Policy and Research, US Department of Health and Human Services; 1993. AHCPR Publication 93-0551.
2. Fava M, et al. for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494.

Potential Causes of TRD

- Misdiagnosis
- Inadequate treatment, undertreatment, or starting treatment too late[1]
- Failure to achieve initial remission[2]
- Nonadherence
- Failure to address concurrent disorders[1]
  - Occult substance abuse
  - Occult general medical conditions (GMCs)
  - Concurrent Axis I or II disorders

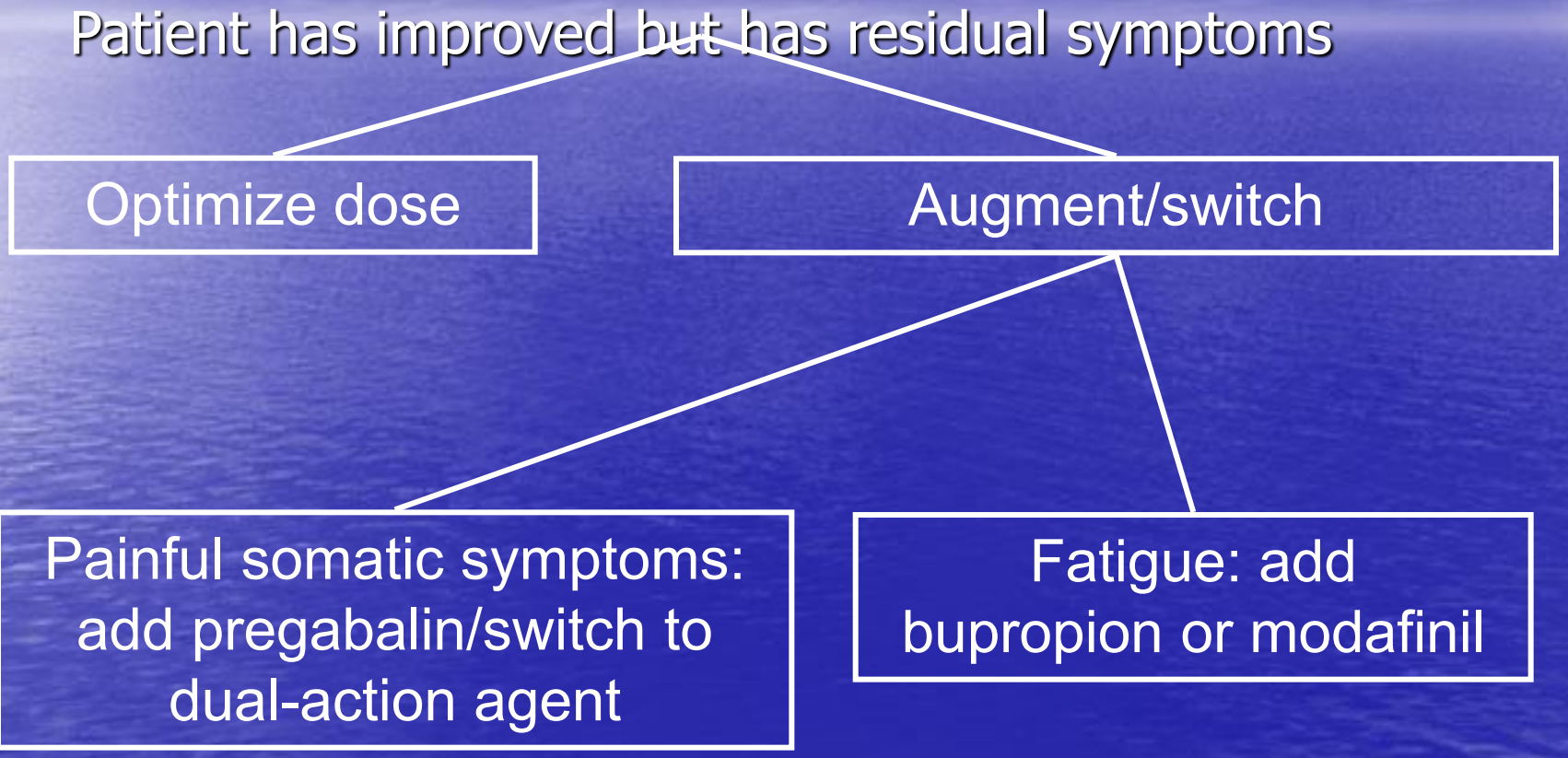
1. Thase ME, Rush JA. *J Clin Psychiatry.* 1997;58(suppl 13):23-29. 2. Judd LL, et al. *J Affect Disord.* 1998;50:97-108.

Assessing Current Treatment and Checking for Nonadherence (1)

- Did the patient receive adequate treatment?
  - An inadequate dose or duration of treatment can prevent remission
    - Experts recommend a minimum trial period between 6 and 12 weeks in length
    - Pharmacokinetics can differ in elderly and pediatric populations
- Is patient nonadherent?
  - Ask patient what they are taking and when
  - ≥50% of patients fail to take antidepressants as prescribed due to lack of understanding of instructions or unnatural fears of side effects/drug dependence
  - Ask about troubling and intolerable side effects, including sexual dysfunction, nausea, akathisia, etc.

Reus VI. Psychiatr Clin North Am 1996.Trivedi MH. Ann Clin Psychiatry 2003.

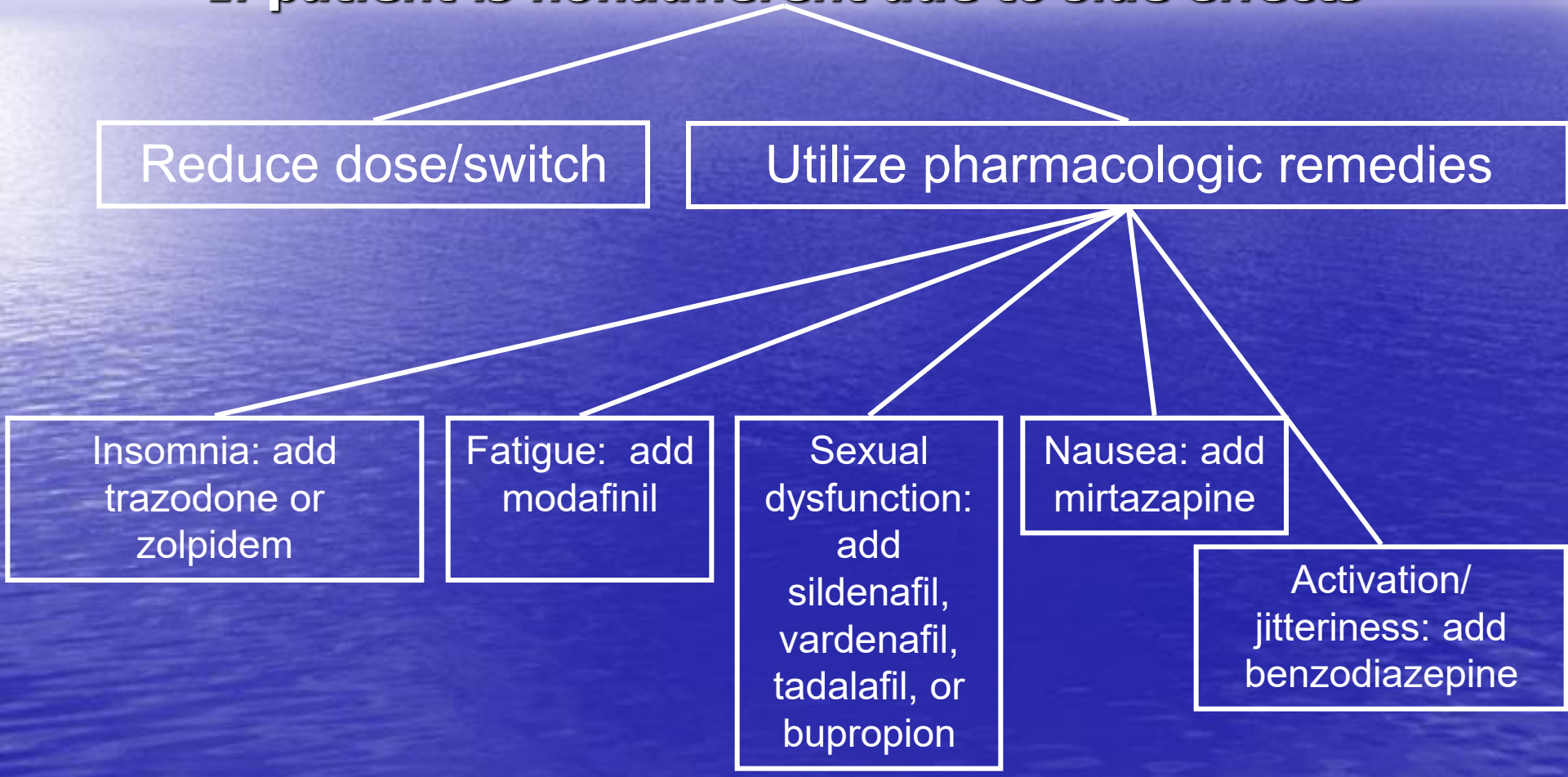
Assessing Current Treatment and Checking for Nonadherence (2)



Stahl SM. Psychopharmacology of antidepressants; 1997.

Assessing Current Treatment and Checking for Nonadherence (3)

If patient is nonadherent due to side effects



Stahl SM. Psychopharmacology of antidepressants; 1997.

Treatment-Resistant Depression: Predictors

- Higher baseline severity/longer duration of illness
- Early onset of illness
- Comorbid anxiety, panic symptoms, substance abuse
- History of childhood abuse
- Lack of social support

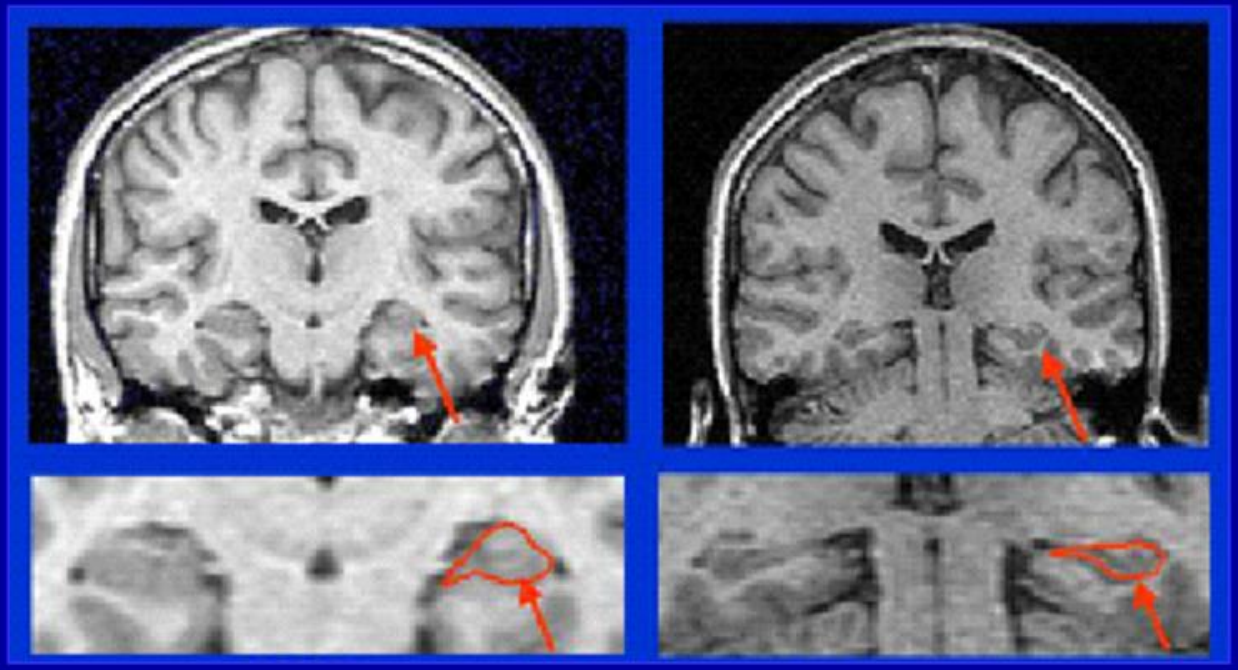
Biologic Treatment Resistance

- Morphologic brain changes and impaired neurogenesis with recurrent depression chronicity[1,2]
- Genetic polymorphisms[3]

1. Henn FA, Vollmayr B. *Biol Psychiatry.* 2004;56:146-150. 2. Manji HK, et al. *Nat Med.* 2001;7:541-547.
3. Neumeister A, et al. *Psychopharmacology.* 2004;174:512-524.

Brain atrophy in depression?

Atrophy of the Hippocampus in Depression

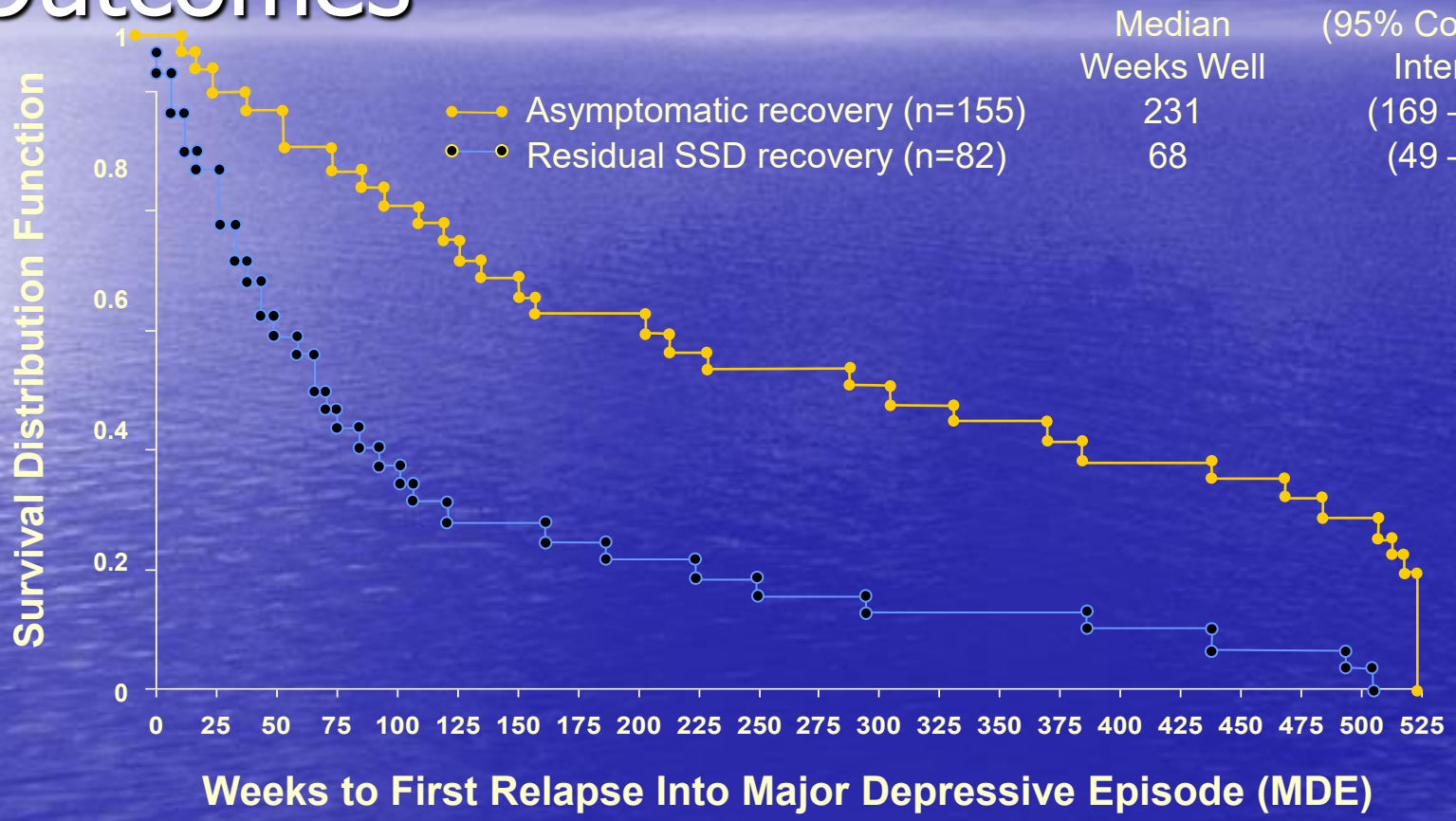


Normal

Depression

Bremner JD, et al. *Am J Psychiatry.* 2000;157(1):115-118.

Failure to Achieve Initial Remission Produces Worse Long-Term Outcomes



SSD=subsyndromal depression; subthreshold depressive symptoms.
Reprinted from Judd LL, et al. *J Affect Disord.* 1998;50:97-108, with permission from Elsevier.

TRD Mortality

- TRD is associated with
  - Increased mortality
  - High risk of suicide (~15% of patients with TRD)[1]
- Patients with well-characterized TRD are likely to report hopelessness and prominent suicidal ideation
  - One third of patients studied reported significant suicidal ideas or gestures[2]
- Suicidal thoughts have a negative impact on the course of depression

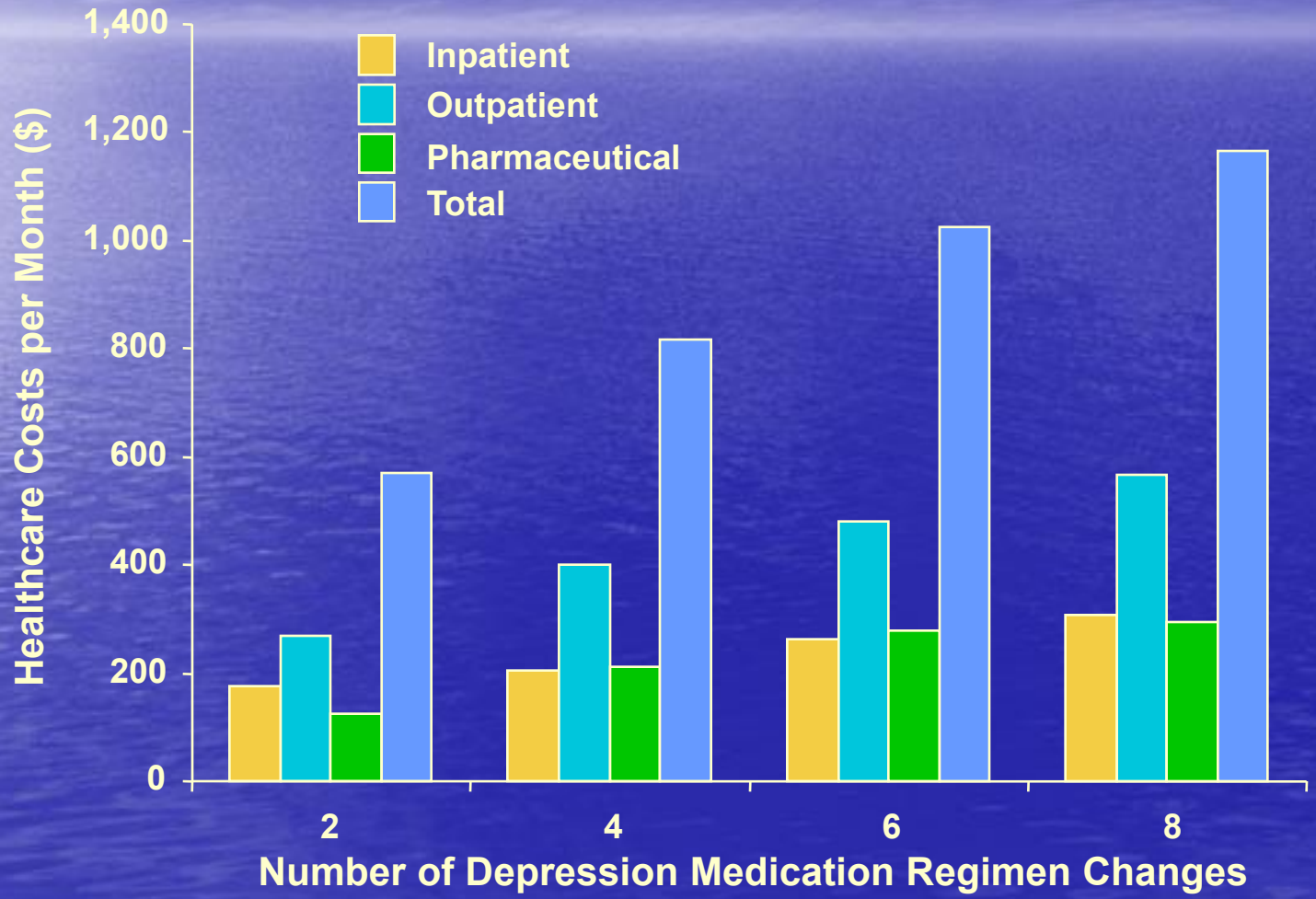
1. American Pharmaceutical Association Web site. Accessed December 18, 2004. 2. Papakostas GI, et al. *J Nerv Ment Dis.* 2003;191:444.

TRD Morbidity

- TRD is associated with
  - Increased economic burden
  - Greater healthcare utilization and costs[1-3]
    - Patients with depression made more than 3× the number of doctor visits than those without depression[2]
    - Hospitalized TRD group had 7× the annual health care costs of the outpatient TRD group and 19× the costs of the comparison group[3]

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

Healthcare Utilization Increases With Greater Degrees of Treatment Resistance



Russell JM, et al. *J Clin Psychiatry.* 2004;65:341-347.

Psychosocial Impact of TRD

- The Longitudinal Interval Follow-up Evaluation (LIFE) scale was used to measure psychosocial functioning in 92 patients with TRD
- Specific impairments noted
  - Mild-to-moderate impairment in work-related activities
  - Good-to-fair interpersonal relations
  - Poor level of involvement in recreational activities
  - Mild impairment of ability to enjoy sexual activity
- However, patients and clinicians rated global social adjustment as poor

Petersen T, et al. *Eur Psychiatry*. 2004;19:196-201.

Clinical Management of TRD

- Polypharmacy is common; which treatments or combinations are best is not known[1,2]
- Preferred treatment steps are not defined[1,2]
- ECT, which may be effective acutely, may be declined, may not be sustained due to adverse events (AEs), and has poor long-term outcomes
  - Side effects and adherence limit treatment effectiveness
  - Greater treatment resistance is associated with lower ECT response and higher post-ECT relapse rates[3,4]

1. Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am.* 2003;26:457-494. 2. Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials.* 2004;25:119-142. 3. Prudic J, et al. *Am J Psychiatry.* 1996;153:985-992. 4. Sackeim HA, et al. *JAMA.* 2001;285:1299-1307.

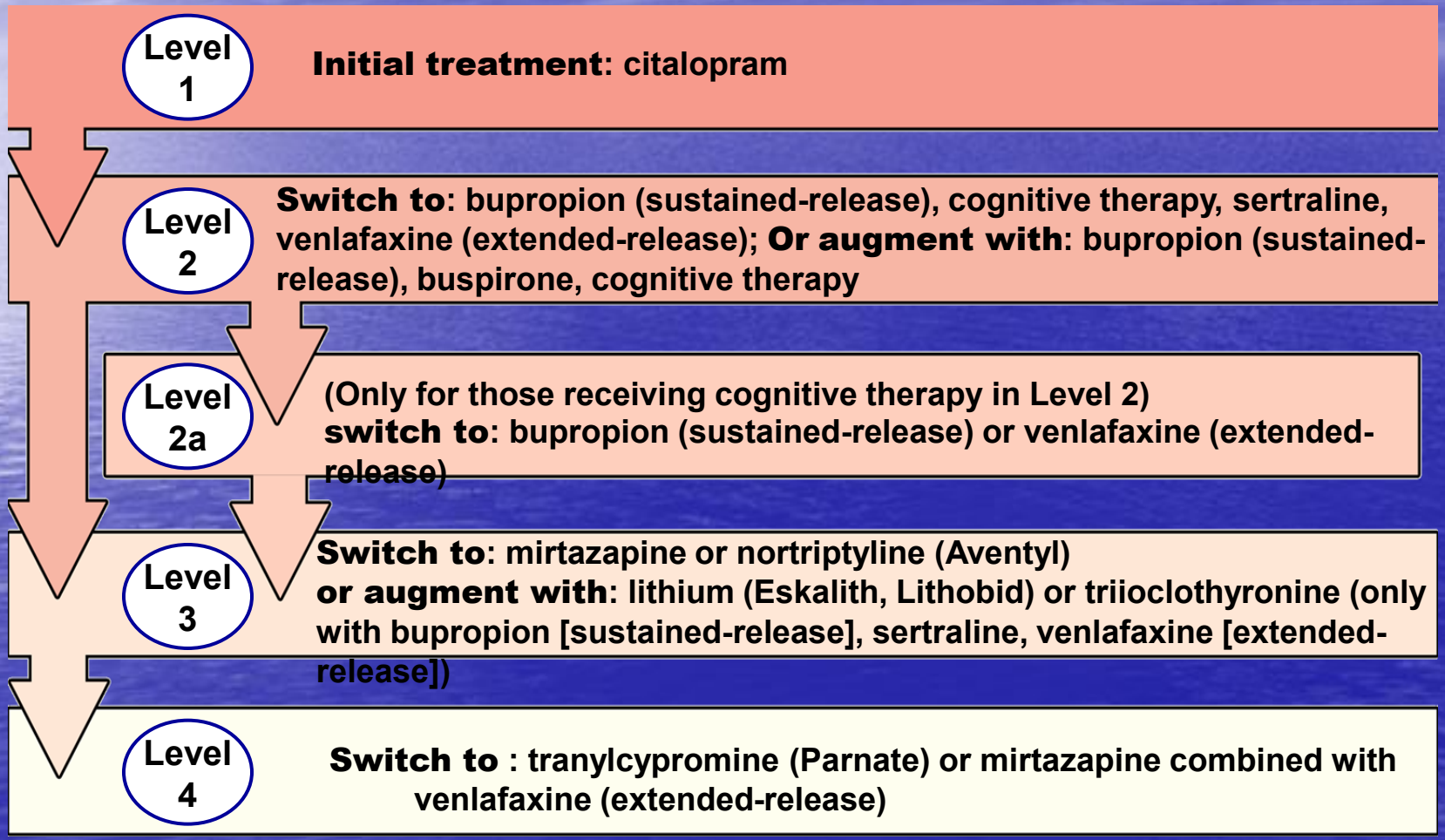
"Treatment-Resistant" Depression: Other Contributing Factors

- Comorbid medical conditions, especially endocrine/metabolic disorders and disturbances of thyroid/adrenal axes
  - Disorders of this nature may affect drug efficacy
  - Pharmacotherapies used to treat comorbid conditions may also affect antidepressant efficacy
- Nutritional deficiencies
  - Folate, thiamine, B6, B12, copper, zinc
- Substance use/abuse
- Sleep deprivation
- Life (social/familial/financial) stress
- Lack of exercise

Reus VI. Psychiatr Clin North Am 1996.

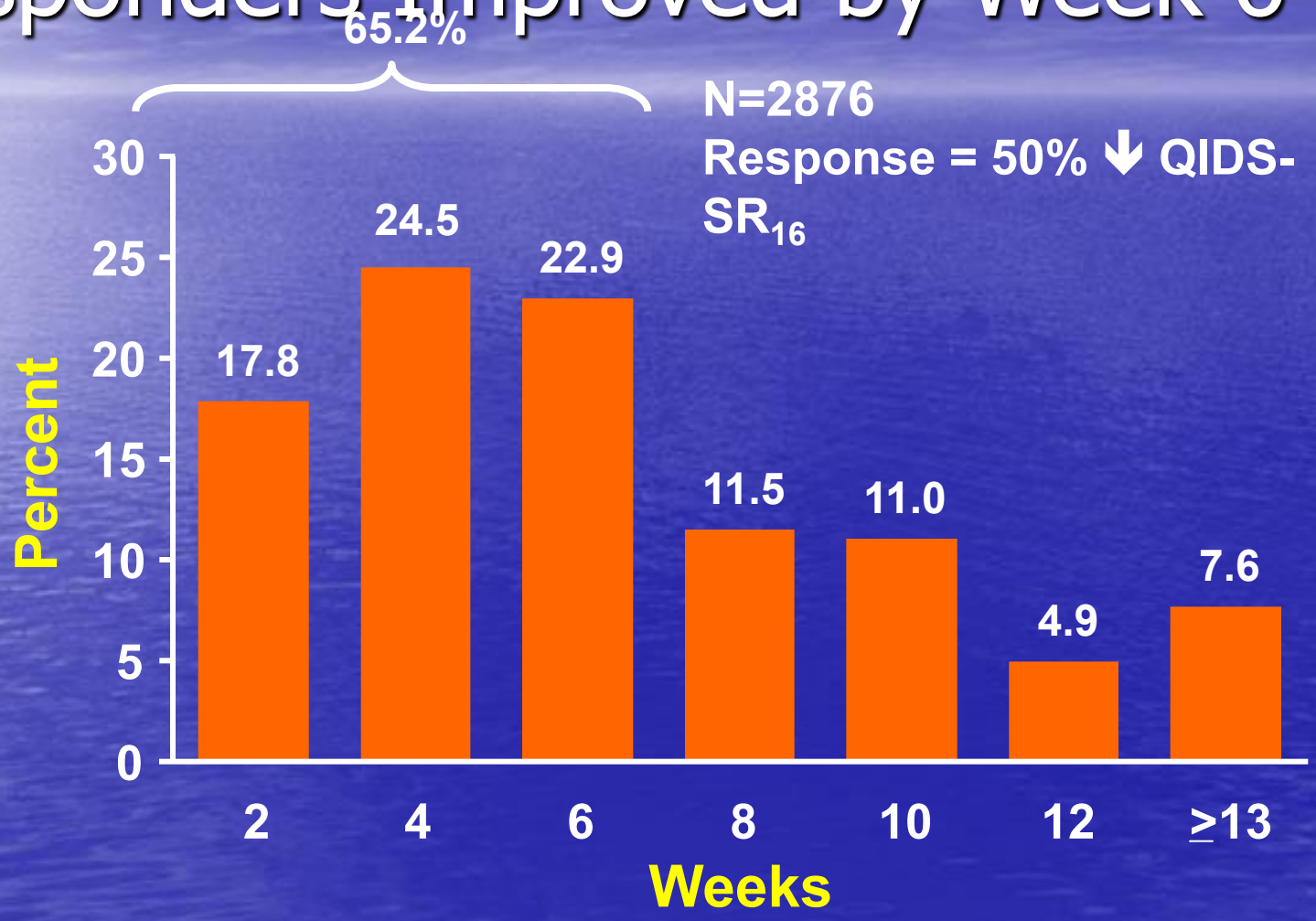
Treatment Algorithm Snapshot

STAR*D Algorithm



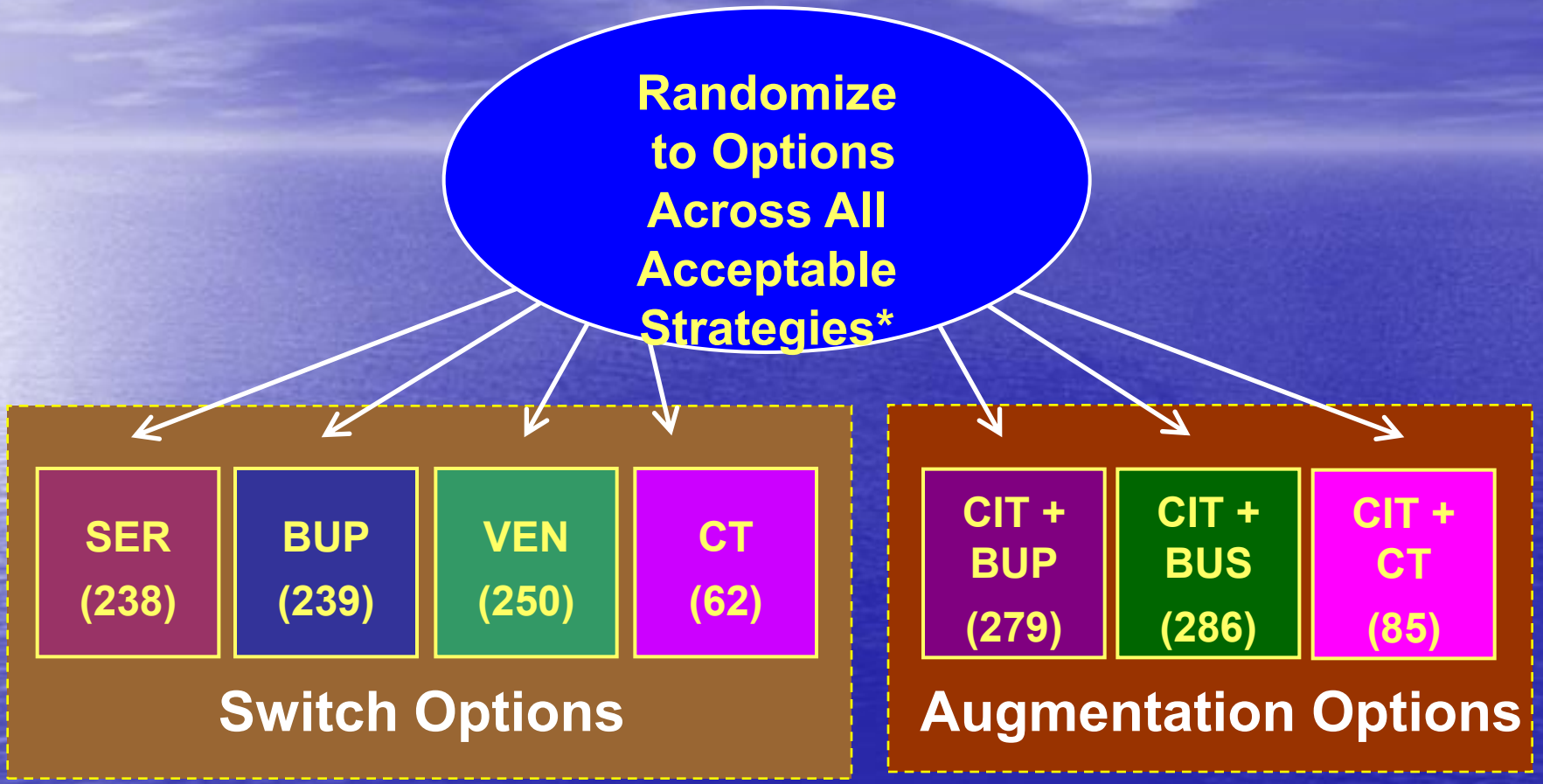
Rush AJ et al. (2003), Am J Psychiatry 160(2):237

Two Thirds of STAR*D Citalopram Responders Improved by Week 6



Trivedi MH et al. (2006), Am J Psychiatry 163(1):28-40

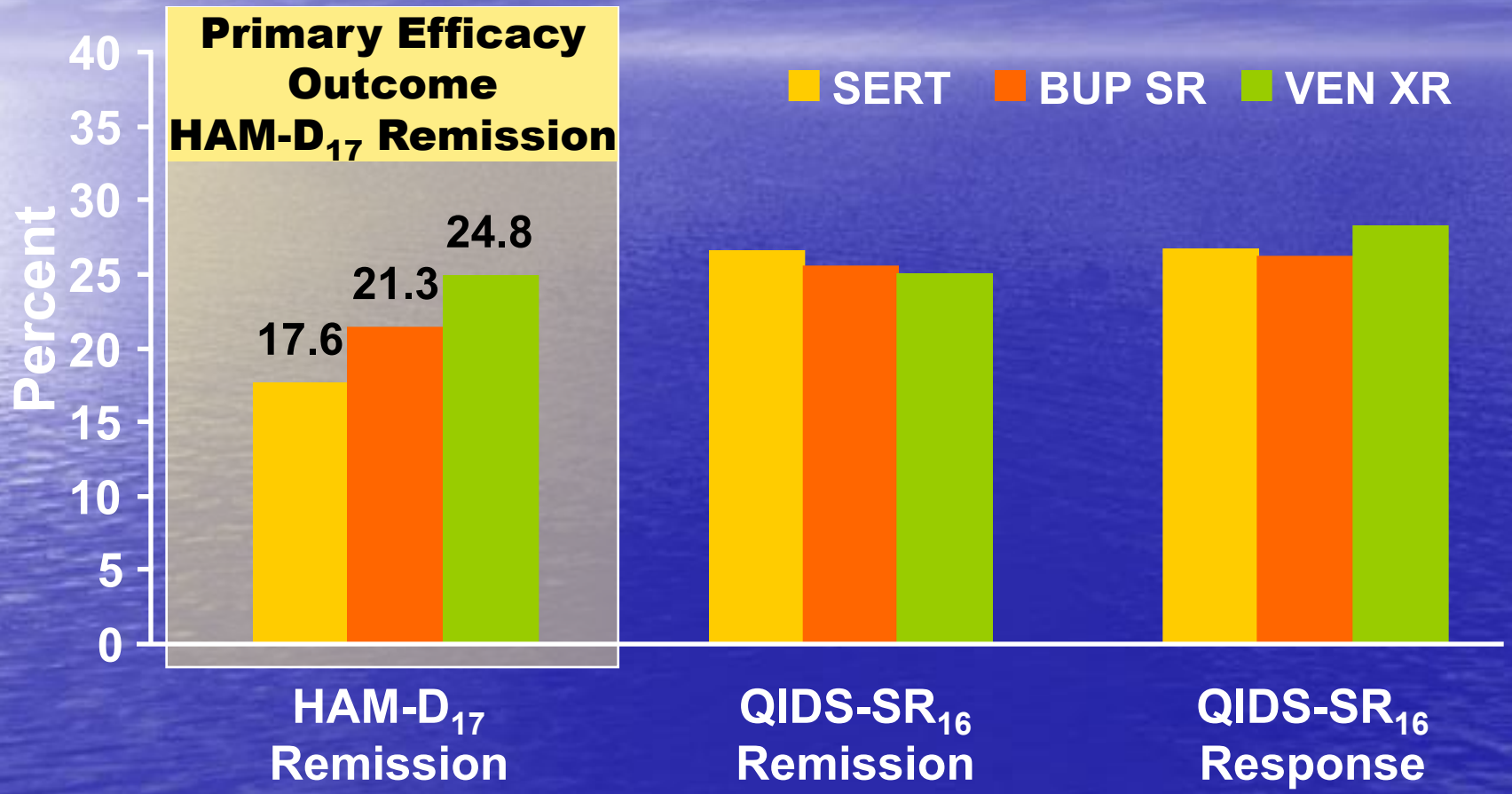
Level 2



*If strategy group is not acceptable to the patient, then he/she is randomized to treatment options within remaining acceptable treatment strategies. If all treatment strategies are rejected, then patient enters naturalistic follow-up; SER = sertraline; VEN = venlafaxine XR; CT = cognitive therapy; CIT = citalopram; BUS = buspirone; Rush AJ et al. (2004), Control Clin Trials 25(1):119-142

Level 2 Medication Switch

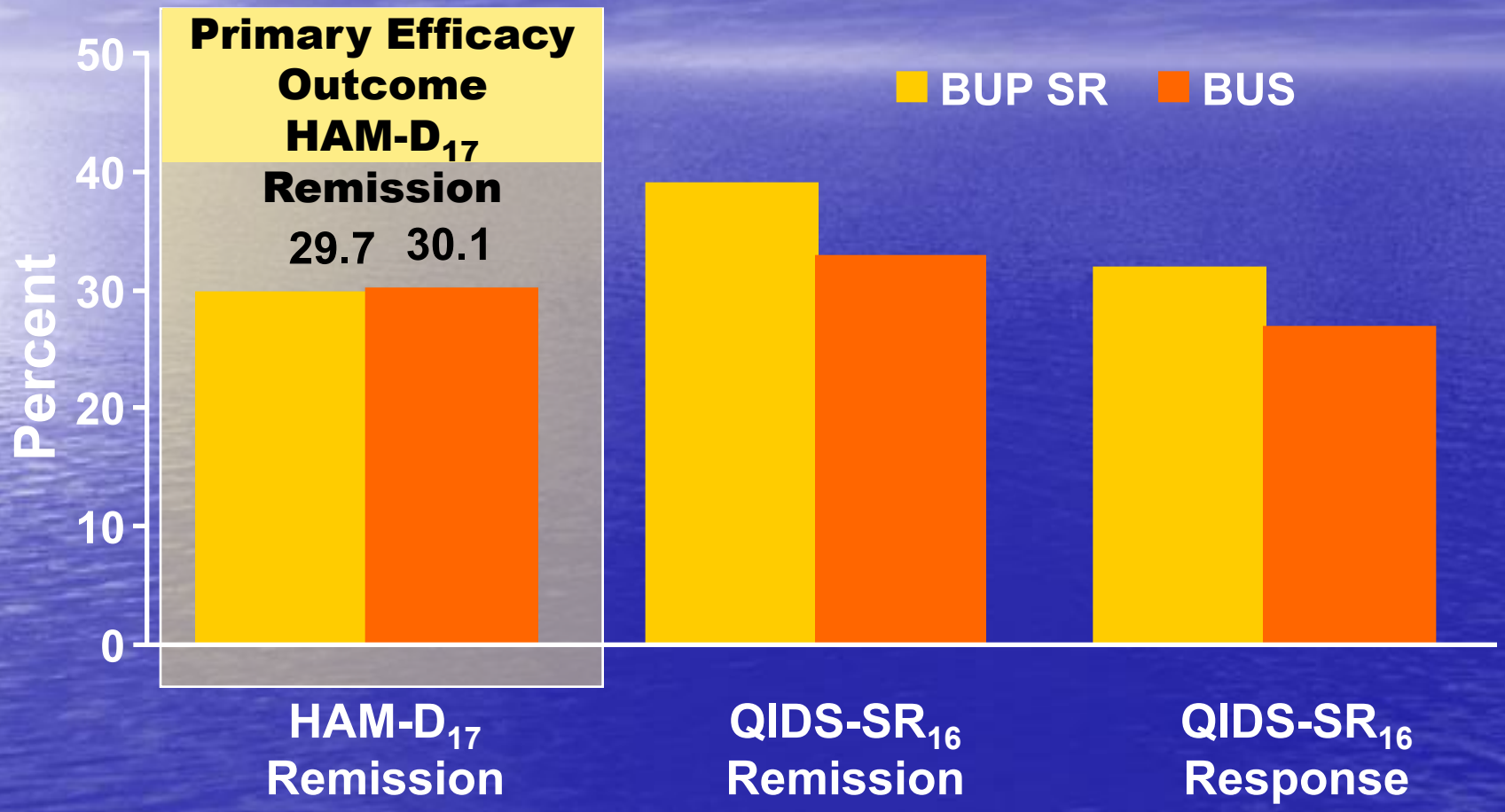
Level 2 Switch: Primary and Secondary Efficacy Outcomes



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

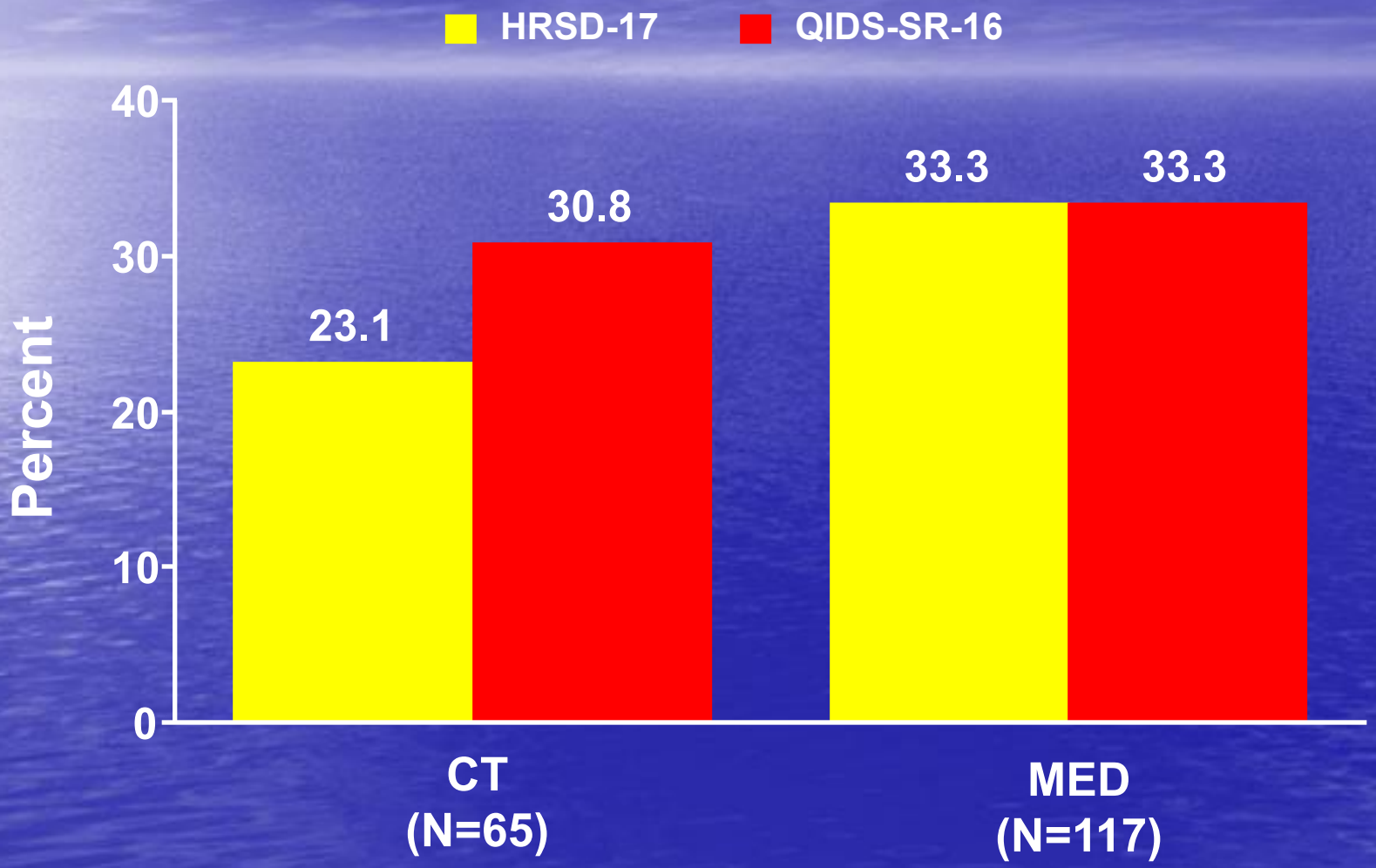
Level 2 Augment: Primary and Secondary Efficacy Outcomes



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

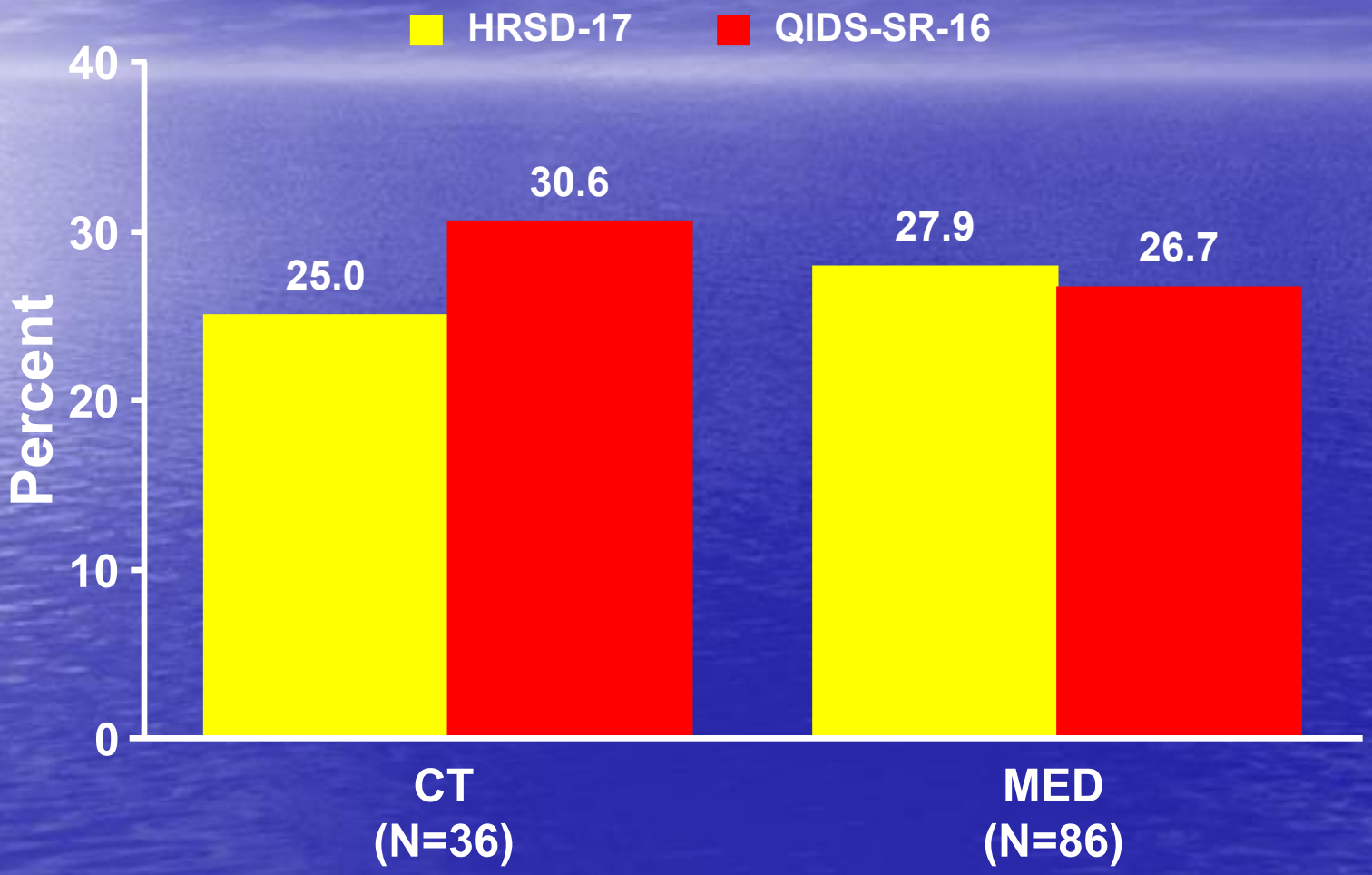
Level 2 Cognitive Therapy Studies

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



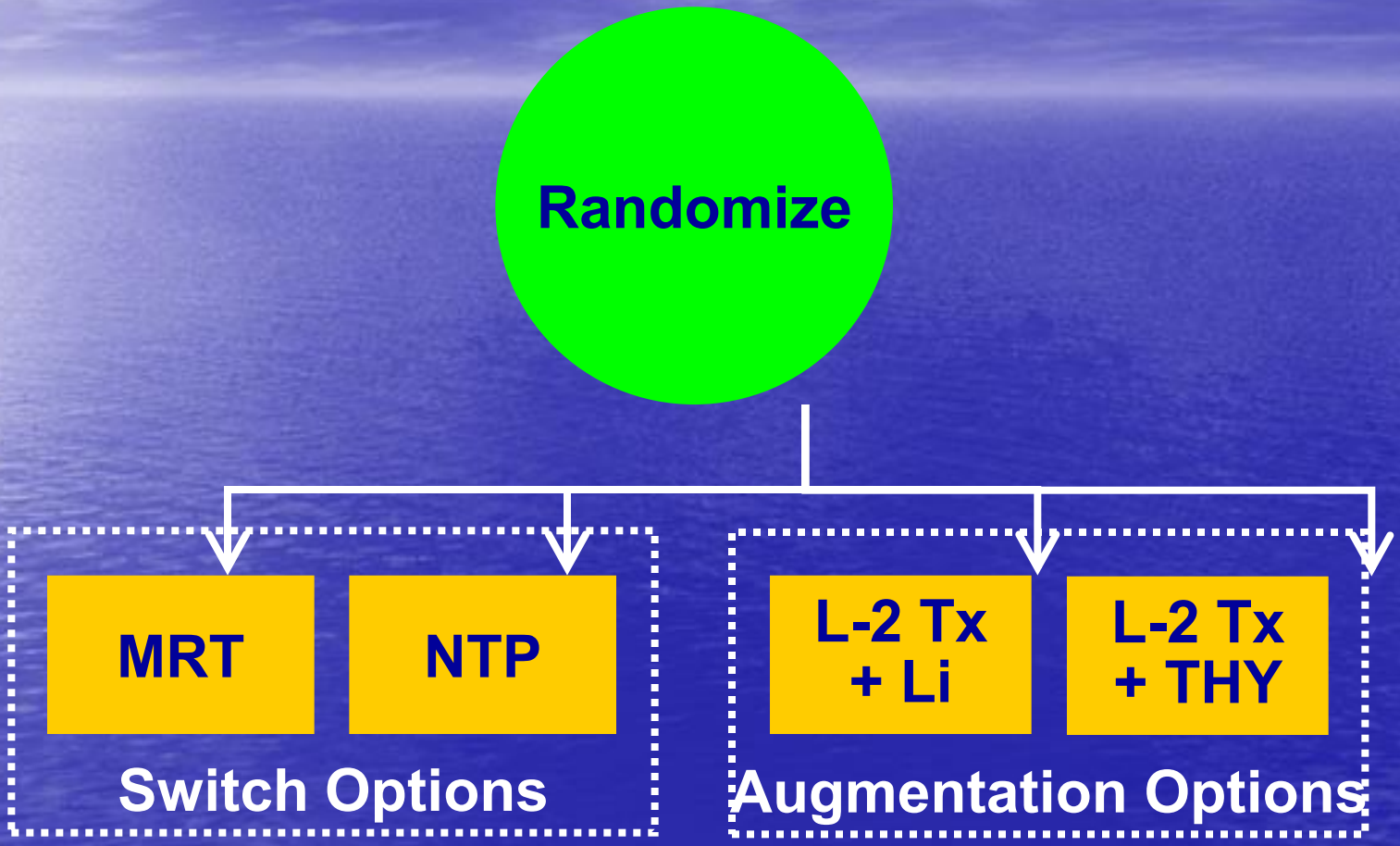
MED = medication augmentation; Thase ME et al. (2007), Am J Psychiatry 164(5):739-752

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



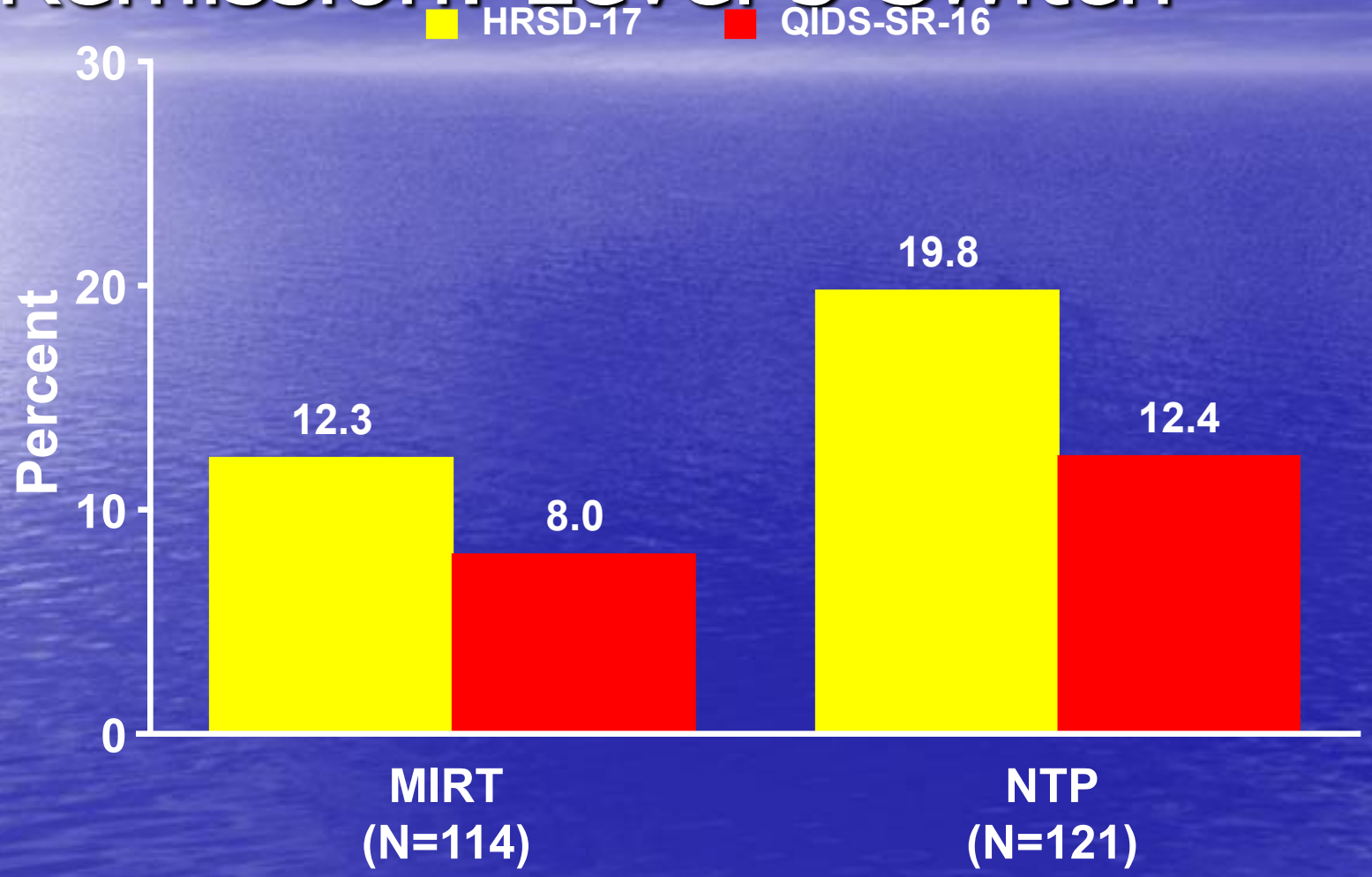
Thase ME et al. In preparation

Level 3



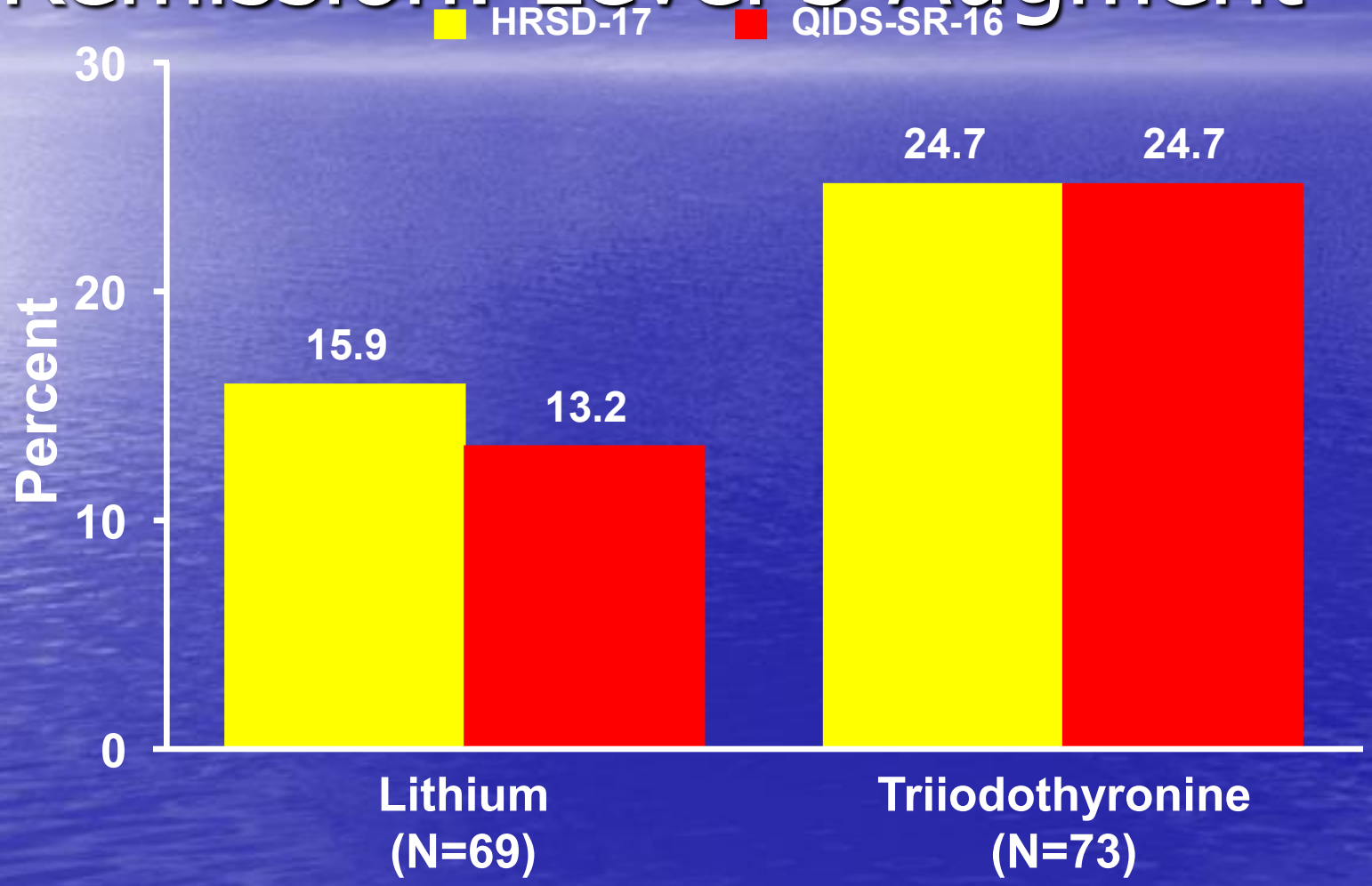
MIRT = mirtazapine; NTP = nortriptyline; Rush AJ et al. (2004), Control Clin Trials 25(1):119-142

Treatment Outcomes Remission: Level 3 Switch



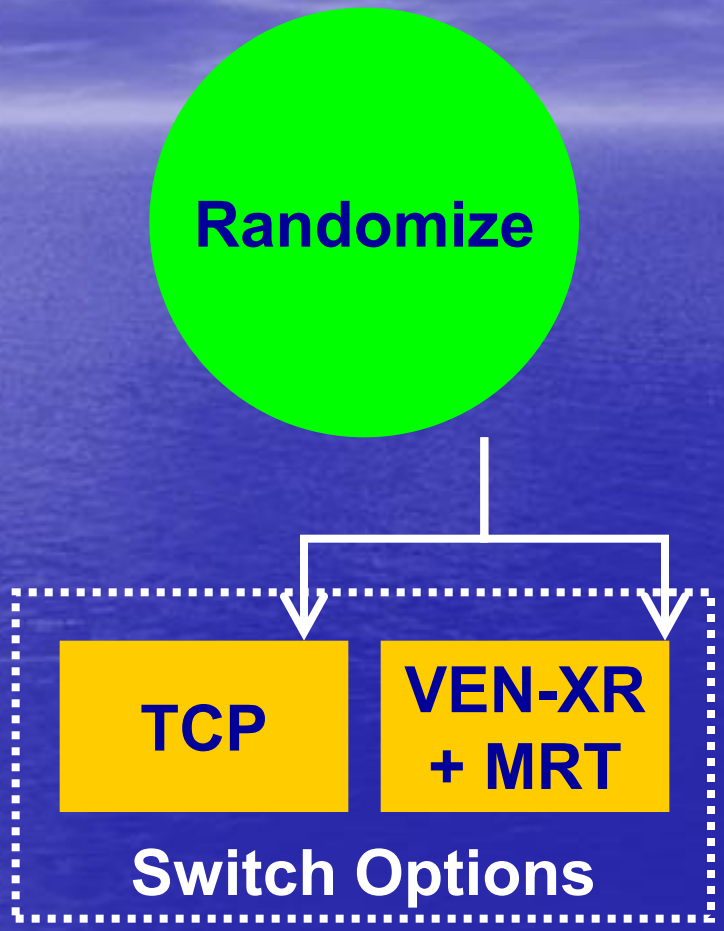
Fava M et al. (2006), Am J Psychiatry 163(7):1161-1172

Treatment Outcomes Remission: Level 3 Augment



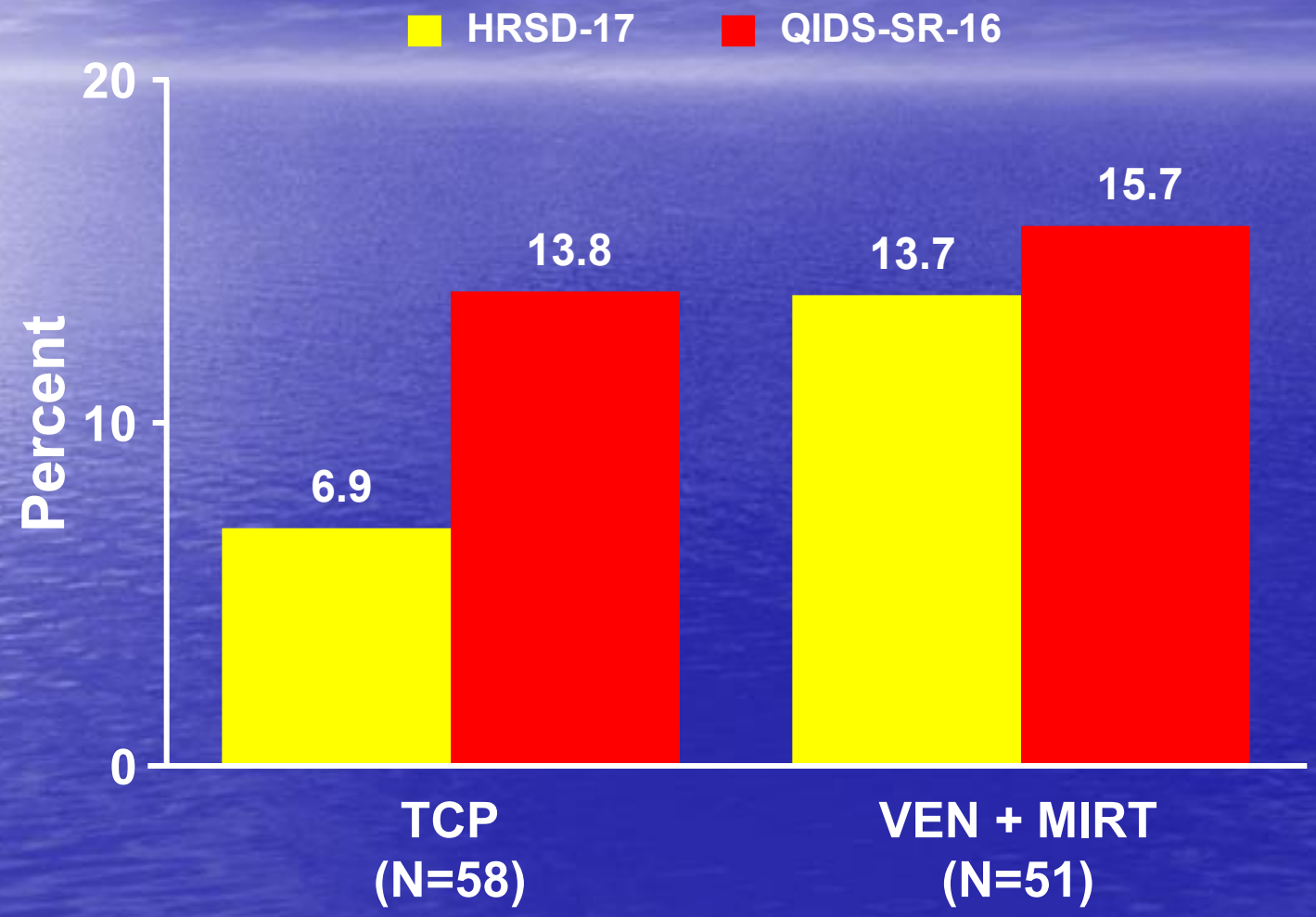
Nierenberg AA et al. (2006), Am J Psychiatry 163(9):1519-1530

Level 4



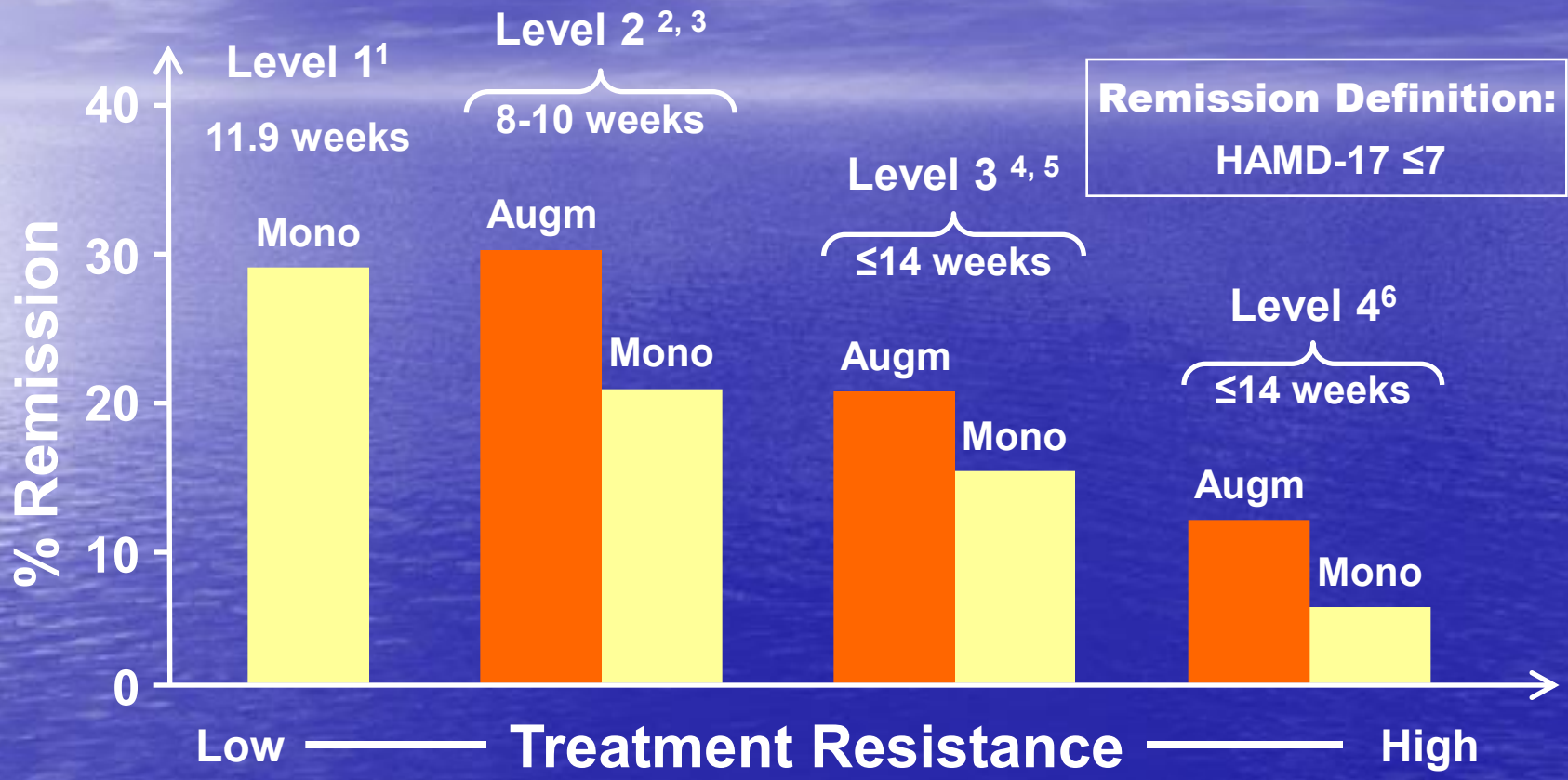
TCP = tranylcypromine; Rush AJ et al. (2004), Contol Clin Trials 25(1):119-142

Treatment Outcomes Remission: Level 4



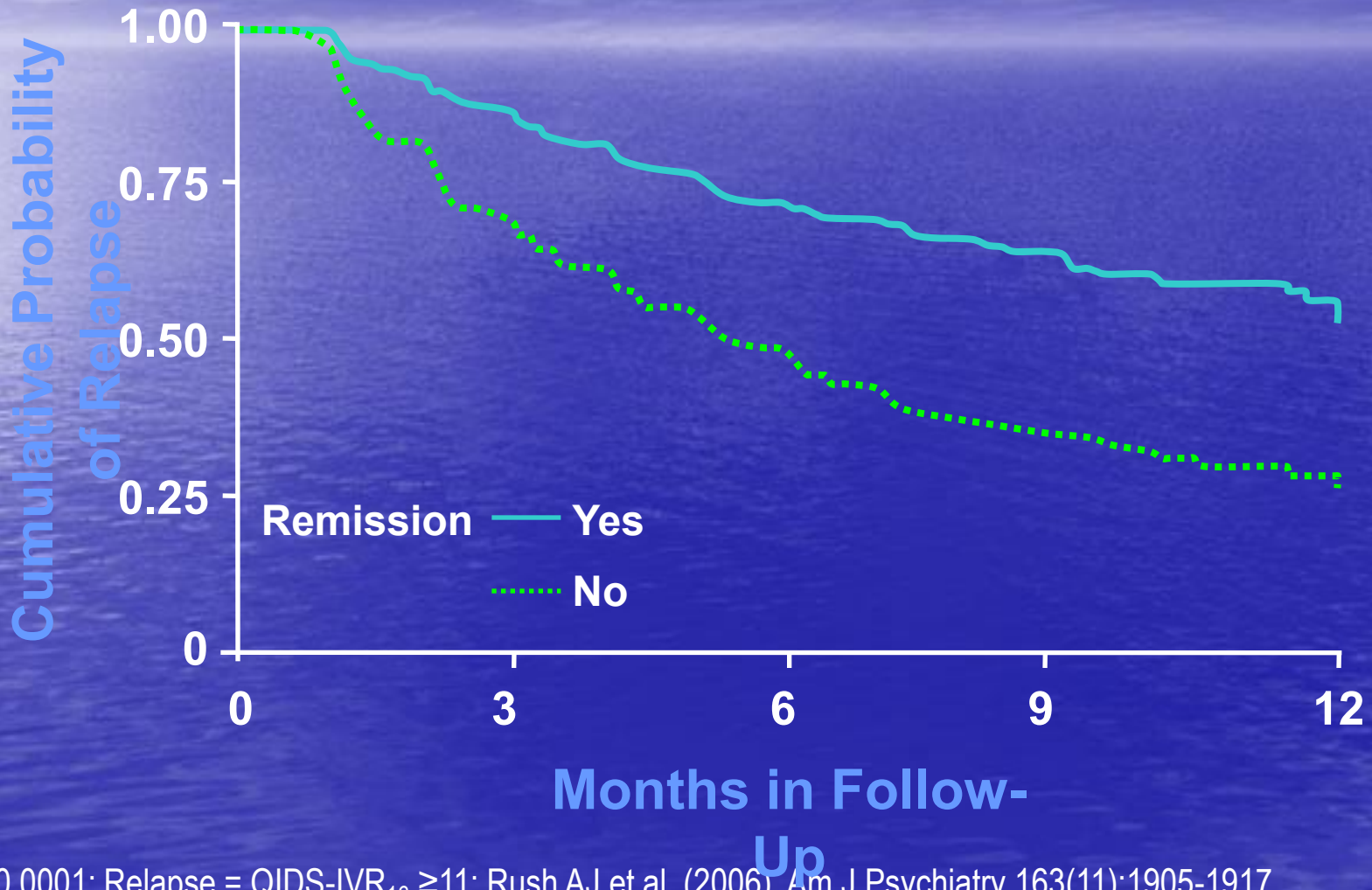
McGrath PJ et al. (2006), Am J Psychiatry 163(9):1531-1541

STAR-D Remission Rates Across All 4 Levels



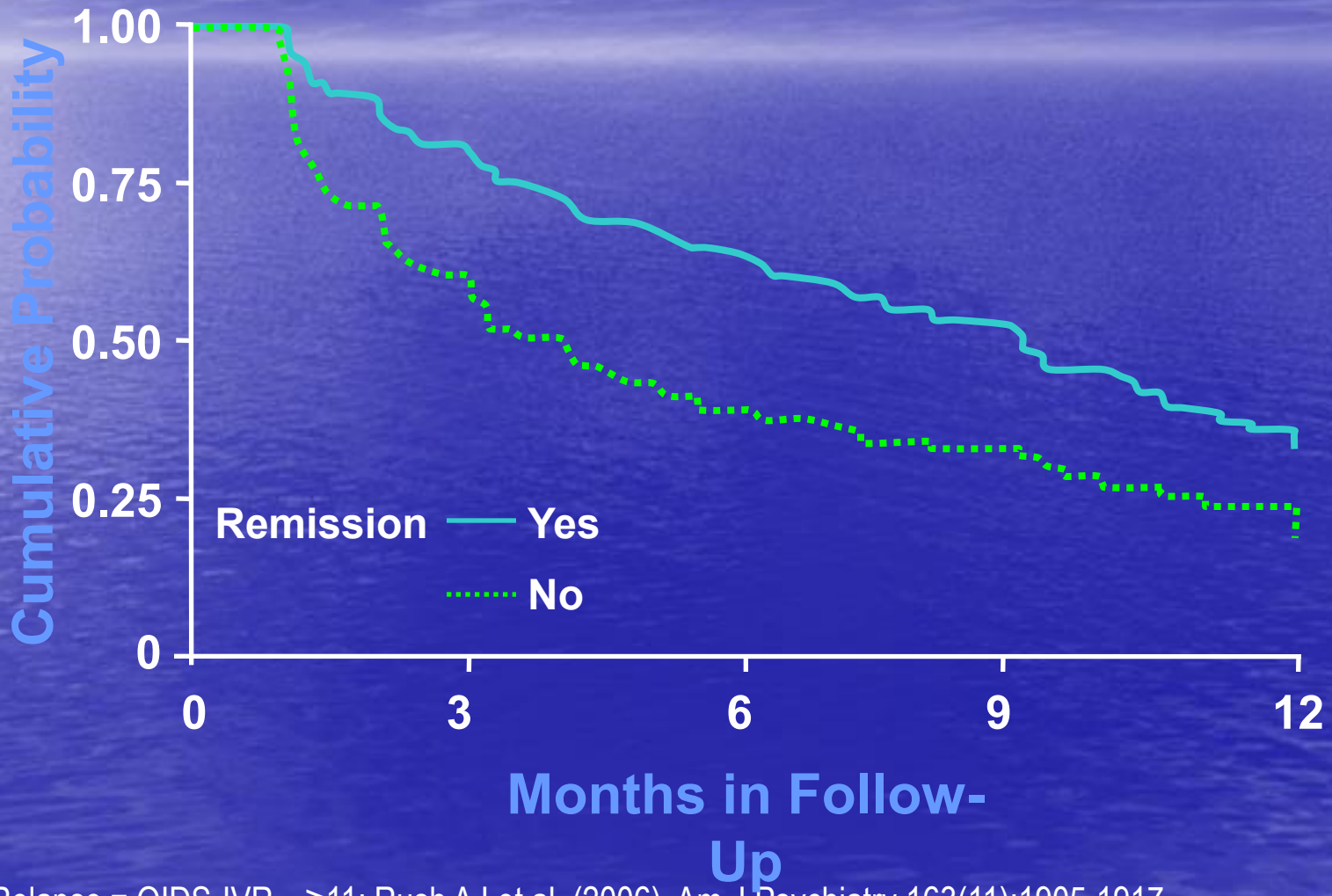
Mono = single medication regimen; Augm = combination medication treatment; [1]Trivedi MH et al. (2006), Am J Psychiatry 163:28-40; [2]Trivedi MH et al. (2006), N Engl J Med 354:1243-1252; [3]Rush AJ et al. (2006), N Engl J Med 354:1231-1242; [4]Nierenberg AA et al. (2006), Am J Psychiatry 163:1519-1530;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



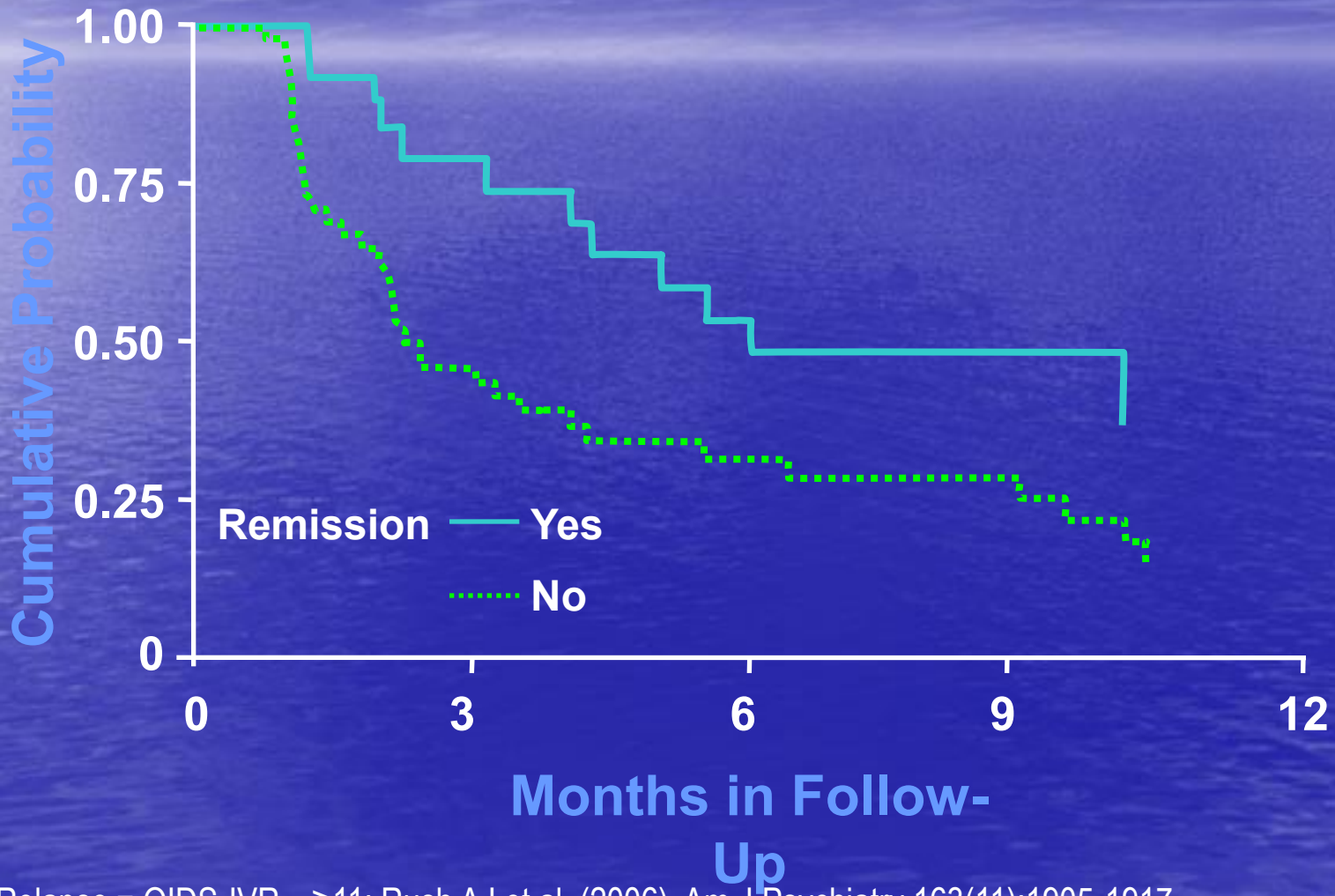
p<0.0001; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Level 2 Follow-Up



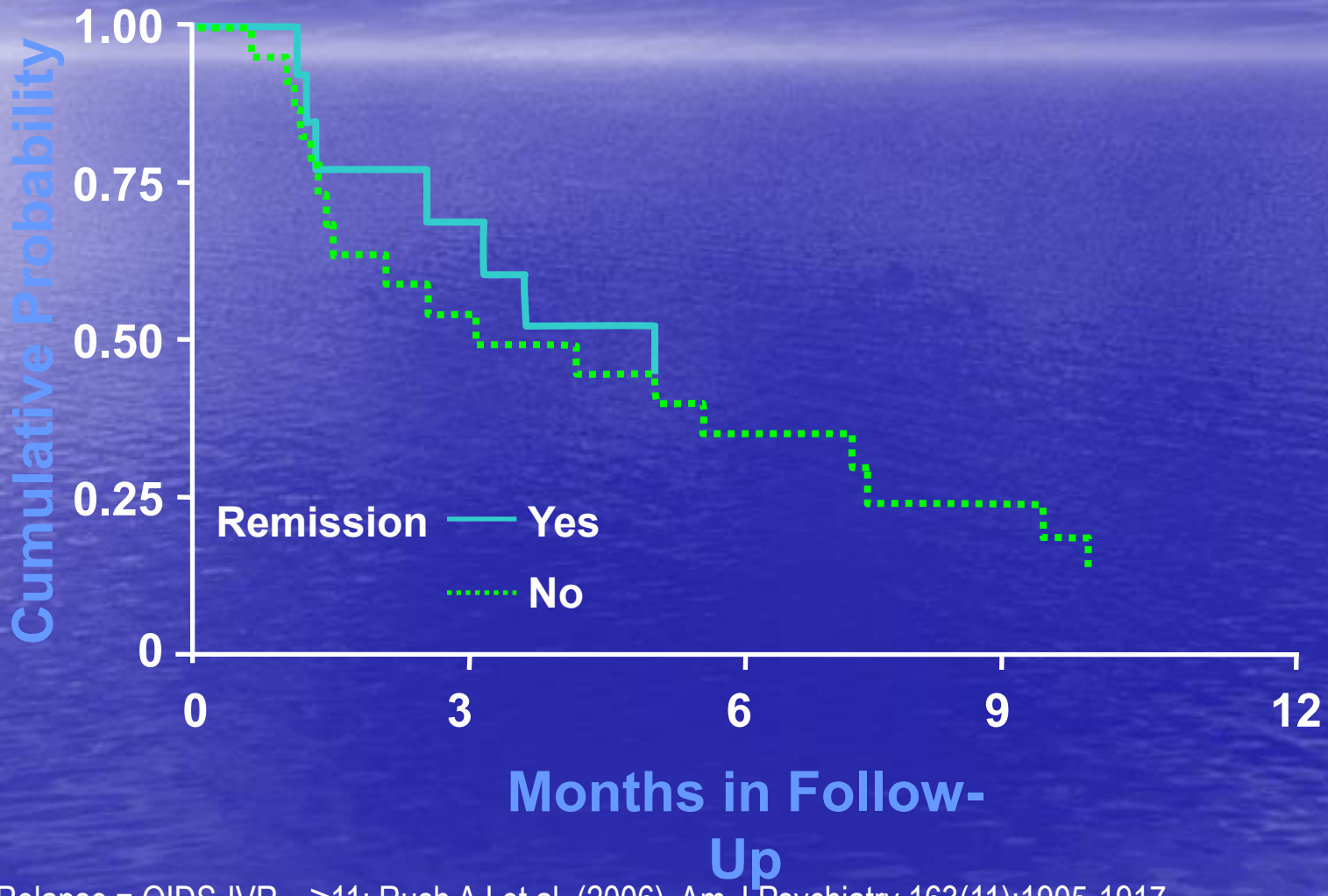
p<0.0001; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Level 3 Follow-Up



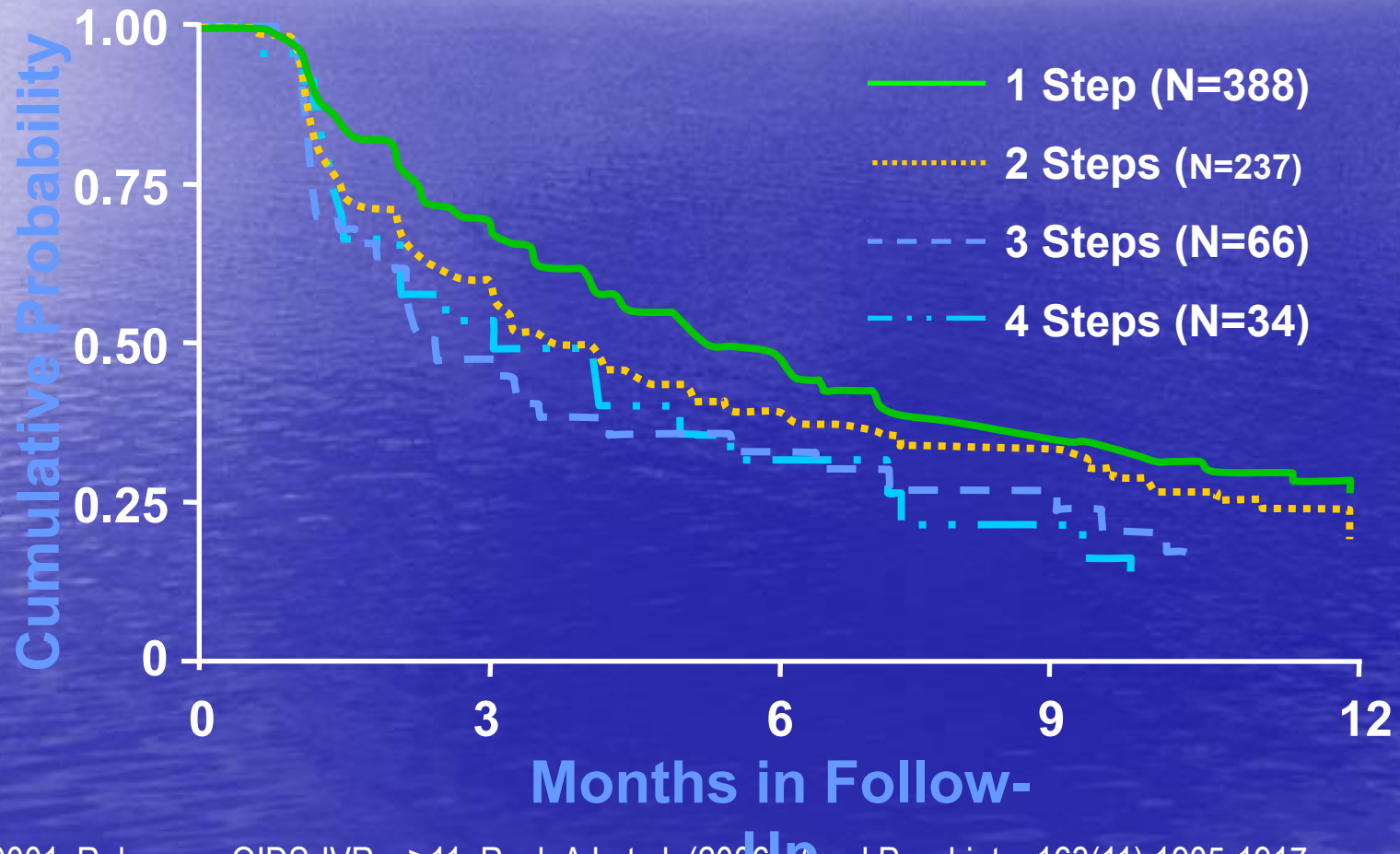
P<0.0132; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

Level 4 Follow-Up



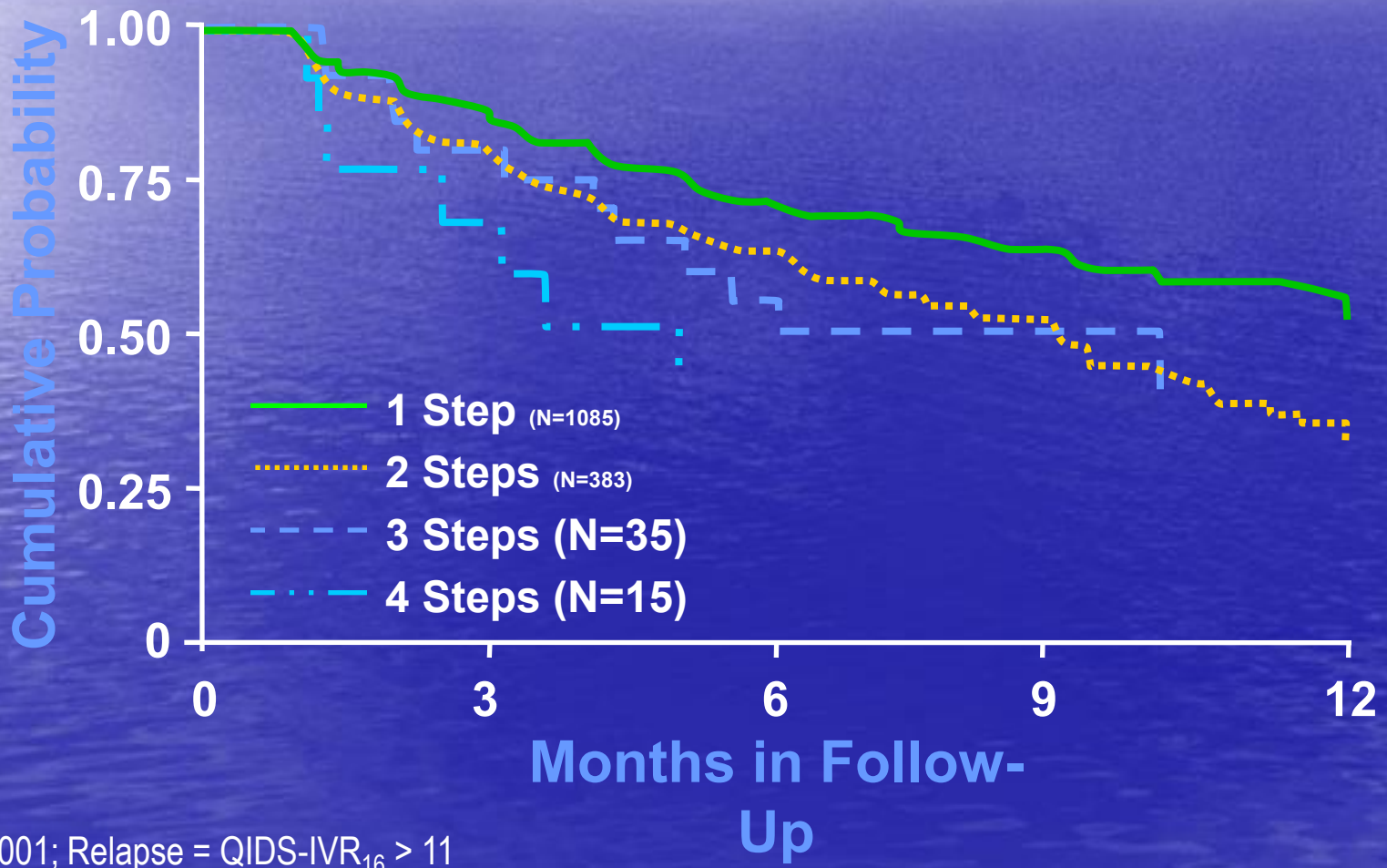
P<0.1387; Relapse = QIDS-IVR$_{16}$ ≥11; Rush AJ et al. (2006), Am J Psychiatry 163(11):1905-1917

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

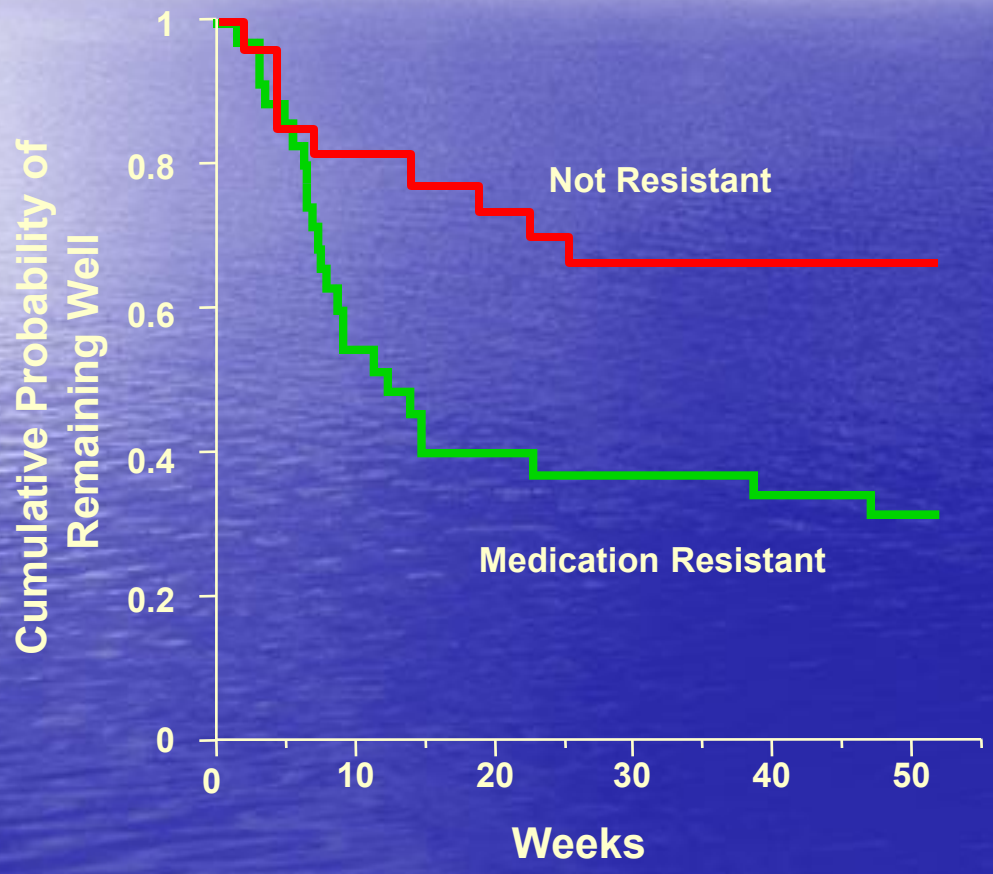
1. Fink M, Bailine S. *Am J Managed Care.* 1998;4:107-112. 2. Weiner RD, Krystal AD. In: Gabbard GO, ed. *Treatments of Psychiatric Disorders.* Washington, DC: American Psychiatric Press; 2001:1267-1293. 3. Kahn DA, et al. *J Psychiatr Pract.* 2000;6:197-211.

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

↓

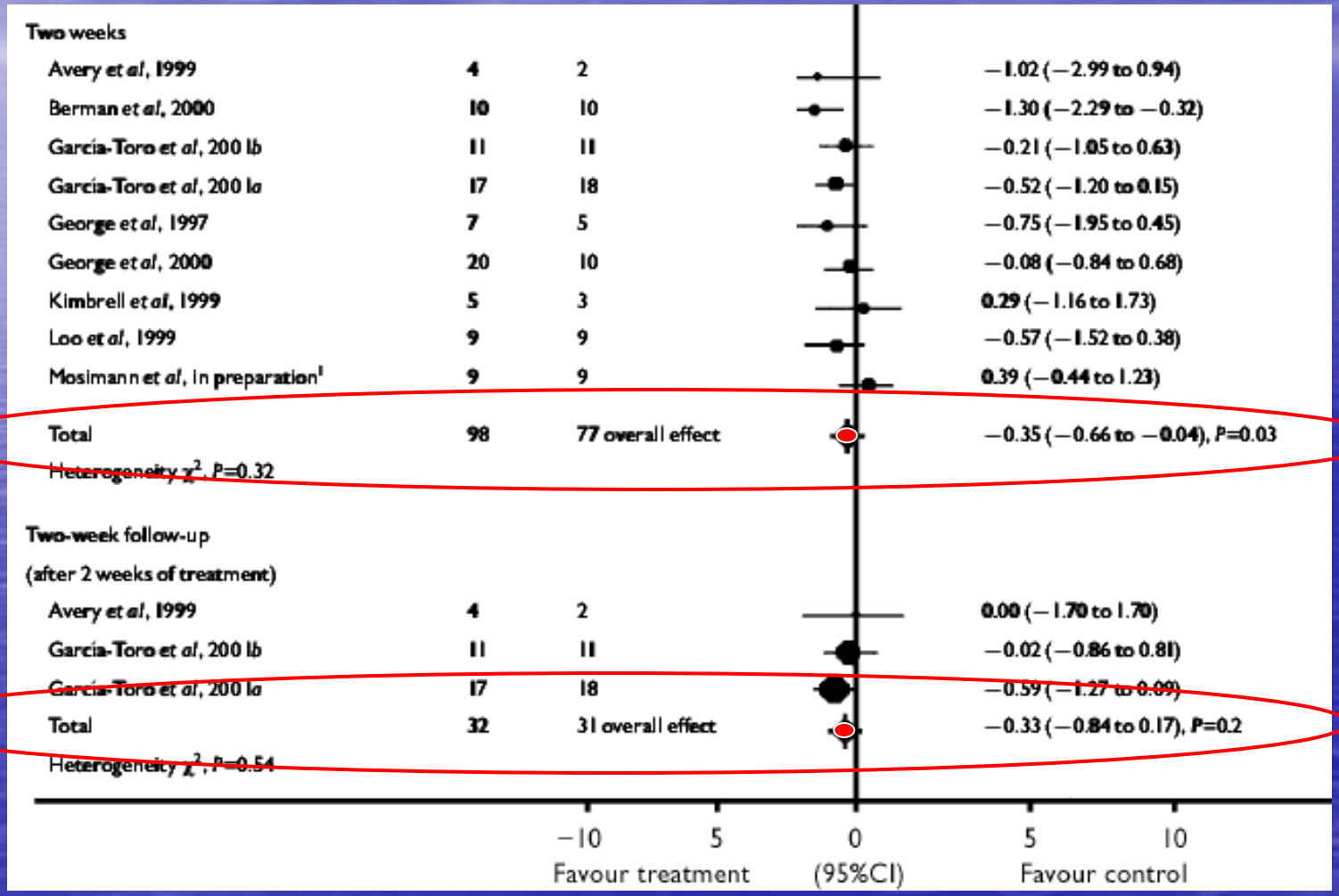
induces current in neurons and

↓

behavioral change

Modest to moderate effects in Sham Controlled studies

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

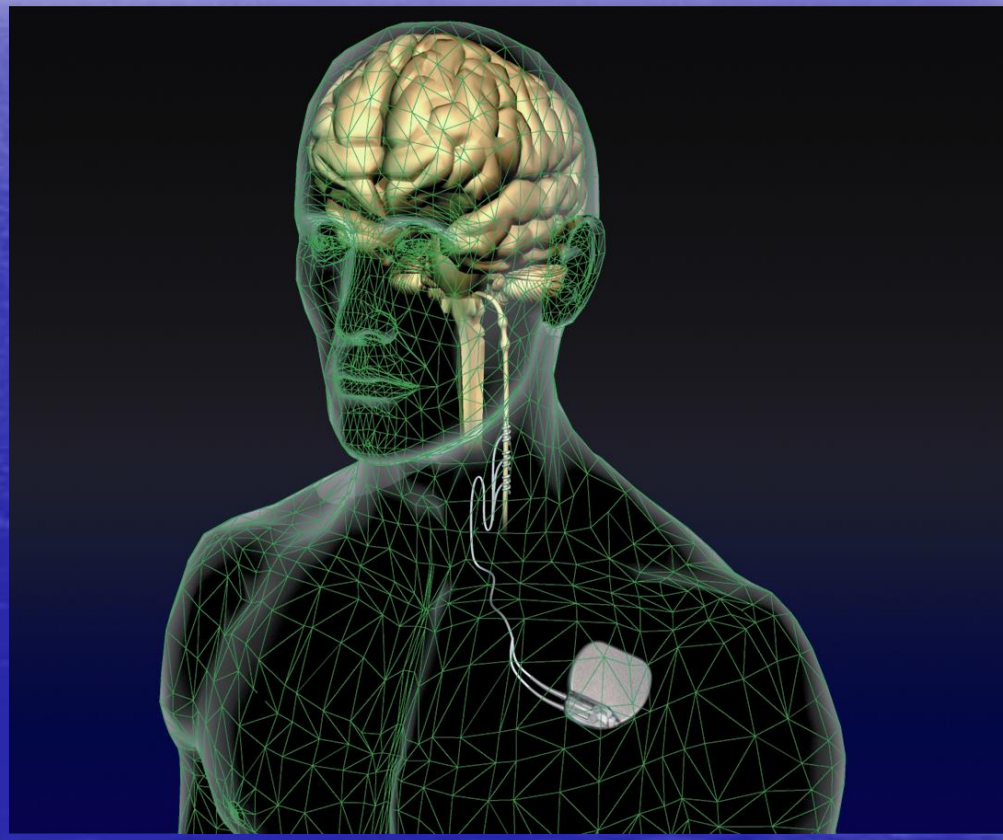


Martin JLR et al, Br J Psychiatry (2003), 182, 480-491.

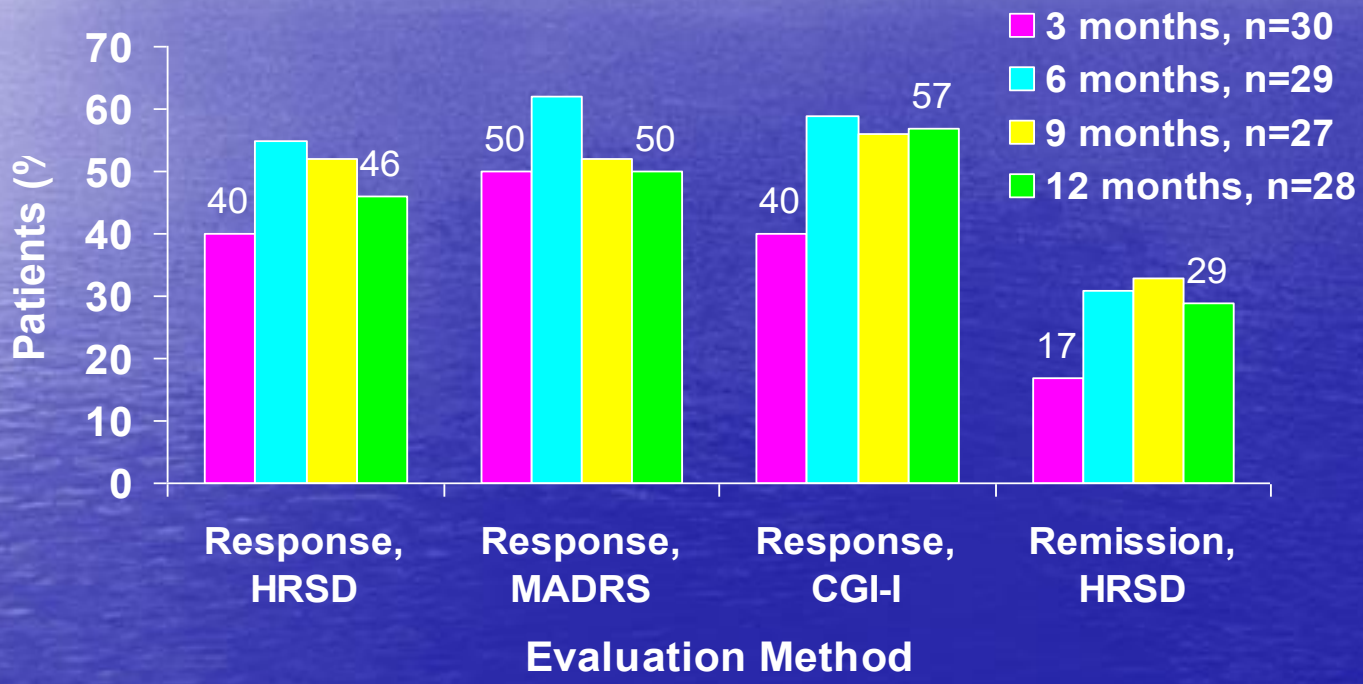
Vagus Nerve Stimulation (VNS)

Limitations

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



VNS Clinical Outcomes: One Year Post-Implantation

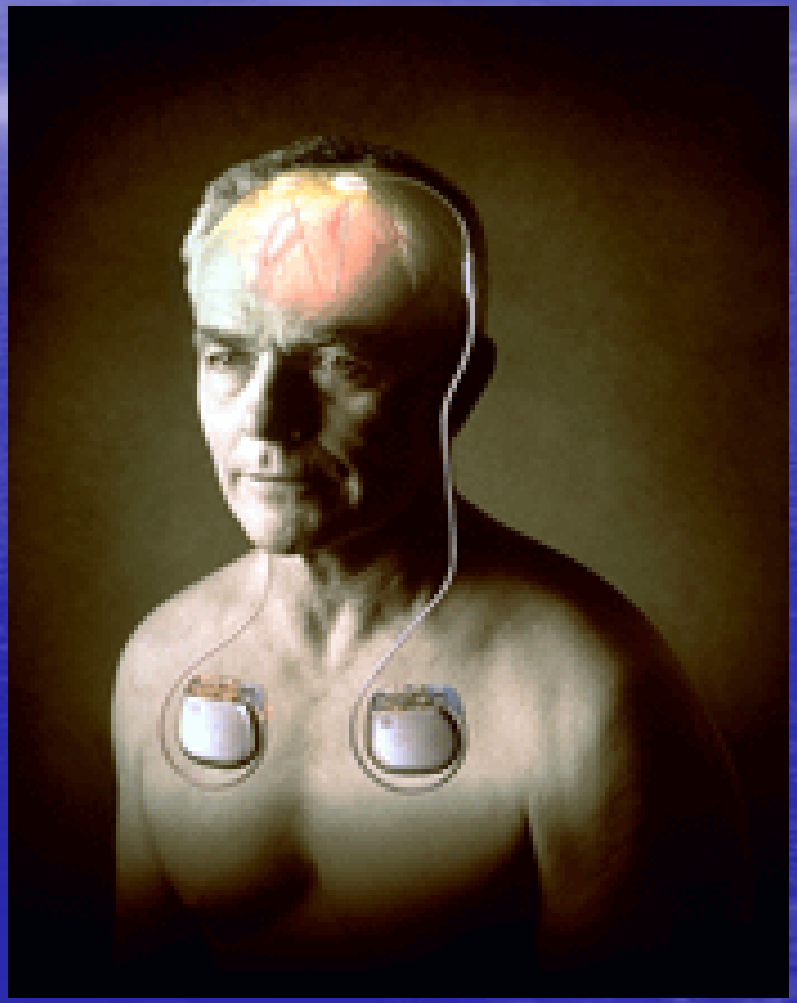


HRSD=Hamilton Rating Scale for Depression, MADRS=Montgomery Asberg Depression Rating Scale, CGI-I=Clinical Global Impression-Improvement. HRSD≤10, for remission. Patients received an additional 9 months of VNS after exiting a 3-month acute study.

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

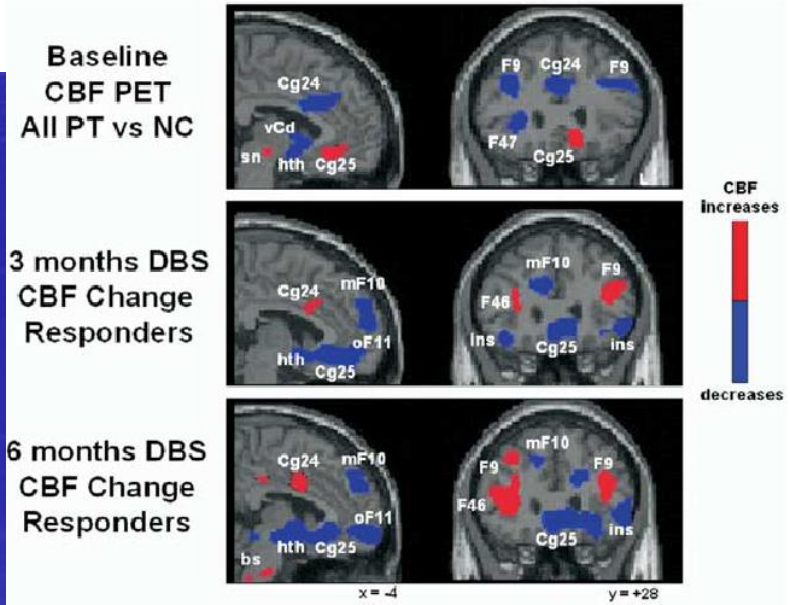
Table 2. Hamilton Depression Rating Scale, HDRS-17, Scores over Time for Each Subject

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