Overview of Treatment-Resistant Depression

Charles DeBattista, MD

Associate Professor of Psychiatry and Behavioral Sciences

Stanford University School of Medicine

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.

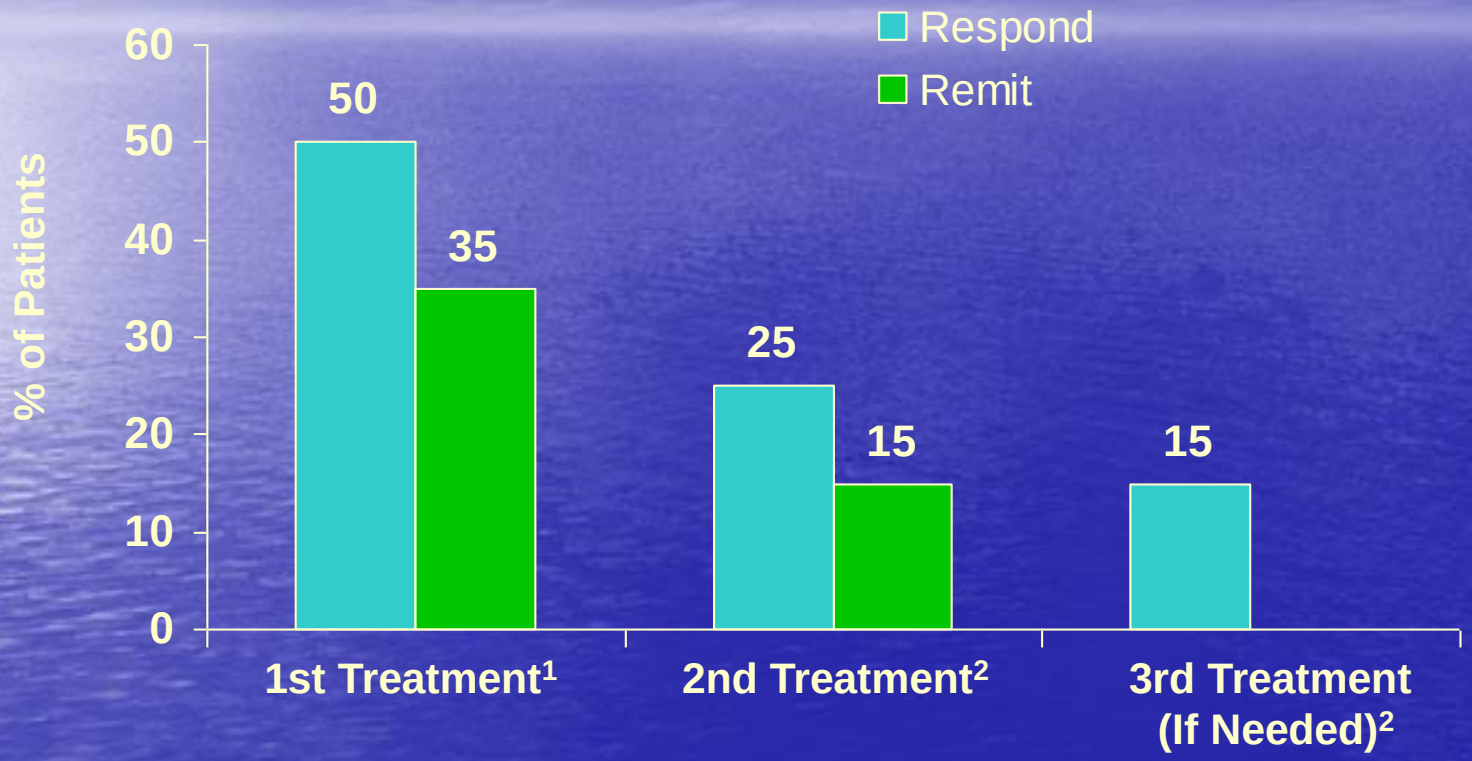
1. World Health Organization Web Site. Accessed July 7, 2005. 2. Greden JF. *J Clin Psychiatry.* 2001;62(suppl 22):5-9. 3. Fawcett J. *Int Clin Psychopharmacol.* 1993;8:217-220. 4. Rowan PJ, et al. *Psychol Med.* 2002;32:903-908. 5. Druss BG, et al. *Am J Psychiatry.* 2000;157:1274-1278. 6. Simon GE.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

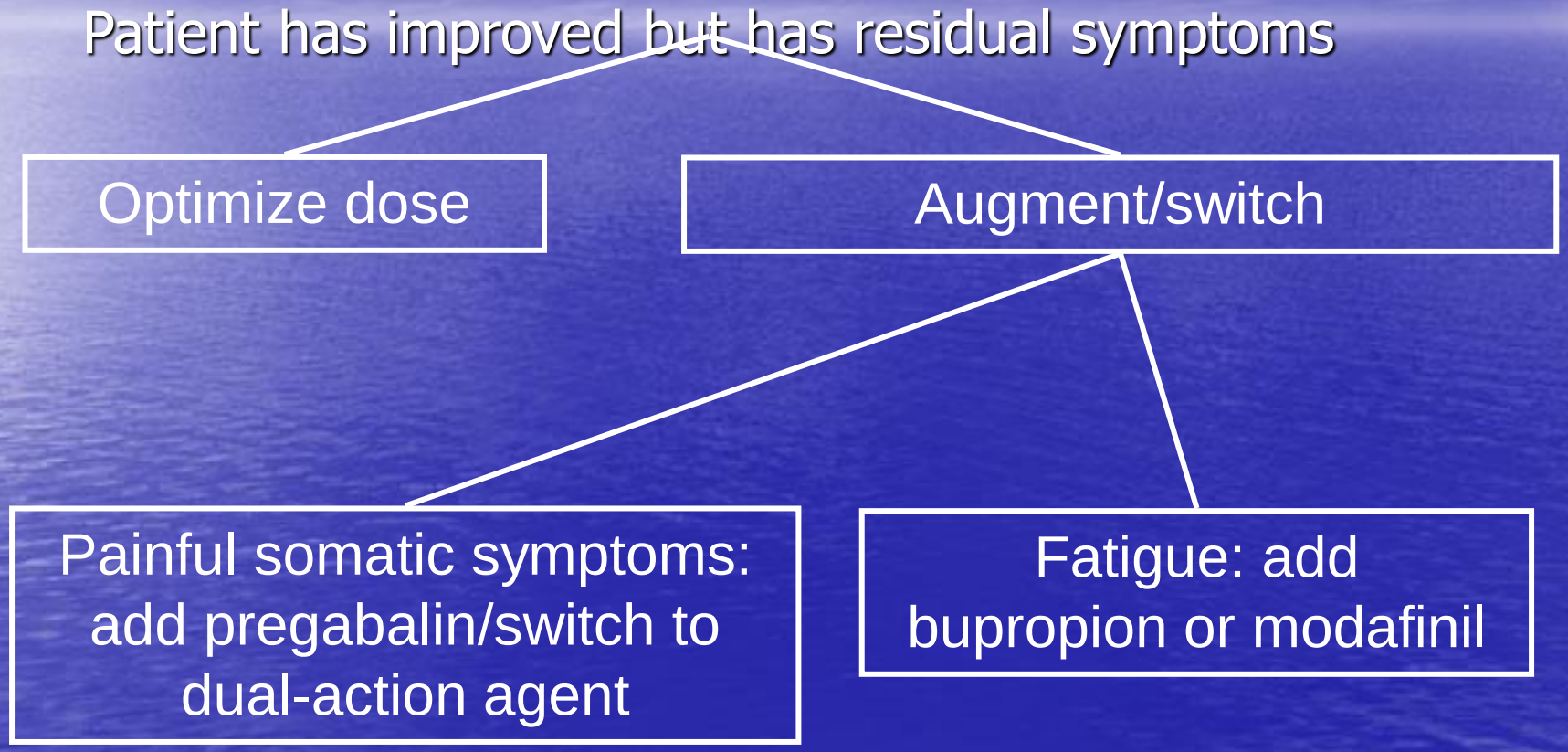
1. Thase ME, Rush JA. *J Clin Psychiatry.* 1997;58(suppl 13):23-29. 2. Judd LL, et al. *J Affect Disord.* 1998;50:97-108.

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.

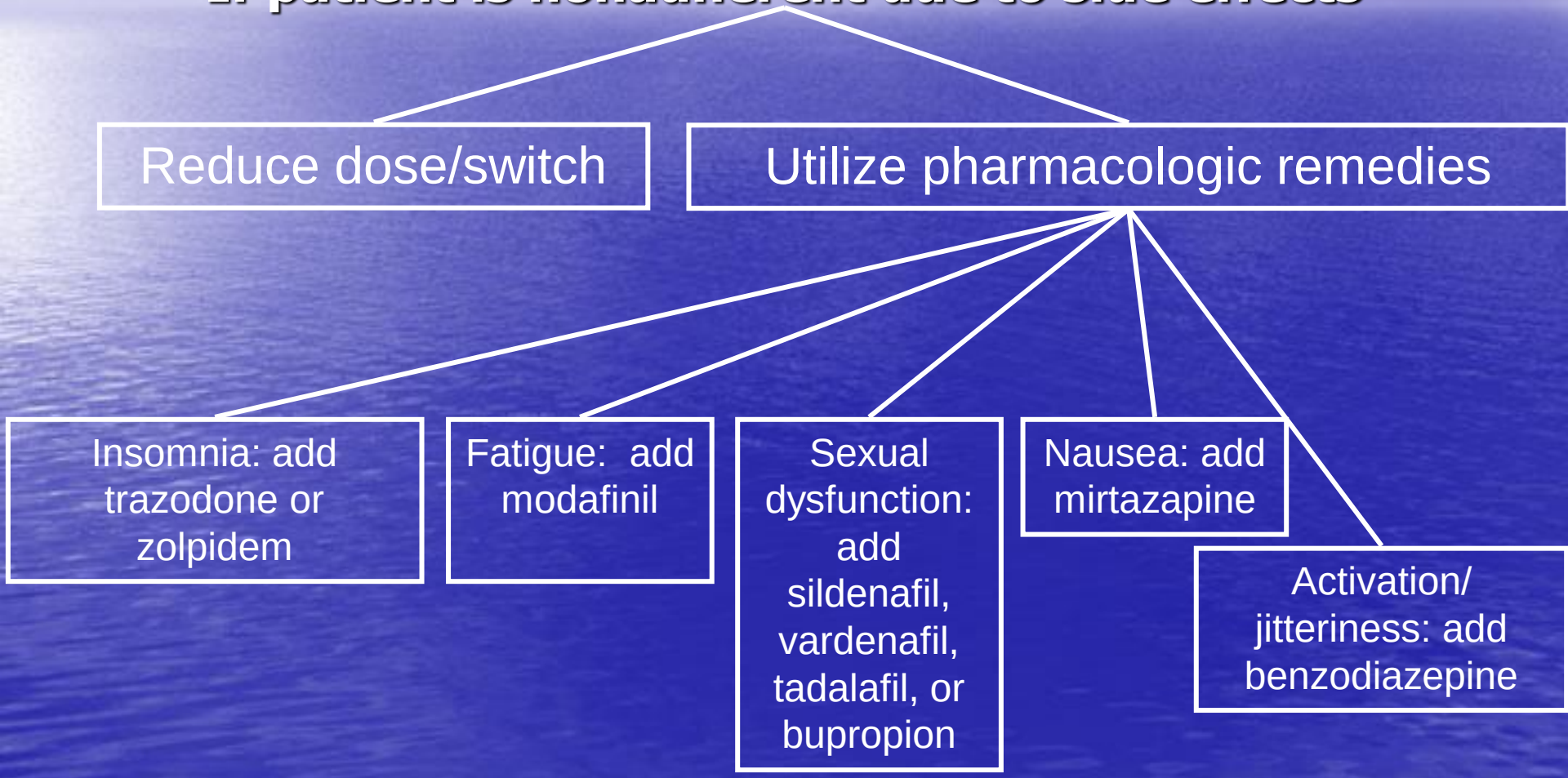
Assessing Current Treatment and Checking for Nonadherence (2)



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

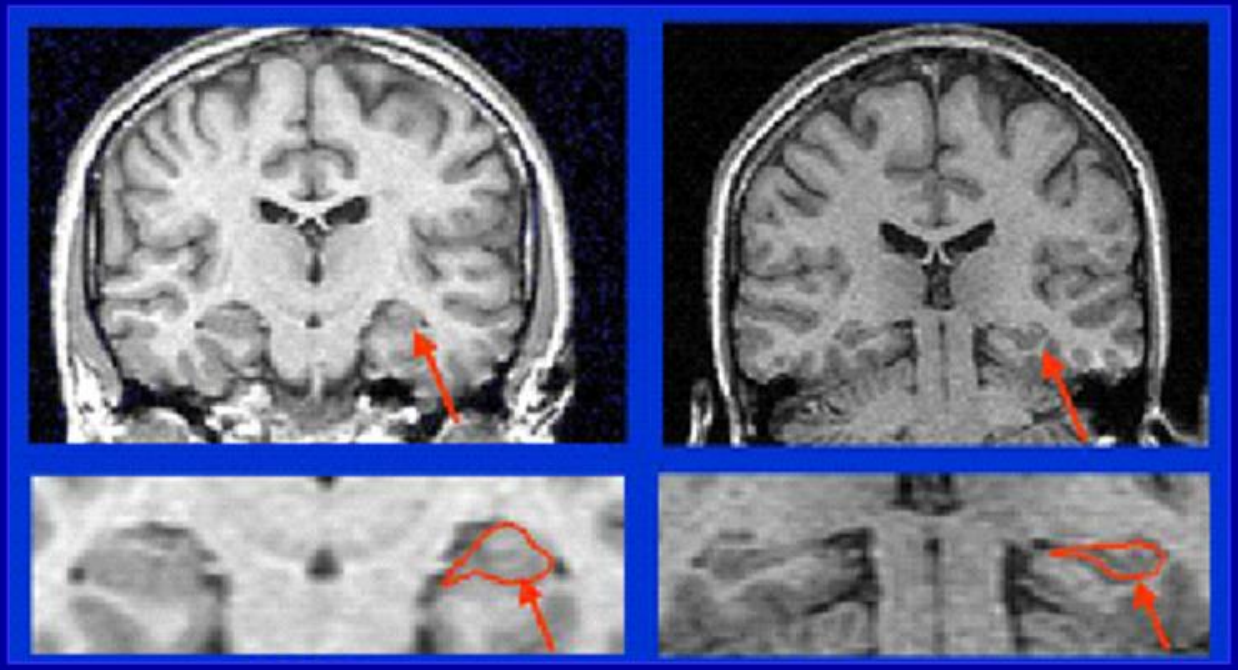
Biologic Treatment Resistance

- 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

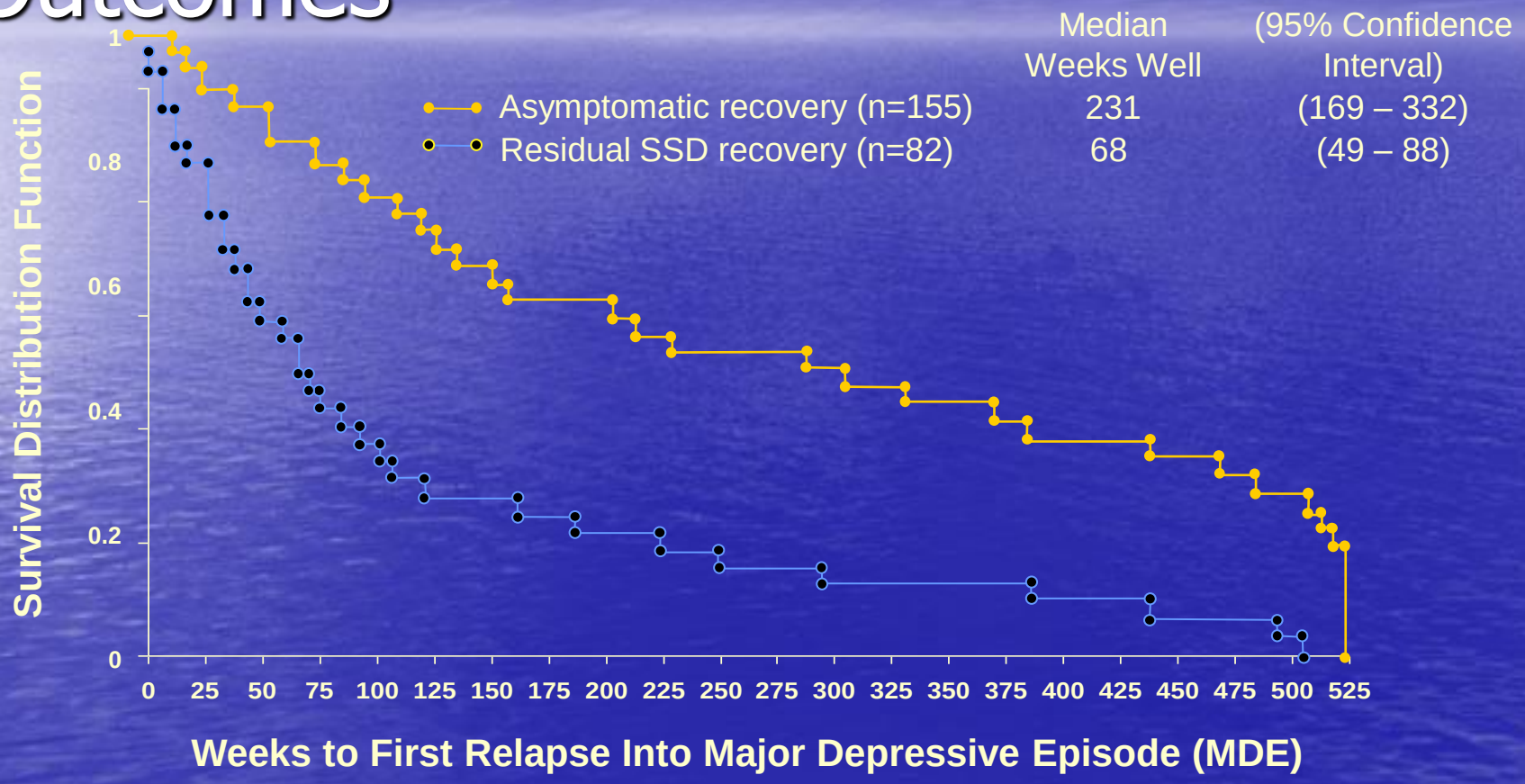


Normal

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

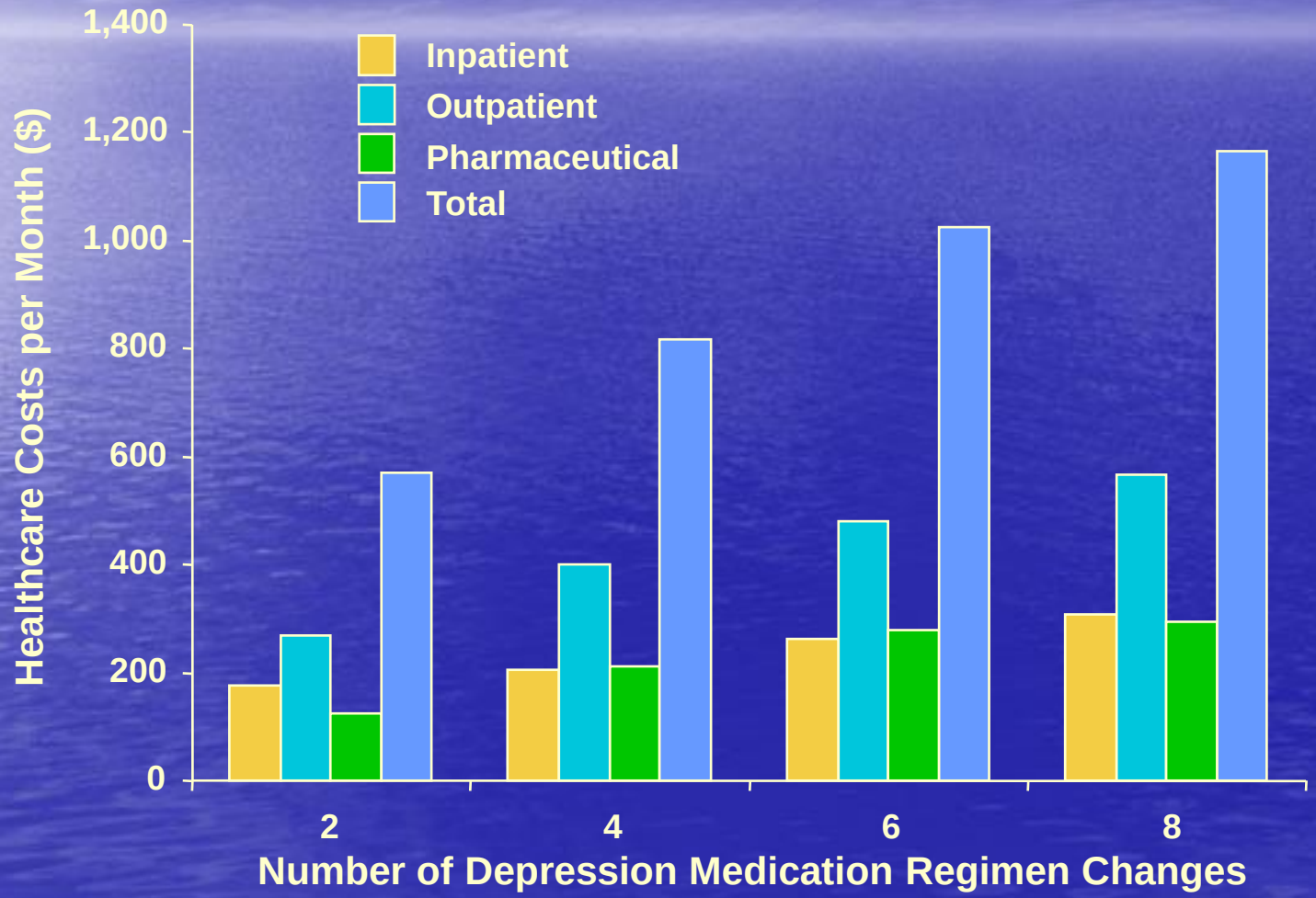
1. American Pharmaceutical Association Web site. Accessed December 18, 2004. 2. Papakostas GI, et al. *J Nerv Ment Dis.* 2003;191:444.

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.

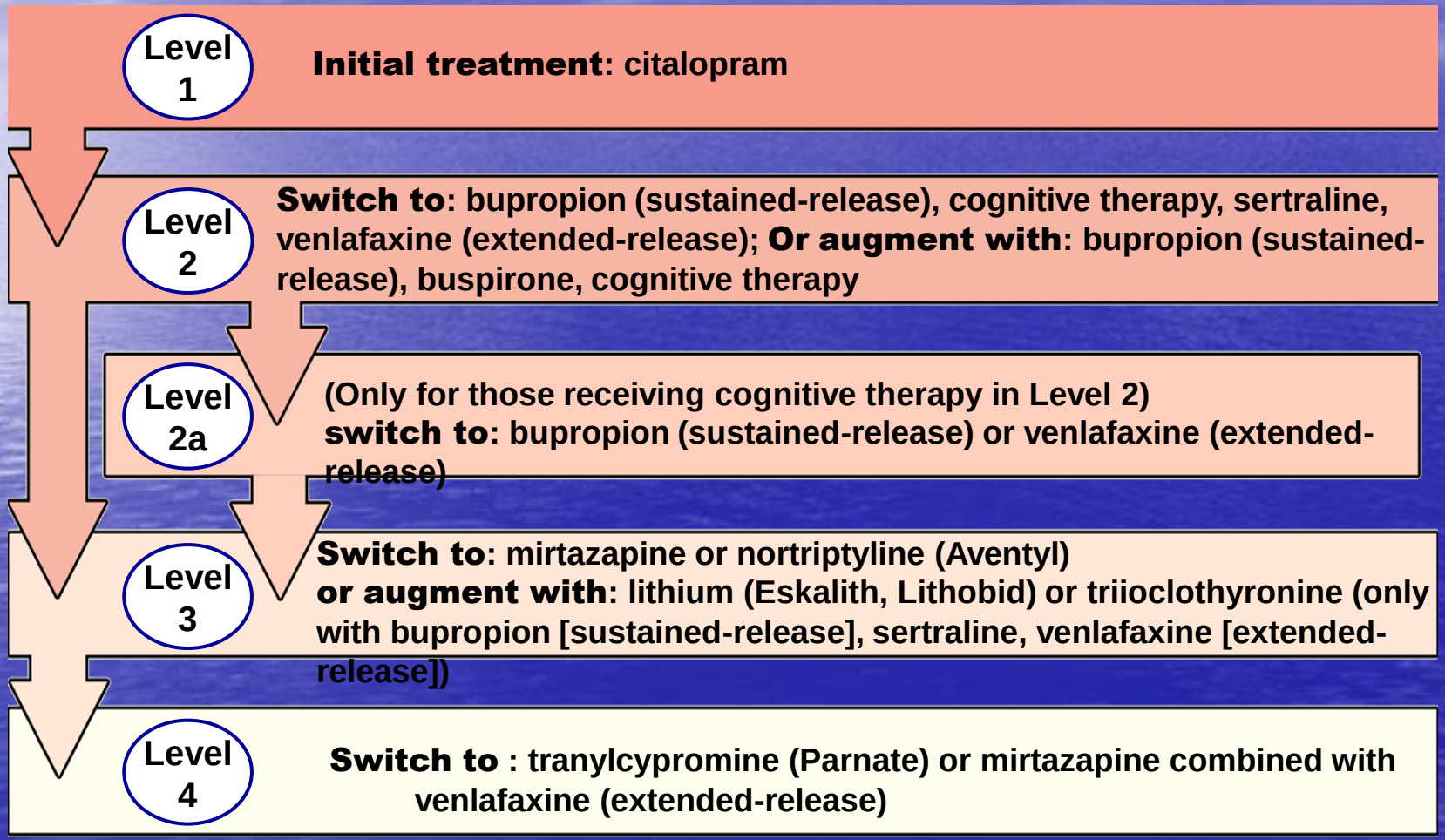
"Treatment-Resistant" Depression: Other Contributing Factors

- 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.

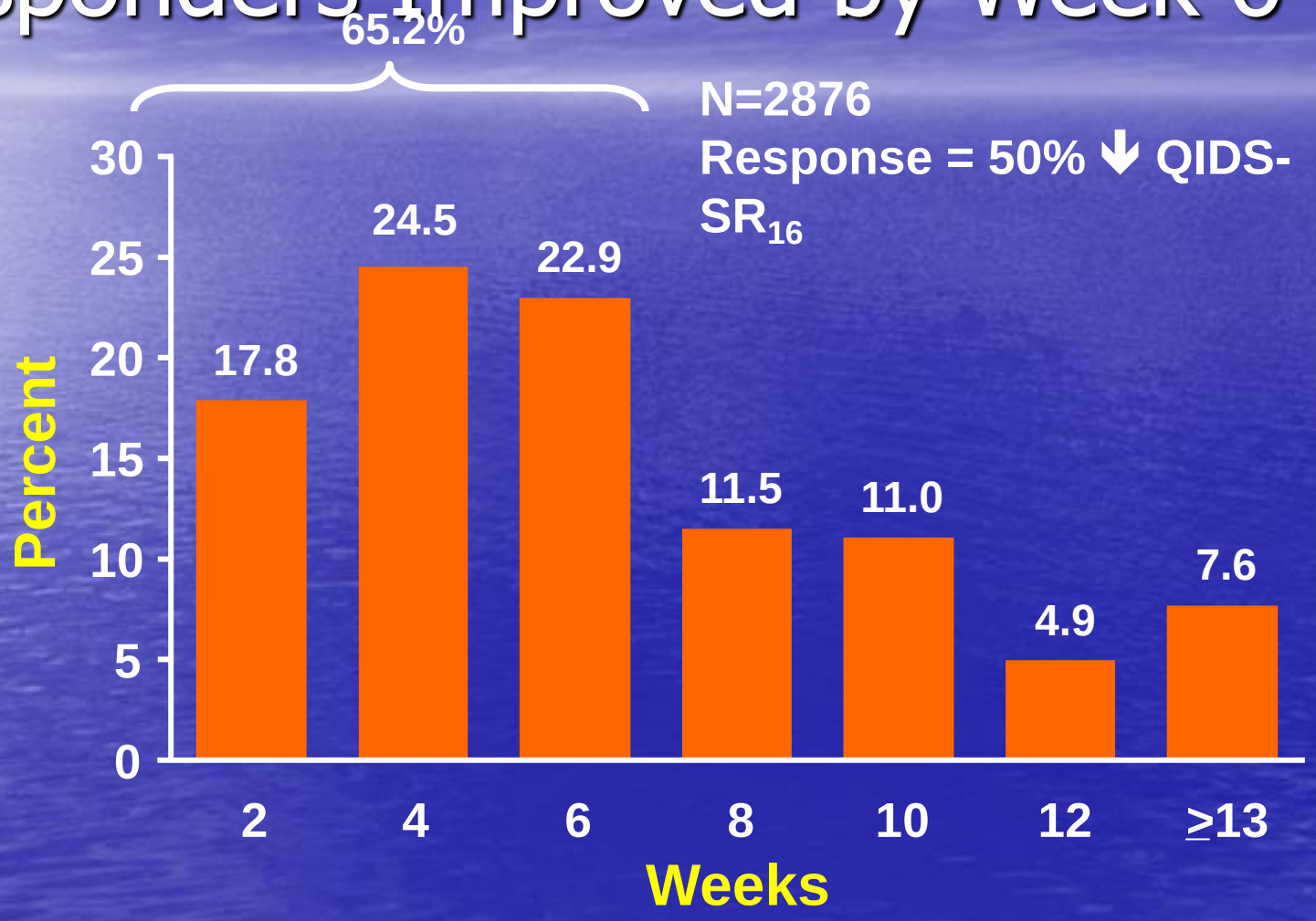
Treatment Algorithm Snapshot

STAR*D Algorithm



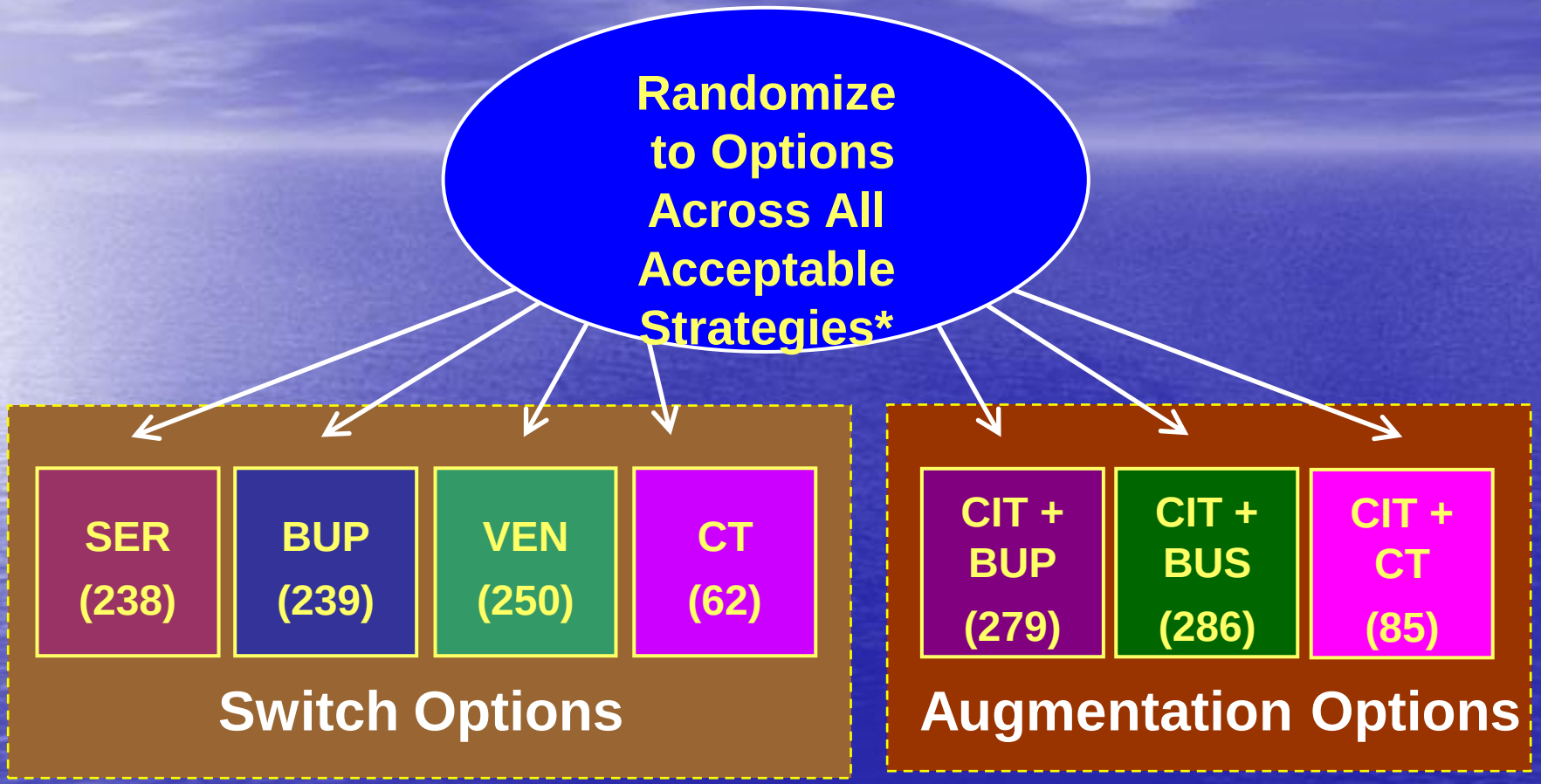
Rush AJ et al. (2003), Am J Psychiatry 160(2):237

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