Improving Major Depressive Disorder (MDD) Treatment Outcomes: Tailoring Strategies for Remission

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Learning Objectives

- Explain patterns of depression recurrence and therapeutic response for patients with major depressive disorder (MDD)
- Identify patients with inadequate response to therapy for MDD
- Apply treatment algorithms to optimize outcomes for patients with major depressive disorder

Depression – Global Burden of Disease

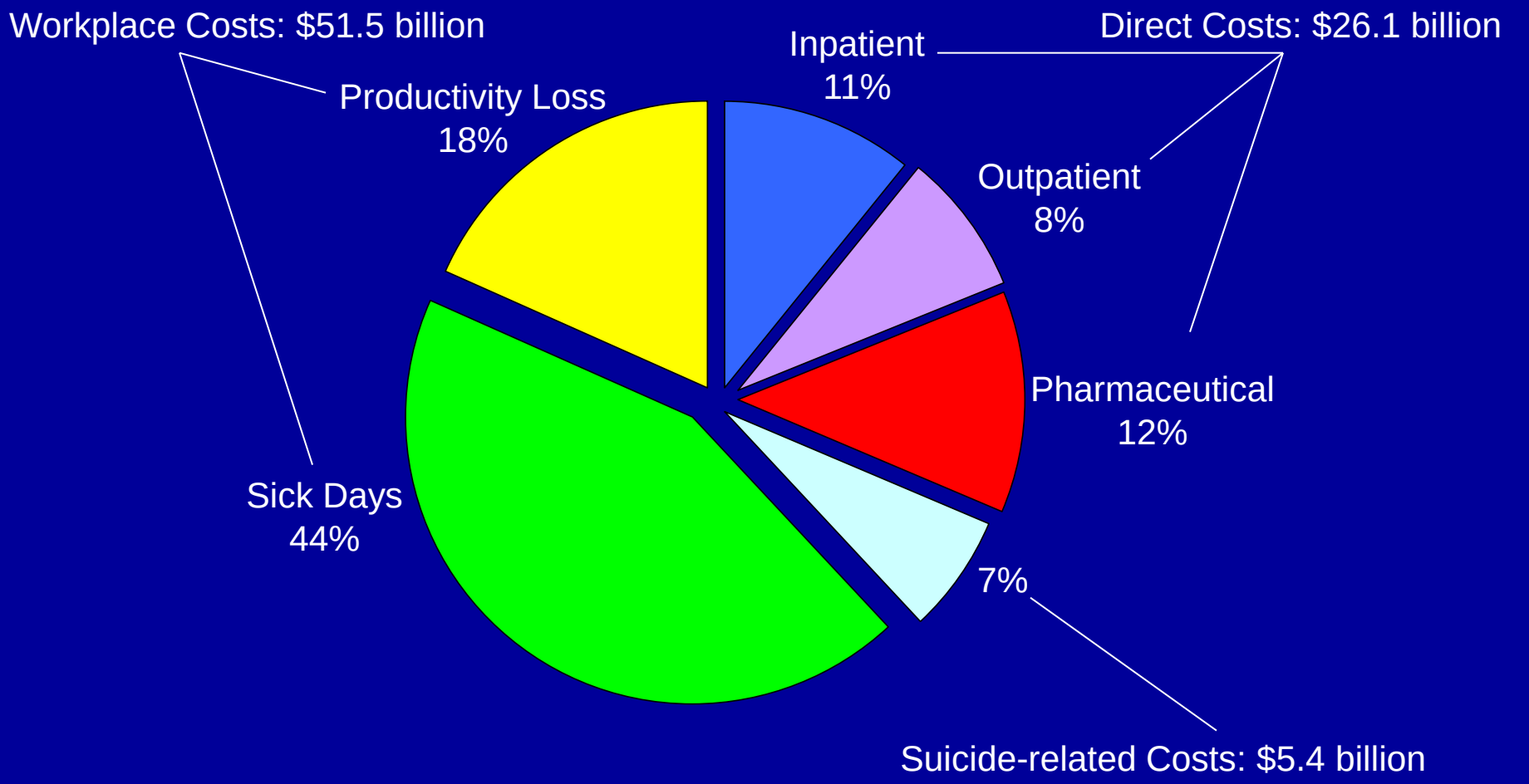
- Depression affects around 120 million people worldwide
- Less than 25% of those affected have access to adequate treatment
- Depression is the third leading cause of burden of disease worldwide (DALYs)

DALY: disability-adjusted life years

World Health Organization. http://www.who.int/en/. Accessed November 2010.

Economic Impact of Depression in the US

Total Cost in US Dollars for the Year 2000 = $83.1 billion



Greenberg P, et al. *J Clin Psychiatry*. 2003;64:1465-1475.

‘Signs’ of Depression

- S—Suicidal preoccupation
- **I—Interest/pleasure (↓)**
- G—Gain/lose weight
- G—Guilty feelings
- E—Energy (↓)
- C—Concentration
- **A—Affect (↓ mood)**
- P—Psychomotor retardation
- S—Sleep disturbance

DSM-IV-TR Major depression:	5 of 9 x 2 weeks 1 of **BOLDED** must be present
DSM-IV Dysthymia:	2 of 6 x 2 years no 2-month hiatus

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*). Washington, DC: American Psychiatric Association; 2000.

Pearls for Psychiatric Management of Patients with MDD

2010 APA Guidelines

- Establish and maintain a strong therapeutic alliance
- Thorough diagnostic assessment
- Evaluate patient safety, suicidal risk
- Evaluate functional impairment and quality of life
- Measurement-based care
- Coordinate care with other clinicians
- Provide patient/family education
- Monitor for response and remission
- Evaluate treatment adherence

APA. Practice guideline for the treatment of patients with major depressive disorder. 2010.

Considerations for Patient Evaluation

- Medical conditions
  - Complete medical evaluation and blood work
- Medications
  - Transplant anti-rejection agents
  - Chemotherapy agents
  - Interferon
  - Steroids
- Psychiatric comorbidities
- Psychosocial stressors and antecedent events
- Rule out bipolarity

APA. Practice guideline for the treatment of patients with major depressive disorder. 2010.

Tools to Improve Accuracy in MDD: Diagnosis and Assessment of Outcomes

Differentiate between tools for diagnosis & those to measure outcomes

Screening Tools	Diagnostic Tools	Monitoring Tools
PHQ-9, PHQ-2	PHQ-9	PHQ-9
CES-D	MINI	QIDS/SR
HADS	SCID-CV	BDI
Zung SDS		CUDOS
MDQ		HADS
CIDI		IDS
		MADRS

Tools listed in yellow are included in handouts

BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Studies Depression Scale; CUDOS: Clinically-Useful Depression Outcome Scale; HADS: Hospital Anxiety and Depression Scale; IDS: Inventory of Depressive Symptomatology; MADRS: Montgomery-Asberg Depression Rating Scale; MINI: Mini International Neuropsychiatric Interview; PHQ-2: Patient Health Questionnaire-2 item; PHQ-9: Patient Health Questionnaire-9 item; QIDS: Quick Inventory of Depressive Symptomatology (clinician and self-report); SCID-CV: Structured Clinical Interview for DSM-IV Axis Disorders-Clinician Version; Zung SDS: Zung Self-Rating Depression Scale; MDQ: mood disorder questionnaire; CIDI: WHO Composite International Diagnostic Interview

Gelenberg AJ. *J Clin Psychiatry.* 2010;71:e01

Measurement-Based Care for MDD

- Systematically using measurement tools to monitor progress and guide treatment choices
  - Regularly scheduled visits
  - Time efficient, validated tools
  - Regularly monitoring symptom improvement, side effects, medication adherence
  - Use a treatment algorithm with established critical decision points

Trivedi M. *J Clin Psychiatry*. 2009;70(S6):26-31.
APA. Practice guideline for the treatment of patients with major depressive disorder. 2010.

Measurement-Based Care for MDD
Assessment Tools

Measurement	Assessment Tool
Symptomatic improvement*	QIDS-C/QIDS-SR (Quick Inventory of Depressive Symptomatology, Clinician Rated/Self-Report PHQ-9 (Patient Health Questionnaire) BDI (Beck Depression Inventory)
Side effects	FIBSER (Frequency, Intensity, and Burden of Side Effects-Rating)
Medication adherence and reasons for nonadherence	BMQ (Brief Medication Questionnaire)

Trivedi M. *J Clin Psychiatry*. 2009;70(S6):26-31.

MDD Treatment Options
Pharmacotherapy

Antidepressant Medications

- Selective Serotonin Reuptake Inhibitors (SSRI)
- Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)
- Norepinephrine-dopamine Reuptake Inhibitors
- Mixed Selective Serotonin Reuptake Inhibitors and Receptor Blockers
- Tricyclic Antidepressants (TCA)
- Monoamine Oxidase Inhibitors (MAOI)

Agents Used Adjunctively

- Lithium
- Thyroid Hormone
- Anticonvulsants
- Psychostimulants
- S-adenosyl methionine (SAMe)
- Atypical Antipsychotics

MDD Treatment Options
Nonpharmacological Therapy

- Psychotherapy
- Exercise
- Neuromodulation
  - Electroconvulsive Therapy (ECT)
  - Transcranial Magnetic Stimulation (TMS)
  - Vagus Nerve Stimulation (VNS)
  - Deep Brain Stimulation (DBS)
- Sleep deprivation with phase advancement

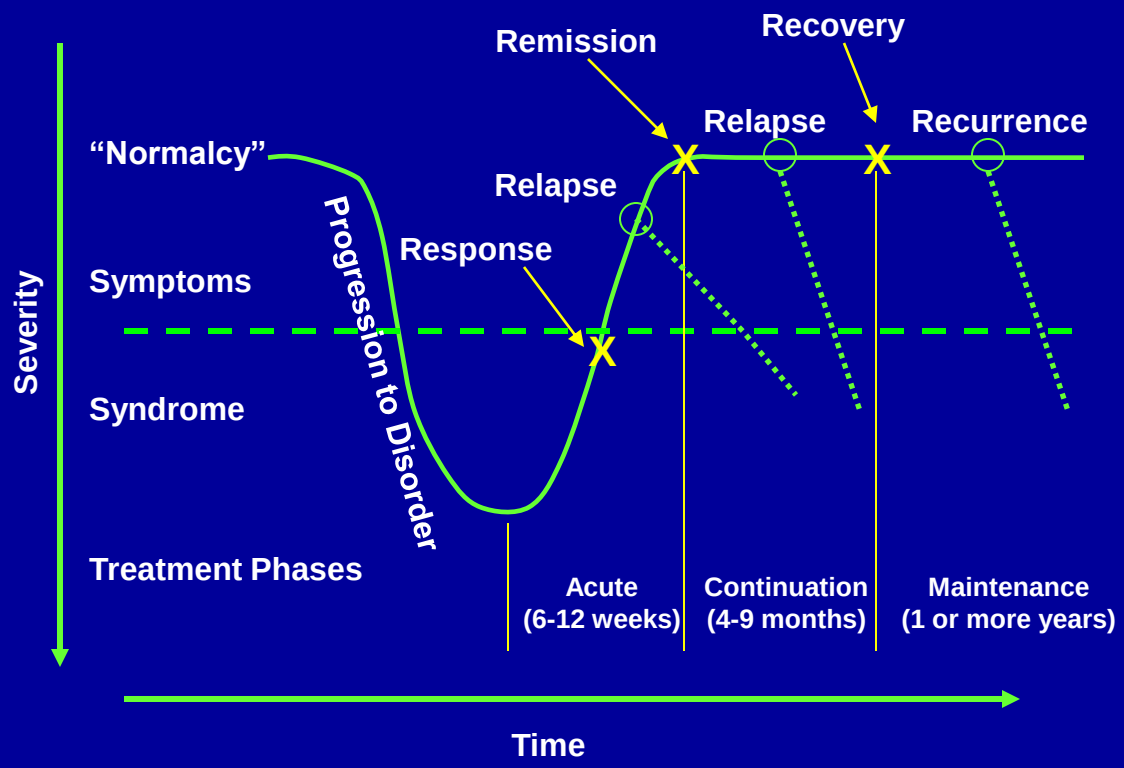
Treating Depression in the 'Real World'

- Remission, not response, is the goal
- Should first treatment fail, either switching or augmenting is reasonable
- For most patients, remission requires repeated trials of **"sustained, vigorously-dosed"** antidepressant medication
- Likelihood of remission substantially decreases after two adequate treatment trials, suggesting need for more complicated regimens and psychiatric consultation

Gaynes B, et al. *Cleve Clin J Med*. 2008;75(1):57-66.

Mission: Remission

- Response
  - ≥ 50% reduction in symptom scores
- Remission
  - Function restored
  - Minimal to no residual symptoms
    - 17-item HAM-D ≤ 7
    - MADRS ≤ 10
- Recovery
  - Remission ≥ 6 months



Keller MB. *JAMA.* 2003;289:3152-3160.
Qaseem A, et al. *Ann Intern Med*. 2008;149:725-733.

Why Target Remission?

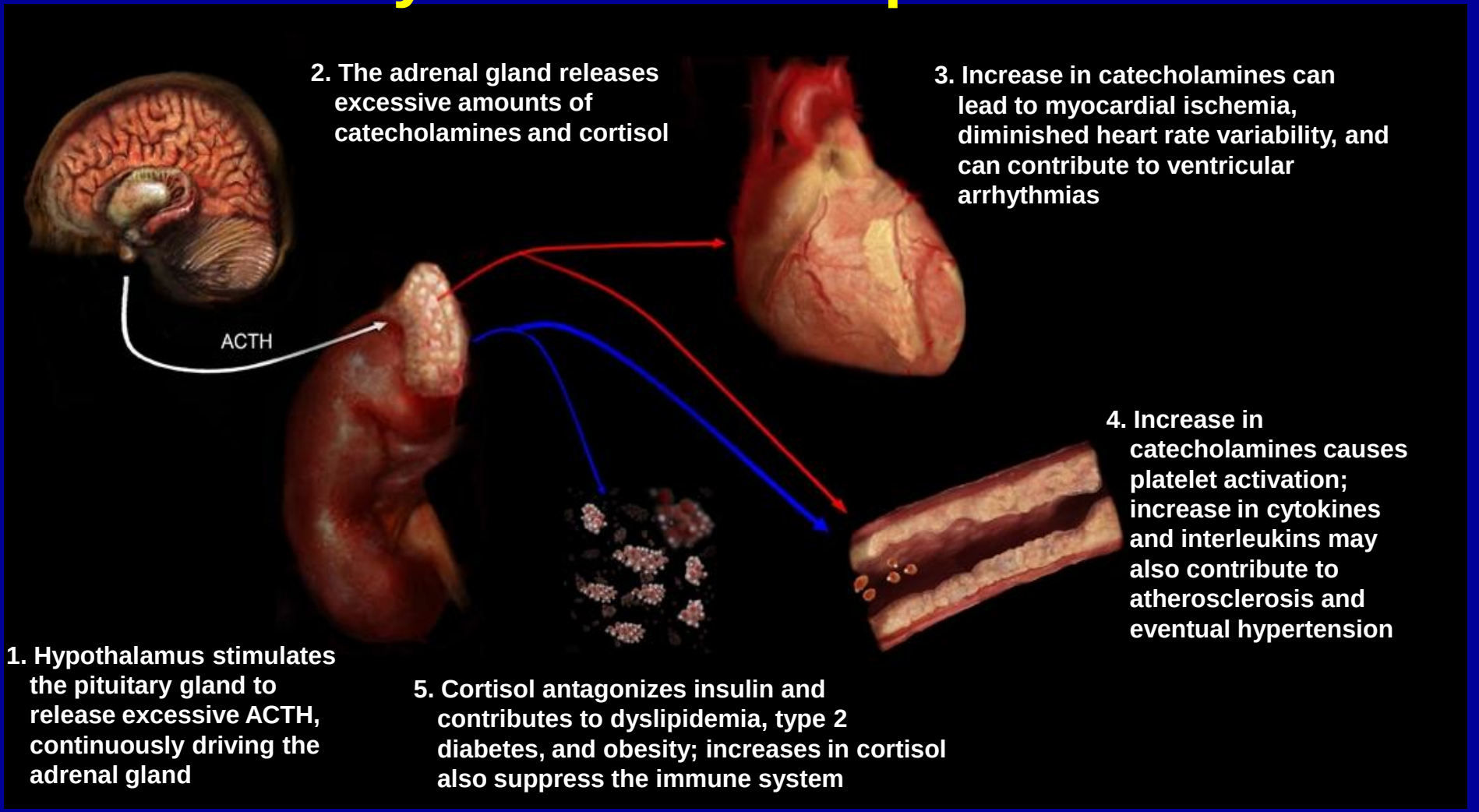
- Compared with patients who achieve full remission, those with **residual symptoms** have:
  - Greater risk of relapse and recurrence
  - More chronic depressive episodes
  - Continued professional and social impairment
  - Shorter duration between episodes
  - Ongoing increased risk of suicide
  - Increased overall mortality
  - Increased morbidity and mortality from comorbid medical disorders, including
    - Stroke, diabetes, myocardial infarction, cardiovascular disease, congestive heart failure, HIV

Papakostas G. *J Clin Psychiatry*. 2009;70(S6):16-25.

Major Depression: A Pathoetiological Risk Factor for Incident Chronic Medical Disorder

- Cardiovascular
- Osteoporosis
- Obesity
- Type II Diabetes Mellitus
- Neurodegenerative Disorders

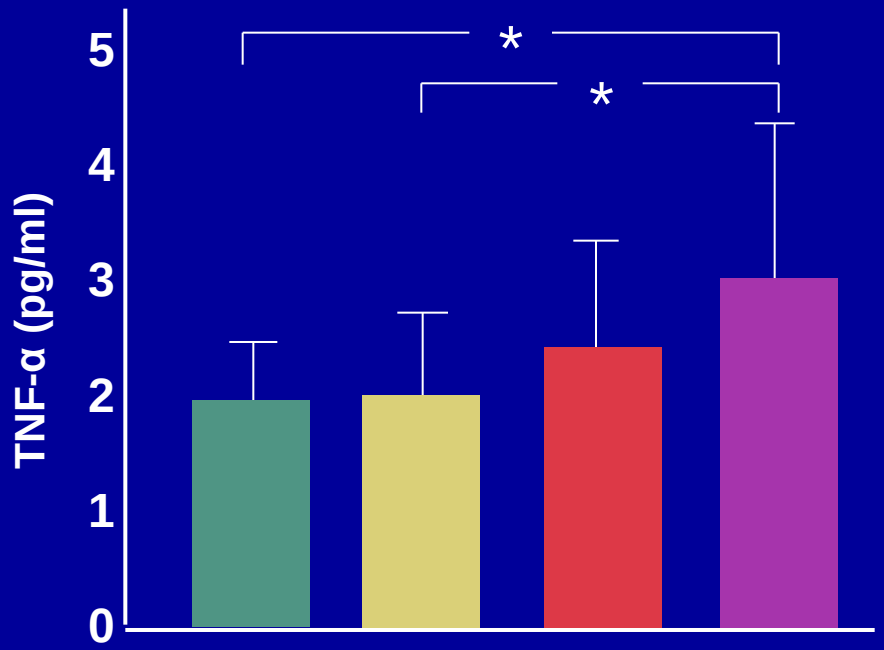
Major Depressive Disorder May Have Systemic Consequences

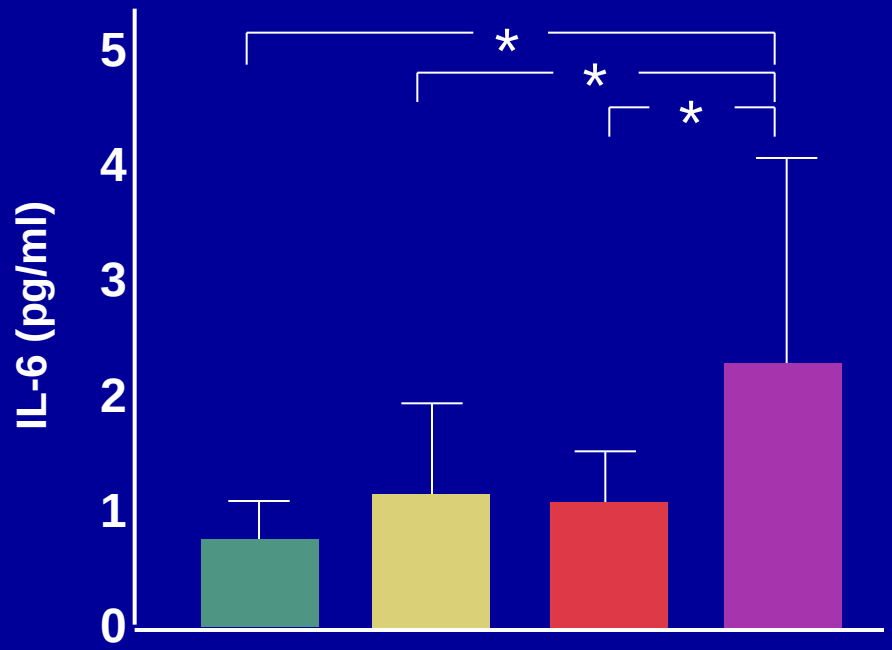


Musselman DL, et al. *Arch Gen Psychiatry.* 1998;55(7):580-592.

Depression Is an Inflammatory Disorder

Healthy comparison subjects (N = 20)
No depression (N = 16)
Lifetime major depressive disorder (N = 12)
Current major depressive episode (N = 10)



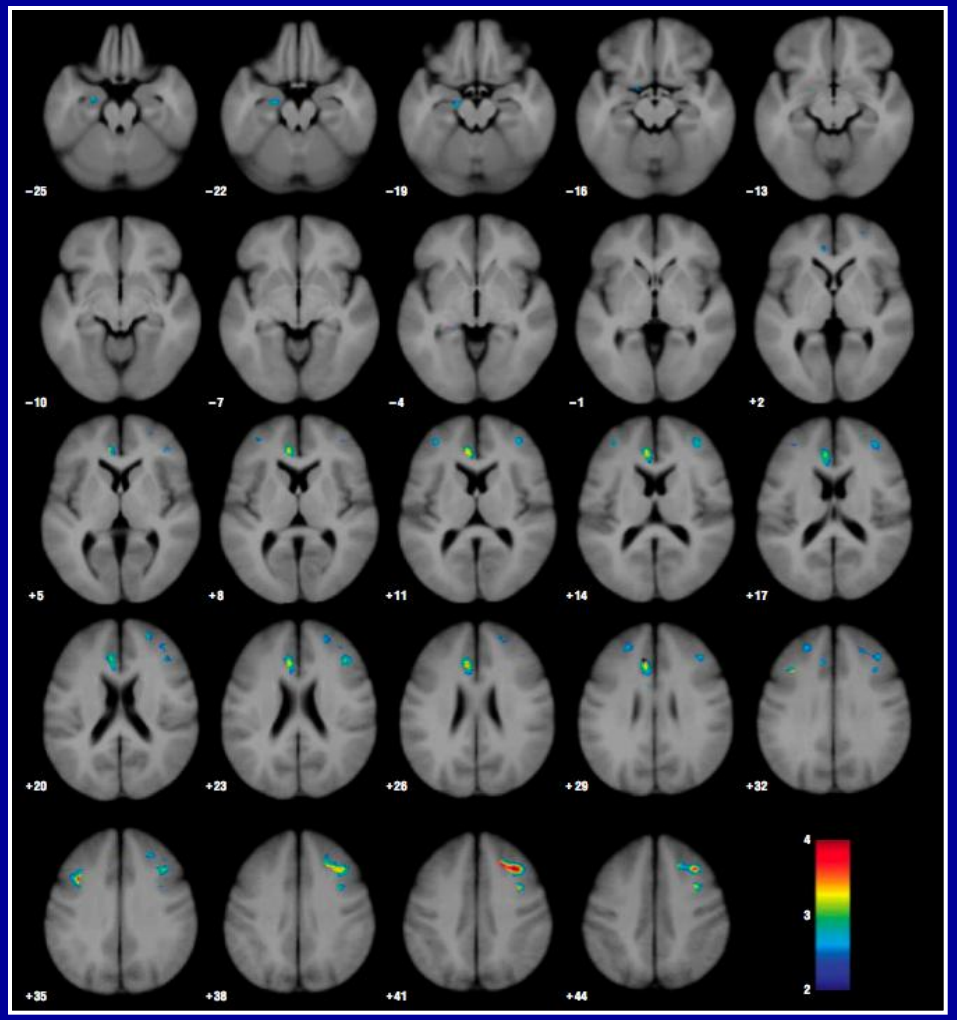


*$P < 0.05$

Kahl KG, et al. *Am J Psychiatry.* 2005;162:168–174.

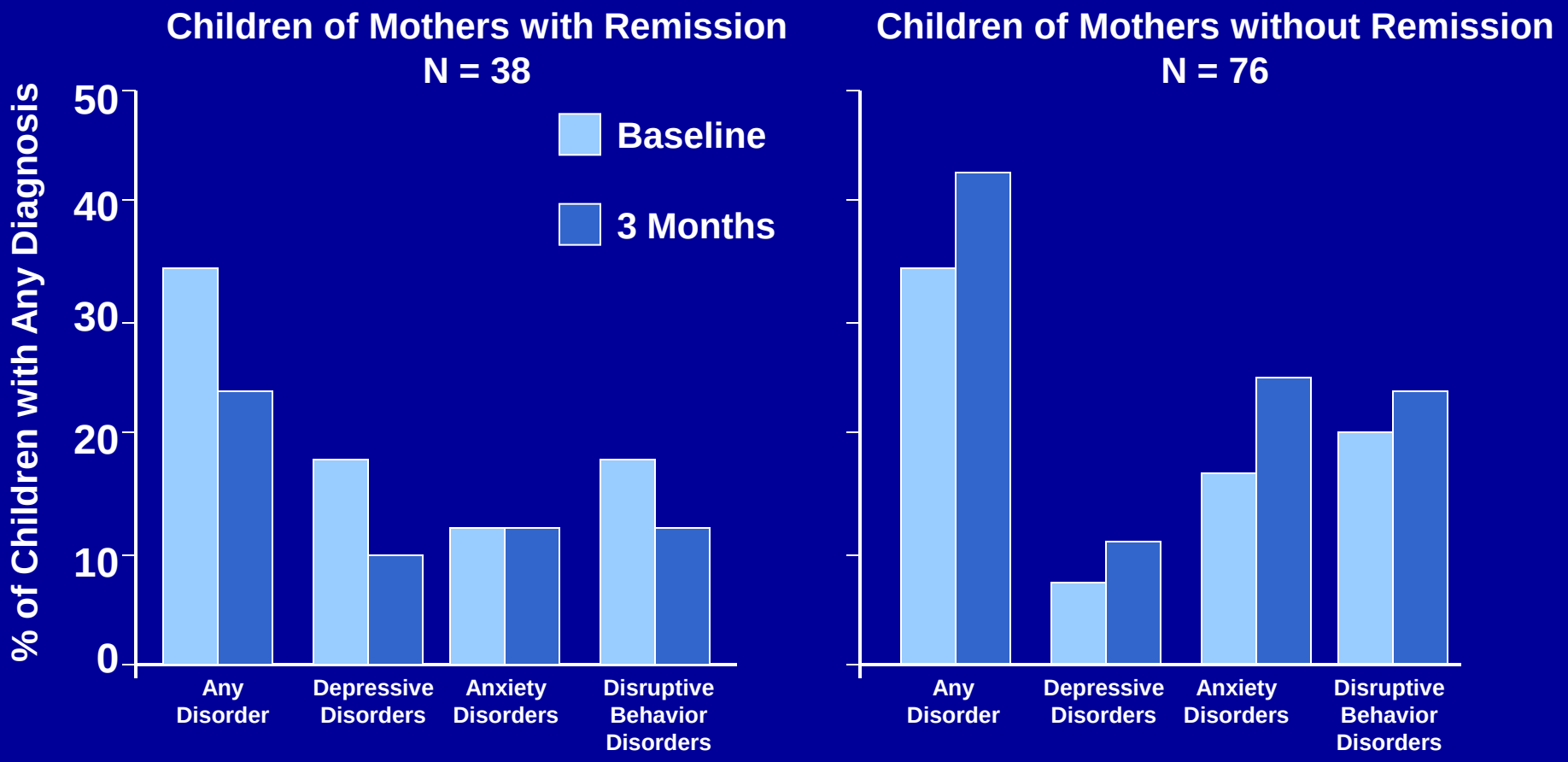
Greater Decline in Gray Matter Volume in Unremitted Compared with Remitted MDD Patients

- 3-year prospective study
- 38 patients vs 30 healthy controls
- Significantly greater decline in gray matter density was noted in non-remitted versus remitted major depressive disorder patients in:
  - Hippocampus
  - Anterior cingulate cortex
  - Dorsomedial prefrontal cortex
  - Dorsolateral prefrontal cortex
- Threshold was set at $P < 0.01$



Maternal Depression
Importance of Remission

Overall **11% decrease** in rates of diagnoses in children of remitted mothers compared with an **8% increase** in children of mothers with continuing depression



Weissman M, et al. *JAMA*. 2006;295(12):1389-1398.

Factors Independently Associated With Greater Chance of Remission (STAR*D)

- Employment
- Greater income
- Greater education
- Caucasian
- Female gender
- No OCD or PTSD
- Greater functioning/quality of life

Trivedi MH, et al. *Am J Psychiatry.* 2006;163:28-40.
Cohen A, et al. *Arch Gen Psychiatry.* 2006;63:50-56.

What Is Treatment-Resistant Depression?

- Failure of a patient to respond to at least 2 antidepressant trials of adequate dose, duration, and treatment adherence

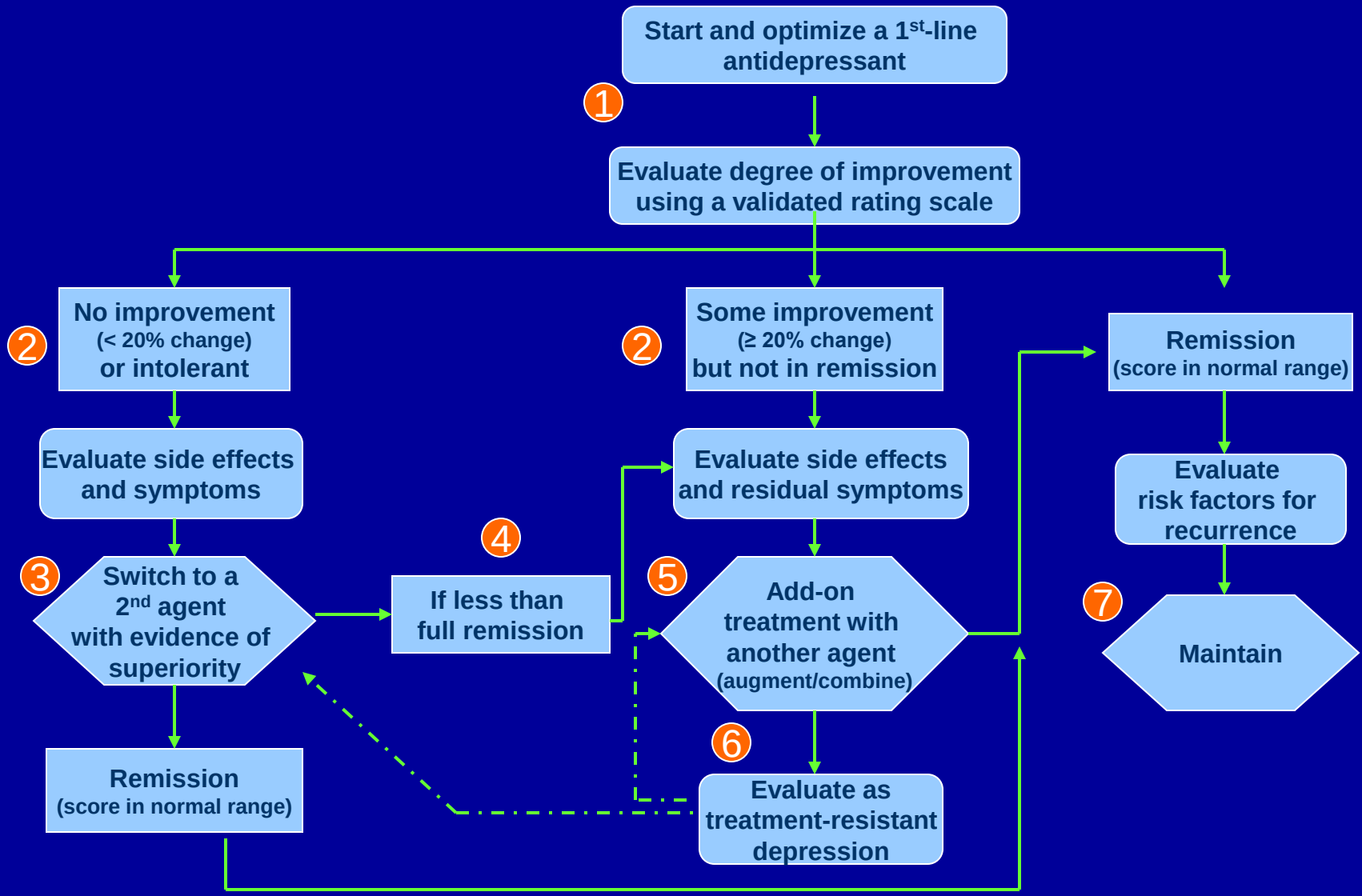
Gaynes B. *J Clin Psychiatry*. 2009;70(S6):10-15.

Factors Associated with Treatment Resistance

- Misdiagnosis (eg, bipolar disorder)
- Depression severity and chronicity
- Specific depressive subtypes
  - Psychotic depression, atypical depression, melancholic features
- Psychiatric comorbidities
  - Anxiety disorders, panic disorder, personality disorder
- Medical comorbidities
- Age at onset before 18 years
- Substance abuse
- Patient noncompliance with treatment
- Pharmacokinetics, pharmacogenetics

Gaynes B. *J Clin Psychiatry*. 2009;70(S6):10-15.

Algorithm for Managing Limited Improvement with First-line Antidepressant



Lam R, et al. *J Affect Disord.* 2009;117:S26-S43.

Strategies for Refractory Depression

- Switch to a different antidepressant (within class or across class)
- Combine the initial antidepressant with a second antidepressant
- Augment the treatment regimen with a non-antidepressant agent

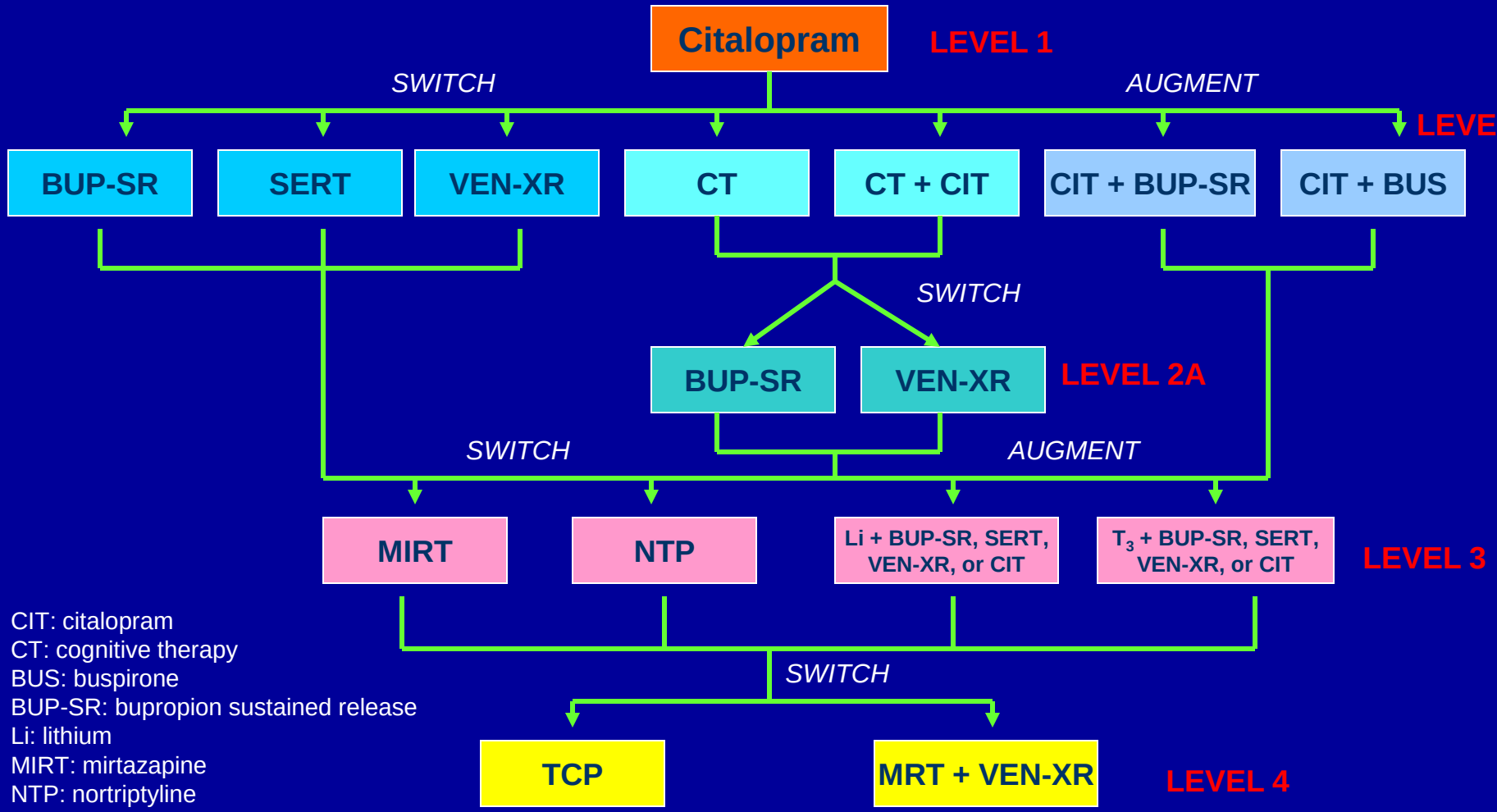
Papakostas G. *J Clin Psychiatry*. 2009;70(S6):16-25.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial (www.star-d.org)

- Primary outcome measured: ***Remission***
- Largest clinical trial of depression to date
  - 7 years (1999–2006)
  - Enrolled 4,041 adult subjects
- Conducted in primary care as well as psychiatric settings (18 vs 23)
- Few exclusion criteria → "real world"

Warden D, et al. *Curr Psychiatry Rep*. 2007;9:449-459.

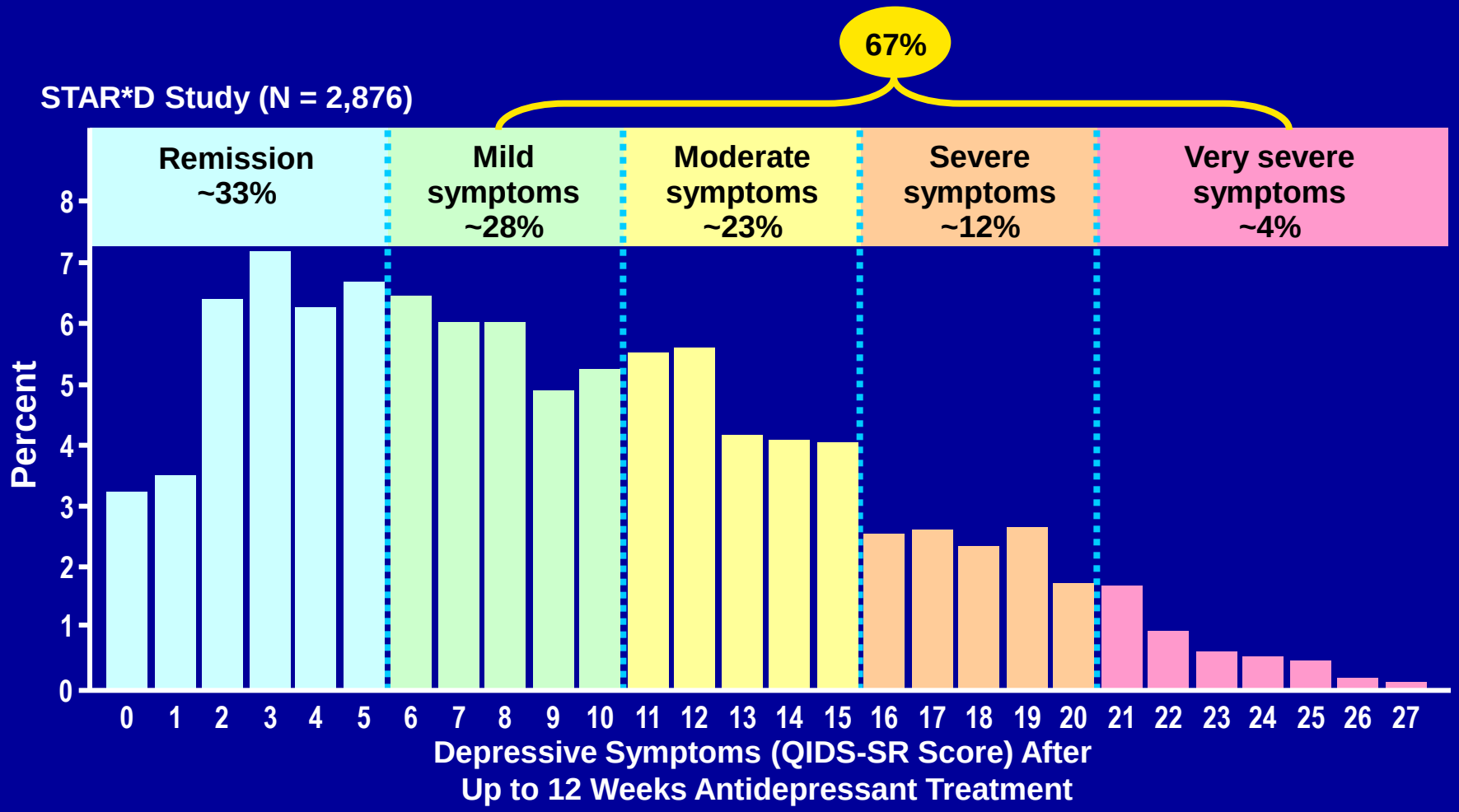
STAR*D Treatment Strategies and Options



CIT: citalopram
CT: cognitive therapy
BUS: buspirone
BUP-SR: bupropion sustained release
Li: lithium
MIRT: mirtazapine
NTP: nortriptyline
SERT: sertraline
T_3:triiodothyronine
TCP: tranylcypromine
VEN-XR: venlafaxine extended release

Adapted from Warden D, et al. *Curr Psychiatry Rep*. 2007;9:449-459.

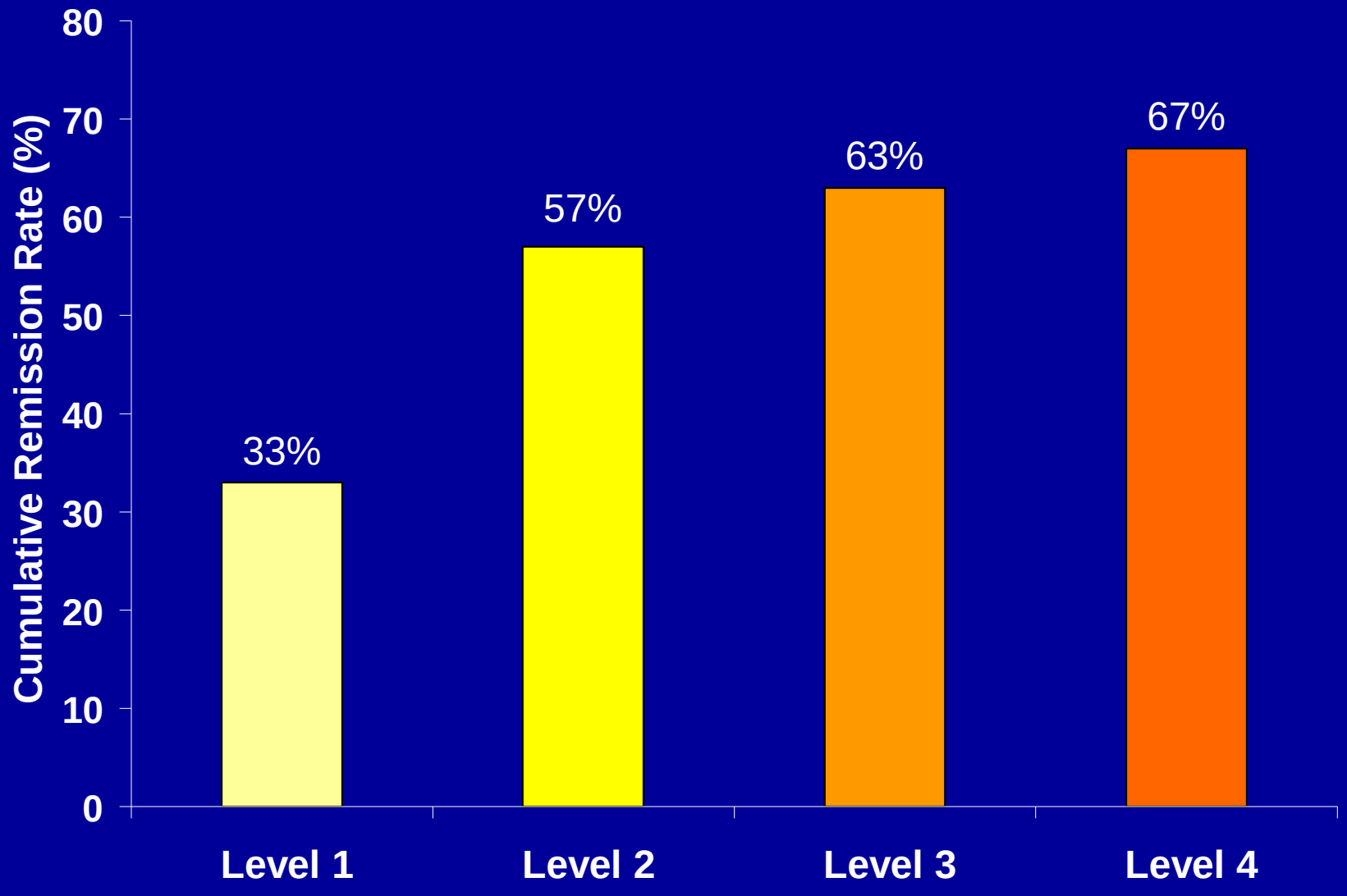
STAR*D: Unresolved Symptoms Following Antidepressant Treatment



STAR*D = Sequenced Treatment Alternatives to Relieve Depression, n = 2,876

Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.

STAR*D Cumulative Remission Rates



Gaynes B, et al. *Clev Clin J Med*. 2008;75(1):57-65.

Atypical Antipsychotic Augmentation Meta-Analysis

16 Trials, 3,480 patients

Atypical antipsychotic (AA) vs placebo

Response

- OR: 1.69 (95% CI 1.46-1.95); *P* < 0.00001
- Overall response rate for AA 44.2% vs 29.9% for placebo

Remission

- OR: 2.00 (95% CI 1.69-2.37); *P* < 0.00001
- Overall remission rate for AA 30.7% vs 17.2% for placebo

Discontinuation for Adverse Events

- OR: 3.91 (95% CI 2.68-5.72); *P* < 0.00001
- Pooled adverse event discontinuation rate for AA 9.1% vs 2.3% for placebo

AAs included olanzapine, risperidone, quetiapine, aripiprazole

Nelson JC, Papakostas G. *Am J Psychiatry*. 2009;166:980-991.

Atypical Antipsychotics: Side Effect Burden

- Metabolic
  - Weight gain
  - Glucose intolerance/Type 2 diabetes
  - Lipid derangements, especially increased triglycerides
- Neurologic
  - EPS (akathisia, parkinsonism, tardive dyskinesia)
- Sedation/somnolence
- Hyperprolactinemia
- Blood dyscrasias

Meyer J. *J Clin Psychiatry*. 2007;68(S14):20-26.

Switch Therapy or Add-on?

Monotherapy switch:

- No drug interactions
- No additive side effects
- Dosing simplicity

Add-on therapy:

- Faster onset of response
- Address specific residual symptoms or side effects
- Psychological advantage
- Late responders

Primarily a clinical decision (lack of evidence) based on whether there is at least a partial response to initial treatment

Lam R, et al. *J Affect Disord.* 2009;117:S26-S43.

Choosing an Add-on Strategy

1st Line	**Level 1 Evidence** • Aripiprazole • Olanzapine • Quetiapine XR • Lithium	**Level 2 Evidence** • Risperidone
2nd Line	**Level 2 Evidence** ▪ Bupropion ▪ Mirtazapine/mianserin ▪ Quetiapine ▪ Triiodothyronine	**Level 3 Evidence** • Other antidepressant
3rd Line	**Level 2 Evidence** ▪ Buspirone ▪ Modafinil	**Level 3 Evidence** • Stimulants

Adapted from Lam R, et al. *J Affect Disord.* 2009;117:S26-S43.

Summary

- > 50% of patients treated for major depressive disorder fail to achieve remission with initial therapy ~'Better is not well'
- Multiple factors are associated with treatment resistance
- STAR*D provides a framework for an evidence-based, individualized treatment plan
- Measurement-based care is essential
- Switch, combination, and augmentation for unresolved depression are evidence-based strategies to achieve remission
- Adjunctive treatment with atypical antipsychotics
  - Effective during acute phase of treatment; side effect burden is a concern
  - Long-term safety and efficacy not known

MDD Case Discussion

Mood Disorder Questionnaire - Rhonda

INSTRUCTIONS: Please answer each question as best you can.	YES	NO
1. Has there ever been a period of time when you were not your usual self and...		
... you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	○	●
... you were so irritable that you shouted at people or started fights or arguments?	○	●
... you felt much more self-confident than usual?	○	●
... you got much less sleep than usual and found that you didn't really miss it?	●	○
... you were more talkative or spoke much faster than usual?	○	●
... thoughts raced through your head or you couldn't slow your mind down?	○	●
... you were so easily distracted by things around you that you had trouble concentrating or staying on track?	●	○
... you had much more energy than usual?	○	●
... you were much more active or did many more things than usual?	●	○
... you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	○	●
... you were much more interested in sex than usual?	○	●
... you did things that were unusual for you or that other people might have thought were excessive, foolish or risky?	○	●
... spending money got you or your family in trouble?	○	●
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	○	●

3. How much of a problem did any of these cause you - like being able to work; having family, money or legal troubles; getting into arguments or fights?

● No problem ○ Minor problem ○ Moderate problem ○ Serious problem

Patient Health Questionnaire 9 (PHQ-9)

Name: Rhonda **Date:** Visit 0 (OB/GYN)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "✔" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	(3)
2. Feeling down, depressed, or hopeless	0	1	2	(3)
3. Trouble falling or staying asleep, or sleeping too much	0	1	(2)	3
4. Feeling tired or having little energy	0	1	2	(3)
5. Poor appetite or overeating	0	1	(2)	3
6. Feeling bad about yourself–or that you are a failure or have let yourself or your family down	0	1	(2)	3
7. Trouble concentrating on things such as reading the newspaper or watching television	0	(1)	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite–being so fidgety or restless that you have been moving around a lot more than usual	0	1	(2)	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	(1)	2	3
Total	**19**			

10. If you checked off any problems, how *difficult* have these problems made it for you to do your work, take care of things at home or get along with other people	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult ✔

Patient Health Questionnaire 9 (PHQ-9)

Name: Rhonda **Date:** Visit 1

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "✔" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	(3)
2. Feeling down, depressed, or hopeless	0	1	2	(3)
3. Trouble falling or staying asleep, or sleeping too much	0	1	(2)	3
4. Feeling tired or having little energy	0	1	(2)	3
5. Poor appetite or overeating	0	(1)	2	3
6. Feeling bad about yourself–or that you are a failure or have let yourself or your family down	0	1	(2)	3
7. Trouble concentrating on things such as reading the newspaper or watching television	0	(1)	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite–being so fidgety or restless that you have been moving around a lot more than usual	0	(1)	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	(0)	1	2	3
Total	**15**			

10. If you checked off any problems, how *difficult* have these problems made it for you to do your work, take care of things at home or get along with other people	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult ✔

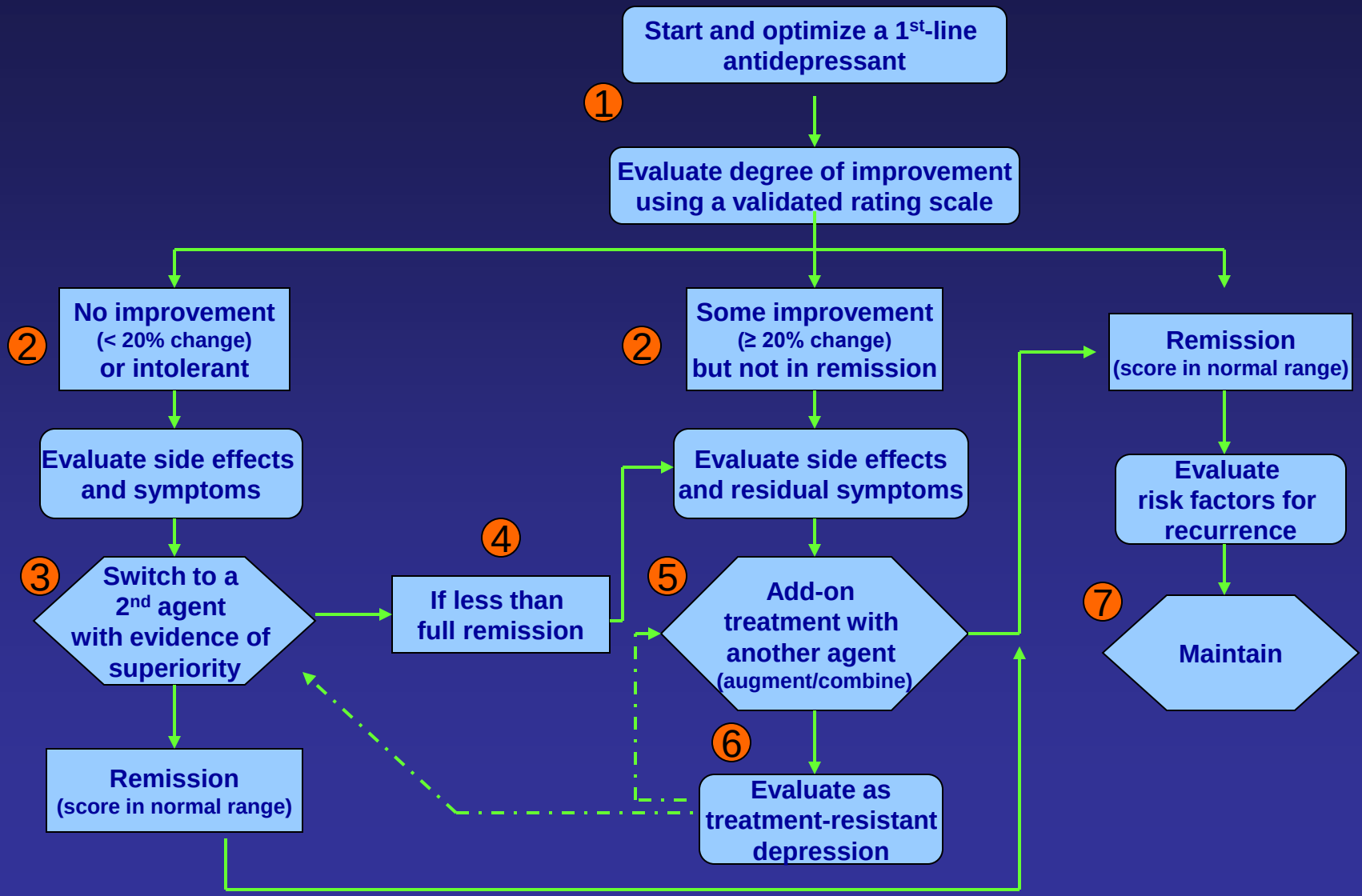
Generalized Anxiety Disorder 7 (GAD-7)

Name: Rhonda **Date:** Visit 1

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "✔" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	(0)	1	2	3
2. Not being able to stop or control worrying	(0)	1	2	3
3. Worrying too much about different things	0	1	(2)	3
4. Trouble relaxing	0	(1)	2	3
5. Being so restless that it is hard to sit still	(0)	1	2	3
6. Becoming easily annoyed or irritable	0	(1)	2	3
7. Feeling afraid as if something awful might happen	(0)	1	2	3
Total	**4**			

Algorithm for Managing Limited Improvement with First-line Antidepressant



Lam R, et al. *J Affect Disord.* 2009;117:S26-S43.