Treatment-Resistant Depression: Definitions and Next Step Recommendations

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Objectives

Discuss:

- Magnitude of the Problem

- Health Care Costs

- Definitions of TRD

Diagnosing Depression

A specific blood test for depression has yet to be developed.

Doctors must use description of symptoms to diagnose and treatment history to determine treatment options.

Other information part of the assessment
- Medical history
- Substance abuse
- Medication use
- Family medical and mental health history

Treatment Resistance in Depression

- ~ 30% remission rates with first-line therapy[1]

- 29%-46% do not respond to pharmacological therapy of adequate dose and duration[2]

- Approximately half of patients who do not respond to the first antidepressant therapy will not respond to a second agent[1]

- Even after multiple interventions, approximately 25% of patients remain depressed, and the likelihood of response to antidepressants decreases with the number of failed treatment trials[3]

[1]AHCPR
[2]Fava et al. 1996
[3]Rush et al. 2006

"resistance," "refractory," and "intractable"

Identifying TRD

- No universally accepted criteria currently exist to diagnose patients as treatment resistant

- Most current definitions of TRD include the concept of multiple failures to respond to adequate treatment trials

- An emerging definition of TRD is failure to respond to adequate trials of 2 different antidepressants

- Two key elements of an adequate treatment trial are:

  – Adequate dose

  – Adequate duration of treatment

- Proper identification requires ruling out other comorbid conditions and assessing factors associated with poorer outcomes

Treatment resistance versus Pseudo-resistance

Major Causes of Pseudo-resistances

1. Inadequate dosing
2. Early discontinuation of treatment prior to completion of an adequate trial
3. Atypical pharmacokinetics that reduce agent effectiveness
4. Patient noncompliance due to adverse effects, and
5. Misdiagnosis of the primary disorder, i.e., other mood disorders or depressive subsets mistreated as unipolar depression.

Reference: Daniel Souery, M.D., Ph.D.; George I. Papakostas, M.D.; and Madhukar H. Trivedi, M.D. Treatment-Resistant Depression J Clin Psychiatry 2006;67 (suppl 6) 16-22.

Depression is Chronic, Patients are non-adherent

Complicated by various factors

- Chronic nature of depression: In Collaborative Depression Study (patients for up to 12 years)

    - 27% patients did not have even a single asymptomatic week during the study

- Non-adherence to treatment: Between 20 to 50 percent depressed patients are non-adherent.

Judd, L. L., H. S. Akiskal, J. D. Maser, P. J. Zeller, J. Endicott, W. Coryell, M. P. Paulus, J. L. Kunovac, A. C. Leon, T. I. Mueller, J. A. Rice and M. B. Keller (1998). "A Prospective 12-Year Study of Subsyndromal and Syndromal Depressive Symptoms in Unipolar Major Depressive Disorders." Arch Gen Psychiatry 55(8): 694-700

Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Arch Intern Med. 2007;167(6):540-550.

Prevalence of TRD – primary care patients in UK

TRD defined if score on BDI-II >14 and have taken an antidepressant for >=6 weeks.

Of 2439 patients who responded, 37% had minimal or greater depressive symptoms even after 12 months of antidepressant medication treatment

Prevalence of treatment-resistant depression

	n	%	95% CI[a]
BDI ≥ 14 and adhered to medication (TRD)	1177	55.3	52.8 to 57.8
BDI ≥ 14 but had not adhered to medication	458	21.5	19.4 to 23.6
BDI < 14 (minimal symptoms)	494	23.2	20.9 to 25.5

[a] CIs have been adjusted for clustering by GP practice. BDI = Beck Depression Inventory. TRD = treatment-resistant depression.

Laura Thomas, David Kessler, John Campbell, Jill Morrison, Tim J Peters, Chris Williams, Glyn Lewis, Nicola Wiles. Prevalence of treatment-resistant depression in primary care: cross-sectional data. Br J Gen Pract. 2013 Dec;63(617):e852-8. doi: 10.3399/bjgp13X675430.

Prevalence of TRD-primary care patients in Canada

Based on case reports filled out by physicians

Number of patients evaluated = 1212

TRD defined by failure to respond to 2 antidepressant (from different classes)

Rate of TRD: 27.1%

Features of patients with TRD:

A. Longer episode duration
B. More likely to receive polypharmacy
C. More antidepressant related side effects
D. More likely to be obese or overweight
E. Less likely to be employed
F. More likely to be prescribed higher doses of medication

Rizvi S et al. Treatment-resistant depression in primary care across Canada. Can J Psychiatry. 2014 Jul; 59(7): 349–357
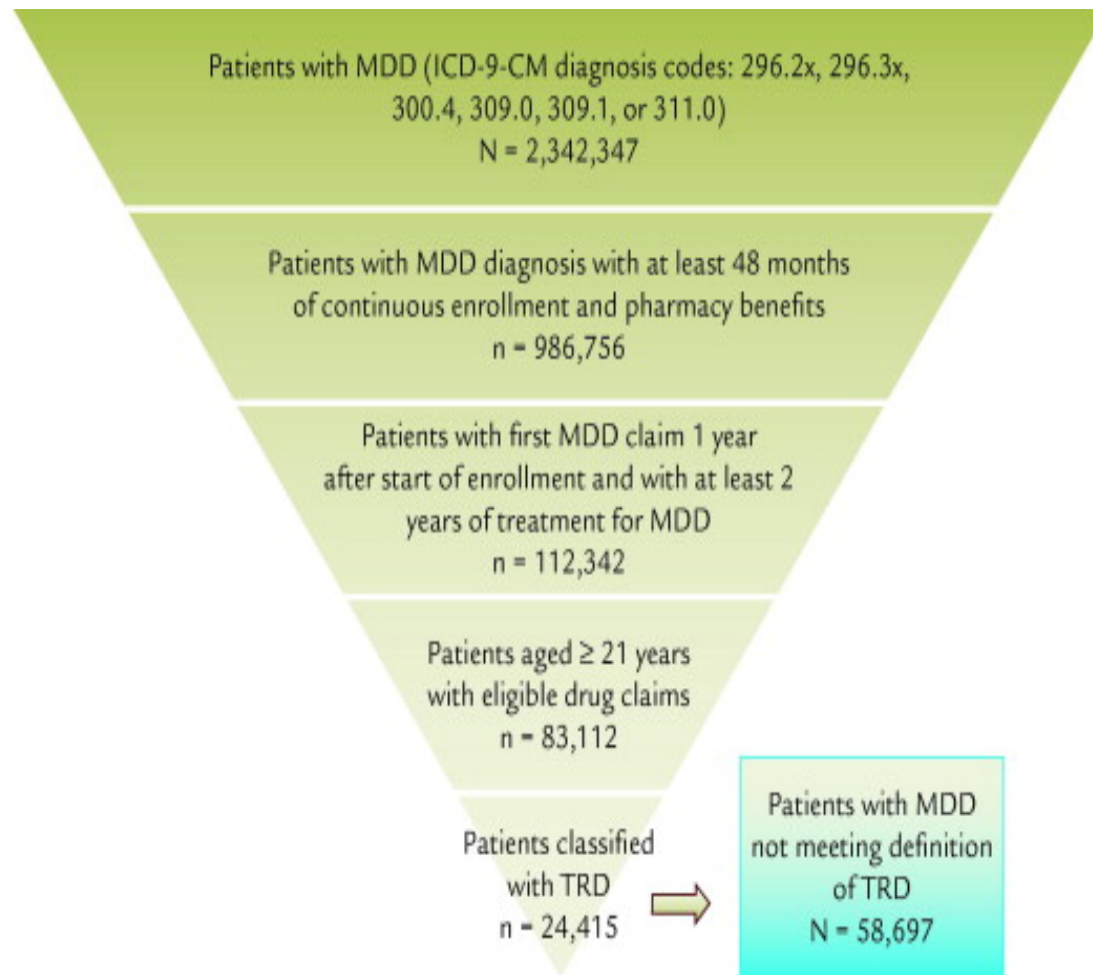
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Risk factors for TRD

Main clinical and biological risk factors for treatment resistant depression.

FACTOR	RISK	REFERENCES
Comorbid anxiety disorder	OR=2.6 [1.8–3,6], $p < 0.001$	Souery et al. (2007)
Current suicidal risk	OR=2.2 [1.6–3], $p < 0.001$	Souery et al. (2007)
Nonresponse to the first antidepressant received	OR=1.6 [1.1–2.5], $p=0.019$	Souery et al. (2007)
Melancholic features	OR=1.5 [1.1–2,], $p=0.018$	Souery et al. (2007)
Bipolarity	OR=1.61 [1.13–2.30], $p=0.008$	Dudek et al. (2010)
Early onset of first depressive episode	OR=2.30 [1.06,-5.0], $p=0.036$	Dudek et al. (2010)
High rate of depressive recurrences	OR=1.52 [1.04–2.22], $p=0.031$	Dudek et al. (2010)
Lack of full remission after a previous episode	OR=10.4 [6.84–15.9], $p=0.001$	Dudek et al. (2010)
Low reward dependence	$F=13.19$, $p < 0.001$	Takahashi et al. (2013a)
Low cooperativeness	$F=5.42$, $p=0.005$	Takahashi et al. (2013a)
High neuroticism	$F=11.10$, $p < 0.001$	Takahashi et al. (2013b)
Low extraversion	$F=26.42$, $p < 0.001$	Takahashi et al. (2013b)
Low openness	$F=5.93$, $p=0.004$	Takahashi et al. (2013b)
Low conscientiousness	$F=4.88$, $p=0.009$	Takahashi et al. (2013b)
Decreased GABA levels in occipital and anterior cingulate cortices	–	Price et al. (2009)
5-HT1A C1019G polymorphism GG genotype+A allele of BDNF G196A (Val66Met) polymorphism	OR=3.178 [1.315–7.68], $p=0.007$	Anttila et al. (2007)
NTRK2 gene polymorphisms (T-Thaplotype)	OR=1,43 [1,16–1,76], $p=0.0008$	Li et al. (2013)
Functional polymorphism of GRIN2B	OR=1.55 [1.18–2.05], $p=0.008$	Zhang et al. (2014)

D. Bennabi et al. / Journal of Affective Disorders 171 (2015) 137–141

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Health Care costs of TRD

Patients with MDD (ICD-9-CM diagnosis codes: 296.2x, 296.3x, 300.4, 309.0, 309.1, or 311.0)
N = 2,342,347

Patients with MDD diagnosis with at least 48 months of continuous enrollment and pharmacy benefits
n = 986,756

Patients with first MDD claim 1 year after start of enrollment and with at least 2 years of treatment for MDD
n = 112,342

Patients aged ≥ 21 years with eligible drug claims
n = 83,112

Patients classified with TRD
n = 24,415

Patients with MDD not meeting definition of TRD
N = 58,697

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Health Care Costs of TRD - continued

	Non – TRD patients		TRD patients		
	Mean	SD	Mean	SD	p Value
Costs/year of Depression Related Medical Services	$910	$2125	$1848	$4737	<0.0001
Costs/year of Other Medical Services	$5464	$10736	$8129	$12645	<0.0001
Costs/year of Depression Related Pharmacy Services	$939	$1250	$2639	$2671	<0.0001
Costs/year of Other Pharmacy Services	$1422	$3370	$2580	$5376	<0.0001
Total Costs/year of depression	$7832	$12754	$13152	$15966	<0.0001

Even after adjusting for covariates*, presence of TRD was associated with **29.3%** (p<0.0001) higher health care utilization costs

* Geographic region, age, gender, insurance type, duration of illness, type of antidepressant medication, non-pharmacological treatments
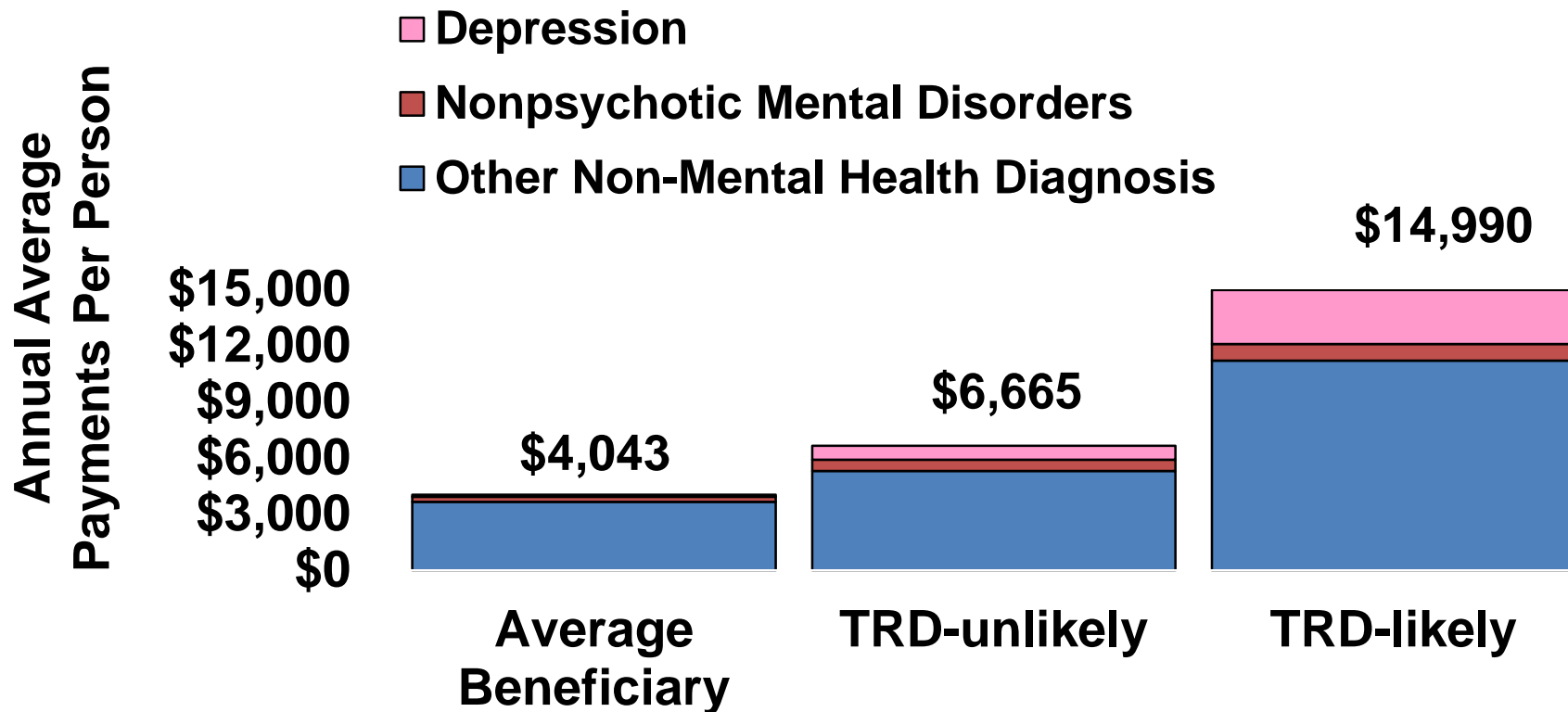
Health Care costs of TRD

Review of published literature

- Higher costs for TRD patients when compared to treatment-responsive depressed patients

- Annual health care costs were $5481 higher in TRD patients

- Annual costs of lost productivity were $4048 higher in TRD patients

Mrazek DA et al. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. Psychiatr Serv. 2014 Aug 1;65(8):977-87. doi: 10.1176/appi.ps.201300059.
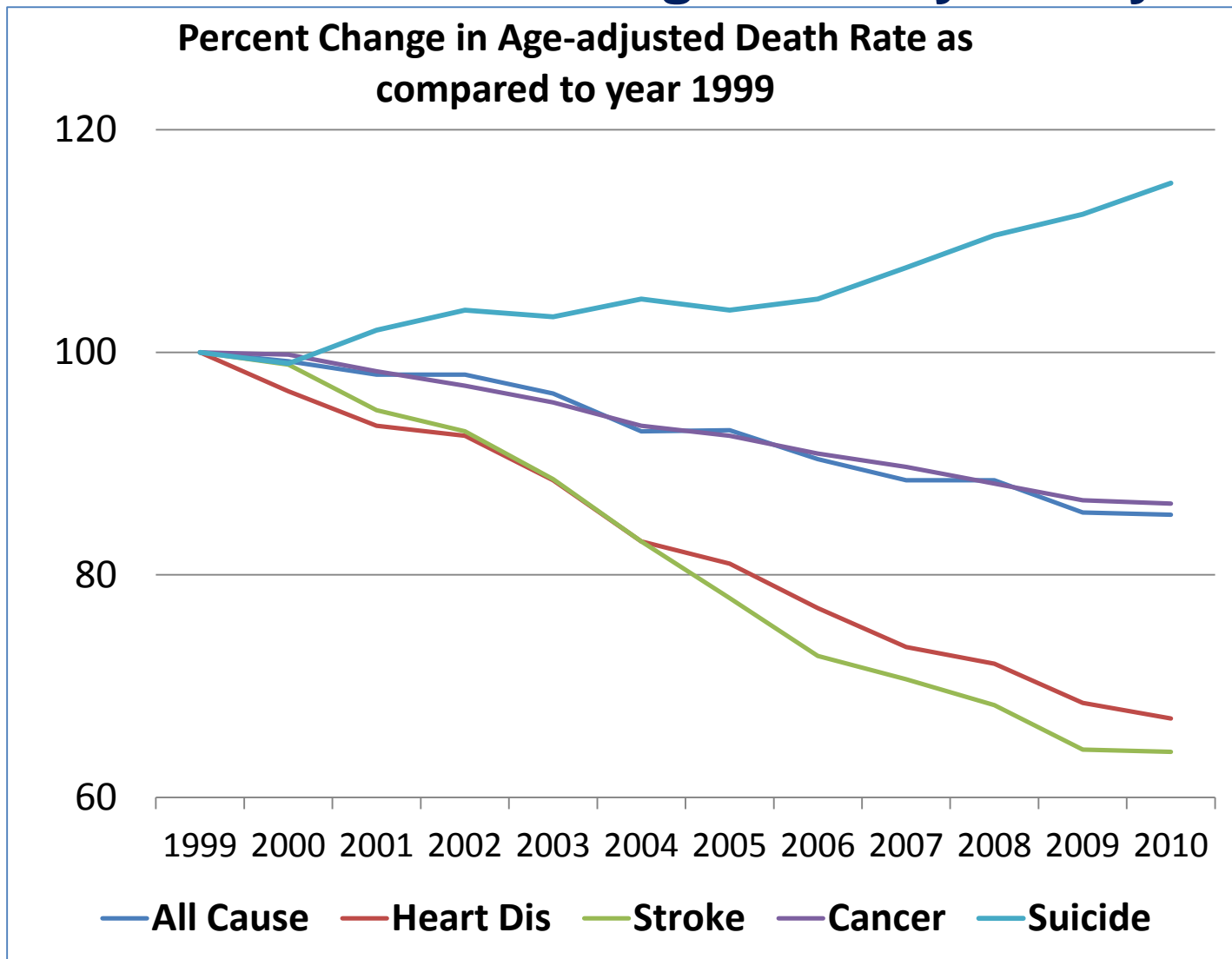
Medical Payments for TRD vs Non-TRD Depressed Patients

Employee Population, 1998 Cost

Legend:
- ■ Depression
- ■ Nonpsychotic Mental Disorders
- ■ Other Non-Mental Health Diagnosis

Annual Average Payments Per Person

- $15,000
- $12,000
- $9,000
- $6,000
- $3,000
- $0

- Average Beneficiary: $4,043
- TRD-unlikely: $6,665
- TRD-likely: $14,990

Corey-Lisle et al. 2002

Suicide rates – increasing mortality over years

Percent Change in Age-adjusted Death Rate as compared to year 1999

Legend: All Cause, Heart Dis, Stroke, Cancer, Suicide

TRD is associated with higher suicide rates

17% (±6%) patients with TRD report prior suicide attempt (1.1±0.2 attempts per patient).

In a study of veterans, completed suicide cases had higher scores on MGH method of treatment resistance staging as compared to matched controls (1.43 in suicide cases vs. 1.1 in non-suicide controls, p<0.001).

Mrazek DA et al. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. **Psychiatr Serv**. 2014 Aug 1;**65**(8):977-87. doi: 10.1176/appi.ps.201300059.

Pfeiffer PN et al. Treatment-resistant depression and risk of suicide. **Suicide** Life Threat Behav. 2013 Aug;43(4):356-65. doi: 10.1111/sltb.12022. Epub 2013 Mar 20.

Methods to define treatment resistance

1. Medication Failure Method

   Categorical approach – TRD present or absent

   Exact number or type of treatment failures necessary prior to establish presence

   of TRD

2. Staging Model Method

   Higher number of treatment failures is associated with greater treatment

   resistance severity

   Multiple staging methods

   A. Thase and Rush method

   B. Massachusetts General Hospital method

   C. European method

   D. Maudsley method

Trevino K, McClintock SM, McDonald Fischer N, Vora A, Husain MM. Defining treatment-resistant depression: a comprehensive review of the literature. Ann Clin Psychiatry. 2014 Aug;26(3):222-32

Thase and Rush method

Thase and Rush staging method: Antidepressant treatment resistance

Stage	Description
Stage 0	Any medication trials, to date, determined to be inadequate
Stage I	Failure of ≥1 adequate trial of 1 major class of antidepressants
Stage II	Failure of ≥2 adequate trials of ≥2 distinctly different classes of antidepressants
Stage III	Stage II resistance plus failure of an adequate trial of a tricyclic antidepressant
Stage IV	Stage III resistance plus failure of an adequate trial of an monoamine oxidase inhibitor
Stage V	Stage IV resistance plus a course of bilateral electroconvulsive therapy

MGH method

Massachusetts General Hospital staging method for treatment-resistant depression

Stage	Description	Points toward resistance score
1	No response to each adequate (≥6 weeks of an adequate dosage of an antidepressant) trial of a marketed antidepressant	1 point per trial (overall score of resistance)
2	Optimization of dose, optimization of duration, and augmentation or combination of each trial (based on the Massachusetts General Hospital or Antidepressant Treatment Response Questionnaire)	0.5 point per trial per optimization/strategy
3	Electroconvulsive therapy	3 points

European method

The European staging method for treatment-resistant depression

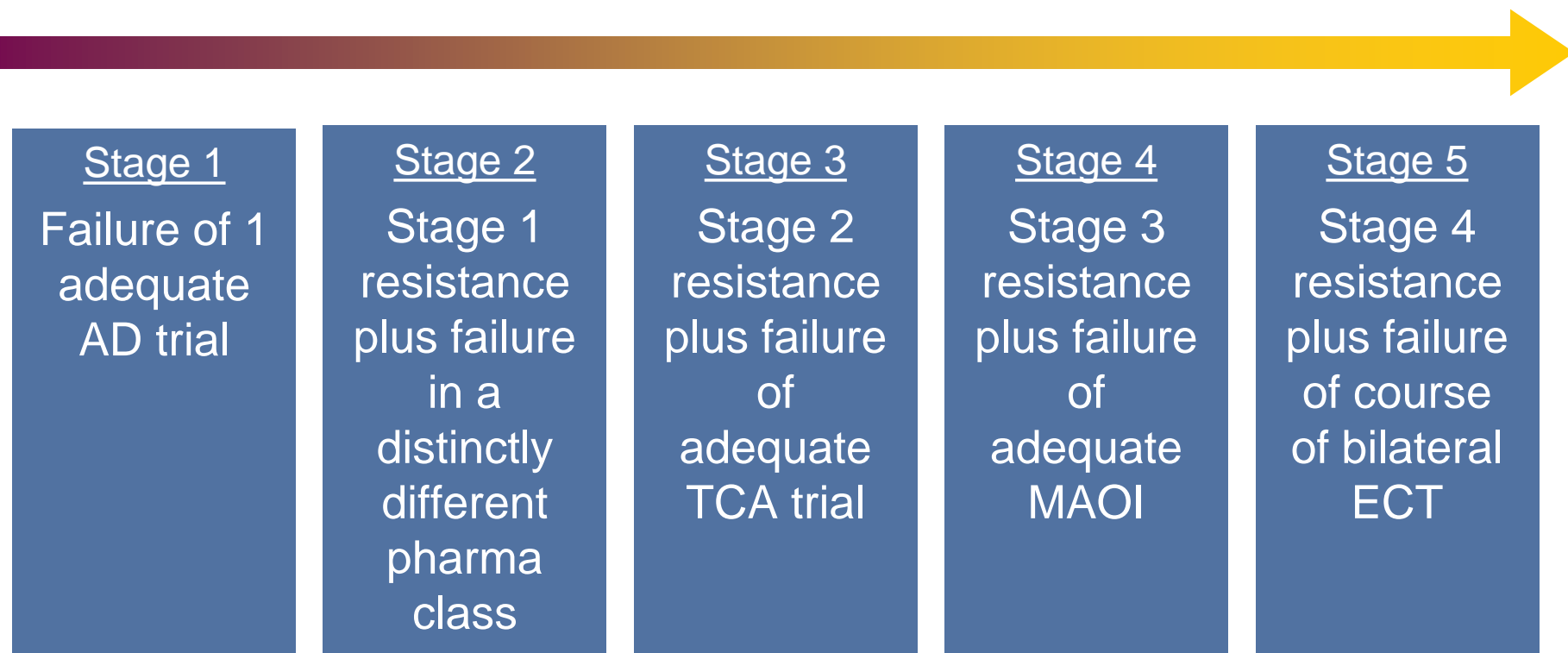| Stage	Definition	Duration of trial
A. Nonresponder	Nonresponse to 1 adequate antidepressant trial of: TCA, SSRI, MAOI, SNRI, ECT, or other antidepressant(s)	6 to 8 weeks
B. TRD	Resistance to ≥2 adequate antidepressant trials	TRD 1: 12 to 16 weeks TRD 2: 18 to 24 weeks TRD 3: 24 to 32 weeks TRD 4: 30 to 40 weeks TRD 5: 36 weeks to 1 year
C. CRD	Resistance to several antidepressant trials, including augmentation strategy	≥12 months

CRD: chronic resistant depression; ECT: electroconvulsive therapy; MAOI: monoamine oxidase inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; TRD: treatment-resistant depression.

Maudsley method

Maudsley Staging Method for treatment-resistant depression: Recommended scoring conventions

Parameter/ dimension	Parameter specification	Score
Duration	Acute (≤12 months)	1
	Sub-acute (13 to 24 months)	2
	Chronic (>24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures		
Antidepressants	Level 1: 1 to 2 Medications	1
	Level 2: 3 to 4 Medications	2
	Level 3: 5 to 6 Medications	3
	Level 4: 7 to 10 Medications	4
	Level 5: >10 Medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		15

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Proposed Staging of Resistance Levels

Stage 1
Failure of 1 adequate AD trial

Stage 2
Stage 1 resistance plus failure in a distinctly different pharma class

Stage 3
Stage 2 resistance plus failure of adequate TCA trial

Stage 4
Stage 3 resistance plus failure of adequate MAOI

Stage 5
Stage 4 resistance plus failure of course of bilateral ECT

- **Stage 2: Based on more recent data, failure with two trials begins treatment resistance**

Thase et al. 1997

# MGH Antidepressant Treatment Response Questionnaire (ATRQ)

Appendix 1. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire[a]

Please indicate the correct answer to the following questions:

(1) Have you received any treatment with medications since the beginning of **THIS CURRENT** episode or period of depression? Please circle the correct answer.   **YES**   **NO**

(2) If **YES**, please review the list below and put a check next to any medication(s) that you have taken for at least 6 or 10 weeks during THIS episode or period of depression.

(3) Of those medication(s) that you have checked from the list, please put a second check next to those that you have taken at a dosage equal to or greater than the minimum dosage listed for that medication.

(4) Of those medication(s) that you have checked from the list, please put a third check next to those that you have taken with another drug (eg, buspirone [Buspar], lithium, psychostimulants such as methylphenidate [Ritalin], atypical antipsychotics such as olanzapine [Zyprexa]) added to augment or boost the antidepressant effect.

(5) Of the medications that you have checked, please write below the name of the one that you feel helped you the most with your depression:

_____

(6) If a rating of 100 is "completely improved" and 0 is "not improved at all," how close to 100 did you get on this medication? Please put a check next to the answer that best applies to you.

_____ a) Less than 25% improved   _____ b) Between 25% and 49% improved   _____ c) Between 50% and 75% improved   _____ d) More than 75% improved

Pharmacologic and Psycotherapeutic Strategies for Depression

OPTIMIZATION

**Switching** **Combination** **Augmentation**
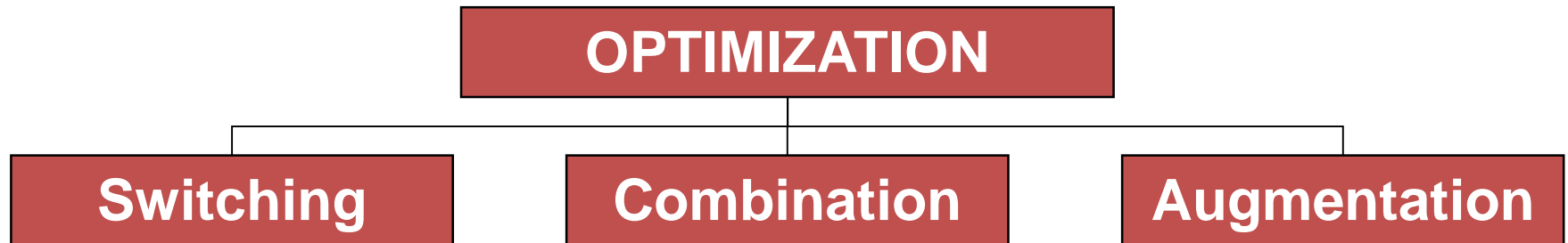
STAR*D: Sequenced Treatment Alternatives to Relieve Depression

- Largest prospective study of a sequential series of treatment for depression ever conducted (N=4000)

- Multicenter, randomized, open-label

- Funded by NIMH

- Investigated treatment options for patients who do not respond to first-line antidepressant therapy in 3 subsequent steps, each 12-14 weeks in duration
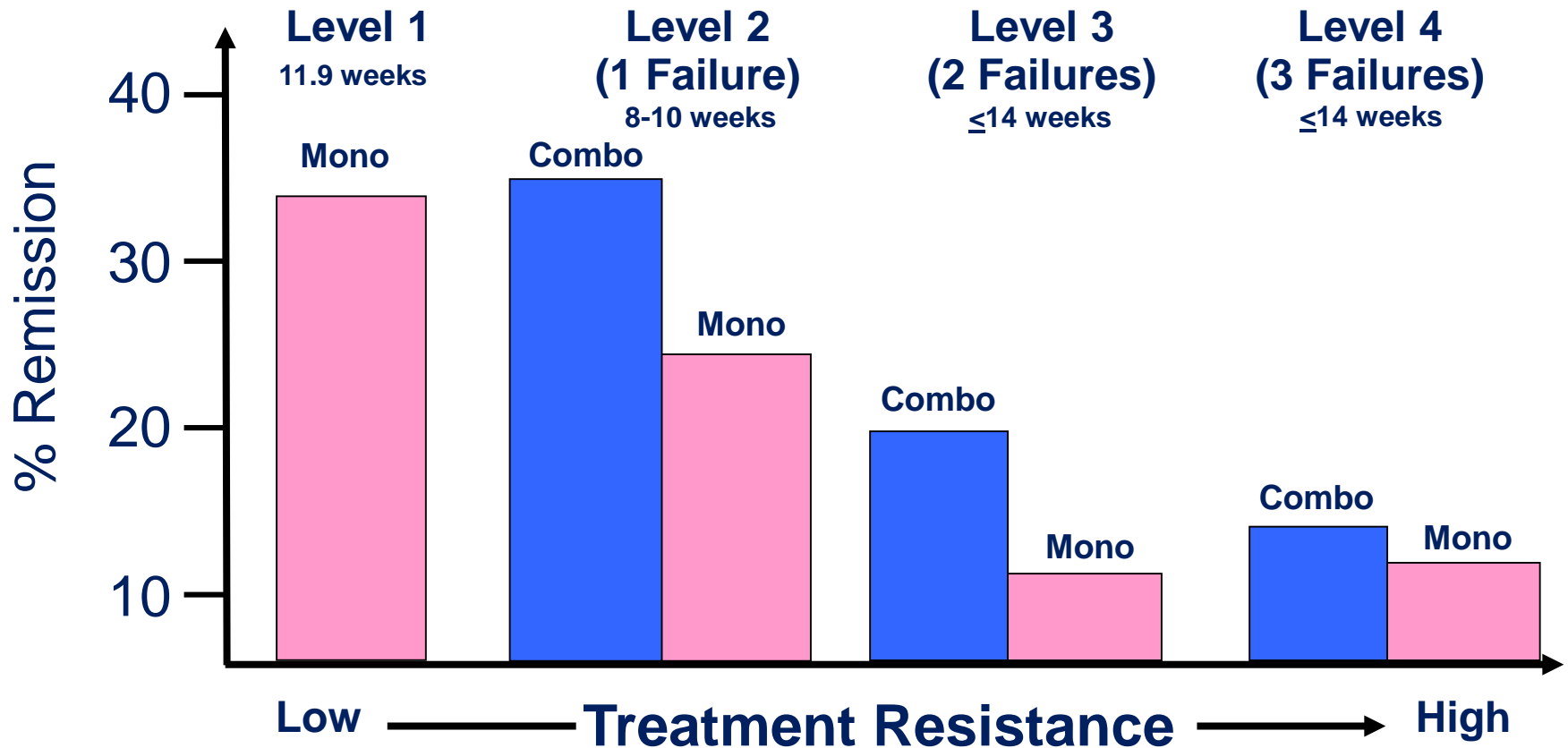
STAR*D Clinical Study Results
Remission Rates (QIDS-SR$_{16}$ ≤5)
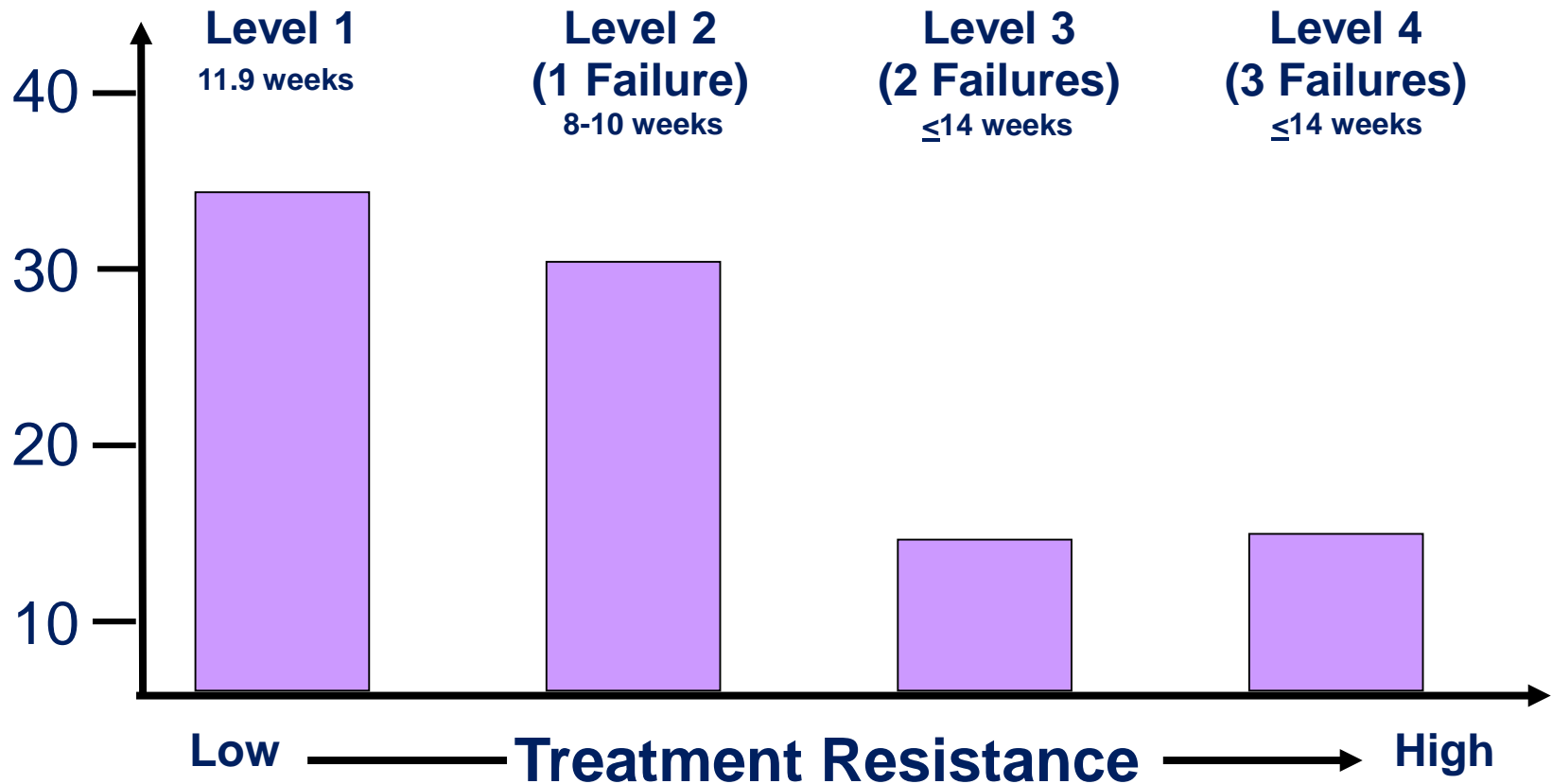
McGrath et al. 2006
Rush et al. 2006
Nierenberg et al. 2006
Trivedi et al. 2006a
Trivedi et al. 2006b

STAR*D Clinical Study Results
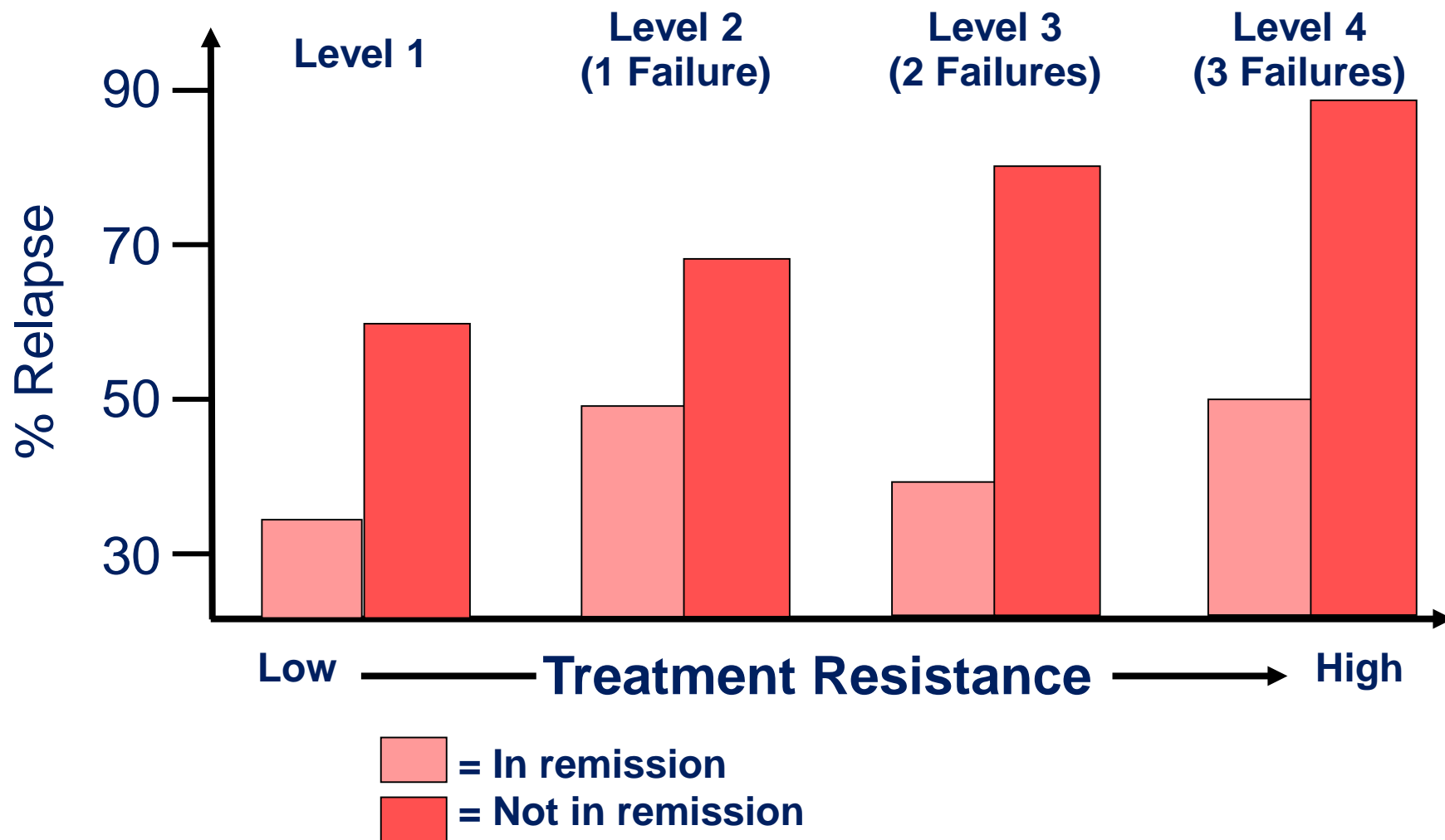# Remission Rates: Combination vs Monotherapy

Level 1
11.9 weeks

**Level 2
(1 Failure)**
8-10 weeks

**Level 3
(2 Failures)**
<14 weeks

**Level 4
(3 Failures)**
<14 weeks

% Remission

40

30

20

10

Mono

Combo

Mono

Combo

Mono

Combo

Mono

Low ——— **Treatment Resistance** ——→ **High**

Mono = monotherapy
Combo = combination treatment

McGrath et al. 2006
Rush et al. 2006
Nierenberg et al. 2006
Trivedi et al. 2006a
Trivedi et al. 2006b

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STAR*D Clinical Study Results
Relapse Rates (QIDS-SR$_{16}$ ≥11)

Rush et al. 2006

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Rate of Combination Antidepressant Treatments Increasing

- Outpatient office-based psychiatric visits in which combination ATD were prescribed from 1996-97 to 2005-06 (adults):

  - Rate increased from 7.8% to 15.8%

  - OR, 2.09 (1.36-3.22); *p* <0.001

- Similar increase seen in pediatric population during similar time period

  - AOR, 1.89 (1.117-3.05); *p* = 0.009

Mojtabai R and Olfson M, Arch Gen Psych 2010
Comer JS, Olfson M, Mojtabai R, JAACAP 2010

Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study

A. John Rush, M.D.

Madhukar H. Trivedi, M.D.

Jonathan W. Stewart, M.D.

Andrew A. Nierenberg, M.D.

Maurizio Fava, M.D.

Benji T. Kurian, M.D.

Diane Warden, Ph.D.

David W. Morris, Ph.D.

James F. Luther, M.A.

Mustafa M. Husain, M.D.

Ian A. Cook, M.D.

Richard C. Shelton, M.D.

Ira M. Lesser, M.D.

Susan G. Kornstein, M.D.

Stephen R. Wisniewski, Ph.D.

Objective: Two antidepressant medication combinations were compared with selective serotonin reuptake inhibitor monotherapy to determine whether either combination produced a higher remission rate in first-step acute-phase (12 weeks) and long-term (7 months) treatment.

Method: The single-blind, prospective, randomized trial enrolled 665 outpatients at six primary and nine psychiatric care sites. Participants had at least moderately severe nonpsychotic chronic and/or recurrent major depressive disorder. Escitalopram (up to 20 mg/day) plus placebo, sustained-release bupropion (up to 400 mg/day) plus escitalopram (up to 20 mg/day), or extended-release venlafaxine (up to 300 mg/day) plus mirtazapine (up to 45 mg/day) was delivered (1:1:1 ratio) by using measurement-based care. The primary outcome was remission, defined as ratings of less than 8 and less than 6 on the last two consecutive applications of the 16-item Quick Inventory of Depressive Symptomatology—Self-Report. Secondary outcomes included side effect burden, adverse events, quality of life, functioning, and attrition.

Results: Remission and response rates and most secondary outcomes were not different among treatment groups at 12 weeks. The remission rates were 38.8% for escitalopram-placebo, 38.9% for bupropion-escitalopram, and 37.7% for venlafaxine-mirtazapine, and the response rates were 51.6%–52.4%. The mean number of worsening adverse events was higher for venlafaxine-mirtazapine (5.7) than for escitalopram-placebo (4.7). At 7 months, remission rates (41.8%–46.6%), response rates (57.4%–59.4%), and most secondary outcomes were not significantly different.

Conclusions: Neither medication combination outperformed monotherapy. The combination of extended-release venlafaxine plus mirtazapine may have a greater risk of adverse events.

(Am J Psychiatry Rush et al.; AiA:1–13)

Week 12:Response and Remission

	BUP + ESCIT	ESCIT + PLB	VEN + MIRT	BUP + ESCIT vs. ESCIT + PLB	VEN + MIRT vs. ESCIT + PLB
	n (%)	n (%)	n (%)	p	p
Remission Last 2 QIDS-SR <6/8	86 (38.9)	87 (38.8)	83 (37.7)	0.9871	0.8095
Remission Last 2 QIDS-SR < 6	82 (37.4)	81 (36.2)	79 (36.2)	0.7796	0.9864
Response	111 (51.6)	113 (51.8)	110 (52.4)	0.9656	0.9100

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Summary

- TRD is common and costly, accounting for a disproportionate share of the illness burden of MDD

- But…

  - Few Options are available

THANK YOU