

Childhood Depression: Etiology, Prevention & Treatment



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**Cognitive-Behavioral Therapy:
In Search of Effective Methods of
Treatment**

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Major Depression

An Important Social Problem



- Common: Point prevalence of 2-7%
- Leading cause of disability worldwide
- 20m Americans affected (compared to 13.5m with coronary heart disease)
- Annual financial toll \$50 billion in USA
- Mortality rate elevated 2.6x

DSM-IV-TR Diagnostic Criteria Major Depression



- Depressed or irritable mood
- Anhedonia
- Weight or appetite change
- Sleep difficulties
- Psychomotor agitation or retardation
- Fatigue
- Worthlessness or guilt
- Concentration or memory problems
- Thoughts of death or suicide

Lifetime Prevalence Major Depression



	Males	Females
• Adolescents	12%	24%
• Adults	14%	23%

Kessler et al. (2005)
Lewinsohn et al. (1993)

Vulnerability for Depression



1. Biological (Genetic) Factors
2. Negative Life Events
3. Early Experience & Insecure Attachment
4. Affect Regulation
5. Social Behavior; Social Support
6. Cognitive Biases / Deficits

Risk of Depression in Children



- Depressed mothers 38%
- Anxious mothers 14%
- Control mothers 7%

Warner et al (1995)

Affective Dysregulation & Stress Reactivity



1. Heightened reactivity to stress (HPA axis)
2. Deficits in regulation of these affective responses

Information Processing in Depression



1. Negative schemas or tacit beliefs
2. Perceptual bias
 1. Increased attention to negative stimuli
 2. Enhanced memory for negative stimuli
3. Negative construct accessibility

Response Latencies on Stroop Task



- Depressed individuals show significantly longer latencies in response to negative words relative to non-depressed controls
- No difference to neutral or positive words
- Pattern same for formerly depressed subjects

Gotlib & McCann (1984)

Gotlib & Cane (1987)

Inhibitory Deficits in Depression



- Depression is characterized by an inability to inhibit the processing of negative material
- Negative material is left in working memory, leading to rehearsal or rumination
- This material becomes “difficult to expel” when no longer adaptive or relevant

Failure of Mood Regulation



- Depressed adults are unable to use positive memories to regulate or repair negative mood states

Joorman et al. (2007)

- What of depressed or at-risk youth?

Cognitive Vulnerability-I



1. Beck Tacit Beliefs or Schema, Cognitive Distortions, Sociotropy, Autonomy, Automatic Thoughts
2. Rehm Self-Control Deficits, Self Reinforcement
3. D'Zurilla Social Problem-Solving Deficits
4. Garber Affect Regulation

Cognitive Vulnerability-II



5. Seligman Learned Helplessness –
 Perceptions of Contingency

6. Abramson Negative Attributional Style

7. Lewinsohn Loss of Social Reinforcement

8. Alloy Depressive Realism;
 Perceptions of Control and
 Worth

Cognitive Vulnerability-III



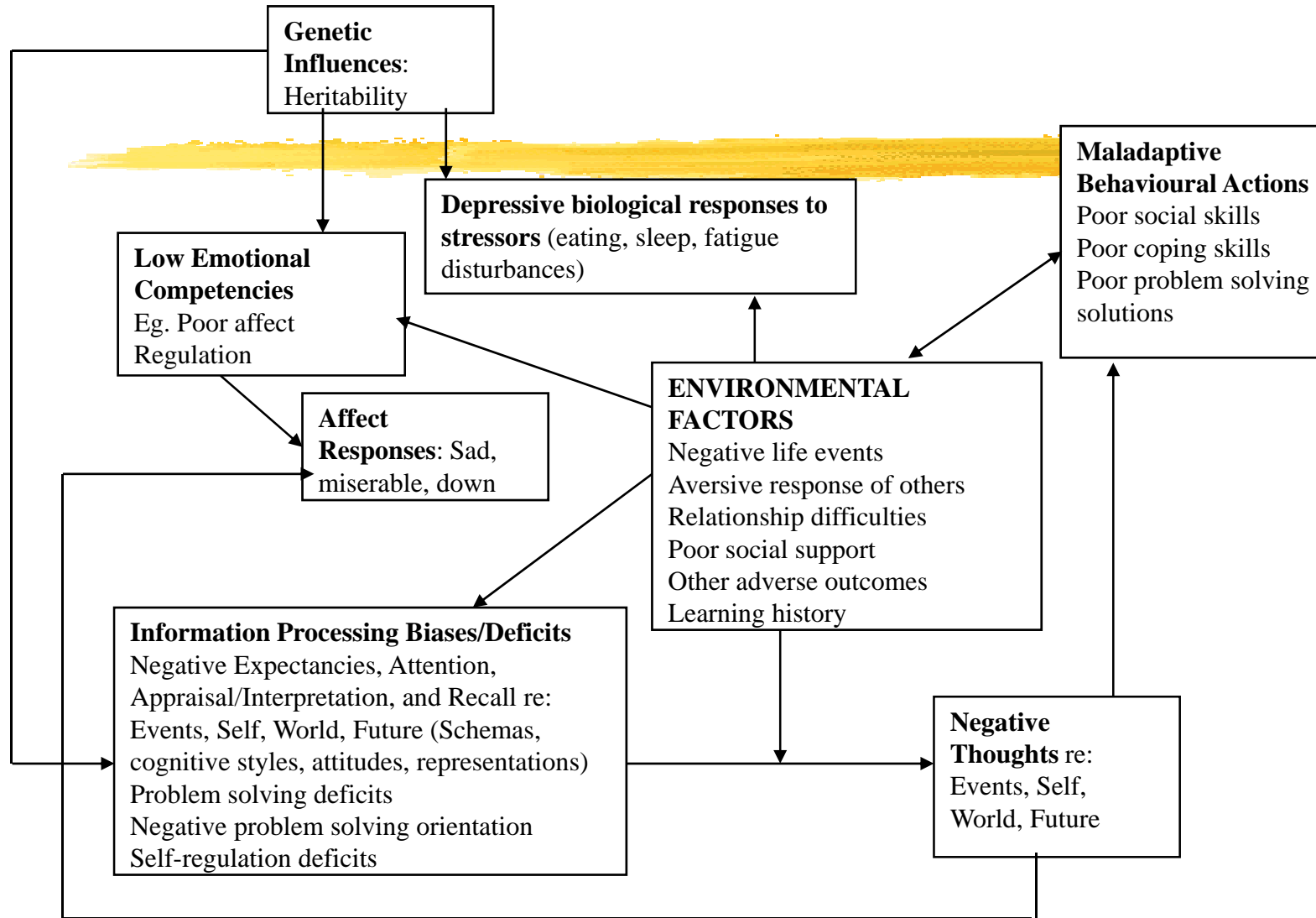
- | | |
|--------------------|--------------------------------|
| 9. Freeman | Decreased mastery and pleasure |
| 9. Joiner | Excessive Reassurance Seeking |
| 10. Nolen-Hoeksema | Ruminative Style |
| 11. Ingram | Self-focused Attention |
| 12. Higgins | Self-Discrepancy |

Cognitive Vulnerability- Summary



1. Tacit Beliefs – Schema
2. Cognitive Distortions (Blockade, Perfectionism)
3. Sociotropy, Autonomy (Self, World, Future)
4. Automatic Thoughts
5. Self-Control Deficits, Self-Reinforcement
6. Social Problem-Solving Deficits (Rational, Motivation)
7. Affect Regulation
5. Helplessness –Perceptions of Contingency
6. Negative Attributional Style (Internal, Global, Stable)
6. Loss of Social Reinforcement, Social Network, Social Skills
7. Perceptions of Control, Worth
9. Accomplishment, mastery
10. Pleasurable events, fun
11. Excessive Reassurance Seeking
12. Ruminative Style, Decreased Solution-Focused Thinking
13. Self-focused Attention
14. Self-Discrepancy (Ideal vs. Actual)

Socio-Cognitive Model of Depression in Children and Adolescents



Socio-Cognitive Model of Depression



- Integrative model of vulnerability
- Distinguishes proximal & distal risk factors
- Attends to both risk & resilience
- Specific predictions; Allows for SEM
- Directs attention to potential mediating variables for developing empirically-supported treatments

TADS

Treatment for Adolescents with Depression Study

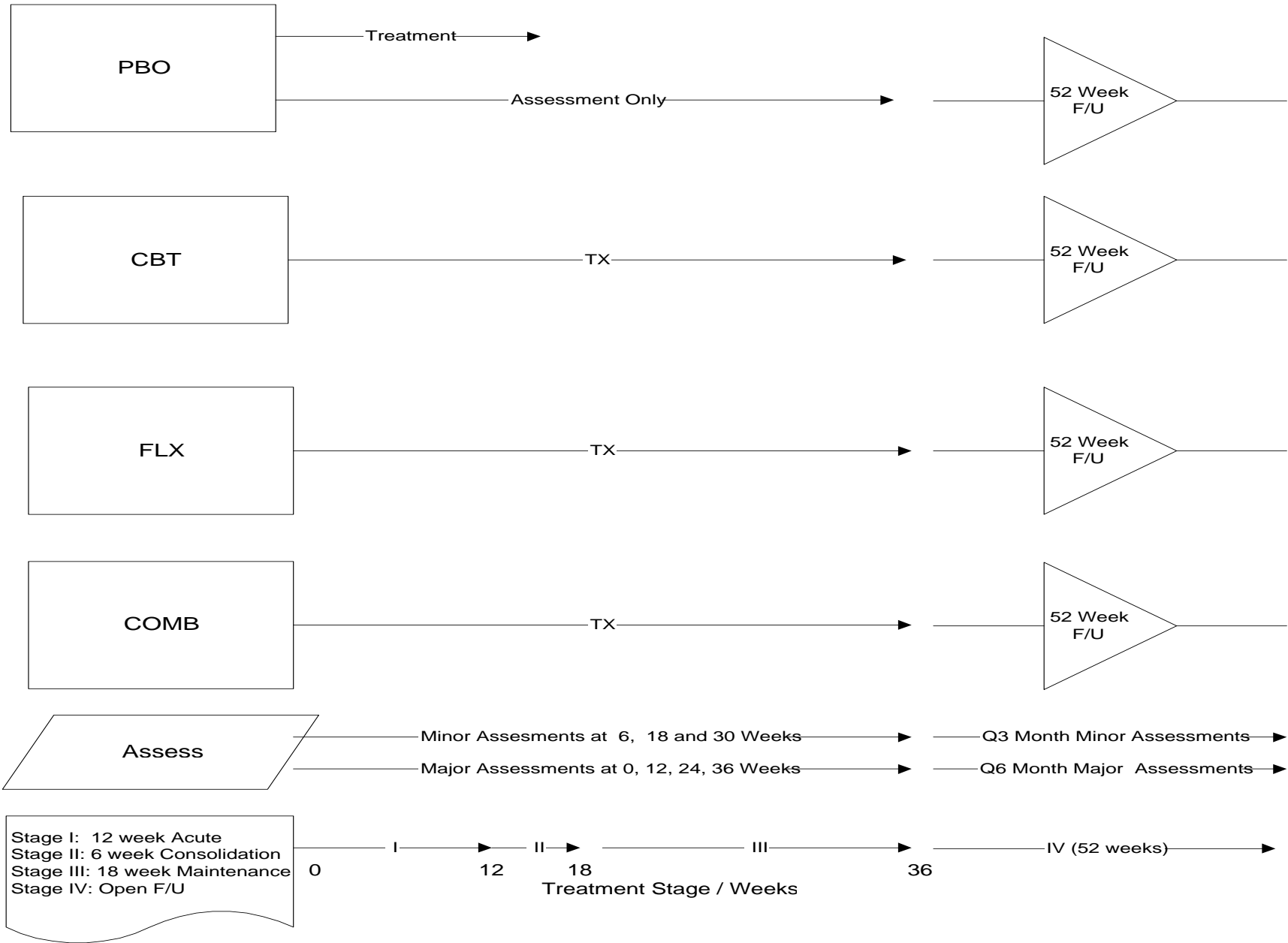


**Rationale, Design,
Methods, & Outcomes**

TADS Study Objectives



A randomized, placebo-controlled trial of 439 adolescents at 13 sites examining the effectiveness, including cost effectiveness, of medication and cognitive-behavioral psychotherapy, alone and in combination, for the acute and long-term treatment of adolescents with DSM-IV Major Depression

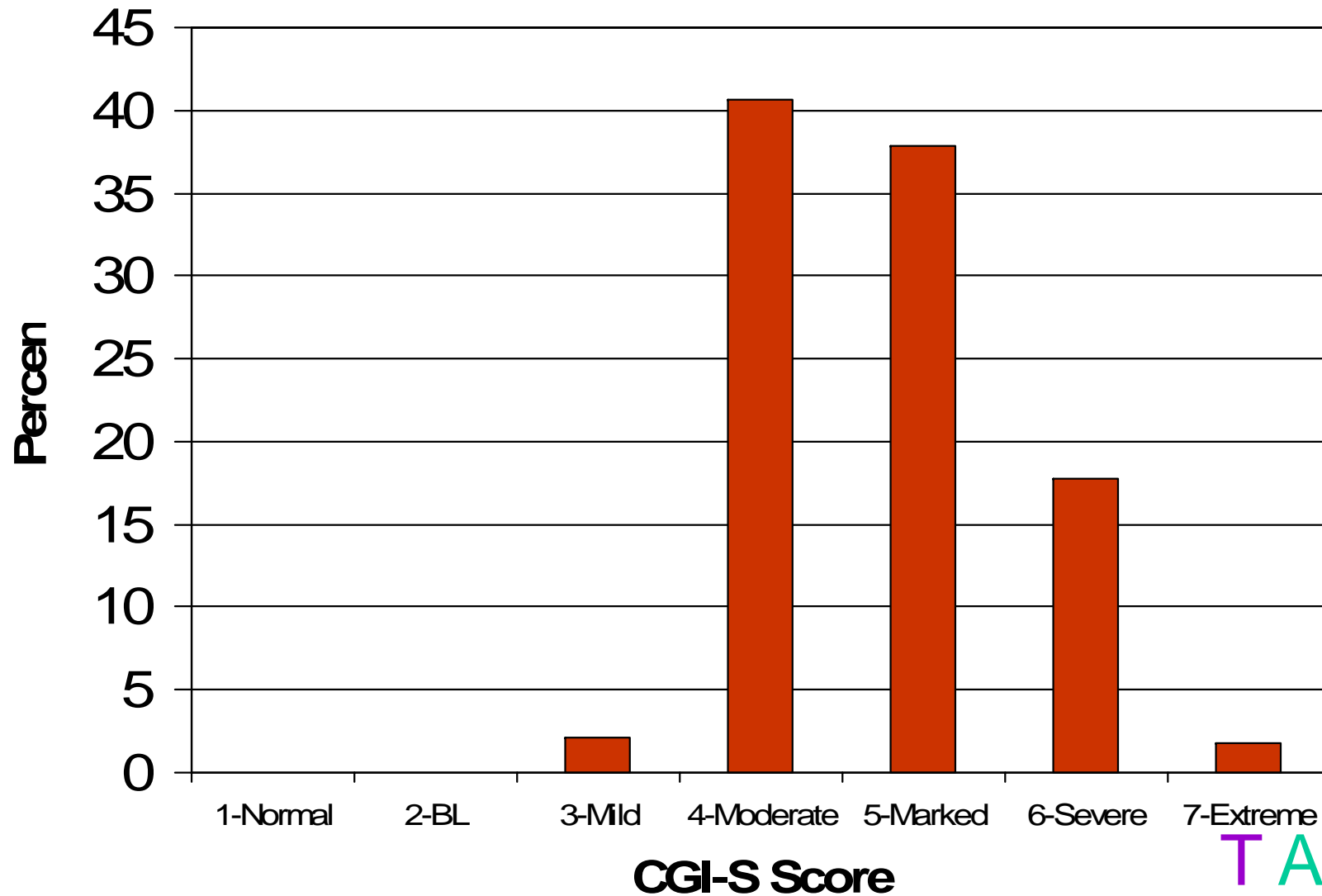


Stages of Treatment



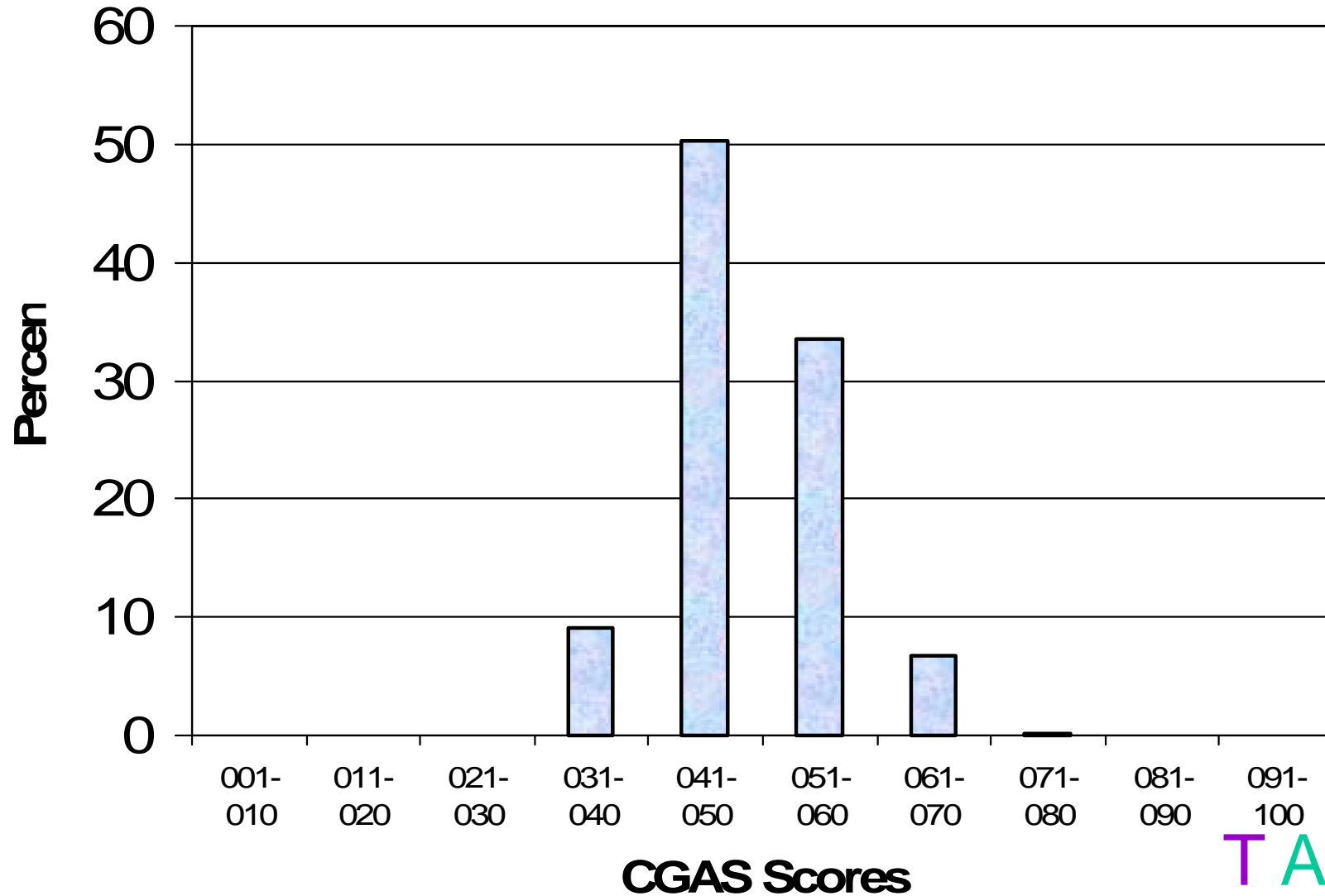
- Stage I Acute Treatment 12 Weeks
- Stage II Consolidation 6 Weeks
- Stage III Maintenance 18 Weeks
- Stage IV Open follow-up 52 Weeks

CGI-S Scores



TADS

CGAS Ratings



Outcome Measures



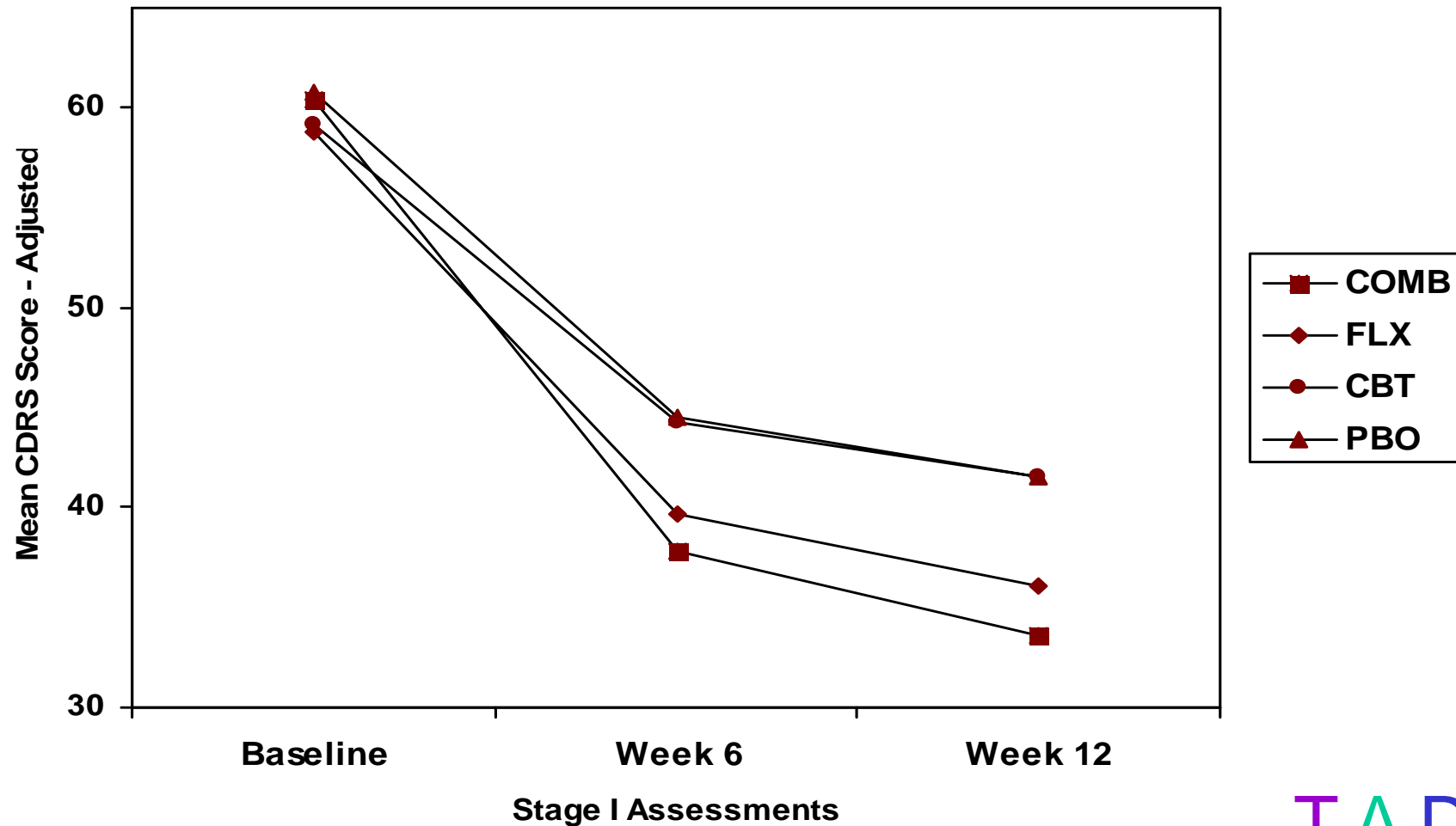
- Children's Depression Rating Scale (CDRS-R)
- Clinical Global Impressions-Improvement (CGI-I)
- Reynolds Adolescent Depression Scale (RADS)
- Suicidal Ideation Questionnaire (SIQ)
- Diagnostic Interview (K-SADS)

Patient Characteristics

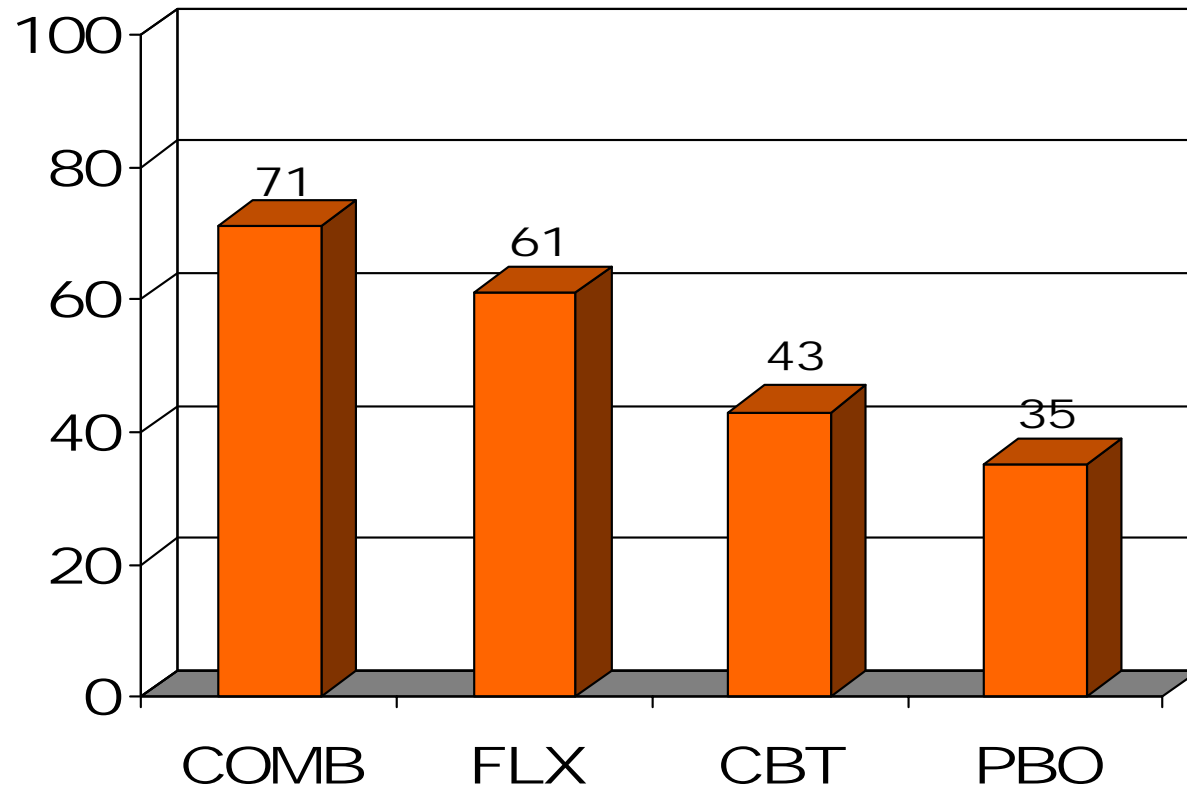


- 439 Subjects
- Average Age = 15 (12-17)
- 54% Male
- 75% White; 13% African American
- 9% Hispanic
- Median Family Income = \$75,000

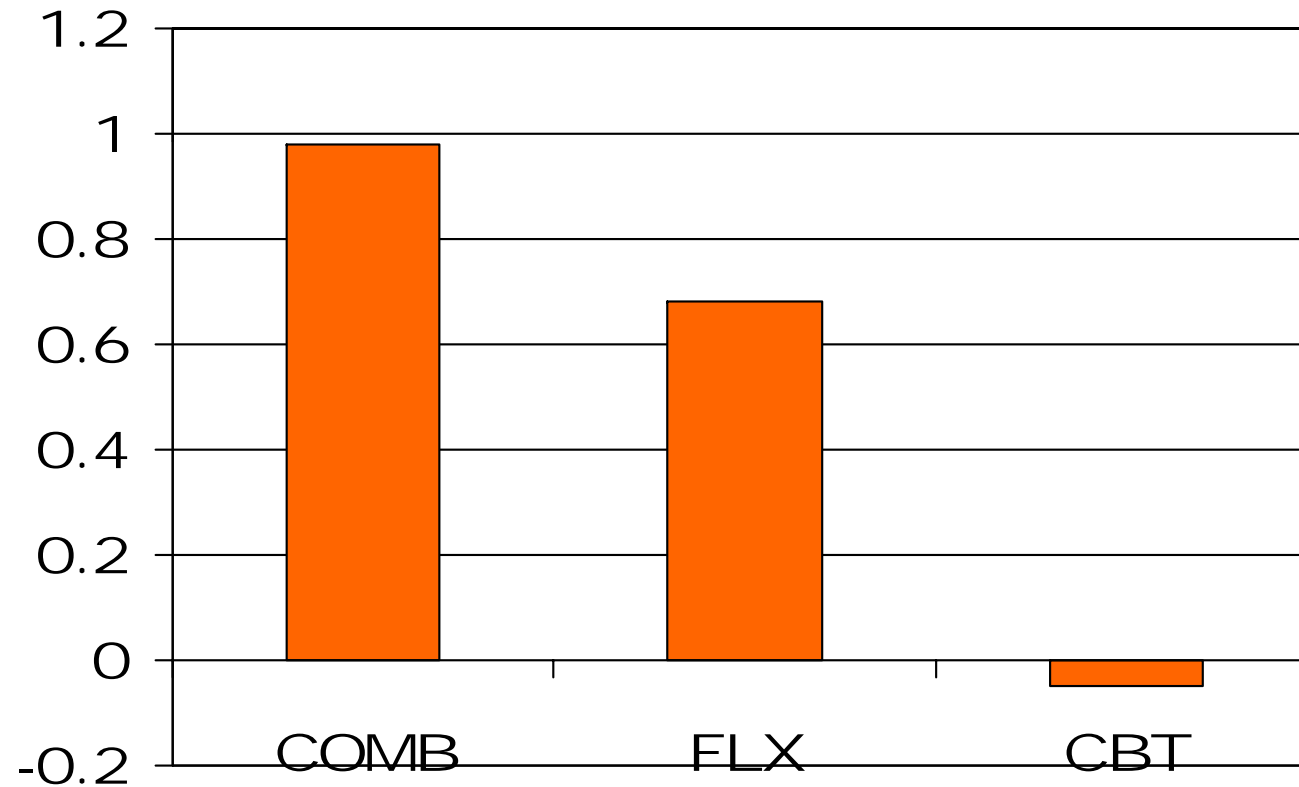
12 Week CDRS: Adjusted Means (ITT)



Treatment Response: Week 12 CGI



Effect Size for CDRS (ITT)



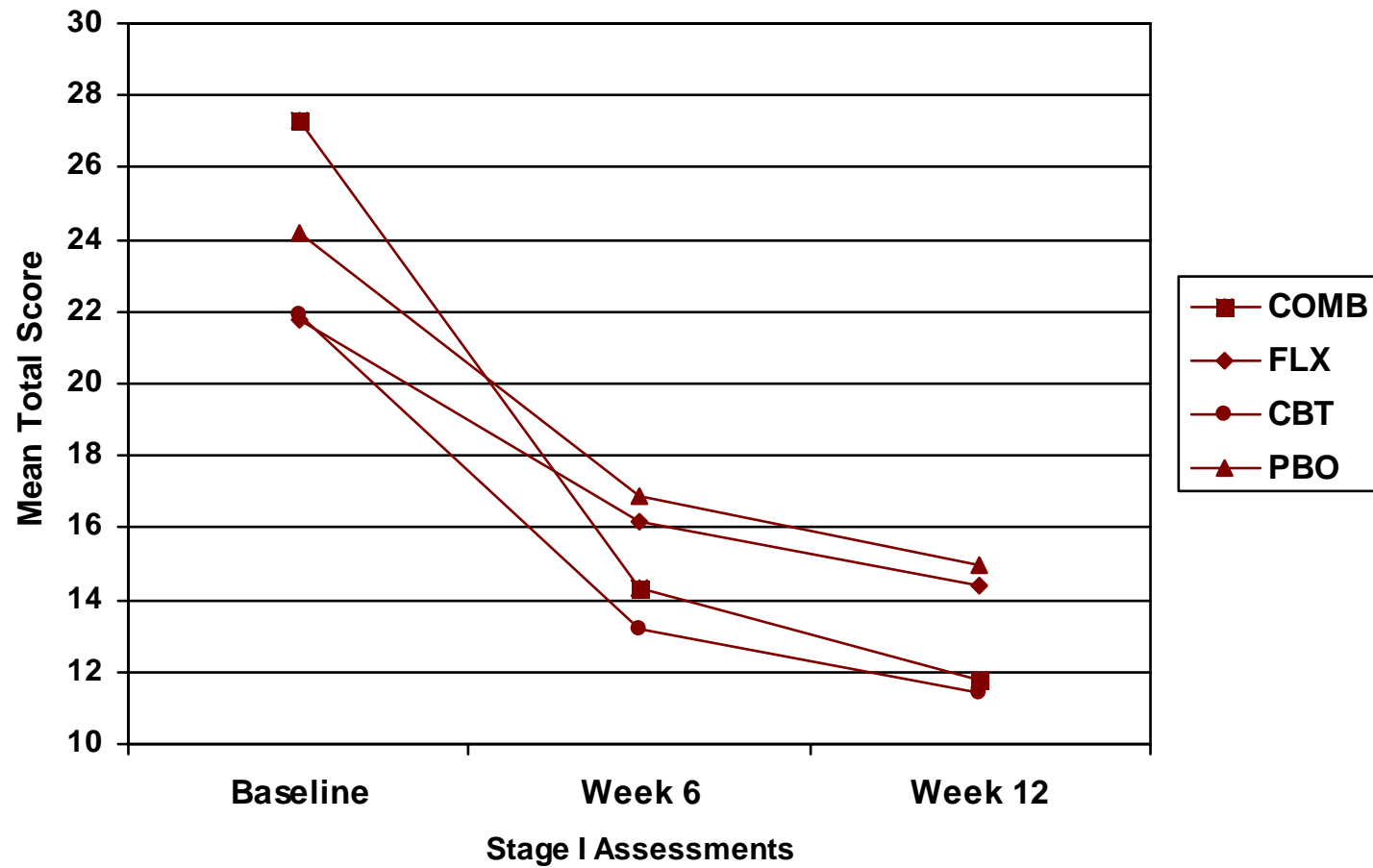
Predictors of Acute Response



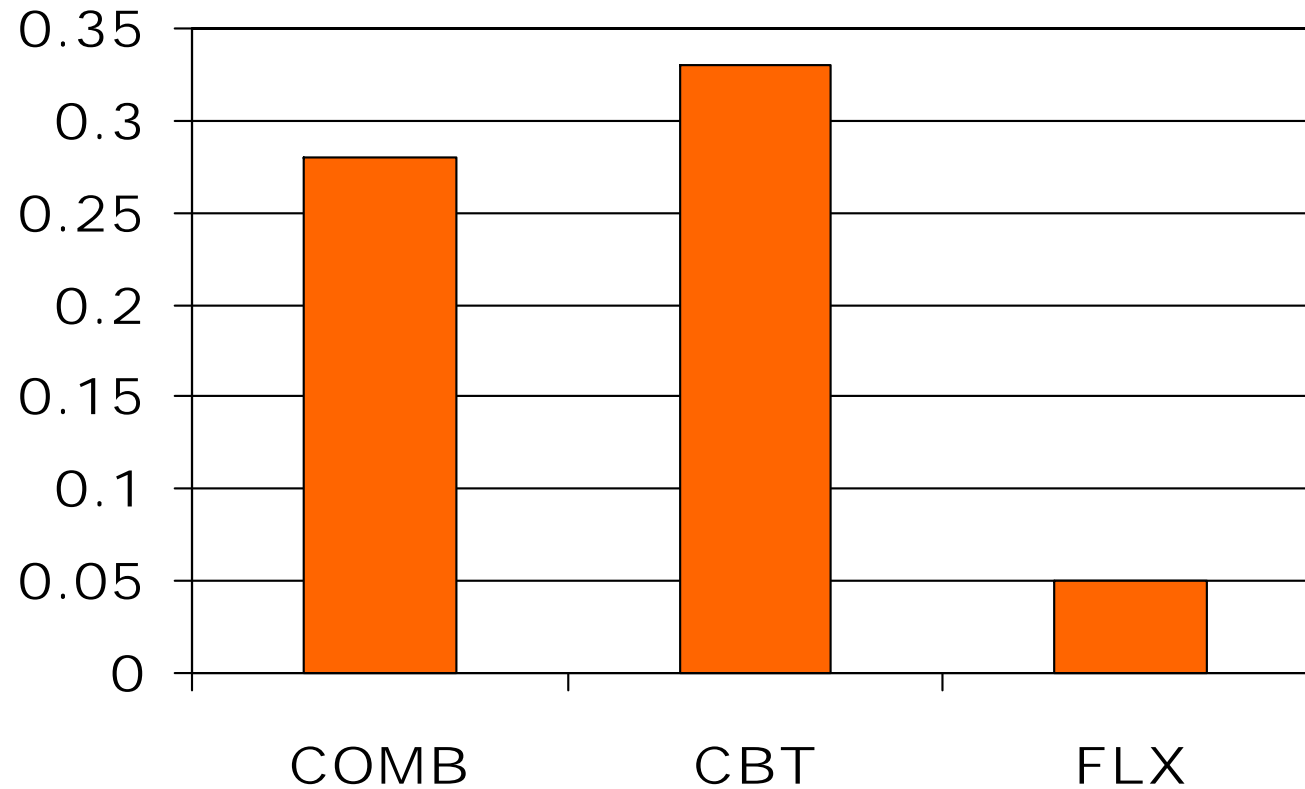
Adolescents were more likely to benefit from treatment if they were:

- Younger
- Less chronically depressed
- Higher functioning
- Less hopeless
- Less suicidal
- Less melancholic
- Fewer comorbid diagnoses
- Had greater expectations for improvement

SIQ : ITT Adjusted Means



Effect Size for SIQ (ITT)



Very Few Suicide Attempts (Stage I)

Treatment	N	Suicide Attempt	SIQ Flag*
FLX	109	1.8% (2)	2
COMB	107	3.7% (4)	3
CBT	111	0.9% (1)	1
PBO	112	0.0% (0)	0
Total Sample	439	1.6% (7)	6

*at baseline

Suicide Events (Stages I-III)

Treatment	N	ITT %	OC %
COMB	107	8.4	7.5
FLX	109	14.7	11.0
CBT	111	6.3	5.4
Total Sample	327	9.8	8.0

TADS Team (2007) *Arch. Gen Psychiatry*. 64: 1132-1144.

ITT = Intent to Treat (all patients randomized to treatment)

OC = Observed Cases (only patients still in assigned arm)

Suicide Events included attempts, preparatory actions, and suicidal ideations per Columbia Suicidality Classification Group

Effectiveness & Safety Conclusions-I



- The combination of FLX and CBT (COMB) is the most effective acute treatment for depressed adolescents
- Fluoxetine alone is effective, but not as effective as COMB
- Fluoxetine accelerates improvement
- Placebo is acceptable in research with depressed youth

Effectiveness & Safety Conclusions-II



- Suicidality decreases substantially with treatment
- Improvement in suicidality is greatest for CBT and COMB and least for fluoxetine alone
- Fluoxetine does not increase suicidal ideation
- Suicide-related events, which are uncommon, may occur more often in FLX treated patients
- CBT may protect against suicide related events in fluoxetine treated patients

Effectiveness & Safety Conclusions-III




- ✓ Taking both risk and benefit into account, the combination of fluoxetine and CBT (COMB) appears superior as a short-term treatment for depression in adolescents

Measures of Functional Impairment



- Child Global Assessment Scale (CGAS)
- Health of the Nations Outcome Scale for Children and Adolescents (HONOSCA)
- Pediatric Quality of Life Questionnaire (PQLQ)

Baseline Association Between Measures of Functional Impairment



	CGAS	HONOSCA	PQLQ
HONOSCA	-.13		
PQLQ	.10	-.20	
CDRS	-.36	.33	-.35

All p's < 0.0001

Treatment Leads to Improved Functioning



- CGAS, HONOSCA & PQLQ improved in all conditions
- CBT = PBO on all measures
- FLX > PBO on CGAS
- ✓ COMB > PBO on CGAS, HONOSCA, and PQLQ

Treatment Effects on Functional Impairment - Conclusion



- ✓ Combining CBT and Fluoxetine results in superior improvement in measures of overall functioning, global health, and quality of life than each treatment in isolation.

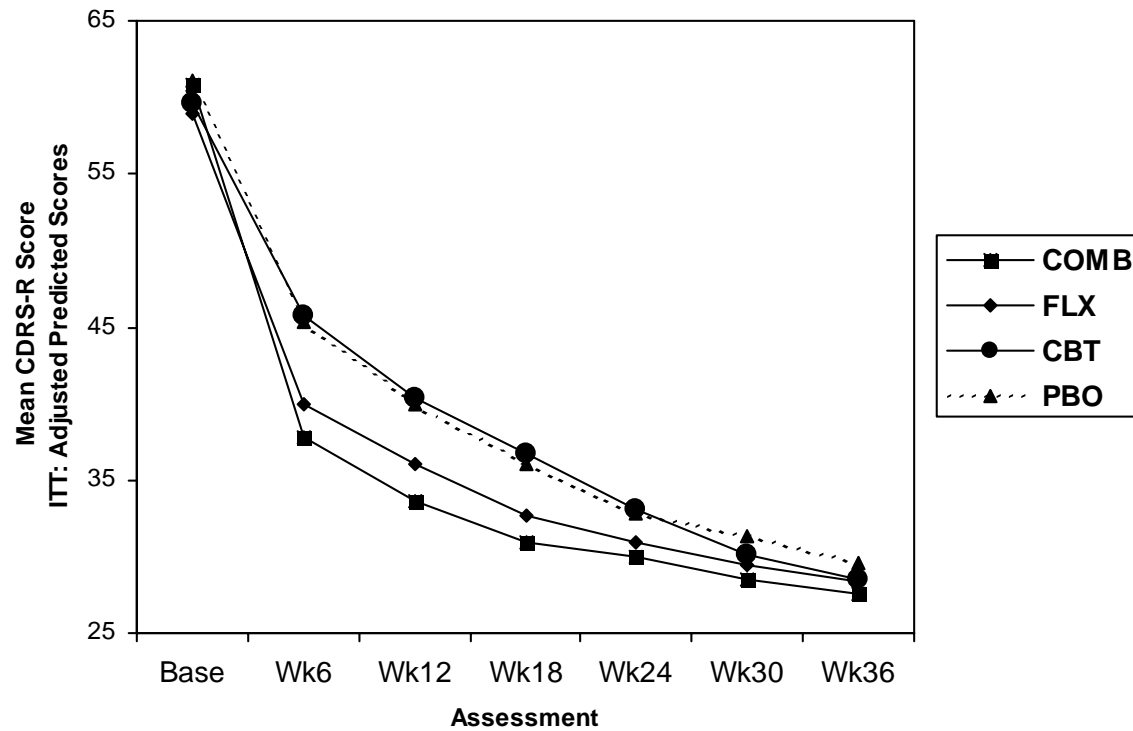
Improvement in psychosocial functioning is rapid and is mediated by improvement of depressive symptoms.

What About Longer Term Outcomes?



- 36 Week Treatment gains are maintained in all arms
- CBT, FLX and Combo converge
- ✓ CBT alone as effective as FLX and Combo
- A delayed treatment effect; time, speed of action

36 week ITT Outcomes (CDRS-R)



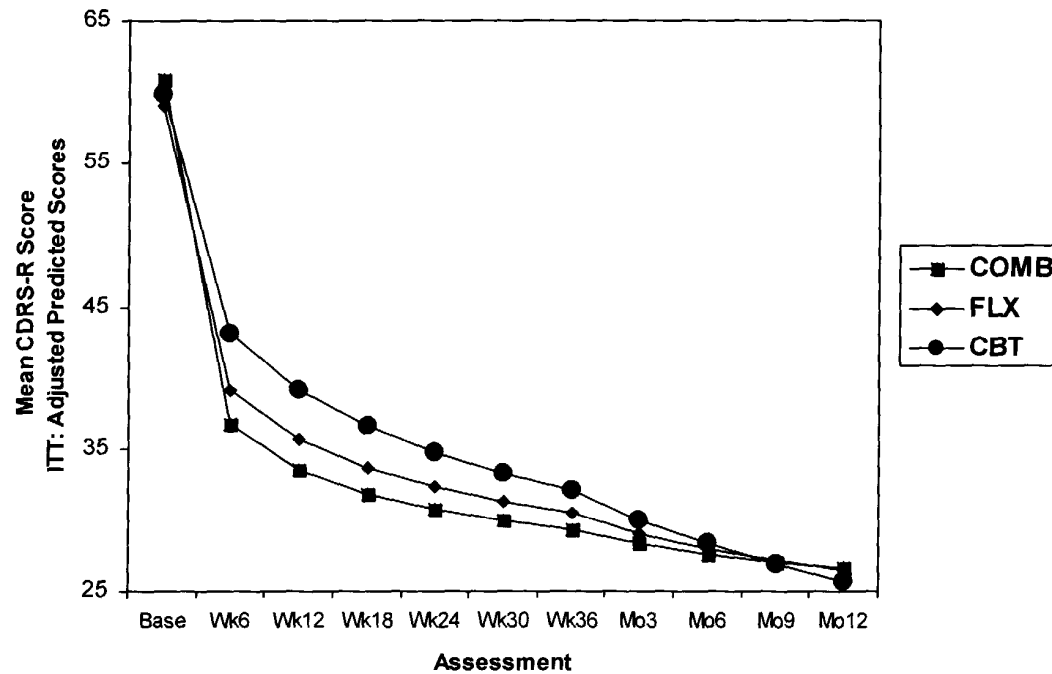
36 Week Rates of Response (CGI)



	Week		
	12	18	36
CBT	48%	65%	81%
Flx	62%	69%	81%
Combo	73%	85%	86%

TADS 12 month follow-up

Figure 1 (N=327): Adjusted Predicted Baseline to End of Stage IV Scores on the CDRS-R




Are Gains Maintained?



- Sustained response defined as two consecutive CGI-I ratings of 1 or 2 ("full response")
- 95 patients (39%) did not achieve sustained response by week 12 (Comb: 29%; Flx: 33%; CBT: 58%)

Yes, It Appears They Are (at least for 36 weeks)



- Sustained response rates during Stages 2 & 3 were Comb: 80%, Flx: 62%, and CBT: 77% (ns)
- Of 147 patients (61%) who achieved sustained response by week 12, CBT patients were more likely than Flx to maintain gains (97% vs 74%). Combo was intermediate (89%)
- Total sustained response at week 36 (Comb: 88%, Flx: 83%, CBT: 75%)

What Can be Said About Maintenance?



- Most depressed youth who do not achieve sustained improvement within 12 weeks will achieve that level with additional treatment— *stay the course* with continuation treatment.
- CBT may help youth who achieve early sustained response maintain their gains

Does CBT Work?

“Robust ” Early Support



- Reinecke et al. (1998)
ES = 1.02 n=6 (CBT only)
- Lewinsohn & Clarke (1999)
ES = 1.27 n=12
- Michael & Crowley (2002)
ES = 0.72 n=14

The Broader View of the Literature

“Curb Your Enthusiasm”



- Weisz, McCarty, & Valeri (2006)

Review of 35 controlled studies (31 of CBT)

Effect size = **.34** $Z=4.57$ $P<.01$

Effects show generality and specificity

“Effects are significant, but modest in their strength, breadth, and durability”

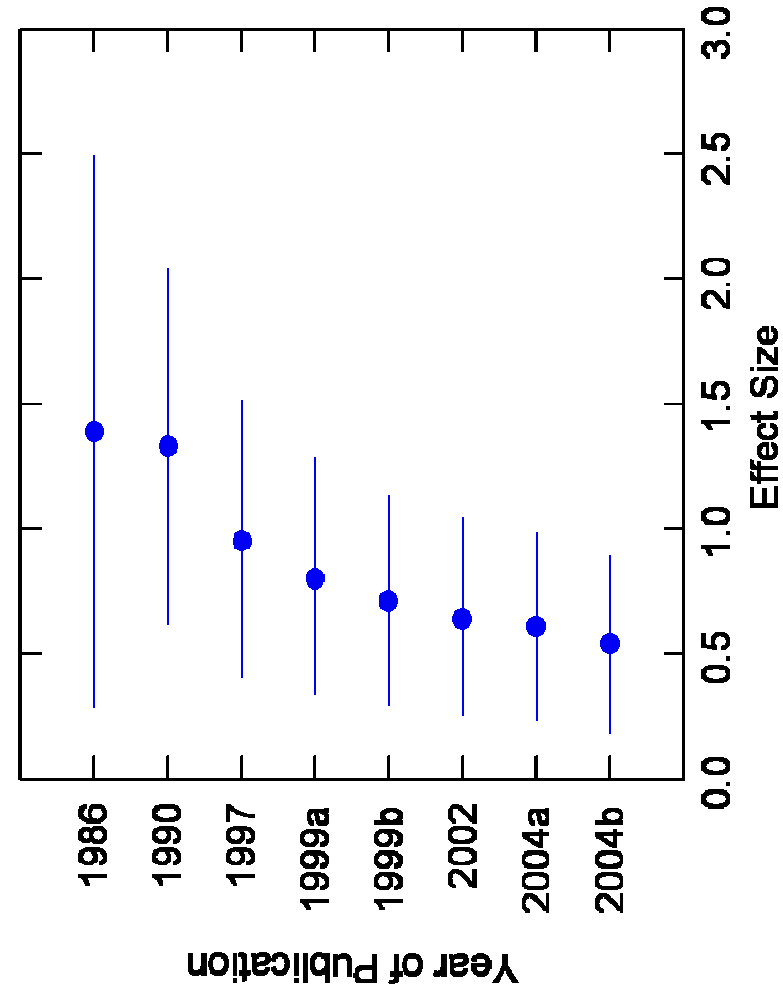
Why the Decline?

(Klein, Jacobs, & Reinecke, 2007)



- A common pattern in outcome research
- Increasingly severe, chronic, comorbid, and functionally impaired participants
- More stringent control conditions, randomization
- Fixed effects requires homogeneity of ES across samples (RRM may be preferred)
- ITT rather than completer analysis
- Reliance on published, peer-reviewed findings


Figure 3. Cumulative effects and 95% confidence intervals for CBT by publication year.



1986 = Reynolds & Coats. 1990 = Lewinsohn et al. 1997 = Brent et al. 1999a = Rossello & Bernal. 1999b = Clarke et al. 2002 = Clarke et al. 2004a = Rohde et al. 2004b = TADS.

What Do We Need to Know?

Basic Science- I



- Interaction of cognitive, biological (genetic, HPA), and social in contributing to risk, onset, course, relapse, treatment response
- Diagnostic validity – We may not be carving nature at its joints
- Comorbidity, negative affectivity

What Do We Need to Know?


Basic Science- II



- Mechanism of link between life events and mood
- Genetic and social predictors of resilience
- Etiology of negative cognitive style
- Development; “sensitive” or “critical” periods

What Do We Need to Know?

Basic Science- III



- Nature, definition of “affect regulation”
- Adverse effects of stress and depression on brain structure and function; plasticity, neurogenesis
- How does treatment effect brain structure and function?
- No genes unequivocally linked with vulnerability

What Do We Need to Know? Treatment



- Many patients experience “low level” symptoms. How should we manage partial responders?
- Most patients relapse at least once. How should we approach relapse prevention? Boosters?
- Moderators-Which treatment for which patient?
- Sequencing and combining of treatments

What Do We Need to Know?

Prevention - I



1. How do we understand “resilience”? How should this guide prevention?
2. What are the effective components? Dismantling.
3. Timing of prevention efforts? Age? Dose?
4. Setting of efforts? Involve parents? Schools?

What Do We Need to Know?

Prevention - II



- Most studies involve youth with a history of depression. How do we prevent the first episode?
- Long-term effectiveness? Wash out in 2 years.
- Effects on co-morbid conditions? Social and academic adjustment?

