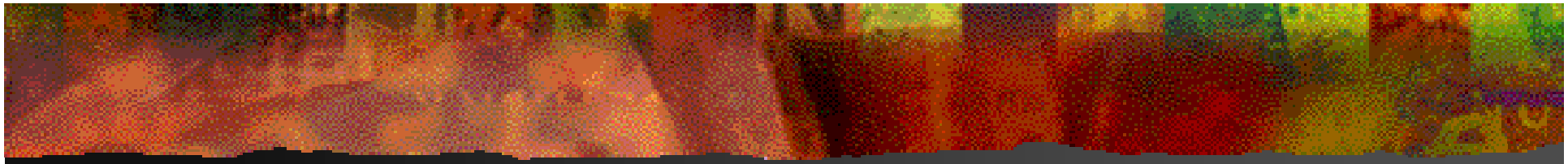

Adolescent Depression: Developing Treatments and Treating Development

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Workshop on the Science of Adolescent Health and Development

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Washington, DC

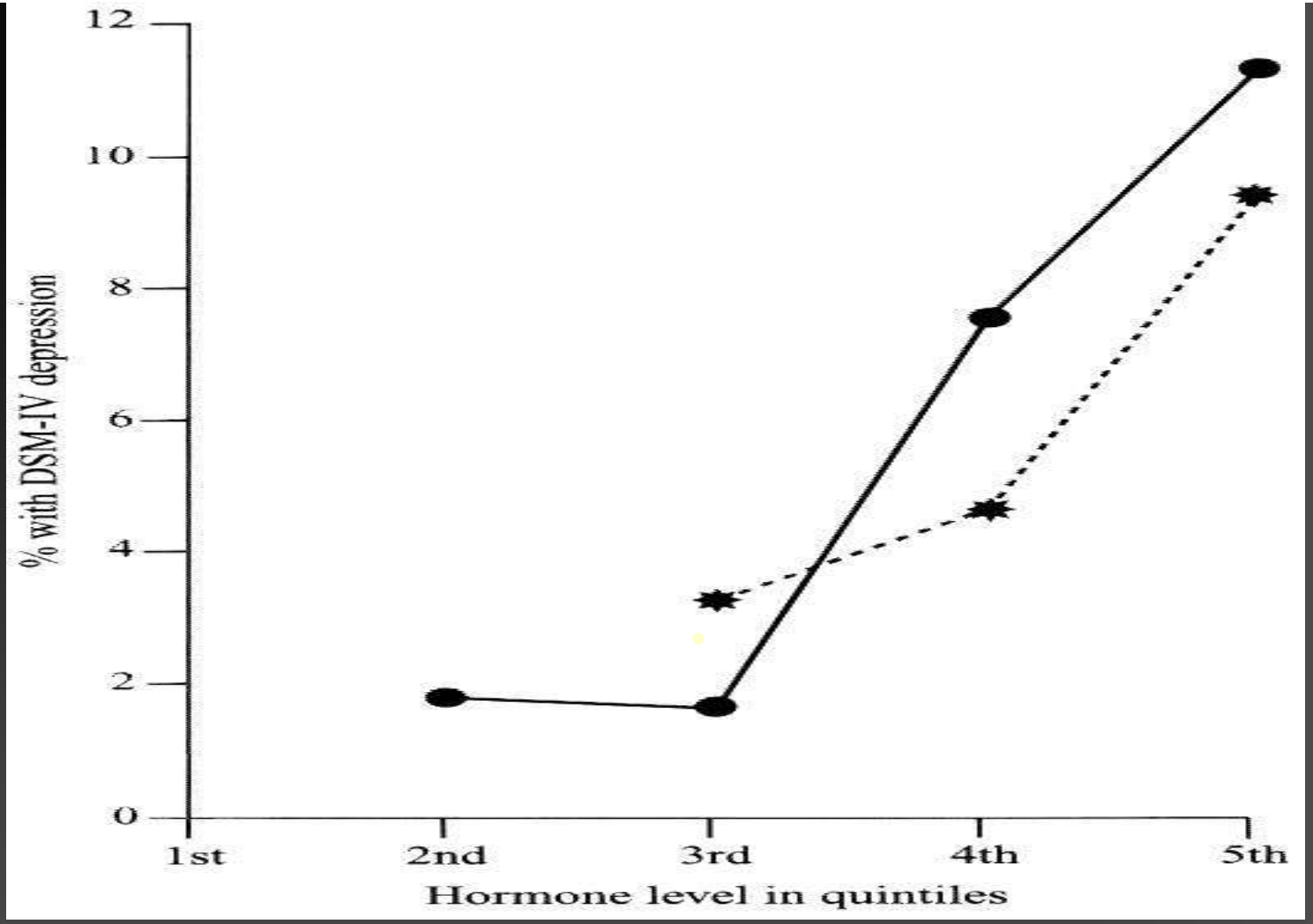
Objectives

- Review salient factors that influence onset and course of adolescent depression
- Review efficacy, adverse events, predictors of outcome of antidepressants, CBT, and IPT
- Discuss how treatment could be improved by broadening context of intervention and outcome
- To include achievement of age appropriate developmental tasks and enhancing overall health

Depression in Children and Adolescents

Point of Prevalence	1-2% in children 3-8% in adolescents
Lifetime risk by end of adolescence	20-30%

After Puberty 2:1 Female:Male Ratio



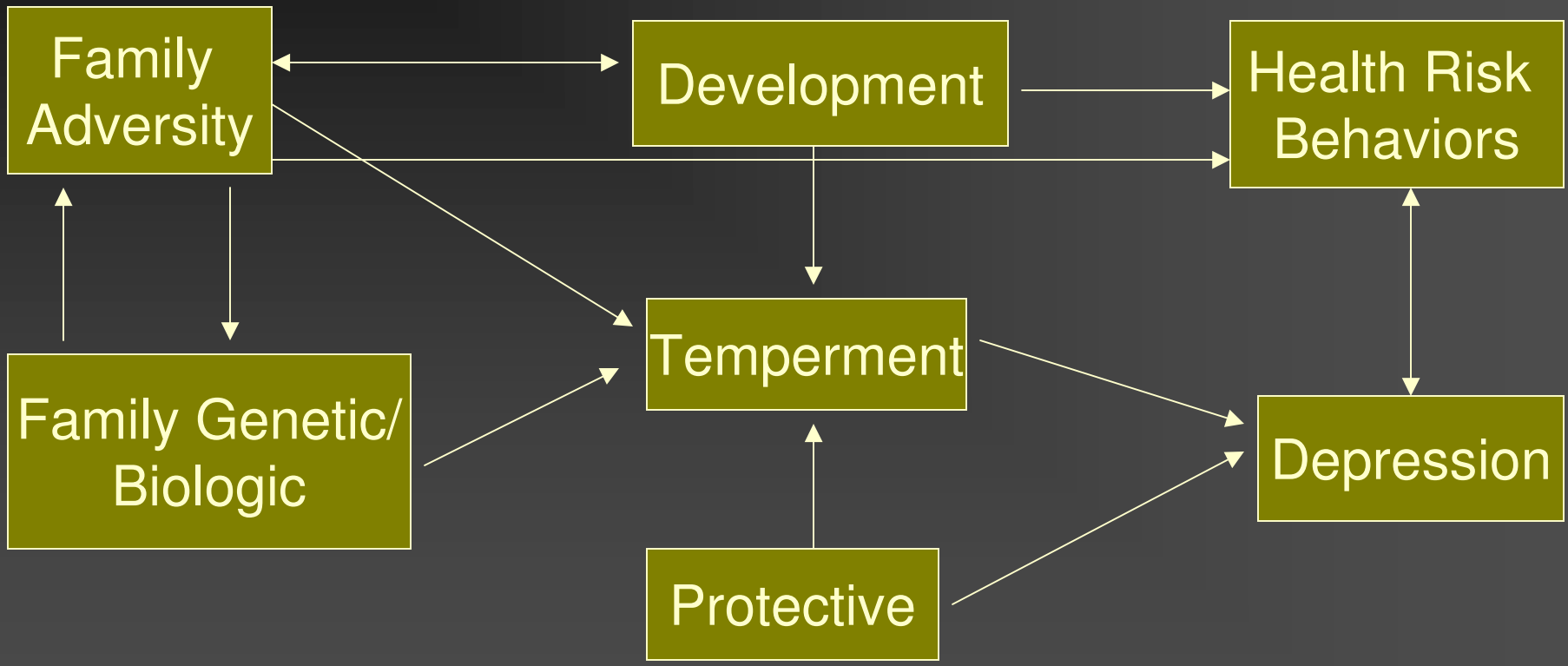
Hormonal effects on depression ([black circle, horizontal bar, black circle], testosterone; (Symbol)**, oestradiol).**

Angold et al. (1999)

Course: Chronic and Recurrent

Episode Length:	8 months
Recurrence rate in 2 years	40%
Recurrence rate in 5 years	72%
Recurrence rate by Adulthood	~100%

Overview of Risk and Protective Factors



Development

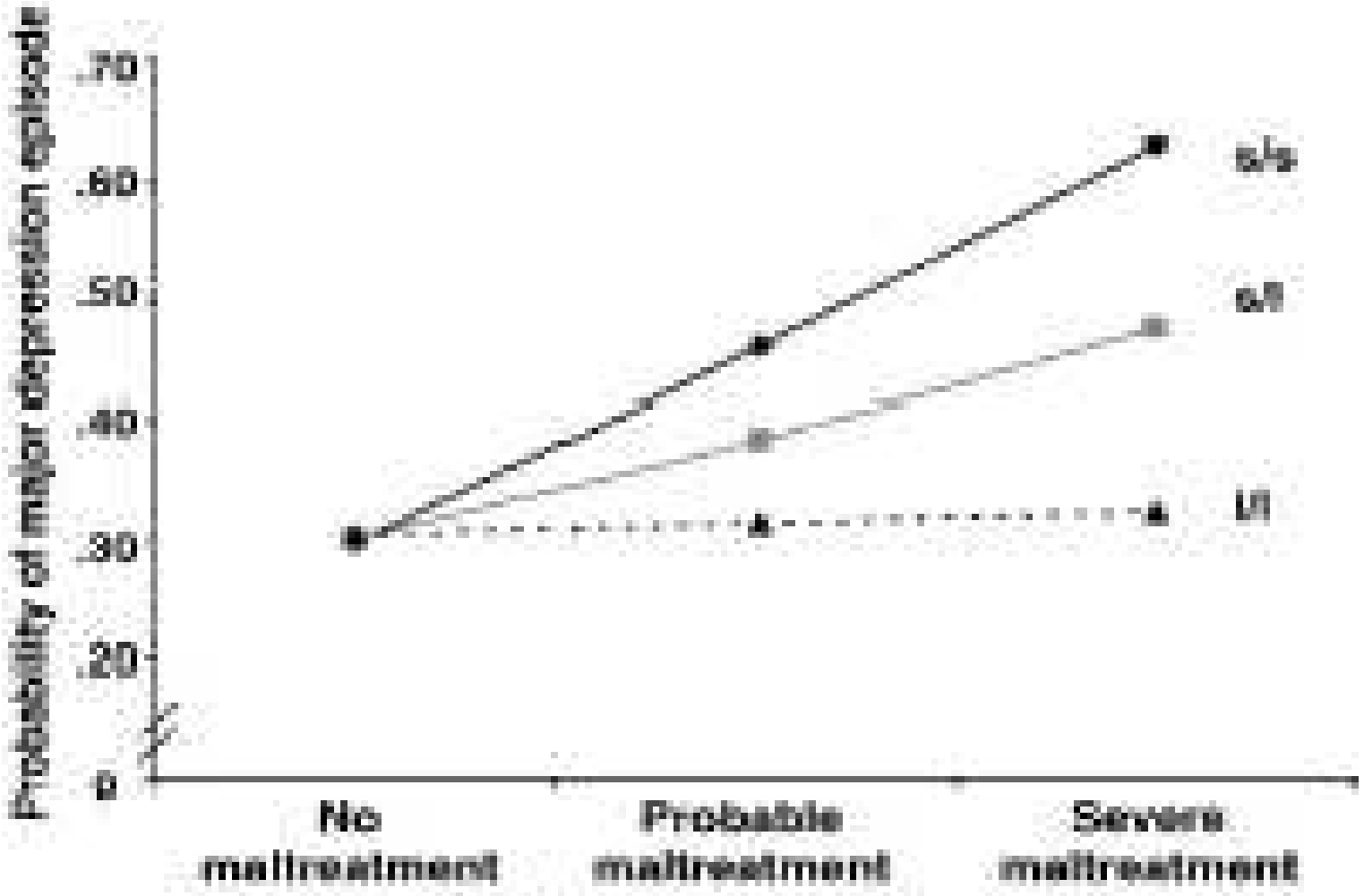
- Early puberty in girls (related to maternal depression, conflict)
- Increased risk-taking and experimentation with sex, thrill-seeking, tobacco and substances
- Increase sleep “deficit”
- Greater parent-child conflict
- Decreased adult supervision
- Cognitive distortions become fixed

Family Adversity

- Parent-child discord
- Abuse/Domestic violence
- Parental criminality
- Parental substance abuse
- Loss

Family Genetic/Biologic

- Parental depression and anxiety
- Adolescents > prepubertal depression re: genetics
- Altered serotonergic/noradrenegic neurotransmission
- Altered serotonin associated with adverse environment



Caspi et al. (2003)

Temperment

- Neuroticism
- Cognitive distortions
- Rumination
- Anxiety

Protective Factors

- Parent-child connection, supervision, expectations
- Family leisure time together
- School-child connection and achievement
- Prosocial peer group

Associated Health Risk Behaviors

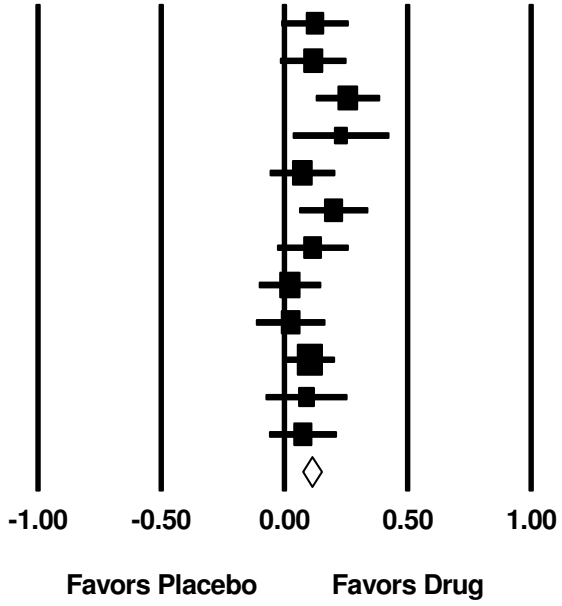
- Related to adversity rather than depression per se
- Tobacco and substance abuse (bidirectional, although depression moderates risk, impact on serotonin)
- Obesity (decreased activity in depression)
- Early sexual experience and pregnancy
- Lower school and occupational attainment

Antidepressant Treatment

- TCAs not efficacious
- SSRIs, NNT 5-10
- Adolescents > children (Venlafaxine, Paroxetine)

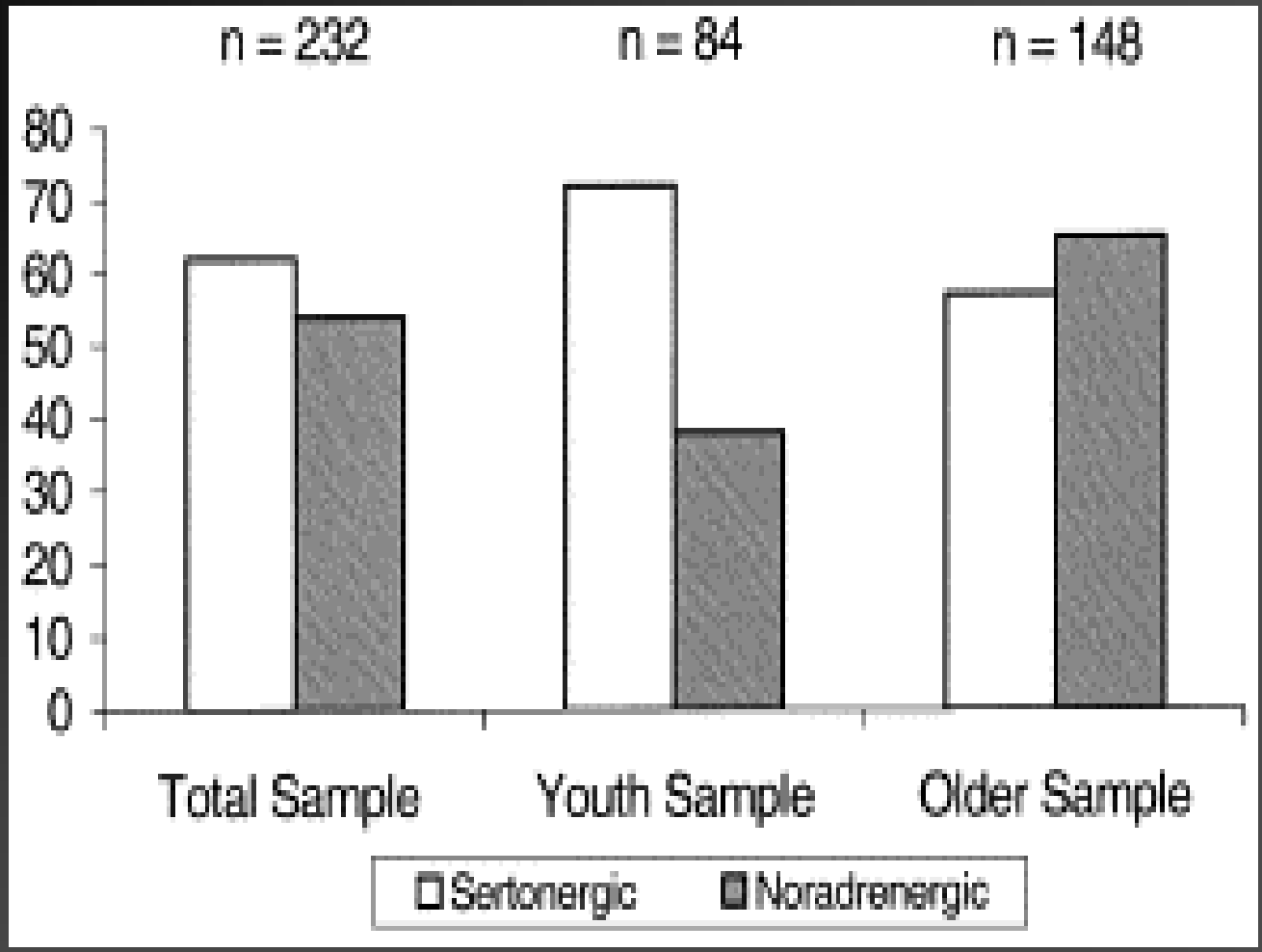
Differences in Response Rates Between Antidepressant and Placebo Groups: MDD Studies

Study name	Outcome	MH risk difference	p-Value
Citalopram (CIT-MD-18)	CDRS (response)	0.124	0.070
Fluoxetine (HCJE)	CDRS-R Response	0.117	0.083
Fluoxetine (TADS)	CGI-I (response)	0.257	0.000
Fluoxetine (X065)	CGI-I (response)	0.229	0.020
Mirtazapine (003-045)	CGI-I (response)	0.073	0.273
Nefazadone (CN104-141)	CGI-I (response)	0.199	0.004
Paroxetine (329)	HAM-D<=8/50% (Response)	0.115	0.115
Paroxetine (377)	MADRS50 (response)	0.022	0.728
Paroxetine (701)	CGI-I (response)	0.025	0.721
Sertraline (A0501001 & A0500175)	CDRS (response)	0.104	0.038
Venlafaxine (382)	CGI-I (response)	0.089	0.287
Venlafaxine (394)	CGI-I (response)	0.074	0.279
		0.113	0.000



Developmental effects on SSRI response

- Younger individuals metabolize SSRIs more quickly
- In young, serotonergic agents > noradrenergic agents; in older, they are equivalent
- In young adults, 5HT transporter s allele does not predict response, in older adults it does



Percentage of patients in remission (i.e., HAM 17 ≤7) by age group and drug type

Mulder et al. (2003)

Citalopram Pharmacokinetics: Steady State Half-Life at 20 mg (hrs)

Isomer	Adolescent[1]	Adult[2]
S	16.9	32.7
R	30.4	54.3

[1]Perel, et al, 2001
[2]Sidhu, et al., 1997

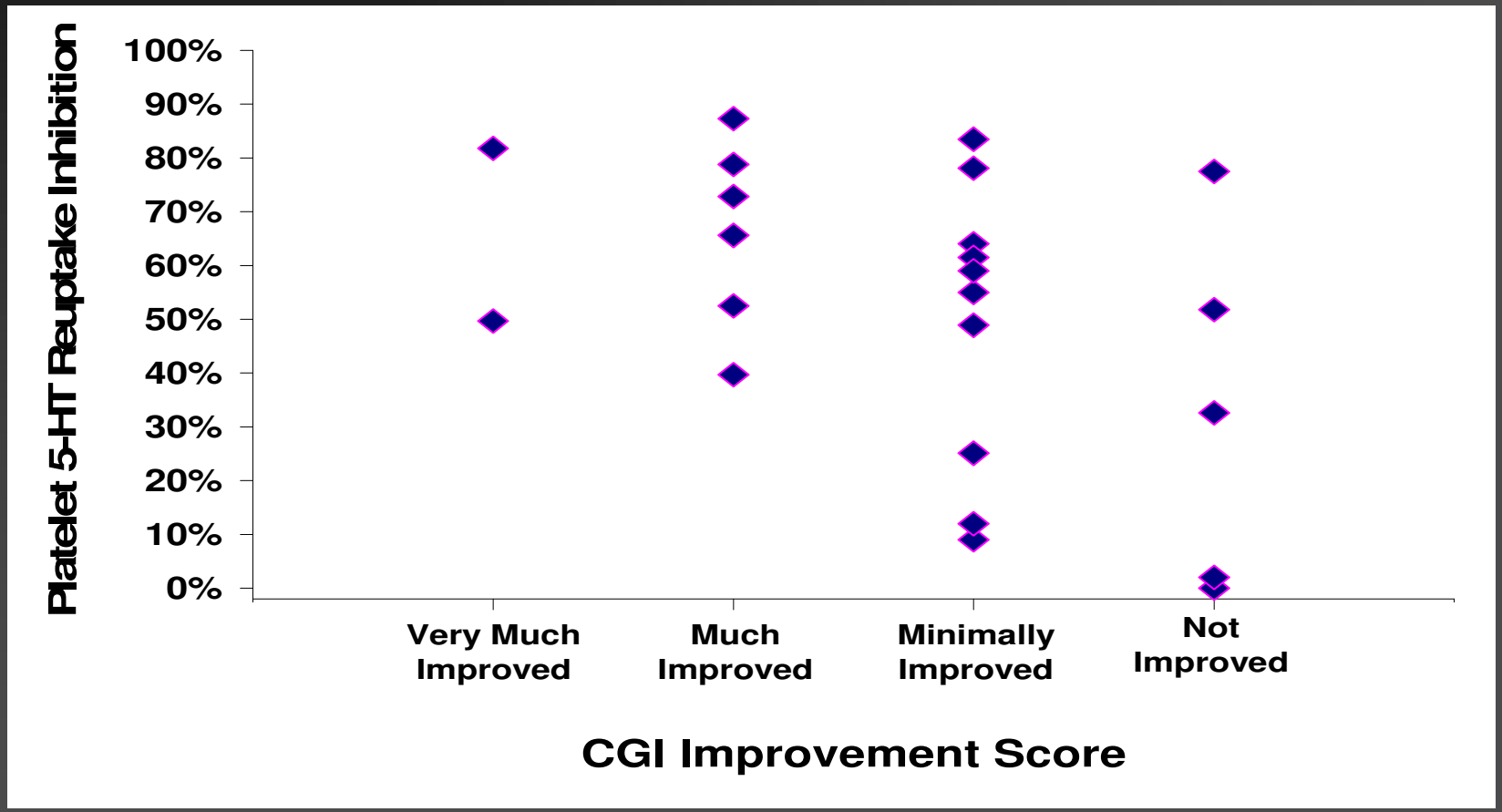
Suicidality and SSRIs

- 1.8-fold increased risk, NNH=50
- Mostly ideation and threats, few attempts, no completion's
- Related to family history, intake ideation and depression, increase in hostility
- ? Withdrawal, akathisia, disinhibition, mixed state

Predictors of Response

- SSRI reuptake inhibition (Axelson et al., 2005)
- Comorbidity
- Chronicity
- Severity
- Family discord
- Adequate dose and duration

Platelet Serotonin Reuptake Inhibition by CGI-Improvement Score

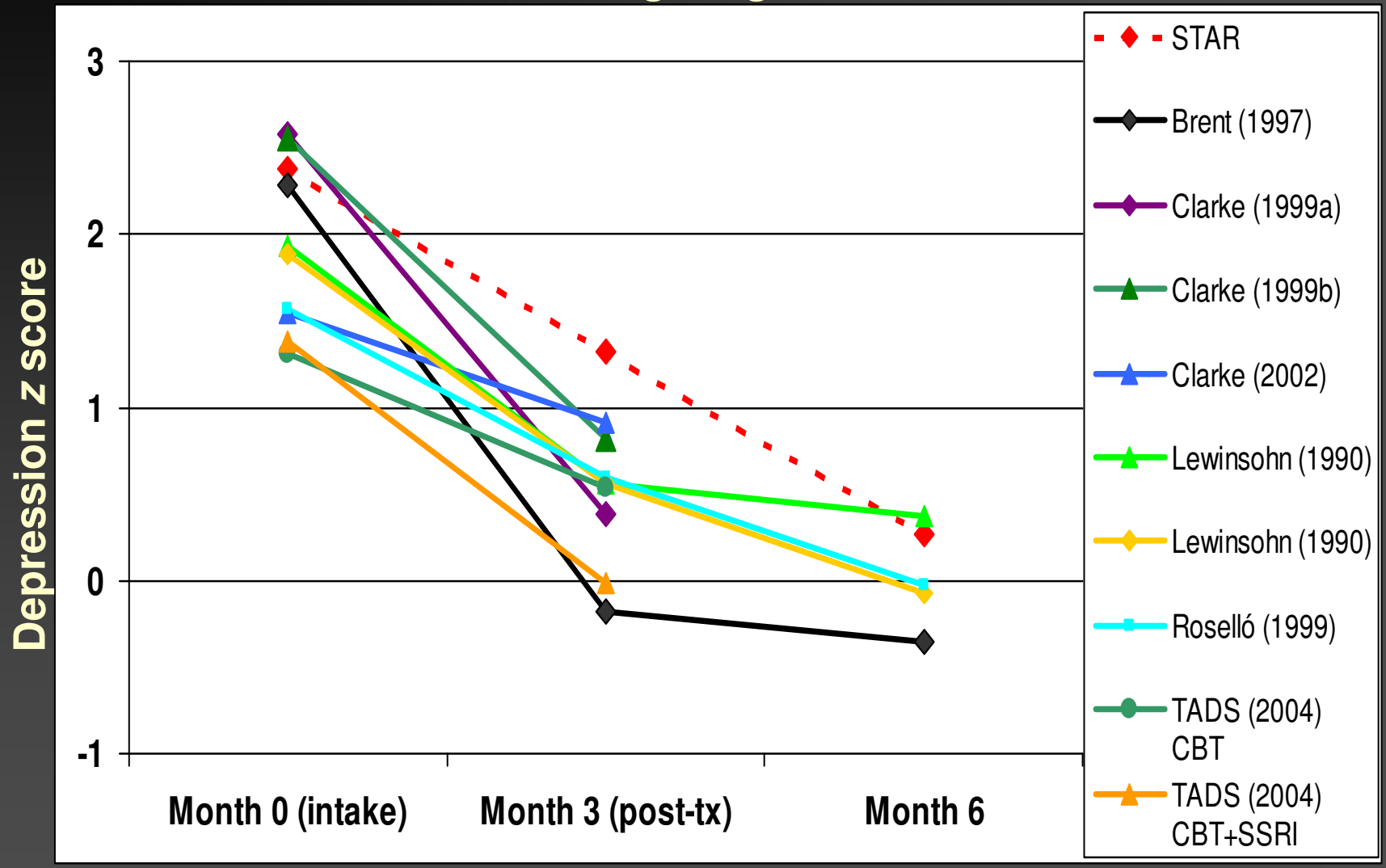


Axelson et al. (2002)

CBT

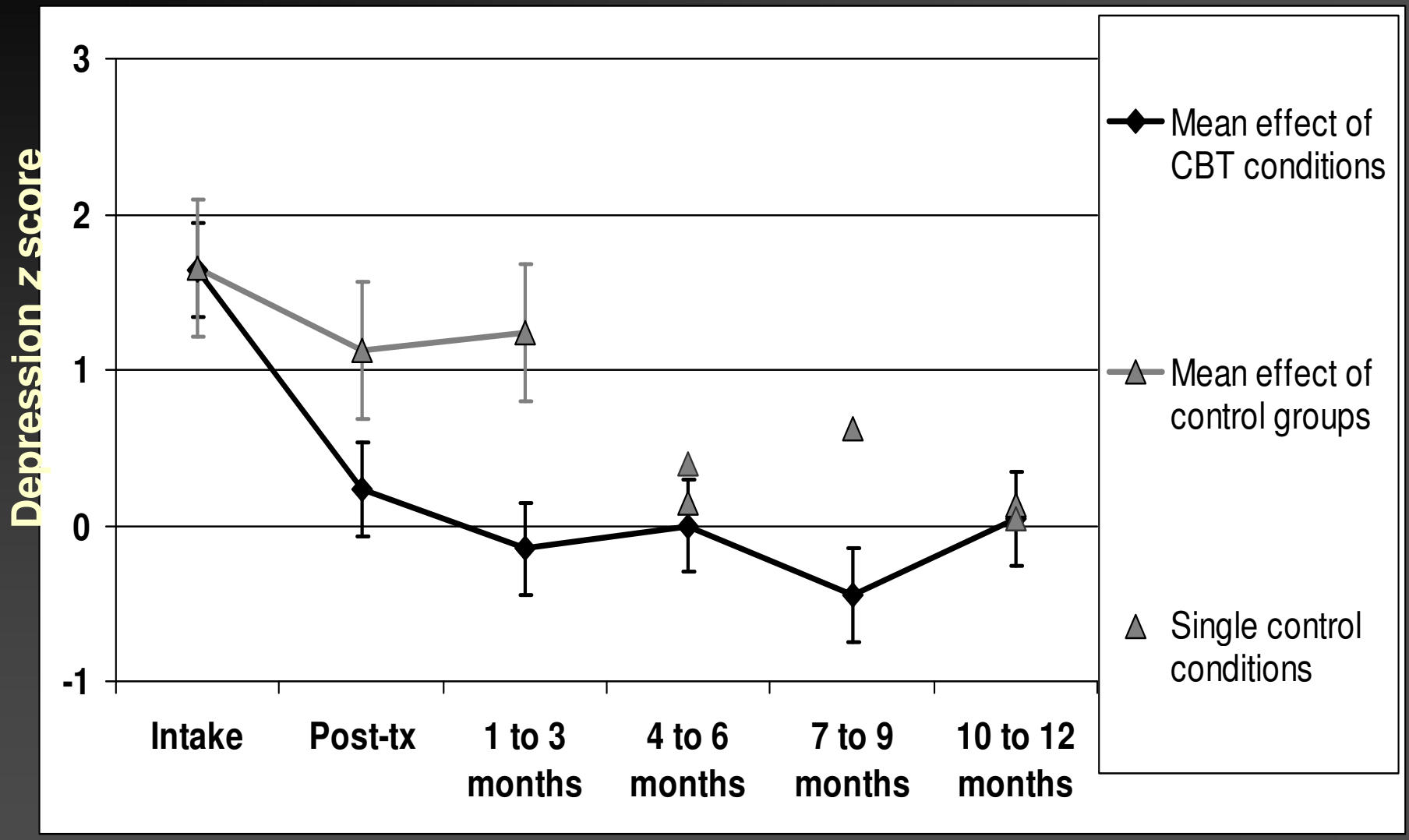
- Behavior activation
- Cognitive restructuring
- Social skills
- Almost all studies CBT > WLC, FT, ST, RL

Converging Evidence:
Data from CBT RCTs Targeting MDD in Adolescents



Weersing & Weisz (2002)

Efficacy of CBT for Youth Depression



Weersing & Weisz (2002)

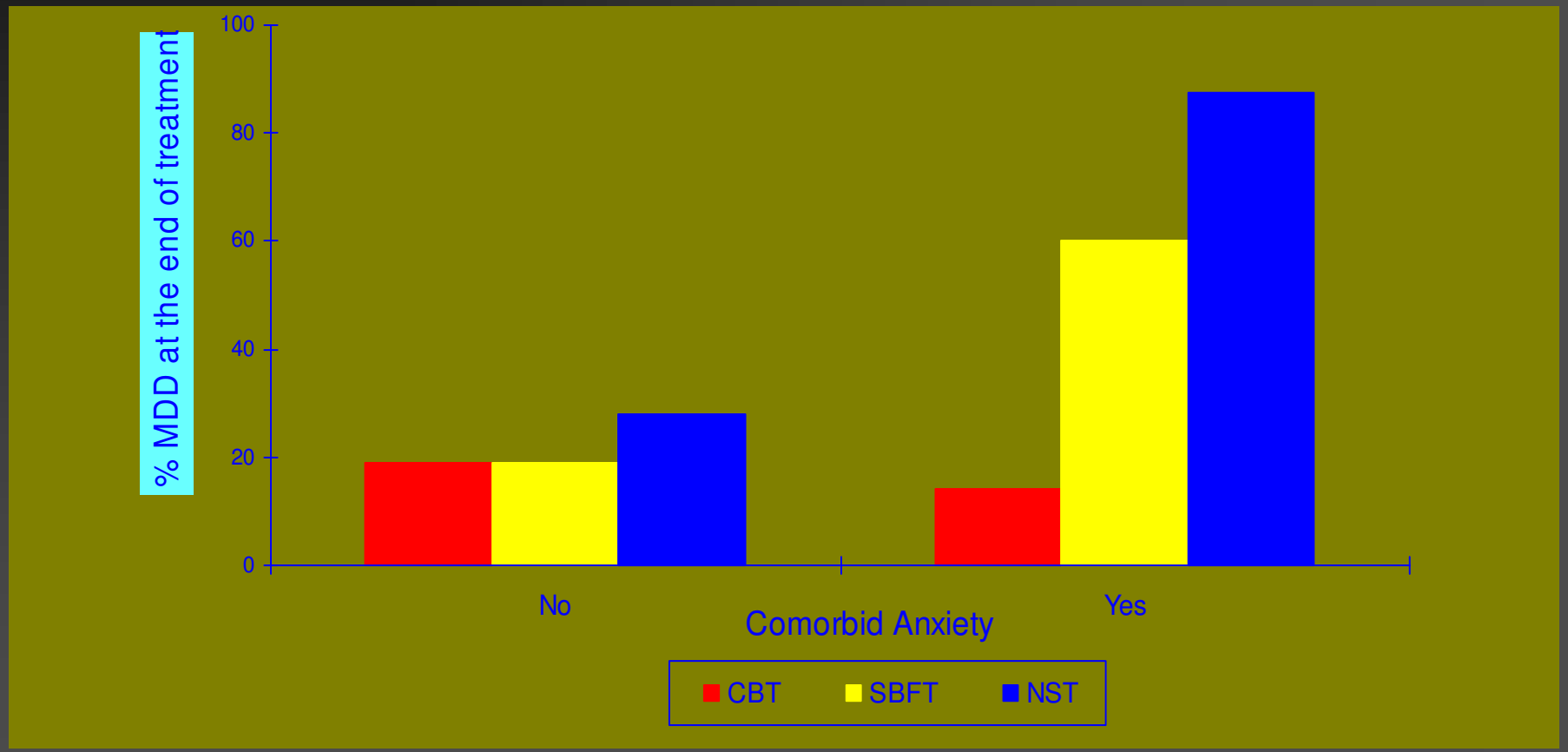
TADS and CBT: Why was CBT=PL?

- CBT used-low dose of many techniques
- Not blind to medication assignment
- Combined treatment recommended, but for CGI-I, adjusted endpoints, more severe depression, CBT + FL = FL

Predictors of Outcome

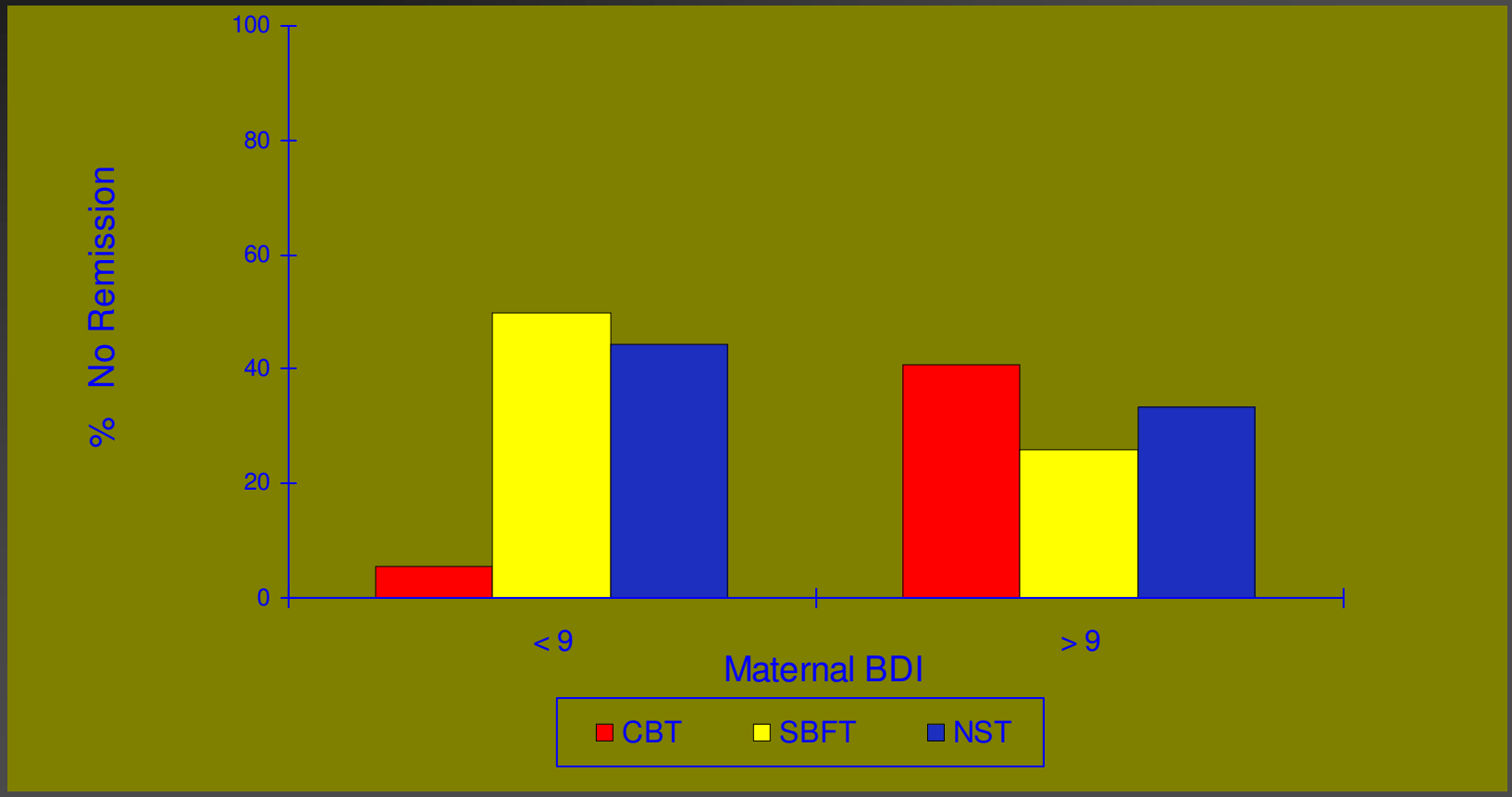
- Age (younger more efficacious)
- Cognitive distortion, hopelessness, severity
- Comorbid anxiety, ADHD, substance abuse
- Advertisement
- Anxiety
- Parental depression
- Sexual abuse
- Change in cognitive distortion predicts response (age moderates)

Depression at the end of Treatment as a Function of Comorbid Anxiety*



* Brent et al. (1998)

Failure to Achieve Remission as a Function of Self-Reported Maternal Depression (BDI)*



* Brent et al. (1998)

IPT

- Focus on interpersonal relations
- Role dispute, transition, peer or parent conflict, loss, single parent family
- Developmentally appropriate
- More severe: IPT > CM
- Relatively easy to disseminate

IPT for Adolescent Depression: % Response

	IPT	CBT	CM	TAU	Prevent Relapse
Rosello 1999	82	59	-		+
Mufson 1999	75	-	46		+
Mufson 2004	50	-	-	34	+

How to Improve Depression Outcome

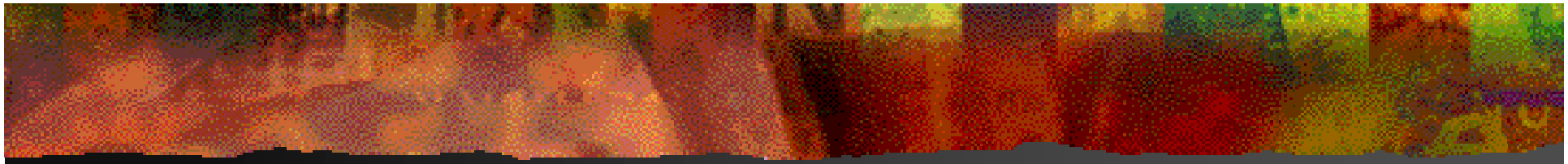
- Adequate dose, duration, continuation
- Education, and address hopelessness, to improve adherence
- Comorbidity (ADHD, substance abuse)
- Parental depression
- Family discord
- Sexual abuse
- Better understand heterogenetics in response (FG, PK, PD, PG, FMRI)

Reducing Intercorrelated risks (? In Continuation Phase)

- Problem-solving, emotion-regulation
- Prosocial peer group
- Modify parental supervision, connection, expectations
- Improve school connection
- Increase physical activity

Recommendations

- Treatment goals should be tied to the accomplishment of adolescent developmental tasks
- Use what is known about non-response to modify treatment
- Importance of contextual protective factors and associated health risks in treatment planning
- Need to study psychosocial and biological factors likely to explain individual differences in treatment outcome



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