

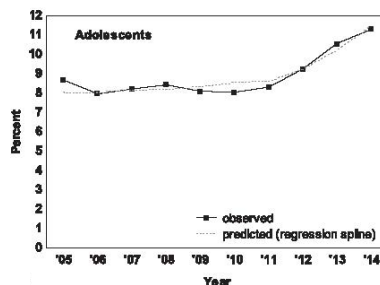


Personalizing Treatment For Adolescent Depression: Challenges And Opportunities

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 University of Minnesota

The Public Health Problem of Adolescent Depression

12-month Prevalence of MDEs in Adolescents in the US



Mojtabai et al, 2016

Psychiatric Diagnoses by Gender in Suicide Victims

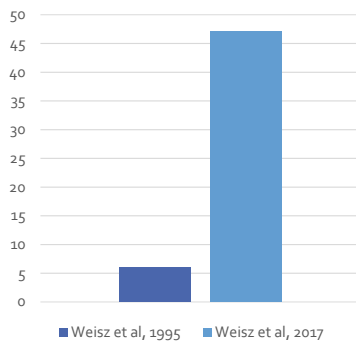
	Males		Females	
	Suicides (n = 119)	Controls (n = 91)	Suicides (n = 21)	Controls (n = 40)
Any psychiatric disorder	82.4	23.1†	81.0	27.5†
Any mood disorder	43.2	7.7†	71.4	15.0†
Anxiety disorder	12.6	1.1**	23.8	10.0
Substance abuse	35.3	4.4†	23.8	2.5*
Conduct/antisocial disorder	34.5	6.6†	10.0	7.5
Past attempt	36.9	1.1†	61.9	0.0†

* p ≤ .05; ** p ≤ .01; *** p ≤ .001; † p ≤ .0001.

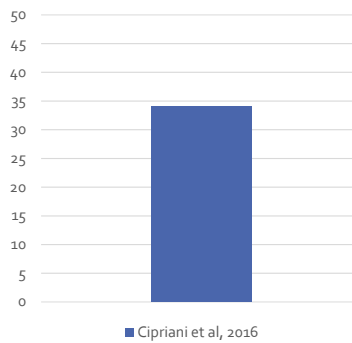
Brent et al, 1999

The Development of Interventions for Pediatric Depression has been a Research Priority

Number of Psychotherapy Trials Targeting Depression



Number of Medication Trials Targeting Depression



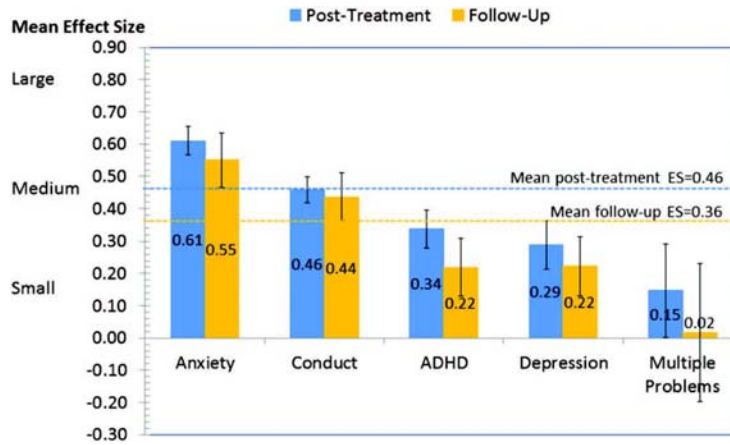
Evidence Base Update for Adolescent Depression Treatment: Summary Table

<i>Level 1: Well-Established</i>	<i>Level 2: Probably Efficacious</i>	<i>Level 3: Possibly Efficacious</i>	<i>Level 4: Experimental</i>	<i>Level 5: Not Effective</i>
Overall CBT Individual CBT Group CBT	Group IPT	Bibliotherapy CBT Family-based interventions	Technology-assisted CBT	
Overall IPT Individual IPT				

Note: CBT = cognitive behavioral therapy; IPT = interpersonal psychotherapy.

Weersing et al, 2017

Effect Sizes for Youth Psychotherapy are Lowest for Depression



Weisz et al, 2017

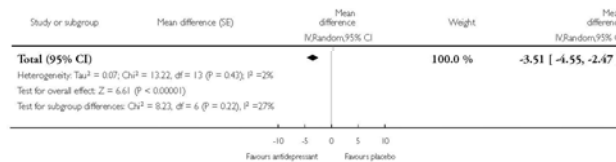
Antidepressants vs. Placebo: Mean Post-Treatment Differences are Small

Analysis 1.1. Comparison 1 Newer generation antidepressant versus placebo (by drug), Outcome 1 Depressive symptom severity (CDRS-R).

Review: Newer generation antidepressants for depressive disorders in children and adolescents

Comparison: 1 Newer generation antidepressant versus placebo (by drug)

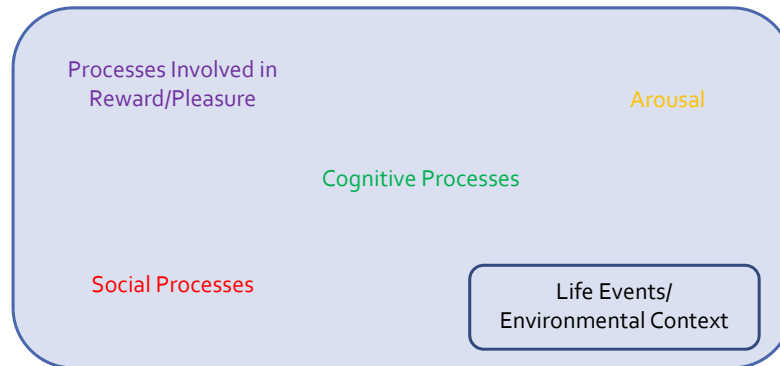
Outcome: 1 Depressive symptom severity (CDRS-R)



Hetrick et al, 2012

Depression is a Heterogeneous Disorder

- Many underlying psychological constructs contributing to the development and maintenance of the disorder:



The Precision Medicine Movement

- To move beyond determining what interventions *work* to identifying which interventions *work for whom*
- To deliver interventions that are:
 - optimally matched to individual characteristics and needs
 - adapted over time to individual characteristics and needs

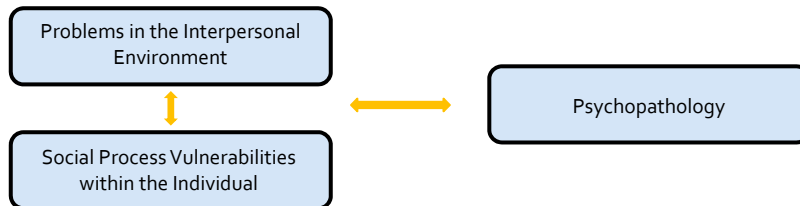
Which Intervention Should You Start With? Models of Psychotherapy Personalization

- The Compensation Model
 - The intervention is most effective for those individuals with the greatest difficulties in the areas targeted by the intervention
- The Capitalization Model
 - The intervention is most effective if it builds on an individual's strengths

Rude & Rehm, 1991

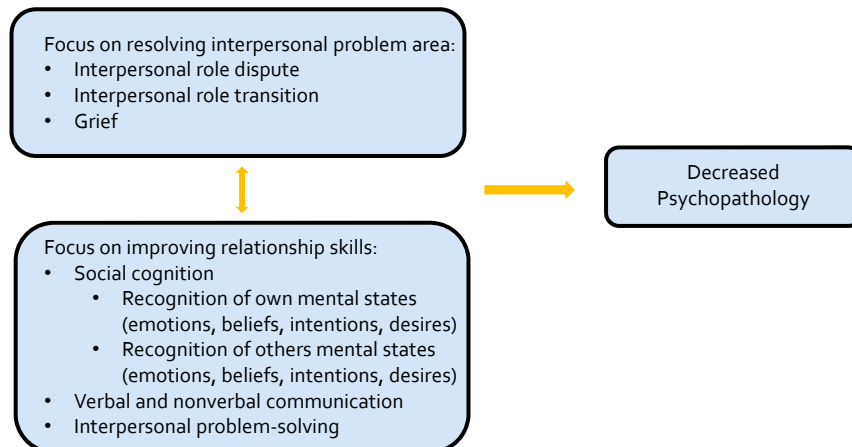
Social Processes:
Compensation or Capitalization Model
for Interpersonal Psychotherapy?

Interpersonal Psychotherapy



Mufson et al, 2004; Weissman et al, 2000

Interpersonal Psychotherapy



Mufson et al, 2004; Weissman et al, 2000

Quality of Interpersonal Relationships & IPT-A

RCT in School-Based Health Clinics (Mufson et al, 2004)

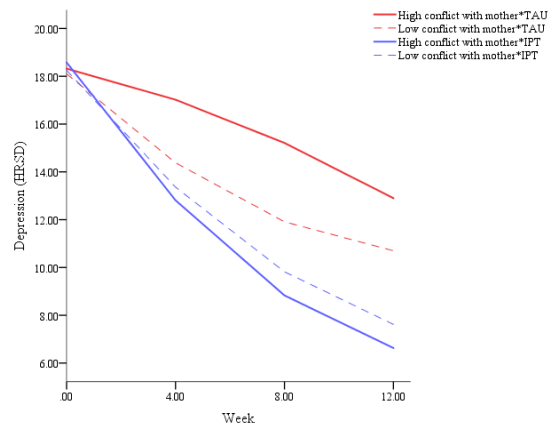
- IPT-A
- Therapy as Usual (TAU): supportive psychotherapy
- 63 adolescents (age 12-18)
 - Mean age = 14.7 (SD = 1.9)
 - 84% female
 - 75% Hispanic, 14% African American, 2% Asian American, and 10% other
- Measures
 - Hamilton Rating Scale for Depression (HRSD)
 - Conflict Behavior Questionnaire (CBQ) – adolescent report on conflict with mothers
 - Social Adjustment Scale (SAS-SR) – family, friendships, school, dating

Gunlicks-Stoessel, Mufson, Jekal, & Turner, 2010

Trajectory of Depression (HRSD) Moderated by Conflict with Mother (CBQ)

RCT in School-Based Health Clinics (Mufson et al, 2004)

- IPT-A
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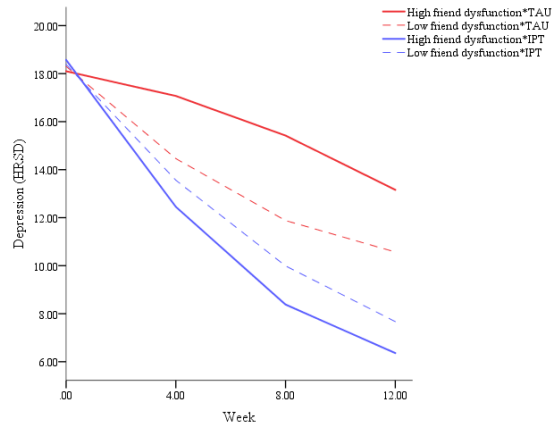


Gunlicks-Stoessel, Mufson, Jekal, & Turner, 2010

Trajectory of Depression (HRSD) Moderated by Social Difficulties with Friends (SAS-SR)

RCT in School-Based Health Clinics
(Mufson et al, 2004)

- IPT-A
- Therapy as Usual (TAU):
supportive psychotherapy
- 63 adolescents (age 12-18)
 - Mean age = 14.7 (SD = 1.9)
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- Measures
 - Hamilton Rating Scale for Depression (HRSD)
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 - Social Adjustment Scale (SAS-SR)



$b = 1.34, t(57) = 3.58, p = .001$

Gunlicks-Stoessel, Mufson, Jekal, & Turner, 2010

Attachment Style

- Attachment theory:
 - When individuals experience distress in response to a stressor, they seek out a significant other to help them regulate their distress and regain a sense of security.
- Two dimensions of attachment style:
 - Attachment Anxiety: an individual's threshold for detecting threats to security or possible rejection
 - Attachment Avoidance: the extent to which people rely on an attachment figure to regulate distress
 - Individuals who are low on both are securely attached.

Bowlby, 1973, 1980; Fraley & Shaver, 2000; Sroufe & Waters, 1977

Attachment Style & IPT-A

RCT (Gunlicks-Stoessel et al, 2016)

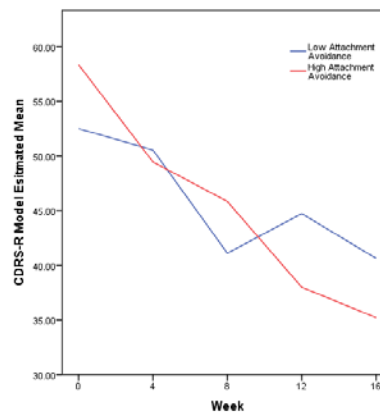
- IPT-A
- Insufficient responders augmented with increase # IPT-A sessions or fluoxetine (SSRI medication)
- 40 adolescents (age 12-17)
 - Mean age = 14.8 (SD = 1.8)
 - 77.5% female
 - 80% white, 7.5% Asian American, 7.5% American Indian/Alaska Native, 5% biracial, 10% Hispanic
- Measures
 - Children's Depression Rating Scale – Revised (CDRS-R)
 - Experiences in Close Relationships – Revised (ECR-R)
 - Attachment Anxiety
 - Attachment Avoidance

Gunlicks-Stoessel, Westervelt, Reigstad, Mufson, & Lee, in press

Trajectory of Depression (CDRS-R) Predicted by Attachment Avoidance

RCT (Gunlicks-Stoessel et al, 2016)

- IPT-A
- Insufficient responders augmented with increase # IPT-A sessions or fluoxetine (SSRI medication).
- 40 adolescents (age 12-17)
 - Mean age = 14.8 (SD = 1.8)
 - 77.5% female
 - 80% white, 7.5% Asian American, 7.5% American Indian/Alaska Native, 5% biracial, 10% Hispanic
- Measures
 - Children's Depression Rating Scale – Revised (CDRS-R)
 - Experiences in Close Relationships – Revised (ECR-R)
 - Attachment Anxiety
 - Attachment Avoidance



$F(1, 29) = 4.38, p < .05$

Gunlicks-Stoessel, Westervelt, Reigstad, Mufson, & Lee, in press

Physiological Response to Interpersonal Stress & IPT-A

- HPA Axis
 - Secretes cortisol under conditions of stress to marshal needed physical and cognitive resources
 - Hyperarousal of the HPA axis generally associated with depression
- RCT (Gunlicks-Stoessel & Mufson, 2016)
 - Individual IPT-A
 - IPT-A with parent involvement
- 15 adolescents (age 12-17)
 - Mean age = 15.2
 - 86.7% female
 - 93.3% Hispanic, 86.7% White, 6.7% African American, and 6.7% biracial
- Measures
 - Pre-treatment parent-adolescent conflict negotiation task
 - Adolescents and parents asked to spend 15 minutes describing and attempting to resolve a conflictual issue
 - Salivary cortisol collected pre-conflict and 10, 20, and 30 minutes post-conflict
 - Children's Depression Rating Scale - Revised

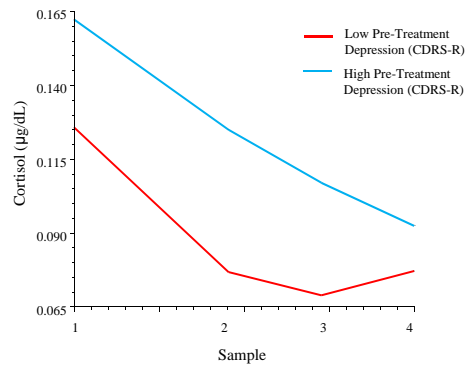
Gunlicks-Stoessel, Mufson, Cullen, & Klimes-Dougan, 2013

Physiological Response to Interpersonal Stress & IPT-A

Cortisol Sample	Timing	Description
1	Immediately prior to conflict task	Anticipation
2	10 mins post-conflict task	Conflict Discussion
3	20 mins post-conflict task	Recovery
4	30 mins post-conflict task	Recovery

Higher Pre-Treatment Cortisol is Associated with Higher Pre-Treatment Depression

Cortisol Sample	Timing	Description
1	Immediately prior to conflict task	Anticipation
2	10 mins post-conflict task	Conflict Discussion
3	20 mins post-conflict task	Recovery
4	30 mins post-conflict task	Recovery

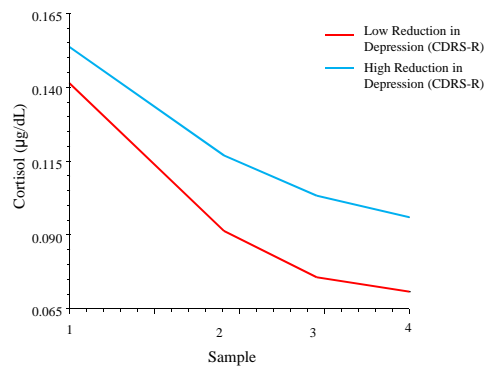


$b = .02, t = 2.20, p < .05$

Gunlicks-Stoessel, Mufson, Cullen, & Klimes-Dougan, 2013

Higher Pre-Treatment Cortisol Predicts Greater Reduction in Depression with IPT-A

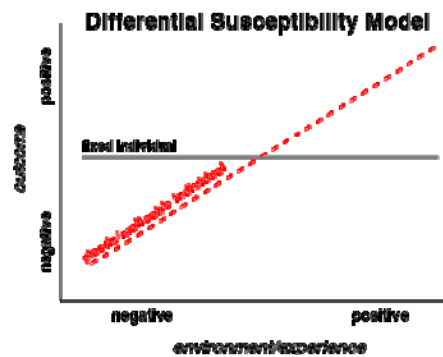
Cortisol Sample	Timing	Description
1	Immediately prior to conflict task	Anticipation
2	10 mins post-conflict task	Conflict Discussion
3	20 mins post-conflict task	Recovery
4	30 mins post-conflict task	Recovery



$b = .66, t = 3.94, p < .01$

Gunlicks-Stoessel, Mufson, Cullen, & Klimes-Dougan, 2013

Differential Susceptibility Theory



Belsky, 1997; Boyce & Ellis, 2005

Personalizing Psychotherapy for Adolescent Depression Based on Aspects of Social Processes

IPT-A

- Particularly effective for adolescents with:
 - High conflict with mothers
 - High levels of interpersonal difficulties with friends
 - High attachment avoidance
 - Greater physiological stress in the context of an interpersonal stressor

- Supports the **compensation** model

CBT

- Particularly effective for adolescents with:
 - Low conflict with mothers
 - Low problems in family relationships

Asarnow et al, 2009; Birmaher et al, 2000; Feeny et al, 2009

However, no studies have looked at the role of social processes in a trial that directly compared IPT-A and CBT.

A Limitation of the Existing Predictor/Moderator Studies

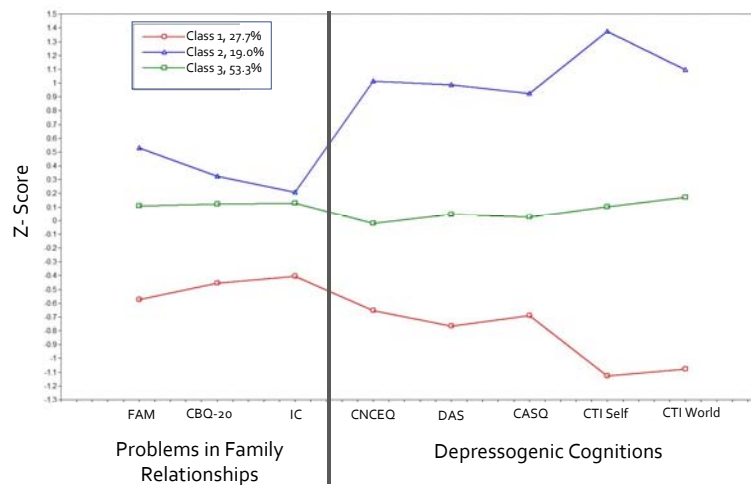
- Most studies have examined a particular predictor/moderator in isolation
- This implicitly assumes that there will be depressed youth who have elevations on only a single risk factor (e.g. interpersonal functioning).
- *To what extent are there youth who exhibit a high level of one risk factor and low levels on other risk factors such that a single risk factor can be used to guide treatment selection?*

Latent Profiles of Cognitive and Interpersonal Risk Factors for Adolescent Depression

Treatment of Adolescents with Depression Study (TADS)

- 439 adolescents (age 12-17)
 - Mean age: 14.6
 - 54.4% female
 - 73.8% White, 12.5% African American, 8.9% Hispanic
- Measures
 - Problems in Family Relationships
 - Family Assessment Measure (FAM)
 - Conflict Behavior Questionnaire – 20 (CBQ-20)
 - Issues Checklist (IC)
 - Depressogenic Cognitions
 - Children's Negative Cognitive Error Questionnaire (CNCEQ)
 - Dysfunctional Attitudes Scale (DAS)
 - Children's Attributional Style Questionnaire (CASQ)
 - Cognitive Triad Inventory (CTI view of the self, view of the world)

Latent Profiles of Cognitive and Interpersonal Risk Factors for Adolescent Depression



Gunlicks-Stoessel, Eckshain, Weisz, Mufson, Reigstad, & Lee, in preparation

Personalizing Initial Intervention Selection: Take Home Points

- In addition to assessment of psychiatric symptoms, intake assessments should include assessment of psychological constructs relevant for depression.
- Social processes show promise as a construct that can be used to guide decisions to treat with IPT-A versus CBT.

Personalizing Initial Intervention Selection: Future Directions for Research

- Clinical trials that include:
 - More than one active intervention
 - Assessment of the psychological constructs that each intervention aims to target for evaluation as possible moderators
 - Assessment of these constructs that move beyond self-report (behavioral, biological markers)
 - Analytic strategies that take into account the role of more than one psychological construct at a time
 - Analytic strategies that translate findings into practice-friendly tools (e.g. cutoff scores on measures)

Personalizing Interventions Over Time

Adaptive Treatment Strategies (ATs)

- Empirically-derived guidelines that recommend when, how, and for whom treatment should change
- Decision rules are based on patient characteristics and outcomes collected during the treatment process, such as patient response and adherence

Collins et al, 2004; Lavori et al, 2000

ATs Require Progress Monitoring

- Systematic and routine assessment and monitoring of symptoms/psychological processes over the course of treatment
- Recommended by practice parameters (AACAP, GLAD-PC)
- Research demonstrates that progress monitoring improves treatment outcomes
- Progress monitoring is rare
 - A review of EMRs from 3 large health care systems: only 32% of depressed adolescents had documentation of symptom monitoring following the initial intake

Harmon et al, 2007; Hawkins et al, 2004; Lambert et al, 2005; Lambert & Shimokawa, 2011; Lambert et al, 2001; Lambert et al, 2002; O'Connor et al, 2016; Whipple et al, 2003

ATs for Medication Management for Depression

- Texas Medication Algorithm Project (TMAP)
- Sequenced Treatment Alternatives to Relieve Depression (STAR*D)
- Treatment of SSRI-Resistant Depression in Adolescents (TORDIA)

Brent et al, 2008; Crimson et al, 1999; Rush et al, 2006

ATs for Psychotherapy for Depression

-

What Do We Need to Know to Develop an ATS for Psychotherapy for Adolescent Depression?

- **When** during the course of therapy should we decide whether to make a change?
- What are our criteria for deciding **whether** to make a change?
- If we make a change, **what** kind of change should we make?

Predicting Post-Treatment Response to IPT-A from Early Change in Depression Symptoms

- What is the optimal time point and depression reduction criterion that best predicts response at the end of IPT-A (12 sessions delivered within 16 weeks)?
- Receiver operating characteristic (ROC) analysis:
 - Area under the ROC curve (AUC) provides an indication of classification accuracy for each time point
 - Conducted for weeks 4, 8, and 12

Gunlicks-Stoessel & Mufson, 2011

What is the Best Time Point for Predicting Post-Treatment Response to IPT-A (12 sessions within 16 weeks)?

Time Point	AUC	SE	<i>p</i> value	95% Confidence Interval for AUC
Week 4 reduction	.78	.08	.01	.63 - .94
Week 8 reduction	.81	.08	.00	.66 - .97
Week 12 reduction	.89	.06	.00	.78 - 1.00

Gunlicks-Stoessel & Mufson, 2011

What is the Best Depression Reduction Criterion for Predicting Post-Treatment Response?

- ROC also provides an indicator of the degree of reduction in depression at a time point that produces the best combined sensitivity and specificity in predicting post-treatment outcome.
- Among adolescents offered 12 sessions of IPT-A within 16 weeks:
 - At week 4, a 20% reduction in depression symptoms signaled that post-treatment response was likely
 - At week 8, a 40% reduction in depression symptoms signaled that post-treatment response was likely

Gunlicks-Stoessel & Mufson, 2011

Two Questions for Developing an ATS Beginning with IPT-A

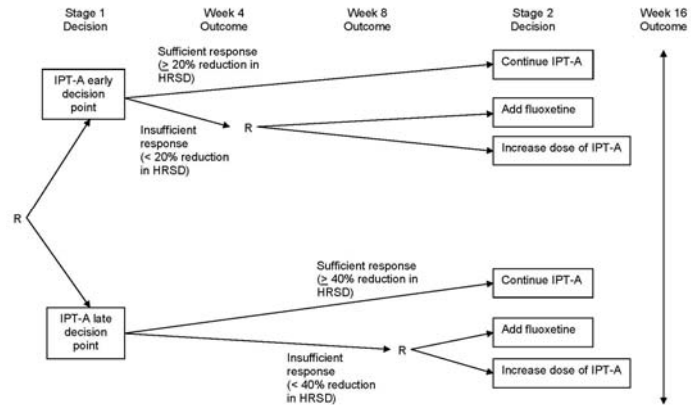
- Is it better to use an early decision point (week 4) or a late decision point (week 8) for identifying potential non-responders to IPT-A?
- Among adolescents who show an initial insufficient response to IPT-A, what kind of change in treatment should be made?
 - Augment
 - Increase the number/frequency of IPT-A sessions
 - Add medication
 - Switch
 - To a different psychotherapy
 - To medication only

Sequential Multiple Assignment Randomized Trials (SMARTs)

- Subjects can be randomized multiple times and these randomizations occur sequentially through time at selected critical decision points
- Results of the SMART trial are used to define the decision rules that make up the adaptive treatment strategy

Lavori & Dawson, 2000, 2003; Murphy, 2005

Pilot SMART Design



K23MH090216 Gunlicks-Stoessel (PI)



Participants (n = 40)

Age	M = 14.8 (SD = 1.8)
Sex	31 (77.5%) female 9 (22.5%) male
Ethnicity	4 (10.0%) Latino/Hispanic 36 (90.0%) not Latino/Hispanic
Race	3 (7.5%) American Indian/Alaska Native 3 (7.5%) Asian 32 (80.0%) White 2 (5.0%) More than one race
Annual income	Mode = \$90,000-\$179,999

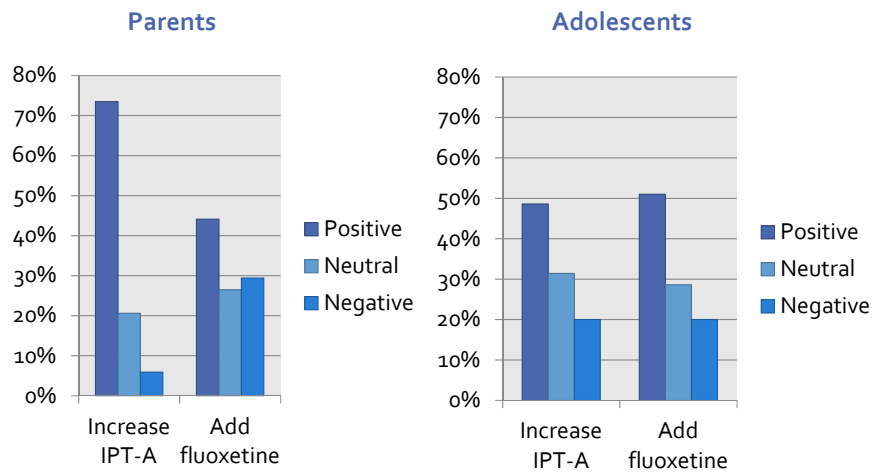
Participants (n = 40)

Depression dx	37 (92.5%) MDD 1 (2.5%) MDD + Dysthymic Disorder 1 (2.5%) Dysthymic Disorder 1 (2.5%) DD NOS
Baseline Depression Severity (CDRS-R)	Range = 38 (mild) – 73 (severe) M = 55.6 (SD = 10.5), t-score = 72
Comorbid dx	9 (22.5%) Generalized Anxiety Disorder 9 (22.5%) Social Anxiety Disorder 2 (5.0%) Panic Disorder 2 (5.0%) Specific Phobia 1 (2.5%) Anxiety NOS 2 (5.0%) Oppositional Defiant Disorder 3 (7.5%) ADHD

Measures

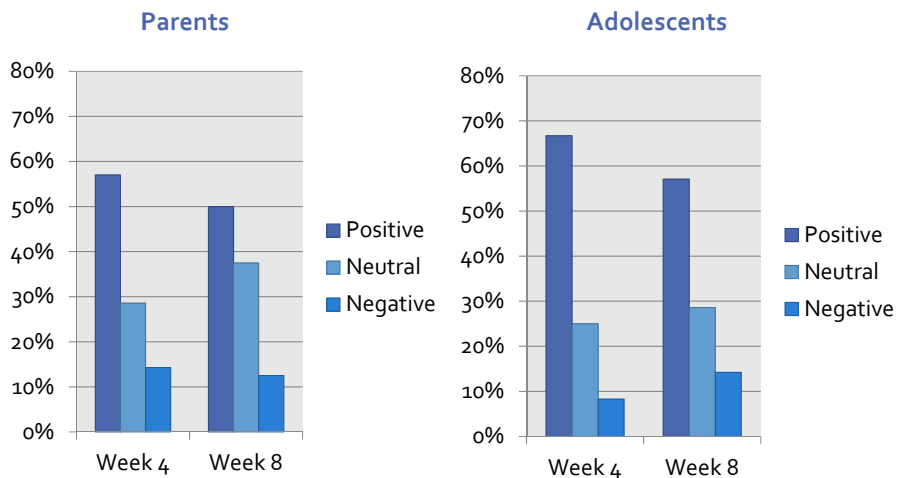
- Acceptability
 - Adaptive Treatment Attitudes Questionnaire
- Clinical outcomes assessed by blinded evaluators
 - Children's Depression Rating Scale-Revised (CDRS-R)
 - Children's Global Assessment Scale (C-GAS)
 - Social Adjustment Scale (SAS-SR)

Pre-Treatment Attitudes



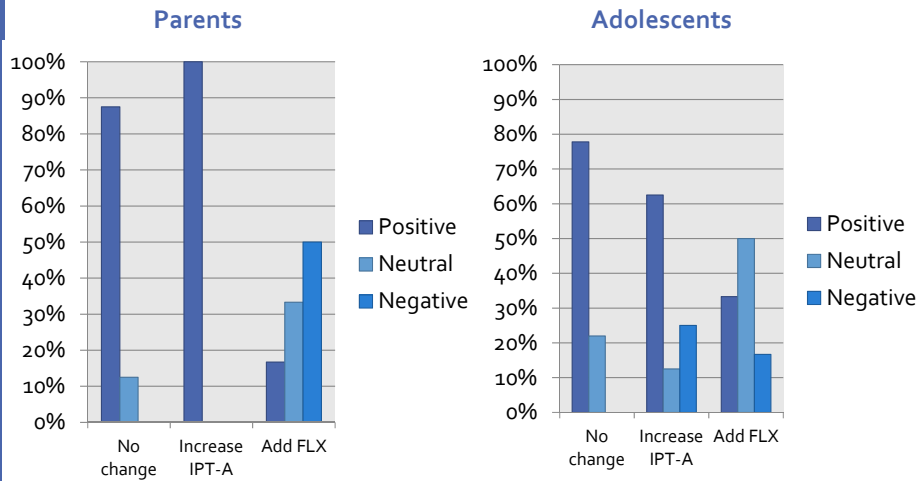
Gunlicks-Stoessel, Mufson, Westervelt, Almirall, & Murphy, 2016

Post-Decision Point Attitudes



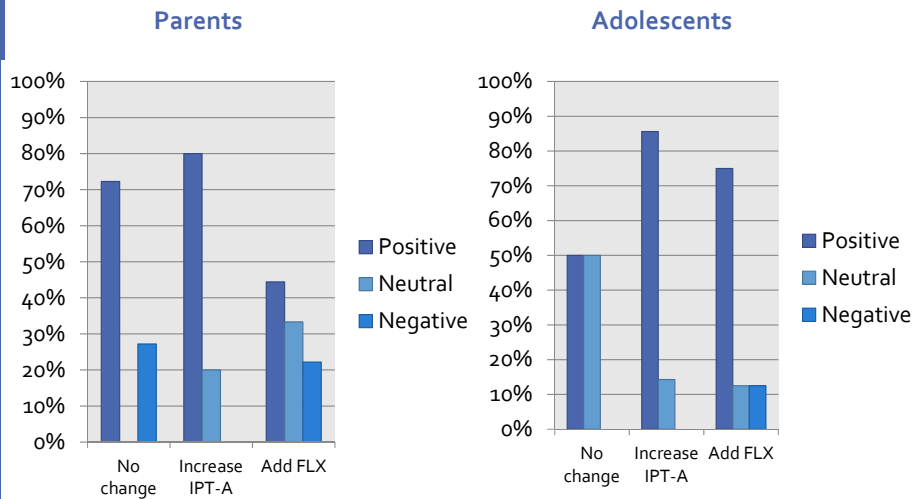
Gunlicks-Stoessel, Mufson, Westervelt, Almirall, & Murphy, 2016

Post-Decision Point Attitudes



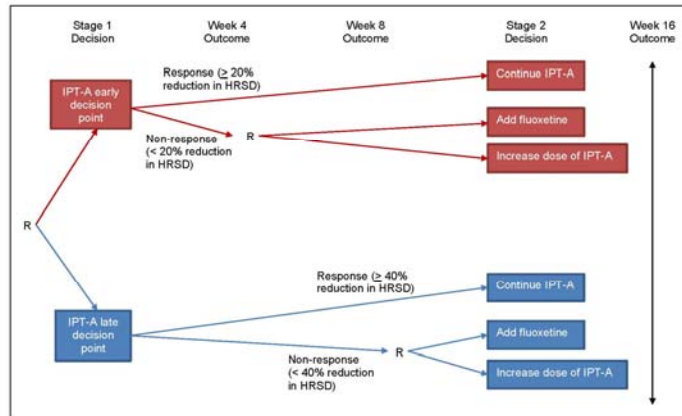
Gunlicks-Stoessel, Mufson, Westervelt, Almirall, & Murphy, 2016

Post-Treatment (Week 16) Attitudes

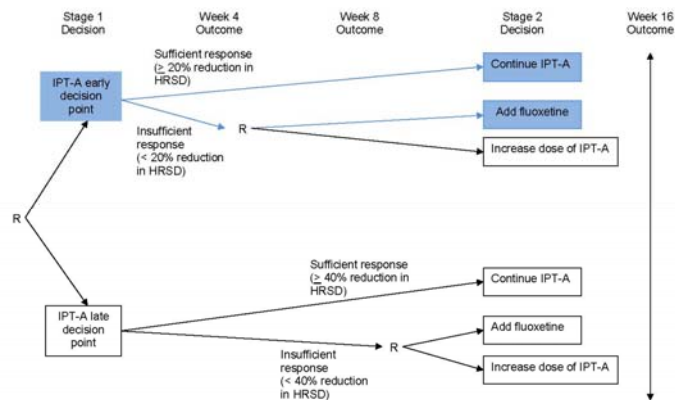


Gunlicks-Stoessel, Mufson, Westervelt, Almirall, & Murphy, 2016

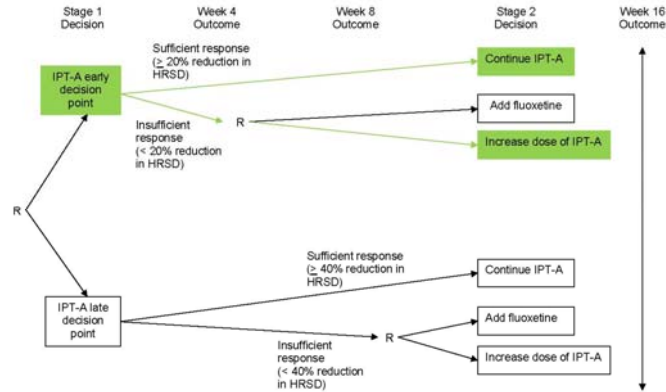
Early Decision Point vs. Late Decision Point



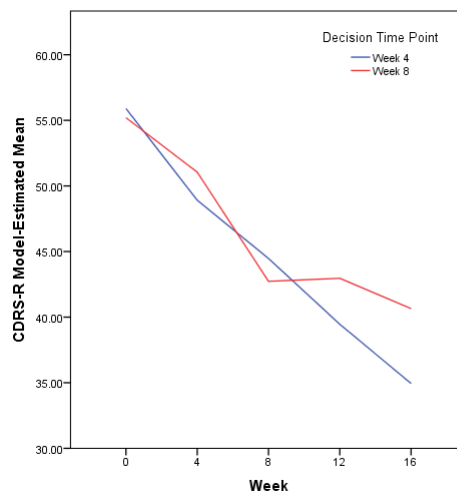
1 of 4 Adaptive Treatment Strategies



1 of 4 Adaptive Treatment Strategies

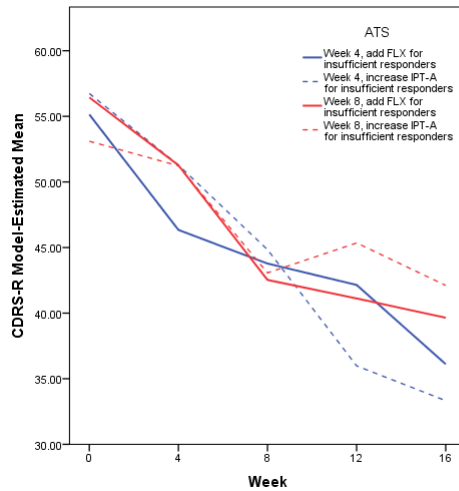


Depression (CDRS-R) by Decision Time Point



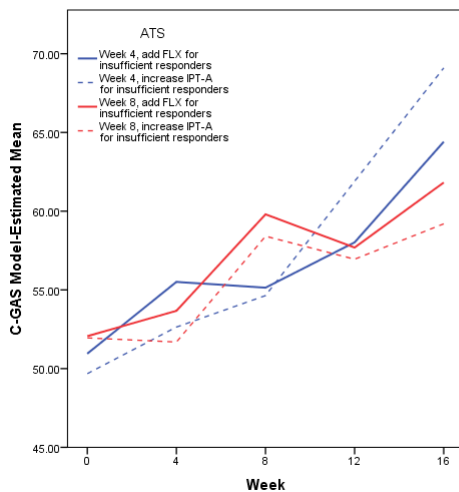
B = 5.72, t = 1.97, p = .049

Depression (CDRS-R)



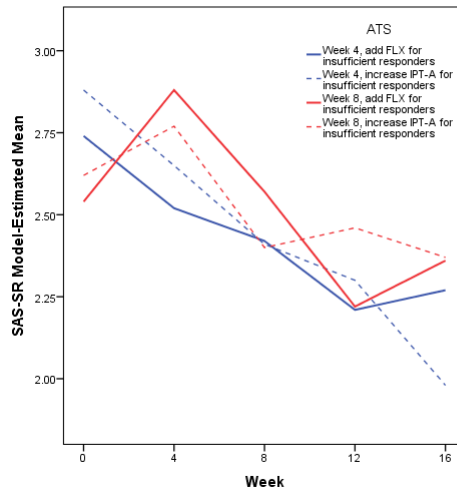
- Week 4 increase IPT-A < Week 8 increase IPT-A
B = 8.78, t = 2.96, p = .003
- Week 4 increase IPT-A < Week 8 add FLX
B = 6.32, t = 2.12, p = .034
- Week 4 add FLX < Week 8 increase IPT-A
B = 5.99, t = 2.09, p = .036

General Psychosocial Functioning (CGAS)



- Week 4 increase IPT-A > Week 8 increase IPT-A
B = -9.90, t = -2.86, p = .004
- Week 4 increase IPT-A > Week 8 add FLX
B = -7.28, t = -2.03, p = .043

Social Impairment (SAS-SR)



• Week 4 increase IPT-A < Week 8 increase IPT-A
 $B = -.39, t = 1.78, p = .077$

• Week 4 increase IPT-A < Week 8 add FLX
 $B = .38, t = 1.82, p = .070$

Adapting Treatment Over Time: Take Home Points

- Progress monitoring is important.
- ATSs are feasible to implement and acceptable to families.
- The timing of when you augment treatment is important:
 - Sooner is better than later
 - This is particularly the case with increasing the frequency of therapy
- Further research is needed to incorporate change in target mechanisms/psychological constructs into ATS algorithms.