Evidence-Based Treatments for ADHD and Mechanisms of Change

(with thoughts on risks for adolescent girls)

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Mechanisms of Change in Developmental Psychopathology

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Objectives

- 1. DP perspectives
- 2. ADHD
  - Impairments, etiology developmental implications
  - Debunk myth that ADHD is a static, categorical, entirely biological entity
- 3. Evidence-based treatments: Meds, behavioral tx's
- 4. For whom do these treatments work (moderators) and through what processes (mediators)
  - Holy grail: Determine actual mechanisms of change
  - What <are> "mechanisms"? Many meanings, but for now, mechanisms are the subset of mediators that truly propel change
- 5. More general risks for adolescent girls
  - When protective factors become risk factors

What is Development? What is "Developmental"?

- **Development**
  - Not just change but progression toward an organized state
  - Webster's:
    - Make "…fuller, more mature, or more organized"
  - Cf. dynamic systems models:
    - Self-organization; attractors re: health/dysfunction outcome

- **Developmental**
  - Not just unfolding from "fixed," preordained initial conditions, but fluid processes incorporating transactional influences across time

Some Tenets of Developmental Psychopathology

- Interplay of normal and atypical
- Continuities/discontinuities across the lifespan
- Role of context in propelling development
- Reciprocal and transactional chains of influence
  - Lack of primacy of any one etiologic/risk factor in isolation
- Multilevel approaches to causation and maintenance
  - Genes to temperament to context to impairment

- APPLICATIONS TO ADHD?

1. ADHD: Key Themes

- **Real condition, but forms a continuum, not pure taxon**
  - Heritable risk pertains to range of symptoms (cf. hypertension)
  - Thus, normal vs. atypical a matter of degree
- **Careful assessment crucial**
  - 10’ office visit not sufficient for thorough evaluation
- **Associated with marked impairment (Hinshaw, 2002)**
  - Academic (school failure; billions in educational costs…and lost work)
  - Social/peer (most peer-rejected condition)
  - Family (reciprocal chains of bidirectional influences)
  - Accidental injury (across the age span; serious risk here)
  - Lowered independence (mildly retarded range despite normal IQ)

Themes - 2

- Such impairment largely independent of comorbidity
  - Yet comorbidity intensifies impairment
- Clearly a syndrome, not a disorder
  - Multiple causal pathways
  - Risk factors interact and transact
  - Reification of categories and taxa—rampant in DSM-IV—is striking in relation to ADHD
- Girls with ADHD
  - Impairments as severe as those of boys
  - Longitudinally, impairments may be more widespread than those of boys; potential for multifinality?

2. Nature of ADHD: Models

- Multiple models proposed over the years
  - E.g., maturational, developmental, motivational, learning, neurobiological, relational, cultural
- Executive function / frontal lobe / fronto-striatal
  - See neuropsychological / neuroimaging findings
  - EF deficits: only a subgroup; academic, not social deficits
- Deficits in inhibition, delay response, reward
  - Barkley (1997), Nigg (2001), Sagvolden et al. (2006)

3. ADHD: Risk, Etiology

- **Heritability and Genes:**
  - **H^2 of ADHD purported to be around .8**
    - **Such figures pertain to parent report of symptoms; but shared method variance/DZ twin contrast effects**
    - **Teacher ratings: Lower figures (still moderate to high)**
  - **Given these estimates, common assumption that ADHD is 'fixed' and largely immutable**
    - **I.e., "parenting can't matter"; parents as shepherds**
    - **Misreading of heritability**

Other Risk Factors

- Low birthweight
  - Predicts ADHD, LD, Tourette's, CP, retardation
- Teratogenic effects
  - FAE: Many are nearly identical to ADHD symptoms
  - Biological + psychosocial effects of alcohol use in parents
- Early parenting: No consistent evidence as causal
  - Middle-class; few prospective studies from early years
- Insecure attachment?
  - Does NOT predict later ADHD
  - Re: aggressive behavior--interactions with temperament, later parenting, family structure/context, yield externalizing behavior (Greenberg et al.)

Risk Factors: Equifinality

- Carlson et al. (1995):
  - In low-income sample, early maternal insensitivity predictive of ADHD symptoms to a greater extent than early temperament
  - Need genetically informative design
- Institutional deprivation (Kreppner et al., 2001)
  - English and Romanian Adoptive Study Team: Inattention/overactivity associated with length of severe institutional deprivation in first 4 years
  - *Specific* effect: Conduct problems and internalizing symptoms not similarly associated with deprivation
  - Yet, different "feel" from typical ADHD presentation
- Hence, *equifinality* apparent

Interaction/Transaction

- Tully et al. (2004): *JCCP*
  - In LBW twins, but not in normal weight, maternal warmth (FMSS) at 5 years predicts lowered risk for subsequent ADHD symptoms
    - Specific: Warmth does *not* protect against risk for lowered IQ
    - Thus, this parenting dimension may buffer risk factor of LBW

- DRD4 susceptibility gene:
  - Appears to produce behavioral manifestations of ADHD, but without associated neuropsychological deficits (Swanson)
  - Perhaps cognitive/EF deficits are not simple "genetic effects" but rather reflect pre/perinatal injury
  - DA genes (DRD4, DAT) = small effect, "susceptibility" genes
  - Epistatic effects and GE interactions?

Developmental Paths

- **Preschool Manifestations (S. Campbell)**
  - **Careful evaluations of 3 and 4 year olds**
  - **Prospective predictions to mid-late childhood:**
    - **PPP = .5! Hence, *multifinality* apparent**
    - **That is, suggestions of (a) "he'll grow out of it" and (b) "medicate today" are each fraught with error**
  - **Predictors of continuation:**
    - **(a) severity of early ADHD**
    - **(b) negativity of early parent/child interaction, controlling for severity of child's ADHD**

4. Intervention: Links to Theory

- General problem: dissociation of treatment research from theoretical formulations
  - Many clinical trials far too atheoretical
  - Maybe ultimate aim of RCT's is, in fact, to see "which treatment wins," but this is a decidedly arid stance

- Need to bring theory to treatment *and* ensure that treatment studies produce higher theoretical yield
  - Hinshaw (2002): *Development & Psychopathology*
  - Kraemer et al. (2002): *Archives of General Psychiatry*
    - Clinical trials designed to answer primary outcome questions, but embedding theory and "right" measures in design can greatly enhance conceptual yield

For example…

- Use of mediator and moderator analyses in clinical and prevention trials
- Hybrid designs: See Howe et al. (2002), *D & P*
  - 1. Intent-to-treat analyses PLUS longitudinal correlational methods (risk, protective, mediator factors measured at several points during the trial) to test mediation
  - 2. Place prevention trial "inside" genetically informative design
    - If linkages between (a) birth parent psychopathology and (b) adoptive parent behavior or evocative child behavior are reduced in treatment but not control group, evidence that genetically mediated transmission is decreased

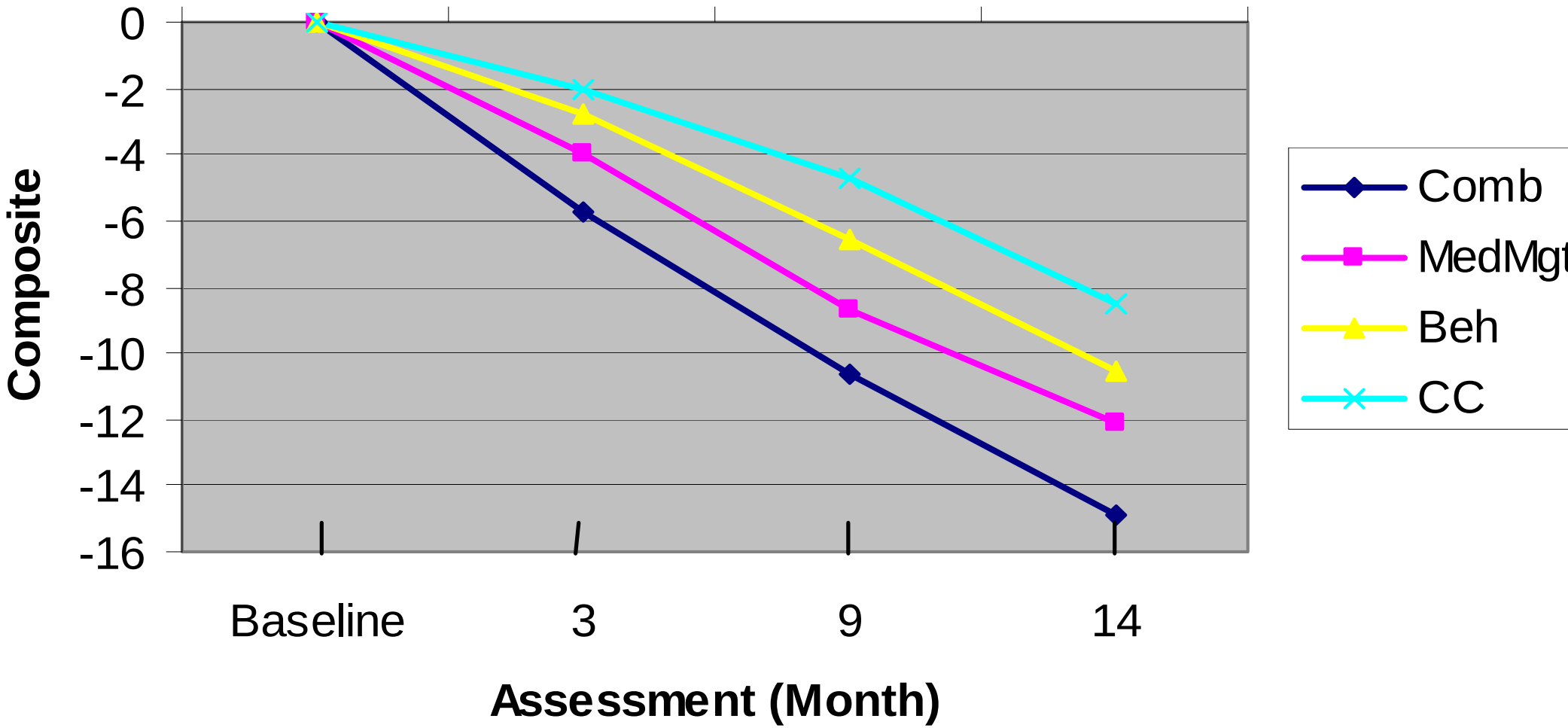
MTA Study

- Major RCT of 4 treatment strategies, delivered for 14 months, to 579 youth with ADHD-Combined, age 7-9
  - Medication management (dose trial + 13 monthly visits)
  - Intensive behavioral tx (parent tx, school consult, STP, class aide)
  - Combined
  - Community comparison/treatment as usual
- Large sample, with intentional inclusion of moderator variables (i.e., baseline SES, comorbidities, etc.) and mediator processes (variables changing during treatment) for exploratory analyses
- Outcome measures:
  - 3 symptom domains (ADHD, internalizing, disruptive)
  - 3 key functional impairments (peer-related, academic, family)
- ITT analyses during active tx, at post-tx (14 mo), and follow-up (24 mo, 36 mo, 6 yr, 8 yr, 10 yr, 12 yr)

Outcomes

- 14 month ITT analyses:
  - For ADHD sx--MedMgt, Comb > Beh, CC
  - For many other primary outcomes, Comb > CC
  - For “excellent response” and for composite outcome across all 6 outcome measures, same order:
    - Comb > MedMgt > Beh > CC

Composite Score
Adjusted for Baseline
Conners et al., 2001



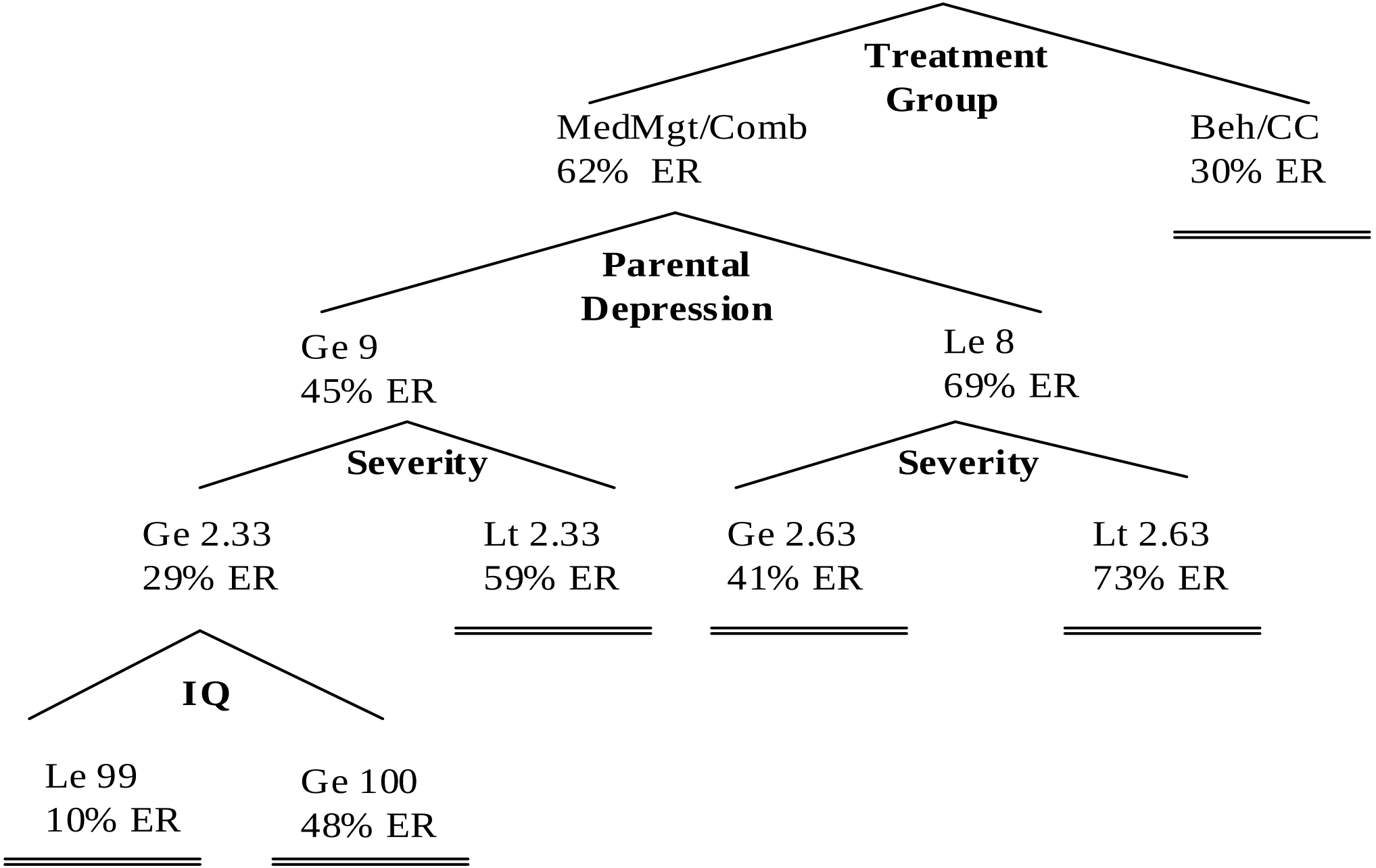
What happens when the RCT ends?

- By 24 mo. (10 mo. after tx ends)
  - Advantage of MedMgt and Comb over Beh and CC for ADHD outcomes was reduced by half
- By 36 mo. and by 6/8 yr:
  - All four randomly assigned groups have nearly identical means
  - This is true for > 20 outcomes, including not only symptoms but also adolescent-relevant, impairment-related d.v.'s
  -
  - See Molina et al. (in press)

During RCT: Moderators of Outcome

MTA Cooperative Group (1999a), *Archives*
Owens, Hinshaw et al. (2003), *JCCP*
Hinshaw et al. (2000), *JACP*

- Logical mediator: Attendance at beh parenting sessions
  - But, it's NOT related to any core outcome
- Moderator variables: Sex, comorbid ODD/CD not moderators
  - Equivalent responses to all 4 tx conditions for boys/girls, comorbid/not
- Yet, comorbid anxiety disorder at baseline predicts relatively better response to Beh and Comb txs
  - Those with ADHD/Anx do as well with Beh as with MedMgt, even better on Comb
- SES: Low SES at baseline predicts relatively better response, regarding social skills outcomes, for Comb tx
- ROC analyses of multiple moderators considered together (Kraemer software)…

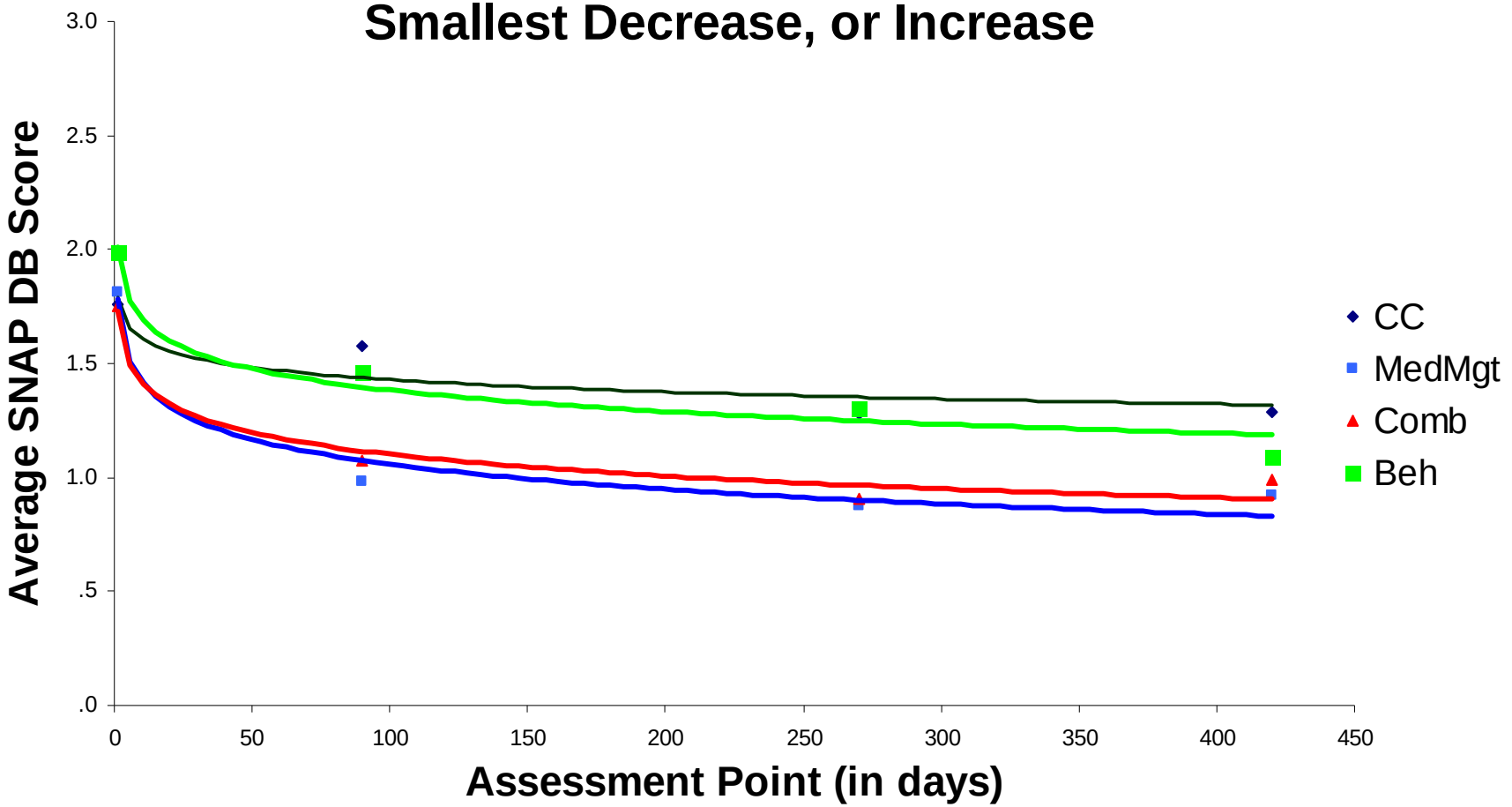

Treatment Group
MedMgt/Comb
62% ER
Beh/CC
30% ER
Parental Depression
Ge 9
45% ER
Le 8
69% ER
Severity
Severity
Ge 2.33
29% ER
Lt 2.33
59% ER
Ge 2.63
41% ER
Lt 2.63
73% ER
IQ
Le 99
10% ER
Ge 100
48% ER

Family discipline as mediator

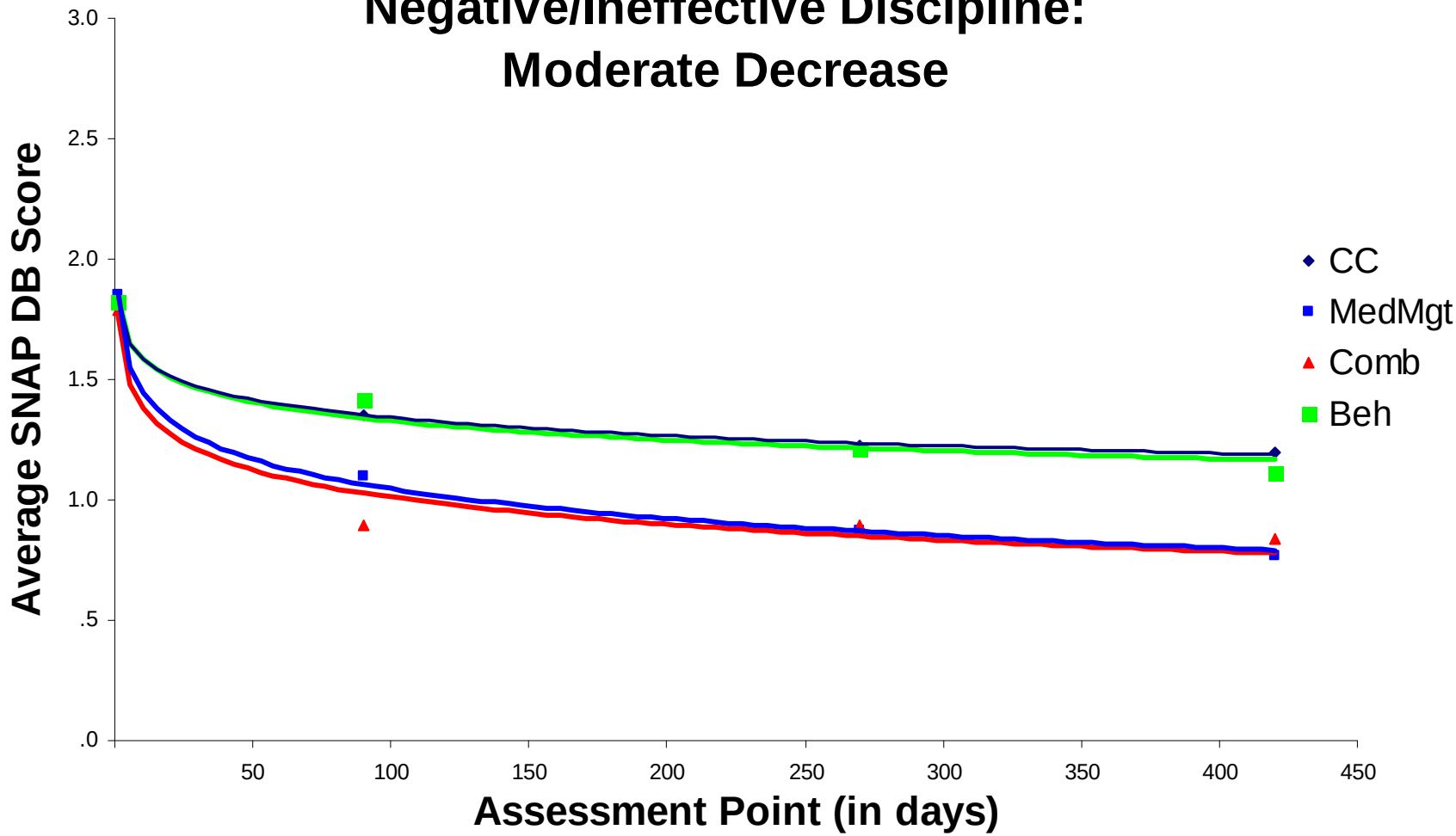
Hinshaw et al., 2000, *JACP*

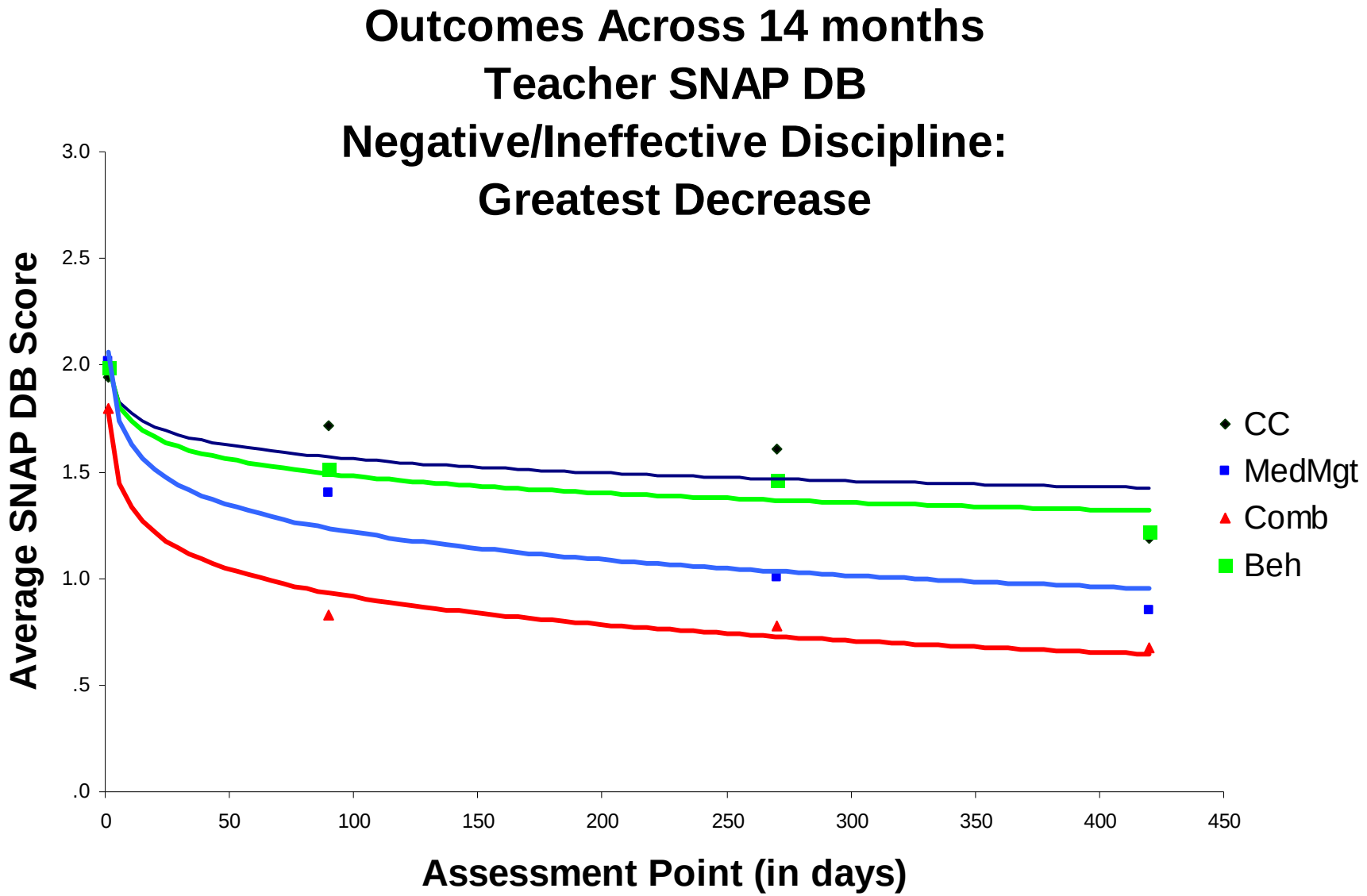
- **Theory:**
  - Family discipline has direct, causal influence on children's externalizing behavior patterns, through coercion, modeling, attachment failure
  - Apply to ADHD, with high heritability?
- **Prediction:**
  - Change in discipline style will serve as mediator of school outcomes--social skill and disruptive behavior--for behavioral tx components
  - Negative/ineffective discipline passes mediator tests
    - Positive parenting and poor monitoring do not

Outcomes Across 14 Months
Teacher SNAP DB
Negative/Ineffective Discipline:
Smallest Decrease, or Increase



Outcomes Across 14 Months
Teacher SNAP DB
Negative/Ineffective Discipline:
Moderate Decrease




Outcomes Across 14 months
Teacher SNAP DB
Negative/Ineffective Discipline:
Greatest Decrease
Average SNAP DB Score
3.0
2.5
2.0
1.5
1.0
.5
.0
0
50
100
150
200
250
300
350
400
450
Assessment Point (in days)
CC
MedMgt
Comb
Beh

Implications

- In Comb, clear improvement in Neg/Ineff. Discipline predicts *normalization* of disruptive behavior at school
  - Not true in other 3 conditions
- Provocative for ADHD
  - See claims that parents of such children do not exert much influence; misreading of heritability statistics
- But, is parenting role causal?
  - In other words, when is a mediator truly a mechanism?
    - MTA is RCT of existing disorder (not preventive intervention), can *etiologic* role for parenting be warranted? Probably not
    - Protective or maintaining factor status still important
    - And, problems with temporal sequence of effects
    - Next trial: manipulate neg/ineffective parenting per se
    - Mechanism research: Iterative sequence of work on basic processes and informed clinical trials

Further Implications

- **Qualitative research:**
  - **Do we even know the right developmental processes to investigate?**
  - **What are the real variables that we need to change, to drive adaptive outcomes?**
    - **Coercive discipline certainly one, but what about longer term?**

- **And, further lesson from MTA: Longer-term trajectories not influenced, on average, by intensive 14 month treatment during childhood**
  - **What mediates and moderates high school completion, avoidance of juvenile hall, desistance from substance abuse, early pregnancy, etc.?**

Conclusions

- **ADHD: Not a static "entity"**
  - **Didn't even delve into types (inattentive, HI, combined)**
- **Dimensional/overlapping with normal distribution**
  - **Need for translational research, linking research on basic attentional, inhibitory, cognitive, emotion processes to ADHD**
- **Multiplicity of causal pathways: Equifinality**
  - **Interactive in ways we are only beginning to know**
  - **Deprivation as well as DA genes as well as other neurobiological risks relevant for different cases**

Conclusions - 2

- **Divergent outcomes for early ADHD: Multifinality**
  - **Thus, what are 'propelling'/maintaining as well as truly protective factors?**
- **Developmental, contextual factors crucial**
  - **Even parenting styles, which may not be causal, are important determinants of outcome**
- **Ultimate questions:**
  - **Unfolding of underlying organization; mechanisms associated with diverging paths and outcomes**

New Directions

- Adolescent psychopathology:
  - Girls, with greater verbal skills, higher empathy, more compliance from early ages, are relatively protected against preadolescent externalizing problems
  - But, these same "protective" factors become risk factors—especially when paired with mood disorder in mother, and/or with general family distress, by the onset of puberty
- That is, despite adolescent girls' overwhelming successes
  - Including 57% of B.A.'s, unprecedented athletic success, etc.…
- Suicide rate for preteens/early teens is going up
- Binge eating much higher than expected (NCS-R)
- Self-harm: seemingly extremely high
- Age of onset of depression dropping
- Aggression/delinquency down in boys but up in girls

"The Triple Bind"

- **Beyond rumination, unproductive coping, sequelae of abuse, earlier puberty (in combination with other risk factors)…what is driving this set of problems in teen girls?**

- **Hypothesis (in new book):**
  - **Combination of "impossible expectations" for girls**
    - **Be nurturing (all girl)**
    - **Be competitive (all boy)**
    - **Do it effortlessly, looking "hot," with alternative identities all co-opted and with many societal structures emphasizing extrinsic as opposed to intrinsic motivation**
  - **This triple-binding set of expectancies leads to internalization, self-focus, and anger**
  - **Harmful for all girls, and especially those with highest vulnerability**
  - **CONTEXT IS ESSENTIAL, INTEGRATED WITH MATURATION, DEVELOPMENT, AND INTERVENTION OPPORTUNITIES**

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