Current Views of the Best Treatments for ADHD: A Decade-plus of Research on Comparing, Combining, & Sequencing Interventions for Childhood ADHD

William E. Pelham, Jr., Ph.D., ABPP Center for Children and Families Florida International University

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#### Disclosures

Past Consultant, scientific advisor, speaker, grant recipient: McNeil/Alza (Concerta) Abbott Shire (Adderall, Adderall XR, guanfacine) Noven (Daytrana) Lilly (Strattera)

MTA principal investigator

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# Center for Children and Families at FIU

- UP scutty: Fink Coles, Joseis A hob, Maggie Blowy, Kell Kart, Daniel Baner, Josef M. S. Sterner, Joseis A. Sterner, S. Sterner, S. Sterner, S. Sterner, Coxe, J. Sterner, S. Sterner, Coxe, J. Sterner, S. Sterner
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- Raiker. SUNY Buffalci Greg Fabiano. Larry Hawk, Karen Morris, Neda Burtman, Koll Pyle Univ, Pitaburgh: Brooke Molina, Tracey Wilson, Nedd Kipp, Carol Waiker, Kat Belendiu, Sarah Bederson, Chisteline Waither, MTA Cooperalive Group (Pitaburgh, UC Berkeley/Irvine, Columbia, NYU, Duke) Memtaric: Charles Cunningham UNC: Patrick Curran

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- Educators

Most common behavioral referral to health care professionals Most common referral/diagnosis in special education Most common behavior problem in regular education classrooms

Most common diagnosis in child mental health facilities

(Barkley, 2006; CDC, 2010, 2011, 2018; Pelham, Fabiano & Massetti, 2005)

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"All of the 'experts' at Jerome Horwitz Elementary School had their opinions about George and Harold. Their guidance counselor, Mr. Rected, thought the boys suffered from A.D.D. The school psychologist, Miss Labler, diagnosed them with A.D.H.D. And their mean old principal, Mr. Krupp, thought they were just plain old B.A.D.!"

## A Variety of Names-Same Disorder-Same Children

- Brain Damage (BD)
- Minimal Brain Damage (MBD)
- · Minimal Brain Dysfunction (MBD) Hyperkinetic-Impulse Disorder
- Hyperkinetic Reaction of Childhood/Hyperkinesis/Hyperactivity—DSM II
- Attention Deficit Disorder (with and without Attention Deficit-Hyperactivity Disorder—DSM III-R, DSM-IV, DSM 5

(Barkley, 2006)

#### ADHD: Core Symptoms--Same **Over Past 50 Years**

Inattention

Impulsivity

Hyperactivity

DSM-5 Definition of ADHD

#### A. Six Symptoms of either Inatt. or Hyp/Impuls. (1) Inattention:

 often fails to give close attention to details or makes careless
mistakes in schoolwork, work, or other activities •often has difficulty sustaining attention in tasks or play activities •often does not seem to listen to what is being said to him or her often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace often has difficulties organizing tasks and activities ·often avoids or has difficulties engaging in tasks that require standard mental effort often loses things necessary for tasks or activities ·is often easily distracted by extraneous stimuli often forgetful in daily activities

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#### DSM-5 Definition of ADHD

(2) Hyperactivity-Impulsivity: often has difficulty playing or engaging in leisure activities quietly

- is always "on the go" or acts as if "driven by a motor"
  often talks excessively

### often blurts out answers to questions before the questions have been completed

- have been completed o noten has difficulty waiting in lines or awaiting turn in games or group situations o often interrupts or intrudes on others (e.g. butts into other's conversations or games) o often runs about or climbs inappropriately

- often fulls about of clinits inappropriately
   often fidgets with hands or feet or squirms in seat
   leaves seat in classroom or in other situations in which
   remaining seated is expected

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#### DSM-5 Definition of ADHD

- B. Some symptoms that caused impairment were present before age 12. C. Some symptoms that cause impairment are present in two or more settings (e.g. at school, work,
- . and at home).
- **D.** There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning. E. Does not occur exclusively during the course of
- Pervasive Developmental Disorder, Schizophrenia or other Psychotic Disorder, and is not better accounted for by a Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder.

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### Comorbidity with ADHD

- · Learning disorders Language and communication disorders
- · Conduct disorder
- Oppositional defiant disorder
- Anxiety disorder Mood disorders
- · Tourette's syndrome; chronic tics

#### BUT....Are DSM Symptoms/Diagnoses important for:

Etiology,

Mechanisms of Dysfunction,

Treatment Conceptualization and Implementation,

and Prediction of outcome in ADHD?

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- · Behavioral functioning at school
- Family functioning at home
- · Leisure activities
- (Barkley, 2006; Fabiano & Pelham, in press)

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### Central Role of Functional Impairment in Treatment Inpairment-that is, problems in daily life functioning that result from symptoms and deficits in adaptive skills is - (1) why children are referred,

- (1) why diminer are released.
   (2) what mediates long-term outcome, and therefore
   (3) what should be targeted in treatment.
   Key domains are peer relationships, parenting/family, and academic achievement
- Assessment of impairment in daily life functioning and adaptive skills is the most fundamental aspect of
- initial evaluation to determine targets of treatment
   Ongoing assessment to evaluate treatment response
- Normalization or minimization of impairment in daily life functioning and maximization of adaptive skills is the goal of treatment--not elimination of symptoms

(Pelham, Fabiano, & Massetti, 2005; Pelham & Fabiano, 2008)



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### Prognosis for ADHD Children Chronic disorder (AAP, 2001, 2011, 2019) extending into adolescence and adulthood

1	One-third:	Tolerable outcome; appear to have mild problems but must constantly work to adapt to their difficulties
	One-third:	Moderately poor outcome: continue to have a variety of moderate to serious problems, including school difficulties (adolescents) or vocational and financial adjustment difficulties (adults), interpersonal problems, general underachievement, problems with alcohol, etc.
	One-third:	Bad outcome; severe dysfunction and/or psychopathology, including sociopathy, repeated criminal activity and resulting incarceration, alcoholism, drug use disorders

(Barkley, Murphy, & Fisher, 2008; Lee et al, 2011; Molina et al, 2009; Molina & Pelham, 2014)

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What is Effective, Evidence-based Treatment for ADHD in Childhood?

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#### Common but Not Evidence-Based Treatments (1) Traditional one-to-one therapy or counseling

- Cognitive therapy Office based "Play therapy" Elimination diets Biofeedback/neural therapy/attention (EEG) training (2) (3) (4) (5) (6) (7)
- Allergy treatments Chiropractics
- (8) Perceptual or motor training/sensory integration training
- (9) Most other OT interventions (e.g., adaptive furniture) (10) Pet therapy
   (11) Dietary supplements (megavitamins, blue-green algae)
- (12) Duct tape

(AAP, 2001, 2011; Pelham & Fabiano, 2008, 2008; Evans et al, 2014)

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- Pediatric drugs are typically more expensive than in adults because of lack of generics—dramatic increases in expenditures in past decade Insurance plans now spend more money on gsychotropics than antibiotics or asthma mede (17% total compared with stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulant stimulants for ADHD being the leading compared to the stimulant stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulant stimulants for ADHD being the leading compared to the stimulant stimulants for ADHD being the leading compared to the stimulants for ADHD being the leading compared to the stimulants for ADHD being the stimula
- cost
- cost 6+% of children in the U.S. took at least one psychotropic in 2005, with 1/5 of those taking 2+meds Steady increases in use of antipsychotic medications (10% increases in 2008) 18% of ADHD children in Medicaid Stimulants are the most prescribed child psychotropic-4%-7% of U.S. child population are medicated daily with stimulants for ADHD—many more than receive BMOD. Two likely causes for the increase
- Two likely causes for the increase



ADHD Medication Usage mber of prescriptions n millions) 2008 39.5 2007 36.6 2006 33.8 2005 31.2 2004 28.4 Treating ADHD The number of prescriptions written for drugs that reat ADHD has risen steadily for the past five years. Source: IMS Health By Keith Simmons, USA TODAY

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Guidelines on Treatments and SDBP Clinical Practice Guideline: Treatment of Complex ADHD in children and Teens AAP Clinical Practice Guideline: Treatment of the School-Aged Child with Attention-Deficit/Hyperactivity Disorder Sequencing (JDBP, 2020) Task Force of APA (2007) says psychosocial first Division 53 reviews of the APA have said since 1998 that there is solid evidence supporting BT For all children and adolescents with complex ADHD, the For an onicitier and behavioral pediatrician should developmental and behavioral pediatrician should prescribe BPT and BCM interventions for home and school to improve impairment in children with ADHD, with adjunctive psychostimulant medication for children for whom impairment is not sufficiently resolved with · For elementary-aged children and adolescents, the Japanese pediatric guidelines (2008) say behavioral/educational first primary care clinician should prescribe FDA-approved medication and behavior therapy—both home and school British guidelines (NICE, 2009) say behavioral first in mild to moderate cases interventions -- to improve target outcomes in children with ADHD · CHADD savs simultaneous behavioral treatments alone AHRQ has said in 30 years of reviews that there is no evidence supporting behavioral treatment For children under 6, behavior therapy (BPT and classroom interventions) should be the first line treatment, with medication (methylphenidate) perhaps as ancillary if BT alone is insufficient and there is moderate to severe Complex ADHD includes ADHD in preschool and Cuidelines of the AACAP (2007) say medication first (and 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, and 5<sup>th</sup>) because behavioral treatments (BT) are not effective AAP 2011 is in the middle adolescent children and any ADHD child with a comorbidity. continued impairment in functioning. CDC says BT for young kids-Russ Barkley says medication! 31 32 33



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(Pelham & Fabiano, 2008; Fabiano et al. 2009)

Why is it Important to Include Parent Training, School Interventions, and Peer-focused Interventions in ADHD Treatment?

- No one is taught how to be a parent and parents of ADHD children have significant stress, psychopathology, and poor parenting skills
- ADHD children have severe academic and behavioral problems in school throughout the grades and teachers are not trained to educate them
- ADHD children often have severely disturbed peer relationships that cannot be sufficiently modified by parents or teachers on their own

(DuPaul & Stoner, 2002; Johnston & Mash, 2001; Milich & Landau, 1982)

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Beneficial Short-term Effects of **Behavioral Treatments** 

- Improved functioning in home (e.g., improved compliance and parent ratings), school (e.g., improvement in classroom disruptive behavior and teacher ratings), and peer settings (e.g., improved positive and negative interactions)
- Evidence for benefit throughout the age range (4 to 15) but fewer studies at younger and older ages Moderate to large effect sizes across treatments and measures
- Benefits independent of comorbidity
- However, room for improvement even after acute clinic-level treatment for many children Less evidence (few studies) for long-term benefits
- How do we maintain benefits from acute treatments and thus emphasis on chronic care model--that is sustained low dose maintenance intervention after acute treatment

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### Main Beneficial Short-term Effects of Pharmacological Treatments

1. Decrease in classroom disruption

- 2. Improvement in teacher and parent ratings of behavior
- Improvement in rule following and compliance with adult requests and commands
   Increase in on-task behavior and daily
- academic productivity and accuracy (but not achievement)
- 5. Improvement in peer interactions
- Improvement on a variety of laboratory tasks of cognition

(Greenhill, 2002)

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- · Parent Training--Use always
- · School Intervention--Use always · Child Intervention--Use when
- indicated because of
- complexity/expense · Medication-Use in low doses as short-term adjunct only when behavioral treatments are insufficient





#### What Do We Know About Comparative and Combined Treatment Studies?

#### Questions the NIMH 1999 MTA Study **Did Not Answer**

- What treatments does a given child need?
- Should behavioral treatment begin before medication (parent preference) or vice versa (physician practice) or should they be implemented simultaneously (as in the MTA).
- What are the best "doses" of psychosocial, pharmacological, and combined treatments?
- If one or the other modality is begun first, how long should it be conducted and at what dose before adding in the second modality?
- What are the implications of different doses and sequences for treatment dosing, benefit, and risk of side effects? These are the questions that families, practitioners, and educators face daily. We have studied them for the past 18 years.

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#### Our Research Program in the Past 20 Years

- Our Research Program in the Past 20 Years Five studies funded by NIMH and IES that examine dose effects and sequencing effects of behavioral and pharmacological tr: (1) Controlled examination of 3 levels of behavior modification (none, low intensity, high intensity) crossed with 4 dose of medication in a summer provide the second second second second second second second provide the second (3) SMART (sequential, multiple, adaptive, randomized trial) design to examine whether to begin freatment with medication or behavior therapy and, when norresponse, whether to add the other modalize on increases the intensity of initial modality (4) Evaluation of Brond effectiveness and need for medication in young with one of the same behavior modification levels as above (with adaptive components) and continuing without tading for 3 years (to pass peak period for medication use) (5) Two phase, linked evaluation of toincare to stimulant medication in the
- peak period for medication use) (5) Two phase, linked evaluation of tolerance to stimulant medication in the STP and school-year settings, with multiple embedded studies of combined and comparative treatments.

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**Dose-Response Effects of Behavior** Modification, Medication, and their Combination in ADHD Children in a Summer Setting

> Pelham, Burrows-McLean, Gnagy, Fabiano, Coles, Hoffman, Massetti, Waxmonsky, Waschbusch, Chacko, Walker, Wymbs, Robb, Arnold, Garefino (NIMH 2002-2007)

(Fabiano et al, 2007; Pelham et al, 2014; Pelham et al in preparation)

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#### Summer Treatment Program Overview · Children grouped by age into groups of 12-16

- Groups stay together throughout the day
- 4-5 paraprofessional counselors work with each group all day outside of the classroom
- One teacher and an aide staff the classroom for each group
- · Treatment implemented in context of recreational and academic activities
- Focus on Impairment and teaching skills--not symptoms
- Parent training incorporated
- Medication is second line treatment

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### Design

- 48-52 ADHD children per summer for 3 summers 4 Medication conditions: placebo and 3 doses of methylphenidate (.15mg/kg, .3 mg/kg, .6 mg/kg, t.i.,d.), with order varying daily within child for 9 weeks
- 3 Behavioral Modification conditions: No behavioral treatment (NBM), low-intensity (LBM) treatment, and high-intensity (HBM) treatment (BM), varying triweekly in random order by treatment group
- 3-4 days per medication X Bmod condition.
- NonADHD comparison group (24/summer).

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### **Results Summary**

oth medication and behavioral treatment produced significant and generally comparable effects on nearly all measures of functioning in recreational and classroom settings.

Relatively low doses of both modalities produced benefit with no SE at the lowest medication dose and considerable SE at the highest dose.

On most measures in both classroom and recreational settings, the combination of the lowest dose of medication (a very low dose-.15 mg/kg per dose) and LBM produced as much and sometimes more change than did the four-limes-higher doses of medication in the NBM condition and HBM without medication

Parents preferred the behavioral treatments or their combination with low-dose

Thus, combined treatment allows low doses of medication and lower doses of behavior modification with excellent outcomes.

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#### Adaptive Pharmacological and **Behavioral Treatments for Children** with ADHD: Sequencing, Combining, and Escalating Doses

William E. Pelham, Jr., Gregory Fabiano, Lisa Burrows-MacLean, James Waxmonsky, Susan Murphy, E. Michael Foster, Elizabeth Gnagy, Andrew Greiner, Timothy Page, William E Pelham, III, Jihnhee Yu, Stefany Coxe, D. (Pelham et al, JCCAP, 2016; Page et al, JCCAP, 2016)

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### **Recruited in Spring of 3** Consecutive years

- Children recruited from schools pediatricians, newspaper, radio, mental health clinics, and parent referrals
- · Baseline assessment in June
- Treatment began in late August/beginning of school
- · Treatment implemented for the school year
- Endpoint measures taken at end of school year

Sample Characteristics

- 146 Children with DSM IV ADHD (74 and 72 in M First and B first) based on T ratings and P ratings and structured interview 80% Combined type diagnosis
- Mean age: 8.4 years
- IQ: 99
- Comorbid ODD/CD: 72%
- Prior Child Medication Treatment: 29%
- Race: 80% Caucasian
- Parent Marital Status: 9% single mothers
- Parent Education: 26% HS or Technical School; 50% AA or BA



#### Specific Aims/Questions

- Is it better to begin treatment for ADHD children with a low dose of Behavior Modification or a low dose of Medication?
- 2) What is the most effective treatment protocol among the four embedded treatment protocols (BB, BM, MB, MM)—that is best pattern of initial treatment and conditional second stage treatment?
- 3) In the event of insufficient response to each initial treatment is it more effective to increase the dose of that treatment or add the other modality?
- 4) What are the relative costs of these treatment strategies?

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#### Indicator of Need for Additional Treatment at 8-week and Subsequent Assessments:

(1) Average performance on the ITB is less than 75% AND(2) Rating by parents or teachers as

impaired (i.e., greater than 3) on the IRS in at least one domain.

Treatment decisions and content are evaluated monthly(or more frequently) and tailored to the specific domains of impairment rated on the IRS

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#### **First Aim/Question**

 Is it better to begin treatment for ADHD children with a low dose of Behavior Modification or a low dose of Medication?

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#### First Aim/Question

 Is it better to begin treatment for ADHD children with a low dose of Behavior Modification or a low dose of Medication?

 It is better to begin with Behavior Modification

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#### Second Aim/Question

- What is the most effective treatment protocol among the four embedded treatment protocols (BB, BM, MB, MM)—that is best pattern of initial treatment and conditional second stage treatment?
- The best protocol was BM; the worse was MB. BB was close to BM (and better on classroom obs.) and MM was only slightly better than MB.

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 In the event of insufficient response to each initial treatment is it more effective to increase the dose of that treatment or add the other modality?

Third Aim/Question

•Additional Bmod was more effective on rule violations than adding Med for BehFirst; additional Med was slightly better than adding Bmod for MedFirst.

•Rule violation rates were nearly twice as high for the two medication conditions as for the two behavioral conditions

















#### Cost Summary

- Behavioral First was significantly less expensive than Medication First
- Behavioral plus Behavioral if necessary was less expensive than Medication plus medication if necessary
- Behavioral plus medication if necessary was less expensive than Medication plus behavioral if necessary
- The incremental costs of behavioral treatment offset by reductions in medication cost when behavioral treatment was implemented first.
- \$4 billion could be saved in US healthcare economy if medication were NOT the first-line treatment for childhood ADHD.

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#### The Effects of Stimulant Medication on Classroom Learning in Children with ADHD

Pelham et al (under review)

#### Participants

- Participants were 240 ADHD children between 6 and 12 years old recruited over four consecutive cohorts from 2013-2016.
- They participated in a year-long NIMHfunded study examining tolerance to stimulant medication with both summer (STP) and school-year components.

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#### Design—STP Classroom Study

- Placebo-controlled cross-over study of methylphenidate (Concerta) in an STP classroom setting in which gradeappropriate, structured lessons were taught in social studies, science, and vocabulary.
- Children received self-contained threeweek modules of each topic on medication and placebo with order randomized across children
- Amount of learning was assessed at the beginning and end of each module.

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#### **Results and Conclusion**

- Children made very large gains in knowledge acquired from excellent instruction in all three content areas
- There were no effects of medication on amount of academic material learned. Medication had expected positive effects on classroom behavior, but this did not translate into improved learning of academic material.
- Results are consistent with the past 50 years of research on medication – no beneficial effects of stimulant medication on achievement in children/teens with ADHD.

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#### **Current Studies**

- Does medication undermine uptake of behavioral treatments and if so, through what mechanism does that happen?
  - E.g., PT finding in SMART trial
  - STP finding in the tolerance study--meds first appeared to worsen response to BEMOD in the STP
  - Teachers whose children started the year on medication in the SMART trial had less appropriate responses to children's classroom behavior at end of the year





Additional Clinical Recommendations for Evidencebased Psychosocial Treatment of ADHD

- Start behavioral and academic interventions at as early an age as possible and continue—reading example and severity of social problems
- Stay in regular contact with family to monitor both behavioral treatments and medication--chronic condition model of treatment
- Make interventions feasible for and palatable for families so they will be maintained in the long run
- Effective treatment requires systems cooperation (e.g., collaboration between families, schools, mental health clinics, primary care, payers) and a public health perspective and effective governmental contingencies for payment to providers

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Downloadable Materials and Videos (Free) on our Websites Unterview of the second of the second of the second and on YouTube) Descent of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the second of the second of the second material second of the secon

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#### Additional Suggestions for Research and Practice in the Future of Treatment for ADHD

- How to improve school district implementation of existing federal laws regarding services for ADHD children - How bad is it? CDC Guideline Notice in 2016.
- Effective treatment requires systems cooperation (e.g., collaboration between families, schools, mental health clinics, primary care, payers) and a public health perspective
- Improvements in MH services for ADHD require policy changes (e.g., federal/state/provincial dollars contingent on EBTs) for which MH professionals must learn and practice lobbying

