

Treatment Resistant Issues

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Learning Objectives

- Review existing agents to treat ADHD
- Identify clinical features and treatment issues as applicable to patients with treatment resistant Attention-Deficit Hyperactivity Disorder (ADHD).
- Evaluate and analyze several ADHD cases
- Apply optimal ADHD medication treatment principles, including medication titration
- Use the Texas Child Medication Algorithm Project (CMAP) guidelines
- Describe essential methods for working with "the toughest" ADHD cases
- Apply evidence-based research findings to the clinical care of patients with ADHD. Tailor individualized treatment plans for patients with ADHD and multiple comorbid disease states and drug related problems to improve treatment outcomes.



ADHD

- Attention-deficit/hyperactivity disorder (ADHD) is a persistent neurodevelopmental disorder that affects **5%** of children and adolescents and **2.5%** of adults worldwide.
- Throughout an individual's lifetime, ADHD can increase the risk of other **psychiatric disorders, educational and occupational failure, accidents, criminality, social disability and addictions.**



Faraone SV, Adamson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiruga JA, Rohde LA, Sonuga-Barke EJ, Tannock R, Franke B. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015 Aug 6;1(202):1. doi: 10.1038/nrdp.2015.20. Review. PubMed PMID: 27181026.

Changes in the DSM-5

- The fifth edition of the DSM was released in May 2013 and replaces the previous version, the text revision of the fourth edition (DSM-IV-TR). There were some changes in the DSM-5 for the diagnosis of ADHD:
 - Symptoms can now occur by **age 12** rather than by age 6;
 - Several symptoms now need to be present in more than one setting rather than just some impairment in more than one setting;
 - **New descriptions** were added to show what **symptoms might look like at older ages**; and
 - For **adults and adolescents age 17 or older**, only **5 symptoms** are needed instead of the 6 needed for younger children.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.

Key Findings: Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD: United States, 2003-2011

- More than 1 in 10 (11%) US school-aged children had received an ADHD diagnosis by a health care provider by 2011, as reported by parents.
- 6.4 million children reported by parents to have ever received a health care provider diagnosis of ADHD, including:
 - 1 in 5 high school boys
 - 1 in 11 high school girls



Visser S, Danielson MJ, Bitsko R, et al. Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD disorder: United States, 2003-2011. J Am Acad Child Adolesc Psychiatry. 2014;53(1):24-46.e2.

ADHD and the family

Heritability

- genotype is 80% (Twin studies)
- phenotype is 40-60% (ADHD Parents will have ADHD child)
- Transmission is 25% (ADHD Children will have and ADHD parent)
- Increased risk of ODD
Correlates with family history of Addiction



Murray & Johnston, J Abnorm Psychol, 2006; Sonuga-Barke et al. Am Acad Child Adolesc Psych, 2002

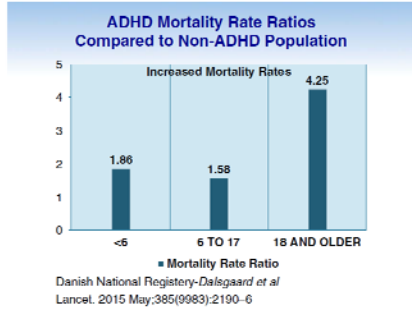


FIGURE 1. ADHD Mortality Rates.⁵

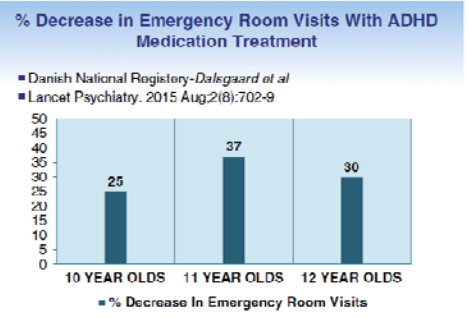


FIGURE 2. Decrease in emergency room visits with ADHD treatment.⁶

Ryan

- 4 year old male
- Lives with mother and father in a home
- He is the youngest of 4 children ages 21, 18, 16
- He was just expelled from his second day care.
- Mother and father both work 2 jobs and Ryan stays with MGM until family is out of work.
- No PMH
- No MEDs

Ryan

- Seen by PCP
- Dx with ADHD
- Started on Focalin 5mg Daily and 2.5mg Noon
- “I don’t feel comfortable to continue”
- Referred to psychiatry

Pharmacotherapy for ADHD

- Stimulants (FDA-approved)
 - Methylphenidate
 - Amphetamine compounds
- Atomoxetine (FDA-approved)
- Alpha agonists (FDA-approved)
 - Guanfacine extended-release
 - Clonidine extended-release
- Combination therapy (FDA-approved)
 - Alpha agonists + stimulants
- Antidepressants
 - Bupropion
 - Tricyclics

Ryan does not look to good

- Not sleeping well
- Not eating well, has lost 10 lbs in 3 weeks
- More irritable with family



Ryan: 3 years later

- Ryan, 7-year-old boy, grade 2
- Mother reports:
 - Does not listen to her, especially in morning
 - Often talks back and does not do what he is told
 - Forgetful, easily distracted
 - Most important problem: parental conflict and stress, doesn't listen at school and poor grades
- Teacher describes problems:
 - Completing work, getting out of seat, waiting his turn
- When you meet Kurt he is quiet but has slight difficulties paying attention

Ryan: : Assessment Findings

- Symptoms of ADHD reported by parents, teacher and child
- Patient interview (Ryan)
 - Complains that teacher is mean; and he can't get all the work done
 - During the interview he fidgets, plays with books in office
- Report cards
 - Below average in all subjects. In danger of having to repeat grade

Dopamine Circuit	Symptom	Narrative
Attention	Inattention	Can't focus Make mistakes Can't stick to task Can't listen Lose Forget
Executive Function	Disorganization	Can't organize Can't prioritize Can't manage time
Motor Control	Hyperactivity	Fidget Can't sit still Busy mind Talk too much
Impulse Control	Impulsivity	Can't foresee consequences Blurts things out Interrupts
Reward	Boredom	Procrastinate Start, but lose interest Can't wait

In terms of the goals of treatment, how likely is it that "remission" might be achieved?

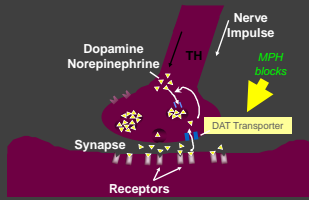
A. Not at all likely
 B. Only slightly
 C. Somewhat
 D. Moderately likely
 E. Highly likely

FDA-Approved Medications for ADHD

- Stimulants
 - Methylphenidate – e.g., Ritalin (LA), Concerta, Focalin (XR), Daytrana, Methylin, Metadate (CD), Quillivant XR
 - Amphetamine – e.g., Dexedrine, Adderall (XR), Vyvanse
- Non-stimulants
 - Atomoxetine (Strattera)
 - Guanfacine XR (Intuniv)
 - Clonidine XR (Kapvay)

Stimulant Medications: Mechanisms

- MPH exerts much of its effect through dopamine uptake blockade by inhibition of dopamine transporter (DAT) of central adrenergic neurons
- By contrast, amphetamines not only block DAT, but also increase catecholamine release as a primary mechanism
- Both increase spontaneously released dopamine that enhances response to environmental stimuli



Stimulant Medications: Efficacy

- Safety and efficacy studies in over 200 controlled studies of ADHD in school-age children
- One of the most robust treatments in psychiatry
- Effective in approximately 70% of children with ADHD—generally equal efficacy across stimulants
- An additional 20% will respond to the next one attempted
- **If the 1st and 2nd choices fail, check for wrong diagnosis and/or previously unrecognized comorbidity**

Froehlich TE, Langshier BP, Epstein JN, Barbaresi WJ, Kautz SK, Kahn RS. Arch Pediatr Adolesc Med. 2007 Sep;161(9):857-64.

Non-Stimulant Medication Mechanism

- Atomoxetine (Strattera) blocks reuptake at the noradrenergic neurons (selective noradrenergic reuptake inhibition – SNRI)
- Guanfacine XR (Intuniv) and Clonidine XR (Kapvay) - alpha-2A adrenergic receptor agonists
 - FDA approved dosing of guanfacine XR 1 to 4 mg daily generally provides symptom benefit lasting 8-14 hours, and up to 24 hours in some children and adolescents receiving a higher dose.
 - For better AM coverage give at night.

May DE, Kratochvil CJ. Drugs. 2010;70(1):

Non-Stimulant Medication Efficacy

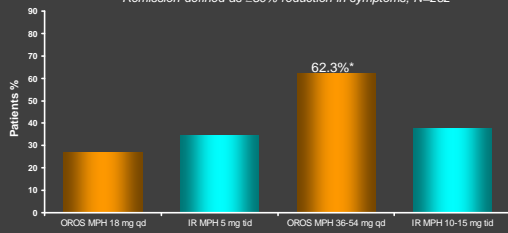
- Head-to-head comparison with OROS-methylphenidate (Concerta):
 - OROS-MPH more effective than atomoxetine
 - (Newcorn et al, Am J Psychiatry, 2008)
 - Effect sizes 0.8-1.0 vs. 0.4-0.5 in stimulant naive

Remission?

Remission At Adequate Doses

36-54 mgs Required to Achieve Remission of Symptoms

Remission defined as $\geq 50\%$ reduction in symptoms, N=282



Greenhill et al. APA, 2004.

Ryan: Treatment Progress

- Treated w/ OROS MPH, 18mg qd, then seen back over after 2 weeks. Parents thrilled, note much improvement at home!
- For the first time in months, a whole week without calls from the teacher!
- You see back in office:
 - No significant side effects noted by parents

Ryan: Audience Answer

Your next move should be to (chose only 1):

- A. Don't fiddle, and leave well enough alone
- B. Increase dose to 27 mg OROS MPH
- C. Increase dose to 36 mg OROS MPH
- D. Switch to another stimulant, e.g., MAS
- E. Switch to atomoxetine
- F. Add behavioural therapy

Optimizing Dosing: Methylphenidate (MPH) in ADHD

Medication	Starting Dose	Maximum Dose	Duration/ Usual Dosing
Ritalin IR	5mg Daily/BID	2mg/kg/day	4hr/BID-TID
Focalin	2.5mg Daily/BID	1mg/kg/day	4-5hr/BID-TID
Focalin XR	5mg Daily	1mg/kg/day	10-12 hour/ Daily
Daytrana	10mg		6-16hr
Concerta	18mg Daily	2mg/kg/day	12 hours / Once
Meditadate CD	20mg Daily		8hr / Once
Ritalin LA	20mg Daily		8hr / Once
Quillivant	<10mg Daily		12hr / Once
Quillichew	<10mg Daily		8hr / Once

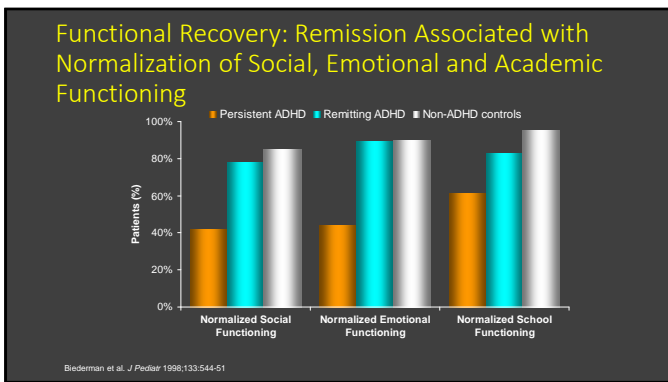
Witem, T. E., & Spence, T. J. (2010). Understanding Attention-Deficit/Hyperactivity Disorder From Childhood to Adulthood. *Postgraduate Medicine*, 122(5), 97-109. <http://doi.org/10.3810/pgm.2010.09.2206>

Optimizing Dosing: Amphetamine (AMPH) in ADHD

Medication	Starting Dose	Maximum Dose*	Duration/ Usual Dosing
Adderall	2.5 to 5mg Daily	1.5mg/kg/day	6hr/BID
Adderall XR	2.5 to 5mg Daily		12hr/Daily
Vyvanse	30mg Daily		12-14 hour/ Daily
Dexedrine tab	2.5 to 5mg BID	1.5mg/kg/day	3 to 5 hr BID-QID
Evekeo	2.5 to 5mg BID		3 to 5 hr BID-QID
Dexedrine span	5mg Daily		6hr/ QD-BID
Dynavel XR (suspension)	2.5 to 5mg BID	1.5mg/kg/day	12hr / Once
Adzenys XR (disintegrating tab)	6.3to 12.5mg BID	Not Established	12hr / Once

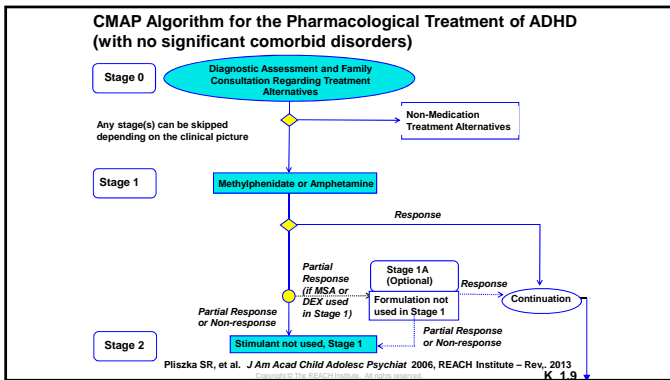
* May exceed FDA Approved Dose (e.g. >20-30mg/day)

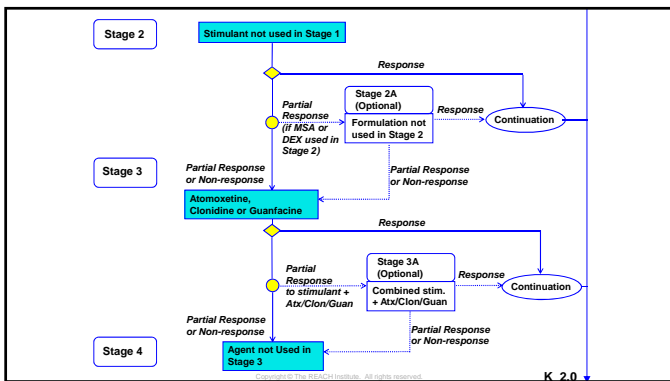
Wilens, T. E., & Spencer, T. J. (2010). Understanding Attention-Deficit/Hyperactivity Disorder From Childhood to Adulthood. Postgraduate Medicine, 122(5), 97-109. <http://doi.org/10.3810/pgm.2010.09.2206>

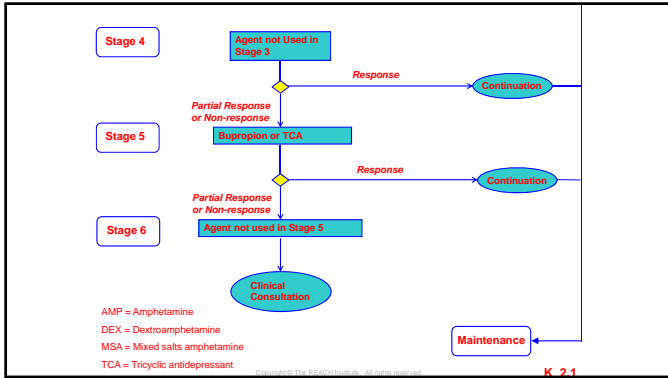


- ### RESOURCE SLIDE: Methylphenidate and Amphetamine: Advantages and Disadvantages
- **Advantages**
 - Can have some immediate onset of action
 - Ability to use drug holidays
 - Multiple options for drug delivery, peak actions, duration of action
 - **Disadvantages**
 - Patients may develop tolerance, psychological dependence
 - May worsen motor and phonic tics
 - Long-term use may suppress growth
 - Cardiac effects???
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Algorithm Tactics

- Response to stimulants is within 1-2 hours
- Evaluate child for 3-7 days (including weekends) for response to each stimulant dose
 - Test all children on at least 3 doses in the first month, seeking goal of “no-room-for-improvement” (remission)
 - Get Rating Scales from each informant at each dose
 - Return for evaluation and “best dose” within 30 days
- Always get input from child, parents, & teachers
- Always use rating scales for assessment & ongoing monitoring
- Ensure adequate patient follow-up – twice yearly is NOT enough!

Ryan: Two Years Later, 9yo

- Intermittent Tx w/ OROS MPH, 36mg qd
- Increasing ODD and aggressive problems, referred by you for behavior therapy
- You see back in office:
 - No significant side effects, except mild appetite decrease, possible irritable mood generally
- You reviewed Vanderbilt rating scales and they are positive for more hyperactivity and inattentive signs.

Ryan: Audience Answer

Your next move should be to:

- A. Decrease dose due to likely irritability SEs
- B. Increase dose to 54 mg OROS MPH
- C. Increase dose to 72 mg OROS
- D. Add clonidine/guanfacine
- E. Switch to another stimulant, e.g., mixed amphetamine salts
- F. Add an atypical antipsychotic

Paul

- 17 year old Male
- 11th grade and struggling to pass this year
- Working in fast-food restaurant
- Last year was suspended and sent to alternative school for smoking giving his girlfriend some of his Focalin.
- Smokes weed on the weekends, and states he has cut down from daily smoking.

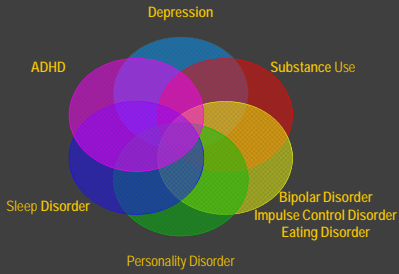
- Mother tells you did better on his stimulant.

Treatment of ADHD in the Context of Substance Abuse

- Atomoxetine (Strattera)
- Guanfacine XR (Intuniv)
- Clonidine XR (Kapvay)
- Lisdexamfetamine (Vyvanse)- all stimulants are labeled with black box warning for abuse
- Bupropion* (Wellbutrin)
- Modafinil* (Provigil)- Schedule IV

*Not FDA approved for ADHD

ADHD and Co-morbid Disorders



Julia

- 16 y/o female, 10th grade
 - h/o ADHD for 8 years
 - Previously stable on short-acting MPH 15 bid
 - Continues to be compliant on medication
- Presents w/increasing symptoms over last 3 months (beginning of September):
 - Irritability, restlessness, always tired, some trouble sleeping, loss of appetite, feels somewhat demoralized lately, no suicidal ideation.

Julia Assessment Information

- Reports no new psychosocial or environmental stresses
- Updated physical exam, blood work, UA, all negative
- Symptoms of anxiety and depression, but did not meet full Anxiety or MDD criterion

Julia

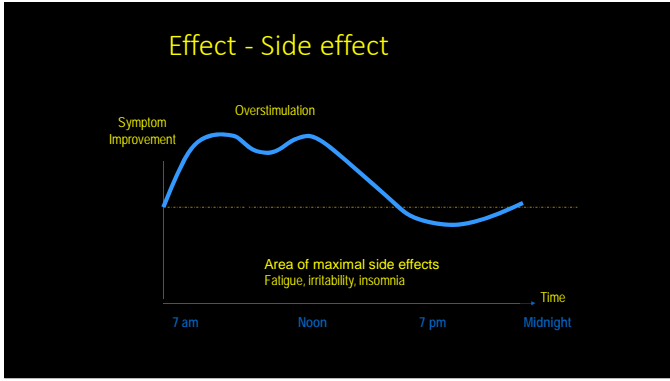
- Julia's most likely diagnosis?
- Your management strategy?

Additional Information

- Julia notes increased problems with homework load, completing homework, high stress high school.
- Julia notes increased inattention problems, worries about college and/or vocation, and doing well on her PSATS
- Julia notes that she feels happy during the summer, during school vacations, weekends, and other times when she has little/no homework.

Julia

- Does this change your diagnosis?
- Your management strategy?
- How does the CMAP algorithm apply to Julia?



Robert

- 10 y/o male at home, an only child
- Most recent problem: threatened to assault teacher
- Several recent suspension, school demanding evaluation
 - Acting up in class, arguing with teacher
 - Hitting and kicking peers
 - Stole money from student's desk
- Normal intellectual functioning by standardized testing, but poor school performance

Robert

- Single mother works late as waitress
 - No contact w/father since birth
 - No h/o trauma or abuse
- Various caregivers (as available): grandmother, aunt, neighbors
- Has been a "handful" since age two
 - Uncontrollable behavior, non-responsive to parental discipline
 - Bullying of younger children when angry
 - Recently stayed out 'til 2am with older teenagers, found and brought home by police
- Previously diagnosed with ADHD, minimal response to long-acting mixed amphetamine salts, 30mg XR

Robert

- Now suspended x 3 days for threatening a teacher. You saw Robert, who was brought in by MGM yesterday, mother not present. Needed "note" to go back to school.
- Physical exam and lab results unremarkable
- Interview with child: angry, blames others for problems, appears sad
- Diagnoses of DSM 5 ADHD and Conduct Disorder based on partner's thorough evaluation
 - Review of past medical records
 - Interview with mother and child
 - Parent and teacher rating forms
 - Psychosis and major mood disturbances ruled out

Robert

- You have never met the mother, since Robert was treated by your partner, who just left the practice. Lucky you, you picked up his cases!
- Mother arranged yesterday's visit as an "emergency", for your note for Robert to go back to school
- You insisted she come in to see you, before your note
- Single parent, age 37, described as "flighty and 'MIA'" by partner in the notes
- Partner notes that mother often does not come to doctor's appointments, usually brought in by maternal grandmother
 - Language problems...MGM from Mexico, speaks only broken English

How would you modify Robert's current management?

- What psychosocial/educational interventions would you recommend for the child/mother?
- How would you optimize his current pharmacologic treatment?

Modified Motivational Interviewing

•LEAP

- Listen
- Empathize, then Educate/Exchange
- Agree
- Partner, Plan and Proceed

LEAP

•LISTEN

- Active listening!
- Don't worry about your response; there is nothing else to do when you are listening than to listen and try to see the problem from the parent's perspective!
 - Be curious – Use COLDER
- Open-ended questions
 - "Can you help me understand..."
 - "How has this affected...?"
 - "What did you imagine caused...?"

LEAP

•EMPATHIZE

- Allow yourself to feel the feeling that is transmitted, along with their words!
 - Heart-string harmonics
- Identify and restate what the parent/youth said, and restate the feeling
- "What has this been like for you?"

LEAP

• ENGAGE / EDUCATE / ENCOURAGE

- Engage & invite them to work together to find solutions – get their permission! “e.g., Would it be okay with you...”
- Educate / encourage in “First principles”
 - Child’s basic needs
 - To FEEL loved (not just “BE” loved)
 - To be IMPORTANT to someone
 - To be GOOD AT something
 - To BELONG to a group of others
 - It takes a parent, plus a village
 - Dx and Treatment

LEAP

• EXCHANGE

- Exchange information...
 - What do you think? What will work for you? How might we do this? What makes sense, what doesn’t?
 - Share with the parent and family your ideas of what might work.

LEAP

• AGREE

- Find areas that you both agree on to focus first
- Enhance child self-monitoring
- Enhance parent support, advocacy: write it out as a “prescription”
- “I can’t do it without you”

• PARTNER, PLAN, & PROCEED

- Parent is the vital, most-important team member
- Shared decision-making
- Mentoring & building parent’s advocacy skills
- Facilitate finding other team members
- On-going problem-solving, modify as needed

Top Ten Tips in Working with "The Tough Cases"

- Listen:
 - Ask about their view of the problem
 - Avoid parental blame or lecturing
- Empathize / Engage / Encourage / Exchange
 - Recognize their efforts, and the challenges they face
 - Look for shame, stigma, maternal depression
 - Educate/encourage in "First Principles"
- Agree
 - Find areas that you both agree on to focus first
- Partnerships with parent and youth are critical
 - Enhance child self-monitoring
 - Enhance parent support, advocacy: write it out as a "prescription"
 - Multiple problems require multiple solutions
 - Medication alone rarely adequate
 - "I can't do it without you"

Top Things to Do and Say, from Parents

DO tell them:

- There is hope for your child's mental health problem;
- You are not alone in dealing with this problem;
- Your child's mental illness is not your fault;
- I understand what you are saying and dealing with; and
- Your child has many strengths

Don't make:

- Dismissive comments minimizing parental complaints
- Blaming comments that directly or indirectly questioned parenting or implied they had caused their child's mental illness

Stimulants: Tips and Pearls

- Effective for both motor and attention symptoms
 - Effects on motor activity may persist longer than effects on attention
 - Higher doses may be needed for attention symptoms than for motor symptoms
- Dosing late in the day may increase the risk of insomnia
- Children who are not growing or gaining weight should stop treatment, at least temporarily
- Some patients respond to or tolerate methylphenidate better than amphetamine, and vice versa
- Half-life and duration of clinical action may be shorter in younger children
- Some patients may benefit from occasional 5-10 mg immediate release added to daily dose of sustained release
- Should not be used in individuals with structural cardiac abnormalities

Solanto, Behv Brain Res. 2002; Stahl, Prescriber's Guide 2005.

Victor

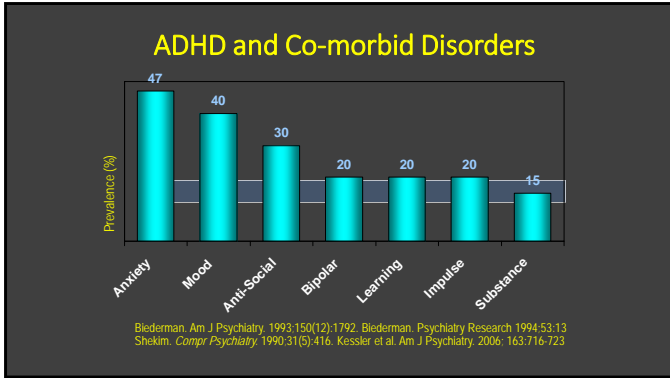
- 15 year old
- Has history of ADHD but has been without medications for several years.
- Declining grades at school and not able to bring them up.
- PCP started on Adderall XR 20mg Daily
- Mother is worried about his change to get college scholarship because she is a single mother.

Victor

- Has been on Adderall XR 20mg for 3 weeks.
- Failing
- Missing school
- Increased worry and tension.
- Mother is crying in your office, she is scared that something is wrong and she is losing her baby boy. He does not want to go to church anymore.
- Victor denies AVH, SI, HI

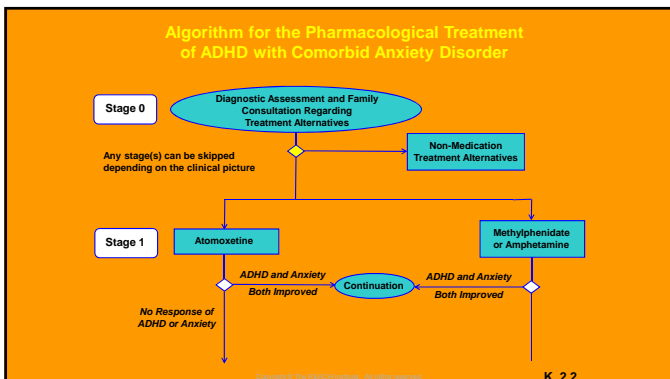
Your next step should be to:

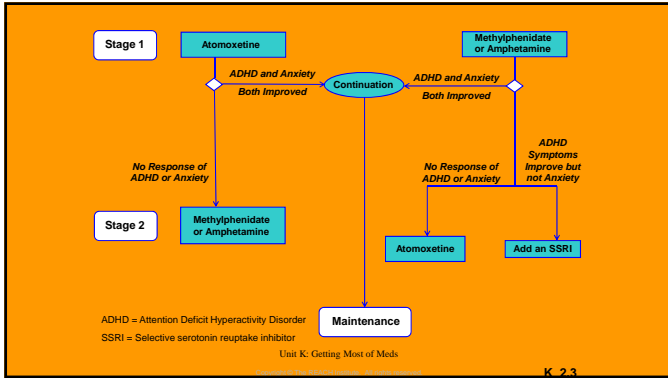
- A. Decrease dose due to likely irritability SEs
- B. Start Trial of SSRI
- C. Increase dose to Adderall XR 30mg
- D. Add clonidine/guanfacine
- E. Start Strattera, consider d/c Adderall XR
- F. Switch to another stimulant, e.g., mixed amphetamine salts
- G. Add an atypical antipsychotic



RESOURCE SLIDES: CMAP Algorithm for the Pharmacological Treatment of ADHD with Comorbid Anxiety Disorder

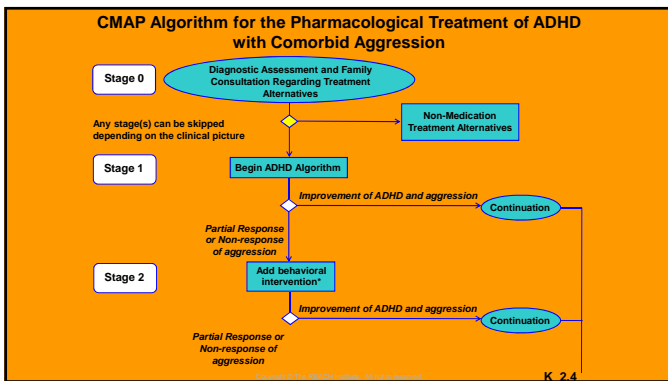
Pliszka SR, Crismon ML, et al. J Am Acad Child Adolesc Psychiatry
2006;45:642-57.

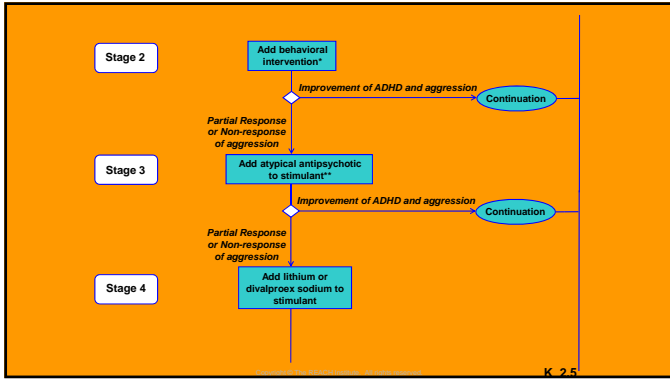


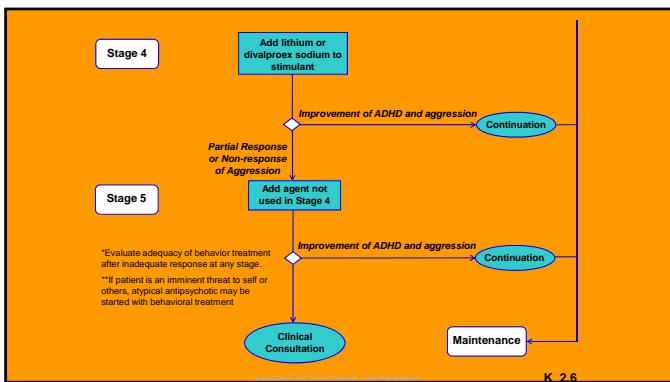


RESOURCE SLIDES:
CMAP Algorithm for the Pharmacological Treatment of ADHD with Comorbid Aggression

Pliszka SR, Crismon ML, et al. J Am Acad Child Adolesc Psychiatry 2006;45:642-57.



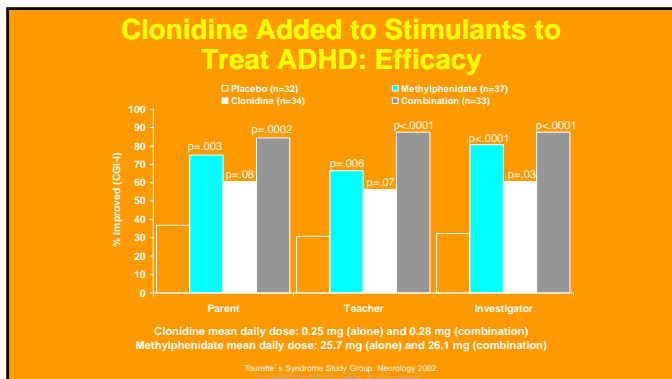


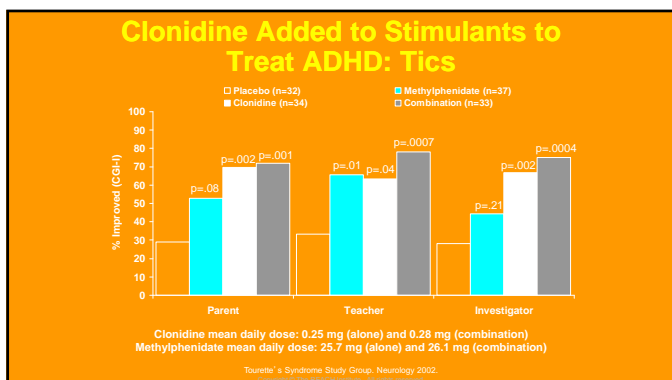


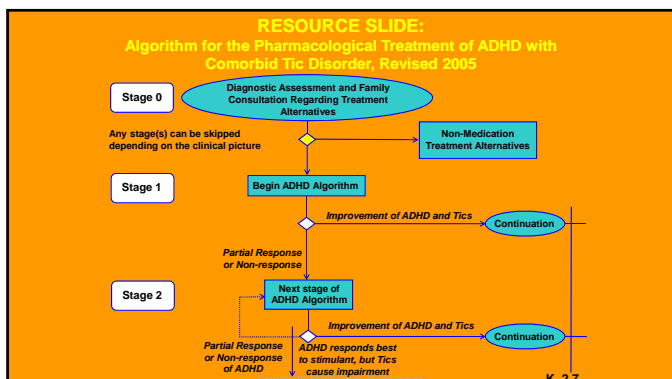
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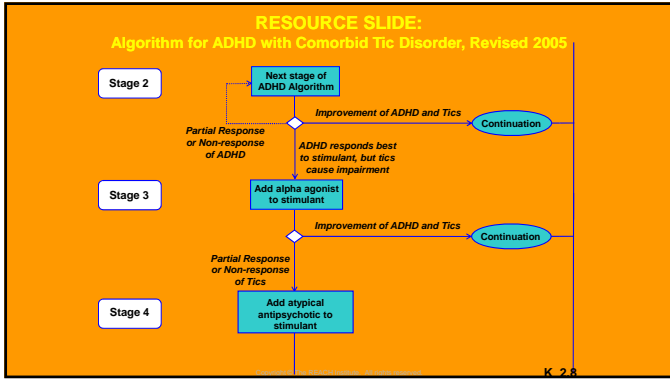
CMAP Algorithm for the Pharmacological Treatment of ADHD with Comorbid Tic Disorder

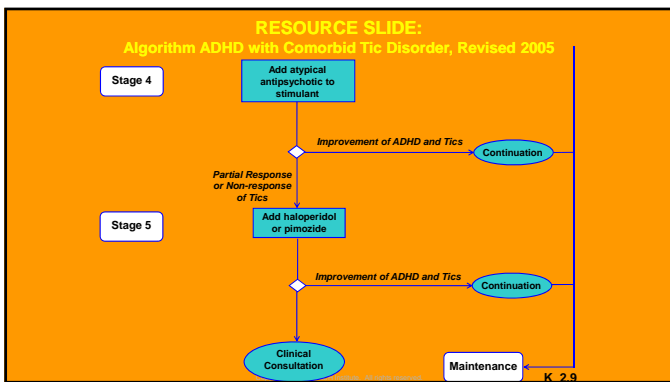
Pliszka SR, Crismon ML, et al. *J Am Acad Child Adolesc Psychiatry* 2006;45:642-57.












Thank you

- Special thanks to educational program 

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