ADHD Plus: Treating ADHD Along with Common Comorbid Disorders

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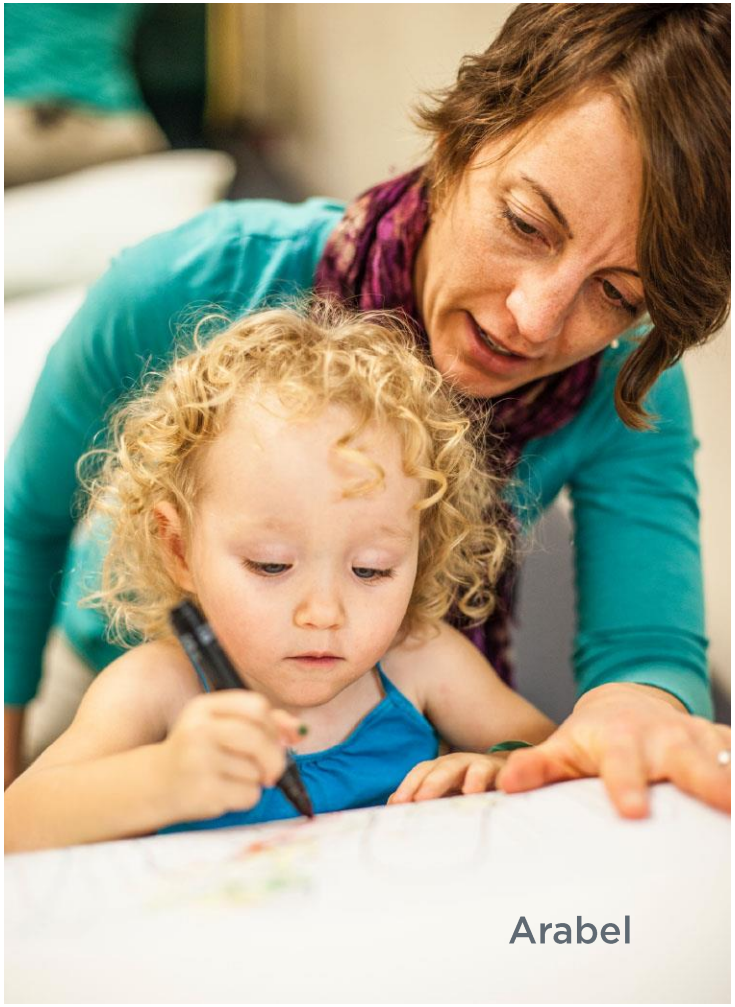
Learning Objectives



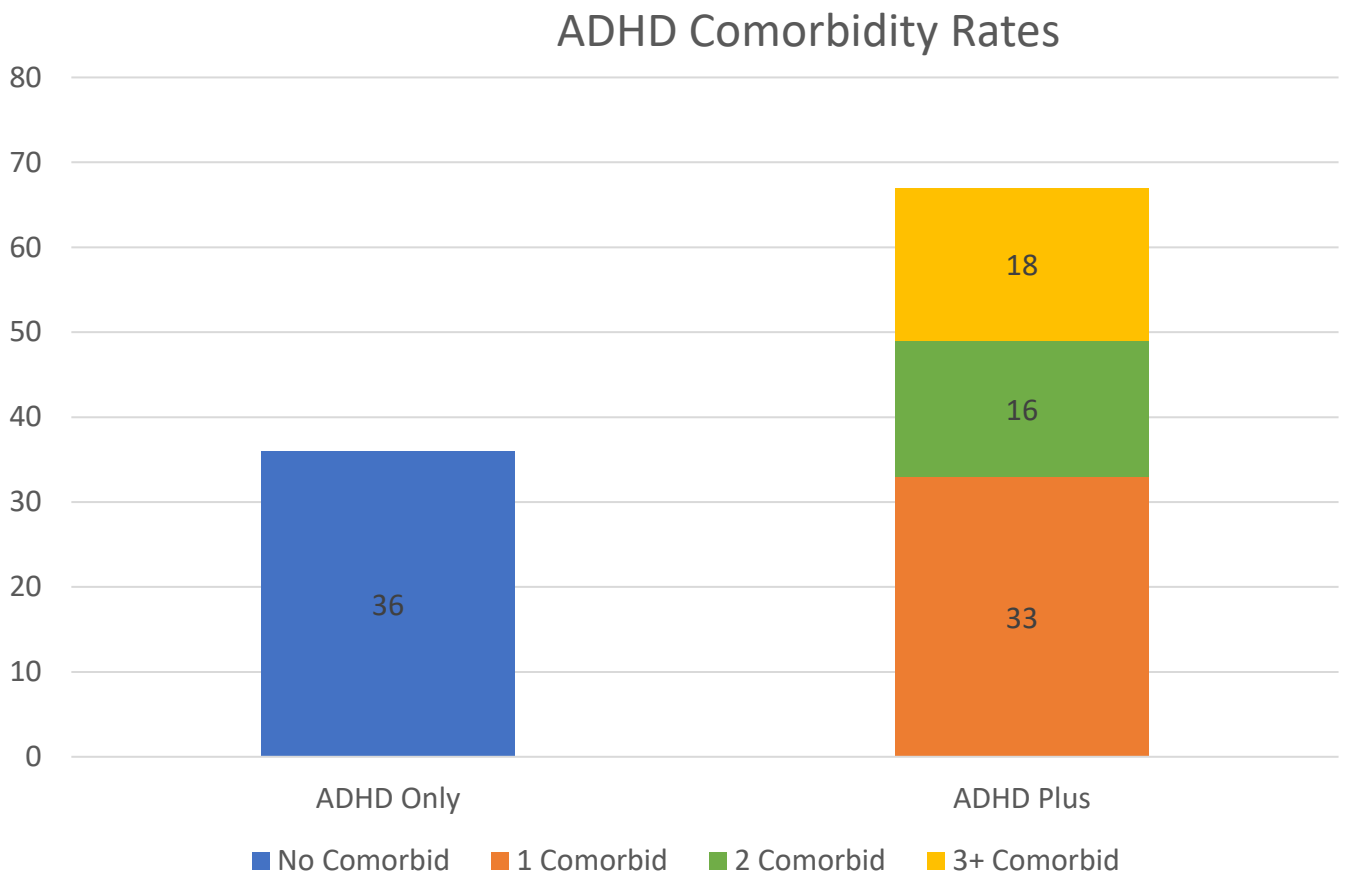
Attendees will understand pathways to comorbidity in ADHD and choices for treatment by:

1. *Considering biological, environmental and treatment interactions contributing to ADHD comorbidity.*
2. *Learning treatment alternatives to address comorbidity and minimize risks of combination treatments.*

ADHD Statistics

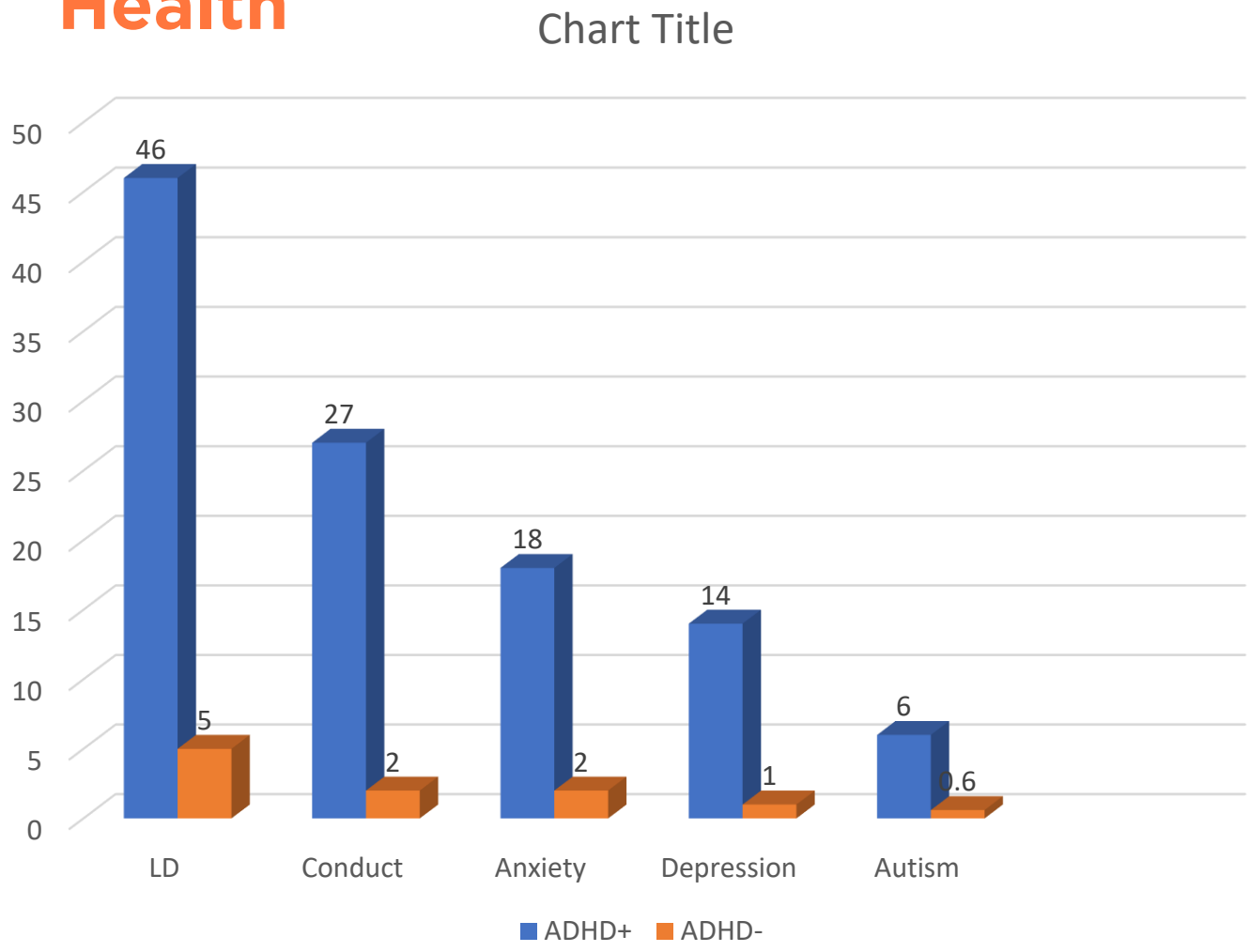
- *Prevalence: 7.8%-11.0%*
- *Boys>Girls*
- *Median age at diagnosis: 6*

https://www.nimh.nih.gov/health/statistics/attention-deficit-hyperactivity-disorder-adhd.shtml Accessed 3/13/20.



Larson, et al – Pediatrics 2011; 127:462-470

Parent Reported Diagnosis: 2007 National Survey of Children's Health



ADHD and Autism

- *In prior version of DSM, ASD was an exclusion criterion for ADHD. Not so in DSM-5.*
- *22-83% of children with ASD meet criteria for ADHD*
- *Shared heritability:*
  - *50-72% of contributing genetic factors overlap*

Sokolova E. J Autism Dev Disord. 2017

How does our understanding of ADHD help with patient education and guiding treatment decisions?

Attention-Deficit/Hyperactivity Disorder (ADHD) is an illness. It Fits Chronic Illness Model (medical analogy: DM Type I)

- *High heritability (74%) supports biological etiology explanation and understanding as an illness*
- *It is expected to be chronic with high persistence (5-75%) – at least through childhood*
- *Often treatable with single drug using measurement-based care after adequate patient education at point of diagnosis*
- *Comorbidity explained: Secondary pathology (ODD, Conduct Disorder, substance use) may be more likely if ADHD is undertreated.*
- *Additional consequences of undertreatment may include academic failure and problems with family and peer relationships, resulting in stress-related emotional problems.*

OR: ADHD is one part of a developmental syndrome related to a primary cause with other developmental consequences

ADHD presenting as just one dimension of developmental problems in autism, FAS and other syndromes with presumed early genetic or toxic cause.

Treatment implications: improvement of ADHD symptoms may be of benefit, but a return to typical development is not expected and ongoing supports will be needed.

ADHD is a common illness, and other common disorders may occur by chance (medical analogy: asthma and migraine)

ADHD, anxiety and depressive disorders are all common and would be predicted to co-occur by chance.

Separate treatments used, but presence of one disorder may complicate treatment of the other.

OR: ADHD is one symptom cluster among several overlapping syndromes related to complex genetic vulnerability and environmental factors (medical analogy: atopic illnesses)

ADHD has polygenic inheritance, and comorbidity is much higher than expected by chance

Characteristic symptom clusters may be seen such as seen with Tourette's – ADHD, OCD, Tics

Treatment implications – Treatments still follow conventional approaches and combination treatments may be necessary for comorbid diagnoses.

Or: Other illnesses can mimic ADHD so that misdiagnosis is possible, and wrong diagnosis can lead to worsening (or at least missed treatment opportunity)

ADHD symptoms that may be better explained as symptoms of Bipolar Disorder, Psychosis, PTSD, substance use

Treat the correct disorder and secondary symptoms resembling ADHD will go away. Children with anxiety, depression, sensory issues or learning disorders may be seen as inattentive.

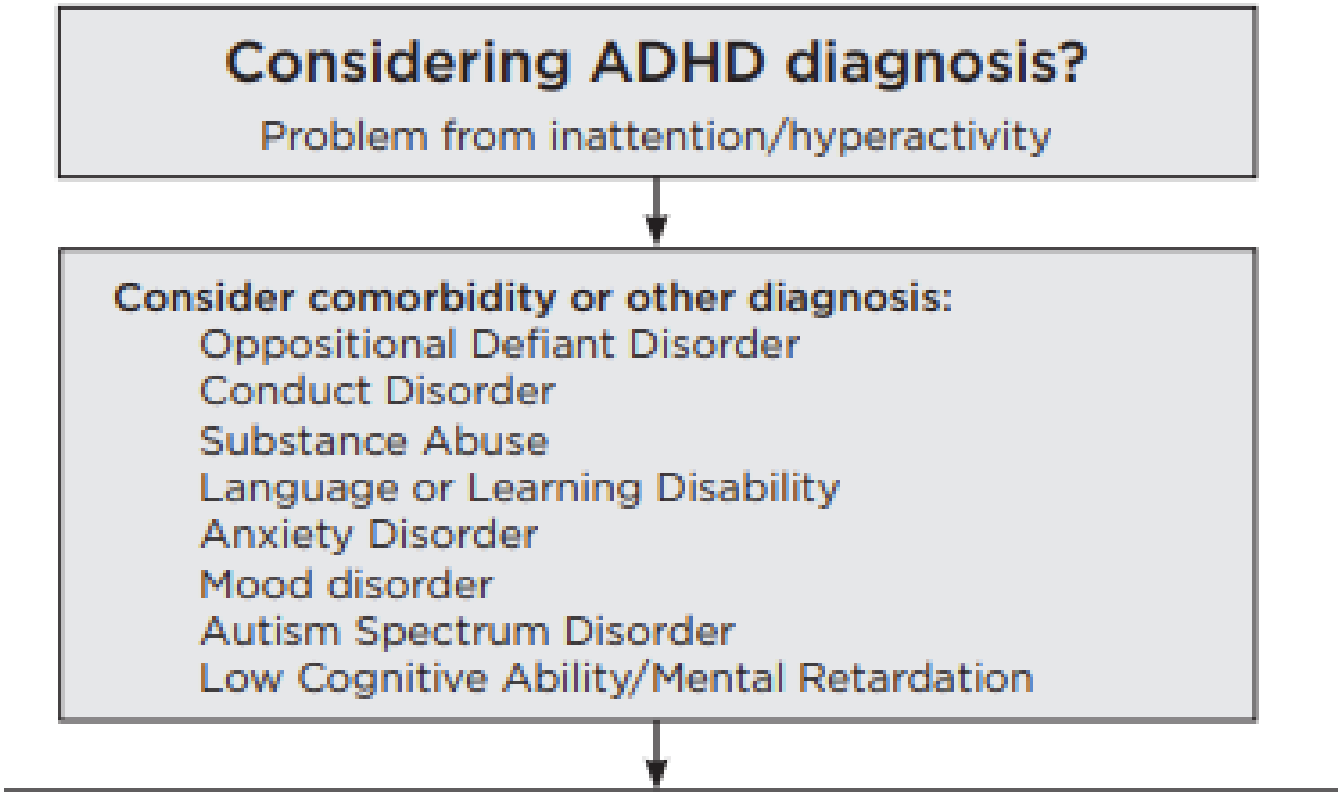
Treatment implications – additional caution may be appropriate with some ADHD treatments (stimulants) in some cases.

Consider psychiatry referral for concerns when treatment response is very unusual or psychotic illness is suspected.

CONCLUSIONS: Clinical management of ADHD must address multiple comorbid conditions and manage a range of adverse functional outcomes. Therapeutic approaches should be responsive to each child's neurodevelopmental profile, tailored to their unique social and family circumstances, and integrated with educational, mental health and social support services.

Pediatrics 2011;127:462–470

From the PAL Care Guide



Evaluation

In addition to gathering information about the presence of ADHD symptoms, screen for developmental problems, oppositional behavior, conduct disturbance, anxiety, depression, trauma and substance use.
The Vanderbilt Rating Scales are very helpful in this regard with comorbid symptom scales!

Follow-up with more thorough assessment in areas where screen is positive. Resources in other Care Guide chapters can be helpful.

Treatment Approaches – ADHD comorbid with:

Learning Disability
Disruptive Behavior Disorders
Neurodevelopmental Disorders
Anxiety Disorders
OCD
PTSD
Mood Disorders
Substance Use Disorders
Tics

Learning Disability

- *Optimize treatment for ADHD – Medication treatment for ADHD can be the first intervention.*

- *Ensure adequate assessment of LD*

- *Support appropriate intervention/accommodation at school*

05/27/2021 - Helping Patients and Families Navigate the Special Education Process - PAL May Newsletter

ODD, Conduct Disorder and Aggression

Oppositional and aggressive behavior is often related to impulsivity. Disruptive behavior can improve with optimized treatment of the ADHD and behavioral treatment may be more successful, so medication treatment for ADHD can be an initial intervention. But don't fall into trap of trying to perfect a medication treatment that isn't helping with behaviors before family will agree to try therapy.

Parent Management Training

Parent Management Training

Parent Management Training includes several evidence-based treatment models such as the Incredible Years parent training (IYPT), Positive Parenting Program (Triple P), and Parent management training – Oregon model (PMTO). The Explosive Child approach - Collaborative Problem Solving (CPS) - has been adapted to inpatient programs.

PMT – cont'd

Young Children: strongly recommend a therapist to teach behavior management skills for parents. More models for this include Parent Child Interaction Training (PCIT), the Barkley method and 1-2-3 Magic.

Child-Directed Play (CDP) described in Care Guide – regularly scheduled individual attention. Narration of child's play activity without controlling or teaching.

Anxiety Disorders

- *Older literature will include OCD and PTSD as anxiety disorders*
- *Stimulants can make anxiety better or worse.*
- *SSRIs can help anxiety, but activation side effect can be more common with younger children, DBDs*
- *Serotonin Syndrome risk with amphetamine + SSRI*
- *Fluoxetine slows atomoxetine metabolism (lower doses may be needed).*
- *Guanfacine and clonidine may help anxiety and ADHD, but perhaps not help a great deal with either.*
- *Atomoxetine "Patients with Concomitant Illness – Does not worsen anxiety in patients with ADHD and comorbid Anxiety Disorders."*
- *It can be a judgement call about which disorder is primary and would be most fruitful to treat first.*

Therapies work well when there is comorbid anxiety.

Multimodal Treatment Study of Children with ADHD (MTA)

- *Multisite RTC funded by NIMH and Department of Education*
- *579 7–9 year old children with ADHD combined type*
- *No exclusions based on comorbidity*
- *Randomized to medication management, behavioral therapy, combined (med mgmt + beh tx), community care for 14 months*

- *Archives of General Psychiatry, December 1999*

MTA Comorbidity

Oppositional Defiant Disorder – 39.9%

Anxiety Disorder – 33.5%

Conduct Disorder – 14.3%

Tic Disorder - 10.9%

Affective Disorder – 3.8%

Mania/hypomania – 2.2%

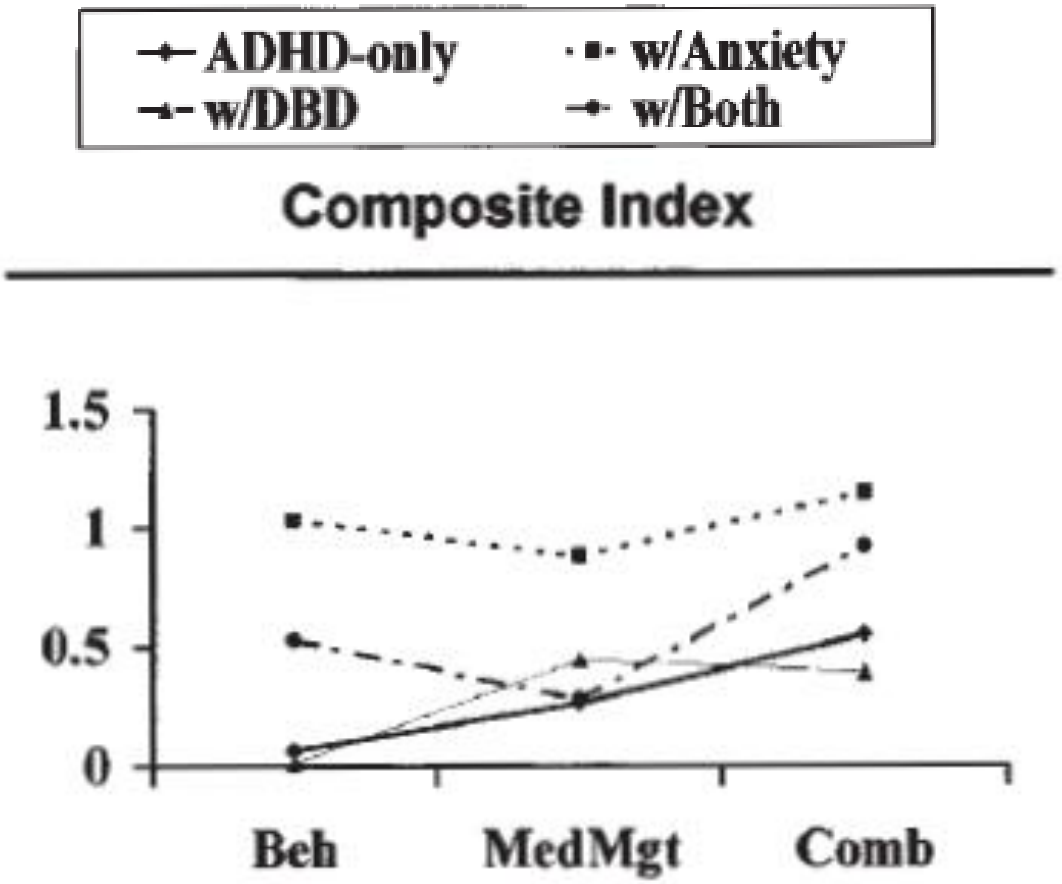
MTA medication treatments by end of study in 289 MM, CT subjects

Methylphenidate 73.4%
D-amphetamine 10.4%
Pemoline 1%
Imipramine 0.3% (1 subject)

Bupropion 0.3%
Haloperidol 0.3%
No medication 3.1% (did best on placebo)

7 reported "severe side effects" of which 6 of 11 were depression, worrying or irritability

MTA Outcomes by Comorbidity x Treatment



J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 40:2, FEBRUARY 2001

Autism and other Neurodevelopmental Syndromes

Stimulant side effects more likely

Response may be less predictable

Treatments targeting other symptoms and comorbidities may be needed (sleep, aggression, depression, anxiety)

ABA therapy

Tic Disorders

- *Stimulants can precipitate or worsen tic disorders, but probably don't "cause" or permanently worsen tic disorders.*
- *Still appears as a contraindication on some methylphenidate product labels but not those most recently approved.*
- *Alpha-2 agonists (clonidine, guanfacine) are ADHD treatments also used for treatment of tics*
- *Antipsychotic medications can treat tics and are likely to reduce ADHD symptoms*
- *Atomoxetine: "Patients with Concomitant Illness - Does not worsen tics in patients with ADHD and comorbid Tourette's Disorder."*

Mood Disorders

Depression

- *Is it a depressive disorder or adjustment disorder?*
- *Stimulants can make depression symptoms better or worse, quickly or slowly. Watch sleep, weight, irritability.*
- *Effective ADHD treatment can make school less stressful with more success experienced and with reduced family conflict.*
- *SSRIs can help depression, but activation side effect can be more common with younger children, DBDs*
- *Bupropion could treat ADHD and depression, but not first line for either (contraindicated with seizure or eating disorders)*

Emphasize therapy (CBT)

Bipolar Disorder

Less common than unipolar depression.

Chronic irritability is not bipolar disorder.

SSRIs, atomoxetine, stimulants can all worsen/precipitate mania, but activation side effect is not mania.

Treat the mood disorder first if diagnosis is clear. (Years of treatment for ADHD before diagnosis is clear is not uncommon.) There is considerable symptom overlap with mania and ADHD. Treatment of mania may reduce ADHD symptoms enough that additional treatment for ADHD is not necessary.

Stimulants are usually safe in bipolar disorder with adequate mood stabilizing treatment.

Substance Use Disorders

Substance use can explain problems with attention

Increased risk for diversion

For adolescents with a history of good stimulant response who are getting more involved in substance use (and less involved in school), discuss decisions about whether to continue treatment.

Viloxazine (Qelbree™)

FDA approved April 2021 for treatment of ADHD in 6-17 year olds.

Norepinephrine Reuptake Inhibitor (NRI), 5HT2B antagonist, 5HT2C agonist

Marketed as antidepressant (Europe) 1976-2002. Orphan designation by FDA in 1984 for narcolepsy/cataplexy.

Two RTCs (vs. imipramine) for enuresis

Viloxazine (Qelbree™)

Black box for suicidal thoughts and behaviors

Most common side effects somnolence, decreased appetite, fatigue, nausea, vomiting, insomnia, irritability

Monitor heart rate and blood pressure, activation of mania or hypomania

Viloxazine (Qelbree™)

Listed drug interaction based on Cytochrome P450 inhibition: CYP1A2 (strong), CYP2D6 and CYP3A4 (weak)

Starting dose 100 mg (6-11 years old), 200 mg (12-17), can titrate weekly to maximum dose 400 mg, though little evidence of better response at higher doses.

Capsules 100, 150, 200 mg - can be sprinkled

Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Fluoxetine, sertraline, escitalopram, fluvoxamine, duloxetine

Approved for treatment of depression, OCD, GAD in youth. SSRIs are first line for medication treatment of depressive and anxiety disorders in youth

Activation side effect

Serotonin Syndrome

What is Activation?

- *A cluster of symptoms that represent a hyperarousal event characterized by impulsivity, restlessness, and/or insomnia.*
- *Not mania, but may have similar symptoms*
- *Starts and stops when antidepressant is started and stopped*
- *More likely in younger, disruptive behavior disorders*
- *Start with very low doses (4-5 mg fluoxetine, 12.5 mg sertraline) and titrate gradually*
- *Are some antidepressants more activating than others? There is little comparative data, but clinical lore is fluoxetine > sertraline, citalopram > duloxetine.*

What is Serotonin Syndrome?

Serotonin syndrome signs and symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

Risk increases when serotonergic drugs are combined - FDA Warning/Precaution for amphetamine products combined with serotonergic antidepressants

Guanfacine and Clonidine

- *α2-adrenergic receptor agonists originally approved for treatment of hypertension, now approved as extended-release forms (Intuniv, Kapvay) for treatment of ADHD*

- *The presynaptic alpha-2 receptors signal that enough norepinephrine has already been released, so agonists tend to decrease sympathetic nervous system arousal.*

- *Can be used alone or in combination with stimulants with complimentary or moderating side effects*

Guanfacine and Clonidine

- *Used for sleep onset (especially clonidine) and to address symptoms outside of stimulant hours*
- *May be helpful in situations where comorbidity with overarousal may be a problem (ASD, PTSD)*
- *Off label treatment for tic disorders*
- *Good safety profile but tell parents not to increase dose on their own or stop it abruptly. Monitor heart rate and blood pressure.*

Atypical Antipsychotics

- *Risperidone and aripiprazole are approved for treatment of irritability and aggression in autism with lower doses often adequate. Aripiprazole is approved for Tourette's Disorder*
- *Several approved to treat mania down to age 10*
- *May reduce aggression in other disruptive behavior disorders but with substantial risk and monitoring burden, mostly related to weight gain*
- *Monitoring for all atypical antipsychotics: AIMS exam at baseline and Q6months due to risk of tardive dyskinesia. Warn of dystonia & NMS risks. Weight checks, fasting glucose/lipid panel Q6months at minimum.*

Summary

- *ADHD with comorbid diagnosis is more common than ADHD alone.*
- *There are a several explanatory models for high rates of comorbidity. Some will fit better than others in explaining diagnosis and choosing treatment*
- *Medication treatment algorithms for each disorder are usually not changed much depending on comorbidity status, but sequencing and combining medications and therapies and interpreting response can be more challenging*
- *Therapies can be very effective for addressing comorbid symptoms without using overly-complicated medication treatments.*

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