

Autism: Update on Diagnoses and Treatment Issues in Primary Care

ABA Therapy and Psychotropic
Medications

Disclosures

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.
- I will be discussing off label use of medications

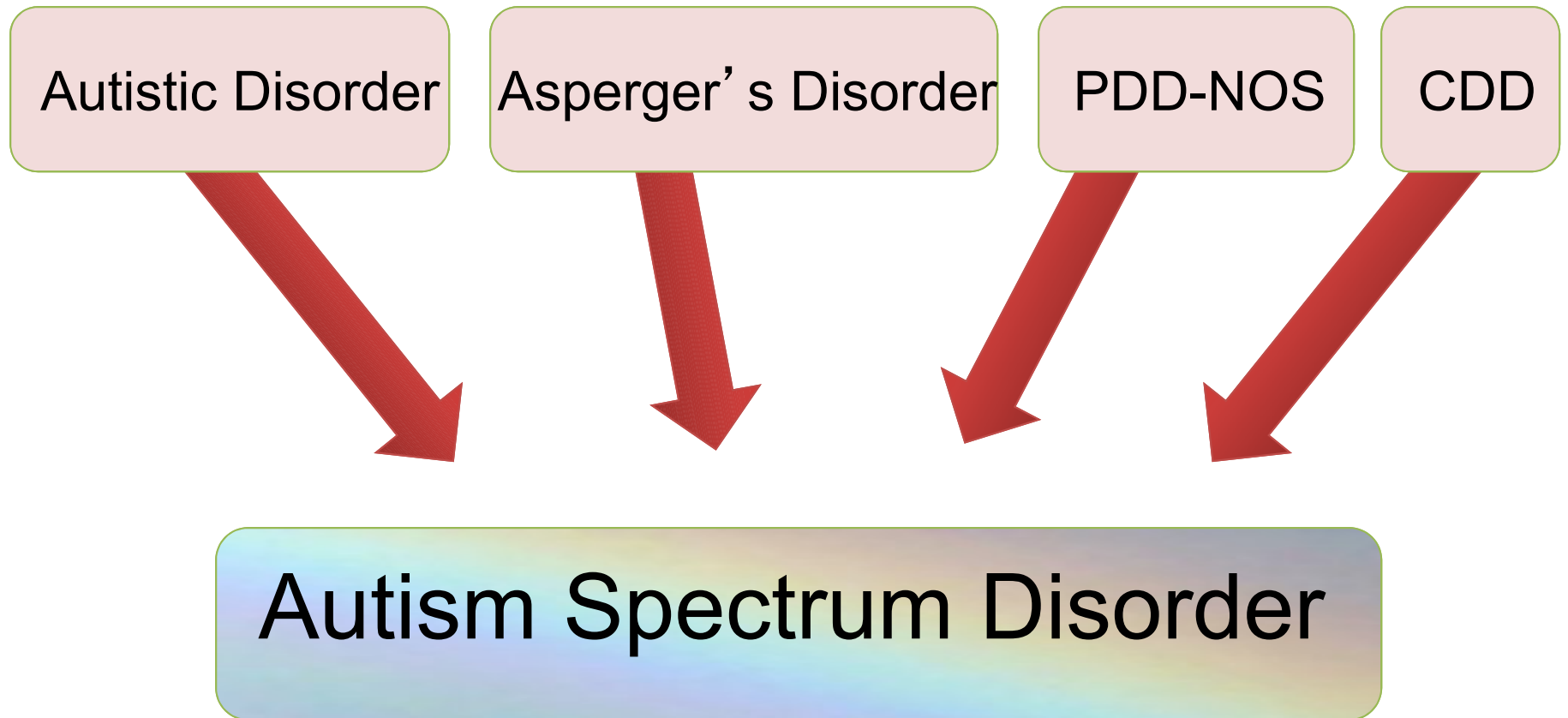
Objectives

- 1) Participants will review the change in autism diagnosis criteria per DSM-5 and implications for diagnosis
- 2) Participants will learn about the role for Applied Behavioral Analysis therapy, including common targets and how best to advocate.
- 3) Participants will learn the evidence base for commonly prescribed psychotropic medications to address core symptoms of autism and related behavioral problems.

Evolving views on Autism

- Results from complex interplay of genetic, environmental and developmental factors
- Disorder involving communication and behavior
- Different “autisms” are now thought to have different clinical courses
- Different pathways, similar presentations
- Similar pathways, different presentations

Autism



Rationale

- *spectrum* concept better captures variability in symptom presentation, time-course and response to treatment
- separation of ASD from typical development is reliable & valid while separation of disorders within the spectrum was not (e.g., Asperger v. PDD-NOS, HFA v. Asperger)
- prevalence estimates frequently reflect *allowable* diagnosis for services (geographic, provider catchment areas) and other biases (racial, SES)

DSM-5 ASD Criteria

A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:

1. Deficits in social-emotional reciprocity
2. Deficits in nonverbal communicative behaviors used for social interaction
3. Deficits in developing and maintaining relationships

B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following:

1. Stereotyped or repetitive speech, motor movements, or use of objects
2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change
3. Highly restricted, fixated interests that are abnormal in intensity or focus
4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment;

C. Symptoms must be present in early developmental period (but may not become fully manifest until social demands exceed limited capacities)

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Methodological Changes

- Age of onset – “present in early developmental period” and do “not become fully manifest until social demands exceed limited capacities.” (C.)
- Reporting sufficient- “currently or by history”
- History sufficient (A. and B.)
- Severity rating – based on “need for support” for each of the two primary symptom categories (A. and B.)
- Increased use of specifiers for fuller picture

Severity

Severity level

Level 3

"Requiring very substantial support"

Social communication

Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others.

Restricted, repetitive behaviors

Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.

Level 2

"Requiring substantial support"

Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others.

Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.

Level 1

"Requiring support"

Without supports in place, deficits in social communication cause *noticeable* impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful response to social overtures of others. May appear to have decreased interest in social interactions.

Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

Specifiers

- Quickly captures and draws attention to major variables that impact presentation and course
- In conjunction with Severity Indicators, better reflects huge individual variability in presentation and disability
- *Specify if:*
 - with or without accompanying intellectual impairment** – huge impact on course and outcomes
 - with or without accompanying language impairment** – de-emphasis on language skills persay; recognition of complexity of social interactions
 - associated with a known medical or genetic condition or environmental factor** (VFCS, Down Syndrome, Fragile X, valproate exposure, etc)
 - with catatonia**

What's not Accounted For

- Speech/Language delays (now a specifier)
- Behavioral difficulties/temper tantrums
- Problems w/ imagination and imitative play
- Social Anxiety/shyness

How are changes impacting diagnosis?

- NIH Prevalence Study (2014) n=6577 (Maenner *et al*)
 - 81.2 % met DSM-5 ASD criteria
 - higher rates w/ intellectual disability (86.6%) than without (72.5%)
 - 10/1K (DSM-5) versus 11.3/1K (DSM-IV)
- Clinic Study (Harstad *et al.* 2014) n=227
 - Median age 3.95 yrs; majority w/ intellectual disability
 - Conclusions: “good model fit across gender and IQ” and will identify “different, albeit overlapping population”

Who is Vulnerable?

- PDD-NOS
- “High Functioning” ASD
- Children < 30 months

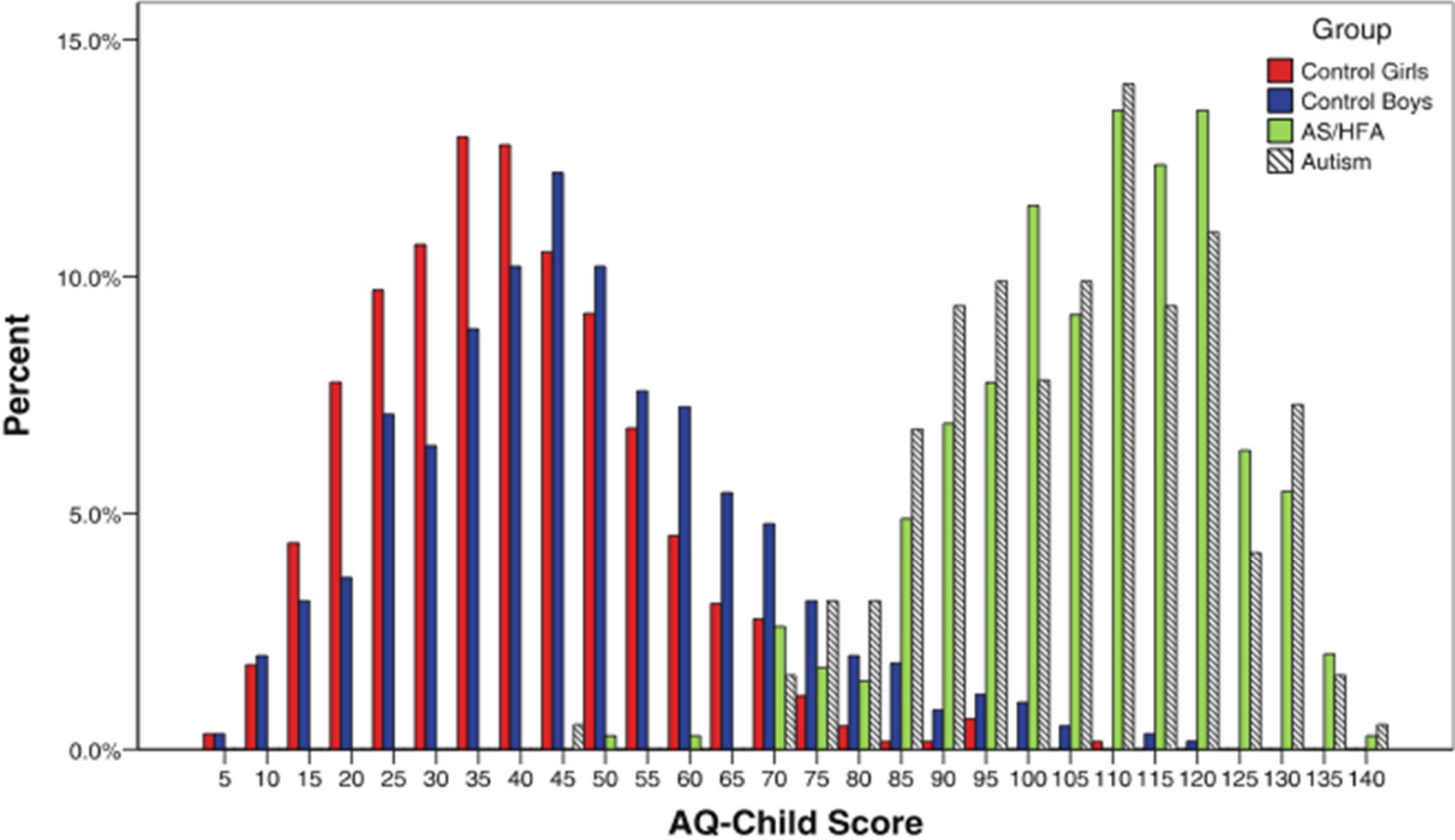
Implications:

- Social Communication Disorder = the new Aspergers?

The Asperger's Debate

- wide variation among expert researchers in how the same patients were being diagnosed
- in epidemiologic studies, evidence of socio-economic and racial bias
- poor stability of autism vs. Asperger's diagnosis over time
- four original cases of Asperger's disorder met DSM-IV-TR diagnostic criteria for autism
- profile of autism assessment scale scores are the same for high functioning autism and Aspergers

Autism vs. Asperger's Similarities



AS=Asperger's Disorder, HFA=high functioning autism
 AQ-CS score >76 is positive

Graph from Auyeung B, et al. J Autism Devel. Disord

PAL Conference - Winthrop - June 2015

For both core deficits related to autism or associated problem behaviors, primary interventions are behavioral and environmental. If insufficient, then consider medication.

Applied Behavioral Analysis

- most widely validated and accepted treatment for ASD
- specific form of behavioral therapy
- systematic application of scientifically validated principles of human behavior to change socially significant behaviors.
- involves use of scientific methodology to reliably demonstrate that behavioral improvements are caused by the prescribed interventions.
- empirically validated approach to improve *behavior and skills deficits* related to core impairments of autism
- expensive and time intensive

Functional Behavior Assessment

- Can be important step in identifying target symptoms and environmental factors that need to be considered in developing ABA treatment plan
- Involves evaluation of environmental variables that maintain challenging behavior
- Identifies effective interventions to reduce challenging behaviors and teach appropriate replacement behavior.
- This is a great thing to ask school to perform as part of IEP assessment

Common ABA Targets

- In framing to parents, schools or insurance company, consider both need for *skill acquisition* and/or *reducing problem behaviors* as goals
- Skills – functional communication, social interaction, flexibility in play, frustration tolerance, self-care, affect regulation, relaxation strategies
- Behavioral targets – tantrums, self-injury, physical aggression, property destruction, self-stimulation, pica, elopement/escape behaviors, inappropriate social interactions/boundaries

What is the state of WA state?

- Washington State Supreme court decision (O.S.T v Regence) ruled against blanket exclusions of ABA, SLP, OT and PT for ASD
- Blanket exclusions violate state and federal mental health parity law (2005)
- WA state Insurance Commissioner in October 2014 ordered private insurers to stop denial for medically necessary mental health treatment based on blanket exclusions (which includes ASD)
- Recent mandate includes review of denials back to 2006 for possible re-imburement.

What is PCP role?

- Refer for initial ASD evaluation (suspected) or confirmation of diagnosis (COE referral – all Medicaid, some private insurance)
- Identify COE near you
(<http://www.hca.wa.gov/medicaid/abatherapy/pages/index.aspx>)
- Advocate at school level for appropriate assessment (FBA, cognitive testing, adaptive functioning) and supports (behavioral support, social skills, SLP, OT, etc)
- Be aware that eligibility and access to ABA are changing rapidly
- Document to services – indicate ongoing challenges related to core deficits of ASD
- At this point, general practitioners cannot write ABA order

Pharmacotherapy for ASD

Things to Consider

- What is the potential risk or impact of behaviors ? (harm to self, harm to others, loss of placement, etc)
- What is the level of behavioral support available?
- Could medication support or augment other interventions?
- Are there psychiatric or medical co-morbidities that need to be considered?
- What is parental level of comfort?
- What is your level of comfort?

Symptom-driven versus diagnosis-driven treatment

- Core symptoms
 - Repetitive behaviors, restricted interests or activities
 - Social communication and social interaction deficits
- Common co-occurring behaviors
 - Irritability/aggression
 - Hyperactivity
 - Sleep problems
 - Self-injury
- Common psychiatric co-morbidities
 - Anxiety
 - Depression
 - ADHD

How does this affect medical decision making?

- Helps set expectations for response to medication
- May influence timeline for treatment and follow-up
- In some cases, may impact dosing
- Important part of conversation about role of non-medication treatments
- Highlights importance of “active” medication management

Challenges in advancing psychopharmacology in ASD

- Lack of widely accepted diagnostic tools for co-occurring psychopathology (anxiety, psychosis)
- Divergence on whether to focus on co-morbid diagnosis (anxiety, depression) OR symptoms domains (aggression)
- Debate about etiology of specific behaviors (e.g. repetitive behaviors)
- Phenotypic and genotypic heterogeneity in ASD population
- High placebo response rates
- Logistical and financial challenges of multi-site trials
- Lack of validated and normed outcome measures

Repetitive Behaviors/Restricted Interests

- Core symptom of ASD
- Multiple etiologies (stereotypy, physical discomfort, anxiety, emotional distress)
- Tend to wax and wane
- Consider degree of impairment and level of distress
- More aggressive treatment indicated if involves self-injury

Psychopharmacology for Repetitive Behaviors

- Risperidone
- Aripiprazole
- Valproic Acid/Divalproex sodium
- SSRIs (citalopram, fluoxetine, clomipramine)

risperidone (Risperdal)

- Effective for reducing repetitive behaviors
- Also effective for irritability and hyperactivity
- Decreases frequency of episodes (delayed “time to relapse” in discontinuation phase of 2 RCTs)
- Low dose (1-2 mg) is typically effective
- High rates of side effects (sedation, weight gain, hyperglycemia, dyslipidemia)

aripiprazole (Abilify)

- Effective for reducing repetitive behaviors
- Also effective for irritability
- Not as clearly effective in decreasing frequency of episodes
- Does not have clearly favorable metabolic side effect profile relative to risperidone (similar to risperidone in one head-to-head trial) (De Hert *et al.* Euro Psych 2011)
- Aggression is more common as side effect versus risperidone
- Weight gain more likely to be an issue in medication naïve, younger and higher baseline weight (Mankowski et al. J Child Adol Psychopharm. 2013)

SSRIs

- Not effective for repetitive behaviors
- High rates of adverse events
- Meta-analysis (Carrasco *et al.* Pediatrics. June 2012) found small but significant effect size disappeared with inclusion of unpublished studies.
- Medications examined = citalopram, fluoxetine, fluvoxamine and clomipramine

Wally

- 15 y/o
- ASD – Level 3 (x2), w/ language impairment, w/ intellectual impairment
- Treatment targets = anxiety, repetitive self-injury, “impulsivity”
- Came to me on high dose sertraline and Intuniv BID
- Parents did not want to try SGA
- Some spikes in behavior
- With time, behavioral support and improved functional communication has done well

Social Withdrawal/communication

- Pentoxifylline (1-hexyl-3,7-dimethylxanthine; serotonin activity) + risperidone
- Risperidone
- Naltrexone
- Lamotrigine

- Oxytocin

Pentoxifylline (akhondzadeh et al; NPBP. 2010)

- Based on evidence of immunologic dysfunction in autism (cytokines, lymphocytes, Igs, TNF synthesis)
- Serotonin affects (synthesis, release, re-uptake)
- DBRCT; n= 40; ages 4-12
- Risp + pento v. risp + placebo
- Improved on ABC-C (irritability, social withdrawal, stereotypic bx, hyperactivity/non-compliance)
- Novel mechanism v. synergy?

Oxytocin

- Insufficient evidence to recommend at this point
- 12 trials currently recruiting
- Timing and dose may important (e.g. impact on up/down regulation of OT receptors at critical times)
- Alternative ways of stimulating endogenous OT are being explored
- Response impacted by timing, gender, trauma, genetics and ??? vasopressin/DDAVP

Irritability

- Risperidone, aripiprazole (FDA Approvals)
- Haloperidol
- Alpha-agonists *
- Olanzapine (side effects)
- Pentoxifylline (+ risperidone)
- Divalproex sodium/valproic acid
- Quetiapine
- Lamotrigine* (AE = insomnia, hyperactivity)

Gavin

- 18 y/o
- ASD – Level 3 (x2), w/ language impairment, w/ intellectual impairment
- Treatment targets = aggression, sensitivity to sounds, behavioral rigidity
- Came to me on quetiapine and clonidine
- History of treatment with paroxetine
- Partial response to quetiapine
- He has done well with addition of very low dose of Haldol

Hyperactivity

- Risperidone, aripiprazole
- Methylphenidate
- Atomoxetine
- Alpha-agonists*
- Naltrexone
- Amphetamines
- Amantadine

Methylphenidate

- Lower response rates than neuro-typical children
- Higher rates of AE (insomnia, decreased appetite, **emotional outbursts**)
- Tolerability improves with higher cognitive function

Atomoxetine

- Better tolerated than MPH
- Most common AE include fatigue, nausea and decreased appetite
- Response improved when combined with parent training but did separate from placebo as stand alone treatment (Handen B, King B. In process)
- Symptoms improvement continued at 6 months

Alpha-agonists

- Some evidence for improving impulsivity (clonidine) and hyperactivity (guanfacine)
- Often tried for before anti-psychotics (irritability or hyperactivity) because of favorable SE profile
- Global functioning improvement with guanfacine
- Several studies underway
- Can take several weeks to months for full affect

Naltrexone

- Can improve hyperactivity and restlessness
- 10 RDBPCs showed no benefit for core symptoms of ASD
- No evidence to support use for SIB

Ethan

- 12 y/o
- ASD – Level 2-3 (x2), w/o language impairment, w/o intellectual impairment
- Treatment targets = ADHD, anxiety, sleep disturbance, eating/feeding issues; question of depression
- Several MPH class trials with irritability at fairly low doses
- Has done well on amphetamines for ADHD
- Did not respond to clonidine or Remeron; activation on citalopram
- Parents did not want to try SGA
- Has done extremely well on lamotrigine

Glutamatergic Agents

- N-acetyl cysteine (NMDA modulator) – 1 small RTC; improved irritability (Hardan A et al. Arch Gen Psych. 2009)
- NMDA antagonists (amantadine, memantine)
 - did not show improvement in multiple RDBPC trials
 - Some promise as adjunct to risperidone

Marijuana

- Unscientific “case studies” / NUPS
- Scientific Basis – altered endocannabinoid signaling in mice with gene abnormality linked to autism and mouse model of Fragile X syndrome
- Erroneous citing of animal literature by mainstream media (Fox, Huffington Post) and online advocacy groups (Mothers for the Medical Marijuana Treatment of Autism, Mothers Advocating Medical Marijuana for Autism)
- Why not?
 - Illegal
 - Untested
 - Increased odds of psychosis (ASD already confers risk)
 - High rates of cannabis abuse in ASD
 - Unrecoverable loss of IQ related to use in adolescence
 - potential negative impacts on sleep, mood, anxiety, memory and executive function

Summary

- There are no medication treatments for core symptoms of ASD
- Medications should be used with appropriate non-medication strategies
- Strongest evidence is for risperidone and aripiprazole targeting irritability and hyperactivity. The potential for serious side effects needs to be considered.
- For hyperactivity alone, methylphenidate is effective but rates of adverse events are high. Alpha-agonists and atomoxetine are reasonable alternatives.
- SSRIs are not effective for repetitive behaviors and rates of activation are high.

Resources

Selected Articles:

An Update on Pharmacotherapy for Autism Spectrum Disorder in Children and Adolescents. Ji *et al.* *Current Opinion Psychiatry* (2015)

Psychotropic Medications in Children with Autism Spectrum Disorders: Review and Synthesis for Evidenced Based Practice. Seigel *et al.* *J Autism Dev Disord* (2012)

Psychopharmacologic Management of Serious Behavioral Disturbance in ASD. K Stigler. *Child Adolesc Psych Clinics N Am* (2014)

ABA Information/Resources:

<http://www.hca.wa.gov/medicaid/abatherapy/pages/index.aspx>

<http://www.feakwa.org/> (Resource Guide)

Joseph

- 18 y/o
- ASD – Level 3 (x2), w/ language impairment, w/ intellectual impairment
- Treatment targets = aggression, irritability, sleep disturbance, question of mood disorder
- History of ADHD and OCD dx and tx – adverse response to stimulants and sertraline
- Severe aggression 10-30x/day
- Parents considering residential placement
- Insufficient response or AE to risperidone, aripiprazole and quetiapine
- Has done very well on combination of VPA and moderate dose of haloperidol