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Medication Considerations in Patients with Autism Spectrum Disorder

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Disclosures

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No conflicts of interest to disclose

Objectives

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By the end of this lesson, you will be able to describe

- The role of psychopharmacology within the context of other treatments in patients with ASD
- Common indications for medication in patients with ASD
- Considerations with medication treatment for patients with ASD

DSM-5 ASD Criteria

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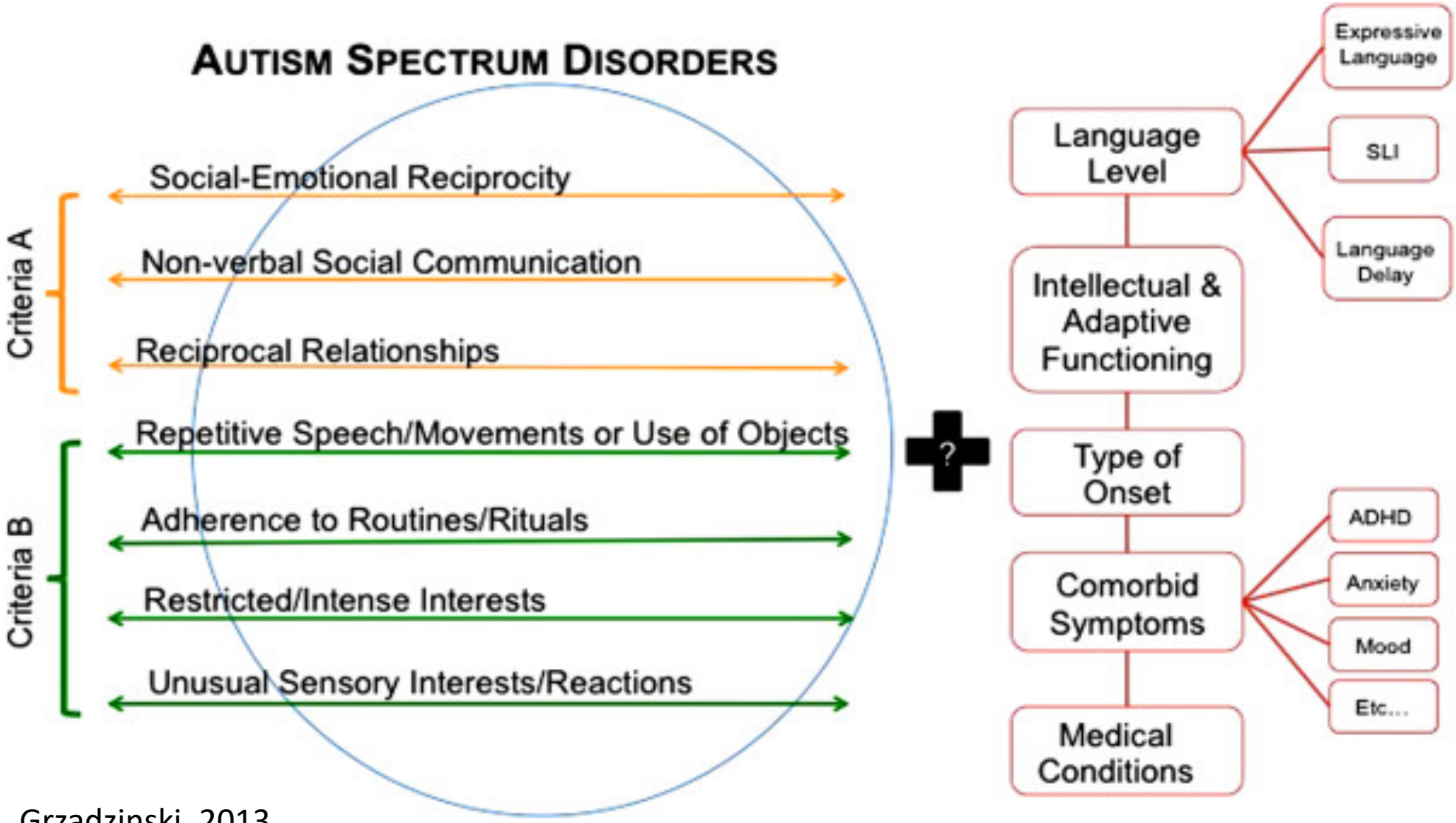

Grzadzinski, 2013

ASD – Core Symptoms Criterion A

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- **Persistent impairment in reciprocal social communication and social interaction** (need all 3)
- Deficits of **social-emotional reciprocity**
    - Example: failure to sustain normal back-and-forth conversation
  - Deficits in **nonverbal communicative behaviors** used for social interaction
    - Example: abnormalities in eye contact (too intense or not at all)
  - Deficits in **developing, maintaining, and understanding relationships**
    - Example: difficulties in sharing in relationship-building play activities
- **Present in "early developmental period"** (but may not manifest until demands>capacities)

ASD – Core Symptoms Criterion B

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- **Restricted, repetitive patterns of behavior, interests, or activities** (2 of 4)
  - **Stereotyped or repetitive motor movements, use of objects, or speech**
    - Example: simple motor stereotypies, like “flapping”
  - **Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior**
    - Example: immense difficulties with transitions, such as changing classes during the school day
  - **Highly restricted, fixated interests** that are abnormal in intensity or focus
    - Examples: memorizing train schedules or bus routes
  - **Hyper- or hypo-reactivity to sensory input** or unusual interest in sensory aspects of the environment
    - Example: intense reactions to sirens or hand dryers

Treating ASD

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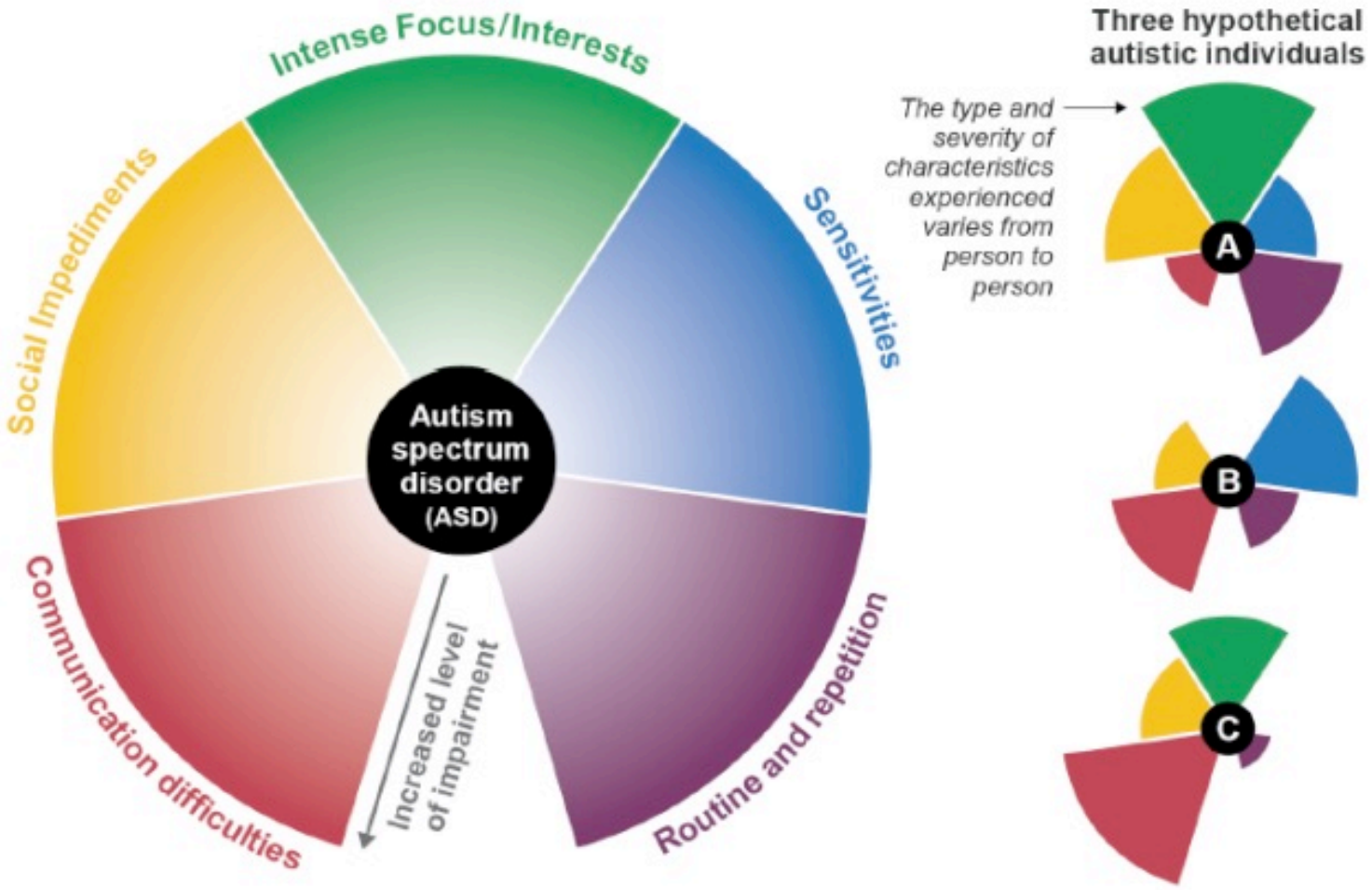
- No “cure” for ASD
- Each spectra provides opportunities for intervention
    - Minimize core deficits
    - Maximize independence

Figure 2: Variation in Autism Spectrum Disorder Characteristics

GAO grouped the characteristics associated with autism into five broad categories, with some overlap between categories.



Source: GAO analysis of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). | GAO-17-109

Co-occurring Conditions in ASD

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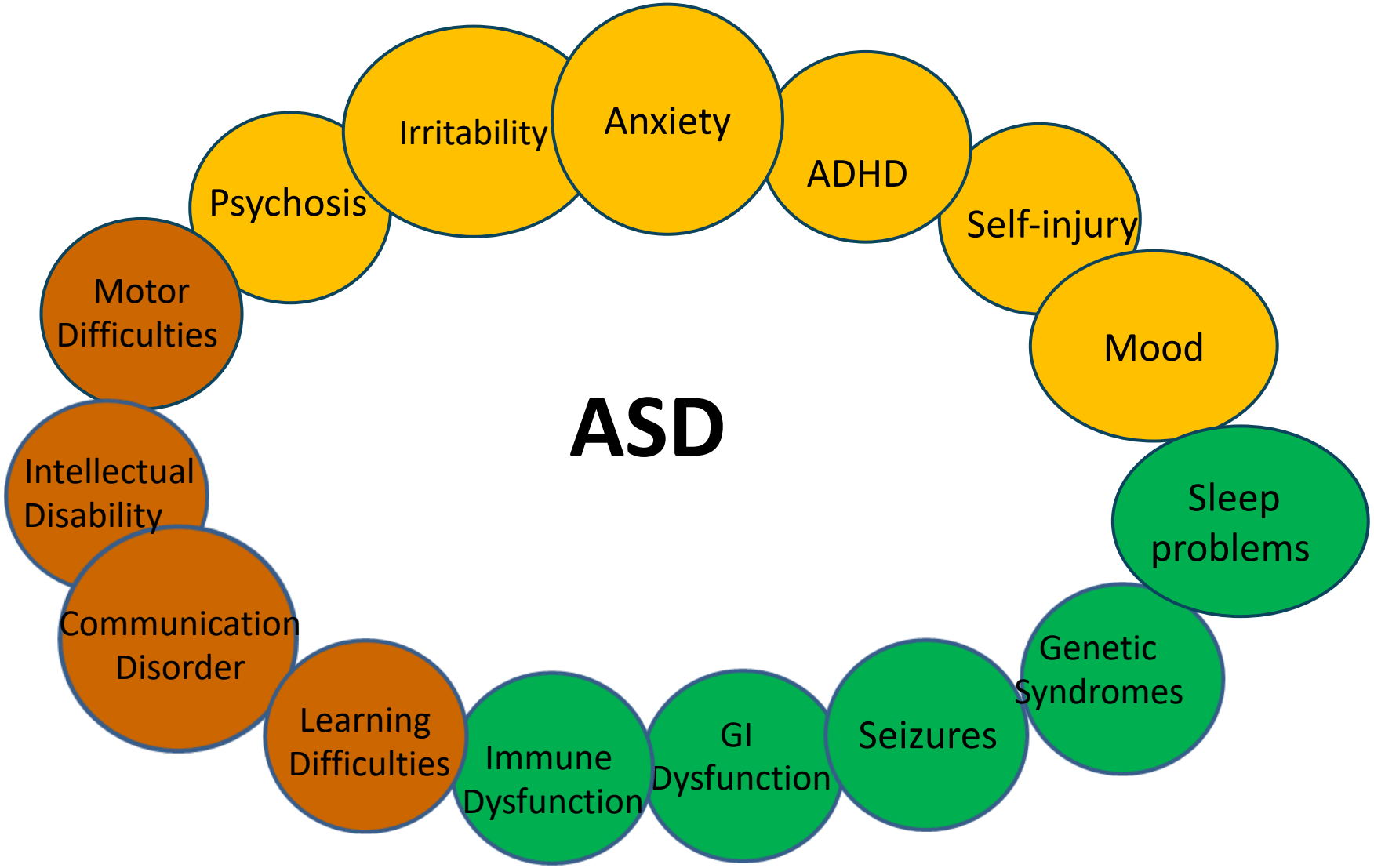

(Some) Components of ASD Treatment

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- **Best evidence: early, intensive behavioral tx**
- **Applied Behavior Analysis**
  - Highly behavior-focused
  - Clinicians need specialized license
  - Strong evidence for all ages
  - Can be evaluated for, administered in schools
- **Environmental interventions** (e.g., addressing sensory overload)
- **Medical care (including assessing sleep)**
- **Developmental services**
- **Medication**

- **Additional Therapy Modalities**
  - Speech and language therapy
  - Occupational therapy
  - Physical therapy
  - DORS supported employment
  - Social Skills
- **School-based Supports**
  - Many different interventions (e.g., ABA, speech, OT)
  - Need ASD **plus** functional impairment to be eligible for IEP
- **Family Support**
  - Parenting intervention
  - Peer/Family navigation
  - Legal advocacy if necessary

Medication and ASD

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- Rules of thumb
  - At this time, no efficacious medications to treat ASD
    - **Negative studies for Core ASD symptoms:**
      - Social impairment: Oxytocin, Memantine
      - Repetitive Behaviors: Citalopram, Fluoxetine
  - **However,** you can **treat symptoms and comorbid conditions**
  - **Rule out medical causes first (i.e., pain, constipation)**
  - Not a substitute for therapy or **environmental changes**
  - Use lower doses
  - Anticipate less predictable responses, particularly where the intellectual disability is more severe

Ex: Nonpharmacologic/Environmental Interventions

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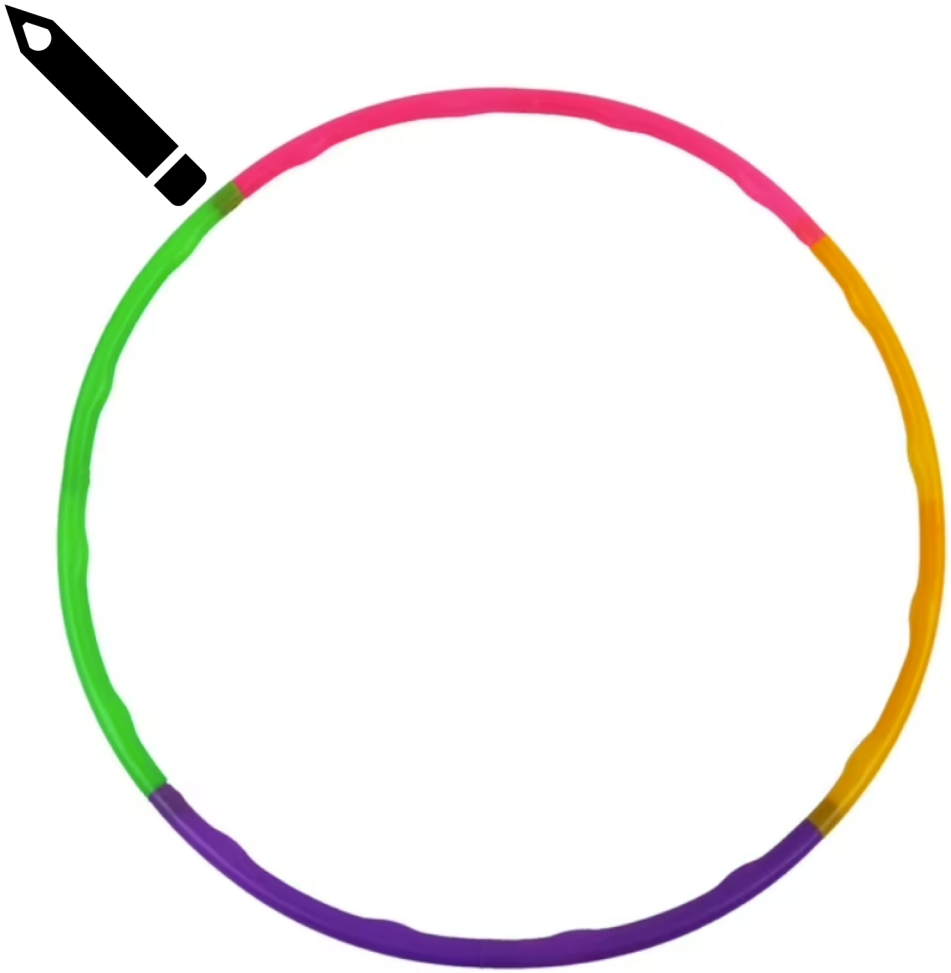

- 15yo with ASD (non-verbal), admitted for aggressive behavior
- Increasing escalation in behavior after chair moved out of room (had been standing/jumping on chair to draw on the ceiling (activity with which he had been preoccupied))
- Discussion about levels of PRN medication for patient
- Prior to giving PRN medication, team created instrument to allow him to safely draw
- Precluded need for PRNs

Common Indications for (Possible) Medication

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- Severe aggressive outbursts (toward self or others)
- Impulsivity/hyperactivity
- Repetitive behaviors
- Anxiety
- Irritability

ASD Comorbidities

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- **ADHD**
  - Only could be diagnosed in kids with ASD with the publication of the DSM-V
  - Symptoms of ADHD in up to 70% of those with ASD
- **Anxiety Disorders**
  - Up to 50% have one or more anxiety disorders
  - Easy to confuse core symptoms with symptoms of OCD
- **Mood disorders**
  - ~25-50% w/Depression, may be challenging to diagnose/overlook as core ASD symptoms (look for increased irritability, repetitive behaviors, SIB)
  - ~7.5% with bipolar d/o (may have earlier age of onset)
- **Sleep problems**
  - Highly prevalent (up to 80%)
  - Can worsen other symptoms, disorders

de Bruin, et al., 2007

ASD and ADHD

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- ADHD can exacerbate behavioral challenges associated with ASD
- **Stimulants**
  - More research on methylphenidate (MPH) than amphetamine preparations
  - Major MPH trials do show benefit for ADHD (hyperactivity in particular) in kids with ASD, not as much for core ASD symptoms (RUPP, 2005)
    - Possibly a **somewhat weaker response in than for kids without ASD**
    - Seems to have greater benefit in kids with less intellectual impairment
    - 0.25 – 0.4mg/kg/day best balances side effects w/benefit, but may need to carefully titrate to higher doses
    - **Higher rates of discontinuation due to adverse effects** (insomnia, appetite suppression)
    - More likely to have side effects of increased irritability and social withdrawal
    - Monitor for worsening of repetitive behavior
    - Monitor for new or exacerbated sleep difficulties
  - Long-acting preparations have been studied as well (Pearson et al., 2013)

ASD and ADHD

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- **Alpha Agonists**
  - Large trial showed significant benefit from guanfacine ER (perhaps even comparable to methylphenidate) for hyperactivity, minimal benefit for attention (Scahill et al., 2017)
    - Doses somewhat comparable to kids without ASD (modal dose of 3mg/day, max of 4-7mg/day)
    - Drowsiness, decreased appetite, and increased irritability were most common adverse effects
  - Immediate release guanfacine and clonidine have also been shown to benefit kids with significant hyperactivity
    - Consider with comorbid sleep difficulties, hyperreactivity/trauma
    - Can be used in combination w/stimulants (facilitate lower stimulant dose)
- **Atomoxetine**
  - Studied with and without combined psychosocial treatment
  - Mean dose between 40-50mg
  - Well tolerated, but can reduce appetite
  - More effects on hyperactivity than inattention

ASD and ADHD

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- Our Advice:
  - Start with a low dose/IR methylphenidate and titrate to 0.25 – 0.4mg/kg/day (in 2-3 divided doses) as tolerated
    - Can transition to longer-acting if tolerated
  - Monitor closely for worsening appetite, insomnia, increased irritability, and social withdrawal
  - If there's no or a partial response:
    - Consider switching to amphetamine preparations
    - Consider switching (to if stimulant side effects are intolerable) or adding an alpha-agonist
  - If that doesn't work, consider atomoxetine

ASD and Anxiety

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- **SSRIs are widely used to treat comorbid anxiety in ASD**
  - Strong data supporting SSRI treatment in adults with ASD
  - Very few good trials exist for kids with ASD, but open-label trials support use for treatment at low doses
- **Side effects**
  - Children with ASD seem to be more sensitive to SSRI side effects
  - Worsening irritability and agitation is much more common
- **Dosing tips**
  - Start with very low doses, titrate slowly, and monitor closely

ASD and Anxiety (Continued)

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- Buspirone (another serotonergic agent-partial agonist of 5-HT_{1A})
  - 2nd line choice (support in open-label trials)
  - Dosed between 10mg and 40mg in 2 divided doses
  - Generally mild side effect profile

ASD and Anxiety

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- Our Advice:
  - Start with a very low dose SSRI, titrate very slowly and to a lower maximum daily dose
  - Monitor closely for worsening irritability, big increases in energy, insomnia
  - If there's no response or intolerable side effects
    - Switch to another SSRI at a very low dose or switch to Buspar

ASD and Repetitive Behaviors

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- Some have theorized that stereotypies and repetitive behaviors may be related to OCD/Anxiety, but appear to be **mechanistically different**
- In two large RCTs, **SSRIs did not separate from placebo**
- SSRI side effects included increases in irritability, energy, insomnia, and hyperactivity
- Some evidence for atypical antipsychotics, but high side-effect burden
- Our advice:
  - If there's evident anxiety, you can target that with medications, but no evidence supports trying to directly address repetitive behaviors
  - Threshold for use of antipsychotics should be high (significant impairment)

Zhou et al., 2021

ASD and Disruptive Behavior/Aggression

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- Start with gaining an understanding of precipitants
- Aggressive outburst can occur in the context of
  - Anxiety (e.g., being confronted with feared situation)/rigidity
  - Depression
  - Hyperactivity/impulsivity
  - Pain
  - Learned prior ‘rewards’
  - Sensory overload
  - Trauma response
- Would use very different strategies depending on **which** of the above is the precipitant

Salpekar & Scahill, 2024

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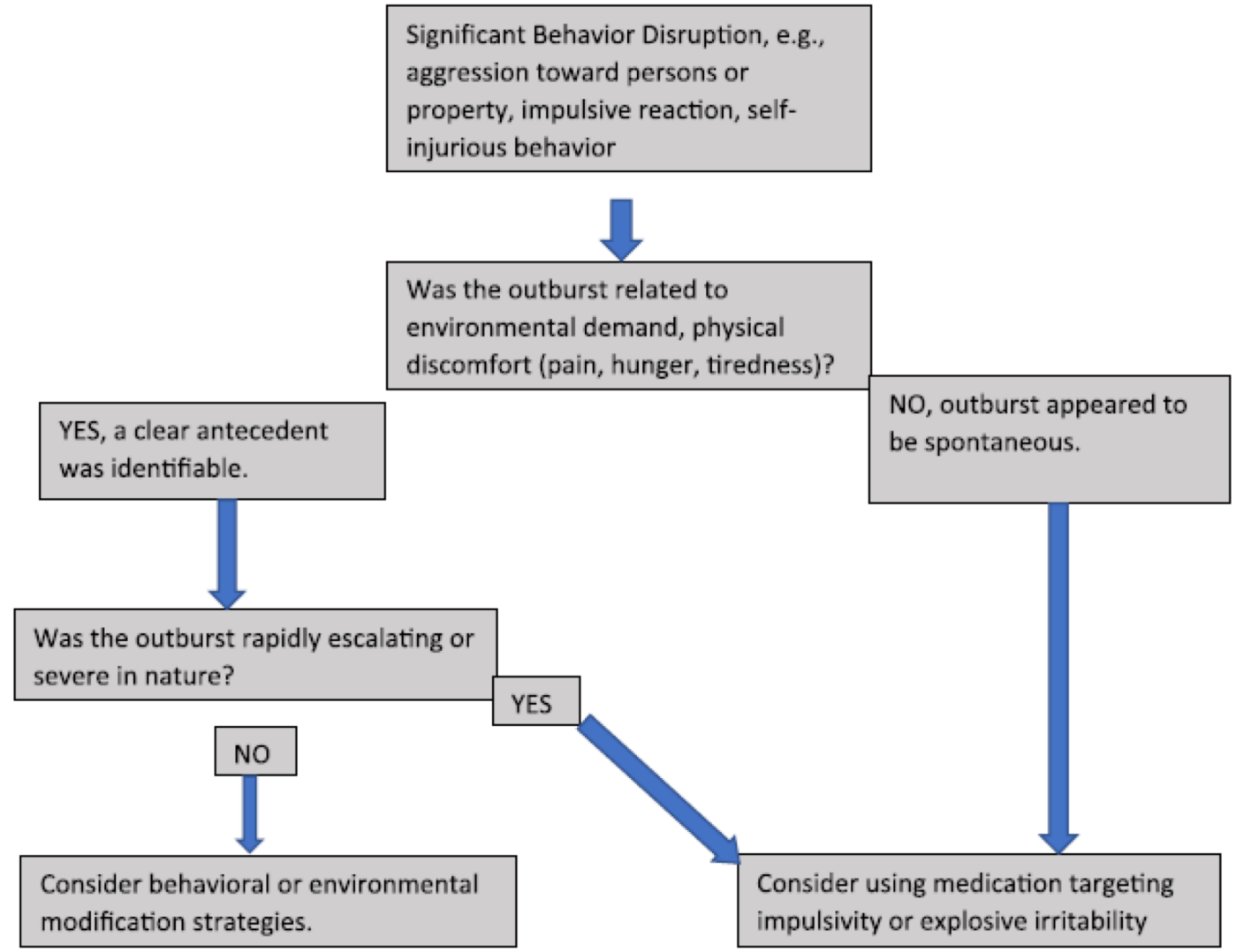

Fig. 1. Sample algorithm for medication decisions.

ASD and Severely Disruptive Behavior

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- FDA approval for “irritability” in ASD for risperidone (ages 5+) and aripiprazole (ages 6+)
  - “Irritability” defined as: severe temper tantrums, aggression, and self-injury
- In the major clinical trials, risperidone and aripiprazole also had helped with hyperactivity and had very modest reductions in stereotypic behavior
- HOWEVER, side effects for both medications are significant
  - Risperidone: severe weight gain, sedation, elevated prolactin levels, EPS (Extrapyramidal symptoms (e.g., abnormal movements/parkinsonism))
  - Aripiprazole: EPS, akathisia, sedation, weight gain
- Only start an atypical antipsychotic for ASD in close consultation with a BHIPP consultant

ASD and Antipsychotic Medications- continued

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- **Aripiprazole**: Start 1-2 mg/day, increase up to 5 mg/day in weekly increments to target dose 5–10 mg/day, max 15 mg/day
- **Risperidone:** Start 0.25mg/day, increase after 3-5 days to 0.5mg/day. Can dose BID. Increase by 0.5mg/day ~q2 weeks, max usually ~4mg/day
- **Monitoring**: BMI, fasting glucose, lipids, LFT (repeat labs at 12 weeks and then q6-12 months), EKG; consider prolactin w/risperidone if symptoms
  - See peer review program for additional monitoring requests: https://health.maryland.gov/mmcp/pap/Pages/Antipsychotics-Review-Programs.aspx

ASD and Severely Disruptive Behavior

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- Our Advice: remember, disruptive behavior is not a core symptom of ASD or a comorbid disorder, the emphasis should be on the **cause** of the disruptive behavior
  - If disruptive behavior arises in the setting of hyperactive/impulsive behavior:
    - Start with methylphenidate
    - Then consider an alpha agonist
  - If disruptive behavior arises in response to anxiety/rigidity
    - Start with an SSRI
    - Then consider buspirone
  - Medication targeting hyperactivity/impulsivity **and** anxiety/rigidity may be necessary (and will likely have a favorable side effect profile to an atypical antipsychotic
  - If you want to consider starting risperidone or aripiprazole, we recommend reaching out for a BHIPP consultation

ASD and Sleep Issues – Recommendations from Sleep Committee/Autism Treatment Network

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- Assess/address medical contributors: (GI d/o, epilepsy, pain, nutritional issues, sleep d/o breathing)
- Behavioral interventions/work with parents first-line
  - ATN has parent-facing toolkit: https://autismcarenetwork.org/toolkits/
  - Includes guidance on routines & sleep hygiene, visual schedules, environmental considerations
  - Includes a separate toolkit related to sleep in teens
- Acknowledges contributors to challenges implementing behavioral interventions for sleep
  - Emotion regulation difficulties, challenges with transitions, difficulties with communication
- Consider pharmacology if behavioral interventions don't work, reach a "crisis point"
  - Toolkit/website includes info sheet on melatonin and sleep

ASD and Sleep Difficulties- Medication

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- Melatonin
  - Evidence for use in ASD and ADHD
  - Relatively short half-life (there are controlled release formulations)
  - Less knowledge about long-term side effects (e.g., effects on puberty)
  - May lower seizure threshold
  - Look for USP Certified brands (only come in 3 and 5mg)
    - Wide variability in amount of melatonin in other preparations
  - Recommend time-limited trial (e.g., 3 months) if possible
- Limited evidence for use of other medications
  - Consider role for medications for comorbid disorders
    - Anxiety (e.g., SSRI)
    - ADHD (e.g., guanfacine/clonidine)

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Thank You!

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