Psychotropic Medications for Challenging Behaviors and Co-occurring Psychiatric Disorders In Autism

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Objectives

- Attendees will learn about the epidemiology of co-occurring psychiatric disorders in ASD.
- Attendees will understand guidelines and strategies that guide pharmacotherapy for challenging behaviors related to autism and common co-occurring psychiatric disorders.
- Attendees will improve their knowledge base regarding use of medication for challenging behaviors and co-occurring psychiatric disorders in children with autism through review of the evidence base and case-examples.

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Psychotropic Trends in ASD

- No medications are effective in treating core symptoms of ASD
- Medication are commonly used in ASD
  - 80% of adults
  - 45% of children (Aman et al. 2003)
- Use of medications increases with age
- Once medications are used, they are more commonly continued
- Polypharmacy is the rule, not the exception (Tsiouris, 2013)
- Atypical antipsychotics, SSRIs, and stimulants most commonly used (Esbensen *et al*. 2009)

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General Considerations

- ASD is a neurodevelopmental "substrate" for other learning, behavioral and emotional challenges
  - enhances likelihood of co-occurring mental health conditions
  - influences effectiveness of "standard" medication treatments
  - Influences rates of side effects and pharmacokinetics
- Atypical manifestations of mental and physical disorders in ASD population
  - Self-injury, irritability, aggression, bizarre movements and behaviors
- Overlap of ASD features and symptoms of other mental health disorders often delays recognition and treatment of co-occurring conditions (Bakken, 2010)

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Psychiatric Comorbidities in Autism

- *Intellectual Disability* – 31.6% (CDC)
- **Anxiety Disorders** – 50% (Rodgers J. Curr Dev Disorder Rep. 2018)
- **Depressive Disorder** –
  - 31% - primary care sample (Saqr *et al*. Autism. 2018)
  - 4X life-time risk (Hudson CC. Jrnl Abnl Child Psych. 2018)
- Bipolar Disorder
- **ADHD**
- **Disruptive Behavior Disorders**
- Psychotic Disorders – ASD is risk factor
  - Catatonia
- Obsessive-Compulsive Disorder

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Psychiatric Comorbidities in Autism

- Presence of co-morbidities increases level of disability burden on families and healthcare expenditures.
- In some cases, co-occurring psychiatric issues are responsible for the majority of the disability (e.g. higher functioning ASD and anxiety)
- Contributes to high rates of psychotropic use in ASD – 80% of children with co-occurring diagnosis are on psychotropic medications

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Symptom-driven versus *diagnosis*-driven treatment

- Core symptoms
  - Repetitive behaviors, restricted interests or activities (B.)
  - Social communication and social interaction deficits (A.)
- Common co-occurring behaviors
  - Irritability (aggression, tantrums, mood lability, SIB)
  - Hyperactivity
  - Sleep problems
  - Self-injury
- Common psychiatric co-morbidities
  - Anxiety
  - Depression
  - ADHD

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Things to Think About When Considering Medications

- 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?

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How does this distinction 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 – no "set and forget it."

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Challenges in advancing psychopharmacology in ASD

- Lack of widely accepted diagnostic tools for co-occurring psychopathology (anxiety, psychosis)
- Difference of opinion 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

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Repetitive Behaviors/Restricted Interests

- Core symptom of ASD (B. Criteria)
- 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

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Medications and Repetitive Behaviors

- Risperidone
- Aripiprazole (Abilify)
- Valproic Acid/Divalproex sodium
- Selective serotonin re-uptake inhibitors (SSRIs) - citalopram, fluoxetine, clomipramine

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Atypical Antipsychotic Medications

- Use of risperidone (Risperdal) and aripiprazole (Abilify) are supported by evidence and experience
- In foundational studies, improvement in RRBs was a secondary outcome measure
- It is hard to predict who will benefit – no predictive phenotype
- Improvement may through indirect mechanism (e.g. mediating hyperactivity, improvement in cognitive and/or behavioral rigidity, etc.)
- Improvement can be seen in other areas (adaptive functioning, hyperactivity, social withdrawal and communication) (Politte *et al*. 2014)

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Selective Serotonin Reuptake Inhibitors (SSRIs)

- Medications examined = citalopram, fluoxetine, fluvoxamine and clomipramine
- Not effective for repetitive behaviors (Cochrane, 2010)
- High rates of adverse events
- Meta-analysis found small but significant effect size disappeared with inclusion of unpublished studies.
  (Carrasco *et al*. Pediatrics. June 2012)
- SSRI use for co-occurring disorders that may manifest at repetitive behaviors (anxiety, OCD, depression) should be considered on case by case basis.

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Wally

- 15 y/o
- ASD – severity level 3 (A. and B. criteria), w/ language impairment, w/ intellectual impairment
- Treatment targets = anxiety, repetitive self-injury, “impulsivity”
- Came to me on high dose sertraline and delayed release guanfacine (Intuniv) twice a day
- Parents did not want to consider an atypical antipsychotic
- RRBs waxed and waned
- With time, behavioral support and improved functional communication has done well

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Social Withdrawal/communication

- Risperidone
- Naltrexone
- Lamotrigine
- Oxytocin

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Oxytocin

- Insufficient evidence to recommend at this point
- Area of active research so stay tuned
- 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

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Irritability

- Risperidone and aripiprazole
  - Best evidence (and FDA approval) for irritability *not* RRBs)
- Haloperidol
- Alpha-agonists *
- Olanzapine (side effects)
- Divalproex sodium/valproic acid
- Quetiapine
- Lamotrigine

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risperidone (Risperdal)

- FDA approval (2006) for irritability (not RRBs) in ASD
- 2 large DBRCTs (McCracken et al. NEJM 2002; Shea. Pediatrics 2004)
- Response rates 57-72% (Politte et al, 2014)
- Can also effective for reducing repetitive behaviors and hyperactivity
- Can see decreases in frequency and severity of episodes
- Low dose (1-2 mg) is typically effective
- High rates of side effects - sedation, weight gain, hyperglycemia, dyslipidemia
- Periodic efforts to lower dose and stop should be part of ongoing care.

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aripiprazole (Abilify)

- FDA approval (2009) for irritability in ASD
- May also reduce repetitive behaviors
- Not as clearly effective in decreasing frequency of aggressive 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)
- Activation/aggression is more common as side effect versus risperidone
- Unique mechanism – partial D2 agonist; selective 5-HT1A agonist; 5-HT2A antagonist
- Weight gain more likely to be an issue in medication naïve, younger and higher baseline weight (Mankowski et al. J Child Adol Psychopharm. 2013)

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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

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Hyperactivity

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

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Methylphenidate

- Good evidence of benefit for hyperactivity in children with ASD (RUPP, 2005)
- Lower response rates than neuro-typical children
- Higher rates of adverse events (AE) – aggression, emotional outbursts, paradoxical activation
- Higher rates of side effects - insomnia, decreased appetite
- Tolerability improves with higher cognitive function
- Start with short-acting preparations
- Long-acting preparations better tolerated
- Due to multi-factorial nature of executive function deficits, frequent re-evaluation is recommended
- As with ADHD w/o ASD, non-ADHD negative behaviors can improve

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Atomoxetine

- Norepinephrine re-uptake inhibitor
- Dosing and response similar to non-ASD populations
- Typically better tolerated than stimulants
- Can take awhile to achieve full effect
- Most common side effects 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)
- Can be effective for co-occurring anxiety for some

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Alpha-agonists

- Some evidence for improving impulsivity (clonidine) and hyperactivity (guanfacine) in ASD
- Often tried for before anti-psychotics (for both irritability and hyperactivity) because of favorable SE profile
- Improvement in target behaviors can improve general functioning
- Effective sleep aide – direct and indirect effects
- Can take several weeks to months for full affect

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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

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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

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Cannabis

- Unscientific "case studies"
- Scientific Basis – altered endocannabinoid signaling in mice with gene abnormality linked to autism and mouse model of Fragile X syndrome
- Erroneous information in mainstream media, internet and online advocacy groups (Mothers for the Medical Marijuana Treatment of Autism, Mothers Advocating Medical Marijuana for Autism)
- Why not "just try it?"
  - It is illegal to give to minors (even CBD oil has enough trace THC to be considered Schedule I by DEA)
  - Untested
  - Increases risk of psychosis (ASD already confers risk)
  - Unrecoverable loss of IQ related to cannabis use in adolescence
  - potential negative impacts on sleep, mood, anxiety, memory and executive function

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ADHD and ASD

- Can compound developmental deficits and behavioral challenges related to ASD
- Gating deficits and stimulus management can compound and mimic ADHD symptoms
- Remember to advocate for and encourage non-medication strategies at school - social skills deficits, organizational and study skills, test accommodations
- Range of ADHD medications can be effective
- Long-acting preparations better tolerated
- Symptoms can persist into adulthood (Johnston, 2012)
  - ADHD alone - fast and inaccurate on attentional switching
  - ASD with ADHD - slower in response (reduced processing speed)

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Anxiety and ASD

- Very common (50%)
- Generalized anxiety and social anxiety are most common (Caamano, 2013)
- Further worsens social communication deficit
- Can be hard to distinguish between repetitive motor symptoms (e.g. compulsions) and RRBs due to autism
- Cognitive and behavioral rigidity attributed to ASD can mask anxiety (especially in younger children)
- Full range of anxiety medications (SSRIs, anti-histamines, benzodiazepines) can be effective but SE are common

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Depression and ASD

- More common in higher functioning ASD – increased psychological awareness; more opportunities to experience impact/limitations of ASD
- ASD can mask and compound symptoms – social withdrawal, constricted affect, irritability
- Consider developmentally appropriate CBT
- SSRIs are most common medication
  - Often effective
  - Start low and go slow
  - Dose range not terribly different with non-ASD populations
  - Treatment response less consistent compared to non-ASD
  - High rates of activation and other SE (GI)

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Suicide and ASD (Hannon *et al.* Clinical Psych Review. 2013; Chen *et al.* Jrnl Clin Psych. 2017)

- ASD is an independent risk factor for suicide attempts
- ASD is a risk factor for depression
- Suicidal behavior and attempts can be masked by repetitive self-injury
- Communication deficits can delay identification
- Cognitive deficits can influence understanding of death, expression of SI (as unhappiness) and risk assessment
- Probably more common in higher function
- Lack of peer, parent and self-acceptance are common factors
- Co-occurring psychiatric issues, bullying and abuse are risk factors – similar to non-ASD

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Psychosis and ASD (Bell *et al*. Br Jrnl Psych. 2018)

- ASD confers risk of psychosis
  - ASD increases risk of developing psychosis (Larson FV. Br Jrnl Psych. 2017; Pina-Camacho. BJ Psych Adv. 2016)
  - ASD present in 30-50% of children diagnosed with severe psychotic disorders (Rappaport *et al*. JAACAP. 2009)
- Both ASD and psychosis are "overlapping" spectrum constructs
- Share physical and genetic vulnerabilities
- No standardized tools to evaluate psychosis in ASD
- More overlap with negative than positive symptoms
- Psychosis often misdiagnosed during times of stress/transition
- ASD deficits in ToM, social functioning and rigid thinking make increase paranoid thinking, reports of hallucinations and impaired reality testing
- Since diagnostic clarity in the exception, not the rule, a symptom based treatment approach is recommended
- Children with ASD are twice as likely to experience treatment failure when AAP prescribed for psychotic symptoms (Downs J *et al*. Jrnl Clin Psych. 2017)

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Sleep Dysfunction and ASD

- 44-83% of children with ASD experience sleep problems
- Huge impact on individual and family function
- Evidence of abnormalities in melatonin synthesis and release
- Insomnia is most common (initial and middle insomnia)
- Less common but important to consider include night terrors, sleep apnea (obstructive and central), RLS and or parasomnias
- Sleep issues have significant impact on daytime behaviors that may be focus of treatment and source of disability
- Medications for behavioral and psychiatric issues can impact sleep
- Sleep medications can impact medical issues (seizures, GI function, OSA)

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Medications for sleep

- Melatonin - large empirical base; studies less consistent; facilitates transition to sleep; increase TST and can improve daytime behaviors; parent report > actual improvement; homeopathic versus hypnotic dosing; rebound may exacerbate middle insomnia
- Anti-histamines - (diphenhydramine, hydroxyzine, doxylamine) no studies; safe and effective; SE common
- Alpha-agonists - no studies; rarely used if sleep is only issue; BP/CV effects are most common SE
- Trazodone - no studies in pediatric ASD populations; SE common; risk of priapism harder to manage due to communication deficits.
- Atypical Anti-psychotics NOT recommended exclusively for sleep
- Gabapentin (Neurontin)

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Summary

- There are no medication treatments for core symptoms of ASD
- Medications should be used with appropriate non-medications 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.

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Environmental Risk Factors for ASD

- Valproic acid
- Prenatal rubella
- Misoprostol (ulcer treatment)
- Chlorpyrifos (insecticide)
- Pollution (proximity to freeways)
- Agricultural pesticides
- Increased paternal age
- Maternal use of SSRIs (Mezzacappa et al. JAMA Peds. 2017)
- Prenatal Ultrasound (Rosman et al. JAMA Peds. 2018)
- Pre-gestational/Gestational Diabetes + Obesity (Li et al. Pediatrics. 2016)
- Herpes Simplex 2 (Mahic et al. mSphere. 2017)

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Primary Care Recommendations for Genetic Testing in ASD

- Heritability estimates in ASD exceed 80%
- 25-40 % of ASD cases have identified genetic abnormality
- Yield of different genetic tests
  - High resolutions karyotype – 5%
  - Micro-array – 10%
  - Exome sequencing – 25%
- Risk in subsequent off-spring (de novo/no genetic cause)
  - One sibling w/ ASD – 10-20% (Ozonoff. 2011)
  - Two siblings w/ ASD – 16-35%

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