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 be introduced to guidelines and strategies of pharmacotherapy for challenging behaviors related to autism and common co-occurring psychiatric disorders.
- Attendees will improve their knowledge of medications for challenging behaviors and co-occurring psychiatric disorders in ASD.

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The role of psychiatry in managing autism

- Always part of multi-disciplinary team - and not always involved
  - SCH – neurology, SLPs, OT, PhD, BCBA, developmental pediatrics, ARNPs, family/resource support team…and psychiatry
- Autism diagnostic evaluations
- Evaluation and management of co-occurring psychiatric disorders and challenging behaviors (aggression, SIB, insomnia) through:
  - Recommending and facilitating access to appropriate psychosocial supports and behavioral therapies
  - Use of medications when appropriate

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General Considerations

- ASD is a neurodevelopmental "substrate" for other learning, behavioral and emotional challenges, so presence of ASD:
  - increases likelihood of co-occurring mental health conditions
  - influences effectiveness of "standard" medication treatments
  - Increased rates of side effects
- Disruptive behavior and emotional symptoms are common manifestations of *both* mental and physical disorders (self-injury, irritability, aggression, abnormal movements and odd behaviors)
- Overlap of symptoms between ASD and common childhood mental health disorders often delays recognition and treatment of co-occurring conditions (Bakken, 2010)

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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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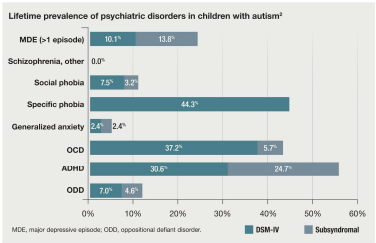
Common Co-occurring Psychiatric Conditions in ASD

(Collins et al. Psych Times. 2019)



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Mental Health Co-morbidity and Risk Factors in ASD

- 79% lifetime prevalence of psychiatric condition in adults with autism (Lever *et al*. Jrnl of Autism and Dev Disord. 2016.)
- ASD confers 5X risk of suicide
- ASD confers 10X risk of schizophrenia spectrum disorder
- Increased risk of bullying, maltreatment and all forms of abuse
- Autism traits can increase exposure to risk factors – increased rates of depression and SI due to social isolation, loneliness and feelings of being a burden
- Many conditions likely underdiagnosed and misdiagnosed due to lack of awareness, diagnostic overshadowing, symptom over-lap and lack of validated screening tools

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ADHD and ASD

- Can compound developmental deficits and behavioral challenges related to ASD
- Low frustration tolerance and sensory issues 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

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Anxiety and ASD

- Very common – may be up to 50%
- Generalized anxiety and social anxiety are most common (Caamano, 2013)
- Exacerbates social communication deficits
- 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 likely to be aware of impact/limitations of ASD
- ASD can mask and/or compound symptoms – social withdrawal, constricted affect, irritability
- Developmentally appropriate CBT is first-line treatment
- SSRIs are most common medication used
  - 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 GI side effects

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Schizophrenia and Autism

- Shared genetic risk
- Symptom overlap
  - language difficulties, poverty of speech, formal thought disorder, over-valued ideas, interpersonal deficits, etc.
  - Intersecting spectrums
- ASD confers increased risk of schizophrenia spectrum disorders
- SSD prodromal and subthreshold conditions complicate diagnosis of both ASD and psychosis
- No validated tools to evaluate psychosis in ASD
- "Atypical" versus "anomalous" perceptions
  - Hallucinations are common in ASD
  - Hallucinations rarely indicate schizophrenia

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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, so risk is compounded with both present
- 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 functioning kids
- 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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Symptom-driven versus *diagnosis*-driven treatment

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

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How does this distinction affect medical decision making?

- Sets 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 the importance of "active" medication management – no "set and forget it."

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Psychotropic Trends in ASD

- No medications are approved for or consistently 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 are most common (Esbensen *et al*. 2009)

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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 behavior support available?
- Could medication support augment other interventions?
- Are there psychiatric or medical co-morbidities that need to be considered?
- What is parent/caregiver level of comfort?
- What is your level of comfort?

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Lack of Specificity in ASD

- **ADHD symptoms/executive function deficits** - methylphenidate, amphetamines, atomoxetine, alpha-agonists, amantadine; (SSRIs)
- **Aggression /Agitation/ Irritability** - alpha agonists, antipsychotics, stimulants, SSRIs, VPA, lithium
- **Anxiety** - SSRIs, hydroxyzine, benzodiazepines, buspirone, quetiapine
- **Sleep** - melatonin, anti-histamines, alpha agonists, trazodone
- **Mood Instability** – AAPs, valproate, lamotrigine, lithium
- **Self-injury** - risperidone, naltrexone

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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 RRBs involve self-injury or create demands on caregivers that put them risk if demands are met.

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Medications for Restrictive and Repetitive Behaviors (RRBs)

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

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Atypical Antipsychotics (AAPs)

- Use of risperidone (Risperdal) and aripiprazole (Abilify) are supported by evidence and experience and are FDA approved
- In foundational studies, improvement in RRBs was a secondary outcome measure
- It is hard to predict who will benefit – no predictive phenotype
- Improvement may be through indirect mechanism (e.g., mediating hyperactivity, improvement in cognitive and/or behavioral rigidity, reducing anxiety, 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)

- Not effective for repetitive behaviors (Cochrane, 2010)
- Medications examined = citalopram, fluoxetine, fluvoxamine and clomipramine
- 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 RRBs (anxiety, OCD, depression) should be considered on case-by-case basis.

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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 – new study at UW/SCH
- Response impacted by timing, gender, trauma and genetics

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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 in ASD
- 2 large DBRCTs (McCracken et al. NEJM 2002; Shea. Pediatrics 2004)
- Response rates 57-72% (Politte et al, 2014)
- May also reduce repetitive behaviors and/or 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
  - Small but real risk of movement side effects – Tardive Dyskinesia can be permanent
- 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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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
- High rates of adverse events (AE) – aggression, emotional outbursts, paradoxical activation
- High 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
- Like ADHD w/o ASD, non-ADHD negative behaviors can also improve

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Atomoxetine

- Norepinephrine re-uptake inhibitor
- Dosing and response similar to non-ASD populations
- Effect size similar to non-ASD populations (different than stimulants)
- Generally, better tolerated than stimulants but less consistently effective
- Can take awhile to achieve full effect
- Most common side effects include fatigue, nausea and decreased appetite
- Can be effective for co-occurring anxiety for some

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Alpha-agonists (clonidine IR/ER, guanfacine IR/ER)

- Evidence of improvement in impulsivity and hyperactivity in ASD
- Often tried for before anti-psychotics (for both irritability and executive function deficits) because of favorable side effect profile
- Improvement in target behaviors can improve general functioning
- Effective sleep aide – direct and indirect effects
- Can take several weeks *at therapeutic dose* to months for full affect

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When to seek consultation?

- Do you need help deciding if medication is appropriate?
  - Have non-medication strategies been inadequate or are they unavailable?
- Do parents need support around *not focusing* on medications?
- Are you out of your comfort zone?
  - Are target symptoms potentially responsive to (other) medications?
- Diagnostic Clarification
  - Do you suspect a co-occurring disorder complicating management of autism?

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Summary of Evidence Base

- Risperidone and aripiprazole generally effective for irritability and hyperactivity but potential for serious side effects needs to be considered.
- For hyperactivity alone, stimulants are generally effective, but rates of adverse events are high. Methylphenidates are typically better tolerated than amphetamines.
- Alpha-agonists are often a good alternatives to AAPs for irritability and stimulants for ADHD symptoms.
- SSRIs are not effective for repetitive behaviors *due to autism* and rates of activation are high.

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Principles of Medication Management in ASD

- No medications are yet identified for core deficits of autism
- Medications treat challenging behaviors and co-occurring disorders
- Individuals with ASD/suspected ASD have increased sensitivity to medications in general
- "start low dose and go slow"
  - therapeutic effects seen at lower doses.
  - Monitor closely for adverse events and side effects
- Re-evaluate medication strategies frequently - no "set it and forget it"

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