Psychopharmacology in Neurodevelopmental Disorders

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DYRK1A syndrome

- Disruptive mutations in Dual-specificity tyrosine-(Y)-Phosphorylation-regulated kinase 1A (DYRK1A).
- Disruption found in 0.1-0.5% of the ASD population
- Common clinical phenotypes (Earl et al., 2017)

>=90%: Intellectual disability or global developmental delay, Speech delay, Motor difficulties, Microcephaly, and Feeding difficulties

**Behavioral disturbances:** Stereotyped behavior (58%), Anxious behaviors (27%), Hyperactive behaviors (33%), Behavioral differences (69%).

⇒ Targets for intervention?

Earl et al., 2017
Behavioral Disturbances

- Frequent in children with an intellectual disability, regardless of the underlying etiology.
- When severe, it can be disabling, create problems in everyday life and can “mask”, or “reveal”, an organic (medical) or psychiatric illness.
- **Myth:** This (behavior) is due to the child’s disability and cannot be treated.
- Common problematic behaviors include sleep disturbances, agitated and aggressive behaviors, and self-injury behavior.

*Ageranioti-Bélanger, et al., 2012*
Diagnostic challenges

- Children/individuals with limited language skills may not be able to explain why they engage in certain “behavior” or report how they feel inside (e.g., physical or emotional pain/discomfort).
- Presenting problem may be similar but due to different etiology (e.g., head banging could be due to pain, sensory, anger or anxiety).
- Medical evaluation to rule out underlying organic (medical) etiology, such as obstructive sleep apnea syndrome, physical discomfort from pain/constipation, etc.
- Psychiatric evaluation to rule out underlying psychiatric disorders, such as depression, anxiety, mood disorder, etc.
- Functional behavior analysis (FBA) will be very helpful for identifying function of behavior.
Process of Functional Behavior Analysis (A-B-C)

1. Obtain a clear description of the behavior (Behavior)
2. Identify factors that predict whether the behavior will or will not occur (Antecedent)
3. Identify the factors or consequences that maintain the behavior (Consequence)
4. Develop a hypothesis about the function of the behavior; make direct observations that provide evidence supporting the hypothesis
5. If appropriate, initiate intervention (behavioral and/or med) and monitor progress

• Common Behavioral Functions
  1) Getting what I want, “tangibles”
  2) Wanting to avoid a task, “escape”
  3) Needing attention, “attention-seeking”
  4) No apparent outside trigger, “autonomic” Could be related underlying medical or psychiatric disorders, such as pain, anxiety, or internally reinforced sensation seeking

O’Neil, 1997
Psychiatric Disorders (e.g., ADHD, anxiety, mood disorders)

- Psychiatric disorders are common in individuals with intellectual developmental disorders (IDD).

- Psychiatric disorders are often under-recognized and under-diagnosed in individuals with IDD due to diagnostic challenges.

- Problem behaviors may “mask” or “reveal” underlying psychiatric disorders in individuals with IDD.

- Presence of comorbid psychiatric disorders often results in severe functional impairment. Could these be targets for psychopharmacologic intervention?
# Examples of Commonly Prescribed Psychotropic Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Risperidone, aripiprazole, quetiapine...</td>
<td>Irritability, aggression, anxiety, psychosis, mood</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Fluoxetine, sertraline, .. Venlafaxine, duloxetine..</td>
<td>Anxiety, depression, sleep</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium, Depakote, Lamotrigine..</td>
<td>Mood, aggression</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Methylphenidate, Adderall, Vyvanse...</td>
<td>Inattention, hyperactivity, impulsivity</td>
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<tr>
<td>Sedatives</td>
<td>Lorazepam, diazepam..</td>
<td>Anxiety, sedation</td>
</tr>
<tr>
<td>Others</td>
<td>Clonidine, guanfacine, buspirone, atomoxetine..</td>
<td>Hyperactivity, impulsivity, anxiety</td>
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</tbody>
</table>
Frequently reported problem behaviors

1. Sleep disturbances
2. Aggression toward others or property
3. Self-injurious behavior
4. Tantrums/Noncompliance
5. Other behaviors (e.g., hyperactivity, impulsivity, elopement, socially inappropriate behaviors, etc.)
Sleep Disturbances

• Very common
• Etiology:
  a) Idiopathic insomnia
  b) Insomnia due to underlying medical (e.g., OSA, restless leg syndrome, pain, etc.)
  c) Insomnia due to underlying psychiatric (e.g., depression, anxiety, mood disorder, etc.)
  d) Side effects (e.g., caffeine, stimulant taken too late into the day, etc.)
Sleep Disturbances

• Assessment
  a) Detailed history, if needed, use sleep questionnaire
  b) Sleep study to rule out Sleep-Wake disorders, such as Obstructive Sleep Apnea or Restless Leg Syndrome

• Treatment
  a) Sleep hygiene
  b) Behavior modification
  c) **Pharmacologic intervention:**
     • Melatonin for delayed sleep onset
     • Specific psychotropic med to address underlying psychiatric etiology (e.g., antidepressant to treat depression or anxiety)
     • Other meds that could be utilized – drowsy antihistamines, clonidine/guanfacine, trazodone, etc.
• Reactive vs. Planned
• Reactive (unplanned) aggression toward others, property, or self
• Acute aggression – investigate physical cause (e.g., dental pain, constipation, ear infection)
• Chronic aggression – FBA to identify “function” of aggression
• Treatment
  a) Evaluate and Treat underlying medical/physical etiology, if any
  b) Behavior intervention
  c) **Pharmacologic intervention:**
     • Specific psychotropic meds if identifiable targets (e.g., ADHD, anxiety, mood disorder, idiopathic insomnia resistant to sleep hygiene)
     • Risperidone/Aripiprazole, approved for irritability associated with ASD
     • Other meds that could be utilized – clonidine/guanfacine for impulsivity, mood stabilizer for emotion dysregulation/explosive behavior, etc.
Self-Injurious behavior (SIB)

Reactive vs. stereotypic/repetitive/autonomic (no function)

Treatment

a) Behavioral intervention

b) Protective gear or physical restraint for severe SIB?
   To consider: ethics, safety, possibility of restraint reinforcing SIB, how to taper restraint successfully.

c) Pharmacologic intervention

   • Most psychotropic meds are not effective for stereotypic or autonomic SIB.
   • Meds used with limited efficacy - Atypical antipsychotics (e.g., risperidone/arianiprazole), Alpha 2 agonists (clonidine/guanfacine), mood stabilizer, OTC N-acetylcysteine (NAC), buspirone (anti-anxiety)
Hyperactivity, impulsivity, noncompliance

May represent underlying ADHD?

Functional Behavior Analysis to identify “function”

Treatment

a) Behavioral intervention

b) School support

c) Parent Management Training

d) Pharmacologic intervention:

• Stimulants and nonstimulant ADHD meds, methylphenidate (Focalin/Concerta), Adderall, Vyvanse, Atomoxetine (Strattera)

• Alpha 2 agonists, guanfacine/clonidine for hyperactivity and/or impulsivity
Anxiety, obsessive compulsive behaviors

Components of anxiety (traditional)
1. Affective – fear
2. Cognitive – thoughts, beliefs
3. Behavioral – avoidance
4. Physiologic arousal
   (heavy breathing, palpitation, sweating)

Expression of Anxiety in individuals with severe ID/Language impairment
a) Affective – ? negative affect (upset/anger)
b) Cognitive – ?
c) Behavioral - ? avoidance, tantrums, agitation
d) Physiologic arousal - ? heavy breathing, palpitation, sweating
Anxiety, obsessive compulsive behaviors

Treatment

a) (cognitive) Behavioral Therapy – exposure/response prevention
b) relaxation skills – deep breathing, counting, etc.
c) Pharmacologic intervention
   • Antidepressants, especially SSRI (fluoxetine, sertraline, citalopram, fluvoxamine, escitalopram, etc.) and SNRI (venlafaxine, duloxetine) are effective to treat symptoms of anxiety
Rhea

• 25 year-old presenting with problem behaviors of pacing all day long, unplugging all electronics, closing all windows and doors.

What questions do you want to ask?

You learned no apparent triggers for this behavior, which happens anytime during the day. Rhea has been engaging in similar behavior on and off for years since she was in her early teen. Her caregivers tried to accommodate her behavior but it became too difficult.
Rhea

- Rhea’s doctor suspected obsessive compulsive disorder and recommended both cBT and medication trial.
- Rhea’s therapist taught Rhea and her family exposure and response prevention strategy, but it was very difficult to engage Rhea in the therapy.
- Rhea’s psychiatrist reviewed benefits and risks with Rhea/parents and started a small dose of fluoxetine (an SSRI). Rhea tolerated the small dose well, and family saw moderate benefit.
Antipsychotics

- Older: Haloperidol (Haldol), Loxapine, Clozapine
- Second generation: Risperidone (Risperdal), Aripiprazole (Abilify), Quetiapine (Seroquel), Olanzapine (Zyprexa), Ziprasidone (Geodon), Paliperidone (Invega)
- Newer: Lurasidone (Latuda), Asenapine (Saphris), Iloperidone (Fanapt), Braxiprazole (Rexulti)

Antipsychotics are the most commonly prescribed psychotropic medications in individuals with ID.

The targets include problem behaviors, such as aggression, SIB, severe stereotypies, hyperactivity and severe temper tantrums.
Antipsychotics: Things to Consider

- Metabolic syndrome?

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<tr>
<th></th>
<th>Baseline</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>annual</th>
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<tbody>
<tr>
<td>BMI</td>
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<td>HbA1c/Fasting glucose</td>
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<td>Lipid</td>
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- Tardive Dyskinesia?
- Long term Efficacy?

Young & Robert 2016
ADHD meds – Stimulants

- Methylphenidate – Ritalin ER, Metadate CD/ER, Concerta, Focalin XR, Daytrana, Cotempla XR-ODT, Quillivant XR
- Amphetamine/Dextroamphetamine – Adderall XR, Dexedrine
- Lisdexamfetamine - Vyvanse

Things to consider

- Effect/efficacy may be lower in individuals with neurodevelopmental disorder
- Tolerability/side effects may be more common in individuals with neurodevelopmental disorder
- Withdrawal/Rebound symptoms
- Appetite/Sleep disturbances
- Cardiac evaluation before trial for those with known/suspected cardiac disease or familial arrhythmia/sudden death at young age
ADHD meds – Non stimulants

- Atomoxetine (Strattera) for both inattention/hyperactivity-impulsivity
- Clonidine IR/ER (Kapvay) for hyperactivity-impulsivity
- Guanfacine IR/ER (Tenex, Intuniv) for hyperactivity-impulsivity

Things to consider:
- Atomoxetine – similar (yet less pronounced) appetite/sleep disturbances than stimulant
- Clonidine/Guanfacine: drowsiness, fatigue, emotional fragility, and irritability during the early phase of treatment

Young & Robert 2016
Anti-depressants: SSRI/SNRI

- Selective Serotonin Reuptake Inhibitors (SSRI) – Fluoxetine (Prozac), Sertraline (Zoloft), Citalopram (Celexa), Paroxetine (Paxil), Fluvoxamine (Luvox), Escitalopram (Lexapro)
- Serotonin Norepinephrine Reuptake Inhibitors (SNRI) – Venlafaxine (Effexor), Desvenlafaxine (Pristiq), Duloxetine (Cymbalta), etc.
- Things to Consider
  - Antidepressants are effective for both anxiety and depression
  - Side effects are generally mild and transient, but be aware of SSRI/SNRI induced “activation syndrome” and serotonin syndrome.
  - Benefit may not be apparent 4 to 6 weeks after dose is optimized.
Questions? Comments?