Advanced Issues in Pharmacology: Aggression and Self-Injury in Adolescents with ASD or Other Disorders

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Potential Sources of Conflict

- None

Broad Intervention Overview

- Environmental
  - Structural
  - Programmatic
- Psychological
  - Cognitive/Behavioral
  - Intrapsychic
- Biological
  - ***Pharmacological***
  - Nutritional

General Points

- To date, **no** pharmacological intervention has been shown prevent or reverse core symptoms of autism spectrum disorder (ASD) or intellectual disability (ID)
- Many (possibly most) children with ASD or ID do not need and are not apt to benefit from medications
- Potent interventions nearly always have potent potential side effect

Possible Targets of Pharmacological Interventions

- Prevention or reversal of underlying problem
  - No likely candidates at present
- Improvement of core symptoms
  - Unclear that any available medications do this
  - No evidence that we can change illness course
- Decrease in core or common accompanying symptoms or behaviors
  - Primary target of current medications

General Precautions

- Most uses described in this talk do **not** have FDA endorsement.
- All described uses are generally accepted practice with experts in child and adolescent psychopharmacology.
- This population seems to be especially prone to side effects.
- When in doubt, seek additional advice.

Current Trends

- New drugs are being used immediately
- **Belief** in drug efficacy and safety is shaky
- Research is expanding but still quite limited
- Focus typically is on symptom reduction, not disorder-specific treatment
- Polypharmacy—i.e., simultaneous use of multiple medications—is quite common

ADVANCING KNOWLEDGE

Who Is Doing Research on Autism and Medications?

- Several common sources of funding
  - NIMH
  - Pharmaceutical Companies
  - Private groups (e.g., NAMI, Autism Speaks)
- Most research occurs in academic centers or with large health care systems

Research Units on Pediatric Psychopharmacology (RUPPs)

- Established in 1996 by the NIMH
- Collaborative effort between government and pharmaceutical industry
- Specific focus on childhood mental disorders, including ASD
- Conducted research on risperidone
- No longer funded for new projects but still publishing previous results

Excellent Resource for Information About Research Trials

- ClinicalTrials.gov
  - Consolidated information source for all large-scale research trials
  - Searchable
  - Currently lists nearly 267,000 trials in all 50 states and 203 countries
  - Currently lists 26 open trials in California for ASD and 22 for ID—none for aggressive or self-injurious behavior and many not involving medications

DECIDING WHETHER MEDICINE MIGHT BE APPROPRIATE

Useful questions when considering medications:

- What behaviors need changing?
- Is a drug apt to help?
- What are the potential risks?
- How will we know if the drug is helping?
- How will we know if we need to stop?

Key Factors in Considering Use of a Drug

- Severity and persistence of behavior
  - Intermittent behaviors are hard to target
  - Milder behaviors may not actually be impairing function
- Age of patient
  - Younger children typically are more subject to behavioral control
  - Brain development now known to extend into at least early 20's

Key Factors in Selecting a Medication

- Whenever possible, look for a cause for the behavior that medicine can alter
- Where feasible, use one medication to address multiple problems, particularly in choosing among similar medicines with differing side effects
- When simply suppressing behavior, *adequate* control may be preferable to *optimal* control

Key Factors (cont.)

- Specificity of desired impact
  - Removing a driving force for undesirable behavior is rare but wonderful
  - General suppression of overall behaviors typically not acceptable to parents or teachers
- Adverse impact of side effects
  - Need to avoid/minimize common side effects
  - Want to identify and deal with emerging side effects sooner rather than later

Behaviors for Which Drugs Are Often Used

- Unmanageable agitation, aggression, or rage
  - antipsychotics, mood stabilizers
  - beta-blockers, antidepressants
- Self-mutilation and head banging (SIBs)
  - antipsychotics, low-dose SSRIs, naltrexone
- Severe impulsivity
  - antipsychotics, lithium, antidepressants, stimulants
- Chronic sleep problems (onset insomnia or EMA)
  - sedating antidepressants, antipsychotics

Behaviors for Which Drugs Are Often Used (cont.)

- Obsessive-Compulsive Behaviors
  - SSRIs
- Perseverative Behaviors
  - antipsychotics, SSRIs
- Labile mood with temper outbursts
  - antipsychotics, low-dose SSRIs, anticonvulsant mood stabilizers

Relatively Poor Medication Targets

- "Asocial inattention," i.e., not attending because not motivated to do so.
- Low social drive, e.g., little interest in peers
- "Odd" or unusual behaviors and interests
- High sexual drive or interest

Stimulants – General Observations

- Seldom used in this population
- Can be helpful in limited circumstances
- Will not help if problems with attention and impulsivity reflect mental age or autism
- Available formulations permit decisions about how big a "window" treatment will create
- Paradoxical increase in agitated motor activity for 6-8 hours well described and not uncommon
- For latest list of FDA-endorsed ADHD medications: www.ADHDMedicationGuide.com

Antidepressants — General Observations

- SSRIs especially effective for obsessive behaviors; low doses may help with anxiety
- Requires little to no monitoring
- SSRIs can produce restless (akathisia)
- **But** all antidepressants now have black-box warning about risk of suicide—first few weeks, cause unknown, magnitude unknown in population.

Antidepressants

- SSRIs
  - citalopram (Celexa)
  - escitalopram (Lexapro)
  - fluoxetine (Prozac)
  - fluvoxamine (Luvox)
  - paroxetine (Paxil)
  - sertraline (Zoloft)
- Other
  - atomoxetine (Strattera)
  - bupropion (Wellbutrin)
  - duloxetine (Cymbalta)
  - imipramine (Tofranil)
  - mirtazapine (Remeron)
  - trazodone (Deseryl)
  - venlafaxine (Effexor)

Antipsychotics — General Observations

- Commonly used in this population, often with good effect
- Widespread effects, including calming, but often rather nonspecific
- Side effects emerging with use of so-called atypical antipsychotics: weight gain, Type-II diabetes, and high cholesterol
- Concerns about increased risk of death (first raised in elderly patients with dementia)

Antipsychotics

- Atypical
  - aripiprazole (Abilify)
  - lurasidone (Latuda)
  - olanzapine (Zyprexa)
  - quetiapine (Seroquel)
  - paliperidone (Invega)
  - risperidone (Risperdal)
  - ziprazadone (Geodon)
- Typical
  - haloperidol (Haldol)
  - thioridazine (Mellaril)

Antipsychotics: Old vs. New

- Old
  - Fairly high risk of acute side effects
  - Risk of tardive dyskinesia ~ 15-20%
  - Modest weight gain
- New
  - Variable risk of acute side effects
  - Low risk of tardive dyskinesia ~ < 2%
  - Variable weight gain, sometimes major
  - Type-II diabetes
  - Hypercholesterolemia

Mood Stabilizers — General Observations

- Scant data on usefulness in individuals with ASD or ID
- Use limited because of need to monitor blood levels

Mood Stabilizers

- Established
  - carbamazepine (Tegretol)
  - lithium (Lithobid, Eskalith)
  - valproic acid (Depakote)
- Of Interest
  - gabapentin (Neurontin)
  - lamotrigine (Lamictal)
  - oxcarbazepine (Trileptal)
  - tiagabine (Gabatril)

alpha-Adrenergic Agonists

- These medications have received scant study
- Typical uses are for their sedative properties to promote sleep and decrease anxiety
- Especially with clonidine, there is a risk of rebound hypertension with skipped doses

alpha-Adrenergic Agonists

- clonidine
  (Catapres, Kapvay)
  - Quite sedating
  - 3-4 doses/day
  - Available as patch
  - Potential for rebound high blood pressure
- Guanfacine
  (Tenex, Intuniv)
  - Less sedating
  - Twice-daily dosing
  - Efficacy relative to clonidine remains unclear

Adrenergic Blockers

- Underlying hypothesis is that some individuals have an "immature" pituitary-adrenal axis resulting in "adrenaline overactivity" that produce meltdowns
- Postulated to have two types:
  - Flight/fright, with reaction to stress promoting flight if possible and aggression if cornered, also called "prey" or "rabbit"—reportedly responsive to beta-blockers
  - Fight, with reaction to stress resulting in directed aggression, also called "predator" or "lion"—reportedly responsive to alpha-blockers.

Adrenergic Blockers (cont.)

- In theory, norepinephrine especially high in predators while epinephrine is much higher in prey
- No controlled, systematic studies. At present "evidence" is strictly anecdotal.
- Safety and efficacy are not established for children or adolescents for either class of medications

Adrenergic Blockers

- beta-Blockers
  - atenolol (Tenormin)
  - bisoprolol (Zebeta)
  - betaxolol (Betopic)
  - metoprolol (Toprol-XL)
  - nebivolol (Bystolic)
  - propranolol (Inderal)
- alpha-Blockers
  - doxazosin (Cardura)
  - prazosin (Minipress)
  - terazosin (Hytrin)

Common Problems to Avoid

- Raising dose too quickly
- Under-medicating for problem
- Over-medicating for problem
- Treating too many target behaviors one at a time, leading to polypharmacy

Case Example #1

- 7-year-old male with well-diagnosed ASD and mild ID with 3-month history of uncontrollable self-pinching, taking small folds of skin and pinching hard enough to bruise while chanting "no more pinching, no more pinching." No known precipitant, constant preoccupation while awake, agitated and dysphoric. No other new symptoms.

Case Example #2

- 8-year-old female with ASD and moderate ID who does well when in Special Day Class (SDC). However, within minutes of being mainstreamed into a second grade class, viciously attacks whoever is closest to her—usually a peer—resulting in her being returned immediately to her SDC.

Case Example #3

- 16-year-old male with ASD and normal cognitive functioning with longstanding ritualistic behaviors such as repeated hand-washing and ordering of objects on his desk. Can become highly assaultive at times, with the teacher insisting it is "out of nowhere." Mostly calm, cooperative, and not a behavioral problem.

Summary

- Medications can be useful for a variety of individuals with autism and related disorders, with and without cognitive delays
- Newer medications are proving to have their own side effects; long-term safety remains to be assessed
- Effective medication demands close, ongoing collaboration between physician and caregivers

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