Psychopharmacology of Aggression Management in Children and Adults

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Objectives

- Differentiate between classifications of aggressive behavior
- Discuss the neurobiology of aggressive behavior
- Compare the various pharmacologic treatment options for aggression
- Design a medication regimen to treat aggression in the patient case provided

Classifying Aggression

- Based on the mode
  - Physical
  - Verbal
- Based on the target
  - Objects (e.g., destroying property)
  - Persons (e.g., screaming, fighting, assault)
  - Self (e.g., head-banging, punching walls)
- Based on the intensity
  - Calm, threatening, assertiveness
  - Raw, primitive, un-modulated

Muscari, ME. Pharmacotherapy of Violent or Aggressive Behavior. October 2006.
Classifying Aggression

- Based on the Time-Frame
  - Acute vs Chronic
- Overt vs Covert
  - Assault vs Manipulation
- Adaptive vs Maladaptive
  - Punching a burglar vs a supervisor
- Patient Age
  - Pediatric (<18 years) vs Adult (18+ years)

Classifying Aggression: Impulsive vs Premeditated

- Premeditated
  - Proactive, goal-directed, predatory
  - Unprovoked by immediate threat, frustration
- Impulsive
  - Unplanned
  - Perception of immediate threat or frustration
  - Negative emotions (fear, anger)
  - Characterized by high autonomic arousal
  - Healthy as a reaction to environmental threats
  - Pathological if disproportional intensity/misdirected

Classifications of Aggression: DSM-V

- Oppositional Defiant Disorder (ODD)
  - Angry/irritable mood, argumentative/defiant behavior, vindictiveness
- Conduct Disorder (CD)
  - ODD + aggression to people or animals, destruction of property, deceitfulness or theft, and serious violation of rules; age <18 years
- Antisocial Personality Disorder (APD)
  - CD when patient is 18+ years
Classifications of Aggression: DSM-V

- **Intermittent Explosive Disorder (IED)**
  - Recurrent, impulsive, aggressive outbursts disproportionate to provocation; age >6 years


Aggression: Related DSM-V Diagnoses

- **Attention-Deficit / Hyperactivity Disorder (ADHD)**
  - A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, not better explained by another mental disorder

- **Borderline Personality Disorder (BPD)**
  - A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood


“Why Is My Patient So Aggressive?”

Causes include:
- Uncontrolled psychiatric disorders
- Neurological or medical disease
- Drug use / abuse
- PTSD
- Intermittent impulsive

http://i.livescience.com/images/i/000/004/598/i02/070606_generic_anger_02.jpg?1296082940
https://slightlychristopher.files.wordpress.com/2013/01/0.jpg
Neurobiology of Aggression

- Imbalance between:
  - Orbital Frontal Cortex (OFC) -> top-down control
  - Anterior Cingulated Cortex (ACC) -> behavioral adaptation
  - Amygdala / Insula -> fear, threat, punishment, reward

- Lower threshold for aggressive responses to external stimuli

- Inadequate regard for consequences of behavior


Receptor Targets of Aggression

- Serotonin (5HT) Transporter
  - activity in ACC and OFC of aggressive patients

- 5HT₂A Receptors
  - binding in physically aggressive, BPD, suicide

- Glutamate / GABA Imbalance
  - Hyperactive response to aversive stimuli

- β-adrenergic / AMPA
  - Modulates emotional memory in the amygdala

- HGH response to α₂-agonist
  - Irritability


Receptor Targets of Aggression

- Testosterone
  - ↑ reported in criminals with personality disorders, alcoholic violent offenders, and spousal abusers
  - Conflicting study in IED males -> no significant association with aggressive behavior

Management: Co-Morbid Conditions

Provide effective treatment of the underlying, co-occurring neurological, medical, or psychiatric condition first

Examples:
- Depression → Antidepressants
- Anxiety → Anxiolytics
- ADHD → Stimulants, α₂-Agonists
- Bipolar Mania → Mood Stabilizers
- Psychosis → Antipsychotic

Managing Aggression as the Primary Condition

Specific pharmacotherapy targeting acute aggressive behavior independent of comorbid diagnosis

- Sedatives
- Anti-Psychotics
- Mood Stabilizers / Anti-Convulsants
- Beta-blockers
- 5-HT1A Receptor Agonists
- Omega-3 Fatty Acids
- Anti-androgens

Comparison by Effect-Size

- Effect Size (ES)
  A quantitative measure of the strength of a phenomenon, based on the primary outcome variable for each study in a meta-analysis
  \[ \text{ES} = \frac{\text{Experimental} - \text{Control}}{\text{SD}_{\text{pooled}}} \]

- Small Effect: <0.2
- Medium Effect: 0.21 – 0.5
- Large Effect: >0.8

*ES ≥0.4 ~ observable change in patient condition
Antidepressants: Adults

- Studied Drug:
- Control Group:
- Diagnosis

Specific Drugs Studied:
Fluoxetine, fluvoxamine, sertraline, amitriptyline, imipramine, citalopram

Proposed Mechanism:
↑ 5-HT activity in OFC / ACC → ↑ regulation of aggressive responses to aversive stimuli

Effect Size for Drug-Class:
Weak evidence for efficacy

Antidepressants: Adults

Desipramine (Norpramin®)

- Clinical Effect:
  ↘ of aggression associated with depression

- Mechanism:
  Inhibition of NE > 5-HT reuptake transporters → ↑ synaptic NE/5-HT concentrations → ↓ of inhibitory α2 autoreceptors / post-synaptic β-receptors

- Adverse Effects:
  - Drowsiness, dizziness, headache, hypotension, xerostomia, blurred vision
  - Cardiac dysrhythmia, QTc-prolongation, sudden cardiac death, NMS, CVA, seizure

- Dose Adjustments:
  Lower initial doses if geriatric, or hepatic impairment
Antidepressants: Bupropion (Wellbutrin®)

- Clinical Effects: ↓ of aggression associated with depression
- Mechanism: Inhibition of DA, NE reuptake transporters → ↑ synaptic DA/NE concentrations in the Nucleus Accumbens / PFC
- Adverse Effects: Insomnia, headache, dizziness, cardiac dysrhythmia, xerostomia, nausea
- Dose Adjustments: Hepatic impairment, moderate-severe → max dose 75mg/day (IR), 100mg/day (SR)

Antidepressants: Fluoxetine (Prozac®)

- Clinical Effects: ↓ of aggression associated with depression
- Mechanism: Inhibition of 5-HT reuptake transporters → ↑ pre-synaptic 5-HT → ↓ of 5-HT autoreceptors → ↑ 5-HT neuron firing
- Adverse Effects: Insomnia, sexual dysfunction, nausea, vomiting, restlessness, anxiety
- Dose Adjustments: Hepatic impairment, moderate-severe → max dose 75mg/day (IR), 100mg/day (SR)

Trials: Antidepressants for Aggression

- Biederman et al, 1989: Desipramine vs Placebo
  - RCT, n= 62, average age 10.4 years, 6-weeks
  - Dx: ADHD, 69% nonresponse to stimulants
  - Effect Size: 0.85 (high >0.51)
- Coccaro et al, 1997: Fluoxetine vs Placebo
  - DB, RCT, n= 40, ages 6-14 years
  - Dx: H ≠ MDD, ≠ Bipolar, ≠ Schizophrenia
  - Conduct scale response 21/37 vs 6/29, p <.01
- ____ et al, Year: Clonidine
  - RCT, n= 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)
Norepinephrine Reuptake Inhibitor: Atomoxetine (Strattera®)

- **AEs:**
  - appetite, emotional lability

- **Studied Population(s):**
  - Primary Dx: ADHD, intolerance, failed response to stimulants
  - Comorbid Dxs: ODD, MDD, GAD
  - 887 subjects, Avg n=214.3; 80.5% male; 10.5 years old

- **Efficacy / Literature:**
  - 4 RCTs, ES=0.18, small-modest effect for long average study duration, sample size

Trials on ***-3 FAs:

- **et al, Year: Trial Intervention**
  - Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
  - Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- **et al, Year: Drug A vs Drug B**
  - RCT, n= 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
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  - Effect Size: 1.1 (large >0.8)

Mood Stabilizers

- **Specific Drugs Studied:**
  - Lithium, valproate, topiramate

- **Mechanism:**
  - L: serotonergic function, noradrenergic function

- **Onset:**
  - Days to weeks

- **Studied Population:**
  - L: Abusive parents, prisoners, suicidal pts

- **Efficacy / Literature:**
  - L: Multiple RCTs demonstrating obsessive/compulsive behavior
  - L: Risk of death by suicide 2.7x less than valproate
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**Anticonvulsants**

- **Specific Drugs Studied:**
  - Carbamazepine (Tegretol®), oxcarbazepine (Trileptal®)
- **Mechanism:**
  - DA activity w/o blocking specific DA receptors
- **AEs:**
  - Hepatotoxicity, pancytopenia, rash, hypersensitivity reactions, electrolyte disturbances, dizziness
- **Studied Population:**
  - C: Alzheimer's, vascular/mixed dementia, borderline
- **Efficacy / Literature:**
  - C: Sole RCT (n=22) → No benefit; Case studies describe benefit; widespread use, more study indicated

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Anticonvulsants

- **Drug:** Oxcarbazepine (Trileptal®)
- **Mechanism:**
  - DA activity w/o blocking specific DA receptors
- **AEs:**
  - Hepatotoxicity, pancytopenia, hypersensitivity reactions, metabolic disturbances
- **Studied Population:**
  - C: Alzheimer’s, vascular/mixed dementia, borderline
  - O: Impulsive aggression w/o comorbid psychiatric dx
- **Efficacy / Literature:**
  - C: Sole RCT (n=22) No benefit; Case studies describe benefit

Benzodiazepines

- **Specific Drugs Studied:**
  - Lorazepam
- **Mechanism:**
  - GABA agonism
- **Onset:**
  - IM formulation: within minutes, peak at 3 hours
- **Studied Population:**
  - Widely used for acute aggression/agitation
- **Efficacy / Literature:**

Trials on ***-3 FAs :

- et al, Year: Trial Intervention
  - Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
  - Dx: ADHD(42), +Tic(67), +CD(26), +PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

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  - RCT, n = 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- et al, Year: Clonidine
  - RCT, n = 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)
Antipsychotics: Risperidone (Risperdal®)

- **Mechanism:**
  - D2, SHT-2A antagonism

- **AEs:**
  - EPS, hyperprolactinemia, weight-gain, sedation, cardiac arrhythmias

- **Studied Populations:**
  - Pediatrics:
    - CD, ODD, ADHD, low IQ
  - Adults:
    - Schizophrenia, PTSD, Borderline

- **Efficacy / Literature:**
  - Peds: Multiples demonstrating efficacy, tolerability, ES: 0.9
  - Adults: Clozapine > Olanzapine > Quetiapine >> risperidone = haloperidol

**Trials on ***-3 FAs:**

- et al, Year: Trial Intervention
  - Meta-analysis of 11 RCTs, n = 150, age 10.6±2.4 years
  - Dx: ADHD(42), tic(67), CD(26), PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- et al, Year: Drug A vs Drug B
  - RCT, n = 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- et al, Year: Clonidine
  - RCT, n = 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)

Antipsychotics

- **Specific Drugs Studied:**
  - Clozapine

- **Mechanism:**
  - SHT-2A antagonism

- **Onset:**
  - Variable by route

- **Studied Populations:**
  - Schizophrenia, PTSD, Borderline

- **Efficacy / Literature:**
  - Data from RCTs
  - C > O > Q >> risperidone = haloperidol
Trials on ***-3 FAs:

et al, Year: Trial Intervention
- Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
- Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
- Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

et al, Year: Drug A vs Drug B
- RCT, n= 67, ages 6-14 years
- Dx: ADHD + ODD, ADHD + CD
- Conduct scale response 21/37 vs 6/29, p <.01

et al, Year: Clonidine
- RCT, n= 8, average age 10.0
- Dx: Autism (PDD)
- Effect Size: 1.1 (large >0.8)

Antipsychotics

- Specific Drugs Studied:
  - Olanzapine
- Mechanism:
  - 5HT-2A, 5HT-2C antagonism
- Onset:
  - Variable by route
- Studied Populations:
  - Schizophrenia, PTSD, Borderline
- Efficacy / Literature:
  - Data from RCTs
  - C > O > Q >> risperidone = haloperidol

Trials on ***-3 FAs:

et al, Year: Trial Intervention
- Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
- Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
- Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

et al, Year: Drug A vs Drug B
- RCT, n= 67, ages 6-14 years
- Dx: ADHD + ODD, ADHD + CD
- Conduct scale response 21/37 vs 6/29, p <.01

et al, Year: Clonidine
- RCT, n= 8, average age 10.0
- Dx: Autism (PDD)
- Effect Size: 1.1 (large >0.8)
**Antipsychotics**

- **Specific Drugs Studied:**
  - Quetiapine
- **Mechanism:**
  - 5HT<sub>2A</sub>, 5HT<sub>2C</sub> antagonism
- **Onset:**
  - Variable by route
- **Studied Populations:**
  - Schizophrenia, PTSD, Borderline
- **Efficacy / Literature:**
  - Data from RCTs
  - C > O > Q >> risperidone = haloperidol

**Trials on ***-3 FAs :**

- et al, Year: Trial Intervention
  - Meta-analysis of 11 RCTs, n = 150, age 10.6±2.4 years
  - Dx: ADHD(42), tic(67), CD(26), PDD(15)
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- et al, Year: Clonidine
  - RCT, n = 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)

**Stimulants**

- **Specific Drugs Studied:**
  - Methylphenidate (Ritalin®, Metadate CD®, Concerta®)
  - Pemoline (Cylert®)
  - d,l-amphetamine (Adderall®)
- **Mechanism:**
  - DA/NE reuptake in neurons of cerebral cortex, subcortical structures
- **AEs:**
  - Insomnia, Appetite, GI pain, HA, dizziness, height/weight suppression
- **Onset:**
  - Minutes - hours
- **Studied Population:**
  - Primary Dx: ADHD (13), AUT (2), MR (1), DB
- **Efficacy / Literature:**
  - Stimulants Overall (ES = 0.78)
  - Methylphenidate (MPH), ES = 0.9, demonstrated efficacy, multiple trials
Trials on ***-3 FAs:

- et al, Year: Trial Intervention
  - Meta-analysis of 11 RCTs, n=150, age 10.6±2.4 years
  - Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
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  - RCT, n=67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- et al, Year: Clonidine
  - RCT, n=8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)

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5-HT$_{1A}$ Receptor Agonists

- Specific Drugs Studied:
  - Buspirone
- Mechanism:
  - Increased serotonergic activity;
- Onset:
- Studied Population:
- Efficacy / Literature:
  - Limited to case reports, open trials
  - Demonstrated reduction in aggressive outbursts

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Trials on ***-3 FAs:

- et al, Year: Trial Intervention
  - Meta-analysis of 11 RCTs, n=150, age 10.6±2.4 years
  - Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- et al, Year: Drug A vs Drug B
  - RCT, n=67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- et al, Year: Clonidine
  - RCT, n=8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)
**β-Blockers**

- **Clinical Effects:**
  - xxx
- **Mechanism:**
  - Non-selective blockade of β-adrenergic receptors normally responsible for ‘fight or flight’ stimulation
- **Adverse Effects:**
  - Drowsiness, dizziness, headache, hypotension, xerostomia
- **Dose Adjustments:**
  - Lower initial doses if renal or hepatic impairment

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**Trials on β-Blockers: Propranolol (Inderal®)**

- **et al, Year: Trial Intervention**
  - Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
  - Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- **et al, Year: Drug A vs Drug B**
  - RCT, n= 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- **et al, Year: Clonidine**
  - RCT, n= 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)

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**Omega-3 FAs**

- **Mechanism:**
- **Onset:**
  - weeks to months
- **Studied Population:**
  - Pts with hx of substance abuse
- **Efficacy / Literature:**
  - DB RCTs – reduced anger, outbursts
Trials on Omega-3 FAs:
- **et al, Year: Trial Intervention**
  - Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
  - Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- **et al, Year: Drug A vs Drug B**
  - RCT, n= 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- **et al, Year: Clonidine**
  - RCT, n= 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)

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**α2-Receptor Agonists**

- Clinical Effects:
  - Reduced oppositional behavior
  - Enhanced frustration tolerance
  - Improved hyperactivity, impulsivity
  - Reduction in AEs from concomitant stimulant therapy

- Mechanism:
  - Agonism at postsynaptic α2-receptors in the prefrontal cortex
  - modulation of sympathetic outflow
  - enhanced executive function

- Adverse Effects:
  - Drowsiness, dizziness, headache, hypotension, xerostomia

- Dose Adjustments:
  - Lower initial doses if renal or hepatic impairment

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**Trials on α2-agonists: Clonidine (Catapres®)**

- **Connor et al, 1999: Clonidine monotherapy**
  - Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
  - Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
  - Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- **Hazel et al, 2003: Stimulant vs +Clonidine**
  - RCT, n= 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- **Jaselskis et al, 1992: Clonidine**
  - RCT, n= 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)
Trials on α₂-agonists: Guanfacine (Tenex®, Intuniv®)

Scahill et al, 2001: Guanfacine monotherapy
- RCT, n= 34, average age 10.0 years, 8-week duration
- Dx: ADHD + tic
- Measured reduction in aggressive behavior
- Effect Size: 0.4 (moderate 0.21 to 0.5)

Anti-androgens

- Specific Drugs Studied:
- Mechanism:
- Onset:
- Studied Population:
- Efficacy / Literature:

Trials on Androgen-Antagonists:

- Meta-analysis of 11 RCTs, n= 150, age 10.6±2.4 years
- Dx: ADHD(42), +tic(67), +CD(26), +PDD(15)
- Effect Size: 0.58±0.16 (moderate 0.21 to 0.5)

- et al, Year: Drug A vs Drug B
  - RCT, n= 67, ages 6-14 years
  - Dx: ADHD + ODD, ADHD + CD
  - Conduct scale response 21/37 vs 6/29, p <.01

- et al, Year: Clonidine
  - RCT, n= 8, average age 10.0
  - Dx: Autism (PDD)
  - Effect Size: 1.1 (large >0.8)
Conclusion

- There is no "magic pill" for the treatment of aggressive behaviors.
- The most effective pharmacotherapeutic management of aggression can vary based on patient specific factors, and the sub-type of aggression.
- Effective treatment of co-morbid psychiatric conditions should be prioritized.

Patient Case

Post-Assessment

- T/F: Patients should always be trialed on an SSRI before resorting to other therapeutic options for aggressive behavior.
- T/F: Aggressive-impulsive behavior is believed to be caused by an imbalance between the prefrontal cortex (control center) and the limbic system (drives).
- T/F: Testosterone antagonists are the most effective treatment option for aggressive-impulsive behavior refractory to other treatment modalities.
References