

Aggression in Youth: Treatment approaches

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Question 1

- 1) A 10 year old boy with serious aggression is treated with risperidone at 2mg/day. Which of the following statements is true:
- A) He is less likely to develop weight gain than an adult
 - B) He is less likely to develop prolactinemia than an adult
 - C) He is less likely to develop weight gain compared to a teenager
 - D) He is more likely to develop weight gain compared to an adult
 - E) He is less likely to develop EPS at dosages of 6mg/day than at 1 mg/day

Question 2

2) Which of the following drugs is not associated with at least one double-blind placebo controlled trial showing efficacy in the treatment of aggression in youth?

- A) Clonidine
- B) Lithium
- C) Carbamazepine
- D) Valproate
- E) Risperidone

Question 3

3) A 14 year old girl treated with risperidone for aggression is found to have a prolactin level of 90 ng/ml. What symptoms or side effects should you ask about?

- A) Increased urination
- B) Decreased urination
- C) Disturbances in sleep
- D) Disturbances in menstruation
- E) None of the above

Question 4

- 4) A 15 year old girl has been treated with lithium for aggression for 3 months. Her trough blood levels have been running from 0.8 to 1.0 meq/L, but a recent level was found to be 1.3 meq/L. She is experiencing no changes in adverse effects. Which explanation is most likely?
- A) She has been drinking alcoholic beverages
 - B) She has been using St John's wort.
 - C) Her family physician has started her on erythromycin
 - D) The blood was drawn at 8 hours after her last dose of lithium
 - E) The blood was drawn 15 hours after the last dose of lithium

Question 5

5) A 12 year old boy seeks revenge against adults who set limits on him. He plans carefully. Are his symptoms likely to be medication sensitive?

A) Yes

B) No

Teaching Points

- Aggression is defined as any behavior intended to be destructive to self, others, or objects & property
- Higher prevalence of aggression is associated with MR, PDD, Conduct Disorder, Bipolar Disorder, PTSD, MDD, ADHD
- Atypical antipsychotics usually first line pharmacological measure to treat aggression
- Acute aggression: Avoid frequent use of stat medications

Outline

- Definition & Subtypes
- Etiology
- Epidemiology
- Assessment
- Prevention
- Treatment: Psychopharmacological & Psychosocial

Aggression: Definition and Subtypes

- Aggression: Any behavior intended to be destructive to self, others, or objects & property
- Subtypes: Acute vs. Chronic; Verbal vs. Physical; Overt (physical assault or temper tantrums) vs. Covert (lying, stealing, cheating, theft); Adaptive vs. Maladaptive
- Maladaptive aggression: Not adaptive for individual, out of proportion of the eliciting precipitants, violates societal rules
- Maladaptive aggression: Types: Reactive-affective-defensive-impulsive (RADI) and Proactive-instrumental-planned-predatory (PIPP).

Connor DF, Carlson GA, et al. Juvenile Maladaptive Aggression: A Review of Prevention, Treatment, and Service Configuration and a proposed research agenda. *J Clin Psychiatry*, May 2006

Ruths S, Steiner H. Psychopharmacologic treatment of aggression in children and adolescents. *Pediatric Annals*, May 2004.

Chronic Aggression in Youth: Final Common Pathway of Multiple Inputs

- Genetic, Organic, Environmental and Learning Disorders, often in concert
- Higher prevalence associated with MR, PDD, Conduct Disorder, Bipolar Disorder, PTSD, MDD, ADHD
- Conduct Disorder and aggression are not synonymous: Aggression is not required for a diagnosis of conduct disorder

Etiology

- Neurotransmitter Theories
 - Lowered serotonin levels
 - Acetylcholine stimulation shown to increase aggression in animals
 - Agents that act on dopamine can increase aggression
- Genetic theories
 - Chromosomes
- Hormonal Theories
 - Testosterone and other hormones implicated

Epidemiology

- 60% referrals to child psychiatry ambulatory clinics: Evaluation & treatment of aggressive children (Connor 2006)
- Violence: Predictor of urgency in pediatric emergency psychiatric settings—62% of child & 32% of adolescent psychiatric emergency visits (Connor 2006)
- Youngsters with maladaptive aggression :
 - Have more school adjustment problems
 - Greater deficits in cognition
 - Experience more peer rejection and victimization
 - Difficulties in ambiguous interpersonal situations, such as reading emotion in people's facial expressions (Jensen 2007)

Assessment

- Thorough psychiatric assessment before initiating treatment
- Assess frequency, duration and severity
- Look for precipitants?
- Assess any alleviating Factors
- Recommended Scales:
 - Overt Aggression Scale (OAS) (Yudofsky et al., 1986)
 - Children's Aggression Scale (Halperin et al., 2003)
 - The Aggression Questionnaire (AQ) (Vitiello et al., 1990)

Prevention programs

- Features of successful prevention programs include:
 - Multimodal interventions: More effective than single-point interventions; simultaneously target child, family, teachers and early childhood education
 - Intensive interventions: Daily-weekly
 - Sufficient duration: 2 years or longer
 - Child & parent interventions focusing on skill-building, problem solving & coping skills
 - Earlier interventions between age 0-6years
 - Individual case management
 - Intensive collaboration among community, school, juvenile justice, family and mental health professionals
- School based violence prevention programs: Effect size 0.36-0.59

Treatment

- Impulsive aggression (Reactive): Medication sensitive
- Predatory or planned, pro-active, or profitable self- controlled aggression: Not medication sensitive (Vitiello 1990)
- Verbal aggression: Not usually medication sensitive (Silver and Yudofsky 1991)

Psychosocial Interventions

- 50% of those who are hospitalized for aggression improve without medication (Malone and Simpson 1998)
 - Especially true of children from stressful home environments or who have violent and criminal parents (Sanchez 1994)
- Other modalities:
 - Psychoeducation
 - Contingency management
 - Social skills training
 - Anger management
 - Parenting skills

Multi-focused Intervention programs

- For older children & adolescents with aggression and juvenile justice involvement
- Effectiveness: Decreased arrest rates by 25-70% (1-4 year outcomes)
- Multidimensional Treatment Foster care (MTFC): 12-26 week program for 12-17 year old youth (serious offenders)—Involves family skills training; individual skills training; intensive supervision at home, school & community; psychiatric consultation & medication management; community liaison; case management (Connor 2006)

Multi-focused Intervention programs

- Multisystemic Treatment: 10-15 week program for 12-17 year old youth; Utilizes parent skills training; individual skills training; family, community and school collaboration; intensive case management (Connor 2006)
- Effect size of multifocused psychosocial treatment programs: 0.4-0.9 (Connor 2006)

Treatment

- Treat the primary diagnosis:
 - ✓ ADHD: stimulants or other agents
 - ✓ MDD: fluoxetine or other SSRIs
 - ✓ Bipolar Disorder: Valproate (VPA) or Lithium or Atypical Antipsychotics (AAPs)
 - ✓ Paranoia or psychosis: AAPs
 - ✓ PTSD : Clonidine or SSRIs

Pharmacotherapy for aggression in youth

- Haloperidol: Conduct Disorder (CD) with Aggression (Campbell 1982)
- Risperidone:
 - CD (RUPP, Findling 2000)
 - MR (Leblanc 2005)
 - Autism (for tantrums, aggression, self,restrictive stereotypic activities RUPP 2005,)
- Lithium: CD with aggression (Malone 2000)
- Valproate: CD with aggression (Steiner 2003)
- Clonidine: ADHD + ODD, CD (Hazzell & Stuart 2003)
- Psychostimulants:
 - ADHD + CD (Farrone 2002)
 - CD alone, Klein 1997)

Use of Atypical Antipsychotics

- Used in as many as 50% of child inpatients mostly for aggression (and not psychosis)
- Increased outpatient usage: 160% in children and 494% teens (Texas Medicaid, 1996→2000, Patel et al 2002)
- Other targeted symptoms
 - ✓ Self-injurious behavior
 - ✓ Repetitive behaviors
 - ✓ Manic symptoms
 - ✓ Psychotic symptoms

TABLE 3. FREQUENCY OF REPORTED ADVERSE EVENTS IN CHILDREN AND ADOLESCENTS WITH SECOND-GENERATION ANTIPSYCHOTICS

<i>Adverse Event</i>	<i>Clozapine (n=206)</i>	<i>Risperidone (n=943)</i>	<i>Olanzapine (n=332)</i>	<i>Quetiapine (n=90)</i>	<i>Ziprasidone (n=26)</i>
Cardiovascular					
Orthostatic Hypotension	25 (12%)	1(0%)	0	0	0
Tachycardia	58 (28%)	16 (2%)	6 (2%)	9 (10%)	0
ECG Changes	0	0	0	3 (3%) (asymptomatic)	0
3/20 qtc >450 ms					
Increased Appetite/ Weight Gain	14 (7%)	159 (17%)	74 (22%)	20 (22%)	1 (4%)
Fatigue/Sedation	82 (40%)	306 (31%)	65 (20%)	22 (24%)	14 (54%)
Sialorrhea	59 (29%)	24 (2.5%)	0	0	0
EPS/Akathisia	13 (6%)	113 (12%)	25 (8%)	1 (1%)	1 (4%)
Enuresis	10 (5%)	34 (4%)	0	0	0
Tardive DYS	0	14 (2%)	0	0	0 transient
Seizures	5 (2%)	3 (0%)	0	1 (1%)	0
Hyperprolactin	0	35 (4%)	24 (8%)	1 (1%)	6 (23)%
Elevated Liver enzymes	1 (0%)	4 (0%)	7 (2%)	0	0

n = number of subjects with reported side effects.

Cheng-Shannon 2004

Rising incidence of obesity in youth

- 1963-1991: Incidence of obesity doubled in youth
- 16% of children aged 6-11 years are overweight : ≥ 95 th percentile of body mass index (BMI: kg/m^2)
- 14.3% at risk of becoming overweight: ≥ 85 th but < 95 th BMI

Prevalence of Obesity in Youth on Antipsychotics

- Cross-sectional naturalistic study
- 151 inpatients, mean age: 19.5 yrs
- In whole study population, obesity (BMI \geq 90th percentile) occurred in:
 - Half of all patients
 - 45% of males
 - 59% of females

BMI = Body mass index

Theisen FM, et al. *J Psychiatry Res.* 2001;35:339–345.

Weight Gain: Long-term Consequences

- Risk of adult obesity and attendant consequences (*Dietz 1998*):
 - Cardiovascular illness
 - Hypertension
 - Osteoarthritis
- Triglyceride increases (*Martin & L'Ecuyer, 2002*)
- Association with Type 2 diabetes
- Psychological effects
 - Isolation

Weight Gain and AAPs in Youth

- Olanzapine and Risperidone cause comparable weight gain in youth (Sikich 2004); Olanzapine worse in adolescents (Ratzoni 2002)
- 12 week study (Correll 2005):
 - 81% Olanzapine
 - 57% Risperidone
 - 43% Quetiapine

Risperidone weight gain across the ages

TABLE 5. Average RIS-Induced Weight Gain as a Percent of BBW by Age Group and by Weeks of Treatment

Weeks of RIS Rx	Average Percent of RIS-Induced Weight Gain/BBW (n*)			
	Ages 5 to 11 Years [†]	12 to 17 Years [†]	33 to 44 Years	71 to 83 Years
4 to 8	5.6 (233)	4.1 (85)	2.1 (1070)	0.5 (56)
9 to 16	7.4 (165)	6.3 (149)	2.9 (60)	0.2 (83)
17 to 56	16.3 (121)	8.1 (95)	3.4 (383)	0.3 (192)

*Pooled data relative to the number of subjects, from Tables 1–3 in relation to the duration of treatment.

[†]Corrected for estimated age-expected weight gain.

BMI in children

$$\frac{\text{weight in lbs}}{(\text{height in inches})^2} \times 703$$

<http://www.cdc.gov/nccdphp/dnpa/bmi/calc-bmi.htm>

Place on growth chart:

BMI <5th percentile :underweight

BMI > 85<95th : at risk for overweight

BMI >95th percentile : **OVERWEIGHT**

Dyslipidemia

- Low potency typicals and OLA, CLOZ, QUET (all 3-ring dibenzodiazepines): ↑ triglycerides (Meyer 2004)
- VLDL levels > 400-500 mg/dL increase risk for acute pancreatitis
- Decreased levels of lipids when switched to Ziprasidone and Aripiprazole in adults

Metabolic syndrome in childhood

- Definition:
 - Abdominal obesity
 - Plasma triglycerides >150 mg/Dl
 - Low HDL cholesterol level (<40 mg/dL for men, <50 mg/dL for women)
 - Blood pressure $>130/85$ mm Hg
 - Abnormal fasting glucose value >110 mg/dl.
- 4% of children & 30% of overweight adolescents in USA meet criteria for metabolic syndrome → DM type 2 & cardiovascular disease.
- Type 2 diabetes mellitus in pediatric population: 8-45% of all diabetes reported among youth

Extrapyramidal Side Effects in Adults

- Occur when 75-80% of D₂ receptors are blocked in basal ganglia
- CLOZ and QUET bind less tightly, hence least EPS.
- RISP and OLA have high 5-HT₂ blockade at low doses but D₂ blockade with increased dosage e.g. 4-5mg/d of RISP or 20-25 mg/d OLA increase risk for EPS (OLA < RISP because of OLA's intrinsic anticholinergic properties).
- TD develops when D₂ blockade is permanent.

EPS with Atypicals

- D₁ & D₂ receptor densities higher in children & teens
- In children, typical APs associated with higher incidence of acute dystonia, NIP, akathisia and withdrawal dyskinesias 12-44% (Connor 2001)
- Neuroleptic-induced Parkinsonism (NIP): OLA, RISP? more common in youth (Sikich 2004)
- Akathisia noticed in 23% of 30 youth on Aripiprazole (Barzman 2004)

Prolactin

- Pituitary cells manufacture prolactin
- Hypothalamic DA tracts are inhibitory to prolactin release; APs block this inhibitory control → ↑ prolactin
- All typical APs associated with prolactinemia
- AAPs, SSRIs, TCAs & some opioids can also cause prolactinemia (2-10 fold increase in first few weeks)
- Different AAPs have differing D₂ receptor occupancy at striatum vs. pituitary and different fat solubility to penetrate BBB (pituitary is on *other side* of BB) → Can have prolactinemia without EPS

Key: DA- dopamine, TAPs- typical antipsychotics, AAPs- atypical antipsychotics, TCA- tricyclic antidepressants, RSP- Risperidone, ARI- Aripiprazole, BBB- blood brain barrier

Diagnosis of Prolactinemia

- >18ng/ml for prepubertal girls and men
- Draw prolactin on 2 separate occasions
- Youth and women more sensitive to effects of increased prolactin
- Relative potency of antipsychotic drugs in inducing hyperprolactinemia (Correll, 2006): Risperidone > Haloperidol > Olanzapine > Ziprasidone > Quetiapine > Clozapine > Aripiprazole

AAPs & Prolactin elevation over time

- Risperidone: Usually transient (Findling 2003, Dunbar 2004): 7.8 ng/mL at baseline to a peak of 29.4 ng/mL at weeks 4-7 of active treatment, 16.1 ng/mL at weeks 40 to 48 (N = 358) and 13.0 ng/mL at weeks 52 to 55 (N = 42). No direct correlation between prolactin elevation and SHAP.
- Olanzapine & ziprasidone → transient increases (elevated at 6 wks) but no longer term studies (Wurdarsky 1999)
- At 12 weeks, 25% of all on AAPs had sexual side effects independent of prolactin levels (Saito 2004)
- Clozapine and quetiapine truly sparing & aripiprazole can reduce levels of prolactin in adults (Goodnick 2002)

APPENDIX
QUESTIONNAIRE USED TO DETECT
SEXUAL SIDE EFFECTS AMONG SUBJECTS

Side Effects Checklist for Adolescents

Please circle true (T) or false (F).

- | | | |
|--|---|---|
| 1. I have unusual discharge from my breasts. | T | F |
| 2. Sometimes my breasts hurt. | T | F |
| 3. I have decreased sexual desire. | T | F |

For girls only

- | | | |
|---|---|---|
| 4. My period is usually regular. | T | F |
| 5. My period didn't come on time in this month. | T | F |

For boys only

- | | | |
|---|---|---|
| 6. My breasts got bigger. | T | F |
| 7. I don't have erections as frequently as I used to. | T | F |
-

Side Effects Checklist for Children

Please circle true (T) or false (F).

- | | | |
|--|---|---|
| 1. I have unusual discharge from my breasts. | T | F |
| 2. Sometimes my breasts hurt. | T | F |

For boys only

- | | | |
|---------------------------|---|---|
| 3. My breasts got bigger. | T | F |
|---------------------------|---|---|
-

Treatment of Prolactinemia

- Incidental lab finding: check for symptoms- repeat & watchfully wait
- If serum prolactin elevated→ then inquire regarding any hormonal contraception, do a pregnancy test to rule out pregnancy, obtain serum TSH and serum creatinine (as contraception, pregnancy, hypothyroidism and renal failure can elevate prolactin)
- If serum prolactin <200 ng/mL→ try reducing antipsychotic dose or change to a more prolactin-sparing drug such as aripiprazole, quetiapine, or, in cases with treatment resistance, clozapine (Correll 2006)

Treatment of Prolactinemia

- If serum prolactin >200 ng/mL or is persistently elevated despite change to a Prl-sparing drug → obtain an MRI scan of the sella turcica to r/o pituitary adenoma or parasellar tumor (Correll, 2006).
- If switch not possible: consider dopamine agonists-bromocriptine (adults start 1.25 bid → 15 qday), cabergoline (in youth 0.25-0.5 mg weekly after levels normalize), amantadine (adult-300 mg in divided doses) (Cohen and Biederman 2001)

Atypical Antipsychotics: Dosing Strategies for Children and Adolescents

Atypical Antipsychotics	Starting Daily Dose	Titration Dose ↑ q3-4 Day (~Min. Days to Antipsychotic Dose)	Usual Daily Dose Range for Aggression ^a		Usual Daily Dose Range for Psychosis	
			Child	Adolescent	Child	Adolescent
Clozapine	6.25-25 mg	1-2 × starting dose (18-20)	150-300 mg	200-600 mg	150-300 mg	200-600 mg ^b
Olanzapine	2.5 mg for children 2.5-5 mg for adolescents	2.5 mg (9-16)	No data available	No data available	7.5-12.5 mg	12.5-20 mg
Quetiapine	12.5 mg for children 25 mg for adolescents	25-50 mg to 150 mg, then 50-100 mg (18-33)	No data available	No data available	No data	300-600 mg
Risperidone	0.25 mg for children 0.50 mg for adolescents	0.5-1 mg (18-20 days)	1½-2 mg	2-4 mg	3-4 mg	3-6 mg
Ziprasidone	10 mg for children 20 mg for adolescents	10-20 mg	No data available	No data available	No data available	No data, in adults, 160- mg

Sources: Dosing suggestions derived from Findling et al. (2000), Goff et al. (1998), Kumra et al. (1996), Sikich (2001), and Shaw et al. (2001).

^a There is little information to guide dosing strategies for aggression. However, for aggressive children treated with risperidone, doses are about half that of the usual antipsychotic dose.

^b In treatment-resistant schizophrenic adults, a serum clozapine level (of the parent compound) greater than 350 mg/dL is generally required for efficacy.

Atypicals and Monitoring:

Routine:

- BMI
- AIMS
- Fasting Blood Glucose, Lipid Profile
- Baseline ECG (ZIP)

Discretionary (Based on Clinical Picture):

- LFTs
- Prolactin

Proposed Criteria for the Definition of Significant Weight Gain/ Changes in Body Composition in Children and Adolescents

Duration of Treatment	Threshold for Significant Change in Body Composition
First 3 Months	>5% of weight increase compared to baseline
Any Duration	<p>≥0.5 increase in BMI Z-score</p> <p>Crossing into the “at risk” weight category (i.e., ≥85 – 94.9 BMI percentile) plus presence of 1 other obesity-related complication, such as hypertension (i.e., ≥90th percentile), dyslipidemia (i.e., fasting cholesterol ≥200 mg/dL, LDL-cholesterol >130 mg/dL, HDL-cholesterol <40 mg/dL, triglycerides ≥150 mg/dL), hyperglycemia (i.e., fasting glucose ≥100 mg/dL), insulin resistance (i.e., fasting insulin >20 μmol/L; Williams et al., 2002), orthopedic disorders, sleep disorders, or gallbladder disease</p> <p>Crossing into obesity (i.e., ≥95th BMI percentile) or abdominal obesity (i.e., ≥90th waist circumference percentile)</p>

Note: BMI = body mass index; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Risperidone

Pediatric Considerations

- “Atypical” only at low doses
- Range of dosing: 0.5-6 mg / day; usually 1.5 mg for CD with aggression; much higher for psychosis with aggression, also with MR (Aman et al 2002)) and Autism (RUPP 2000)
- Half life =3- 20 hrs; TMax=1.5hrs; Metabolized: CYP 2D6, 3A4
- Dosing:start 0.25 mg a day for children and 0.5mg a day for adolescents and titrate up q 3-4 days.
- Antiaggression Dose: 1-4 mg a day
- Side effects include mild and transient sedation, headache, rhinitis (Findling et al 2004)
- In overdose→ Tachycardia, hypotension, prolonged QTc
- Rare: Leukocytopenia, Questionable: Elevation of LFTs: 2° to weight gain and fatty deposits (Kumra 1997); LFT monitoring not necessary (Findling)

Risperidone: Pediatric Considerations

- Weight gain common (~20 lbs /6 months: reversible when discontinued (Lindsay et al 2004); not related to serum leptin (Martin et al 2004)
- Children vs. teens may be more likely to experience EPS: 25 % of youth score mod-severe on AIMS at 4 mg (Sikich 2001)
- Potential for hyperprolactinemia: Ask regarding this
- May be used with psychostimulants for better control of hyperactivity with no difference in weight gain (Aman 2004)
- Monitor BMI, lipids, glucose

Quetiapine: Pediatric Considerations

- Weak binding of the D2 receptor→ virtually no EPS or prolactinemia
- Half-life=6-7 hrs, T_{max}=1.5 hrs, Metabolized by CYP3A4
- Dosing: 12.5 mg a day for children & 25 mg a day for adolescents.
- No data on antiaggressive dose; 800 mg is antipsychotic dose in adults

Side Effects

- Sedation, dry mouth
- Some weight gain, rare hypertriglyceridemia, hyperglycemia and Diabetes Mellitus
- Tachycardia
- Cataracts - Not over normal incidence in adults (Fraunfelder 2004)
- Overdose→ tachycardia, ataxia, hypotension, EPS, anticholinergic

Ziprasidone: Pediatric Considerations

- Half-life: 7 hrs; T_{Max} : 6-8 hrs; Metabolized by aldehyde oxidase and Cyt3A4; absorption increases 2-fold with food
- Dosing: 10 mg for prepubertal children and 20 for teens; 160 mg is antipsychotic dose in adults
- QTc prolongation as a real side effect upheld by FDA: May occur at 160mg/day (10 msec $>$ others; can't use with other agents that prolong QTc (including mesoridazine, thioridazine, pimozide, droperidol, halofantrine, class IA and III antiarryhtmics))

Ziprasidone: Pediatric Considerations

- Monitor potassium, and magnesium-- No cases of torsades de pointes reported so far, but 3 of 20 youth had QTc>450 msec (Blair 2005)
- Transient sedation, dyspepsia, EPS ↑ with dosage; reports of prolactinemia, akathisia, agitation, headache, orthostatic dizziness, nausea (in adults, Keck 2003)- *focus on information for children*
- Weight neutral or loss: Improved cholesterol and triglyceride profiles (Cohen 2003)
- In overdose → QTc prolongation, hypotension

Olanzapine: Pediatric Considerations

- Atypical only at lower doses (< 20mg)
- Half-life 30 hrs, T_{max}=5hrs; Metabolized by UGTs, CYP1A2
- Dosing: 2.5-5mg a day for children; 10mg for adolescents on; 10-20 mg is antipsychotic dose in adults

Side Effects

- Sedation
- Moderate Prolactinemia in teens at 20 mg-ASK
- Weight gain hyperglycemia, hyperlipidemia, DM
- EPS increases with dosage
- Rare: ?abnormal LFTs

In overdose → pinpoint pupils

Monitor BMI, lipids / glucose

Aripiprazole: Pediatric Considerations

- Aripiprazole: Partial agonist at the D_2 and $5-HT_{1A}$ receptors & an antagonist at the $5-HT_{2A}$ receptor.
- Half-life: 7.5 hrs; T_{Max} : 3-5 hrs; C_{max} : 30-40% higher in women Metabolized by 2D6 and 3A4
- Dosage range: 2.5mg-15mg a day.
- Dosage of 2mg/kg/day → Vomiting and somnolence (Findling)
- Pharmacokinetics are linear
- Side effects include: sedation 33%, akathisia 23% (Barzman 2004) headache, vomiting, light headedness, dyspepsia
- Modest ↑ in weight; no EKG changes, may ↓ prolactin levels

**PERFORM AIMS
PRETREATMENT & THEN
EVERY 6 MONTHS**

Lithium

- Different preparations have different absorptions; peaks with slow release preparations that have slower absorption and lower peak; may decrease GI upset
- Not bound to plasma or tissue proteins; no hepatic metabolism
- Peak levels in brain (similar to blood) after 24 hrs
- Equilibrium established in 5 days
- Renal excretion; directly related to GFR; sodium depletion can cause Li retention

Lithium pre-treatment assessment

- History of thyroid disease, cardiac disease (sick sinus function), renal disease (contraindicated in acute renal failure, but used in chronic renal failure and on hemodialysis at reduced doses)
- Labs: TSH, BUN, creatinine, CBC, electrolytes, UA, EKG, creatinine clearance

Lithium preparations & dosage

- Preparations:

- ✓ Lithium carbonate: 150,300 & 600 mg cap; 300 mg tablet
- ✓ Slow release Li (Lithobid or generic): 300 mg tablet
- ✓ Eskalith CR: Controlled release tablet (450 mg)
- ✓ Lithium citrate syrup (5ml=300 mg lithium)

- Dosage:

Weller's child chart

Weight (kg)	Total Dose (mg/day)
<25	600
25-40	900
40-50	1200
50-60	1500

(J Am Acad Child Adolesc Psychiatry 1998 Jan;37(1):60-65)

Lithium adverse effects

- Thyroid: Hypothyroidism, goiter
- Renal: Impaired concentration (enuresis)
- WBC: May increase to 12-15,000/mm³
- EKG: ST, T wave changes; occasional U wave, “Sick Sinus Syndrome;” make sure to EKG in toxicity
- GI: Early symptoms (nausea, diarrhea) if late toxicity
- CNS: Headache, fatigue, tremor, ataxia
- Weight gain, acne, worsening psoriasis
- Younger children more prone to side effects

Important Drug Interactions: Lithium

- Tetracycline, thiazides, ACE inhibitors: ↑ lithium levels
- NSAIDs increase lithium levels by 12-66%
- Caffeine, theophylline, aminophylline: May increase lithium excretion → lowered plasma levels

Lithium Toxicity

- Individualize to lowest levels 0.6-1.2 meq/ml
- Blood draw: Trough levels done 12 hrs after last evening dose (before the morning dose!)
- At 1.5 meq/ml: Impaired concentration, lethargy, muscle weakness, slurred speech, nausea, irritability, seizures

Valproate preparations

- Depakene: Valproic acid (n-dipropylacetic acid)
Preparations: 250mg in 5 ml syrup or 250 mg capsules
- Depakote (Enteric coated sodium divalproex): Valproic acid + Na valproate (pro-drug)
Preparations: 125, 250 & 500mg tablets
- Depakote ER- 250 & 500 mg
- Divalproex sprinkles in capsule: may remove sprinkles from capsule to sprinkle on food.
Preparations: 125 mg capsules

Valproate & plasma proteins in adults

- Highly bound to plasma proteins
- ASA, Naproxen displaces VPA
- VPA displaces Carbamazepine, Diazepam, Phenytoin
- Clinical response when serum level is 50mg/dL

Valproate Metabolism & Pre-assessment

- Metabolism: Glucuronidation; Mitochondrial β -oxidation 35% (usual pathway with monotherapy), no toxic metabolites
- Assess for a history of liver disease, bone marrow suppression, malnutrition, pancreatitis
- Labs: CBC with differential count, Platelets, AST, bilirubin, alkaline phosphatase

Adverse Reactions

- Common side effects: GI distress (may be minimized by ingesting food), diarrhea, sedation and rash.
- Serious side effects: hepatotoxicity, pancreatitis, association with polycystic ovarian syndrome, peripheral neuropathy, low platelets, SIADH, hyponatremia, blood dyscrasias and Stevens Johnson syndrome
- Avoid use in females of child bearing age: Teratogenicity resulting in Neural tube defects in child.

Therapeutic Regimen

- Initiate treatment @ 15 mg/kg/day with upward titration by 5-10 mg/kg/day every week not to exceed 60mg/kg/day
- May want to use BID dosing
- Therapeutic levels: 50-125mcg/dl; Clinical response generally occurs within 2 weeks of attaining serum level of 50 mcg/dl
- Depakote ER conversion:

Depakote(daily mg)	Depakote ER (daily mg)
500-625	750
750-875	1000
1000-1125	1250
1250-1375	1500
1500-1625	1750
1875-2000	2000

Carbamazepine

- Was not found superior to placebo in reducing aggressive behavior in children with CD.
- Dose range: 20-30mg/kg/day.
- Therapeutic Blood levels: 6-12 mcrograms/ ml.
- Common side effects: GI distress, sedation,dizziness, lethargy, elevated liver enzymes.
- Serious adverse reactions: blood dyscrasias, aplastic anemia, life-threatening rashes, SIADH, hepatitis, pancreatitis and pulmonary hypersensitivity.

Ruths, Steven and Steiner, Hans Psychopharmacologic treatment of aggression in children and adolescents. *Pediatric Annals*, May 2004.

Carbamazepine

- Many potential drug-drug interactions¹
- Extensive induction of CYP 450 and UGTs
- 10,11- epoxide metabolite believed to be responsible for CYP induction and probably bone marrow suppression¹
- Monitoring of blood levels of Carbamazepine and CBC are necessary¹
- Monitor drug blood levels weekly for the first 1-2 months, then biweekly for another 2 months.²
- A patient who has been stable on CBZ for one year may be monitored every 3-4 months thereafter.²
- Check CBC, liver function, electrolytes and renal function after one month, then quarterly for the first year.²

1. Ruths, Steven and Steiner, Hans Psychopharmacologic treatment of aggression in children and adolescents. *Pediatric Annals*, May 2004.

2. Albers et al. *Handbook of Psychiatric Drugs*. 2005 Edition

Carbamazepine

- CBZ should be used only after other mood stabilizers have been tried and failed or if there is evidence of familial response (due to toxic side effect profile and lack of efficacy data)

Ruths, Steven and Steiner, Hans Psychopharmacologic treatment of aggression in children and adolescents. *Pediatric Annals*, May 2004.

Possible Algorithm for use of medication in aggression in youth

- Select an AAP
- Start low, Go slow
- Wait 2 weeks at therapeutic dose, if known for youth, before determining it is a failure
- If first AAP fails, try a second
- If partial response, then add a mood stabilizer. (Tray Part II 2003)
- If stable with no aggression for 6 mos, consider discontinuing slowly

Psychostimulants

- May be effective in reducing antisocial behavior by improving the function of the reticular activating system.
- Twenty eight studies showed that treatment with stimulants resulted in significant reduction of aggression-related behaviors in patients with ADHD. Findings were independent from effects on core ADHD symptoms
- Larger effect size for overt vs. covert aggression.

Ruths S, Steiner H. Psychopharmacologic treatment of aggression in children and adolescents. *Pediatric Annals*, May 2004.

For further slides of
psychostimulants and
clonidine and guanfacine see
ADHD lecture

SSRIs may be useful (see depression lectures)

- Central serotonin is inversely related to impulsive aggression and violence.
- Low levels of CSF 5-hydroxyindolacetic acid (5-HIAA), a metabolite of serotonin have been found in children with disruptive behavior disorders who reported aggression towards others.
- Citalopram found to significantly reduce impulsive aggression and irritability in children and adolescents without MR and established aggression.
- Consider side effect profiles of SSRIs when prescribing.

Ruths, Steven and Steiner, Hans Psychopharmacologic treatment of aggression in children and adolescents. *Pediatric Annals*, May 2004.

TRAAAY guidelines

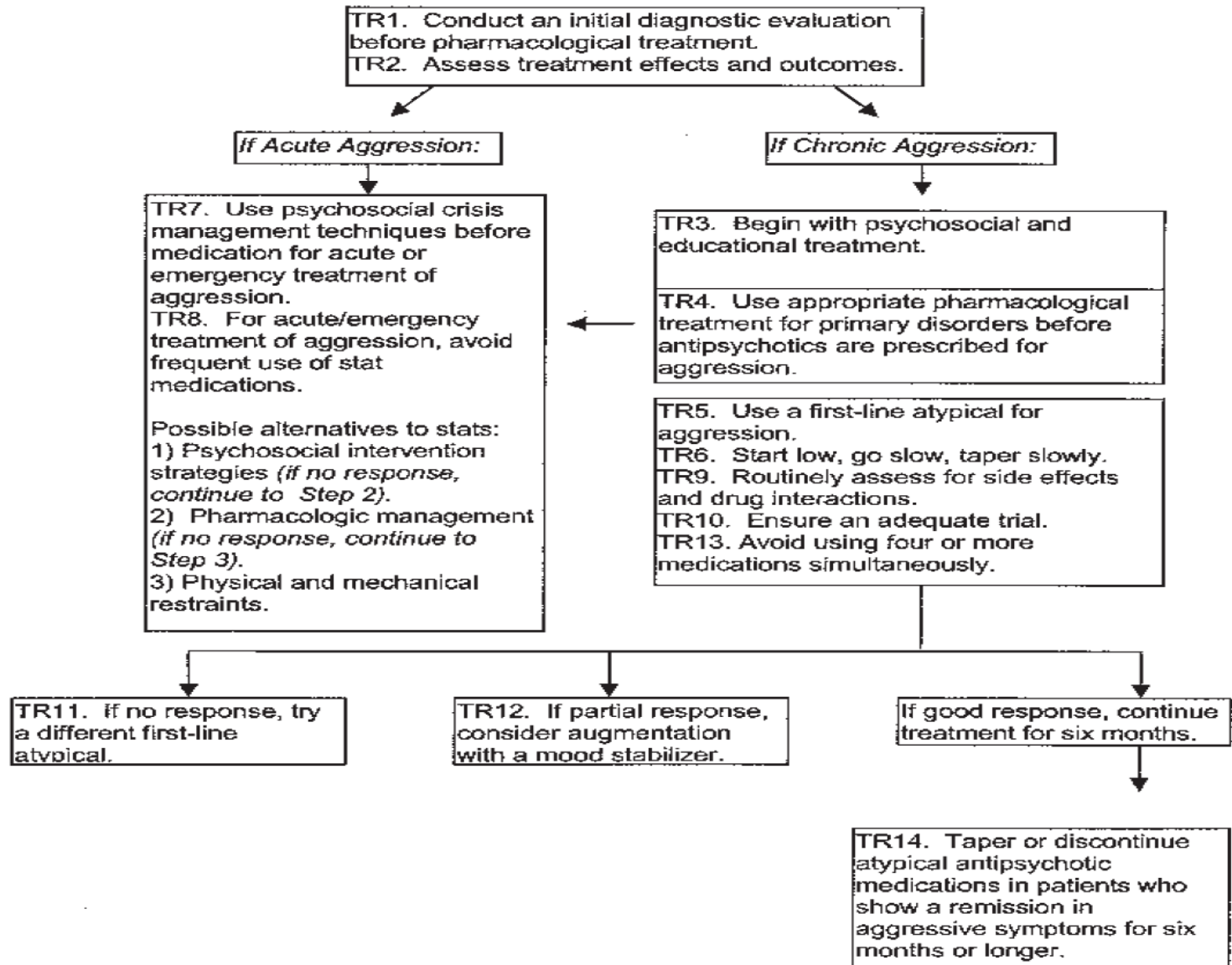


Fig. 1 Flow chart depicting the systematic application of the Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAAY).

Question 1

- 1) A 10 year old boy with serious aggression is treated with risperidone at 2mg/day. Which of the following statements is true:
- A) He is less likely to develop weight gain than an adult
 - B) He is less likely to develop prolactinemia than an adult
 - C) He is less likely to develop weight gain compared to a teenager
 - D) He is more likely to develop weight gain compared to an adult
 - E) He is less likely to develop EPS at dosages of 6mg/day than at 1 mg/day

Question 2

- 2) Which of the following drugs is not associated with at least one double-blind placebo controlled trial showing efficacy in the treatment of aggression in youth?
- A) Clonidine
 - B) Lithium
 - C) Carbamazepine
 - D) Valproate
 - E) Risperidone

Question 3

- 3) A 14 year old girl treated with risperidone for aggression is found to have a prolactin level of 90 ng/ml. What symptoms or side effects should you ask about?
- A) Increased urination
 - B) Decreased urination
 - C) Disturbances in sleep
 - D) Disturbances in menstruation
 - E) None of the above

Question 4

- 4) A 15 year old girl has been treated with lithium for aggression for 3 months. Her trough blood levels have been running from 0.8 to 1.0 meq/L, but a recent level was found to be 1.3 meq/L. She is experiencing no changes in adverse effects. Which explanation is most likely?
- A) She has been drinking alcoholic beverages
 - B) She has been using St John's wort.
 - C) Her family physician has started her on erythromycin
 - D) The blood was drawn at 8 hours after her last dose of lithium
 - E) The blood was drawn 15 hours after the last dose of lithium

Question 5

5) A 12 year old boy seeks revenge against adults who set limits on him. He plans carefully. Are his symptoms likely to be medication sensitive?

A) Yes

B) No

Answers

- 1-D
- 2-C
- 3-D
- 4-D
- 5-B