Aggression and Its Treatment in Youth

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Question 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 less likely to develop weight gain compared to a teen-ager

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

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

A 14 year old girl treated with risperidone for aggression is found to have a prolactin level of 90 ng/m. 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

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

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

Definition and Subtypes of Aggression

- Simple definition- hostile or offensive action or words.
- Aggression often implies intent to harm another person or damage an inanimate object.
- Subtypes: Acute vs. Chronic, Verbal vs. Physical, Overt vs. Covert, Adaptive vs. Maladaptive, Reactive-affective-defensive-impulsive (RADI) vs. Proactive-instrumental-planned-predatory (PIPP).

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

Chronic Aggression in Youth is the 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- (e.g. aggression is not required for a diagnosis of conduct disorder)

Etiologies of Aggression

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

Assessment

- A thorough psychiatric assessment before initiating treatment
- Assess frequency, duration and severity
- Precipitants?
- 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

Treatment

- Impulsive aggression (Reactive) is medication sensitive
- Predatory or planned, pro-active, or profitable self- controlled aggression is not medication sensitive (Vitiello 1990)
- Verbal aggression is not usually medication sensitive (Silver and Yudofsky 1991)
- Overt Aggression (physical assault or temper tantrums) v. Covert Aggression (lying stealing cheating, theft)

Treatment

- Treat the primary diagnosis

  e.g. ADHD:stimulants or other agents

  MDD: fluoxetine or other SSRIs

  Bipolar Disorder: VPA or Lithium or AAPs

  Paranoia or psychosis: Atypical Antipsychotics

  PTSD :Clonidine or SSRIs

Psychosocial Interventions

50% of those who are hospitalized for aggression improve without medication (Malone and Simpson 1998)

-Especially 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

Drugs with proven efficacy in aggression in youth

- Haloperidol (CD with Aggression, Campbell 1982)
- Risperidone CD (RUPP, Findling 2000), MR (Leblanc 2005) Autism (for tantrums, aggression, SIB,restrictive stereotypic activities RUPP 2005,)
- Lithium (CD with aggression Malone 2000)
- VPA (CD with aggression, Steiner 2003)
- Clonidine (ADHD + ODD, CD, Hazzell and Stuart 2003)
- Psychostimulants (ADHD + CD Farrone 2002, CD ALONE, Klein 1997)

Use of Atypical Antipsychotics (AAPs)

- Used in as many as 50% of child inpatients mostly for aggression 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

Side Effects With AAPs

Relatively Common	Less Common	Rare
Sedation/fatigue Weight gain	EPS	Sexual Side Effects Dyslipidemia Diabetes QTc (Geodon3/20> 450 on EKG ,Blair 2005) TD NMS

EPS = extrapyramidal symptoms; TD = tardive dyskinesia
NMS = neuroleptic malignant syndrome

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

Adverse Event	*Clozapine (n=206)*	*Risperidone (n=943)*	*Olanzapine (n=332)*	*Quetiapine (n=90)*	*Ziprasidone (n=26)*
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
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
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.

3/20 qtc >450 ms

transient

Cheng-Shannon 2004

Rising incidences of obesity in youth

- 1963-1991 incidence of obesity doubled in youth
- 16% of children between the ages of 6 and 11 are Overweight : $\geq$95th percentile of body mass index (BMI: kg/m^2)
- 14.3% at risk of becoming overweight :$\geq$85th < 95th BMI

Prevalence of Obesity in Young Patients on Antipsychotic Therapy

- Cross-sectional naturalistic study
- 151 inpatients, mean age: 19.5 yr
- In whole study population, obesity (BMI ≥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)*, e.g.:
  - Cardiovascular illness
  - Hypertension
  - Osteoarthritis
- Triglyceride increases *(Martin & L'Ecuyer, 2002)*
- Association with Type 2 diabetes
- Psychological effects

  isolation

Weight Gain and AAPs and Youth

Olanzapine and Risperidone cause comparable weight gain in youth (Sikich 2004) and olanzapine worse in adolescents (Ratzoni 2002)

12 wk week study:

81% OLA, 57% RISP, 43% QUET (Correll 2005)

RISP 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

	Average Percent of RIS-Induced Weight Gain/BBW (n*)			
Weeks of RIS Rx	**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.

Safer D 2004

BMI in children

weight in lb

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height (“)x height (“)

x 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 dibenzodiazepine derivitives) are associated increased triglycerides (Meyer 2004)
- VLDL levels above 400-500 mg/dL increase risk for acute pancreatitis
- Decreased levels of lipids when switched to ZIP and ARI in adults

Metabolic syndrome in childhood

- **Definition**=abdominal obesity, plasma triglycerides >150 mg/dL, a low HDL cholesterol level (<40 mg/dL for men, <50 mg/dL for women), a blood pressure of over 130/85 mm Hg and an abnormal fasting glucose value >110 mg/dL.
- 4% of children and 30% of overweight adolescents in USA meet criteria for a metabolic syndrome ---> DM type 2 and cardiovascular disease.
- Type 2 diabetes mellitus in the pediatric population represents 8 to 45% of all diabetes reported among youth

Extrapyramidal Side Effects in Adults

- Occurs 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 S2 blockade at low doses but D2 blockade with increased dosage

  e,g,, 4-5mg/d of RISP or 20-25 mg/d OLA increased risk for EPS

  but OLA < RISP because of OLA's intrinsic anticholinergic properties.
- TD develops when D2 blockade is permanent.

EPS With Atypicals

- D1 and D2 receptor densities higher in children and teens
- In children, typical APs associated higher incidence of acute dystonia, NIP, akathesia and withdrawal dyskinesias 12-44% (Connor 2001)
- NIP OLA, RISP? more common in youth (Sikich 2004)
- Akathesia 23%/30 in ARI with youth (Barzman 2004)

Prolactin

- Pituitary cells manufacture prolactin
- Hypothalamic DA tracts are inhibitory to prolactin release

  Block the blocker---more prolactin flows
- All TAPs are associated with prolactinemia (used to be believed that this was associated with efficacy)
- AAPs, SSRIs TCAs and some opioids also can cause prolactinemia (2-10 fold increase in first few weeks)
- **Different AAPs have differing D2 receptor occupancy at striatum v pituitary and different fat solubility to penetrate BBB: (pituitary is on *other side* of BB) so can have prolactinemia w/o EPS**

Key: DA- dopamine, TAP- typical antipsychotics, AAP- atypical antipsychotics, TCA- tricyclic antidepressants, RSP- risperdal 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 having effects of increased prolactin

AAPs and Prolactin over time in youth

Risperidone -usually transient (Findling 2003, Dunbar 2004) 7.8 ng/mL at baseline to a peak of 29.4 ng/mL at weeks 4 to 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 and ziprasidone transient increases (elevated at 6 wk studies 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 and 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

Saito 2004

Treatment of Prolactinemia

- Incidental lab finding - check for sexual symptoms- repeat and watchful waiting
- If it is true prolactinemia, reduce dose or switch to a different atypical antipsychotic
- If a switch is not possible, consider dopamine agonists: bromocriptine (adults start 1.25 bid->15 q d), cabergoline (in youth 0.25-0.5 mg weekly after levels normalize), amantadine (adult 300 mg 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, 160mg

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 Clinical Monitoring:

Routine:

- BMI
- AIMS
- FBG, Lipid Profile
- Baseline ECG (ZIP)

Discretionary (Base on Clinical Picture)

- LFTs
- Prolactin

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 by *2D6, 3A4
- Dosing:start 0.25 mg a day for children and 0.5mg a day for adolescents and titrate up q 3-4 dys.
- 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- secondary to weight gain and fatty deposits (Kumra 1997)- LFT monitoring is not necessary- Findling
- 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 to severe on AIMS at 4 mg (Sikich 2001)
- Potential for hyperprolactinemia - ASK-
- 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, Tmax=1.5 hrs, Metabolized by 3A4
- Dosing: 12.5 mg a day for children and 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)
- In overdose-> tachycardia, ataxia, hypotension, EPS, anticholinergic

Ziprasidone
Pediatric Considerations

- **Half-life =7 hrs TMax= 6-8 hrs Metabolized by aldehyde oxidase and 3A4: absorption incr 2-fold with food**
- **Dosing: 10 mg for prepubertal children and 20 for teens.160 mg is antipsychotic dose in adults**
- **Side Effects**
- **QTc prolongation as a real side effect upheld by FDA:Occurs at 160mg 10msecs>others; can't use with other agents that prolong QTc (e.g., mesoridazine,thioridazine, pimozide, droperidol, halofantrine, IA and III antiarryhtmics)**
- **Monitor potassium, and magnesium-- but no cases of torsades de pointes reported so far, but 3/20 youth exceeded 450 millsecs in EKG (Blair 2005)**
- **Transient sedation, dyspepsia, EPS increases with dosage and 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, Tmax=5hrs Metabolized by UGTs, CYP1A2**
- **Dosing: 2.5-5mg a day for children and 10mg for adolescents on basis pharmacokinetics PMID: 10770461 . 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 functions as a partial agonist at the D_2 and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptor.**
- **Half-life 7.5 hrs TMax3-5 hrs *Cmax is 30%-40% higher in women Metabolized by 2D6 and 3A4**
- **Dosage range: 2.5mg-15mg a day.**
- **2mg/kg/day -> vomiting and somnolence. (Findling)**
- **Pharmacokinetics are linear**
- **Side Effects include: sedation 33%, akathesia 23% (Barzman 2004) headache, vomiting, light headedness, dyspepsia**
- **Modest increase in weight; no EKG changes, may reduce prolactin levels**
- **Study of aggression with CD in 6-17 year olds showed a good response rate at 0.1mg/kg/day (Findling, 2003 study in process)**

PERFORM AIMS PRETREATMENT AND EVERY 6 MONTHS

Lithium

- Different preparations have different absorptions and peaks with slow release preparations have slower absorption and lower peak and may decrease gi upset
- Not bound to plasma or tissue proteins and no hepatic metabolism
- Peak levels in brain (similar to blood)but 24 hrs later
- Equilibrium established in 5 days
- Excretion is directly related to GFR
- Na and Li are handled by the kidney so that Na
- depletion causes Li retention: conversely high Li leads to Na excretion Think of "Taco Tantrums"

Lithium Pre-treatment

- 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, lytes, UA: EKG, Creatinine Clearance

Lithium carbonate in 150,300 and 600 mg capsule and 300 mg tablet

Slow release=Lithobid or generic in a 300 mg tablet

Eskalith CR is a controlled release tablet in a 450 tablet

Lithium citrate is a syrup 5ml=300 mg lithium carbonate

Weller's child chart

Weight (kg)	Total Dose (mgs per 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--->hypothyroid, goiter
- Renal---> impaired concentration (enuresis)
- WBC---> Increase to 12-15,000
- EKG->ST, T wave, occasional U wave, “Sick Sinus Syndrome” * get EKG in toxicity
- GI-> early symptoms (nausea, dh) if late *toxicity
- CNS-> headache, (fatigue, tremor, ataxia)
- Weight gain, acne, can worsen psoriasis,
- Younger children are more prone to side effects

Important Lithium Drug/Drug Interactions

Tetracycline, thiazides, ACE inhibitors increase lithium levels

NSAIDs increase lithium levels 12-66%, Rx Sulinac

Caffeine, theophylline, aminophylline can increase lithium excretion leading to lowered plasma levels

Lithium Toxicity

- Individualize to lowest levels 0.6-1.2 meq/mL
- Blood draw trough 12 hrs after last evening dose before the morning dose!
- At 1.5-> impaired concentration, lethargy, muscle weakness, slurred speech, nausea, irritability, seizures

VPA forms

Depakene= valproic acid= n-dipropylacetic acid: Preparations:(250mg in 5 mls syrup or 250 mg capsules)

Depakote=enteric coated Na divalproex =valproic acid + Na valproate (pro-drug) Preparations:((125, 250 & 500mg tablets)

Depakote ER- 250 and 500 mg- need conversion table

Divalproex sprinkle in capsule: may remove sprinkles from capsule to sprinkle on food. Preparations**:(125 mg capsules)**

VPA and plasma proteins in adults

- Highly bound to plasma proteins
- ASA, Naproxin displaces VPA
- VPA displaces CBZ, DZP,PHT
- Clinical response when serum level is 50mg/dL

VPA Metabolism

- Glucuronidation UGT2B7, UGT1A3 40%
- Mitochondrial b-oxidation 35%-usual pathway with monotherapy, no toxic metabolites
- Microsomal CYPs: 10% CYP2A6 and CYP2C9,CYP219 produces 4-en and 2,4-en VPA toxic metabolites

Depakote Pre-medication evaluation

- Assess for a history of liver disease, bone marrow suppression, liver or kidney disease, malnutrition, pancreatitis
- Labs CBC with diff, Plts, AST, bilirubin alkaline phosphatase

Adverse Reactions

- Common side effects include: GI distress (may be minimized by ingesting food), diarrhea, sedation and rash.
- Serious side effects include: hepatotoxicity, pancreatitis, polycystic ovarian syndrome, SIADH, hyponatremia, blood dyscrasias and Stevens Johnson
- Beware of use in girls capable of child bearing. Neural tube defects are possible in the unborn child.

Albers et al*. Handbook of Pyschiatric Drugs.* 2005 Edition

Therapeutic Regimen

- Initial 15 mg/kg/dy with progression of 5-10 mg/kg/day weekly not to exceed 60mg/kg/day
- May want to use BID dosing
- Putative therapeutic level 45-145mcg/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

Additional Clinical Considerations

- Clinical response generally occurs within 2 wks of attaining serum level of 50 mcg/dL
- Don’t use ASA for analgesia

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 interactions[1]
- Extensive induction of CYP 450 and UGTs
- 10,11- epoxide metabolite believed to be responsible for CYP induction and probably bone marrow suppression[1]
- Monitoring of blood levels of Carbamazepine and CBC are necessary[1]
- 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 Pyschiatric Drugs.* 2005 Edition

Carbamazepine

- Because of the toxic side effect profile and lack of efficacy data, it is recommended that CBZ be used only after other mood stabilizers have been tried and failed or if there is evidence of familial response.

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 the effects on core ADHD symptoms
- Larger effect size for overt vs. covert aggression.

Ruths, Steven and Steiner, Hans 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.

Question 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 less likely to develop weight gain compared to a teen-ager

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

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

A 14 year old girl treated with risperidone for aggression is found to have a prolactin level of 90 ng/m. 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

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

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