Pediatric Psychopharmacology

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Question 1

- Which drug is least likely to cause weight gain?
- A-lithium
- B-methylphenidate
- C-risperidone
- D-valproate
- E-quetiapine

Question 2

- The drug of choice in teenage depression is:
- A-sertraline
- B-fluoxetine
- C-bupropion
- D-venlafaxine
- E-none of the above

Question 3

- Which statement is true
- A- Youth like taking psychotropic medication
- B-Parents always monitor psychotropic adherence carefully
- C-Psychiatrists should not investigate the “meaning” of medication in a child’s life
- D-Youth and parents attach “meaning” to medication-taking
- E-Only parents attach “meaning” to medication-taking

Question 4

- Which medication is the drug of choice for ADHD?
- A-atomoxetine
- B-clonidine
- C-guanfacine
- D-psychostimulants
- E-antipsychotics

Question 5

- Which statement is true about youth and pharmacokinetics and pharmacodynamics
- A- Young children have lower GFRs than adults
- B- Young children tend to metabolize drugs slower than adults
- C-Young children are relatively insensitive to atypical antipsychotics
- D-Young children generally need lower daily doses than adults of drugs metabolized by the liver
- E-Young children generally need higher daily doses than adults of drugs metabolized by the liver

*Overview

- History and special considerations
- Antidepressants
- Stimulants/alpha-2 agonists
- Mood stabilizers
- Antipsychotics

History of Pediatric Psychopharmacology

- 1937- Bradley uses benzedrine to treat behavioral disorders in children
- 1950- MPH is used to treat hyperactive children
- 1953- 1st reported use of CPZ in children
- 1965- TCA's are used to treat children with major depressive disorder
- 1969- Haloperidol is used in childhood psychosis

History of Pediatric Psychopharmacology

- 1970- Lithium is used in children & adolescents with mania
- 1971- 1st reported use of imipramine in school phobia treatment
- 1978- Haloperidol approved for use in tx of tic disorders in children
- 1979- 1st reported use of clonidine in the tx of tic d/o and disruptive behavior problems

History of Pediatric Psychopharmacology

- 1989- Double-blind study of clomipramine to treat OCD
- 1990- 1st reported uses of fluoxetine in children w/ OCD or major depression
- 1992- Multicenter trial of clomipramine tx for OCD
- 1994- MTA study of ADHD begun

History of Pediatric Psychopharmacology

- 1994- FDA mandates that new drug applications must include available data on children
- 1995- Risperidone first used in children with various disorders
- 1996- Clozapine systematically studied, and found to be safe and effective in children & teens
- 1998- FDA Modernization Act

History of Pediatric Psychopharmacology

- 2000- Ziprasidone includes pediatric trial in its application
  - Found efficacious in a prospective multisite DB-PC trial for Tourette's d/o
    - Sallee: *JAACAP*, March 2000

*Children are not small adults (usually)

- Young children may not be able to describe their internal states
- Young children cannot view themselves in relation to others
- Developmentally relevant vocabulary must be developed for working with children and families
- Physiologically different
  - start low, go slow, but higher doses may be tolerated and req'd, on a mg/kg basis

Children are not small adults (usually)

- liver metabolism, GFR are more efficient in children
  - GFR reaches adult rates by about 12 mos.
- Neurotransmitter development
  - 5 HT levels stay relatively constant throughout life
  - NE levels increase w/age
    - diff'l response in child vs. adult to TCA
    - does not explain response in ADHD

*Children are not small adults (usually)

- Neurotransmitter development, cont'd
  - DA: decrease in receptor density beginning @ age 3
- Lack of long-term safety data for most drugs
  - in fact, prolonged use may be harmful in very young children (VPA, Ph, Brbs in preschoolers)
- Most long-term data are extrapolated from animal studies

*Children are not small adults (usually)

- Gender differences may exist
  - In adolescence, girls' body fat increases more than boys'--this may affect distribution and half-life
- Pharmacodynamic and pharmacokinetic differences exist
  - In general, many psychotropics metabolized by the liver have shorter half-lives in children due to altered distribution, requiring more frequent dosing

*Children are not small adults (usually)

- Pharmacodynamic and pharmacokinetic differences, cont'd.
  - Higher doses w/ less toxicity (digoxin)
  - Therapeutic levels in adults may be toxic in children (TCA's)
  - Lower plasma levels may be sufficient for a desired therapeutic effect (haloperidol) due to more sensitive DA receptors
  - Young adolescent males may be at particular risk for acute dystonic reactions, compared to adults

ADHD Treatments

- MTA study: *Arch Gen Psychiatry*/ 56: 1073-1086, Dec 1999
  - 579 children with ADHD-CT; 7-9.9 yrs; 6 sites; 14 month parallel-design
  - 4 different treatment groups:
    - Medication mgmnt (immediate release methylphenidate)
    - Intensive behav treatment (parent, school, child components)
    - Meds + Behav Tx
    - “Usual” community care

ADHD Treatments

- MTA study: cont'd.
  - All 4 groups showed sizable reduction in symptoms over time
  - *ADHD symptoms*: Combo. and med-only groups had significantly greater improvement than those given intensive behav tx or "usual" community care (UCC)

ADHD Treatments

- MTA study: cont'd.
  - *Non-ADHD symptoms*: (social skills, parent-child relations, oppositional-aggressive behavior, internalizing symptoms, academic achievement)
    - The 3 MTA-delivered treatments were very similar, with the combined treatment arm being consistently superior to UCC.

ADHD Treatments

- MTA study: cont'd.
- *Combined behavioral intervention and stimulant medication--(multimodal treatment), yielded no statistically significantly greater benefits than medication management "alone" for the core symptoms of ADHD*

*ADHD Treatments (medication options)

- Established Treatments
  - Psychostimulants
  - TCAs
  - Bupropion
  - Atomoxetine
- Probable Efficacy
  - Venlafaxine
  - Alpha-2 agonists

ADHD Treatments (medication options)

- Efficacious but usually inadvisable
  - Carbamazepine
  - MAOIs (moclobemide, selegiline)
  - Conventional neuroleptics
  - Newer antipsychotics
  - Nicotine

ADHD Treatments (medication options)

- Possible efficacy
  - Beta-blockers
- Likely ineffective
  - SSRIs
  - Caffeine
  - St. John's Wort

ADHD Treatments (medication options)

- Potentially deleterious
  - Lithium
  - BDZ
  - Antihistamines
  - Buspirone

Medication	Tablet size	Dosage *	Half-life (hrs)	Side effects
d-, l-Amphetamine (Adderall, Benzedrine, Biphetamine) ***(AMPH)***	**5-30 mg tablets, double-scored**	**0.15- 0.5 mg/kg/d** Literature range (0.1-1.5 mg/kg/d)	**Serum: 12-20** **Behavior: 3-7**	**Similar for all stimulants: headache, stomach ache, irritability, appetite suppression, sleep problems, dysphoria, Ņzoned outÓ effect, hyperfocus**
d-Amphetamine (Dexedrine) ***(AMPH)***	**5 mg (IR) 5, 10, 15 mg (spansule)**	**0.15- 0.5 mg/kg/d** Literature range (0.1-1.5 mg/kg/d)	**Serum: 12-20** **Behavior: 2-7**	**See above**
Methylpheni-date (MPH) (Ritalin, Methylin, Metadate)	**5, 10, 20 mg** **Metadate-ER avail in 10 and 20 mg**	**0.3- 1.0 mg/kg/d** Literature range (0.3-2.0 mg/kg/d)	**Serum: 3- 6** **Behavior: 2-6**	**See above**
Methylpheni-date (Concerta: OROS-MPH), (Metadate-CD: Diffucaps-MPH)	**18, 36, 54 mg** **20, 40, 60 mg blisterpack**	**0.3- 1.0 mg/kg/d** Literature range (0.3-2.0 mg/kg/d)	**Behavioral: 10-14 hrs**	**Possibly less rebound than shorter-acting;** **Once-daily dosing**

*ADHD Treatments (medication options)

- Bupropion (Wellbutrin/ Zyban)
  - Minimal 5-HT effects
  - Inhibits NE, DA uptake
  - May have special use with comorbid depression or substance abuse
  - 1 open and 3 controlled studies in children
    - not quite as robust an effect as stimulants

*Bupropion, cont'd.

- Side effects
  - Skin rash -occ very serious
  - Seizures (lower with SR preparation)
    - 0.3%-0.4%; risk increases with doses> 450 mg TDD, or > 150 mg/ dose
  - Psychosis, agitation
  - Sleep problems
  - Appetite suppression
    - ? paradoxical effect in combo. with stimulants
      - Callaghan, *JAACAP*, July 1999

*Bupropion, cont'd.

- Dose
  - Begin with 37.5 mg in AM
  - Slow titration to 100-250 mg TTD (total daily dose. 3-7 mg/kg/d)
    - Peaks in 2 hours, $T_{1/2}$= 8-14 hrs
    - Use SR or XL when possible

ADHD Treatments (medication options)

- Tricyclic Antidepressants (TCAs)
  - 15 DB-placebo controlled studies show efficacy in children
    - Imipramine, amitriptyline, desipramine, clomipramine
  - Uncontrolled studies show benefit of nortriptyline, protriptyline

ADHD Treatments (medication options)

- Tricyclic Antidepressants (TCAs)
  - Strong effects on H/I symptoms
  - Wkr cognitive effects than stimulants
  - May lv behind some attnl probs
  - Can be used as adjunctive strategy
    - Can help with sleep, appetite probs

*Clonidine (Catapres)

- Alpha-2 adrenergic agonist
- May have role for H-I symptoms and aggression (not inattention)
  - Special utility in DD population
- Slight placebo-med differences have been found in small controlled studies
- Side effects often limit its usefulness

  especially sedation

*Clonidine (Catapres)

- Dose:
  - Start with EKG, baseline labs (LFTs, CHEM 8, TSH, CBC, FBS)
  - 0.05 mg @ HS
  - 3-5 mcg/kg/d, in 3-4 divided doses
  - Max daily dose 0.9 mg
  - Patch may be used: start with 0.1mg to non-hairy site on back; doses > 0.6mg not helpful; change q 7 d. Mark date.

*Clonidine (Catapres)

- Useful in ADHD with co-morbid tic d/o
- Monitor BP and pulse
  - Serious bradycardia in 0.3% of adults.
  - Rebound tachycardia and HTN
    - Children between doses
    - If d/c'd abruptly
  - *If tx'd for more than 1 month, d/c at a rate of 0.05 mg q3-7 days*

*Clonidine (Catapres)

- May reduce HR variability
- Relative contraindication : Depression since 1/20 can develop as a side effect especially if family hx
- MPH/ CLON combination
  - Not systematically studied, but found to be very helpful, esp. w/ comorbid insomnia
  - 1994: 40% of pts w/ ADHD tx'd with CLON were also on stimulants.
  - 3 fatalities, 1 LTE in kids on MPH/ CLON
    - See *JAACAP* 38:5, May 1999, pp614-622, for debate on this often-used combination
    - Deemed to be safe

*Guanfacine (Tenex)

- Similar MOA to clonidine, with some impt diffs: -cleaner drug
  - Alpha 2A agonist, but weaker alpha 1, alpha 2B, alpha 2C activity
  - Less beta-adrenergic, histamine, 5-HT, beta-endorphin, and DA effects
- Less hypotension, sedation, rebound HTN

*Guanfacine (Tenex)

- Longer duration, so less frequent dosing necessary ($T_{1/2}$= 17 hrs.); peaks in 2-3 hrs
  - start with 0.5 mg qD, then increase 0.5 mg q3-4 days if necessary
  - optimal dosing: 2.5-3.5 mg TDD, div TID or QID.
  - MDD=4 mg/day
- May have role in inattention, impulsivity, tics
- Less evidence than Clonidine

*Guanfacine (Tenex)

- Sedation , BP changes are common (25-30%), but usually transient
- No reports of sudden death thus far
- Monitor for behavioral activation/ disinhibition
- Controlled studies underway
  - Scahill, et al: *Am J Psychiatry* 158:7, July 2001

Antidepressant and Antianxiety Medications

Brand Name	Generic Name	Approved Age
Anafranil	clomipramine	10 and older (for OCD)
BuSpar	buspirone	18 and older
Effexor	venlafaxine	18 and older
Luvox	fluvoxamine	8 and older (for OCD)
Paxil	paroxetine	18 and older
Prozac	fluoxetine	7 and older (OCD/Depression)
	nefazodone	18 and older
Sinequan	doxepin	12 and older
Tofranil	imipramine	6 and older (for bed-wetting)
Wellbutrin	bupropion	18 and older
Zoloft	sertraline	6 and older (for OCD)

TCAs

- History
- Mechanisms of action
- Imipramine, nortriptyline, amitriptyline, desipramine, clomipramine
- Anticholinergic,Cardiac, Sudden death (DMI- 4? Cases)

Major Depression - TCAs

- Historically most used; 60%-80% response reported in open studies
- Meta-analysis by Hazell 2002 showed modest efficacy in teens
- Adverse effects- anticholinergic, cardiac
- Sudden death? Can be lethal in overdose

*Major Depression - SSRIs

- Open studies also suggest efficacy
- Positive controlled studies (mostly fluoxetine) (Emslie et al, 1997, 2002, TADS 2005)
- However, many unpublished negative studies
- Safer in overdose- no deaths reported
- Fewer adverse effects
- Long term use not studied
- Considered first line due to above

*SSRIs

- Fluoxetine, 1988, approved 1/3/03 for ages 7-17
- Mechanisms of action - serotonin reuptake inhibition
- Serotonin selectivity: Citalopram >> paroxetine > sertraline > fluvoxamine > fluoxetine
- Fluvoxamine - OCD 8-17 yo
- Sertraline - OCD 6-17 yo

*SSRIs in Children Recommendations

- Monitor Suicidality
- Rule out bipolar depression
- Minimize side-effects (nausea,diarrhea, appetite changes, headaches, restlessness, tremor, and changes in sleep)
- Prevent drug interactions
- Avoid withdrawal

*Fluoxetine

- CYP 2D6 mediated
- May interact with CBZ, benzos, Li, Haldol, CZP
- May be higher rates of behavioral activation
  - Jain, 1992 - 28% d/c due to irritability, hypomanic sxs
  - Riddle, 1990 - 50% with activation in OCD/dep population (motor restlessness, sleep disturbance, excitation)

*Fluoxetine in Pediatric Depression

- A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression.
- Emslie et al., 1997.*Arch Gen Psychiatry* 54:1031-1037
- N=96, 7-17 yo, 48 vs. 48
- 56% response vs. 38% placebo response
- 6% with manic-like sxs

*Sertraline in Pediatric Depression

- Wagner, et al, 2003
- N = 376, 51 sites
- Age 7-17, MDD
- Response = CGI-I of 1 or 2
- SERT = 69%, PBO - 59%
- Significant difference on change in CDRS-R scores (but only -22.8 vs -20.2)

*Paroxetine in Pediatric Depression

- JAMA August, 2004
- Placebo controlled data: TADS study in progress
  - CBT, CBT + meds, meds only
  - Fluox + therapy =
  - Fluox alone =
  - Therapy alone =
  - Placebo alone =

*Paroxetine in Pediatric Depression

- JAMA August, 2004
- Placebo controlled data: TADS study in progress
  - CBT, CBT + meds, meds only
  - Fluox + therapy = 71%
  - Fluox alone = 61%
  - Therapy alone = 44%
  - Placebo alone = 35%

*Paroxetine in Pediatric Depression

- Keller et al., 2001
- N = 275, adolescents with MDD
- Paroxetine vs. IMI vs. Placebo, 8 weeks
- Paroxetine (66%) > IMI (52%) = Placebo (48%)
- 31% IMI discontinuations (cardiac)

*Fluvoxamine

- FDA approved 1997 - pediatric OCD
- 50 - 300 mg/day (BID)
- Dry mouth, sleep problems
- 3A4 inhibitor : Boosts benzos, contraindicated with some antihistamines

*Fluvoxamine

- OCD (Riddle et al, 2001):
  - N = 120, 8-17 yo
  - Fluvoxamine = 42%
  - Placebo = 26%
- PDD (McDougle et al, 2000):
  - 34 children with PDD spectrum d/o
  - No benefit over placebo

RUPP studies for Anxiety

- NEJM (2001), 344:1279-1285
- Generalized anxiety, social phobia, separation anxiety
- Ages 6 - 18
- Placebo = 29%
- Fluvoxamine = 76%
- “Mild improvement” included as responders

*Citalopram

- Highly selective for serotonin receptors
- 10 - 40 mg QD
- May decrease heart rate by 5 bpm
- Wagner et al, 2001
  - Placebo controlled trial for MDD
  - N = 174, 7-17 yo
  - Active > placebo

*SSRIs - Adverse Effects

- GI, sedation
- Neuropsychiatric (akathisia)
- Major interactions- unique to each SSRI

(e.g. paroxetine and fluoxetine potent inhibitors of CYP2D6 and fluvoxamine is a modest inhibitor, or fluvoxamine is potent inhibitor of CYP1A2 and CYP2C19)

*SSRIs in Adolescents

- Paroxetine - recent “ban” in U.K.
- US FDA followed suit…
- Venlafaxine reported to have similarly increased rates of “suicidal gestures and behavior”
- Children with unique reactions to antidepressants?
- First presentation of BD is often depression in adolescence!

*SSRI Induced Mania

- Case reports and study by Martin 2004
- Differentiate from “behavioral disinhibition”
- Risk factors - peripubertal, “bipolar-like” depression, psychosis, family history of mania
- About 5%

Other Antidepressants

- Bupropion (SR)
- Nefazodone
- Venlafaxine (XR)
- Mirtazapine

*Major Depression - Medication Augmentation

- Lithium - two open trials, 42% response
- Thyroid replacement - anecdotal in children
- Other antidepressant classes not well studied (bupropion, venlafaxine, nefazodone, etc)

*Major Depression - Treatment Strategies

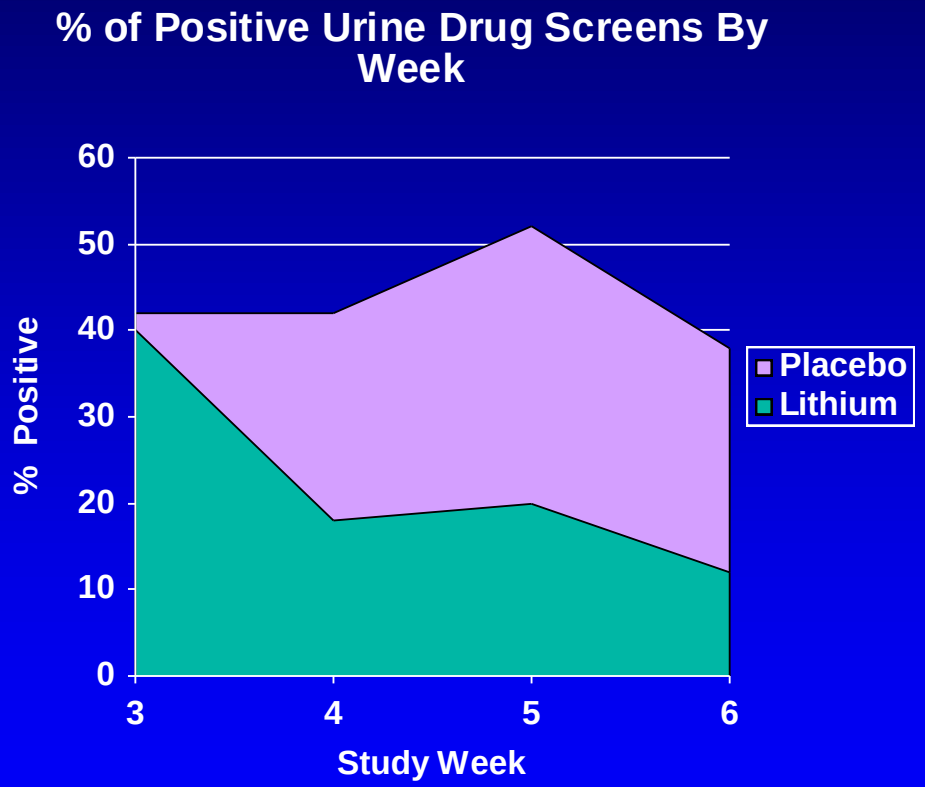
- Fluoxetine is DOC, if AEs, select another med based on adverse effect profile, ease of ingestion, other medical conditions, drug interactions. Also consider family history of response, insurance panel.
- Start low, go slow if possible
- TCAs: monitor serum levels, EKGs
- Establish target symptoms and monitor
- May use CDI, parent rated questionnaires

Other Uses for Antidepressants in Children and Adolescents

- IMI - enuresis (10-40% response)
- Bupropion - ADHD?
- Bulimia - SSRIs (fluoxetine)
- PTSD, PDD, selective mutism

*Lithium in Adolescent Bipolar Disorder + Substance Abuse

- Double blind, placebo controlled study, n = 25 adolescents with BD x 6 wks
- Weekly and random lithium levels and urine drug screens
- Li < Placebo for % Positive drug screens
- Li > Placebo for CGAS scores



Geller, et al., (1998) *J Am Acad Child Adolesc Psychiatry* 37:171-178

*Lithium in Childhood Bipolar Disorder

- Helps adolescent bipolar disorder with substance abuse* **(Geller et al. 1997)**
- Open studies suggest clinical efficacy in adolescents **(Kafantaris et al., 2004; 2005)**
- Baseline CBC, renal, thyroid panel
- Recommended serum level = 0.6-1.2 meq/L, monitor Q 6 months
- High relapse rates (>90% in 18 months) with Li discontinuation **(Stober et al, 1990)**

* double blind placebo controlled

*Lithium Adverse Effects

- Acne, psoriasis worsened
- Weight gain
- Cognitive impairment
- Sedation, tremor, headache
- Gastrointestinal irritation
- Thyroid dysfunction
- Polyuria, polydipsia, enuresis

*Markers of Poorer Lithium Response in Child & Adolescent Bipolar Disorder

- Overall, literature suggests 50% - 66% response
- Prepubertal onset Axis I disorder (esp. ADHD) (40% vs. 80% for no prepubertal disorder) (Strober 1988; Strober 1999)
- Mixed states (Himmelhoch & Garfinkel 1986)
- Greater genetic diathesis, very early onset, developmental immaturity (Strober et al. 1988)
- Personality disorder in adolescents (Kutcher et al. 1990)

*Valproate in Child & Adolescent Bipolar Disorder

- No studies of prepubertal bipolar disorder
- Open studies in adolescent bipolar disorder (**Wagner et al., 2004)**
- More effective than lithium in adolescent mixed mania? (Strober, 1997)
- Baseline CBC, platelets, LFTs
- Recommended serum level 80-120 mcg/mL, monitor every 6 months

Polycystic Ovarian Syndrome

- First reported in female epilepsy population on valproate
- 80% of PCO cases treated before 20 y.o.
- May be secondary to obesity, hyperandrogenism (Bauer et al., 2002)
- Valproate associated with new-onset oligomenorrhea with hyperandrogenism (Joffe 2006)
- Monitor for weight, hirsutism, amenorrhea

*Carbamazepine in Childhood Bipolar Disorder

- No controlled studies
- Open study: helps childhood mania (Hsu et al. 1986; Kowatch et al., 2000)
- Baseline - CBC, differential, platelets, LFTs ± EKG
- Children 10 - 20 mg/kg/day
- Adolescents 400 - 1400 mg/day
- Serum level 4 -12 ug/mL (from epilepsy)
- Monitor labs every 6 months

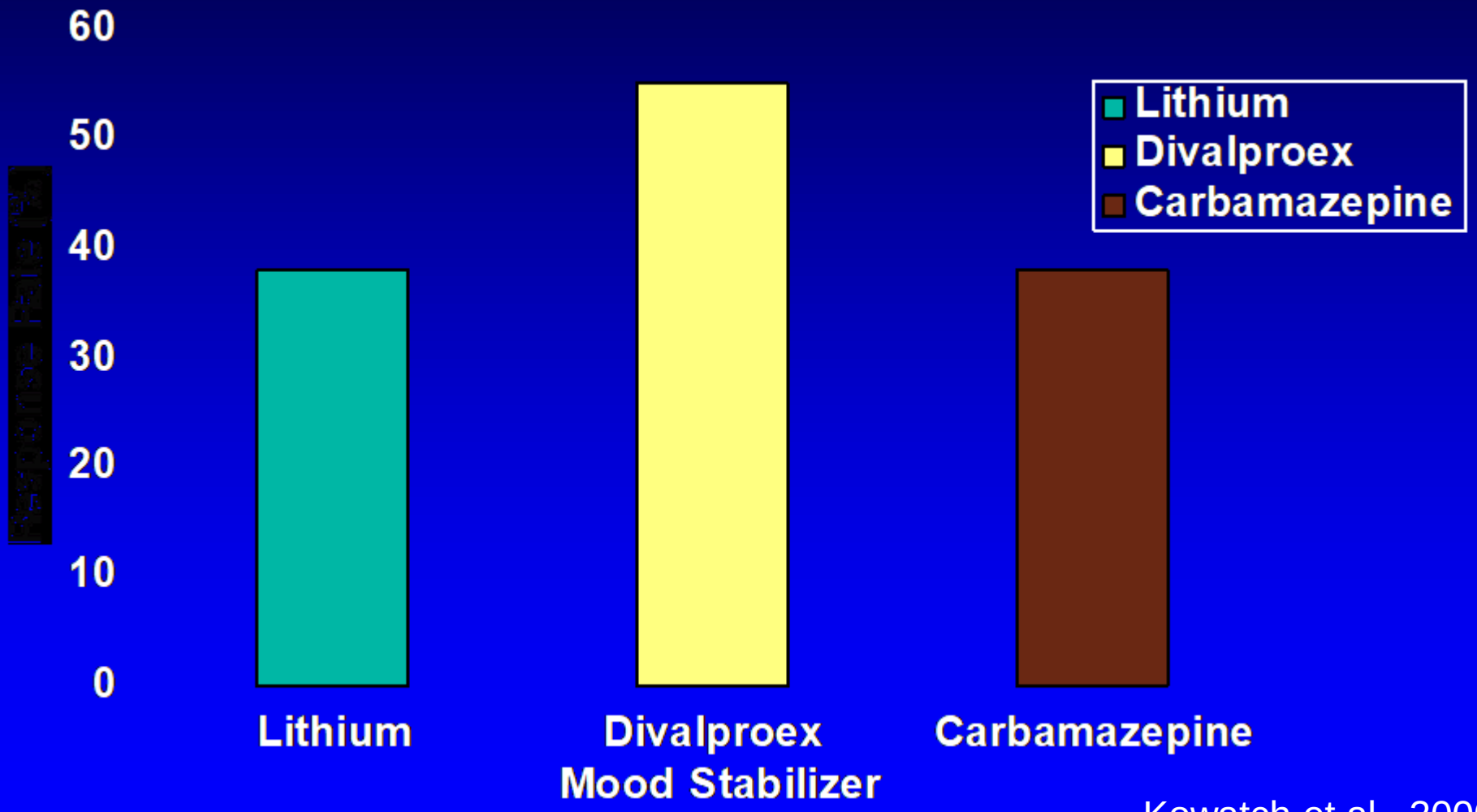
*Carbamazepine Adverse Effects

- Leucopenia
  - Benign (1/10)
  - Aplastic anemia (1/100,000)
  - Discontinue if WBC < 3K, neutrophils < 1K
- Rash
  - Benign (1/10)
  - Stevens-Johnson(1/100,000)
  - Discontinue if any rash

*Effect Size of Mood Stabilizers in Pediatric Bipolar Disorder

- Kowatch et al., 2000
- Children/adolescents with BPI or II
- N=42, mean age 11.4 years
- Randomized to 6 weeks open Rx
- Lithium, divalproex, carbamazepine
- Response = >50% reduction in Y-MRS
- Effect size: DVPX = 1.53, Li = 1.06, Carb = 1.00

*Response Rate of Mood Stabilizers in Pediatric BD



Kowatch et al., 2000

*Atypical Antipsychotics in Adolescent BD

- Potentially useful adjunctively to mood stabilizers and in monotherapy
- Olanzapine
  - Short term adjunctive use for acute mania (Soutullo et al., 1999; Chang & Ketter, 2000)
  - 1.25 - 5 mg QHS
  - Monotherapy efficacy (Frazier et al, 2000; DelBello et al., 2005; Tohen et al., 2005) at 2.5 - 20 mg QD
- Risperidone
  - May ↓ aggression, mania (Frazier et al., 1999; Biederman et al, 2005)
  - .5 - 1.0 mg BID
- Clozaril - treatment refractory BD

*Atypical Antipsychotics in Adolescent BD

- Quetiapine
  - Effective in adolescent mania when added to divalproex (DelBello et al., 2002) at 400 mg/day
  - Large, DBPC multisite study underway
- Ziprasidone
  - Very little evidence for efficacy in pediatric BD
- Aripiprazole
  - Chart reviews suggest efficacy (Barzman et al., 2005)
  - DBPC multisite study underway

*Other Anticonvulsants in Adolescent BD

- Gabapentin
  - ? useful adjunctively (Soutullo, et al., 1998)
  - Minimal adverse effects
  - No efficacy in adults
  - May be helpful for insomnia, comorbid anxiety
- Topiramate
  - One negative study vs. placebo (DelBello et al., 2004)
  - Anecdotal - cognitive problems, weight loss
  - May be useful adjunctively for weight loss/mood improvement

*Other Anticonvulsants in Adolescent BD

- Lamotrigine
  - Rash rates lower with lower titration schedule
  - Positive open study for adolescent bipolar depression (Chang et al., 2006) at 100 - 150 mg/day
  - Unknown maintenance efficacy in children
- Oxcarbazepine
  - Negative study vs. placebo in pediatric mania (Wagner et al., 2005)
  - May be more effective than placebo in prepubertal children

L-thyroxine

- T4 - precursor to active form, T3
- Decreases rapid cycling in adults with subclinical hypothyroidism
- Lithium may cause increased TSH
- Start .025 mg QD and titrate by .025 mg up to .075 - .1 mg. Check TSH after one month.

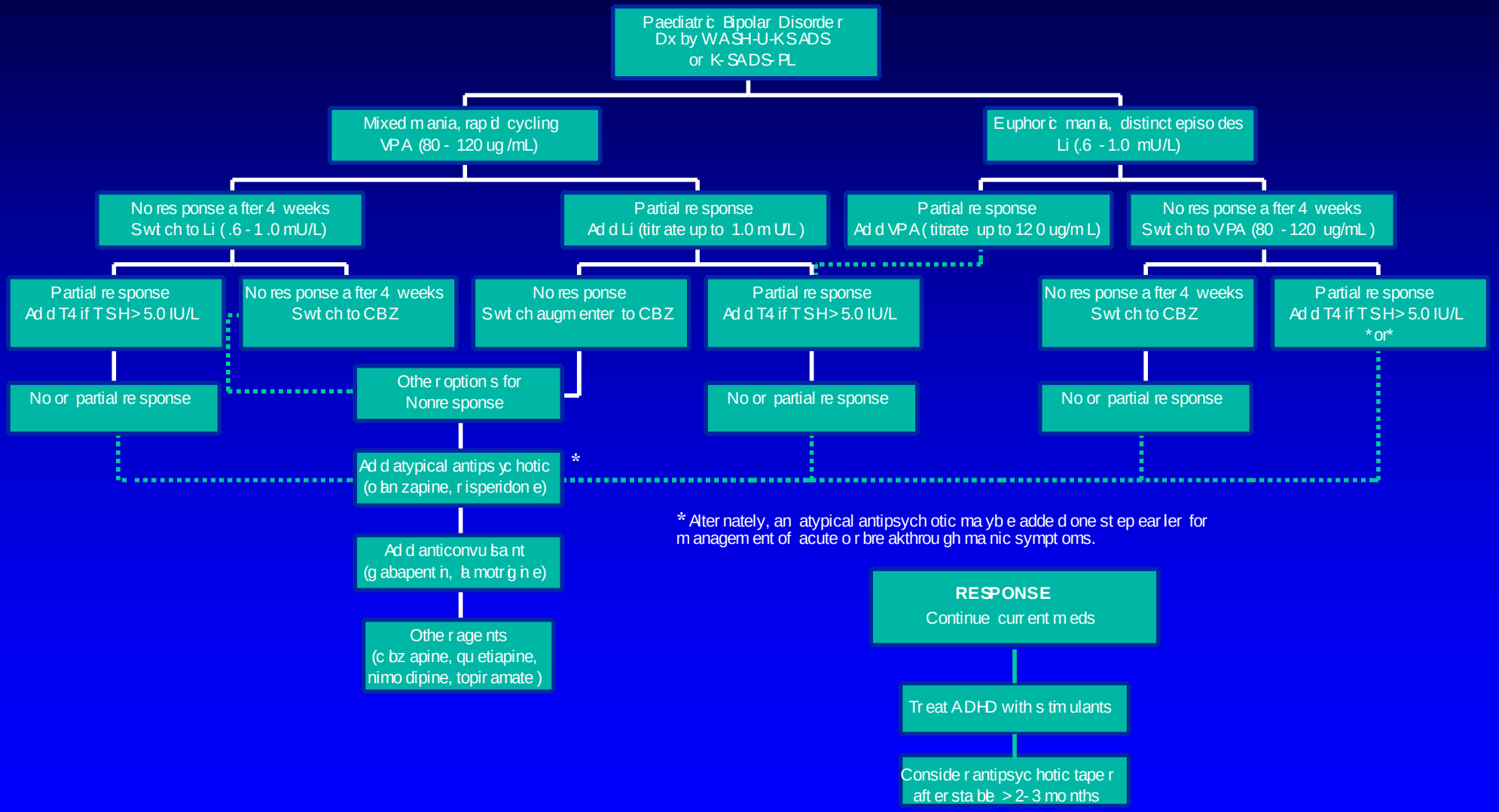
Omega 3 Fatty Acids in Childhood BD

- Adjunct to mood stabilizers (adults) (Stoll, et al., 1998)
- Anecdotal reports in children
- Aim for 3 - 5 g/day, QD or BID
- EPA:DHA = 2:1
- Avoid castor liver oil, tuna
- Concomitant Vitamin E (prevents oxidation)

*Combined Pharmacotherapy in Adolescent BD

- Rule rather than exception
- Avoid redundancy
- Care with SSRIs or stimulants- ensure adequate mood stabilization
- Be aware of other meds (Accutane, antibiotics, OCPs)

*Treatment Algorithm for Pediatric Bipolar Disorder



*Pediatric Uses of Antipsychotics

- Schizophrenia
- Mood disorders
  - depression with psychotic features
  - bipolar d/o (with or w/o psychotic features)
- Pervasive developmental d/o
- Mental retardation
- Movement d/o (Tourette's, tics, chorea)
- Disruptive behavior disorders, aggression

*Pediatric Use

- Target symptoms
  - psychosis
  - mania
  - aggression
  - self-injurious behavior
  - hyperactivity

*Pharmacokinetics

- $T_{1/2}$ varies greatly
  - clozapine $t_{1/2}$ 12 hrs
  - risperidone $t_{1/2}$ 24 hrs (w/ metabolite)
  - olanzapine $t_{1/2}$ 21-54 hrs
  - quetiapine $t_{1/2}$ 6-12 hrs
  - ziprasidone $t_{1/2}$ 5-10 hrs
  - children may require more frequent dosing,

Clozapine

- 1st intro'd in 1989
- $H_1 = M_1 > 5\text{-}HT_{2c} > 5\text{-}HT_{2A} > D_4 > D_2$
- Kumra et al (1996): n = 21, 6-wk randomized, DB comparison to haloperidol
  - ages 6-18 yrs; all previously poor responders
  - Clzpn dose range was 25-525 mg/d (mean dose 176 +/- 149 mg)
  - Haldol range was 16 +/- 8 mg

Clozapine, cont'd.

- Helpful in both positive and negative symptoms
- 1/3 of patients had significant side effects
  - seizures
  - weight gain
  - neutropenia (none had agranulocytosis)
  - other prominent side effects: sialorrhea, tachycardia, BP changes, constipation

Clozapine, cont'd.

- More prospective studies are needed
- Clinical experience with children is hard to come by, but improving
- Should be strongly considered in selected cases
  - Criteria are similar to adults
    - schizophrenia or psychosis refractory to 2 previous antipsychotics
    - intolerable side effects to previous agents

*Risperidone

- 1st intro'd in 1994
- 5-HT_{2A} >> $alpha_1$ > D_2 > 5-HT_{2c}
- some D1, D3, D4 activity
- Many open-label studies and case series
  - most work thus far in the DD population
  - frequently used in agitation, aggression, and psychotic states
  - dose range: 2-6 mg TDD (total daily dose)

*Risperidone, cont'd.

- Findling, et al. (2000): n = 20; Conduct d/o,10 wk, RAN, DB, p-c study, 2 parallel arms
- outcome measures: RAAPP, CGI, CPRS, CBCL; AIMS and other mvmnt scales
- dose range: 0.75- 1.5 mg QD
- significant changes from baseline were on *conduct* (p=0.0005), *psychosomatic problems* (p=0.04), and *delinquent behavior* (p=0.04)

*Risperidone, cont'd.

- Side effects were mild, and included weight gain (4.2 +/- 0.7 kg)
- No parkinsonian or dystonic side effects; 1 case of restlessness was noted
- Other studies shown prolactin increases, tardive dyskinesias, acute dystonias (Mandoki, 1995)

*Olanzapine

- 1st intro'd in 1996
- Similar profile to clozapine, but with relatively more 5-HT_{2A}, and less D4 blockade
- Emerging role in pediatric bipolar disorder (Tohen et al, 2005), childhood schizophrenia (Kumra et al, 2000), and autistic spectrum disorders.

*Olanzapine

- Begin at 1.25-2.5 mg hs for children, 2.5-5 mg for adolescents
- increase in 1.25- 2.5 mg increments (only if necessary) q3-4 days
- no proven benefit above 20 mg TDD, after which it resembles typical agents…though some clinicians report anecdotal success.

*Olanzapine, cont'd.

- Major side effects: Wt.gain can be substantial, lipidopathies, type II DM, constipation, BM suppression (rare)
- Less likely to cause prolactin changes than risperidone
- No reports of seizures, blood dyscrasias
- No completed controlled studies thus far in children

*Quetiapine

- 1st intro'd in 1997
- H_1>alpha$_1$ >5-$HT_{2A,2C,1A}$ > D_2
- Possible role in schizophrenia, psychosis and agitation.
- Very little EPS, with moderate weight gain (5-HT_{2c} > H_1) and sedation (H_1)

*Quetiapine, cont'd.

- McConville, et al (1998): n=10, open label trial ; aged 12-17 yrs, BP/SCHZ
- Dose steadily increased to 400 mg TDD (div. BID)
- Results were favorable after 3 weeks

*Quetiapine, cont'd.

- Possible role for adjunctive therapy in clozapine related weight gain and type II DM amelioration (Reinstein, et al. 1999)
  - n=65, non-random, 10 month retrosp. chart review
  - Quetiapine- clozapine combo. showed a tendency to induce weight loss ($p<0.001$), & improve glycemic control ($p<0.0001$) in pts who were on previously on clozapine only.

Quetiapine, cont'd.

- Cataracts seen in animal studies mainly
- May cause behavioral disinhibition
- Lmtd. initial results in autistic children are not promising, with little efficacy, and generally poor tolerability noted after 16 weeks; (Martin, et al, 1999)

*Ziprasidone

- Intro'd Feb. 2001
- Prominent 5-HT_{2A} blockade (also 5-$HT_{1A, 1D, 2C}$, and D_2)
- T 1/2 similar to quetiapine (5-10 hours)
- Steady state in 1-3 days
- Dose 40-160 mg TDD

*Ziprasidone, cont'd.

- Sallee, et al. (2000): n=28, boys & girls aged 7-17 yrs with TS or CTD; DB, p-c, randomized, multi-center trial for 56 days
- Dose range 5-40 mg TDD (gradual up-titration, div BID); Mean TDD = 28.2 +/- 9.6 mg
- Outcome measures: Yale Global Tic Severity Scale (YGTSS)

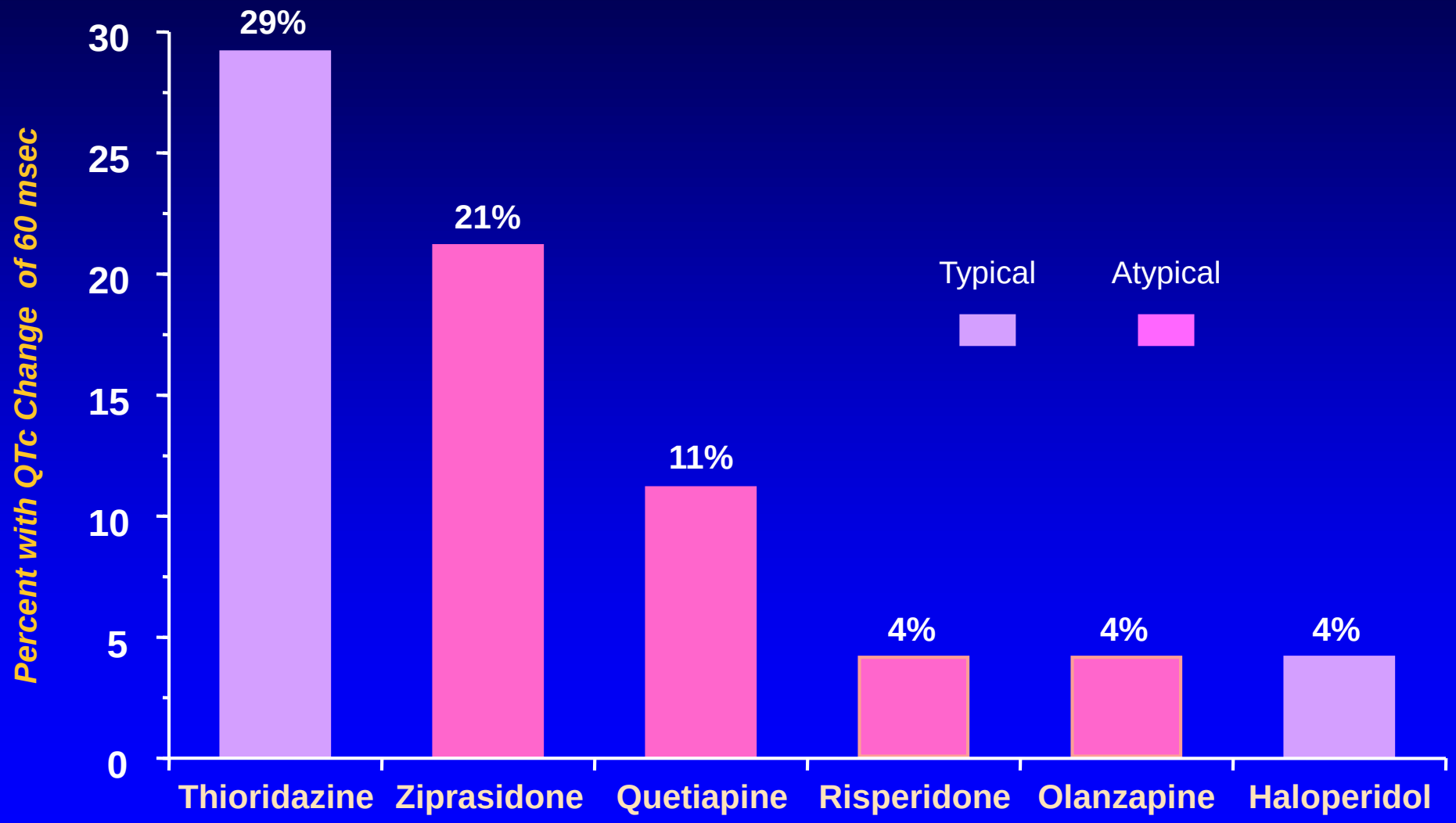
*Ziprasidone, cont'd.

- Results: mean YGTSS change from baseline was significant in the ZIP-tx'd group (*p=0.016*), compared to placebo
- Side effects: transient mild sedation; transient prolactin elevation
- No mvmnt disorders nor weight changes were noted
- No clinically significant changes in BP, pulse,
- Some reports of QTc changes (Blair 2005)

*Ziprasidone, cont'd.

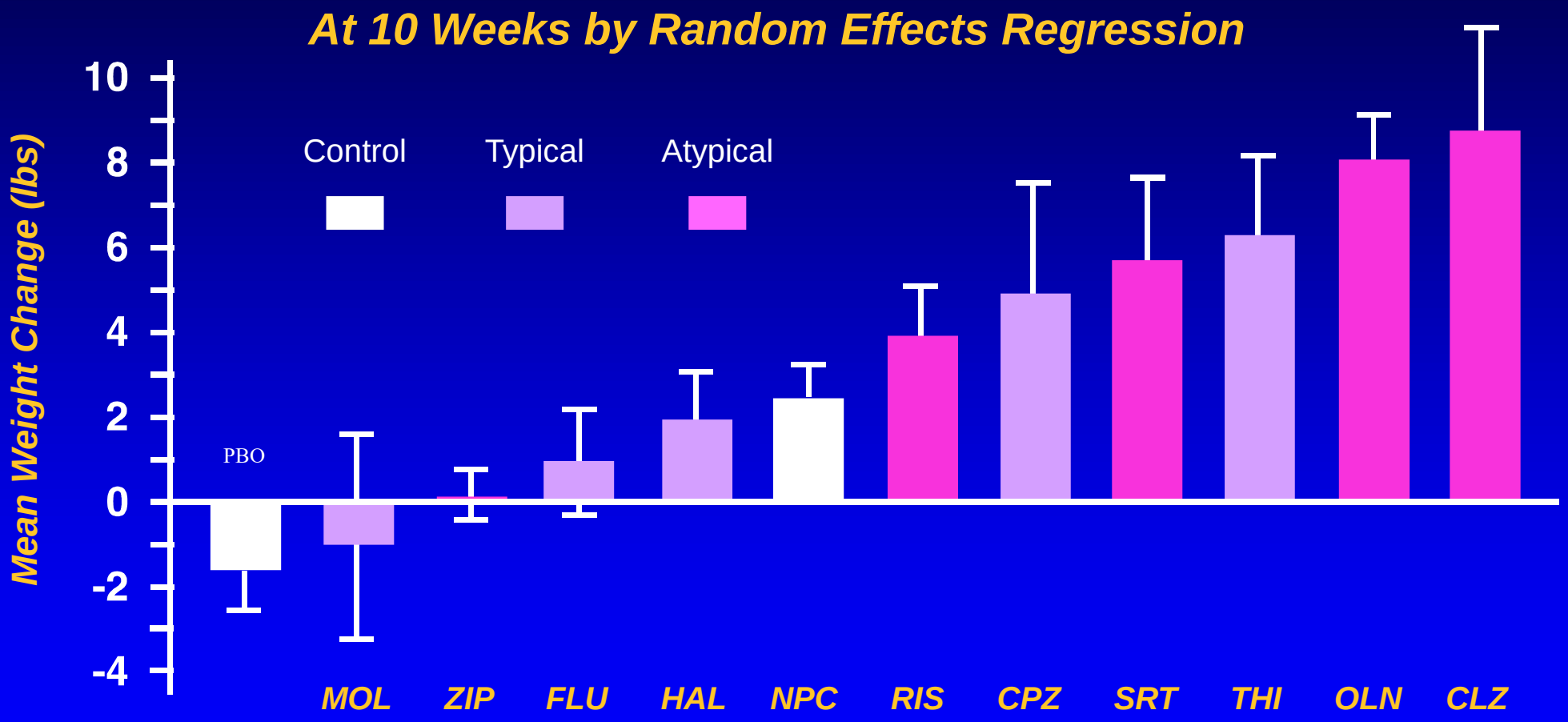
- QTc changes do not currently appear to be problematic, though longer studies in children need to be done
  - Initial data in adults shows modest increase of 5.9-9.7 msec in random ECGs (doses 80-160 mg/day)
  - rare QTc > 500 msec (0.06% zip vs. 0.23% placebo)
  - effect on QTc unchanged in the presence of metabolic inhibition (CYP 3A4 substrate)

Antipsychotic-Induced QTc Prolongation in adults



Adapted from: FDA Background on Ziprasidone 2000:5.

Antipsychotic-Induced Weight Gain in Adults



PBO = Placebo; NPC = Non-Pharmacological Control. Allison DB, et al. Am J Psychiatry 1999;156:1686-96.

*Atypicals and EPS

- Less frequent, but still happens
  - Reduce dose, add benztropine, or change to a different atypical agent
- akathisia
  - Above measures; may need to add clonazepam or inderal
- If anti-EPS agent used, attempt taper over several weeks to avoid anticholinergic side effects

*Antipsychotics - Conclusions

- Atypicals have received widespread use in children and adolescents, despite a general lack of controlled trials
- Initial experience has been favorable
- More investigation remains to be done

Psychological issues in pharmacologic mgmt.

- ? % of all rx are not filled or are taken improperly- rates of adherence maybe only 25-30%
- Why is psychological management important?
- Parent issues:
  - Ambivalence re: need for meds
  - Inadequate parental surveillance of adherence

Psychological issues in pharmacologic mgmt.

- More Parent Issues:
  - Misunderstanding of doses, serum levels, and onset of effects
  - Internet info and misinfo
  - All of our actions have meaning to the patient and family
    - What language do we use to explain the theoretical nature of their child's illness?

Psychological issues in pharmacologic mgmt.

- Meanings, cont'd
  - Many patients (esp teens) attach meaning to the medication itself
  - Once taken, it b/c psychologically incorporated into the patient's view of himself/herself, and can change their sense of identity
  - The meaning and significance of a drug can affect the way patients view the drug, the prescriber, and themselves (*Lieberman & Tasman, 2000)*

Question 1

- Which drug is least likely to cause weight gain?
- A-lithium
- B-methylphenidate
- C-risperidone
- D-valproate
- E-quetiapine

Question 2

- Drug of choice in teenage depression is?
- A-sertraline
- B-fluoxetine
- C-bupropion
- D-venlafaxine
- E-none of the above

Question 3

- Which statement is true
- A- Youth like to take psychotropic medication
- B-Parents always monitor psychotropic adherence carefully
- C-Psychiatrists should not investigate the “meaning” of medication in a child’s life
- D-Youth and parents attach “meaning” to medication-taking
- E-Only parents attach “meaning” to medication-taking

Question 4

- Which medication is the drug of choice for ADHD?
- A-atomoxetine
- B-clonidine
- C-guanfacine
- D-psychostimulants
- E-antipsychotics

Question 5

- Which statement is true about youth and pharmacokinetics and pharmacodynamics
- A- Young children have lower GFRs than adults
- B- Young children tend to metabolize drugs slower than adults
- C-Young children are relatively insensitive to atypical antipsychotics
- D-Young children generally need lower daily doses than adults of drugs metabolized by the liver
- E-Young children generally need higher daily doses than adults of drugs metabolized by the liver

Answers

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