Pediatric Psychopharmacology: General Principles

Shashank V. Joshi, MD

Kiki D. Chang, MD

Stanford University School of Medicine

Goals of this talk

- By the end of this lecture, participants will be able to
  - Discuss the major differences between child and adult psychopharmacology
  - Know specific medications' indications, dose ranges and side effects
  - Discuss a differential diagnosis for the triad of neuromuscular changes, autonomic instability, and altered mental status
  - Develop an awareness of the psychological factors in medication management

Overview

- History of Pediatric Psychopharmacology and FDA process
- General approach to Children and Teens
  - Similarities and differences with adult patients
- NMS, 5-HT syndrome
- Specific agents for acute states
- Other factors in child & adolescent psychopharmacology

All of these are reasonable first line interventions for non-emergent acute agitation in children EXCEPT:

- A) Haldol, 0.5 mg PO
- B) Thorazine, 25 mg IM
- C) Ativan, 1mg PO
- D) Benadryl, 25 mg PO

Which one is true about pharmacokinetics in younger children?

- A) Psychotropics tend to have longer half-lives in younger children
- B) GFR is less efficient than in adults
- C) More fatty tissue in younger children allows meds to be stored somewhat longer in the body
- D) Half-lives may be shortened due to altered kinetics, compared to teens

Which is true regarding neurotransmitter development?

- A) 5-HT receptor density increases with age
- B) DA receptor density stays constant throughout life
- C) NE receptor density increases with age
- D) Attending Psychiatrists tend to get denser with age

All of the following are true in pediatrics, ***except ?***

- A) Stimulants have the most studies to justify their use
- B) Both free and bound portions of medication are psychoactive
- C) Children and teens may require more frequent dosing of medication, compared to adults
- D) There are now at least 3 SSRIs with FDA indications in pediatric patients

General Approach

- Children are not small adults (usually)
- Establish a diagnosis, or diagnostic category
- Parents and teachers are essential collaborators
- All physician's actions have meaning to patients, and families, (*especially teens)*

History of Pediatric Psychopharmacology

- Realm of pediatricians
- Child Psychiatry itself has developed over the past 100 years
  - In parallel with the psychological study of normal child development

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
- 2002- Best Pharmaceuticals for Children Act (BPCA)
- 2003-4 : SSRI-suicidality link leads to new FDA prescribing guidelines

History of Pediatric Psychopharmacology

- 2004- Atomoxetine becomes 1st non-stimulant developed for ADHD treatment
- 2006-7: Risperidone gets pediatric indication for autism symptoms, short-term treatment of bipolar disorder, and childhood-onset schizophrenia (COS)
- 2007: Aripiprazole gets pediatric indication for COS

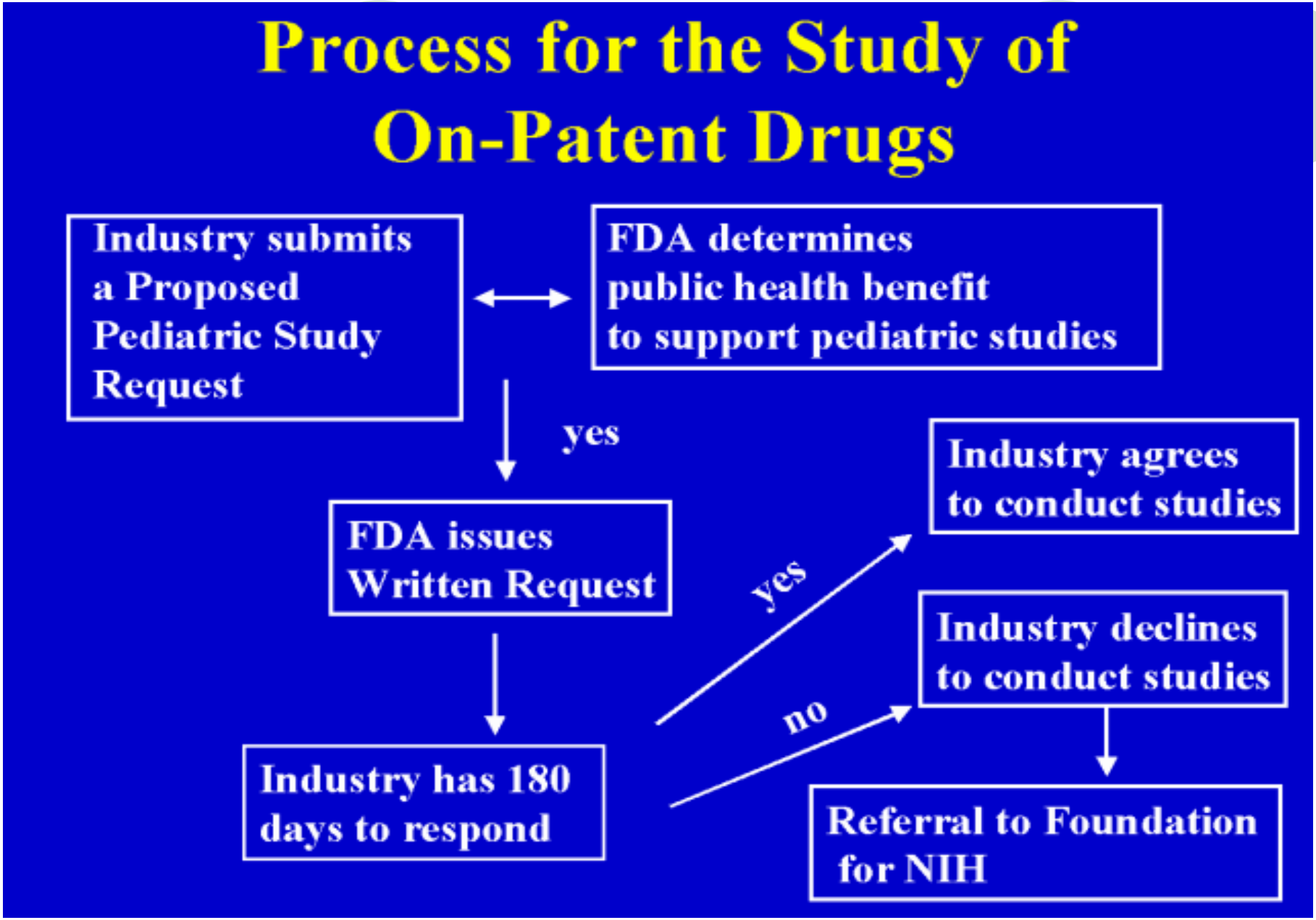
Best Pharmaceuticals for Children Act

- Signed into law January 4, 2002
- Provides processes for studying "off-patent" as well as "on-patent" drugs
- Re-authorized pediatric exclusivity incentives as they apply to drugs* approved under Section 505 of the Federal Food, Drug and Cosmetic Act
- Sunsets October 1, 2007

*most biologic pharmaceuticals are approved under the Public Health Service (PHS) Act and therefore do not qualify for pediatric exclusivity

Best Pharmaceuticals for Children Act

- Provides opportunity for FDA and NIH to collaborate on the drug development process, for drugs that may be administered to children
- provides processes for studying "off-patent" drugs, as well as "on-patent" drugs


Process for the Study of On-Patent Drugs
Industry submits a Proposed Pediatric Study Request
FDA determines public health benefit to support pediatric studies
yes
FDA issues Written Request
Industry has 180 days to respond
yes
Industry agrees to conduct studies
no
Industry declines to conduct studies
Referral to Foundation for NIH

Children are not small adults (usually)

- Young children may not be able to describe their internal states
- 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, PhBrb 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 have shorter half-lives in children due to altered distribution, sometimes requiring more frequent dosing

Children are not small adults (usually)

- Pharmacokinetics:
  - the disposition of the drug to determine drug concentration at the effector site
- Pharmacodynamics:
  - the drug's action at the effector site and the end response

Children are not small adults (usually)

- Pharmacodynamic and pharmacokinetic differences, cont'd.
  - Because V_d (the volume into which the drug distributes into the body, when the body is at equilibrium) is linearly related to body wt, less drug may be available for delivery than expected. (mg/kg dosing attempts to correct for this)

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)

Children are not small adults (usually)

- Pharmacodynamic and pharmacokinetic differences, cont'd.
  - Young adolescent males may be at particular risk for acute dystonic reactions, compared to adults
  - Some drugs induce their own metabolism, and this may result in lower levels than expected

Children are not small adults (usually)

- Plasma protein binding
  - Remember, most meds are reversibly bound to albumin, and only the free unbound portion is active and available for tissue distribution.
    - different sites for acidic drugs (globulin) and basic drugs (*a-1* glycoprotein)
    - b/c *a-1* glycoprotein is an acute phase reactant, its increased presence during infection and physical stress may result in decreased free medication.
- Cytochrome P450: ***As important in children as in adults.***

Acute pediatric interventions for psychiatric symptoms

- Acute agitation *(always offer medication by p.o. route 1st, unless there is an acute safety threat)*
- *1st Assess Clinical Presentation and Etiology*
- *If medication is warranted, proceed with caution and confidence*
  - Risperidone, 5-18 yrs: 0.25 mg – 1 mg/dose PO
    - Max of 6 mg (rarely need to go above 2 mg, except in extreme cases
    - Watch for extrapyramidal / parkinsonian side effects
    - liquid form is 1mg/cc); well-tolerated, in general, but watch for _____?____
  - Haloperidol, 3-6 yrs: 0.25 - 1 mg/dose PO,
    - max of 0.15 mg/kg/day if needed
    - 6-12 yrs: 0.25-2 mg/dose q4-8 hrs; max dose 0.15 mg/kg/day
    - Age >12 yrs: 0.25-5 mg/dose PO; 2-5 mg/dose IM; rpt q 1 hr PRN

Acute pediatric interventions for psychiatric symptoms

- Risperidone seems better for non-agitated delirium and confusion, haloperidol for agitated delirium (Karnik NS, Joshi SV, Paterno C, Shaw RJ: “Subtypes of Pediatric Delirium: A Treatment Algorithm”, *Psychosomatics* 48:253-257, June 2007)

Acute pediatric interventions for psychiatric symptoms

- Main side effects of Haldol-- hypotension, lowers seizure threshold
- acute dystonia
  - (tx: 25-50 mg IM diphenhydramine)
- avail as PO (tabs or syrup) or IM
- NB! Hypo/ hypertension, drug interax (trazodone, CNS depressants), EPS

- Neuroleptic Malignant Syndrome

Acute pediatric interventions for psychiatric symptoms

- Acute anxiety: Lorazepam, 0.5-4 mg/dose, p.o. or IV/IM
  - onset 20-30 minutes, duration 6-8 hours
  - (NB! Respiratory depression, paradoxical agitation (esp. brain damaged patients, DD population)) Flumazenil is the antidote, 0.01mg/kg (max 0.2 mg), q 1 min, max cumulative dose of 1 mg; max hrly dose of 3 mg--*does not reverse narcotics*

Acute pediatric interventions for psychiatric symptoms

- Acute agitation *(always offer medication by p.o. route 1st, unless there is an acute safety threat)*
  - Chlorpromazine (Thorazine): PO (quick thinking ~1mg/kg/dose) or 2.5-6 mg/kg/day, div q4-6 hrs
- Teens:
  - P.O. / I.M. (quick thinking, average starting dose ~25-50 mg)
    - q4-6 hrs
    - dose range, 50-200 mg/day
    - Adult max : 2000mg
  - IM / IV: 2.5-4mg/kg/day div. q6-8hrs
    - max IM / IV dose, 5-12 yrs: 75 mg
    - ***As last resort*** : PR, 1mg/kg/dose, q6-8hrs
  - CPZ side effects: sedation, hypotension, lowered seizure threshold, NMS

Acute pediatric interventions for psychiatric symptoms

Very acute agitation: Droperidol, 0.03-0.07 mg/kg/dose IM (may give IV over 2-5 minutes), max dose 2.5 mg; onset in 3-10 minutes, pks in 10-30 minutes; duration 2-4 hrs

(Caution! Hypotension, tachycardia, bronchospam, laryngospasm are [rare] side effects)

Only administer where there are strict monitoring parameters in place

NMS (Neuroleptic Malignant Syndrome)

- true psychiatric emergency
- incidence: 0.02-2%
- autonomic instability, severe EPS/rigidity, hyperthermia
- more common in pts. treated w/Lithium and antipsychotics
- Untreated, may lead to LOC, rhabdomyolysis, and death

Acute pediatric interventions for psychiatric symptoms

- Risk factors for NMS
  - Being female (3:2)
  - Previous hx of NMS
  - High-potency agents
  - Older age
  - Concomitant mood d/o
  - Presence of dementia or delirium

Acute pediatric interventions for psychiatric symptoms

- Risk factors for NMS, cont'd
  - presence of dementia or delirium
  - dehydrated state
  - rapid dose titration
  - concomitant use of other psychotropics
- usually within 2 weeks of initiation of tx
  - After large dose increase
  - *may occur at any time during tx, however*

Acute pediatric interventions for psychiatric symptoms

- NMS (Neuroleptic Malignant Syndrome), cont'd
  - Mgmt: Call NMS Hotline (24/7, staffed by MD)
    - http://www.nmsis.org/services.shtml
    - 888-667-8367 (U.S.)
    - 315-464-4001 (outside U.S.)
    - Stop antipsychotic! *GET MEDICAL BACKUP*
    - cooling blankets, external sponging, fanning, gastric/colonic lavage
    - *antipyretics generally not helpful*
    - Respiratory / CV status (continuous monitoring)
    - Neurologic / fluid and electrolyte status

Acute pediatric interventions for psychiatric symptoms

- NMS (Neuroleptic Malignant Syndrome), cont'd
  - ICU team: Neuromuscular paralysis for severe hyperthermia and rigidity
  - BDZ for reducing rigidity
  - Dantrolene or Bromocriptine if severe
    - DNTRLN: 1-5 mg/kg IV
    - BRMCRPTN: 2.5-5 mg PO, q4-6h; max dd 40-100mg
  - CPK, WBC for ongoing monitoring, not diagnosis

Acute pediatric interventions for psychiatric symptoms

- NMS (Neuroleptic Malignant Syndrome), cont'd
  - Differential diagnosis
    - Serotonin syndrome
      - selective **serotonin** reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), and to a lesser extent, opioids, sumatriptan, and other serotonergic agents, usually when used in combination
      - altered mental status, neuromuscular abnormalities, and autonomic dysfunction
    - Malignant Hyperthermia
      - A severe, potentially fatal increased body energy consumption after exposure to certain anesthetic drugs.
      - **Genetic** susceptibility
        - Family history of death during **general anesthesia** or having a high body temperature during or after general anesthesia are the most likely indicators that a person may be susceptible to MH. The June 15, 2005, issue of *JAMA* includes an article about **genetic testing** (Torpy, et al: *JAMA*; Vol. 293 No. 23, June 15, 2005)

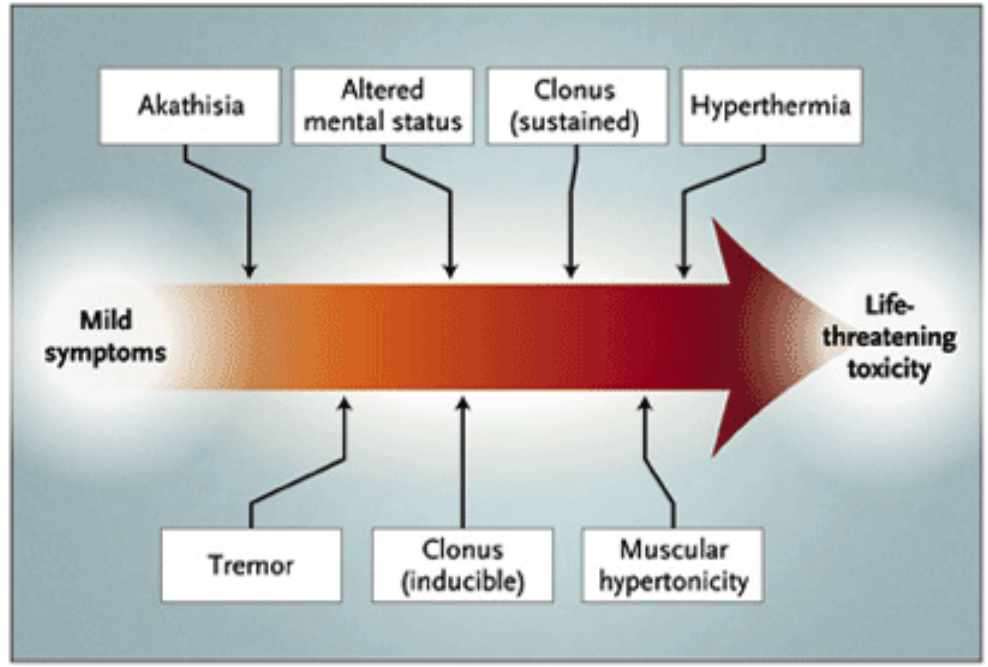
Case report:

- G. is an 11-year-old Asian female patient with high-risk, Philadelphia chromosome positive, acute lymphoblastic leukemia (ALL), which was diagnosed 2 years before her admission for bone marrow transplantation. She was seen for initial psychiatric consultation because of anxiety before transplantation and her anxiety resolved after the transplant was completed. G. was treated with busulfan and cyclophosphamide, and then she received bone marrow transplantation from her infant brother. She soon developed painful mucositis, and she was treated with continuous infusion of fentanyl. G. was simultaneously given antibacterial, antifungal, and antiviral antibiotics, cyclosporine, and the 5-HT3 antagonist, ganisetron.

Case report, cont’d:

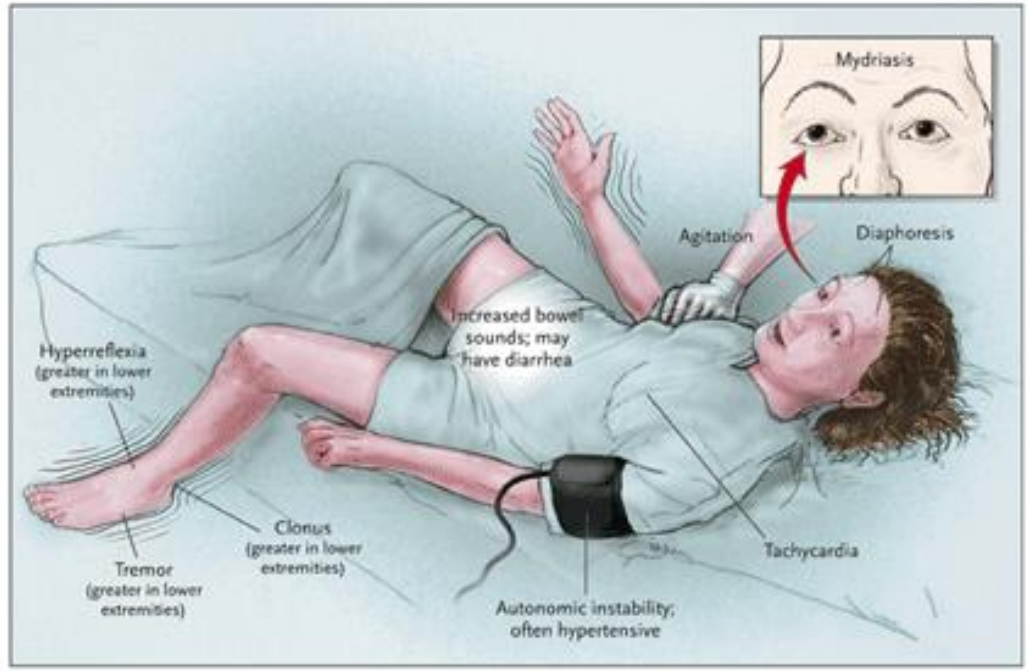
- Two weeks later, G. developed veno-occlusive disease with renal and hepatic involvement. She became irritable and dysphoric with restricted affect, poor eye contact, and impaired attention that was consistent with early delirium, but no changes were made in her treatment. She became acutely confused 5 days later, with visual hallucinations, marked anxiety, tremulousness, ataxia, and myoclonus. Because the **serotonin** syndrome was suspected, granisetron was discontinued, and fentanyl changed to hydromorphone. G.'s confusion abated by the next day, myoclonus resolved, and her medical condition briefly stabilized, but her condition deteriorated, with progressive renal and hepatic failure. G. died 6 weeks later.

Case report, cont'd:



Boyer & Shannon, **NEJM:352 (11):1112-1120** March 17, 2005

Case report, cont'd



Boyer & Shannon, **NEJM:352 (11):1112-1120** March 17, 2005

Case report, cont'd

Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.

Drugs associated with the serotonin syndrome

Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolide (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)
Other: lithium

Drug interactions associated with severe serotonin syndrome

Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron

Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolide and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

Boyer & Shannon, **NEJM:352 (11):1112-1120** March 17, 2005

Psychological issues in pharmacologic management

- ? % of all rx are not filled or are taken improperly
  - Ans: About 50%, on average, across pediatric specialties
  - Depends on frequency of dosing and length of time meds are needed, ease of use, taste, cost, and understanding of necessity, among other reasons
- Why is psychological management important?
- Parent issues:
  - Ambivalence regarding need for medication, guilt about having “caused” the condition
    - Feelings of “inadequate” parenting
    - Feeling responsible for “poor” gene contribution
  - Inadequate parental surveillance of adherence

Psychological issues in pharmacologic management

- More Parent Issues:
  - Misunderstanding of doses, serum levels, and onset of effects
  - Internet information and misinformation
  - General public perception (see *Psychiatr Serv* 58:613-618, May 2007)
  - 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 management

- Meanings, cont'd
  - Many patients (especially teens) attach meaning to the medication itself.
  - Once taken, the "pill" is 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)*

Psychological issues in pharmacologic management

- Prescriber Issues
  - Dual Working Alliance crucial for successful outcomes
    - Child / teen may be easier to work with than parent
  - Potential for conflict of interest when conducting clinical trials
  - Many adult relationships need to be cultivated to promote best working alliance, maximum adherence, and best clinical outcomes
    - Parent
    - Teacher
    - Primary Therapist
    - Primary Care Provider / Other referring specialist

1. All of these are reasonable first line interventions for non-emergent acute agitation in children EXCEPT:

- A) Haldol, 0.5 mg PO
- B) Thorazine, 25 mg IM
- C) Ativan, 1mg PO
- D) Benadryl, 25 mg PO

2. Which one is true about pharmacokinetics in younger children?

- A) Psychotropics tend to have longer half-lives in younger children
- B) GFR is less efficient than in adults
- C) More fatty tissue in younger children allows meds to be stored somewhat longer in the body
- D) Half-lives may be shortened due to altered kinetics, compared to teens

3. Which is true regarding neurotransmitter development?

- A) 5-HT receptor density increases with age
- B) DA receptor density stays constant throughout life
- C) NE receptor density increases with age
- D) Attending Psychiatrists tend to get denser with age

4. All of the following are true in pediatrics, ***except ?***

- A) Stimulants have the most studies to justify their use
- B) Both free and bound portions of medication are psychoactive
- C) Children and teens may require more frequent dosing of medication, compared to adults
- D) There are now at least 3 SSRIs with FDA indications in pediatric patients

Answers

1. B
2. D
3. C
4. B

References:

- Martin, et al: Pediatric Psychopharmacology: Principles and Practice, Oxford U. Press, NY, 2003
- Joshi SV: **“**Teamwork**:** The therapeutic alliance in child and adolescent psychopharmacology”, *in:* Martin A & Bostic J (eds.), *Child & Adolescent Psychiatry Clinics of North America;* 2006; Vol 15 ; 239-264
- Lieberman, JA and Tasman A: Psychiatric Drugs, WB Saunders, Philadelphia, 2000
- Lewis O: Psychological factors affecting pharmacologic compliance, *Child & Adol Psy Clin of North Amer* 4(1), 15-23, 1995
- Tosyali,MC and Greenhill LL: Child & Adolescent “Psychopharmacology- Important Developmental Issues”, *Pediatric Clin of North Amer* 45(5), 1021-33,1998

References:

- Wilens TE: Straight Talk about Psychiatric Medications for Kids, revised ed, Guilford Press; NY, 2003
- Bakerman S, et al: Bakerman's ABC's of Interpretive Lab Data, 3rd ed, Interpretive Lab Data, Inc, Myrtle Beach, SC, 1994
- Keltner NL & Folks DG: Psychotropic Drugs, 2nd ed , Mosby, St. Louis, 1997
- Fuller MA & Sajatovic M: Psychotropic Drug Information Hndbk., Lexi-Comp, Cleveland, 2001
- Tasman A, et al.: The Doctor-Patient Relationship in Pharmacotherapy ; Guilford Press, NY 2000
- Riddle MA, et al. Pediatric psychopharmacology. *J Child Psychol Psychiatry*. Vol 42(1) pp.73-90, 2001