

Child Psychopharmacology: Issues, Controversies, Safety & Efficacy

Texas Association of School Psychologists

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Kubiszyn 10-8-2010 (TASP)

Please respond to these items (1=SA to 5=SD)

- 1) Psychotropic drugs work by restoring a chemical imbalance in the brain.
- 2) An FDA indication means a drug is safe and effective.
- 3) An FDA warning means a drug is unsafe.
- 4) Ped. psychotropic drugs are prescribed primarily by child psychiatrists.
- 5) Most ped. psychotropic drugs for conditions other than ADHD are prescribed "off-label."

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10 items continued...

- 6) Behavioral treatment of ADHD enables lower doses of drugs to be used.
- 7) In Texas it's OK to recommend drug treatments to parents as long as you do NOT prohibit the child from attending school.
- 8) Ped. psychotropic drug treatments are MORE effective than psychosocial treatments.
- 9) Ped. psychosocial treatments are safer than psychotropic Tx.
- 10) Psychotropic drugs should NEVER be prescribed for school-aged kids.

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PART 1: HISTORY, ISSUES & CONTROVERSIES

- Brief History
- Rx to more and younger kids,
- off-label, polypharmacy,
- ethical/legal issues
- Direct to consumer marketing,
- Conflicts of Interest
- Publication bias

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PART 2: SAFETY & EFFICACY

- Basic terminology, concepts, mechanisms
- Comparative pediatric safety & efficacy data
 - short and long-term safety of drug and psychosocial treatments.
 - FDA warnings/advisories & PHTs
 - Side effects
 - short & long-term drug & psychosocial efficacy for
 - Symptoms
 - Functional outcomes

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Brief History

- "Fidgety Phil" - 1865
- 50s - early 90s
- 70s & 80s
- 1997-Food and Drug Administration Modernization Act (FDAMA); 6 mos. patent exclusivity
- 1998-"Pediatric Rule": required ped subjects for new drugs or for existing drugs if a new indication, form of dosage, dosage regimen, or route of administration is requested

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RUPP

- 1998-Research Units in Pediatric Psychopharmacology (RUPP), sponsored by the National Institute of Mental Health (NIMH).
 - increasingly sophisticated and methodologically complex (e.g., a placebo washout phase to minimize placebo responders in the trial, crossover designs, long-term follow-ups),
 - government-sponsored (with support from drug manufacturers),
 - large scale, multi-site RCTs (MTA, TADS, POTS, PATS, CAMS)
 - relative effectiveness of psychotropic drug Tx vs. psychosocial Tx, and combinations of drug and psychosocial Tx

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Warnings & Controversies:

- 2003 FDA/ADA Advisory about AAPs (weight gain, metabolic disorders)
- 2004 FDA suicidality black box warning for ADs, > dozen warnings/advisories since then
- mid-2000s direct marketing, conflict of interest allegations, withheld data, publication bias

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Is pedi psychotropic Rx increasing?

- Dramatic increase in pedi Rx the last decade:
 - 500% in antipsychotic Rx alone ! (Olfson, M., Blanco, C., Liu, L., Moreno, C., & Laje, G., 2006; Patel, N. C., Sanchez, R. J., Johnson, M. T., & Crimson, M. L., 2002)
 - 2004-Medco study: 5.3% of sample of 300,000 youth took psychotropics (all classes)
 - 1st time psychotropic meds (all classes) exceeded spending for antibiotics and asthma meds *combined*
 - 17% - psychotropic
 - 16% - antibiotic and asthma
 - 11% - skin conditions
 - 6% - allergies
 - <http://www.drugtrend.com/medco/consumer/drugtrend/trends/jsp>

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And they're younger and younger (Olfson, M. Crystal, S, Huang, C. & Herhard, T. (2010).

- Claims for privately insured children 2 - 5 years, with 12 months of continuous service enrollment (n = 400,196, 2001 755,793, 2007)
- AP use increased from 0.78 to 1.59/1000
- For what DX were APs prescribed?
 - 28.2% PDD or IDD/MR
 - 23.7% ADHD
 - 12.9% disruptive behavior disorders
- Less than half received a mental health assessment (40.8%), a psychotherapy visit (41.4%), or a visit with a psychiatrist (42.6%)

"Conclusions: Despite increasing rates of antipsychotic use by very young children, provision of formal mental health services remains sparse. These service patterns highlight a critical need to improve the availability of specialized and well integrated mental health care for very young children with serious mental health problems." (p.13)

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Off-label prescribing & polypharmacy

- Off-label Prescribing – Rx for a condition or age group that has not been approved by the FDA
 - Safety?
 - Efficacy?
- Polypharmacy – Rx of more than one drug, at least one of which is typically off-label
 - we cannot predict adverse events or side effects for an individual drug (i.e., monotherapy),
 - the task becomes even more complex when two or more drugs are prescribed (i.e., polypharmacy).

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Polypharmacy for adults

- **Safe & Effective?**
 - most data are from open label studies, lithium is best supported but least used (Fava & Rush, 2006)
 - Antonuccio, Yury, Valenstein, & Matuszak (2008)
 - Efficacy data "extremely limited". (p.3)
 - Safety? Of 22 studies, 3 had no safety data, 8 had a safety section, 3 had a comparison with a placebo group, 16 had safety statistics, and 17 had a description of the adverse effects or events
- **How common?** National Ambulatory Medical Care Survey - 13, 079 visits to office-based psychiatrists:
 - visits with 2 or more meds (42.6% in 1996-1997 to 59.8% in 2005-2006) p <.001
 - visits with 3 or more meds (16.9% to 33.2%) p <.001

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Polypharmacy for children

- **Safe & Effective?**
 - "Often these prescriptions are without demonstrated efficacy in youth, but the hope is that they will be effective because they were shown to be effective in adults..." (p.345)
 - (Julien, Advocat & Comaty, 2008)
 - Safety?
- **How common?**
 - 1.6 million youths took 2 or more psychotropics in 2006, including 280,000 under 10 years old (Julien, Advocat & Comaty, 2008)
 - Florida Medicaid fee for service receiving an AAP
 - 7% of U-12 and 8% older kids received at least 2 AAPs
 - Constantine, R. J., Boaz, T & Tandon, R. (2010)

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School-related legal/ethical Issues

- Federal legislation
 - IDEIA Child Medication Safety Act
- State legislation
- Ethical issues

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IDEIA: (25) Prohibition on Mandatory Medication

- "(A) in general. The State educational agency shall prohibit State and local educational agency personnel from requiring a child to obtain a prescription for a substance covered by the Controlled Substances Act (21 U.S.C. 801 et seq.) as a condition of attending school, receiving an evaluation under subsection (a) or (c) of section 1414 of this title, or receiving services under this title.
- (B) Rule of Construction. Nothing in subparagraph (A) shall be construed to create a Federal prohibition against teachers and other school personnel consulting or sharing classroom-based observations with parents or guardians regarding a student's academic and functional performance, or behavior in the classroom or school, or regarding the need for evaluation for special education or related services under paragraph (3).

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Tx House Bill 1406 (6/03)

- amends the Education Code to prohibit a school district employee from
 - recommending that a student use a psychotropic drug,
 - suggesting any particular diagnosis, or
 - using a parent's refusal to consent to administration of a psychotropic drug to a student or to psychiatric evaluation or examination as ground for barring a student's attendance in a class or participation in a school-related activity.

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Tx House Bill 1406 (6/03)

- does NOT prohibit appropriate referrals under
 - certain federal provisions,
 - recommendations by a school nurse, physician, or mental health professional for an evaluation by an appropriate medical practitioner, or
 - discussions by a school employee with a parent or another district employee about any aspect of the student's behavior or academic progress.

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Off-limits

- Recommending specific drugs, dosages, cocktails
- Administer/dispense/supply drugs,
- Tell clients to stop/start/modify drug regimens
- other than
 - DOD-trained psychologists in the military,
 - Dually licensed psychologists (MD/PhD, PhD/NP, etc.)
 - in NM or LA if appropriately trained (2 yrs. Postdoc) , licensed, and/or certified

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Within limits, but be careful!

- Discussing changes in behavior, academics
- Discussing Dx & Tx issues and options
- Outcomes evaluation
- Discussing medication resources:
 - “no one has exclusive rights to nor ownership of knowledge” (p.34)
 - (Preston & Ebert, 1999)
- Sharing research-based knowledge regarding medications, being careful to cite references
- Safer to refer clients to the info and review technical aspects with them (i.e. be the knowledge broker)

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Ethical Issues

- “...psychologists take reasonable steps to avoid harming their clients/patients.” (APA, 2002)
- Competency
- Informed consent
- Confidentiality

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Other issues and controversies

- direct to consumer marketing
- financial conflicts of interest,
- selective release, publication

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Conflict of Interest?

Campbell, et al. (2007). A National Survey of Physician-Industry Relationships. *New England Journal of Medicine*, 356,1742-1750.

Benefit	No. of Respondents (%) ^a
Drug samples	1255 (78)
Gifts	1391 (83)
Food or beverages in workplace	1366 (83)
Tickets to cultural or sporting events	122 (7)
Reimbursements	542 (35)
For admission to CME meetings (free or subsidized)	382 (24)
For meeting expenses (e.g., travel, food, lodging)	260 (15)
Payments	456 (28)
For consulting	282 (18)
For serving as a speaker or on a speakers' bureau	278 (14)
For serving on an advisory board	139 (9)
For enrolling patients in clinical trials	55 (3)
Any of the above relationships	1554 (94)

^a Percentages were weighted to adjust for the probability of selection within each specialty and for nonresponse.

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Conflicts of Interest?

- Unreported Big Pharma funding between 2000-2007 NY Times, (June 2008).
 - Joseph Biederman, MD - \$1.6 million
 - Timothy Wilens, MD - at least \$1.6 million
 - Thomas Spencer, MD - at least \$1 million
- Big Pharma funded researchers commonly are the most prominent and respected researchers
 - Also are journal editors and reviewers, serve on FDA Advisory groups and panels, shape practice, policy & research agendas
 - Psychiatry's "Civil War"
- Alternatives? What would happen without them?

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Selective release of findings

- Study findings are considered proprietary
- **Canadian Medical Association Journal (CMAJ) (March 2004)**
 - "An internal document ... GlaxoSmithKline (GSK) to withhold clinical trial findings (Study 329) in 1998 that indicated the antidepressant paroxetine ... had no beneficial effect in treating adolescents."
- subsequent law suit by New York Attorney General, Eliot Spitzer settled out of court
- Jureidini et al. (2008)-study 329 was negative for all 8 outcome measures and positive for harm.

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Selective publication of findings

- Turner, Matthews, Linardatos, Tell, & Rosenthal (2008)
- Findings:
 - Reviewed 74 FDA-registered studies
 - 38 studies viewed by FDA as positive, 37 were published;
 - 25 studies viewed by FDA as negative or questionable, 3 were published
 - Based on the published studies it appeared that more than 90% of the trials conducted were positive.
 - FDA analysis showed that 51% were positive
- "...failure to submit manuscripts on the part of authors and sponsors, from decisions by journal editors and reviewers not to publish, or both. (p.159)"

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PART 2: SAFETY & EFFICACY

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Basic psychopharmacology terminology and concepts

- Pharmacokinetics (PK)
- Pharmacodynamics (PD)
- Basic neural anatomy and physiology
- Putative mechanisms of action (MOA)

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Pharmaco...what?

- Pharmacokinetics
 - Study of the time course of a drug and its metabolites in the body after administration by any route.
 - How the body/brain affects the drug
- Pharmacodynamics
 - Study of the biochemical and physiologic effects of drugs and their mechanisms of action.
 - How the drug affects the body/brain

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Pharmacokinetics (ADME)

- Absorption
- Distribution
- Metabolism
- Excretion
 - There are ADME developmental differences
 - Knowledge of how these factors differ at different ages, as well as for gender, ethnicity, genetic make up, and other factors would, in theory, enable individualized drug treatment

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Pharmacodynamics

- The mechanisms by which the drug exerts its influence (largely unknown!)
- Isn't it just correcting "a chemical imbalance!"

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Forest Pharmaceuticals (2005) How Lexapro (escitalopram) works.
www.forest.com/english/bout_lexaprohow_works/asp. Retrieved October 25, 2005.

"...there is an imbalance of serotonin—too much serotonin is reabsorbed by the first nerve cell, so the next cell does not have enough; as in a conversation, one person might do all the talking and the other person does not get to comment, leading to a communication imbalance.

LEXAPRO blocks the serotonin from going back into the first nerve cell. This increases the amount of serotonin available for the next nerve cell, like a conversation moderator. The blocking action helps balance the supply of serotonin, and communication returns to normal."

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Putative Mechanisms of Action

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Figure 1

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Some neurotransmitters (NTs)

- Serotonin *
- Norepinephrine *
- Dopamine *
- GABA
- Acetylcholine
- Glutamate

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QUICK REFERENCE TO PSYCHOTROPIC MEDICATION®

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ANTIDEPRESSANTS

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Amitriptyline	Amitriptyline	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Imipramine	Imipramine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Nortriptyline	Nortriptyline	75-150 mg	15-20 hr	5-HT ₂	++	++	0
Desipramine	Desipramine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Protriptyline	Protriptyline	75-150 mg	10-15 hr	5-HT ₂	++	++	0
Trimipramine	Trimipramine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Doxepin	Doxepin	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Levomepromin	Levomepromin	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Phenelzine	Phenelzine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Tranylcypromine	Tranylcypromine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Maprotiline	Maprotiline	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Fluoxetine	Fluoxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Paroxetine	Paroxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Citalopram	Citalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Escitalopram	Escitalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Fluvoxamine	Fluvoxamine	100-300 mg	15-20 hr	5-HT ₂	++	++	0
Venlafaxine	Venlafaxine	75-225 mg	5-10 hr	5-HT ₂	++	++	0
Duloxetine	Duloxetine	60-120 mg	10-15 hr	5-HT ₂	++	++	0
Desvenlafaxine	Desvenlafaxine	50-100 mg	10-15 hr	5-HT ₂	++	++	0
Levomefepipron	Levomefepipron	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Phenelzine	Phenelzine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Tranylcypromine	Tranylcypromine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Maprotiline	Maprotiline	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Fluoxetine	Fluoxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Paroxetine	Paroxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Citalopram	Citalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Escitalopram	Escitalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Fluvoxamine	Fluvoxamine	100-300 mg	15-20 hr	5-HT ₂	++	++	0
Venlafaxine	Venlafaxine	75-225 mg	5-10 hr	5-HT ₂	++	++	0
Duloxetine	Duloxetine	60-120 mg	10-15 hr	5-HT ₂	++	++	0
Desvenlafaxine	Desvenlafaxine	50-100 mg	10-15 hr	5-HT ₂	++	++	0
Levomefepipron	Levomefepipron	150-300 mg	10-15 hr	5-HT ₂	++	++	0

MOOD STABILIZERS

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Lithium	Lithium	900-1800 mg	8-12 hr	5-HT ₂	++	++	0
Valproic acid	Valproic acid	750-1500 mg	10-15 hr	5-HT ₂	++	++	0
Carbamazepine	Carbamazepine	800-1600 mg	10-15 hr	5-HT ₂	++	++	0
Lamotrigine	Lamotrigine	200-400 mg	24-36 hr	5-HT ₂	++	++	0
Topiramate	Topiramate	600-1200 mg	10-15 hr	5-HT ₂	++	++	0
Zinc	Zinc	15-30 mg	10-15 hr	5-HT ₂	++	++	0
Magnesium	Magnesium	100-200 mg	10-15 hr	5-HT ₂	++	++	0
Selenium	Selenium	50-100 mcg	10-15 hr	5-HT ₂	++	++	0
Copper	Copper	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Iron	Iron	45-65 mg	10-15 hr	5-HT ₂	++	++	0
Zinc	Zinc	15-30 mg	10-15 hr	5-HT ₂	++	++	0
Magnesium	Magnesium	100-200 mg	10-15 hr	5-HT ₂	++	++	0
Selenium	Selenium	50-100 mcg	10-15 hr	5-HT ₂	++	++	0
Copper	Copper	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Iron	Iron	45-65 mg	10-15 hr	5-HT ₂	++	++	0

ANTICHOLINERGIC

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Atropine	Atropine	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Scopolamine	Scopolamine	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Benztropine	Benztropine	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Trihexyphenidyl	Trihexyphenidyl	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Procyclidine	Procyclidine	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Benztropine	Benztropine	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Trihexyphenidyl	Trihexyphenidyl	1-2 mg	10-15 hr	5-HT ₂	++	++	0
Procyclidine	Procyclidine	1-2 mg	10-15 hr	5-HT ₂	++	++	0

ANTISEROTONINERGIC

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Pargoline	Pargoline	100-200 mg	10-15 hr	5-HT ₂	++	++	0
Phenelzine	Phenelzine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Tranylcypromine	Tranylcypromine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Maprotiline	Maprotiline	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Fluoxetine	Fluoxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Paroxetine	Paroxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Citalopram	Citalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Escitalopram	Escitalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Fluvoxamine	Fluvoxamine	100-300 mg	15-20 hr	5-HT ₂	++	++	0
Venlafaxine	Venlafaxine	75-225 mg	5-10 hr	5-HT ₂	++	++	0
Duloxetine	Duloxetine	60-120 mg	10-15 hr	5-HT ₂	++	++	0
Desvenlafaxine	Desvenlafaxine	50-100 mg	10-15 hr	5-HT ₂	++	++	0
Levomefepipron	Levomefepipron	150-300 mg	10-15 hr	5-HT ₂	++	++	0

PSYCHO-STIMULANTS

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Methylphenidate	Methylphenidate	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Amphetamine	Amphetamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Dextroamphetamine	Dextroamphetamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Mephentermine	Mephentermine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Modafinil	Modafinil	100-400 mg	10-15 hr	5-HT ₂	++	++	0
Adrafinil	Adrafinil	100-400 mg	10-15 hr	5-HT ₂	++	++	0
Phenethylamine	Phenethylamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Propylphenylamine	Propylphenylamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Amphetamine	Amphetamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Dextroamphetamine	Dextroamphetamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Mephentermine	Mephentermine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Modafinil	Modafinil	100-400 mg	10-15 hr	5-HT ₂	++	++	0
Adrafinil	Adrafinil	100-400 mg	10-15 hr	5-HT ₂	++	++	0
Phenethylamine	Phenethylamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0
Propylphenylamine	Propylphenylamine	10-60 mg	10-15 hr	5-HT ₂	++	++	0

ANTISEROTONINERGIC

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Pargoline	Pargoline	100-200 mg	10-15 hr	5-HT ₂	++	++	0
Phenelzine	Phenelzine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Tranylcypromine	Tranylcypromine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
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Phenelzine	Phenelzine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Tranylcypromine	Tranylcypromine	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Maprotiline	Maprotiline	150-300 mg	10-15 hr	5-HT ₂	++	++	0
Fluoxetine	Fluoxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Paroxetine	Paroxetine	20-40 mg	15-20 hr	5-HT ₂	++	++	0
Citalopram	Citalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Escitalopram	Escitalopram	10-30 mg	35-40 hr	5-HT ₂	++	++	0
Fluvoxamine	Fluvoxamine	100-300 mg	15-20 hr	5-HT ₂	++	++	0
Venlafaxine	Venlafaxine	75-225 mg	5-10 hr	5-HT ₂	++	++	0
Duloxetine	Duloxetine	60-120 mg	10-15 hr	5-HT ₂	++	++	0
Desvenlafaxine	Desvenlafaxine	50-100 mg	10-15 hr	5-HT ₂	++	++	0
Levomefepipron	Levomefepipron	150-300 mg	10-15 hr	5-HT ₂	++	++	0

ANTISEROTONINERGIC

Brand	Generic	Daily Dose	Half-life	Receptor	ACM	SE	AE
Pargoline	Pargoline	100-200 mg	10-15 hr	5-HT ₂	++	++	0
Phenelzine	Phen						

So, is it “just a chemical imbalance?”

“...there is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no “real” monoamine deficit.”
(Stahl, *Essential Psychopharmacology* (2009).

“Some have argued that depression may be due to a deficiency of NE or 5-HT because the enhancement of noradrenergic or serotonergic neurotransmission improves the symptoms of depression.

However, this is akin to saying that because a rash on one’s arm improves with the use of a steroid cream, the rash must be due to a steroid deficiency”.

(Delgado & Moreno, 2000)

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Current thinking

- NT modification is necessary, but not sufficient for a Tx effect
- NT modification enables 2nd messenger action (postsynaptic internal cell membrane), also necessary but not sufficient
- That enables 3rd messenger action (postsynaptic cell nucleus) that affects genetic “switches” and transcription (necessary and sufficient)

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Safety and Efficacy

General issues :

“Primum Non Nocere” (First, Do No Harm), Hippocratic Oath, The Ethics Code of the American Psychological Association (APA)

“...psychologists take reasonable steps to avoid harming their clients/patients.”

Safety by class of drug

- FDA warnings/advisories
- Side effects

Efficacy by disorder for symptoms & fx outcomes

- Short-term
- Long-term

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General issues: Are psychiatric drugs safe?

- All drugs can be toxic
- What are the adverse events and/or side effects of these drugs:
 - For which children/disorders?
 - At what dosages and dosage regimens?
 - And are they transient or reversible?
 - When prescribed “off-label”
 - In combination with other drugs (polypharmacy)?
 - Within the specific cultural milieu?

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General issues: Are psychosocial treatments safe?

- Iatrogenic effects (PHTs)
- Cultural influences?

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Psychosocial Tx, on balance...

- meta-analyses consistently demonstrate the positive effects of psychotherapy compared to no treatment or placebo (Westen, Novotny, & Thompson-Brenner, 2004).
- Comparable to a variety of medical treatments (Barlow, 2004; Brown et al., 2008; Kubiszyn, Carlson & DeHay, 2005; Lipsey & Wilson, 2001; Weisz, Jensen & McLeod, 2005).
- “There are well over 500 ‘brands’ of psychotherapy, most of which have not been examined in controlled trials.” Eisner (2000)
- no formal equivalent of medicine’s (FDA) to conduct Phase I or Phase II trials, offer approvals or warning/advisories

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Potentially Harmful Treatments (PHTs) Lilienfeld (2007)

- “Some psychologists have assumed that ‘doing something is always better than doing nothing’ and that therapy is at worst innocuous” (p.62)
- “Although emerging data indicate that several psychological treatments may produce harm in significant numbers of individuals, psychologists until recently paid little attention to the problem of hazardous treatments” (p. 53).
- PHTs include critical incident stress debriefing, recovered memory techniques, grief counseling for individuals with normal bereavement reactions, and attachment therapies.

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ADHD drugs

Stimulants
Non-stimulants

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Stimulants: FDA Warnings & Advisories

(Kubiszyn T., in press. Pediatric Psychopharmacology. In: T. Kehle & M. Bray (Eds.) Oxford Handbook of School Psychology)

- 1999, pemoline (Cylert) possible liver damage and liver toxicity in the pediatric population
- 2/2005, sudden unexplained death (SUD) associated with the use of Adderall
- 2/2007, **all ADHD drugs** (stimulants and non-stimulants) an increased risk of significant cardiovascular events (e.g., SUD) and for the possible emergence of psychotic/manic symptoms

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Non-stimulants:

Atomoxetine (Strattera)-FDA warnings/advisories

- 12/04, potential liver damage in pediatric patients
- 9/05, increased risk for suicidality (suicidal ideation or action)
- 10/06, increased risk for cardiac (SUD) and psychiatric events
- 2/07, increased risk of significant cardiovascular events (e.g., SUD) and for the possible emergence of psychotic/manic symptoms

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SIDE EFFECTS: How side effect data currently are reported:

- List:
 - “Commonly reported side effects included sedation, irritability, gastrointestinal upset...”
- Summary:
 - “No serious adverse events were reported, although 17 of 63 subjects discontinued participation by the end of the fourth week.”
- Probabilistic data (e.g., FDA PI tables):
 - GI upset - drug = 10%, placebo = 2%
 - Headache - drug = 5%, placebo = 5%
 - Irritability - drug = 20%, placebo = 2%

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SE Tables: CAUTIONS & LIMITATIONS

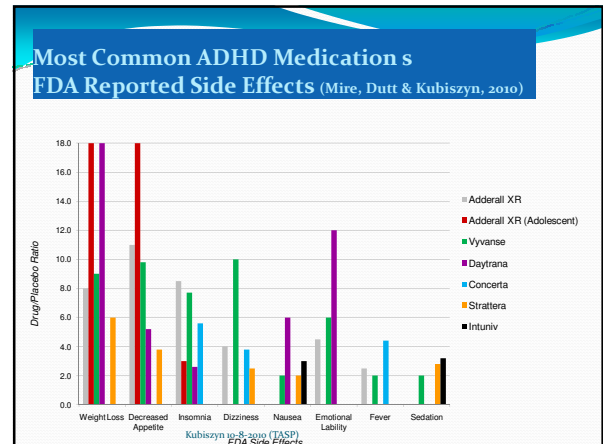
- The data set:
 - All side effect data were reported for monotherapy (no polypharmacy side effects were reported on the FDA/CDER website)
 - All reported drug-placebo ratios have been based on data publicly available on the FDA/CDER website
 - Most of these data are from short-term studies (some as short as 3-4 weeks)
- Side effects, like therapeutic effects, cannot be predicted for individual patients
- The data we report in these presentations should be considered suggestive, not definitive
- Close monitoring for any side effects in the pediatric population, not just those that occurred more often in the FDA studies, is strongly encouraged

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Most Commonly Occurring Side Effects Reported on FDA Website (Mire, Dutt & Kubiszyn, 2010)

	Weight Loss	Decreased Appetite	Insomnia	Dizziness	Nausea	Emotional Lability	Fever	Sedation
Adderall XR	X	X	X	X		X	X	
Adderall XR (Adolescent)	X	X	X					
Vyvanse	X	X	X	X	X	X	X	X
Daytrana	X	X	X		X	X		
Concerta			X	X			X	
Strattera	X	X		X	X			X
Intuniv					X			X

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Antidepressants (ADs)

Tricyclics (TCAs)
 Selective serotonin reuptake inhibitors (SSRIs)
 Serotonin-norepinephrine reuptake inhibitors (SNRIs)
 Monoamine oxidase inhibitors (MAOIs)
 Other

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- ### ADs: FDA Warnings/Advisories
- 1/02, nefazodone (Serzone) warning of potential liver abnormalities and liver failure
 - 10/03, possible increases in suicidality associated with SSRIs and other ADs (mirtazapine or Remeron, nefazodone, and venlafaxine or Effexor)
 - 10/04, black box warning for all ADs, increased risk of suicidality
 - 11/06, triptans (for migraine headaches) taken with either SSRIs or SNRIs could lead to a potentially life-threatening serotonin syndrome (all ages)
 - 2/07, young adults included in another warning about increased suicidality
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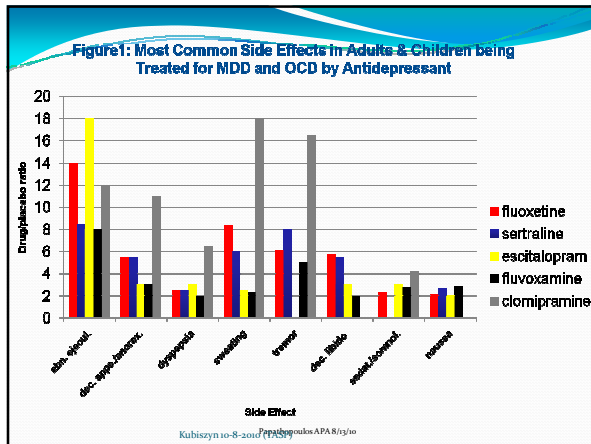
- ### The FDA data: IMPORTANT
- AD side effect data were either aggregated (adult and child together) or adult data alone
 - i.e., No side effect percentages exclusively for pediatric population
 - FDA PIs typically reported that SEs did NOT differ by age, or listed SEs that were more common for the pedi subjects
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FDA Reported Side Effects (Papatthopoulos, Gerondale & Kubiszyn, 2010)

Most Frequently Occurring Side Effects

	SIDE EFFECT							
	Abnormal ejaculation	Decreased appetite/anorexia	Dyspepsia	Sweating	Tremor	Libido decreased	Sedation/somnolence	Nausea
Fluoxetine	X	X	X	X	X	X	X	X
Sertraline	X	X	X	X	X	X	-	X
Escitalopram	X	X	X	X	-	X	X	X
Fluvoxamine	X	X	X	X	X	X	X	X
Clomipramine	X	X	X	X	X	-	X	-

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TCA AD side effects

- no longer recommended for any of the internalizing disorders (Birmaher and Brent, 2003; LaBellarte & Ginsburg, 2003)
 - Cardiotoxic effects include
 - QTc prolongation (a delay in normal heart rhythms that may lead to arrhythmia and sudden death)
 - Desipramine (Norpramin) has been associated with at least six sudden pediatric deaths & imipramine (Tofranil) with least three sudden deaths in the pediatric population (Green, 2007)
 - Syncope (loss of consciousness with interruption of awareness of oneself and one's surroundings)
 - Anticholinergic effects: dry mouth, urinary retention, constipation, nausea, blurred vision, memory impairment and confusion

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MAOI AD side effects

- dizziness, headache, orthostatic hypotension (dizziness and fainting when quickly standing after being seated), insomnia, sedation, fatigue, dry mouth, and GI disturbances
- Hypertensive crisis possible if ingested with foods containing tyramine (cheese, some types of beans, yeast derivatives, and alcohol)

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Antipsychotics

Typical - 1st generation
Atypical - 2nd generation

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Typical (1st gen.) APs – FDA warnings/advisories

- 7/00, thioridazine (Mellaril) dose-related association with QTc prolongation (associated with cardiac arrhythmias and possible sudden death)
- 9/07, haloperidol (Haldol), potentially serious cardiotoxic effects, including QTc prolongation
- 6/08, haloperidol, pimozide, and other typical APs - possibility of death in the elderly population when given to patients with dementia

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Atypical (2nd gen.) APs – FDA warnings/advisories

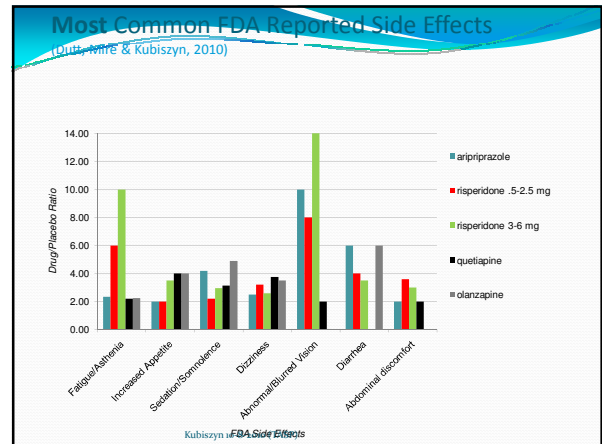
- Clozapine (Clozaril)
 - 1994, increased risk (about one to two percent of all patients) for agranulocytosis (a potentially fatal blood disorder) and seizures
 - 4/05, increased risk of myocarditis (an inflammation of the heart muscle), and other adverse cardiac and respiratory events
- All Atypical APs
 - 11/03, increased risk of hyperglycemia and diabetes mellitus associated with the use of atypical antipsychotics
 - 6/05, increased risk of death in elderly patients with dementia

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FDA Reported Most Common Side Effects: Atypical Antipsychotics (Dutt, Mire & Kubiszyn, 2010)

	Fatigue/Asthenia	Increased Appetite	Sedation/Somnolence	Dizziness	Abnormal/Blurred Vision	Diarrhea	Abdominal discomfort
aripiprazole (Abilify)	X	X	X	X	X	X	X
risperidone 5-2.5 mg (Risperidal)	X	X	X	X	X	X	X
risperidone 3-6 mg	X	X	X	X	X	X	X
Quetiapine (Seroquel)	X	X	X	X	X	-	X
Olanzapine (Zyprexa)	X	X	X	X	-	X	-

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Atypical (2nd gen.) APs = side effects

- Metabolic, endocrine, neurological effects
 - metabolic effects including significant weight gain, insulin resistance, and the development of type II diabetes (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, 2004).
 - clozapine and olanzapine - greatest risk
 - ziprasidone and aripiprazole may have the lowest risk (Allison et al., 2001; Julien et al., 2008).

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Metabolic effects: The SATIETY study (pediatric weight gain and metabolic changes) Correll et al., 2009

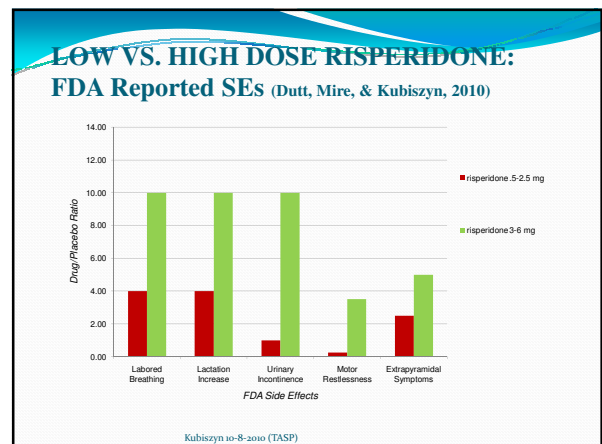
- Non-randomized, multiple Dx, 1st time AAP users, median = 10.8 weeks
- Weight increases of:
 - 8.5 kg with olanzapine (n = 45),
 - 6.1 kg with quetiapine (n = 36),
 - 5.3 kg with risperidone (n = 135), and
 - 4.4 kg with aripiprazole (n = 41) compared to
 - 0.2 kg in the untreated comparison group (n = 15).
- Metabolic changes:
 - Total cholesterol increase greatest for olanzapine & quetiapine
 - Triglycerides increase greatest for risperidone

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Atypical (2nd gen.) APs = side effects

- Endocrine side effects include prolactin elevation, (especially for risperidone) and related menstrual irregularities and amenorrhea, as well as gynecomastia (development of abnormally large breasts in males), sexual dysfunction and cardiovascular effects, including QTc prolongation which can lead to arrhythmias and fatalities.
- Neurological side effects include sedation & somnolence, seizures, and extrapyramidal symptoms at higher doses

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"Mood Stabilizers"

Anticonvulsants (ACVs)
Antipsychotics (APs)
Lithium (Li)

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Mood stabilizers (lithium & ACVs) – FDA warnings/advisories (1)

- 1980s, lithium - hepatic, pancreatic & teratogenic effects
- lamotrigine (Lamictal)
 - 3/97 - not indicated for use in children below 16 years of age, potentially life-threatening, severe rash (Stevens -- Johnson syndrome and toxic epidermal necrolysis)
 - 10/05 alert about multiorgan sensitivity, often preceded by fever and rash.

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Mood stabilizers (lithium & ACVs) – FDA warnings/advisories (2)

- 7/06, divalproex (Depakote) –
 - potentially fatal liver damage, especially in children under the age of two who are treated with multiple anticonvulsants, who have congenital metabolic disorders, who have mental retardation along with seizures, and in those who have an organic brain syndrome
 - possible cases of fatal hemorrhagic pancreatitis in both children and adults
- 12/07, carbamazepine (Tegretol) increased risk (about 10 times higher) of Stevens-Johnson syndrome and toxic epidermal necrolysis when used to treat individuals of Asian descent
- 1/08, all ACVs, doubling of the risk of suicidality (ideation and actions) for patients taking any one or more of 11 anticonvulsant/antiepileptic drugs

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Lithium side effects

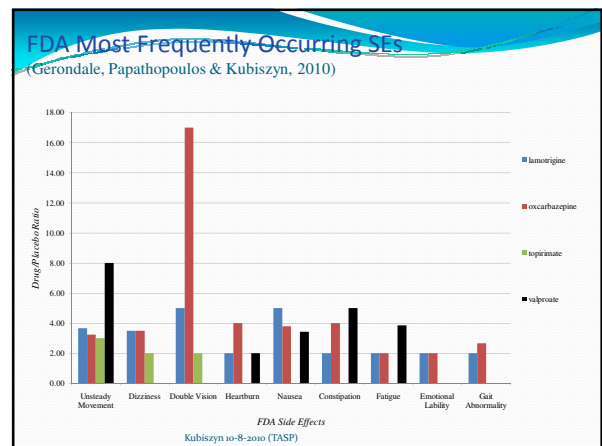
- Early emerging - tremor, polyurea (excreting larger than average amounts of urine), nausea and gastrointestinal complaints, weight gain, and headache
- Later emerging - these side effects as well as thyroid and renal (kidney) abnormalities, dermatologic abnormalities, fatigue, and leukocytosis (an abnormal increase in white blood cells) (Connor & Meltzer, 2006)

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FDA Most Frequently Occurring SEs (Gerondale, Papatopoulos & Kubiszyn, 2010)

	SIDE EFFECT									
	Unsteady Movement	Dizziness	Double Vision	Heartburn	Nausea	Constipation	Fatigue	Emotional Lability	Abnormal Gait	
lamotrigine	X	X	X	X	X	X	X	X	X	X
oxcarbazepine	X	X	X	X	X	X	X	X	X	X
topiramate	X	X	X							
valproate	X			X	X	X	X			

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FDA Reported ACV Idiosyncratic SEs

(Gerondale, Papatopoulos & Kubiszyn, 2010)

	Anorexia	Abnormal Thinking	Difficulty w/Memory	Increased Sweating	Urinary Tract Infection	Amnesia	Bronchitis	Difficulty W/Concentration	Amblyopia
lamotrigine					6				5
oxcarbazepine				6					
topiramate			10					5	
valproate	24	12				5	5		

- ### EFFICACY
- Symptoms vs. functional outcomes
 - Short vs. long term
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- ### What does "efficacy" really mean?
- Depends on whom you may ask
 - Clinicians, who consider data from:
 - Personal experience
 - drug reps,
 - colleagues,
 - newsletters,
 - journals,
 - FDA, other governmental agencies
 - Result: wide range of opinions
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- ### What does "efficacy" really mean (p.2)?
- Researchers, who consider data from:
 - Clinical trials
 - Open-label
 - Randomized controlled trial (RCT)
 - Random assignment
 - Placebo controlled
 - Double blind RCT
 - Result: considerable consensus
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- ### The placebo effect
- Administration of an inert agent (e.g., a sugar pill) that
 - Is designed to look like and taste like the real drug/treatment
 - The patient believes is the real drug/treatment, and
 - Is administered under normal clinical conditions and expectations
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- ### Drug Efficacy – FDA Pediatric Indications
- ADHD – many
 - ODD/CD – none
 - Tic disorders-two
 - OCD – four
 - Non-OCD Anxiety – none
 - Depressive Disorders-one
 - BPD – four
 - ASD - one
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ADHD: FDA Indications (Kubiszyn, in press)

Trade Name	Generic Name	Approved Age
Adderall	amphetamine	3 and older
Adderall XR	amphetamine (extended release)	6 and older
Concerta	methylphenidate (long acting)	6 and older
Dexedrine	dextroamphetamine	3 and older
Dexrostat	dextroamphetamine	3 and older
Metadate/Metadate ER	Methylphenidate (extended release)	6 and older
Ritalin/Ritalin SR	methylphenidate (sustained release)	6 and older
Daytrana	methylphenidate	6-12
Vyvanase	lisdexamphetamine	6-12
Non-Stimulant Medications		
Strattera	atomoxetine	6 and older
Tenex/Intuniv	guanfacine	6 and older

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Evidence-Based ADHD Treatments

- (1) Behavior modification
-175 studies
- (2) CNS stimulant medication
>300 studies
- (3) The combination of (1) and (2).
>25 studies

Moderate to large effect sizes across treatments
(Pelham & Fabiano, 2008; Greenhill & Ford, 2002; Hinshaw et al, 2002; Fabiano et al, in press)

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A recent reference for the drug-psychosocial Tx efficacy comparison

- Brown, R. T., Antonuccio, D. O., DuPaul, G. J., Fristad, M. E., King, C. E., Leslie, L. K. et al. (2008). *Childhood Mental Health Disorders: Evidence Base and Contextual Factors for Psychosocial, Psychopharmacological, and Combined Interventions*. Washington, DC: American Psychological Association.
- As well as more recent RCTs

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Comparisons by effect size & strength of evidence base: Criteria (Brown et al., 2008)

1) Effect Size (Cohen, 1988)		2) Evidence Base	
Strong	.81 +	Strong	Replicated RCT or large # single-subject studies
Moderate	.51 - .80	Moderate	RCT or replicated single-subject study
Small	.21 - .50	Small	Comparison Group only
Weak	.20 or less	Weak	No Control Group

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Brown et al. Criteria applied to ADHD (Short-term)

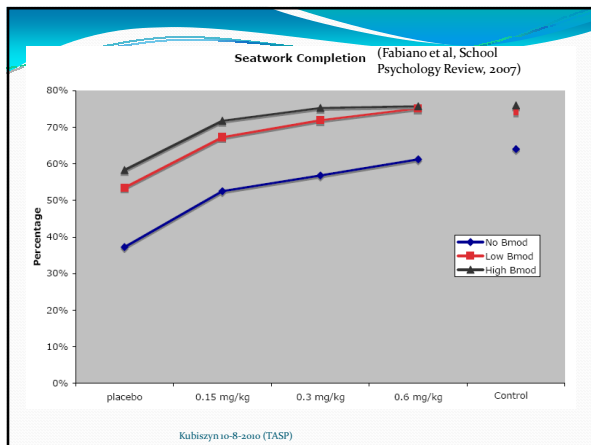
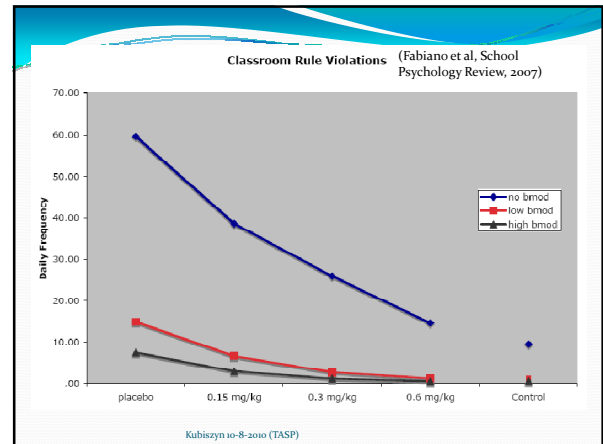
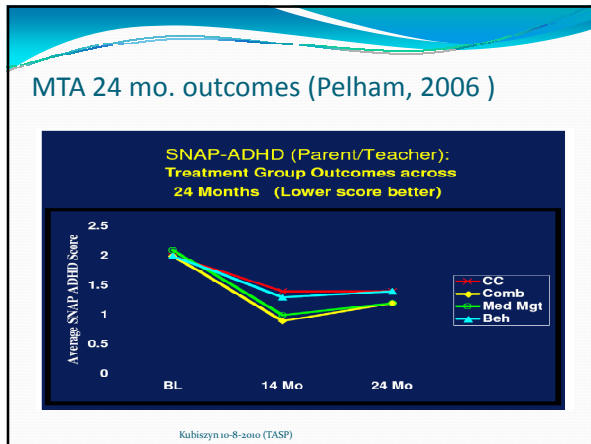
These criteria mapped to	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Psychosocial-Behavioral Combination	Moderate	Strong	Mod-small (weak-achiev.)	Strong
Stimulants	Moderate	Strong	Mod-weak	Strong
Tricyclics	Small	Strong	Small	Small
Bupropion	Small	Moderate	--	--
Clonidine	Small-Weak	Strong	Small	Strong
Atomoxetine	Small	Strong	Weak	Strong

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ADHD (Long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Psychosocial-Behavioral Combination	Small	Moderate	Small (weak-family)	Moderate
Stimulants	Moderate	Strong	Mod-small (weak-achiev.)	Strong
Tricyclics	Small	Small	Small	Small
Bupropion	--	--	--	--
Clonidine	--	--	--	--
Atomoxetine	Moderate	Strong	--	--
Guanfacine	Moderate	Strong	--	--

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MTA 8 year follow up (Molina et al., 2009)

- Findings**
 - Type or intensity of Tx for ADHD in childhood does not predict future functioning.
 - At 8 years youth with ADHD still had significantly more academic, social and other problems (run-ins with police, as well as more depression, and psychiatric hospitalizations) than peers w/o ADHD
 - youths who maintained gains for two more years after the end of the trial tended to be functioning the best at eight years.
 - A majority (61.5 percent) of those medicated at the end of the 14-month trial stopped taking medication by the eight-year follow-up
 - Children who were no longer taking medication at the eight-year follow-up were generally functioning as well as children who were still medicated
- Conclusion**
 - a child's initial clinical presentation, including ADHD symptom severity, behavior problems, social skills and family resources, may predict how they will function as teens more so than the type of treatment they received.

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Oppositional Defiant and Conduct Disorders (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Behavioral	Strong-Mod.	Strong	Strong-Mod	Mod-small
CBT & MST	Strong	Small	-	-
Combination	Mod-small	Moderate	Small-weak	Moderate
Lithium	Moderate	Moderate	--	--
Antipsychotics	Moderate	Moderate	--	--
Divalproex Sodium	Small	Moderate	--	--
Methylphenidate	Small	Moderate	--	--
Atomoxetine	Moderate	Moderate	--	--

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ODD & CD (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Behavioral	Weak	Moderate	--	--
CBT & MST	Strong	Small	-	-
Combination	Small	Moderate	Weak	Moderate
Lithium	--	--	--	--
Antipsychotics	--	--	--	--
Divalproex Sodium	--	--	--	--
Methylphenidate	--	--	--	--
Atomoxetine	--	--	--	--

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Tic Disorders-FDA Indications

- Haloperidol (Haldol) –ages 3 and up (for Tourette's syndrome)
- Pimozide (Orap) – ages 2 and up (severe Tourette's syndrome) who have not responded adequately to other APs.

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Tic Disorder – Medication (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Clonidine	Small-Weak	Moderate	Small-weak	Moderate
Guanfacine	Mod-small	Moderate	Small-weak	Moderate
Haloperidol	Moderate	Strong	--	--
Pimozide	Small	Strong	--	--
Risperidone	Moderate	Strong	--	--
Ziprasidone	Mod – Small	Moderate	--	--
Atomoxetine	Small	Moderate	--	--

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Tic Disorder-Drug (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Clonidine	--	--	--	--
Guanfacine	--	--	--	--
Haloperidol	--	--	--	--
Pimozide	--	--	--	--
Risperidone	--	--	--	--
Ziprasidone	--	--	--	--
Atomoxetine	--	--	--	--

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Tic Disorders – Psychosocial (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
HRT	Strong – Small	Moderate	Small	Moderate
ERP	Moderate	Small	--	--
Contingency Management	Small	Moderate	--	--
Combination	--	--	--	--

HRT: habit reversal training
ERP: exposure & response prevention

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Tic Disorders – Psychosocial (Long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
HRT	--	--	--	--
ERP	--	--	--	--
Contingency Management	--	--	--	--
Combination	--	--	--	--

HRT: habit reversal training
ERP: exposure & response prevention

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OCD – FDA indications

- SSRIs
 - fluvoxamine (Luvox) - 8 and older
 - sertraline (Zoloft) - 6 and older
 - fluoxetine (Prozac) - 7 and older
- TCA
 - clomipramine (Anafranil) - 10 and older.

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Obsessive-Compulsive Disorder (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Exposure-based CBT Individual	Strong	Strong	Small	Strong
Exposure-based CBT: Group	Strong	Moderate	Weak	Moderate
CBT + SSRI	Strong	Moderate	--	--
SSRIs and Clomipramine	Mod-Small	Strong	Moderate	Strong

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POTS OCD study (2004)

- Remission rates at conclusion of study:
 - 53.6% for combined treatment
 - 39.3 percent for CBT
 - 21.4 percent for sertraline
 - 3.6 percent for placebo
- Effect Size for CBT alone was larger than that of sertraline alone (.97 and .67, respectively)
- The authors conclude that "...children and adolescents with OCD should begin treatment with CBT alone or with CBT plus an SSRI"

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OCD (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Exposure-based CBT Individual	Moderate	Weak	--	--
Exposure-based CBT: Group	--	--	--	--
CBT + SSRI	--	--	--	--
SSRIs and Clomipramine	Moderate	Weak	--	--

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Non-OCD Anxiety disorders

- FDA indications: None

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Non-OCD Anxiety Disorders (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Individual CBT	Strong	Strong	Strong	Strong
Individual + Parent CBT	Strong	Strong	Strong	Strong
Combination	-	-	--	--
SSRIs	Strong-Small	Strong	Strong-Small	Strong

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Non-OCD Anxiety (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Individual CBT	Strong	Weak	Strong	Weak
Individual + Parent CBT	Strong	Weak	Strong	Weak
Combination	-	-	--	--
SSRIs	--	--	--	--

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CAMS (Walkup et al., 2008)

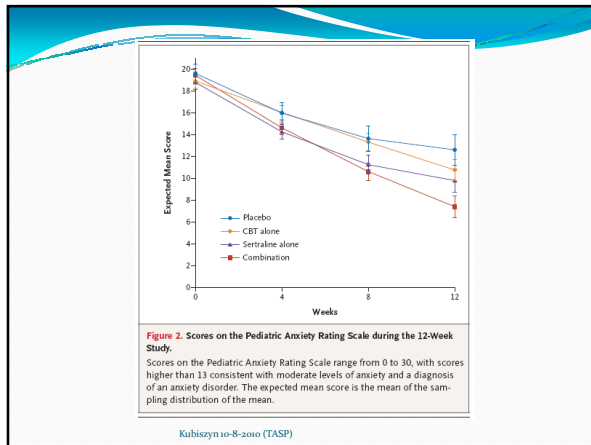
- Multi-site RCT (7 sites)
- N = 488, 7-17 year, w/GAD, SAD, or SoP
- Phase 1 -12-week trial CBT (14 sessions), sertraline (up to 200mg/day), and their combination w/PBO
- Phase 2 was a 6-month open extension for patients who had a response in phase 1.

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CAMS (cont.)

- Results:
 - CGI improvement
 - 80.7% for combination therapy (P<0.001),
 - 59.7% for CBT(P<0.001)
 - 54.9% for sertraline (P<0.001)
 - Combination therapy was superior to both monotherapies (P<0.001).
 - Pediatric Anxiety Rating Scale-similar outcomes
 - less insomnia, fatigue, sedation, and restlessness associated with CBT than with sertraline
 - No serious adverse events

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Major Depression – FDA Indications

- SSRI
 - fluoxetine (Prozac) - 7 to 17-year-olds
 - Escitalopram (Lexapro)- 12 and up
- MAOI
 - phenelzine (Nardil) -ages 16 years and older

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Depressive Disorders (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
IPT-A	Small	Strong	Small	Strong
CBT	Small	Strong	--	--
MST	Small – Weak	Moderate	--	--
Fluoxetine + CBT	Strong	Moderate	--	--
Fluoxetine	Small	Strong	Weak	Strong
Other SSRIs/TCAs	Weak	Strong	Weak	Strong

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Depressive Disorders (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
IPT-A	--	--	--	--
CBT	Small	Strong-Mod	--	--
MST	--	--	--	--
Fluoxetine + CBT	--	--	--	--
Fluoxetine	Small	Moderate	--	--
Other SSRIs/TCAs	--	--	--	--

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BPD – FDA Indications

- lithium - 12 and older
- Atypical Antipsychotics (2nd generation)
 - risperidone (Risperdal) – ages 10-17-mania
 - aripiprazole (Abilify) - ages 10 to 17-mania
 - Olanzapine (Zyprexa) – ages 13-17-mania (2009)
 - quetiapine (Seroquel) – ages 10-17-mania (2009)

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Bipolar Disorder – Psychosocial Treatment (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
CFF-CBT	Strong	Weak	Strong	Weak
FFT	Moderate	Weak	--	--
MFPG	--	--	Strong-small	Moderate
IFP	Moderate	Moderate	--	--

CFF-CBT: child & family focused CBT
 FFT: functional family Tx
 MFPG: multi-family psychoed. group
 IFP: individual family psychoed.

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BPD – Psychosocial Treatment (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
CFF-CBT	--	--	--	--
FFT	--	--	--	--
MFPG	--	--	--	--
IFP	--	--	--	--

CFF-CBT: child & family focused CBT
 FFT: functional family Tx
 MFPG: multi-family psychoed. group
 IFP: individual family psychoed.

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Bipolar Disorder – Medication monotherapy (Short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Lithium	Strong-Mod	Mod-weak	Strong	Weak
Risperidone	Strong	Mod-Weak	--	--
Aripiprazole	Strong	Mod-Weak	--	--
Divalproex sodium	Strong-Mod	Mod-weak	Strong	Weak
Topiramate	Strong-Mod	Mod-Weak	Strong	Weak
Quetiapine	Strong	Moderate	--	--
Carbamazepine	Strong	Moderate	--	--
Olanzapine	Strong-Mod	Mod erate	--	--

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BPD – Medication monotherapy (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Lithium	--	--	--	--
Risperidone	--	--	--	--
Aripiprazole	--	--	--	--
Divalproex sodium	--	--	--	--
Topiramate	--	--	--	--
Quetiapine	--	--	--	--
Carbamazepine	--	--	--	--
Olanzapine	--	--	--	--

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Bipolar Disorder – polypharmacy (short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Divalproex Sodium + risperidone	Strong	Moderate	Strong	Moderate
Lithium + Risperidone	Strong-Mod	Moderate	Strong	Moderate
Lithium + Divalproex Sodium	Strong	Weak	Strong	Weak
Divalproex Sodium + quetiapine	Moderate	Moderate	--	--

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BPD – polypharmacy (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Risperidone	--	--	--	--
Divalproex Sodium + risperidone	--	--	--	--
Lithium + Risperidone	--	--	--	--
Lithium + Divalproex Sodium	--	--	--	--
Divalproex Sodium + quetiapine	--	--	--	--

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ASD – FDA Indications

- risperidone (Risperdal) – ages 5-16
 - aggression, self injury, and temper tantrums

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Autism Spectrum Disorder (short-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Psychosocial Combination	Strong	Strong	Strong	Strong
Methylphenidate	Small	Strong	Weak	Weak
Risperidone	Strong	Strong	Strong	Strong
Clomipramine	Small	Moderate	--	--
Fluoxetine	Small	Moderate	--	--

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ASD (long-term)

	Primary Symptoms		Functional Outcomes	
	Effect Size	Evidence Base	Effect Size	Evidence Base
Psychosocial Combination	Small	Small	Small	Small
Methylphenidate	--	--	--	--
Risperidone	--	--	--	--
Clomipramine	--	--	--	--
Fluoxetine	--	--	--	--

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Schizophrenia – FDA Indications

- Aripiprazole (Ability) – ages 10-17
- Risperidone (Risperdal) – ages 13-17
- Olanzapine (Zyprexa) – ages 13-17 (2009)
- Quetiapine (Seroquel) – ages 13-17 (2009)
- Thioridazine (Mellaril) – ages 2 and up who have failed trials of psychosocial intervention and other APs
- Haloperidol (Haldol) – ages 3 and up for psychotic disorders and explosive aggression who have failed psychosocial interventions and other APs

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Resources: Where can we get accurate information?

- Preferred:
 - Government sponsored websites, brochures
 - e.g., FDA/CDER, NIH, NIMH
 - Peer-reviewed publications
 - E.g., JAMA, NEJM, JAACAP JCAP

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FDA web pages

Main page

- <http://www.fda.gov/default.htm>

Center for Drug Evaluation and Research

- <http://www.fda.gov/cder/index.html>

Alpha list of drugs with Healthcare Professional, Patient, and Consumer Information Sheets, Medication Guides, and Information Pages

- <http://www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm>

Medication Guides

- http://www.fda.gov/cder/Offices/ODS/medication_guides.htm

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FDA web pages (p.2)

MedWatch

- <http://www.fda.gov/medwatch/index.html>

MedWatch Online Voluntary Reporting Form (3500)

- <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>

Video Webcasts

- <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/viewbroadcasts.cfm>

Drugs@FDA (search by name)

- <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>

- **Bibliography? tkubiszyn@uh.edu**

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Where can we get accurate information (p.2)?

- Be careful with:
 - Industry-sponsored websites, brochures, ads
 - Industry sponsored talks
 - Non-government websites
 - Self-help books
 - Articles in popular magazines
 - Advocacy materials

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Where we've been today

- Hx, Issues, controversies
- Basic psychopharm terms and concepts
- Drug safety
- Drug & psychosocial Tx efficacy evidence
- Resources

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Please respond to these items (1=SA to 5=SD)

- 1) Psychotropic drugs should NOT be used with school-aged kids.
- 2) An FDA indication means a drug is safe and effective.
- 3) An FDA warning means a drug is unsafe.
- 4) Ped. psychotropic drugs are prescribed primarily by primary care physicians.
- 5) Most ped. psychotropic drugs for conditions other than ADHD are prescribed "off-label."

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10 items continued...

- 6) Behavioral treatment of ADHD enables lower doses of drugs to be used.
- 7) In Texas it's OK to recommend drug treatments to parents as long as you do NOT prohibit the child from attending school.
- 8) Ped. psychotropic drug treatments are more effective than psychosocial treatments.
- 9) Ped. psychosocial Tx are safer than psychotropic Tx.
- 10) Psychotropic drugs work by restoring a chemical imbalance in the brain.

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CONGRATULATIONS!

- We're Done!
- Questions? Contact me at
- tkubiszyn@uh.edu

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