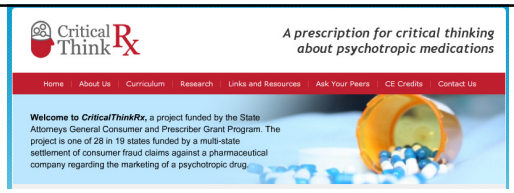

A Critical Curriculum on Psychotropic Medications

Critical Think Rx

A Critical Curriculum on Psychotropic Medications

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Critical Think Rx
www.CriticalThinkRx.org

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Module 5

Specific Drug Classes: Use, Efficacy, Safety

4

Part A

Overview: Psychotropic Drugs Used with Children and Adolescents

5

"Psychotropic" or "psychoactive" drugs

affect the central nervous system and alter feeling, thinking, and behaving

6

"Approved use" means…

FDA has reviewed limited data on safety and efficacy for one indication, usually in one population

A "label" for the drug is established to guide dosage and describe observed side effects

FDA Drug Approvals List

7

Fewer than 10% of psychotropic drugs are FDA-approved for any psychiatric use in children

8

Focus: Stimulants

9

Stimulants approved by FDA for pediatric use

Brand Name	Generic Name	Psychiatric Indication	Age group
Adderall, Adderall XR, Dexedrine, Dextrostat	amphetamine, dextroamphetamine	ADHD, narcolepsy	3 +
Concerta, Ritalin, Daytrana, Metadate Focalin, Focalin XR	methylphenidate, dexamethylphenidate	ADHD	6 +
Vyvanse	lisdextroamphetamine		
Strattera (*not considered a stimulant*)	atomoxetine		

10

Stimulants act quickly

Stimulants change behavior *within one hour* in 60-70% of children who take them

11

Long-term evidence of benefits doubtful

APA Report noted lack of data supporting long-term efficacy or safety

- Stimulants show minimal efficacy in general life domains of the child, including social and academic success

(APA Working Group on Psychoactive Medications for Children and Adolescents, 2006; MTA Cooperative Group, 2004)

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Short-term desirable effects of stimulants at usual doses

- ✓Increase alertness and wakefulness
- ✓Induce sense of well-being (euphoria)
- ✓Improve accuracy on brief physical and mental tasks

(Bezchlibnyk-Butler & Jeffries, 2005)

Effects misconstrued as therapeutic in children

- ✓Increased repetitive, persistent behavior
- ✓Decreased exploration and social behavior
- ✓Increased compliance

(Breggin, 1998)

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Undesirable *behavioral* effects of stimulants

- Nervousness, restlessness
- Insomnia
- Agitation
- Depression, "zombie" look
- Irritability, Aggression
- Psychological dependence
- Mania, Psychosis

(Bezchlibnyk-Butler & Jeffries, 2005)

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Undesirable *physical* effects of stimulants

- Increased blood pressure
- Dizziness, headaches
- Palpitations
- Stomach cramps, nausea
- Apetite/weight loss
- Stunted growth
- Cardiac arrest

(Bezchlibnyk-Butler & Jeffries, 2005)

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Stunted growth

Decreases in growth averaging ¾" and 6 lbs. without evidence of rebound 3 years after stopping treatment

(Swanson et al., 2007)

17

Emergency room visits

2,500 children visited ERs in 2004 after taking stimulants for ADHD, most due to accidental overdoses

- 1 in 4 children had heart or blood pressure symptoms including palpitations, chest pain or fainting

CDC

(Waters, 2007)

18

2006: FDA warning on stimulants

- ✓increased risk of sudden death in patients with heart problems
- ✓increased aggression, mania and/or psychotic symptoms (including hallucinations)

The New York Times

August 22, 2006

F.D.A. Strengthens Warnings on Stimulants

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Definite risk of tolerance and dependence

Stimulants prescribed to children are Drug Enforcement Administration (DEA) "Schedule II Drugs," indicating a high risk of tolerance and dependence

RITALIN LA® is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep RITALIN LA® in a safe place to prevent misuse and abuse. Selling or giving away RITALIN LA® may harm others, and is against the law.

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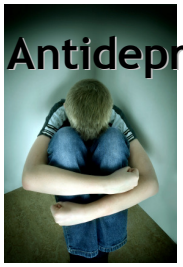
Focus: Antidepressants



21

FDA-approved antidepressants for pediatric use

Brand Name	Generic Name	Psychiatric Indication	Age group
Sinequan	doxepin	OCD	12+
Anafranil	clomipramine		10+
Luvox	fluvoxamine		8 +
Zoloft	sertraline		6 +
Tofranil	imipramine		
Prozac	fluoxetine	Depression, OCD	7 +

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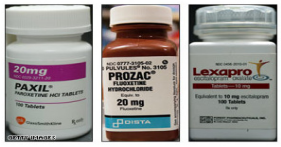
CDC: Antidepressants most prescribed drugs in U.S.



Antidepressants such as Paxil, Prozac and Lexapro are among America's most-prescribed drugs.

CNN.com /health 2007

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But are they effective?

Meta-analyses of drug vs. placebo studies show 75-82% of the response was duplicated by placebo

- 57% of studies submitted to FDA failed to show a difference between drug and placebo

(Moncrieff et al., 2004; Kirsch et al., 2002; Kirsch & Sapirstein, 1998)

24

Unimpressive evidence from FDA's complete adult database

"[I]n 189 trials of 53,048 adult subjects with psychiatric disorders … Approximately 50% of subjects who received active drug and 40% of subjects who received placebo were designated as responders."

(Stone & Jones, 2006)

The entire scientific case for antidepressants rests on this 10% difference—which may result from biases in the conduct of clinical trials

25

FDA analysis of pediatric trials concurs

Only 3 of 15 published and unpublished randomized controlled trials show SSRIs as more effective than placebo in depressed children

None of the studies found drugs better on client- or parent- rated measures

(Laughren, 2004)

26

No evidence that older antidepressants (tricyclics or MAO inhibitors) have any efficacy with depressed youths

(Somers-Flanagan & Somers-Flanagan, 1996)

27

Short-term desirable effects at usual doses

- ✓Increased physical activity
- ✓Elevated mood
- ✓Decreased expressions of distress such as crying, hopelessness
- ✓Improved sleep and appetite

(Bezchlibnyk-Butler & Jeffries, 2005)

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Undesirable *behavioral* effects of antidepressants

- Anxiety, nervousness
- Agitation, irritability
- Mood swings, mania
- Aggressiveness
- Thoughts of suicide
- Attempted or actual suicide

(Antonuccio et al., 1999; Preda et al., 2001; Healy, 2003)

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Undesirable *physical* effects of antidepressants

- Gastrointestinal distress (nausea, vomiting, stomach pain, constipation, diarrhea)
- Sexual problems (loss of libido, anorgasmia, erectile dysfunction)
- Sleep disruption (insomnia, hypersomnia)
- Urinary retention
- Blurred vision
- Weight gain
- Headaches, dizziness

(Antonuccio et al., 1999; Preda et al., 2001; Healy, 2003)

30

Six clusters of withdrawal effects likely upon abrupt discontinuation of SSRI antidepressants

1. Neurosensory (vertigo, tingling & burning)
2. Neuromotor (tremor, spasms, visual changes)
3. Gastrointestinal (nausea, vomiting, diarrhea, weight loss)
4. Neuropsychiatric (anxiety, depression, crying spells, irritability, suicidal thinking)
5. Vasomotor (heavy sweating, flushing)
6. Other (insomnia, vivid dreaming, fatigue)

(Schatzberg et al., 2006)

31

Antidepressants double risk of suicidality

U.S. Food and Drug Administration

2005: FDA issues "black box" warning of "Suicidality in Children and Adolescents":

"Antidepressants increase the risk of suicidal thinking and behavior (suicidality)"

- *(22 RCTs testing 9 antidepressants: **2.3%** rate of serious suicidal events among drug-treated children, vs. **1.2%** among placebo treated—no completed suicides)*

32

"Activation" syndrome: A more common risk

FDA also warns of ***increased agitation, irritability, aggression, worsening anxiety, severe restlessness, and other unusual behaviors*** in youth treated with antidepressants

(Breggin, 2006)

33

Concern over "prescription cascade"

Continued exposure to the drug can lead to effects misinterpreted as psychiatric symptoms (such as mania), leading to increases in dosage or additional drugs—when reducing or stopping the drug would relieve the patient's discomfort

(Breggin, 2006)

34

Focus: Anticonvulsant Drugs

35

Anticonvulsants on U.S. market (antiepileptics, antiseizure drugs)

Brand Name	Generic Name	Yr of intro
Tegretol, Equetro	carbamazepine	1968, 2004
Neurontin	gabapentin	1993
Lamictal	lamotrigine	1994
Depakene, Depakote	valproate	1995
Topamax	topiramate	1997
Trileptal	oxcarbazepine	2000

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Anticonvulsants FDA-approved for pediatric seizure disorders

Brand Name	Generic Name	Approved Indications	Age
Tegretol, Equetro	carbamazepine	NO PSYCHIATRIC INDICATIONS	Any
Gabitril	iagabine		12 +
Depakote Depakene	divalproex sodium, valproate		10 +
Topamax	topiramate		
Neurontin	gabapentin		3 +
Lamictal	lamotrigine		2 +
Trileptal	oxcarbazepine		

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Anticonvulsants widely promoted as "mood stabilizers"

Use started in 1980s-1990s due to dissatisfaction with lithium and antipsychotics in treatment of Bipolar Disorder

Use spread rapidly with the promotion of "mood stabilizer" expression and of Bipolar Disorder diagnosis in children

(Healy, 2006)

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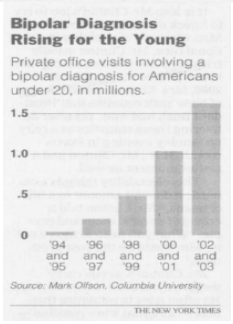
The New York Times

Bipolar Illness Soars as a Diagnosis for the Young

40-fold increase in less than a decade



(Moreno et al., 2007)

40

Polypharmacy without psychotherapy

More than 90% of children diagnosed with Bipolar Disorder received more than 1 psychoactive drug

Less than 40% received psychotherapy

(Moreno et al., 2007)

41

Scant empirical support

No studies confirm the efficacy and safety of anticonvulsants to treat Bipolar Disorder in children and adolescents

*"Despite the frequent use of antiepileptic drugs in the treatment of **juvenile bipolar disorder**, migraine, and neuropathic pain, the data are insufficient to make recommendations regarding the efficacy of antiepileptics in these conditions in children and adolescents."* *(Golden et al., 2006)*

(Kowatch et al., 2000, 2005; National Institute of Mental Health, 2000; Ryan, Bhatara & Perel, 1999)

42

Most trials are open, small, and show limited response in youth

Half of all participants in an open trial of lithium, divalproex, or carbamezepine did not respond to treatment

- 58% received *at least one* mood stabilizer *plus* a stimulant, an atypical antipsychotic, or an antidepressant

(Lopez-Larson & Frazier, 2006)

43

Desired behavioral effects of anticonvulsants

✓Reduce aggression and impulsivity

✓Calm restlessness and excitability

(Bezchlibnyk-Butler & Jeffries, 2005)

44

FDA U.S. Food and Drug Administration U.S. Department of Health and Human Services

2008: FDA warns anticonvulsants *double risk* of suicidal behavior or ideation

Risk is highest in treatment of epilepsy—which rules out psychiatric status as confounding variable

45

Undesired *behavioral* effects of anticonvulsants

- Depression, sedation
- Hostility and irritability
- Anxiety, nervousness
- Hyperactivity
- Abnormal thinking
- Confusion and amnesia
- Slurred speech
- Sedation, sleepiness

(Bezchlibnyk-Butler & Jeffries, 2005)

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Undesired *physical* effects of anticonvulsants

- Nausea and dizziness
- Vomiting and abdominal pain
- Headaches and tremors
- Fatal skin rashes
- Hypothyroid
- Blood disorders
- Pancreatitis, liver disease
- Birth defects and menstrual irregularities
- Withdrawal seizures

(Bezchlibnyk-Butler & Jeffries, 2005; Gonzalez-Heydrich et al., 2003)

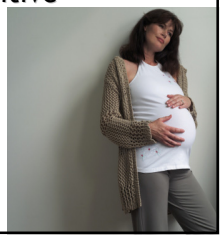
47

Birth defects of concern given new patient profiles

Anticonvulsants cross placenta and increase the risk of fetal malformations and cognitive impairments in children exposed in utero

- *Highest rates for valproate and carbamazepine*

(Adab et al., 2006)



FDA black-box warnings

Depakote	Liver toxicity (particularly for under 2 yrs of age); birth defects; pancreatitis
Tegretol	Aplastic anemia and agranulycytosis (severe reduction in white blood cells)
Lamictal	Serious rash requiring hospitalization; Stevens-Johnson Syndrome for under 16 yrs of age (fatal sores on mucuous membranes of mouth, nose, eyes and genitals)
All anticonvulsants	Suicidal ideation and behavior

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50

"Atypical" (newer, 2nd generation) antipsychotics on U.S. market

Brand Name	Generic Name	Yr of intro
Clozaril	clozapine	1989
Risperdal	risperidone	1994
Zyprexa	olanzapine	1996
Seroquel	quetiapine	1997
Geodon	ziprasidone	2001
Abilify	aripriprazole	2002
Invega	paliperidone	2007

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FDA-approved psychiatric indications of atypicals

Risperdal	Autism, bipolar mania, schizophrenia	5 +
Abilify	Schizophrenia	10+
Clozaril	Treatment resistant schizophrenia	Adults only
Zyprexa	Bipolar mania, schizophrenia	
Seroquel		
Geodon		
Symbyax		
Invega		

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FDA-approved psychiatric indications of typicals for children

Brand Name	Generic Name	Psychiatric Indication	Age
Orap	pimozide	Tourette's Disorder (for Haldol non-responders)	12 +
Haldol	haloperidol	Schizophrenia, Tourette's Disorder	3 +
Mellaril	thioridazine	Schizophrenia	2 +

Typicals make up less than 5% of FL Medicaid prescriptions of antipsychotics

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"Typical" & "Atypical" antipsychotics

Since 1950s, antipsychotics were used to treat psychoses, despite high toxicity and limited effectiveness

Newer, expensive "atypical" antipsychotics were heavily promoted in the 1990s as safer and more effective

54

Yet, newer no better than older…

The NEW ENGLAND JOURNAL of MEDICINE

2005: largest-ever schizophrenia treatment study finds atypicals neither more effective *nor* better tolerated than older drug

- 75% of patients quit either drugs within 18 months due to inefficacy or intolerable side effects

(Lieberman et al., 2005)

55

Non-psychotic diagnoses in children treated with atypicals

Diagnosis	% of Florida Medicaid children on antipsychotics (2006)
ADHD / Conduct Disorder	48
Nonpsychiatric, Anxiety, Other Psychiatric	27
Bipolar / Depression	13
Schizophrenia / Psychosis	8
Austism / Mental Retardation	4

St. Petersburg Times (2007)

56

"Aggression" said to account for most of the antipsychotic prescribing in children and adolescents

(Patel et al., 2005)

57

But do antipsychotics effectively control aggression?

The latest randomized-controlled trial found ***placebo more effective*** than either a typical (haloperidol) or atypical (risperidone) antipsychotic to reduce aggression in patients with intellectual disability

Trial had no drug company sponsorship

(Tyrer et al., 2008)

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"Antipsychotic drugs should no longer be regarded as acceptable routine treatment for aggressive behavior in people with intellectual disability."

(Tyrer et al., 2008)

59

Few pediatric clinical trials of atypicals for *any* indication

As of 2006, only a few studies of direct AAP comparisons with placebo

Most studies are short-term (3-6 weeks) and results favor the funder's drugs

(McDonagh et al., 2006)

60

"There are no studies that have shown (atypicals) are safe, or for that matter, that they are effective for children…The bottom line is that the use of psychiatric medications far exceeds the evidence of safety and effectiveness."

Ronald Brown, Chair,
2006 American Psychological Association
Task Force on Psychotropic Drug Use in Children

St Petersburg Times (2007)

61

Dopamine-blocking action of all antipsychotics explains

- ✓indifference, sedation, drowsiness, apathy
- ✓reduced spontaneity and affect
- ✓reduced ability to monitor one's state
- ✓increased abnormal movements
- ✓cognitive and motor impairments
- ✓confusion and memory problems
- ✓depression, mood swings, agitation

(Bezchlibnyk-Butler & Jeffries, 2005)

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Desirable effects of antipsychotics at usual doses

- ✓suppress psychotic symptoms (delusions, hallucinations, agitation)
- ✓suppress manic symptoms (euphoria, expansiveness, irritability)

(Bezchlibnyk-Butler & Jeffries, 2005)

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Effects misconstrued as therapeutic

- ✓increased indifference
- ✓reduced spontaneity and affect
- ✓reduced ability to monitor one's state
- ✓increased compliance with social norms

(Bezchlibnyk-Butler & Jeffries, 2005)

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Undesirable *behavioral* effects of antipsychotics

- Cognitive and motor impairments
- Sedation, drowsiness
- Confusion and memory problems
- Anxiety
- Depression, mood swings
- Abnormal thinking
- Hostility, aggression

(Bezchlibnyk-Butler & Jeffries, 2005)

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Undesirable *physical* effects of antipsychotics

- Weight gain, high blood sugar
- Abnormal movements (all body parts)
- Diabetes
- Cardiac problems
- Liver problems, jaundice
- Neuroleptic malignant syndrome
- Death

(Bezchlibnyk-Butler & Jeffries, 2005; Lindenmayer et al., 2003; Meyer, 2001)

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Hormonal dysfunctions

Elevated prolactin levels cause:

- ✓sexual and menstrual disturbances
- ✓infertility
- ✓decreased bone density

(Bezchlibnyk-Butler & Jeffries, 2005; Correll & Carlson, 2006; Patel et al., 2005)

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Extrapyramidal symptoms (abnormal movements)

Akathisia: inner distress, rocking, pacing, agitation

Dystonia: sudden, bizarre muscle spasms

Dyskinesia: rhythmic movements of face, mouth and tongue, sometimes of hands and feet

Parkinsonism: rigid muscles, loss of facial expression, unsteady gait, drooling

(Campbell, Rapaport & Simpson, 1999)

68

Tardive dyskinesia risk highest for typical antipsychotics

Long-lasting abnormal movements affect 12% to 35% of children who receive typical antipsychotics for more than 3 months

(Campbell, Rapaport & Simpson, 1999)

69

Weight gain and diabetes

50% of patients on antipsychotics gain 20% of their weight (primarily as fat)

Weight gain linked to "metabolic syndrome"

3 Schizophrenia Drugs May Raise Diabetes Risk, Study Says

By ERICA GOODE
Published: August 25, 2003

The New York Times

(Bezchlibnyk-Butler & Jeffries, 2005; Correll & Carlson, 2006; Patel et al., 2005)

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Neuroleptic malignant syndrome

Can occur with any antipsychotic agent, at any dose, at any time

Symptoms: extreme muscular rigidity, high fever, & altered consciousness

1-2% rate per year

Fatal if untreated

(Bezchlibnyk-Butler & Jeffries, 2005; Silva et al., 1999)

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3 atypicals suspected in nearly 4,500 deaths reported to FDA, 1998-2005

Clozaril: 3,277 deaths
Risperdal: 1,093 deaths
Zyprexa: 1,005 deaths

(Moore, Cohen & Furberg, 2007)

72

FDA "black-box" warnings

All atypicals	Increased mortality in frail elderly
Clozaril	Serious risk of agranulocytosis (severe drop in white blood cells), seizures, myocarditis, and other cardiovascular and respiratory effects
Seroquel	Risk of suicidality in children and adolescents

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"For many adults, and a small number of children, these agents can be an important component of treatment. However, it's so rare to find an example where evidence-based alternatives were exhausted prior to starting an atypical antipsychotic in a child that I have not found one yet in three years of searching."

Mark E. Helm, MD, MBA
Medical Director, Evidence-Based Prescription Drug Program
University of Arkansas Medical Sciences
College of Pharmacy, 2007

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Part B

Lawsuits against drug makers shed light on illegal promotion and serious risks

The New York Times
December 18, 2006

Drug Files Show Maker Promoted Unapproved Use

By ALEX BERENSON

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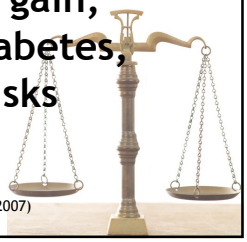
States sue drug makers for illegal marketing of unapproved uses

to recover money states paid to purchase atypical antipsychotics and the costs of medical care for the people injured by these drugs

(Pringle, 2007; Kesselheim & Avorn, 2007)

Patients sue, charging that drug makers did not adequately warn about severe weight gain, pancreatitis, diabetes, and other risks



(Pringle, 2007; Kesselheim & Avorn, 2007)

The New York Times

January 5, 2007

Lilly Settles With 18,000 Over Zyprexa

By ALEX BERENSON

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Zyprexa lawsuits

2007: Several states sue Eli Lilly for downplaying or hiding data linking use of the drug to weight gain and hyperglycemia

- *Most of those states' Medicaid spending on antipsychotics is for Zyprexa*

79

2007: Zyprexa settlements top $1.2 billion, *so far*

Eli Lilly has paid more than **$1.2 billion** to settle 30,000+ Zyprexa lawsuits

- The settlements required data on rates of adverse effects be kept *secret*

(Berenson, 2008)

80

2008: Feds, Eli Lilly negotiate $1 billion Zyprexa fine

If a deal is reached, it would be the largest fine ever paid by a drug company for breaking the federal laws governing how drugmakers can promote their medicines

The New York Times
Thursday, February 7, 2008

Lilly Considers $1 Billion Fine To Settle Case

81

Department of Justice

FOR IMMEDIATE RELEASE
FRIDAY, SEPTEMBER 28, 2007
WWW.USDOJ.GOV

2007: Bristol-Myers Squibb pays $515 million over illegal marketing and pricing of Abilify, Serzone, other drugs

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Litigation has

- ☑ exposed shady practices of pharmaceutical manufacturers
- ☑ uncovered previously hidden data about adverse events
- ☑ helped doctors reassess risks and benefits of some drugs and think critically about the available "evidence"

(Kesselheim & Avorn, 2007)

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Part C

Conclusions and Recommendations

84

Evidence "poor" for the use of psychotropics in children

- *Little or no evidence of efficacy and safety* of long-term use of these drugs in children
- *Clear evidence of harm* and risk of serious adverse events, including death
- *Risk-benefit ratio especially poor* for antidepressants, anticonvulsants, and antipsychotics

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Need to rethink risk-benefit ratio

Risks for adverse events, including death, increase with the number of concomitant drugs administered

Risks for adverse events are higher in children, who are receiving adjusted adult dosages of drugs rarely studied in children

(Brown & Sammons, 2002; Riddle, Kastelic & Frosch, 2001; Vitiello, 2001) 86

Side effects leading to multiple medications?

After initial medication, side effects may be viewed as mental disorders and drugged, in a "prescribing cascade" of polypharmacy that keeps children at risk with no sign of behavioral improvement

87

Available evidence does not justify use of psychotropic drugs as **first-line** treatments for children and adolescents

Reassess all cases?

Given known risks and dearth of valid studies showing benefits, cases of children receiving psychiatric medications should be reassessed

Children are involuntary patients. To support continuing psychotropic drug treatment, ***rock-solid*** rationale should be provided in every single case

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A Critical Curriculum on Psychotropic Medications

Module 5

The End

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