Children and Psychotropic Drugs: How Good Is The Evidence?

Steve Balt, MD, MS
Private Practice, San Rafael and Walnut Creek, CA
Editor-in-Chief, *The Carlat Psychiatry Report*
Supervising psychiatrist, John Muir Medical Center

Disclosure

Dr. Balt DOES have an interest in selling a technology, program, product and/or service to CME/CE professionals:

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The headlines

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For 'the

U.S. NEWS | August 11, 2013, 10:39 p.m. ET

U.S. Probes Use of Antipsychotic Drugs on Children

Federal health officials are reviewing antipsychotic drug use on children in the Medicaid system

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By LUCETTE LAGNADO

Federal health officials have launched a probe into the use of antipsychotic drugs on children in the Medicaid system, amid concern that the medications are being prescribed too often to treat behavioral problems in the very young.

The inspector general's office at Department of Health and Human Services says it

The headlines

The headlines

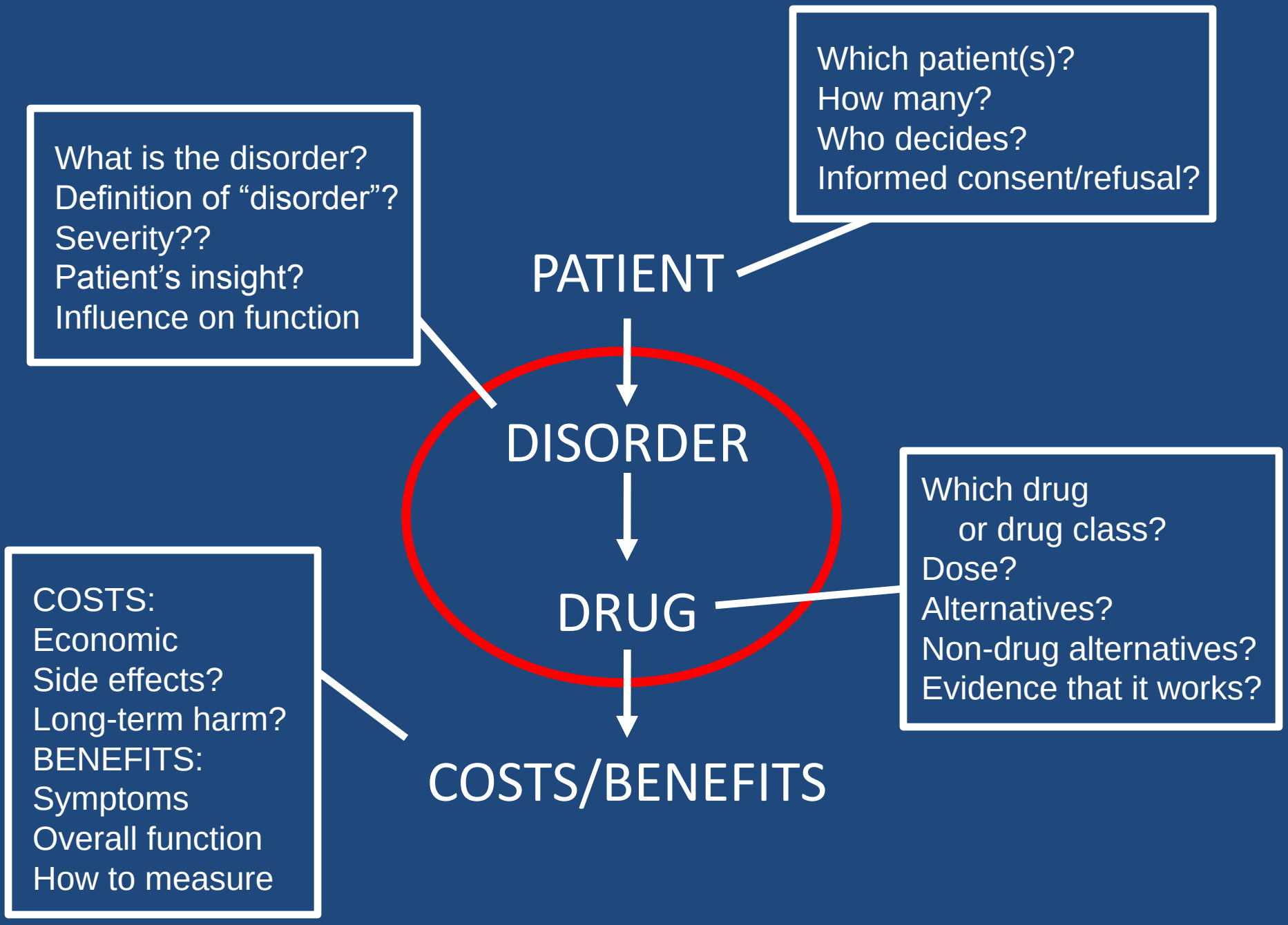
Is this acceptable?

A PATIENT…

… with a DISORDER…

… receives a TREATMENT…

… which has certain COSTS and BENEFITS


Which patient(s)?
How many?
Who decides?
Informed consent/refusal?
What is the disorder?
Definition of “disorder”?
Severity??
Patient’s insight?
Influence on function
PATIENT
DISORDER
DRUG
COSTS/BENEFITS
Which drug
or drug class?
Dose?
Alternatives?
Non-drug alternatives?
Evidence that it works?
COSTS:
Economic
Side effects?
Long-term harm?
BENEFITS:
Symptoms
Overall function
How to measure

What is a psychiatric disorder?

and

How do we know what works to treat it? (and who tells us?)

DSM

DSM-IV Definition of Mental Disorder

Features

A	a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual
B	is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning) or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom
C	must not be merely an expectable and culturally sanctioned response to a particular event, for example, the death of a loved one
D	a manifestation of a behavioral, psychological, or biological dysfunction in the individual
E	neither deviant behavior (e.g., political, religious, or sexual) nor conflicts that are primarily between the individual and society are mental disorders unless the deviance or conflict is a symptom of a dysfunction in the individual

Other Considerations

F	no definition adequately specifies precise boundaries for the concept of "mental disorder"
G	the concept of mental disorder (like many other concepts in medicine and science) lacks a consistent operational definition that covers all situations

"… a manifestation of a behavioral, psychological, or biological dysfunction…"

"… conflicts that are primarily between the individual and society [are not] mental disorders unless the conflict is a symptom of a dysfunction in the individual."

"A disease is what the medical profession recognizes as such." -- Edward Jellinek, 1960

"Pretty soon everyone's going to have a mental disorder, or two, or three, and it's time we reconsider how we want to define them." -- Allen Frances, 2013

Disease Model

"Disorder": The Disease Model of Psychiatry

- A known or presumptive biological basis
- Markers often present upon physical exam, labs, imaging, etc

- Targeted to reverse/correct the pathophysophysiology of the disease

- improvement in function
- stabilization
- reversal of pathology

But what's the biological basis?

Do we <u>create</u> more pathophysiology than we treat?

Other interpretations/definitions

Harmful dysfunction (Wakefield, 1992) (vs *harmful function*?)

- "A mental disorder is a mental condition that (a) causes significant distress or disability, (b) is not merely an expectable response to a particular event, and (c) is a manifestation of a mental dysfunction."

"Ecological" or **"systems"** or **"interactionist"** approach

Values play an ineliminable role in the diagnosis of childhood disorders

- e.g., ADHD may have conferred an adaptive advantage ("hunter in a farmer's world")
- e.g., "reading disorder" or "mathematics disorder" (subsumed under "specific learning disorder" in *DSM-5*)
- e.g., conduct disorder may be construed as a *moral* problem, not a medical one

“Our society has decided that pain, suffering, murder, aggression are bad. Getting along with others, respecting the law are good. And these are the same values that medicine has to pursue. In some ways it’s irrelevant if disorders are classified as illness or vice.”

-- Benedetto Vitiello, NIMH

Background: California, like most states, has a "mental health parity" law.

The law's mandates: California's law generally requires health plans to eliminate mental health-specific benefit limits and cost-sharing requirements, such as higher co-payments and deductibles and limits on numbers of covered benefits which have traditionally made mental health benefits less comprehensive than other health benefits. Additionally, the law requires that every insurer that provides hospital, medical or surgical coverage shall provide coverage for the diagnosis and medically necessary treatment of those with covered conditions, including:

- Outpatient services
- Inpatient hospital services
- Partial hospital services
- Prescription drugs, if the health plan covers prescription drugs

Covered Conditions:

- Schizophrenia
- Schizoaffective disorder
- Major depressive disorders
- Obsessive-compulsive disorder
- Bipolar disorder

- Anorexia nervosa and bulimia nervosa
- Panic disorder
- Pervasive developmental disorder
- Certain serious emotional disturbances of a child

While this list does not include all mental health disorders, it does include almost all mental illnesses which would require numerous physician or therapy visits and/or hospital days.

I would like the above-mentioned claims (copies attached) reviewed again.

I have attached my first letter requesting review dated N
letter from Dr. _____, who is treating _____ at ____

…SED is not a diagnosis…

It appears as though XXX. (who wrote the attached appeal denial) and XXX (whom I spoke with yesterday) need education on a section of Mental Health Parity Law that went into effect in July 2000 under California State Assembly Bill 88. I refer specifically to the Seriously Emotionally Disturbed (SED) criteria. SED is not a diagnosis; there is not code that can be put on the paperwork for it. SED is a term used when a set of criteria are met.

I have attached a section of text from Section 1374.72 of AB88 explaining SED and would like for the following to be considered in this appeal:

1374.72 (e) – ___ has been diagnosed with ADHD (combined type), Anxiety Disorder NOS that results in behavior inappropriate to his age

Text from Paragraph 2 of Subdivision (a) in Section 5600.3 of the Welfare and Institutions code is included as well. I would like to note the following:

5600.3 (2) __ has two identified disorders from DSM-IV that results in behavior inappropriate to his age;

(A) as a result, ___ has substantial impairment in self-care, school functioning, family relationships, ability to function in the community;

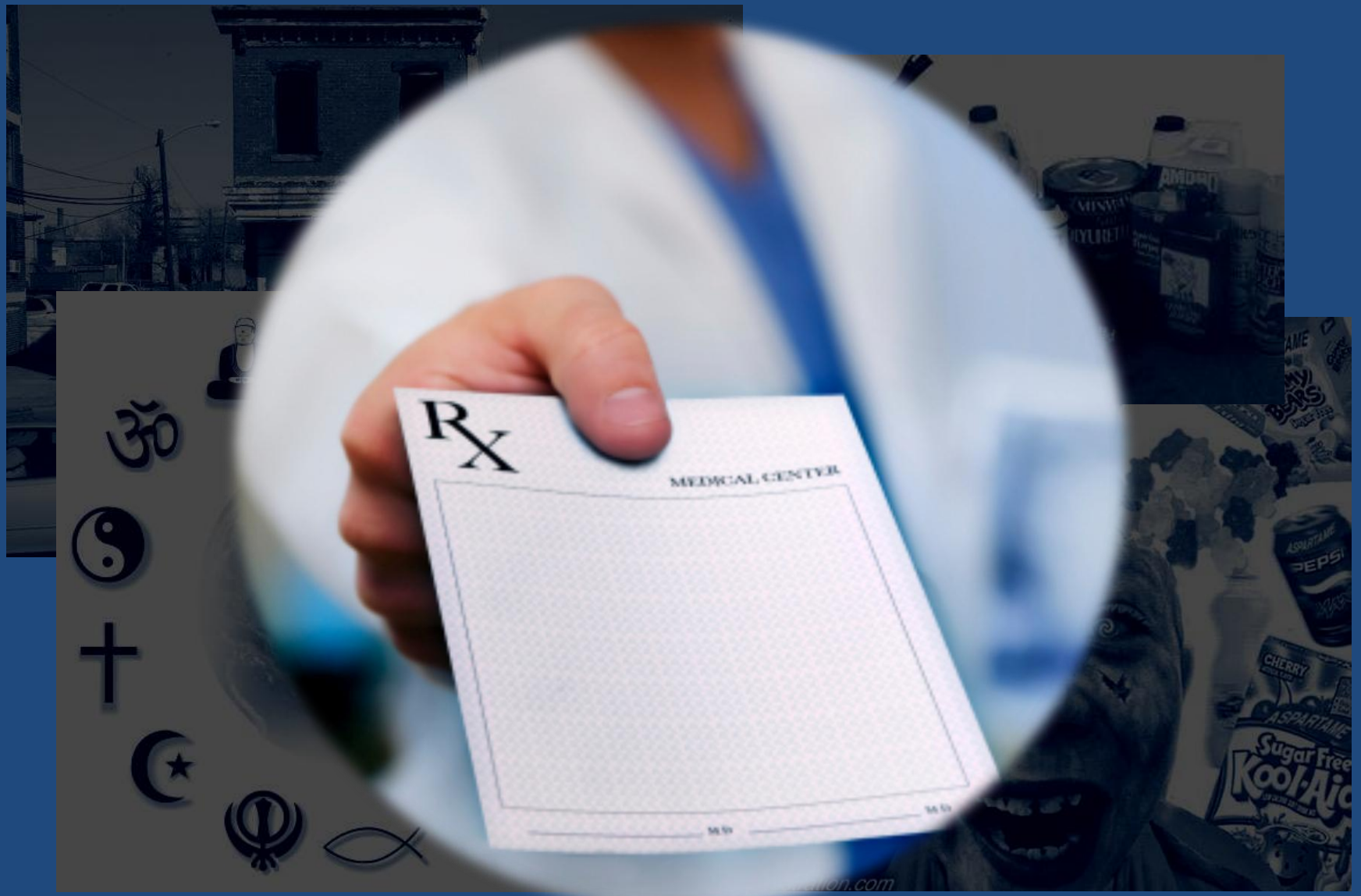
(ii) the disorders and impairments have been present for ____ years and will

…has two identified disorders from DSM-IV…

(C) ___ meets the special education eligibility requirements

How else can we conceptualize “disorder”?

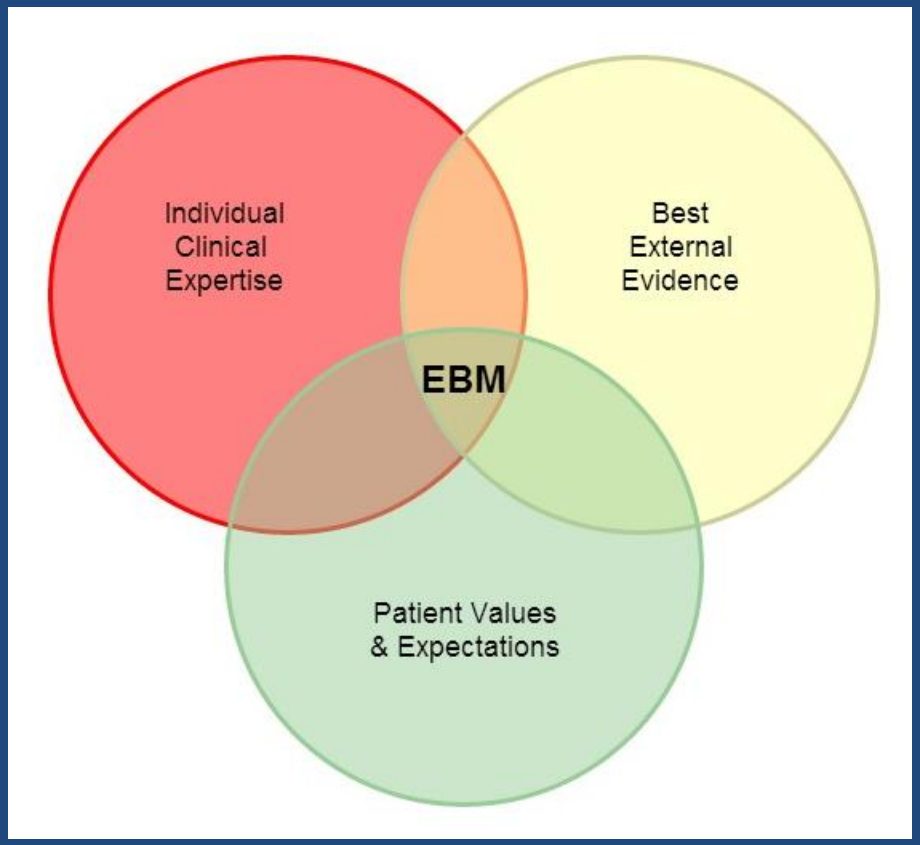
How else can we conceptualize “disorder”?



How do we know what *works* for a given disorder?

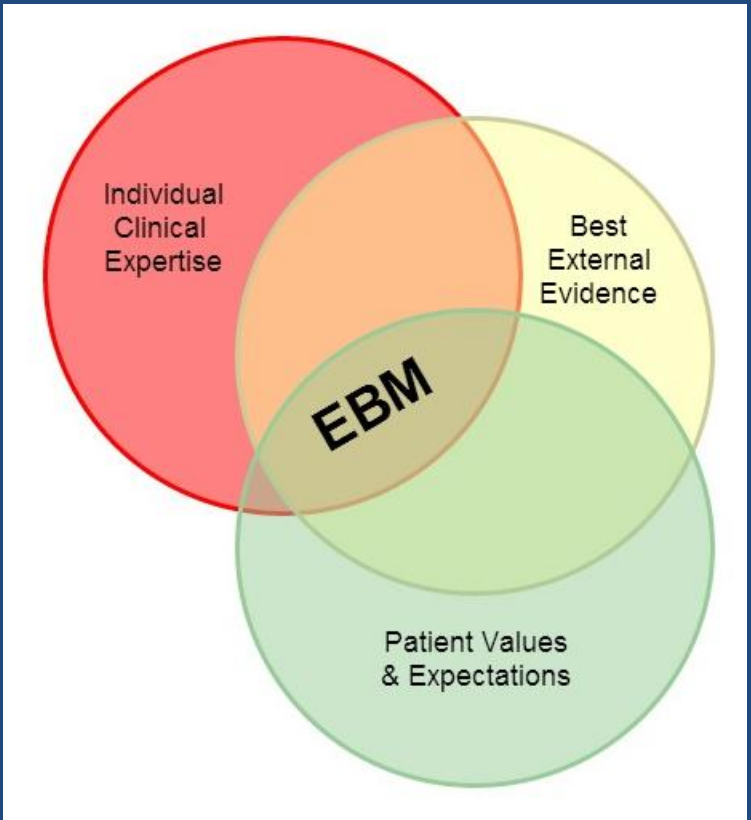
Evidence-Based Medicine

(circa 1995)



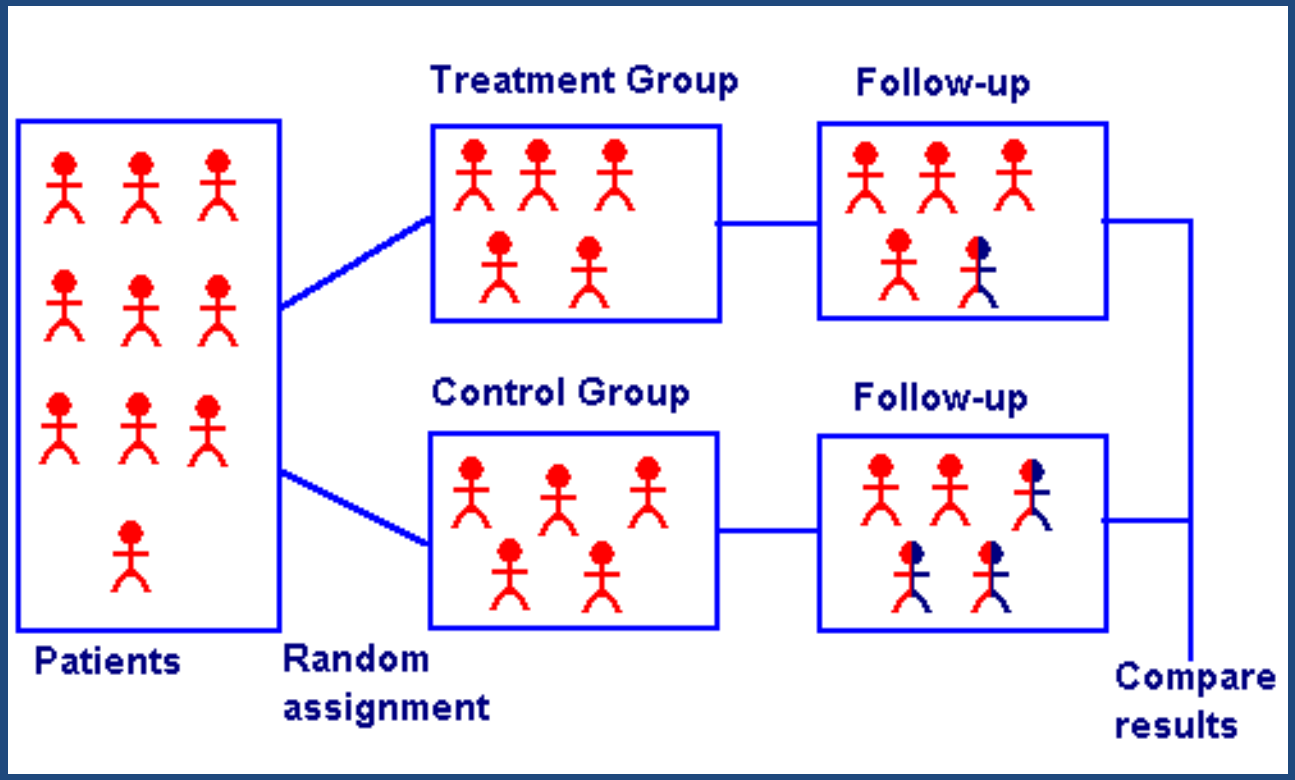
Evidence-Based Medicine

(circa 2013)



Evidence-Based Medicine

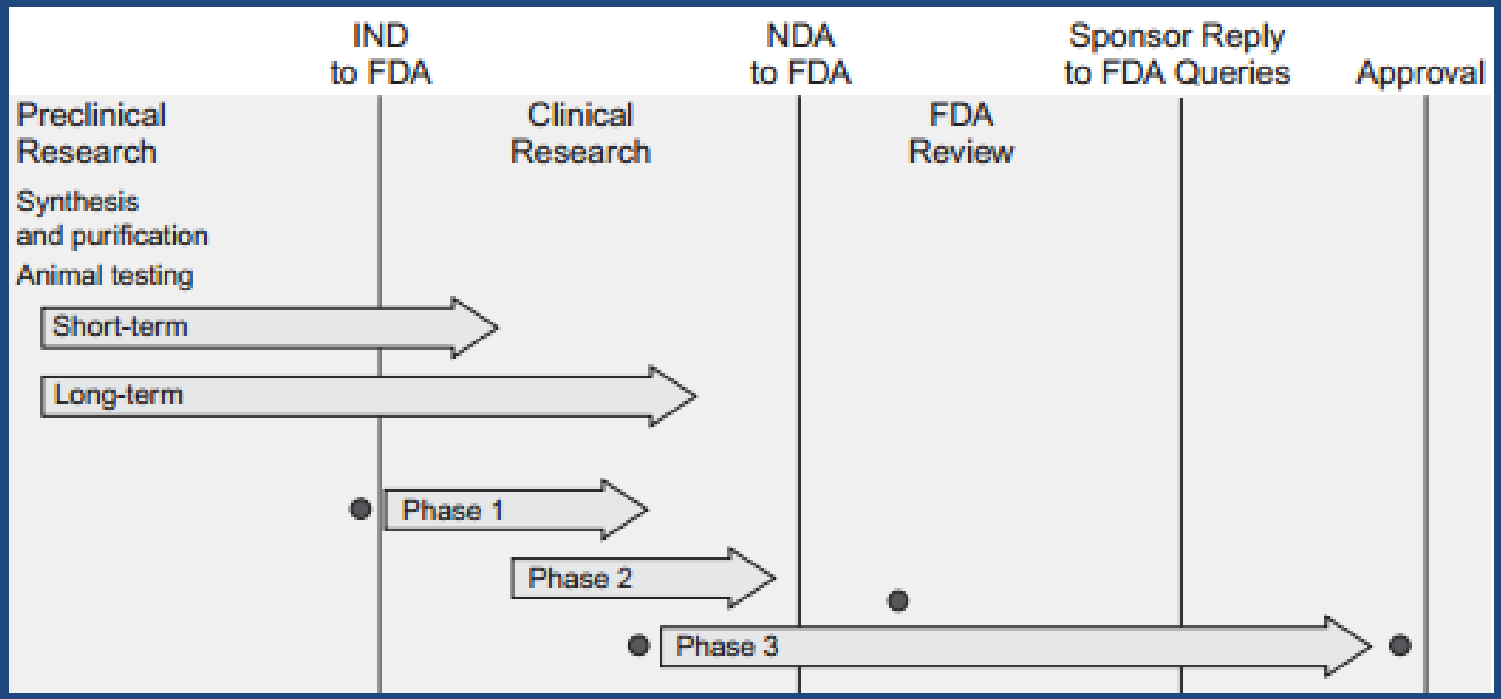
The randomized controlled trial



Randomized controlled trials are at the heart of the drug approval process

All prescription drugs must be approved by the US **Food and Drug Administration (FDA)**

Drug Approval - Stages



Average time from NCE (new chemical entity) to FDA approval:
8.1 yrs (1960s) → 14.2 yrs (1990s)
Cost of developing a new drug estimated at $802 million in 2001

Drug Approval

PRE-CLINICAL TESTING

2-4 YEARS

- Molecules are tested in the laboratory, both *in vitro* and in animals (*in vivo*)
- Biological activities are measured
- Toxicities are also evaluated

ELSEVIER

European Journal of Pharmacology

Volume 572, Issues 2–3, 31 October 2007, Pages 160–170

Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test

Takeo Ishiyama, Kumiko Tokuda, Tadashi Ishibashi, Akira Ito, Satoko Toma, Yukihiro Ohno[1]

Pharmacology Research Laboratories, Dainippon Sumitomo Pharma Co. Ltd., Enoki 33-94, Suita, Osaka, 564-0053, Japan

Abstract

Lurasidone (SM-13496) is a novel atypical antipsychotic with high affinities to dopamine D_2, serotonin 5-HT_7, 5-HT_{2A}, 5-HT_{1A} receptors and α_{2C} adrenoceptor. In this study, the effects of lurasidone on the rat passive-avoidance response and its impairment by the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801

Drug Approval

PHASE I TRIALS

2-3 YEARS

- Drug is given to healthy volunteers (usually <100) to establish safe dosages, adverse effects, and abuse potential

PHASE II TRIALS

1-2 YEARS

- Drug is given to several hundred (300-500) people with the illness for which the drug will be marketed
- Efficacy, safety, tolerability
- Therapeutic effects are measured

Drug Approval

PHASE III TRIALS

2-4 YEARS

- *Randomized controlled trials* (RCTs) are performed; patients with the indicated diagnosis are given either placebo (or active comparator) vs. drug
- The FDA requires only TWO positive phase III trials, even if more trials are negative

What is a "positive" trial?

- The drug-treated group has a statistically significant improvement over the placebo-controlled group on a symptom rating scale

- "Efficacy" = response (usually measured as a >50% reduction in symptoms) of drug is better than that of placebo (usually to a significance of $p < 0.05$)
- *Not* "effectiveness" = the extent to which the drug achieves its intended effect in the usual clinical setting

Drug Approval

NEW DRUG APPLICATION (NDA)

When phase III trials have provided sufficient data on safety and efficacy, a sponsor can make a new drug application; this essentially asks the FDA for approval to market the drug for a specific indication and in a specific age group

Problems with Clinical Trials

ASSUMPTIONS MAY NOT BE CORRECT

- "Real" patients rarely resemble the subjects in drug trials
- Drug effects are usually highly correlated with the patient's/subject's knowledge that he/she is taking a drug
- Investment of time/energy/money in the treatment process is significant

SHORT DURATION

- Any benefit of drug might "wear off" by the end of the trial

Problems with Clinical Trials

NARROWLY SELECTED COMPLAINTS AND BEHAVIOR

- Clinical scales (CDRS, MADRS, HAM-D, HAM-A, YBOCS, etc)
- Clinical Global Impression (CGI)

PLACEBO CONTROLS vs ACTIVE CONTROLS

WHAT IS THE BIOLOGY OF MENTAL ILLNESS IN THE FIRST PLACE?

- No biological markers exist
- Is our use of drugs “disease-centered” or “drug-centered”? (Moncrieff & Cohen, 2005)

THE PARACHUTE PROBLEM

- If it has to be proven through a clinical trial (“of sufficiently large N”), then how valuable is it anyway?

CHILDREN'S DEPRESSION RATING SCALE (CDRS)

The Children's Depression Rating Scale (CDRS) is a 16-item measure used to determine the severity of depression in children 6-12 years of age. Items are measured on 3-, 4-, 5-, and 6-point scales. The CDRS is derived from the Hamilton Rating Scale for Depression (HAM-D); a score of 15 on the CDRS is equivalent to a score of 0 on the HAM-D. Assessment information is based on parent, child and schoolteacher interviews.

1. **Depressed Mood (0-5).** Affect may be aroused (e.g., sad, forlorn, gloomy, anguished) or suppressed. Note nonverbal behavior (e.g., facial expression, eye contact, body posture). Child may or may not verbalize feelings of sadness.

   0=No information

   1=Definitely not depressed-facial expression and voice animated during interview

   2=Doubtful-mild suppression of affect during interview and/or some loss of spontaneity

   3=Mild-overall some loss of spontaneity. Child looks unhappy during parts of interview. May still be able to smile when discussing nonthreatening areas

   4=Moderate-may have a moderate restriction of affect throughout most of the interview and have brief periods where looks unhappy

   5=Severe-child looks sad, withdrawn with little verbal interaction throughout interview. May look like crying

2. **Weeping (0-3).** Information usually from parents, teachers, but occasionally from child.

   0=No information

   1=Normal for age

   2=Suggestive statements that child cries more frequently than peers

   3=Cries frequently-more than reasonable for age or provocation

3. **Self-Esteem (0-5).** The child's ability to describe self is very concrete at 6 and 7, becoming more sophisticated at 9 and 10. Note affective tones around the child's responses. Inappropriate guilt rates 3 or 4.

   0=No information

   1=Child describes self in mostly positive terms

   2=Doubtful evidence of lowered self-esteem

   3=Child describes self using a mixture of attributes, with both affectively positive and negative tones

5. **Suicide and Suicide Ideation (0-5).**

   0=No information

   1=None

   2=Has thoughts about suicide-usually when angry

   3=Recurrent thoughts of suicide

   4=Thinks about suicide and names methods or if depressed, strongly denies thinking about suicide

   5=Suicide attempt within the last month or actively suicidal

6. **Irritability (0-5).** Information usually from Parents, nurses, etc., and direct observation. This can range from whining, "chip on the shoulder" attitudes to temper outbursts and other direct displays of hostility and anger. Rate on frequency of irritable behavior. Some children may directly display whining, irritable behavior during the interview.

   0=No information

   1=Normal

   2=Occasional-slightly more than normal

   3=Episodic

   4=Frequent

   5-Constant

7. **Schoolwork (0-5).** Consider current function as opposed to usual or expected function. Expected function should take into consideration the intelligence of the child and specific learning disabilities, cultural and family expectations.

   0=No information

   1=Performing at or above the expected level.

   3="Not working to capacity" or recent disinterest in schoolwork with minimal interference with performance

   4=Doing poorly in most subjects or evidence of a recent major interference with performance

Clinical Global Impression (CGI)

1. **Severity of illness**
   Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?
   0 = Not assessed
   1 = Normal, not at all ill
   2 = Borderline mentally ill
   3 = Mildly ill
   4 = Moderately ill
   5 = Markedly ill
   6 = Severely ill
   7 = Among the most extremely ill patients

2. **Global improvement:** Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.
   Compared to his condition at admission to the project, how much has he changed?
   0 = Not assessed
   1 = Very much improved
   2 = Much improved
   3 = Minimally improved
   4 = No change
   5 = Minimally worse
   6 = Much worse
   7 = Very much worse

3. **Efficacy index:** Rate this item on the basis of **drug effect only**.
   Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.
   EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		**Side effects**			
		None	*Do not significantly interfere with patient's functioning*	*Significantly interferes with patient's functioning*	*Outweighs therapeutic effect*
Marked	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
Moderate	Decided improvement. Partial remission of symptoms	05	06	07	08
Minimal	Slight improvement which doesn't alter status of care of patient	09	10	11	12
Unchanged or worse		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

Problems with Clinical Trials

NARROWLY SELECTED COMPLAINTS AND BEHAVIOR

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THE PARACHUTE PROBLEM

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Problems with Clinical Trials

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score >15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.[6]

Meta-analysis

Our statistical apprach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Department of Obstetrics and Gynaecology, Cambridge University, Cambridge CB2 2QQ
Gordon C S Smith *professor*
Department of Public Health, Greater Glasgow NHS Board, Glasgow G3 8YU
Jill P Pell *consultant*
Correspondence to: G C S Smith gcss2@cam.ac.uk

BMJ 2003;327:1459–61

Problems with Clinical Trials

SPECIFICS TO CHILDREN/ADOLESCENTS

-Most practitioners extrapolate findings from adults to children
    -Children are "therapeutic orphans"
-Use of psychotropics in children has, in general, *preceded* research
-Do children/adolescents have the same "disorders" as adults?
    -Examples: bipolar disorder, depressive disorders, some anxiety disorders
-Safety issues in children
    -Interference with immature neurotransmitter systems; ↑ risk of substance abuse/dependence due to sensitization; suicidality
-Ethical issues in children
-Early recognition/intervention trials

Who Pays For Gathering The Evidence? (*i.e.*, who tells us what works?)

Industry

1997: **FDA Modernization Act (FDAMA)**: incentives to pharmaceutical industry

- pharmaceutical companies gain 6 additional months of patent exclusivity in return for conducting specific studies in children ("carrot")
- "Pediatric Rule" (1998): required pediatric effectiveness + safety data for all new drugs which may have *potential* use in children, and all supplemental applications for new indications, dosages, and dosage forms ("stick")
- industry has funded most placebo-controlled efficacy trials of stimulants and antidepressants
- EU has enacted similar incentives

1998-2008: >300 studies:

Cost of additional studies: $5-44 million (median $12.3 million)
Return for 6 months of exclusivity: $9-508 million (median $140 million)
Range of return/cost ratios ("return on investment"): -0.68 to +73.63

Antidepressant: cost $35M, return $242M (ratio = 7)
ADHD medication: cost $3.7M, return $5.3M (ratio = 2.3)

Li et al, *JAMA*, 2007

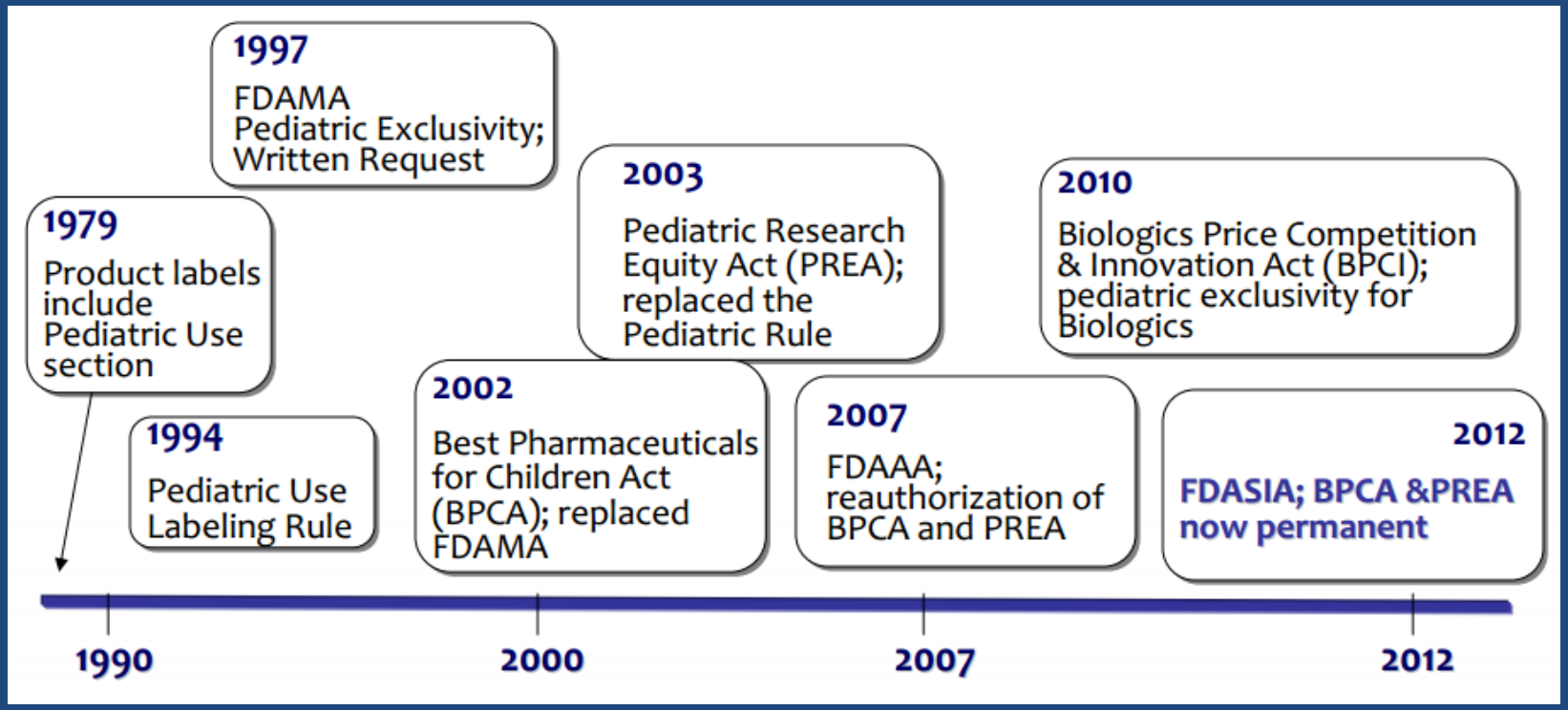
Industry

- Exclusivity is granted for completing specific studies within a certain period of time, *but not necessarily for demonstrating efficacy*"
- The types of studies conducted under pediatric exclusivity tend to be more for ADULT use than pediatric

The 135 drugs granted exclusivity between 1998-2006 included 5 of the 10 best-selling drugs in 2005: Lipitor, Zocor, Nexium, Prevacid, and Zoloft.

Collectively, sales of these five drugs amounted to $24.1 billion that year (Boots et al, 2007)

Industry



FDAMA → Best Pharmaceuticals for Children Act (BPCA) - *voluntary*

Pediatric Rule → Pediatric Research Equity Act (PREA) - *mandatory*

Industry

2002: **Best Pharmaceuticals for Children Act (BPCA) -- *voluntary***

- Authorizes FDA to request studies of approved and/or unapproved pediatric indications, including drugs used off-label in pediatric population
- 6-month patent exclusivity
- The NIH maintains a "priority list" of drugs needing study; the NIH conducts studies on priority drugs *if manufacturers decline to do so*.
- Reauthorized in 2007

2003: Pediatric Research Equity Act (PREA)

- Triggered by a new drug application (NDA) for a new indication *(except* orphan indications), dosage form, dosing regimen, or route of administration
- Authorizes FDA to *require* pediatric assessment even for drugs meant for adult use, when the medication is potentially relevant to pediatric use
- Requires studies only on indication(s) under review

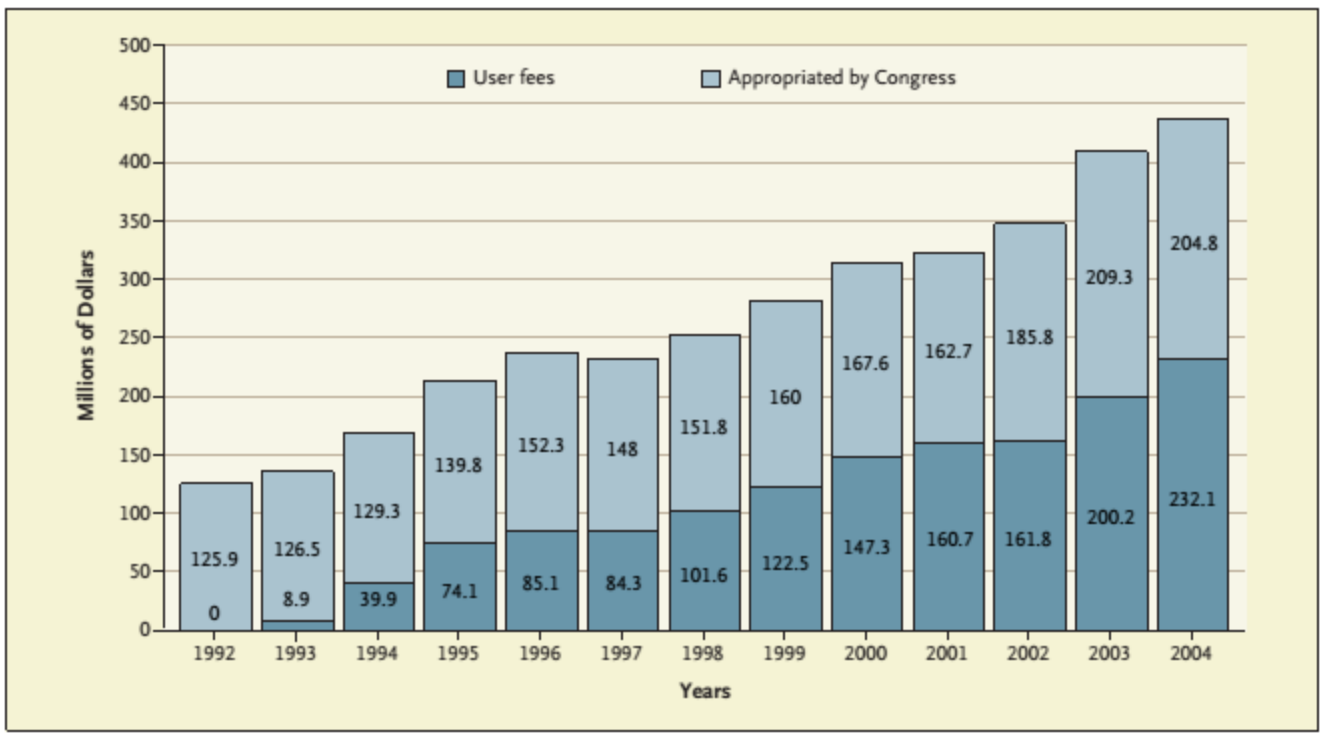
Before BPCA and PREA, >80% of drugs approved for adult use were being used in children, without establishment of safety or efficacy.

Industry

And let us not forget…

1992: Prescription Drug User Fee Act

- FDA collects fees from drug manufacturers (“sponsors”), averaging $500 million per drug, to review the data for drug approval
- User fees make up >50% of the budget of the Center for Drug Evaluation and Research (CDER)



Public

NIH Research networks (mid-1990s)

- Pediatric Pharmacology Research Units (PPRUs)
  - to study the efficacy of drugs used in general pediatrics
- Research Units on Pediatric Psychopharmacology (RUPPs)
  - to study the efficacy of off-label psychiatric medications
  - (examples: fluvoxamine in OCD, risperidone in autism)

Effectiveness studies

- ADHD (MTA Cooperative Group)
- adolescent depression (TADS Team)
- comparisons of antipsychotics in youth with schiz (TEOSS Study)
- cost-effectiveness (MTA, TADS, TEOSS)

Other areas

autism and PDDs
epidemiology
meta-analyses
bioethics
long-term illness trajectories

What Else Can Be Done?

- Pharmacoepidemiologic studies
- Better assessment instruments for children; measurements of functional outcomes
- Research into effectiveness of psychosocial interventions; psychosocial interventions as “active controls”
- Inclusion criteria for pediatric studies based on *symptoms* rather than categorical *diagnoses*
- “N=1” studies
- Large ,“simple” observational studies
- Active surveillance (vs. spontaneous reporting) of adverse events; registries
- Others?

Take-Home Points

- Know what you're calling a "disorder" and why!
- Always search for alternative explanations/interventions
- Think about the evidence *for* or *against* anything you do
- Funding sources don't always reveal bias, but they do help to determine what research will be funded
- Always ask for the information you need to do your job better; and if you can't get an answer, *always ask why not!!!*

Thank You

Steve Balt, MD, MS
www.stevebalt.com
www.thoughtbroadcast.com