FDA Flawed Gate keeping

Testimony
Vera Sharav
President
Alliance for Human Research Protection
June 12, 2007

U.S. DHHS. Agency for Healthcare Research & Quality (AHRQ)

"Systematic reviews are the building blocks underlying evidence-based practice;

they focus attention on the strengths and limits of evidence from research studies about the effectiveness and safety of a clinical intervention."

FDA Prozac Safety Review, 1990

The firm's analysis of suicidality does not resolve the issue. The firm acknowledged that its clinical trials were not designed to study this and that the quality and specificity of data to be gleaned from these trials to address suicidality were poor. The data presented in some tables showed higher percentages of suicidality among fluoxetine patients than among tricyclic or

"The data showed higher percentages of suicidality among fluoxetine patients than among tricyclic or placebo patients...apparent largescale underreporting

Interestingly, the proportion of patients with treatment-emergent suicidality on fluoxetine in this study was similar to that reported by Teicher et al.

Because of apparent largescale underreporting, the firm's analysis cannot be considered as proving that fluoxetine and violent behavior are unrelated.

David J. Graham, MD, MPH

"the division does not see it as a real issue, but rather as a public relations problem."

Date: October 3, 1990	Time: 10:00 AM
Conversation With:	Martin Brecher, M.D.
Title/Affiliation:	Medical Officer Division of Neuropharmacological Drug Products
Telephone Number:	(301) 443-4020
Regarding	PAROXETINE: Suicide-Ideation and Violence-Ideation; Efficacy Review

CONFIDENTIAL

"In summary, I don't consider these data to represent a signal of risk for suicidality for either adults or children."

Thomas P. Laughren, M.D., FDA Team Leader, Psychiatric Drug Products, Division of Neuropharmacological Drug Products, HFD-120

October 25, 1996

Thomas Laughren, 2006

"the pooled estimates of studies of the adult population support the null hypothesis of no treatment effect on suicidality."

But the data shows relative risk for suicidal behavior:

Age <25:	RR = 2.30	(1.04 - 5.09)
Age 45 - 54:	RR = 2.29	(0.73 - 7.14)
Age 45 - 64:	RR = 1.75	(0.68 - 4.48)

FDA: Clinical review: relationship between antidepressant drugs and suicidality in adults. Nov. 17, 2006:44.
http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf

FDA drug safety standard for approval

An FDA “determination that a drug is ‘safe for use’ is not a finding of fact, but an opinion.”

“risks have not been reliably assessed.”

“too few patients are exposed to a drug during commercial development to capture adverse drug induced phenomena”

FDA Memo. Dr. Paul Leber to Dr. Robert Temple, Dec. 6, 1996

FDA efficacy standard for approval

"the measure of treatment effects obtained in clinical experiments that assess treatment effects on rating scales are not easily understood in terms of meaningful clinical benefit."

"Moreover, the risks associated with the use of a drug at the time [of approval]…are invariably fewer than its actual risks."

FDA Memo. Dr. Paul Leber to Dr. Robert Temple, Dec. 6, 1996

FDA-approved Lethal drugs

1991 Halcion (triazolan) withdrawn in UK
1997 Fen-pehn (diet)
1998 terfenadine (antihistamine)
2000 Rezulin (troglitazone)
2000 Lotronex (alosetron)
2000 Propulsid (cisapride)
2001 Baycol (cerivastatin)
2001 Organon (rapacuronium)
2004 Vioxx (rofexoxib)
2005 Adderall XR (amphetamine) withrawn in Canada
2005 Pemoline
2005 Tysabri (natalizumab)

Efficacy “Proof in principle”

FDA review of Zyprexa premarketing trials:

"inappropriate design"

"inappropriate sample of patients”

“ill-suited titration;" “high incidence of dropouts”

“the evidence of efficacy submitted to the FDA provided only "proof in principle" of the drug's acute antipsychotic action.”

Dr. Paul Leber to Dr. Robert Temple, Aug 18, 1996

Risperdal *NEJM*, 2002

Children aged 5-17: 8-week placebo controlled trial

Adverse Events	Risperdal (n= 49)	Placebo (n=52)
Fatigue	59%	27%
Drowsiness	49%	12%
Constipation	29%	12%
Skin irritation	22%	14%
Drooling	27%	6%
Dyskinesia	12%	6%
Tremor	14%	2%
Tachycardia	12%	2%
Muscle rigidity	10%	2%
Respiratory infection	10%	4%
Sore throat	10%	2%

Risperdal children aged 5-12
Pediatrics, 2004

8-week placebo CRT	Risperdal (n=40)	Placebo (n= 39)
Any Adverse Effect	100%	79.5%
Somnolence	72.5%	7.7%
Abdominal pain	20%	7.7%
Constipation	12.5%	2.6%
Apathy	12.5%	0
Tachycardia	12.5%	0
Flu-like symptoms	10%	5.1%
Fatigue	10%	2.6%
Weight gain	10%	2.6%
Tremor	10%	0
EPS	27.5%	12.8%

FDA TRANSPARENCY, 2006
Secret Science

FDA approved Risperdal for “irritability” in Autistic children, October 2006

1. FDA engaged in secret scientific review
2. No disclosure of data for independent review
3. No advisory committee
4. No public hearing or discussion

Risperdal Label, 2006

	RISPERDAL® (n=76)	**Placebo** (n=80)
Somnolence	67%	23%
Appetite increased	49%	19%
Confusion	5%	0%
Saliva increased	22%	6%
Constipation	21%	8%
Dry mouth	13%	6%
Fatigue	42%	13%

Table 4 Incidence of Treatment-Emergent Adverse Events in Two 8-Week, Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

There was a higher incidence of extrapyramidal symptoms (EPS) in the RISPERDAL® group (27.6%) compared with (10.0%) in the placebo group

Risperdal label

	RISPERDAL® (n=76)	**Placebo** (n=80)
Central & peripheral nervous system		
Tremor	12%	1%
Dystonia	12%	6%
Dizziness	9%	3%
Automatism	7%	1%
Dyskinesia	7%	0%
Parkinsonism	8%	0%
Upper respiratory Infection	34%	15%
Weight increase	5%	0%
Tachycardia	7%	0%

Adverse events reported since marketing

- anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pituitary adenomas, pulmonary embolism, and precocious puberty.

- There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®.

U.S. DHHS. Agency for Healthcare Research & Quality

Bipolar depression:

"The data are sparse and conflicting about the efficacy of atypical antipsychotics for patients with major depression with psychotic features compared to conventional therapy."

AHRQ: Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics, 2007

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

FDA approval basis: Science or Commerce?

"This supplemental new drug application provides for the use of Seroquel® in the treatment of major depressive episodes associated with bipolar disorder."

"We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the attached agreed-upon labeling text."

Thomas P. Laughren, M.D. Director. Division of Psychiatry Products
Office of Drug Evaluation I Center for Drug Evaluation and Research, 2006