The depressing news about antidepressant use in children and adolescents

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Pediatric major depression

- Two weeks or more of persistent depressed mood plus at least 4 symptoms
- Relatively common, particularly in adolescents
- Causes impairment at school, with peers, family
- Suicide attempts and completed suicide

Pediatric major depression

- Same symptoms as adults
- Runs in families with adult depression
- Same course as adults
- So: should respond to antidepressant medications as adults

Prologue: Tricyclic antidepressants in children and adolescents

Imipramine in prepubertal major depressive disorders.
Archives of General Psychiatry. 44(1):81-9, 1987 Jan.
Two complementary strategies were used simultaneously: a five-week, double-blind, placebo-controlled design (N = 38), and a plasma level/clinical response study (N = 30).
Response rates in the double-blind study were similar in both groups (imipramine, 56%; placebo, 68%).

Prologue: Tricyclics

- In the 1980's tricyclic antidepressants were thought effective for pediatric depression and prescribed widely.
- In 1992 a review of placebo controlled trials found that none were effective.
- 12-13 controlled trials to date: NONE SHOW EFFICACY GREATER THAN PLACEBO

FDA extends patent to drug companies that test drugs in children-1997

- 6 month extension if drugs tested in children
- Worth a great deal of money to drug companies
- Only have to test not find efficacy or even report results to public

Two controlled trials of fluoxetine by Emslie et al, 1997 and 2003

Results

	Placebo	Fluoxetine	p-value
Study 1			
30% reduction in CDRS-R	15/47 (32%)	28/48 (58%)	p=0.013
CDRS-R total score change from baseline	-10.5	-20.2	p=0.002
Study 2			
30% reduction in CDRS-R	54/101 (53%)	71/109 (65%)	p=0.093
CDRS-R total score change from baseline	-14.9	-22.1	p<0.001

Controlled trial of Paxil (paroxetine) 2001 Keller et al.

- Double blind randomized trial in adolescent depression comparing placebo, paroxetine, and imipramine
- 275 adolescents
- 8 weeks duration

Controlled trial of Paxil (paroxetine) 2001 Keller et al.

P<.05	Placebo	Paxil
Very much improved or much improved	48.3%	65.6%
Hospitalized, suicidal gesture, other serious	2%	12%

Efficacy of Sertraline in the Treatment of Children and Adolescents With Major Depressive Disorder Two Randomized Controlled Trials

Karen Dineen Wagner, MD, PhD; Paul Ambrosini, MD; Moira Rynn, MD; Christopher Wohlberg, MD, PhD; Ruoyong Yang, PhD; Michael S. Greenbaum, MD; Ann Childress, MD; Craig Donnelly, MD; Deborah Deas, MD; for the Sertraline Pediatric Depression Study Group

***JAMA.* 2003;290:1033-1041. (August)**

Conclusion The results of this pooled analysis demonstrate that sertraline is an effective and well-tolerated short-term treatment for children and adolescents with MDD.

JAACAP, December, 2003

Depression and Bipolar Support Alliance Consensus Statement on the Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents

[SPECIAL COMMUNICATION]

Coyle, Joseph T M.D.; Pine, Daniel S M.D.; Charney, Dennis S M.D.; Lewis, Lydia; Nemeroff, Charles B M.D.; Carlson, Gabrielle A M.D.; Joshi, Paramjit Toor M.D.; Reiss, David M.D.; Todd, Richard D M.D., PH.D.; Hellander, Martha J.D.; BiPolar Support Alliance Consensus Development Panel

Accepted July 29, 2003.

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Depression and Bipolar Support Alliance Consensus Statement on the Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents[SPECIAL COMMUNICATION]Coyle, Joseph T M.D.; Pine, Daniel S M.D.; Charney, Dennis S M.D.; Lewis, Lydia; Nemeroff, Charles B M.D.; Carlson, Gabrielle A M.D.; Joshi, Paramjit Toor M.D.; Reiss, David M.D.; Todd, Richard D M.D., PH.D.; Hellander, Martha J.D.; BiPolar Support Alliance Consensus Development Panel

Recent studies (Brent et al., 1997; Clarke et al., 1999; Jayson et al., 1998; Kazdin, 2000), both of cognitive-behavioral therapy and interpersonal psychotherapy (Curry, 2001), as well as of selective serotonin reuptake inhibitors (SSRIs) (Emslie and Mayes, 2001; Emslie et al., 1997; Keller et al., 2001; Nixon et al., 2001; Wagner et al., 2001), document the utility of these treatments for major depression in youngsters. In particular, at least five large randomized controlled trials document superiority of an SSRI over placebo (Donnelly and Wohlberg, 2001; Emslie and Mayes, 2001; Wagner et al., 2001), with one of these studies also demonstrating superiority over a tricyclic antidepressant (Keller et al., 2001).

Depression and Bipolar Support Alliance Consensus Statement on the Unmet Needs in Diagnosis and Treatment of Mood Disorders in Children and Adolescents[SPECIAL COMMUNICATION]Coyle, Joseph T M.D.; Pine, Daniel S M.D.; Charney, Dennis S M.D.; Lewis, Lydia; Nemeroff, Charles B M.D.; Carlson, Gabrielle A M.D.; Joshi, Paramjit Toor M.D.; Reiss, David M.D.; Todd, Richard D M.D., PH.D.; Hellander, Martha J.D.; BiPolar Support Alliance Consensus Development Panel

Although the identification, reporting, and monitoring of adverse drug events have not been carried out systematically in children and adolescents, some cautions are applicable, given potential interactions between pharmacological effects and development. For example, the tricyclic antidepressants, which are associated with adverse cardiac events and lethality when taken in overdose, may have unique cardiac effects in children (Emslie et al., 1999; Ryan and Varma, 1998). Given their lack of efficacy in placebo-controlled trials of major depression (Birmaher et al., 1996b), tricyclic antidepressants should be avoided in this population. Similarly, there is concern that the use of valproic acid in developing girls may be associated with polycystic ovaries (Geller and Luby, 1997; Ryan et al., 1999). Antipsychotic drug therapy in children and adolescents is often associated with marked weight gain and extrapyramidal side effects. Moreover, limited evidence documents efficacy in any pediatric mood disorder. Children may develop akathisia on antipsychotics and SSRIs, which can be misconstrued as ADHD (Hamilton and Opler, 1992; King et al., 1991). The long-term effects of lithium on renal and thyroid function, particularly in children, are also a concern (Geller and Luby, 1997; Hagino et al., 1995; Ryan et al., 1999). Systematic monitoring of drug therapy, particularly when multiple medications are involved, should include patients, parents, and clinicians as collaborators to increase the likelihood of recognizing adverse drug reactions.

So, things were looking pretty dang good for the pharmacotherapy of depression in children and adolescents December 9, 2003!

- Several drugs (Prozac, Paxil, Zoloft, Celexa) safe and effective!
- Endorsed by leading medical scientists!
- Results published in the leading peer reviewed medical journals!

December 10, 2003. WARNING TO ALL PHYSICIANS AND PHARMACISTS
Medicine and Healthcare Regulatory Agency-GREAT BRITAIN

Summary of advice

In patients under 18 years old:

* Paroxetine, venlafaxine, sertraline, citalopram and escitalopram are now contraindicated in paediatric MDD in the under 18s.
* There are no data on the safety and efficacy of fluvoxamine in paediatric MDD. Safety and efficacy in adults cannot be extrapolated to those under 18 and therefore this product should not be used in this age group.
* The balance of risks and benefits of fluoxetine in the treatment of MDD in under 18s appears to be favourable.

Level 1 – Overview of regulatory status and CSM advice relating to major depressive disorder in children and adolescents

	Fluoxetine	Sertraline	Citalopram	Escitalopram	Fluvoxamine	Paroxetine	Venlafaxine
Drug class	SSRI	SSRI	SSRI	SSRI (active constituent of citalopram)	SSRI	SSRI	SNRI
Licensed indications Children and adolescents	None	Obsessive compulsive disorder	None	None	Obsessive compulsive disorder	None	None
Efficacy in major depressive disorder (MDD) in children and adolescents	Demonstrated in controlled clinical trials	Not demonstrated in controlled clinical trials	Not consistently demonstrated in controlled clinical trials	No data from clinical trials	No data from clinical trials	Not demonstrated in controlled clinical trials	Not demonstrated in controlled clinical trials
Safety profile in MDD trials in children and adolescents	Mania and hypomania more frequently reported than in adults, perhaps as a result of differing inclusion criteria in clinical trials. No increased rate of self-harm and suicidal thoughts compared with placebo.	Rate of events including agitation, anorexia, insomnia and suicidal thoughts and self harm increased compared with placebo.	Increased rate of self-harm compared with placebo in 1 of 2 trials.	No data from clinical trials	No data from clinical trials	Increased rate of self-harm and suicidal thoughts compared with placebo.	Increased rate of self-harm and suicidal thoughts compared with placebo.
CSM advice in relation to MDD in children and adolescents	**Risk/benefit balance is favourable.**	**Risk/benefit balance is unfavourable.**	**Risk/benefit balance is unfavourable.**	**Risk/benefit balance is presumed unfavourable. (Extrapolation from citalopram.)**	**Risk/benefit balance is not assessable – safety and efficacy in adults cannot be extrapolated to under 18 year olds.**	**Risk/benefit balance is unfavourable.**	**Risk/benefit balance is unfavourable.**

MHRA Review

Sertraline - Major depressive disorder

Key efficacy trials - Primary efficacy data from 2 identically designed short term placebo controlled trials.

Objectives:-To evaluate the safety and efficacy of sertraline compared with placebo in children and adolescent (6-17 years of age) outpatients with MDD.

Design:- Multicentre, randomised, double-blind, placebo controlled, flexible-dose trial of sertraline in children (6-11 years) and adolescents (12-17 years) with MDD. Double-blind phase was 10 week duration. Dose range 25-200mg/day.

Participants:-Subjects with a current episode of MDD (as defined by DSM-IV), and a Revised Children's Depression Rating Score (CDRS-R) of $\geq$ 45, and Clinical Global Impression – Severity (CGI-S) $\geq$ 4.

Outcome measures:-Primary efficacy variable was change from baseline in the CDRS-R total score.

Results

Patient numbers

	Randomised		**Completed**	
	Sertraline	**placebo**	**sertraline**	**placebo**
Study 1	97	91	65	77
Study 2	92	96	78	79

MHRA Review-Efficacy

Primary efficacy variable (ITT population)

Study 1	All patients	6-11 yrs	12-17yrs	Study 2	All patients	6-11 yrs	12-17yrs
Sertraline n=93	-25.9	-27.0	-24.6	Sertraline n=92	-28.8	-30.4	-27.2
Placebo n=88	-22.1	-24.8	-19.5	Placebo n=91	-25.6	-27.9	-23.3
p-value	0.084	0.504	0.084	p-value	0.170	0.473	0.227

MHRA Review

Summary of responder analysis (ITT population) Study 1

Study 1	Sertraline			Placebo			p-value for estimated contrast
	N	n	N/n (%)	N	n	N/n (%)	
Responders - CDRS- R*	93	58	62.4	88	50	56.8	0.464
Remitters**	81	37	45.7	80	40	50.0	0.732
Remitted responders***	81	34	42.0	80	35	43.8	0.969

*Responders were defined as subjects with at least a 40% decrease in the adjusted CDRS-R total score from baseline to endpoint. The adjusted CDRS-R score was defined as CDRS-R total score minus 17 (the minimum possible CDRS-R total score).

**Remitters were defined as subjects who no longer met DSM-IV criteria for a current major depression episode at endpoint.

***Remitted responders were defined as CDRS-R responders who were also remitters.

MHRA Review-Efficacy

Summary of responder analysis – ITT population Study 2

	Sertraline			Placebo			p-value for estimated contrast
	N	n	N/n (%)	N	n	N/n (%)	
Responders - CDRS- R*	92	69	75.0	91	55	60.4	0.033
Remitters**	86	61	70.9	85	52	61.2	0.259
Remitted responders***	86	56	65.1	85	46	54.1	0.239

*Responders were defined as subjects with at least a 40% decrease in the adjusted CDRS-R total score from baseline to endpoint. The adjusted CDRS-R score was defined as CDRS-R total score minus 17 (the minimum possible CDRS-R total score).

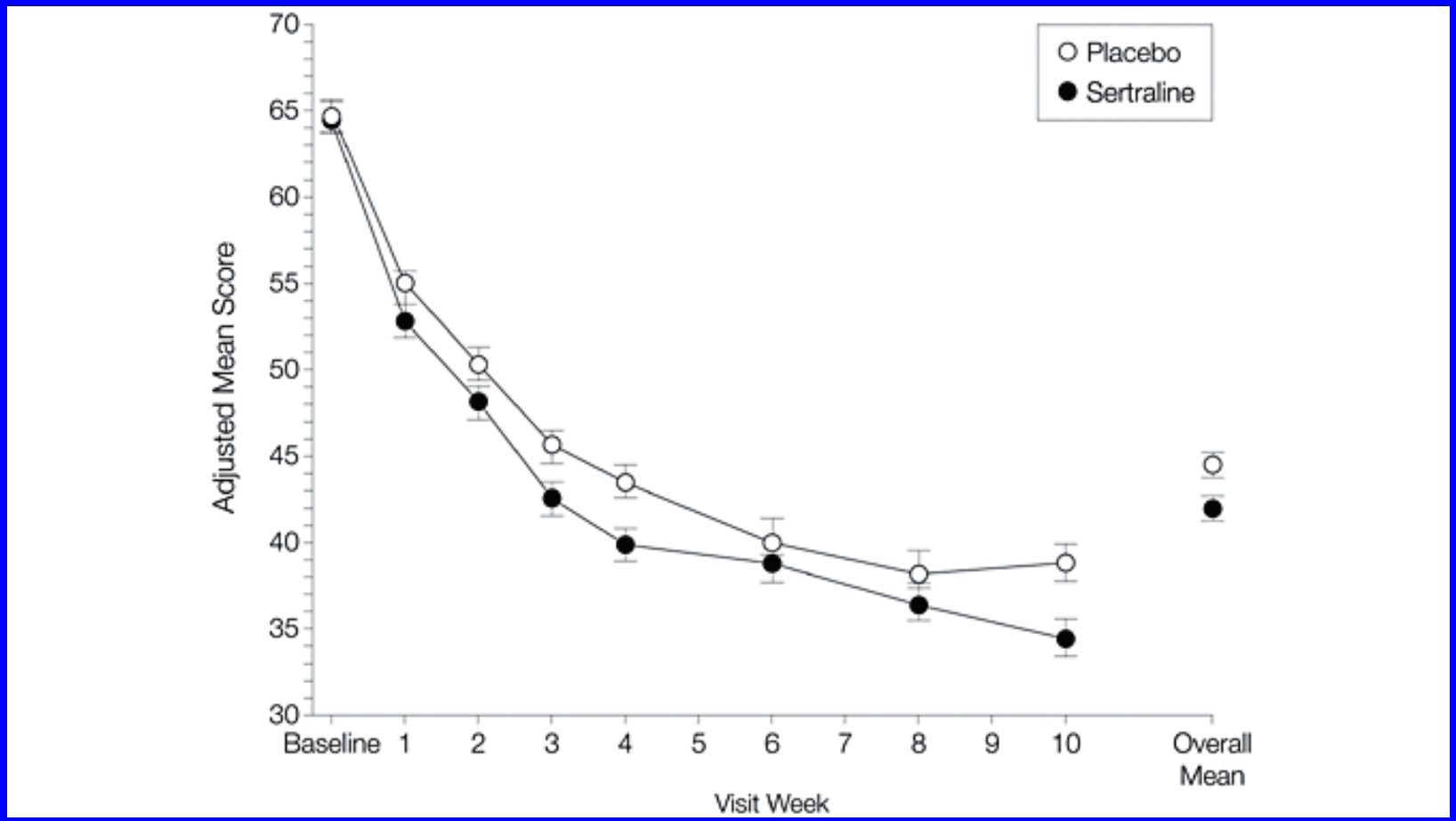
**Remitters were defined as subjects who no longer met DSM-IV criteria for a current major depression episode at endpoint.

***Remitted responders were defined as CDRS-R responders who were also remitters.

JAMA article (same 2 studies but data pooled)

- 69% sertraline and 59% placebo met responder criteria ($p<.05$)
- “the number needed to treat to expect a difference in response between sertraline and placebo is 10”

Wagner et al, JAMA, 2003:290:1033-1041 (same two studies but data pooled)



MHRA Review-Safety

Safety - data from clinical trials are available for 189 patients treated with sertraline at doses of 25-200 mg for up to 10 weeks. 135 patients completed 10 weeks of treatment. There were no deaths in the studies. There are few data on long term safety. Agitation, anorexia and insomnia were among the adverse events that were reported more often by sertraline treated patients than by placebo treated patients.

In the two placebo-controlled trials with depression there was a higher rate of discontinuation from sertraline compared to placebo for suspected adverse events, especially amongst children. Overall there were 17 discontinuations from the sertraline group for adverse events and 4 from the placebo group. Fifteen of these 17 discontinuations in the sertraline group were for psychiatric adverse events compared with two out of the four in the placebo group. The commonest reasons for discontinuation of treatment were: aggressive reaction (sertraline 3), agitation (sertraline 3), hyperkinesia (sertraline 2), suicidal thoughts (sertraline 3) and suicide attempt (sertraline 2, placebo 1).

Suicide related events were reported in 2.7% (5/189) of sertraline treated patients and 1.1% of (2/184) of placebo treated patients.

Tolerability

The mean dosage of study drug administered to patients who completed 10 weeks of double-blind treatment was 131 mg/d of sertraline and 144 mg/d of placebo equivalent, and the median duration of exposure to study drug was the same in both treatment groups (68 days). Sertraline in the dosage range of 50 to 200 mg/d was generally well tolerated. In the majority (>90%) of patients, adverse events were mild or moderate in intensity. There were 4 adverse events that occurred in at least 5% of sertraline-treated patients and with an incidence of at least twice that in placebo patients: diarrhea, vomiting, anorexia, and agitation (Table 3). Seventeen sertraline-treated patients (9%) discontinued the study because of adverse events; 13 of these patients were children. Seven sertraline-treated patients and 6 placebo patients had adverse events that met the established criteria for a "serious" adverse event, including suicide attempt (2 sertraline and 2 placebo), suicidal ideation (3 sertraline), and aggressive reaction (1 sertraline), as well as medical hospitalizations (1 sertraline and 4 placebo). There were no clinically important differences between the 2 treatment groups with respect to laboratory test, vital sign, physical examination, or electrocardiographic findings. The mean change in body weight from baseline to the final visit was –0.38 kg among patients treated with sertraline and +0.78 kg among placebo patients (*P* = .001).Wagner et al, JAMA, 2003:290:1033-1041

Wagner et al, JAMA, 2003:290:1033-1041 (same two studies but data pooled)

- Results:…"5 placebo (3%) prematurely discontinued the study"…
- Discussion: …"the number of suicide attempts was the same in each treatment group….Our trials showed a lack of significant difference in suicidal ideation between (groups) as measured by the CDRS-R".

February 2004

- FDA (USA) presents independent analyses of drug trials showing increased suicidality in adolescents receiving SSRI type antidepressants.
- Results questioned by academic child psychiatry community
- Blind analysis of data by experts at Columbia University begun

Lancet, April 2004.

Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data

Findings Data for two published trials suggest that fluoxetine has a favourable risk-benefit profile, and unpublished data lend support to this finding. Published results from one trial of paroxetine and two trials of sertraline suggest equivocal or weak positive risk-benefit profiles. However, in both cases, addition of unpublished data indicates that risks outweigh benefits. Data from unpublished trials of citalopram and venlafaxine show unfavourable risk-benefit profiles.

Lancet Editorial, April, 2004

Depressing research

It is hard to imagine the anguish experienced by the parents, relatives, and friends of a child who has taken his or her own life. That such an event could be precipitated by a supposedly beneficial drug is a catastrophe. The idea of that drug's use being based on the selective reporting of favourable research should be unimaginable. In this week's issue of *The Lancet* (p 1341), however, a meta-analysis by Craig Whittington and colleagues suggests that this is what has been happening for research into the use of antidepressants in childhood. Their results illustrate an abuse of the trust patients place in their physicians. They also represent an abuse of the trust placed by trial volunteers in the medical and pharmaceutical establishments.

Lancet, April 2004.

- “The story of research into selective serontonin reuptake inhibitor (SSRI) use in childhood depression is one of confusion, manipulation, and institutional failure.”

BMJ, April, 2004 Review of SSRI data in pediatric depression

Summary points

- Investigators' conclusions on the efficacy of newer antidepressants in childhood depression have exaggerated their benefits
- Improvement in control groups is strong; additional benefit from drugs is of doubtful clinical significance
- Adverse effects have been downplayed
- Antidepressant drugs cannot confidently be recommended as a treatment option for childhood depression
- A more critical approach to ensuring the validity of published data is needed

Re-analysis of definitive suicidal ideation/behavior in drug trials by FDA using data from re-analysis by Columbia University group (September 2004)

Table 10: Summary of the overall risk estimates of the primary outcome (outcome 3) by drug across all indications and in MDD trials.

Drug	Relative Risk (95% CI), all trials, all indications	Relative Risk (95% CI), MDD trials
Prozac	0.92 (0.39, 2.19)	0.89 (0.36, 2.19)
Paxil	2.65 (1.00, 7.02)	2.15 (0.71, 6.52)
Zoloft	1.48 (0.42, 5.24)	2.16 (0.48, 9.62)
Celexa	1.37 (0.53, 3.50)	1.37 (0.53, 3.50)
Effexor	4.97 (1.09, 22.72)	8.84 (1.12, 69.51)
Remeron	1.58 (0.06, 38.37)	1.58 (0.06, 38.37)

In summary, the members of the advisory committees:

- endorsed FDA's approach to classifying and analyzing the suicidal events and behaviors observed in controlled clinical trials and expressed their view that the new analyses increased their confidence in the results;
- concluded that the finding of an increased risk of suicidality in pediatric patients applied to all the drugs studied (Prozac, Zoloft, Remeron, Paxil, Effexor, Celexa Wellbutrin, Luvox and Serzone) in controlled clinical trials;
- recommended that any warning related to an increased risk of suicidality in pediatric patients should be applied to all antidepressant drugs, including those that have not been studied in controlled clinical trials in pediatric patients, since the available data are not adequate to exclude any single medication from an increased risk;
- reached a split decision (15-yes, 8-no) regarding recommending a "black-box" warning related to an increased risk for suicidality in pediatric patients for all antidepressant drugs;
- endorsed a patient information sheet ("Medication Guide") for this class of drugs to be provided to the patient or their caregiver with every prescription;
- recommended that the products not be contraindicated in this country because the Committees thought access to these therapies was important for those who could benefit; and
- recommended that the results of controlled pediatric trials of depression be included in the labeling for antidepressant drugs.

Response of the American Academy of Child and Adolescent Psychiatry

- Opposed “black box warnings”

FDA Black Box Warning October 15, 2004

- A total of 24 trials involving over 4400 patients were included. The analysis showed a greater risk of suicidality during the first few months of treatment in those receiving antidepressants. The average risk of such events on drug was 4%, twice the placebo risk of 2%. No suicides occurred in these trials. Based on these data, FDA has determined that the following points are appropriate for inclusion in the boxed warning:

FDA Black Box Warning

- Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with MDD and other psychiatric disorders.
- Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.

FDA Black Box Warning

- Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).

FDA Black Box Warning

- In addition to the boxed warning and other information in professional labeling on antidepressants, MedGuides are being prepared for all of the antidepressants to provide information about the risk of suicidality in children and adolescents directly to patients and their families and caregivers. MedGuides are intended to be distributed by the pharmacist with each prescription or refill of a medication.

Summary

- All SSRI's, including fluoxetine are considered to increase risk of suicidal ideation/behavior
- "2-3%" above and beyond risk from the disorder itself
- True even in studies of disorders other than major depression; no known risk markers.
- Risk is greatest in first week.
- Some risk during withdrawal (particularly Paxil?).

Treatment for Adolescents with Depression Study (TADS)

(JAMA, Aug. 18, 2004)

- NIMH sponsored trial
- 439 adolescents with major depression
- 13 US academic and community clinics between 2000 and 2003

Treatment for Adolescents with Depression Study (TADS)

- Randomized, controlled, blind trial of:
  - Placebo
  - Fluoxetine
  - Cognitive behavioral therapy (CBT)
  - CBT + fluoxetine

Treatment for Adolescents with Depression Study (TADS)

- Two primary outcomes:
- Children's Depression Rating Scale Revised total score
- Clinical Global Impression score: Much improved or very much improved

Treatment for Adolescents with Depression Study (TADS)

- On the main outcome of decreased CDRS score no significant difference between fluoxetine and placebo

Treatment for Adolescents with Depression Study (TADS)

	Much improved or very much improved
Placebo	34.8%
Fluoxetine	60.6%
CBT	43.2%
Fluoxetine+CBT	71%

TADS trial comparing fluoxetine, CBT, and placebo--suicidality

Table 3. Harm- and Suicide-Related Adverse Events

	Total No. of Patients	Intent-to-Treat Cases	
		Harm-Related	Suicide-Related
Active Treatment vs Placebo			
CBT with fluoxetine			
No. (%) of patients	107	9 (8.41)	6 (5.61)
OR (95% CI)		1.62 (0.56-4.72)	1.60 (0.44-5.85)
Fluoxetine alone			
No. (%) of patients	109	13 (11.93)	9 (8.26)
OR (95% CI)		2.39 (0.87-6.54)	2.43 (0.73-8.14)
CBT alone			
No. (%) of patients	111	5 (4.50)	5 (4.50)
OR (95% CI)		0.83 (0.25-2.81)	1.27 (0.33-4.87)
Placebo			
No. (%) of patients	112	6 (5.36)	4 (3.57)
SSRI vs No SSRI			
SSRI			
No. (%) of patients	216	22 (10.19)	15 (6.94)
OR (95% CI)		2.19 (1.03-4.62)	1.77 (0.76-4.15)
No SSRI			
No. (%) of patients	223	11 (4.93)	9 (4.04)
CBT vs No CBT			
CBT			
No. (%) of patients	218	14 (6.42)	11 (5.05)
OR (95% CI)		0.73 (0.36-1.49)	0.85 (0.37-1.94)
No CBT			
No. (%) of patients	221	19 (8.60)	13 (5.88)

Abbreviations: CBT, cognitive-behavioral therapy; CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

TADS trial: Psychiatric-Related Adverse Events

CBT+ Flu	Flu alone	CBT alone	Placebo
12	20 OR 2.57 significant	1	9

How did all this happen?

- The pharmaceutical industry
- The regulators
- Academic child psychiatrists

Pharmaceutical industry

- Only published positive studies and no obligation to publish negative studies
- Manipulation of physicians to prescribe drugs for “off-label” indications

The regulators (FDA)

- Wyeth (maker of Effexor) sent out strong warning label for children based on their studies
  - Watered down by FDA
- Suppressed Paxil evidence by its own epidemiologist
- Investigation of FDA ongoing by House and Senate

Academic child psychiatry

- Drug treatment for depression very good for marketing of psychiatry
- Strong investment in biologic model of depression
- Strong alliance with drug companies:
  - Willingly signed non-disclosure agreements
- Fundamental violation of academic ethics

New York Times
GlaxoSmithKline, for instance, has acknowledged that just one of its nine studies of Paxil in children and adolescents has been published - a study that made only passing mention of suicide and concluded that the drug was effective against depression. According to the F.D.A., the combined results of all nine trials show that the drug is not effective against depression in patients under 18.

Dr. Graham Emslie, a professor of psychiatry at the University of Texas Southwestern Medical Center who was a researcher in four of GlaxoSmithKline's studies of Paxil, said he suspected that the other studies went unpublished at least in part because the results were unfavorable. "Some of these studies were finished a couple of years ago," Dr. Emslie said. "But negative trials tend not to get published.“

According to Dr. Emslie, other companies have withheld negative studies of S.S.R.I.'s. "I know of at least a half-dozen other studies of antidepressant treatments in children and adolescents that have been completed but as yet have not been published," he said. "More than enough time has passed for these to be published at least in abstract form." He refused to identify the companies or the drugs involved because **he, like other researchers involved in similar research, has signed contracts promising secrecy.**

March 2004

- Editorial in CMAJ by E. Jane Garland, Clinical Head, Mood and Anxiety Disorders Clinic, B.C. Children's Hospital

tors. Those researchers, including myself, who *did* see results of negative paroxetine industry trials were prohibited by nondisclosure contracts from discussing them.

JAACAP, December, 2003

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Analyzing the evidence

- Field is moving too fast to rely on textbooks or even “reviews”
- Most comprehensive evidence to date is from the BMJ and Lancet articles
- Only papers with data should be read; authoritative reviews without data and tables should be shunned.

Analyzing the evidence

- It is clear that there is bias towards publication of positive results
  - We must be skeptical
- It is clear that researchers have minimized reporting of behavioral side-effects, esp. suicidality
  - We must be skeptical

Analyzing the evidence

- Best source for data and advice are the regulatory authorities
  - Null hypothesis bias
  - Less influenced by drug companies
  - Access to data the rest of us chumps will never see!

The fallout

- Major journals have now required all trials to be registered publicly at the beginning or they will not be published
- GSK (Paxil) sued by New York State Attorney; now has put all its data on its website for public viewing.
- US House and Senate investigations of FDA and drug companies.

Quality Assurance, Italian Style
Commando Carabinieri per la Sanita

Clinical recommendations

- SSRI's should not be first choice of treatment as outpatient (remember huge placebo effect)
  - Psychotherapy
  - Watchful waiting
- Fluoxetine approved by FDA and MHRA (only SSRI) (no drug approved in Canada)
  - Would use only this SSRI.

Clinical recommendations

- Must take seriously possibility of suicidality and behavior problems caused by SSRI and monitor
- Must inform patients and families of findings of regulatory agencies and of controversy surrounding SSRI's

What to do?

- Fluoxetine ONLY SSRI approved by FDA.
- Fluoxetine ONLY SSRI with positive risk benefit ratio according to British regulatory authority
- SO: I use ONLY fluoxetine.

If you prescribe fluoxetine…

- Explain risk of fluoxetine induced suicidal ideation/attempts (2-3 per 100 adolescents)
- Know their recent history of suicidal ideation/attempts
- See patient weekly when initiating fluoxetine

If you prescribe fluoxetine…

- If they become suicidal or suicidality worsens: is it the fluoxetine?
- Stop fluoxetine if in doubt

Plan for management of major depression: key principles

- Miserable illness that requires support and monitoring NOW
- Very variable course with spontaneous remissions
- No treatment even moderately effective

  -TADS—possibly CBT+Fluoxetine?

Plan for management of major depression: key principles

- Access to Psychiatry for consultation and management limited and not timely
- So: it is up to the pediatrician/family doctor/CLSC to manage depression

Plan for management of major depression

- Confirm it is major depression
- Initiate referral to Psychiatry
- Educate patient and family about depression
- Find psychotherapist
  - Can family afford private psychologist?
  - Training centers for psychotherapy
  - CLSC's, Youth Centres, etc.

Plan for management of major depression

- If patient goes to psychotherapist: arrange f/u with you in 1-2 months to check progress
- If no psychotherapist:

Plan for management of major depression: no psychotherapist

- See patient regularly and frequently (weekly?)
- Offer reassurance that patient will get better
- Improve self-esteem and remove guilt/blame
- Encourage patient to resume activities—pts. often in negative spiral “Try it and we will discuss next visit”

Plan for management of major depression: no psychotherapist

- And if they are no better after 2-3 months
  - They will have moved up the waiting list and be seen in Psychiatry
- Add fluoxetine.

And so to end on a depressing note…

With a cautionary tale for the optimistic who like to be the first on the block to use a new drug…

Cymbalta
(Duloxetine, Eli Lilly)
Approved August, 2004 by FDA

598 **Psychiatric Disorders** — *Frequent:* initial insomnia; irritability, lethargy, nervousness,
599 nightmare, restlessness, and sleep disorder; *Infrequent:* completed suicide, mania, mood swings,
600 pressure of speech, sluggishness, and suicide attempt.