Global Business Masquerading as Science

—The Human Laboratory—

Dec. 3, 2006

Prof. David Healy

Pocket Reference to SOCIAL PHOBIA

by
The WPA social phobia task force

Editor: S.A. Montgomery

so small

...yet so effective

Ativan

more successfully controls anxiety than any previous benzodiazepine

British Journal of Psychiatry (1991), 158, 737–742

Annotation

The Marketing of 5-Hydroxytryptamine: Depression or Anxiety?

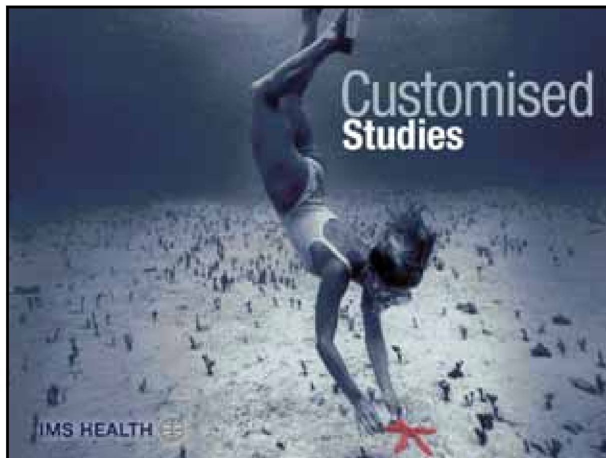
DAVID HEALY

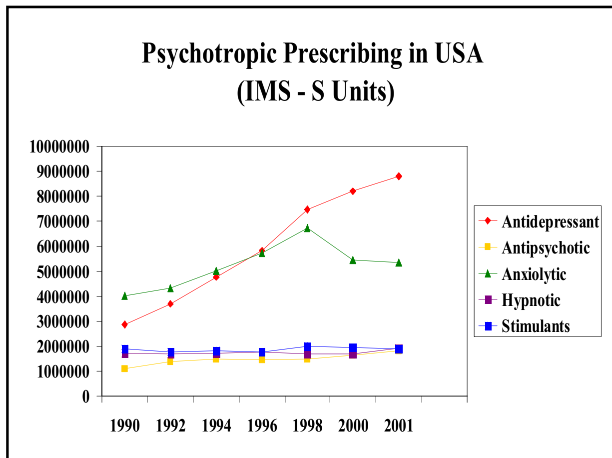
The discovery that tricyclic antidepressants blocked the re-uptake of both noradrenaline and 5-hydroxytryptamine (5-HT) was a significant step on the road to the development of the monoamine hypotheses of depression (Healy, 1987). The subsequent demonstration that the de-aminated metabolites of amitriptyline and imipramine, nortriptyline and desipramine, were antidepressants tilted the balance toward noradrenaline as the pertinent neurotransmitter, as these latter drugs were clearly inhibitors of noradrenergic rather than 5-HT uptake.

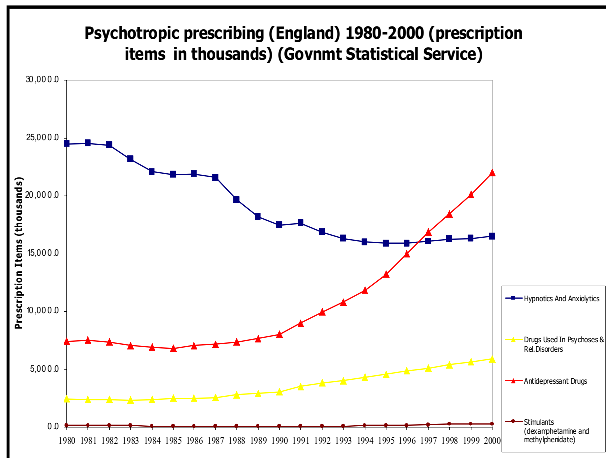
In 1964, Ciba Geigy chlorinated imipramine, in an attempt to produce a more effective antidepressant. However, not only was the resulting chlor-imipramine no more effective, it seemed to be markedly more

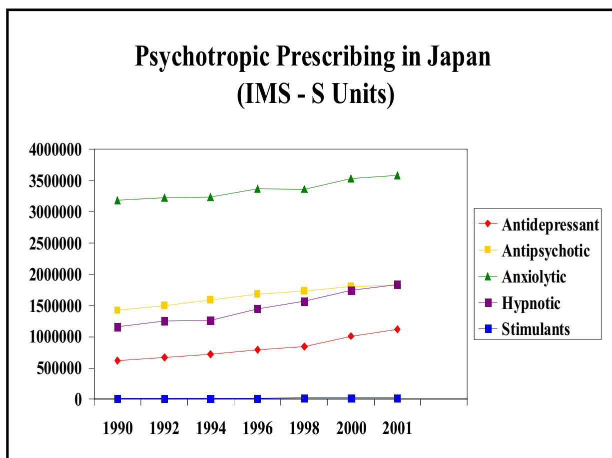
the market for phobic/anxious depressions was at this time targeted by producers of monoamine oxidase inhibitors (MAOIs), whose sales had slumped as a result of both the MRC comparative trial of antidepressants in 1965 and the recognition of the 'cheese effect'. Clomipramine was subsequently marketed as anti-obsessional and it was for this indication that it was licensed by the FDA in 1990.

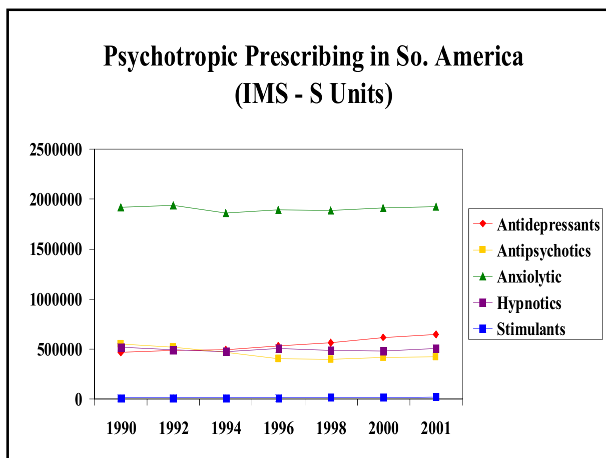
Whether the promotion of clomipramine as anti-obsessional was as market orientated as this analysis may suggest is uncertain, but the outcome today is that it and other 5-HT re-uptake inhibitors are marketed as specific for obsessive–compulsive disorders (OCD). It has been suggested that a large part of this impression derives from the fact that drugs



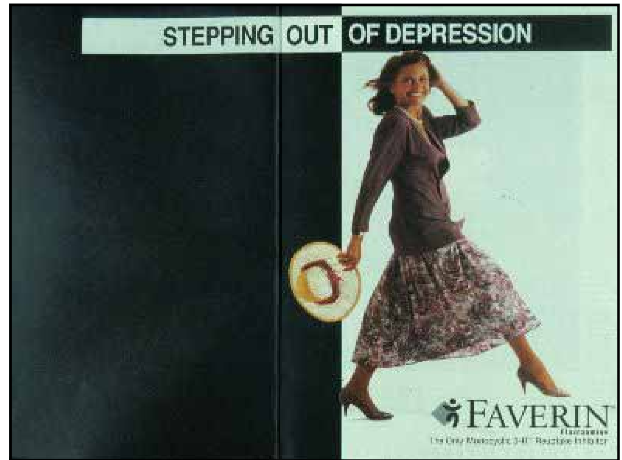


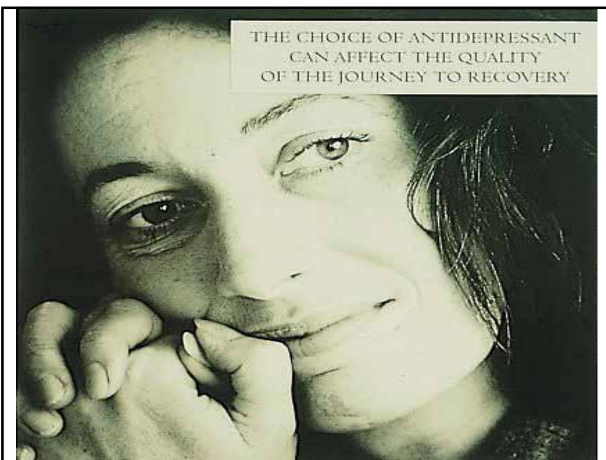


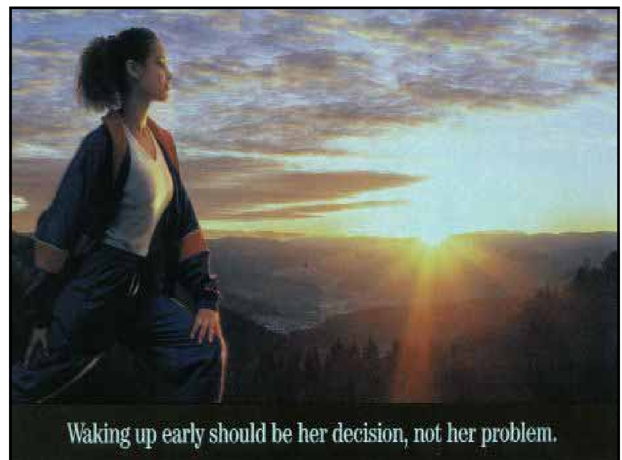




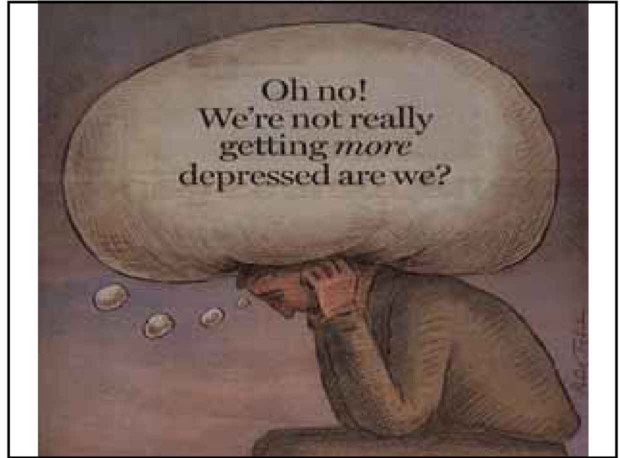
"Doctor,
I feel awful"


STEPPING OUT OF DEPRESSION
FAVERIN


THE CHOICE OF ANTIDEPRESSANT
CAN AFFECT THE QUALITY
OF THE JOURNEY TO RECOVERY

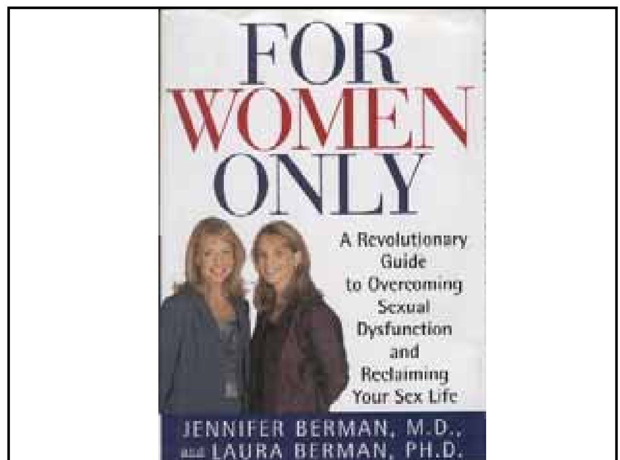

Waking up early should be her decision, not her problem.

"Doctor,
I feel awful"


Oh no!
We're not really
getting *more*
depressed are we?

DOLORAX
Born to Shop?
DOLORAX

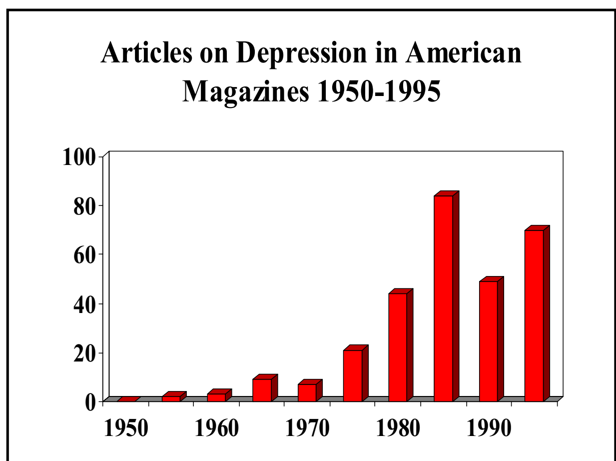
WHAT'S AN ORGASM, MUMMY?
I DUNNO— ASK YER FATHER

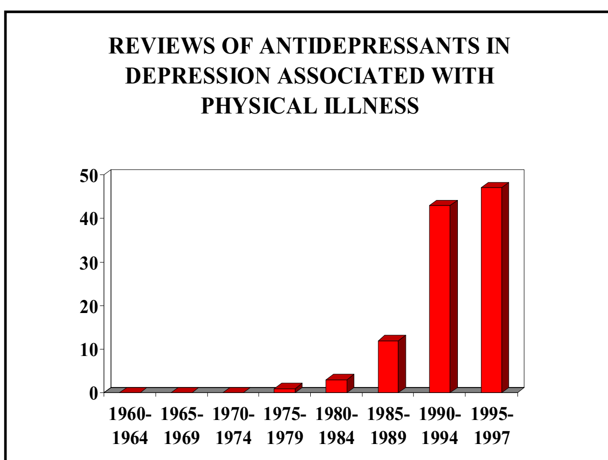

FOR
WOMEN
ONLY
A Revolutionary Guide to Overcoming Sexual Dysfunction and Reclaiming Your Sex Life
JENNIFER BERMAN, M.D.,
and LAURA BERMAN, PH.D.

Q: I'm 27 years old, with two young boys and a 33-year-old husband with the libido of a 15-year-old. For most women, it would be a dandy situation, but for me, sex has become a hassle (yet another one of those things I just don't have time for). He approaches me every day, and my walls go up immediately. I'm just not interested, and I know that hurts his feelings.

I keep trying to tell him that it's me, not him, with the problem. Every time we try to make love, it takes forever for me to get aroused and then it seems like the act just takes forever. I feel terrible about this. I should point out that my youngest son is 7 mos old and was breastfed until about a month or so ago, so I'm assuming that could have something to do with it. We always had a healthy sex life before the boys were born. Is it fatigue or should I have my hormones checked? I've been on Micronor (because of the nursing) but I'm wondering if I should switch to a pill with testosterone now that I'm no longer nursing or pumping. Where's the best place to start?

A: I suggest that you speak to your gynecologist about getting your testosterone levels checked. Also, if you are using birth control pills, that can effect your libido. You may consider taking DHEA 50mg as well.



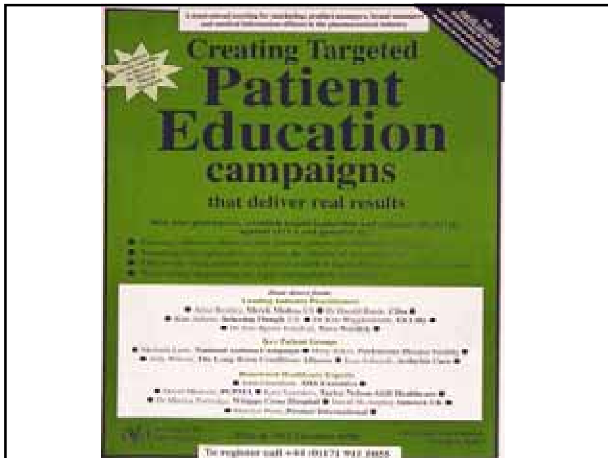


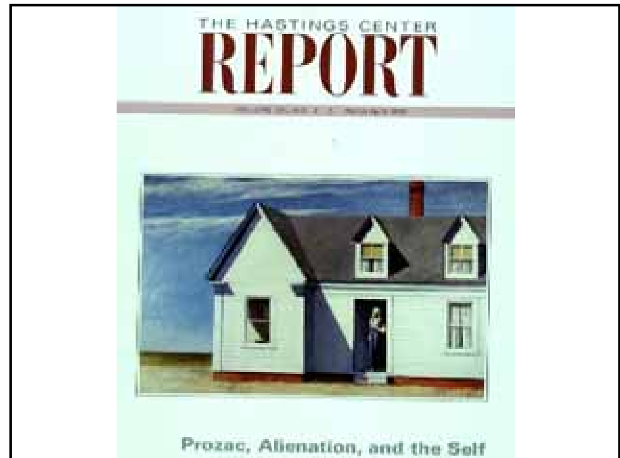
Dear David,

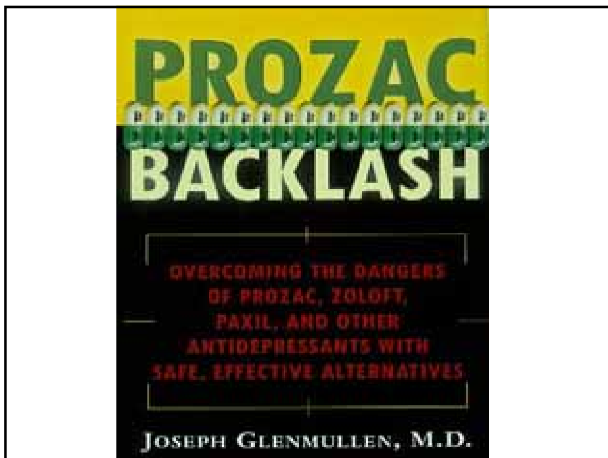
Many thanks for your letter of September 13, 1993 along with a copy of your article in J. Psychopharmacology 7 (4) (1993) 378 - 388. I hope to be able to convince management to order a sizeable quantity of reprints. It would be helpful, if you could let me know the price / copy for 5000 / 10 and 20 thousand copies.

I tried to reach you by phone today and will try again next week.

Best regards,







Glenmullen is a master of textual exegesis. quoting fragments from other physicians that distort their larger meanings. Use of his and others' personal testimonials is a reminder of medicine's authoritarian past. where the long and dishonorable tradition of "In my experience" means one patient. "In my series" stands for 2 patients and "In patient after patient after patient" equals 3 patients. The alternative is the scientific method. where hypotheses tested in randomized- controlled trials lead to incremental advances in knowledge….

Glenmullen's emphasis on discontinuing antidepressant medications will encourage discontinuation by some who are best served by continuing their SSRI maintenance medication. Relapse will follow discontinuation. sometimes into severe depressions. some of which will likely lead to suicide. Glenmullen's misrepresentations and distortions are dangerous and violate one of medicine's oldest dictums: Premium nil nocere (First. do no harm).

John Greist, Professor of Psychiatry, UNIV. of WISCONSIN Medical School

The title of this book appears appropriate as the term "backlash" has the connotation of over reaction to an event. This book presents a highly unbalanced view of a variety of areas of the treatment of depression and the use of SSRIs. Selected components of research studies, case vignettes, investigative reporting and personal opinion are used to present a slanted view of the status of antidepressant treatment. The boundaries between these sources of information are often unclear and much of the apparent "data" presented is in fact incorrect or quoted out of context.

While it is clear that a more balanced point of view would probably not sell as well in book form it is a disservice to people with mental illness to present such unbalanced information. Many of the points presented are not new or even controversial. Patients should be adequately diagnosed, treated appropriately following accepted guidelines and adequately informed of the risks and benefits of treatment…

Graham J. Emslie, Professor of Psychiatry, UNIVERSITY of TEXAS S.W Medical Center

Dr. Glenmullen's book "Prozac Backlash" is introduced at a time when psychiatric research documents the devastating effects of mental depression. The large body of accumulated research on depression also notes the development of treatments that have been demonstrated to be effective and safe for the alleviation of depression. Continued use of treatments for depression reduces depression-related pain and suffering for those who experience depression. Even the Surgeon General of the US has made adequate treatment of depression a priority.

Dr. Glenmullen is critical of this research. the diagnostic criteria developed by the American Psychiatric Association, the Food and Drug Administration. the pharmaceutical industry, and clinical investigators. He recommends treatments that for the most part are not adequately studied as alternatives to established methods of treating depression.

I am concerned that individuals who suffer from depression and who would likely benefit from established and well researched treatments might opt instead for the remedies suggested by Dr Glenmullen. I acknowledge that we do not know the cause(s) of depression or how treatments work. Answers to these important questions, however, can only come from further research.

David L. Dunner. Professor of Psychiatry UNIVERSITY of WASHINGTON

Throughout the book, Dr Glenmullen presents his assertions as fact. And although many of Dr. G s assertions are rooted in fact, he tends to overstate his case, going beyond the published research on side effects of SSRI medications, and into pure speculation.

Most of the SSRI-related side effects discussed in Dr G's book do exist. Additionally, it is true that some primary care physicians and internists may, at times, overprescribe or unnecessarily prescribe psychotropic medications to their patients. However, by depending on selective case studies to support his claims, Dr. G causes great harm to both patients who need and do well on medications: and to prospective patients.

Dr. Glenmullen' s take-away message - that these agents dangerous and cause serious problems, including death - goes well beyond what is appropriate. As such, it is an irresponsible detriment and deterrent to those seeking help for depression and it borders on inflammatory journalism.

Harvey L Ruben, Professor of Psychiatry
YALE UNIVERSITY

My foremost concern with Prozac Backlash is that it is misleading in nature. As a result of reading the book, it is possible that people with depression may be steered away from safe and effective treatments like Prozac, Zoloft, and Paxil, towards treatments whose safety and efficacy is still unclear (eg St John's Wort)

Dr G. is creating a great disservice by claiming that SSRIs are over-used and often misused when in fact millions of people have taken & derived benefit from these medications. Further, the very medications that Dr G. claims are overused are well studied, scrutinized and closely regulated.

I am also disheartened that Dr. G bolsters many of the arguments and proves his hypotheses by borrowing liberally from others' work including my own. In cases where Dr. G. quoted studies published by me, he tended to quote from the work out of context to fit his need;. At no point did Dr. G. consult me directly to question my studies, two of which he conveniently uses to prove his argument.

The book contains little, if any, truly helpful information for patients, and is a great disservice to people with depression. Patients should always discuss any medication questions with their physicians, particularly if they are considering switching from an SSRI to an over-the-counter herbal medication. It can be extremely dangerous to stop medication completely, or to mix a psychotropic with St John' s Wort.

Anthony J. Rothschild, Prof. of Psychiatry
UNIVERSITY of MASSACHUSETTS

April 6, 2000 Jamie Talan NEWSDAY BY FAX: 516-843-2873
Dear Ms. Talan:

In the new book *Prozac Backlash,* Dr. Joseph Glenmullen discredits not only the work of the U .S. Food and Drug Administration he attacks the work of research scientists, academic medical institutions and doctors.

The book preys on the fear of people with clinical depression, and may prompt some people to abandon their medication and seek medically unproven alternatives for a debilitating disease with potentially life-threatening consequences.

Because you often cover mental health issues, we thought you might be interested to know about this book.

If we can offer you any information, or some balance to a story you may be planning, we would be more than happy to oblige. **We can arrange for interviews with spokespeople from Eli Lilly and Company, as well as with independent researchers from the medical community.**

We are attaching some commentary on the book for your review. Thank you for your consideration. I will contact you tomorrow morning. Please feel free to call me in the interim - at 212/732-6111, Ext. 213.

Sincerely, Robert Schwadron

CHAMBERLAIN
COMMUNICATIONS
GROUP, INC.

April 6, 2000

Eli Lilly – F.O.I. REQUEST

103 Healy long term strategy.

Thank you for the message outlining your strategy to counteract Dr David Healy's claims re: Prozac and violence.

Send a letter to Healy designed to get him to stop discussing a study that he has never done.

Have a third party expert in the audience at BAP to ask Healy questions when he presents.

Just last Thursday Healy was quoted in a Cincinnati paper saying Prozac causes violence and suicide…X has asked that we go back to legal and determine if we can sue Healy under UK law.

104 Huge turn out… Good talk. Lesson no sponsor if Healy present in future.

Dear David

I am delighted you are able to participate in our satellite symposium… In order to reduce your workload to a minimum we have had our ghostwriters produce a first draft based on your published work. I attach it here…

Dear David
Rereading your M/S antidepressant psychopharmacology at the crossroads, I felt that it was a pity to try and modify it as it reads so well, on the other hand we need to bring across one or two points that are not accentuated in your M/S. We have decided therefore to publish "crossroads" as it is..but also to publish the original manuscript. SK has kindly agreed to author this one. We would however like your talk to be more on the first manuscript… in order to bring out the main commercially important points.
Best regards

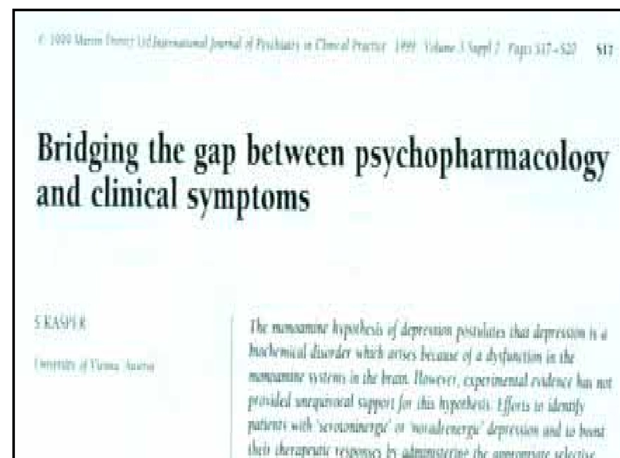
International Journal of Psychiatry in Clinical Practice 1999 Volume 3 Suppl 2 Pages S9–S15 S9

Antidepressant psychopharmacotherapy at the crossroads

D HEALY

North Wales Department of Psychological Medicine, Bangor, Wales

The original treatments for nervousness involved compounds containing a large number of ingredients aimed at covering all possible ailments that might afflict an individual. The development of modern pharmacotherapy has involved progress towards greater selectivity and specificity which has led to highly selective dopamine antagonists in schizophrenia and both selective serotonin and noradrenaline re uptake inhibitors in depression. Progress in terms of selectivity and specificity however suggests that pharmacological and clinical specificity differ. Pharmacologically

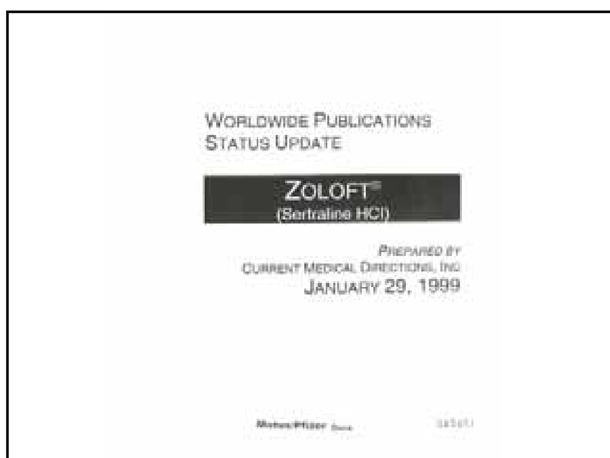

International Journal of Psychiatry in Clinical Practice 1999 Volume 3 Suppl 2 Pages S17–S20 S17

Bridging the gap between psychopharmacology and clinical symptoms

S KASPER

University of Vienna, Austria

The monoamine hypothesis of depression postulates that depression is a biochemical disorder which arises because of a dysfunction in the monoamine systems in the brain. However, experimental evidence has not provided unequivocal support for this hypothesis. Efforts to identify patients with 'serotoninergic' or 'noradrenergic' depression and to boost their therapeutic responses by administering the appropriate selective


WORLDWIDE PUBLICATIONS
STATUS UPDATE

ZOLOFT®
(Sertraline HCl)

PREPARED BY
CURRENT MEDICAL DIRECTIONS, INC
JANUARY 29, 1999

Current Medical Directions
"to deliver scientifically accurate information strategically developed for specific target audiences"

CMD writes up studies, review articles, abstracts, journal supplements, product monographs, expert commentaries and textbook chapters. It conducts meta-analyses, and organizes journal supplements, satellite symposia, and consensus conferences as well as advisory boards for its clients

[CMD] "strives to exceed the expectations of our clients and to assist them in achieving their strategic objectives".

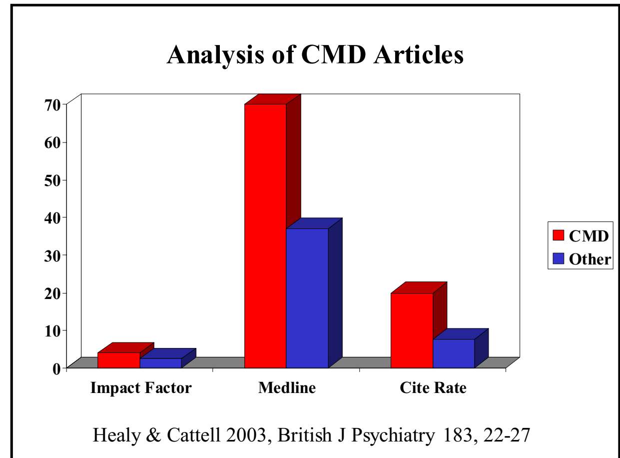
Page 12 of 25

Prepared by Current Medical Directions, Inc.

ANXIETY

POST-TRAUMATIC STRESS DISORDER

Author—Title	Vendor	Status
Author TBD—(640) Sertraline vs. placebo in PTSD	Paladin	Poster presented at ECNP, 1997. Paper is completed, but revisions are needed.
Author TBD—(671) Title TBD	Paladin	Poster presented at ECNP, 1998. First draft completed, but additional analyses needed. Both 640 and 671 studies to be submitted soon. One will go to *New England Journal of Medicine* and the other to *JAMA*.



Healy & Cattell 2003, British J Psychiatry 183, 22-27

THERAPEUTIC AREAS	
DEPRESSION	15
DYSTHYMIA	7
PANIC DISORDER	8
POST-TRAUMATIC STRESS DISORDER	2
GEN ANXIETY DISORDER	2
OBSESSIVE COMPULSIVE DISORDER	1
DIFFERENTIATION BETWEEN SSRIs	17
OUTCOMES RESEARCH	10
SERTRALINE IN ELDERLY	10
SERTRALINE IN CHILDREN	6
SERTRALINE IN WOMEN	4
PHARMACOKINETICS	2
PEDOPHILIA	1

Dear David,

Thank you very much for all your hard work on this article. I'm afraid we've run into a legal wall with our libel lawyer reluctant for us to publish your piece… I remain supportive of publication but obviously can't do this against legal advice.

Our lawyer has several questions that he wants us to address at this stage. He isn't ruling out publication, but we need to reassure him about the facts first.

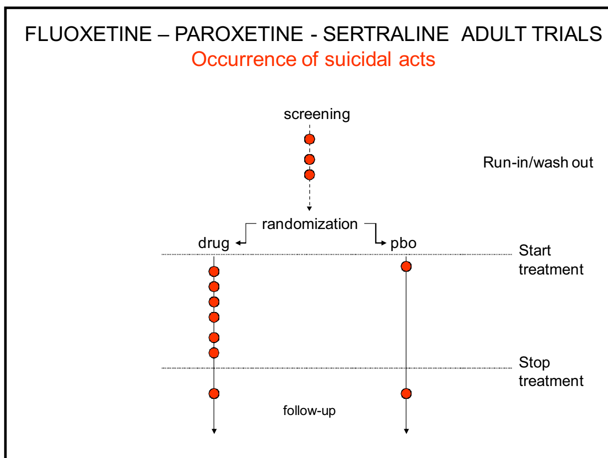
Best wishes,

KA

Editor British Medical Journal

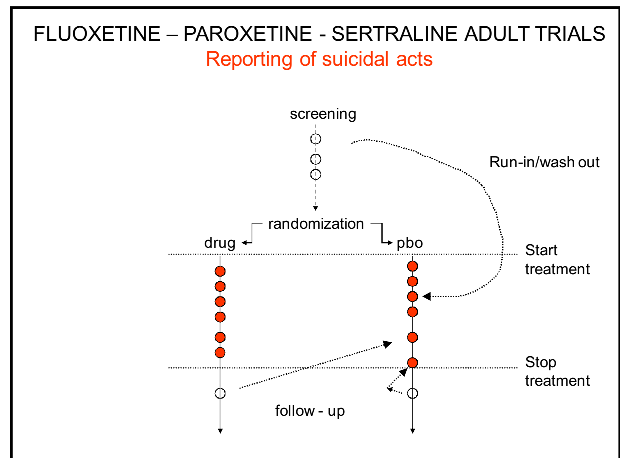
FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

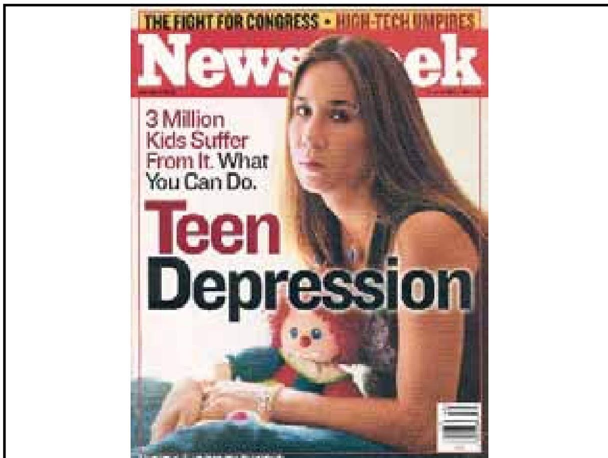
Occurrence of suicidal acts



FLUOXETINE – PAROXETINE - SERTRALINE ADULT TRIALS

Reporting of suicidal acts





Alderman et al 1998 – "sertraline is **safe** and likely to be **effective** in pediatric patients." (9%)

Ambrosini, Wagner et al 1999 – "sertraline is **effective, safe and well tolerated**" (5.7%)

Keller, Wagner et al 2001 – "study provide[s] evidence of the **safety & efficacy** of paroxetine in the treatment of adolescent depression (5.4%)

Wagner et al 2002 – "these results indicate that treatment of children and adolescents with paroxetine is **safe and generally well-tolerated**.

Geller, Wagner et al 2002 – "paroxetine is a **safe and effective** treatment for OCD in pediatric pts"

Wagner et al 2003 – "sertraline is an **effective and well tolerated** treatment for children and adolescents with MDD"

Ovid: KEL...: J Am Acad Child Adolesc Psychiatry, Volume 40(7).July 2001 762-77   Page 1 of 16

Journal of the American Academy of CHILD & ADOLESCENT PSYCHIATRY

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Volume 40(7)   July 2001   pp 762-772

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

[Articles]

KELLER, MARTIN B. M.D.; RYAN, NEAL D. M.D.; STROBER, MICHAEL PH.D.; KLEIN, RACHEL G. PH.D.; KUTCHER, STAN P. M.D.; BIRMAHER, BORIS M.D.; HAGINO, OWEN R. M.D.; KOPLEWICZ, HAROLD M.D.; CARLSON, GABRIELLE A. M.D.; CLARKE, GREGORY N. PH.D.; EMSLIE, GRAHAM J. M.D.; FEINBERG, DAVID M.D.; GELLER, BARBARA M.D.; KUSUMAKAR, VIVEK M.D.; PAPATHEODOROU, GEORGE M.D.; SACK, WILLIAM H. M.D.; SWEENEY, MICHAEL PH.D.; WAGNER, KAREN DINEEN M.D., PH.D.; WELLER, ELIZABETH B. M.D.; WINTERS, NANCY C. M.D.; OAKES, ROSEMARY M.S.; MCCAFFERTY, JAMES P. B.S.

SB CONFIDENTIAL - FOR INTERNAL USE ONLY

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

American College of Neuropsychopharmacology

EXECUTIVE SUMMARY

PRELIMINARY REPORT OF THE TASK FORCE ON SSRIs AND SUICIDAL BEHAVIOR IN YOUTH

January 21, 2004

ACNP TASK FORCE

Graham Emslie, M.D., Co-Chair of the ACNP Task Force
J. John Mann, M.D., Co-Chair of the ACNP Task Force
William Beardslee, M.D., Prof of Child Psychiatry, Harvard,
Jan Fawcett, M.D., Professor of Psychiatry, U of New Mexico
Andrew Leon, Ph.D., Professor of Public Health, Cornell
Herbert Meltzer, M.D., Professor of Psychiatry, Vanderbilt
Fredrick Goodwin, M.D., Psychopharm. Res. Center, GWU;
David Shaffer, M.D., Professor of Child Psychiatry, Columbia
Karen Wagner M.D., Ph.D., Prof of Psychiatry, U of Texas;
Neal Ryan, M.D., Professor of Psychiatry, U of Pittsburgh.

GYMR knows how to grab the attention of D.C. and national reporters – reporters who set the agenda for media in communities nationwide.

Our media events are successful because we have a nose for news. We know how to take the language of science and medicine and transform it into the more understandable language of health. We advise clients of the best dissemination strategy for their news and make sure that the message they deliver is compelling, documented and contributes to other national dialogues in a real and

The goal of marketing is
To own the market
Not just to sell the product

There must be a fundamental opposition
between marketing and science in that:

Marketing proceeds by building consensus
while
Science proceeds by fracturing consensus

UNMET NEEDS

Bipolar disorder 5%

Under-acknowledged and under-researched

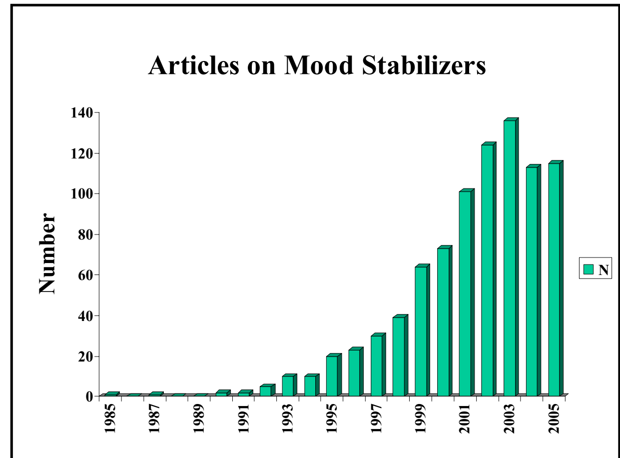
My doc and I decided not to have antidepressants

Identify triggers ….

My feelings of persecution are really …

In my most recent episode I used a mood scale ..

DEPAKOTE®
valproate semisodium
Fast, effective mood stabiliser
Anti manic effects in 1–4 days[1]



Level the symptoms of acute mania associated with bipolar disorder...
with an effective tool for MOOD STABILIZATION.

zyprexa
olanzapine

An Introduction to Bipolar Disorder and Manic Depression

Lilly

Staying Well ...
with bipolar disorder

Remember...

- Bipolar disorder is often a life-long illness needing life-long treatment
- Symptoms come and go, but the illness stays
- People feel better because their medication is working
- Almost everyone who stops taking their medication will get ill again
- The more episodes you have, the more difficult they are to treat

Anything or Nothing

Self-guide for People with Bipolar Disorder

THE RIGHT MEDICINE AT THE RIGHT TIME

Medicines are crucially important in the treatment of bipolar disorders. Studies over the past 20 years have shown beyond the shadow of doubt that people who receive the appropriate drugs are better off in the long-term than those who receive no medicine.

THE RIGHT MEDICINE AT THE RIGHT TIME

Medicines are crucially important in the treatment of bipolar disorders. Studies over the past 20 years have shown beyond the shadow of doubt that people who receive the appropriate drugs are better off in the long-term than those who receive no medicine.

All studies of life expectancy on antipsychotics
Show a doubling of mortality rates
And a reduction of life expectancy

All studies of prophylaxis with mood stabilizers
Show a doubling of suicidal act risk compared to placebo

Valproate and other mood stabilizers
are among the most teratogenic in medicine

Mood Diary

Month 01

- +2 Very productive, everything to excess (phone calls, writing, tea, smoking), charming and talkative.
- +1 Self-esteem good, optimistic, sociable and articulate, good decisions and get work done.
- 0 Mood in balance, no symptoms of depression or mania. Life is going well and the outlook is good.
- -1 Slight withdrawal from social situations, concentration less than usual, slight agitation.
- -2 Feeling of panic and anxiety, concentration difficult and memory poor, some comfort in routine.

Healy

The Creation of Psychopharmacology

NEWS 5

Pictures bring home the horrors of bone disease

JAPAN

MANIC-DEPRESSIVE ILLNESS WAS

10 per million new cases per year

300 new cases per year

8 Times less common than Schizophrenia

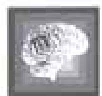
BIPOLAR DISORDER IS

5% + of Japan

5,000,000 Japanese

As common as Depression

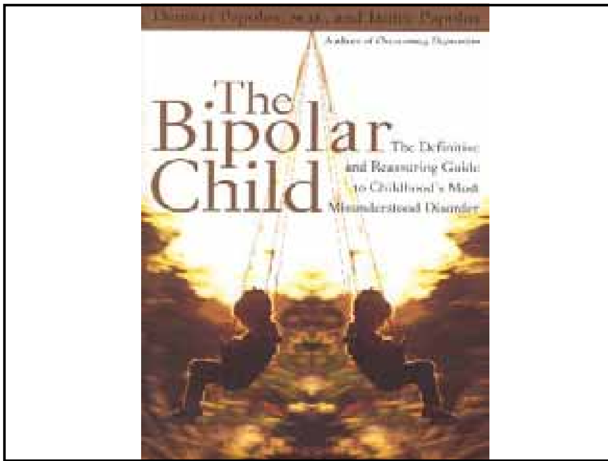
10 times commoner than Schizophrenia

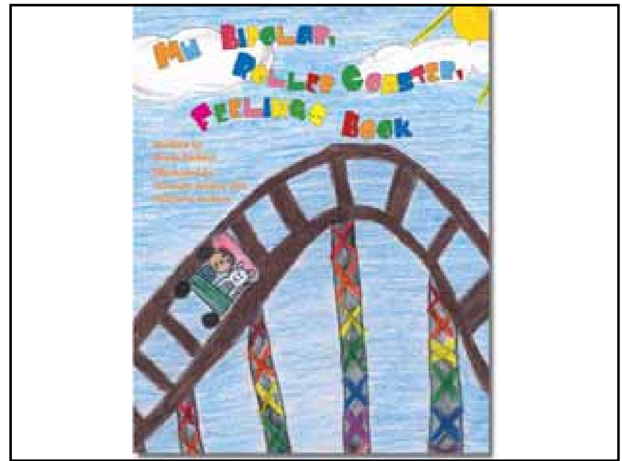


Classic Text No. 58

Manic-depressive illness in children: an early twentieth-century view by Theodor Ziehen (1862–1950). Introduction

CHRISTOPHER BAETHGE
IRA GLOVINSKY
ROSS J. BALDESSARINI





Name:________________ My Mood Chart for ____________

In the **morning** I felt: (circle all the ways you felt)

Sad/Depressed | Scared/Anxious | Sick/Yuck! | Good/ O.K. | Happy | Hyper/Silly | Angry/Irritable

In the **afternoon** I felt:

Sad/Depressed | Scared/Anxious | Sick/Yuck! | Good/ O.K. | Happy | Hyper/Silly | Angry/Irritable

In the **evening** I felt:

Sad/Depressed | Scared/Anxious | Sick/Yuck! | Good/ O.K. | Happy | Hyper/Silly | Angry/Irritable

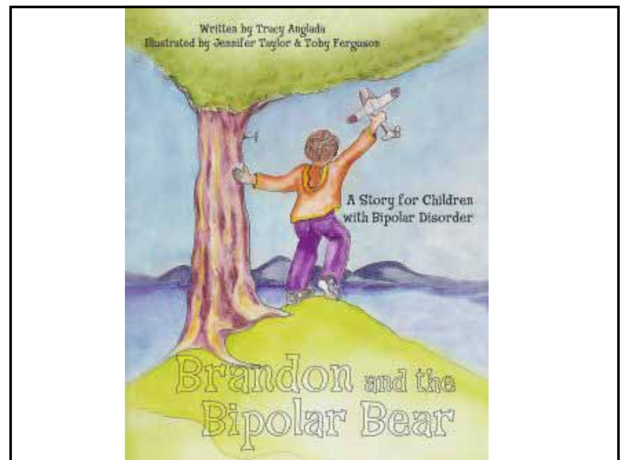
Last night I fell asleep at____:____ **This morning I woke up at ____:____**

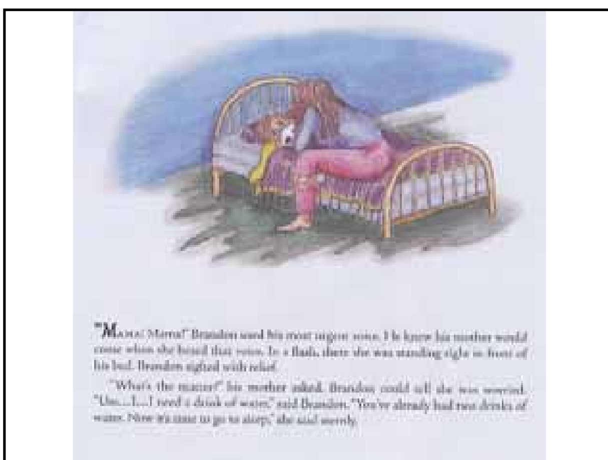
Today I took all my medicine: (circle one) **on time late early oops! forgot:______**

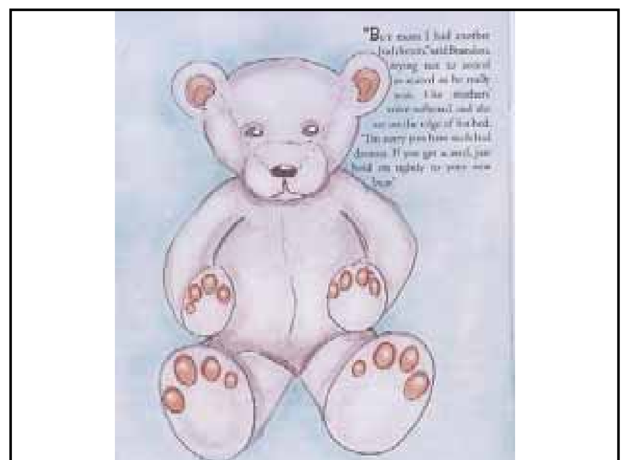
Last night I took my medicine: (circle one) **on time late early oops! forgot:______**

New medicine I started or medicine I stopped: ____________

Something I want to tell my doctor: ____________



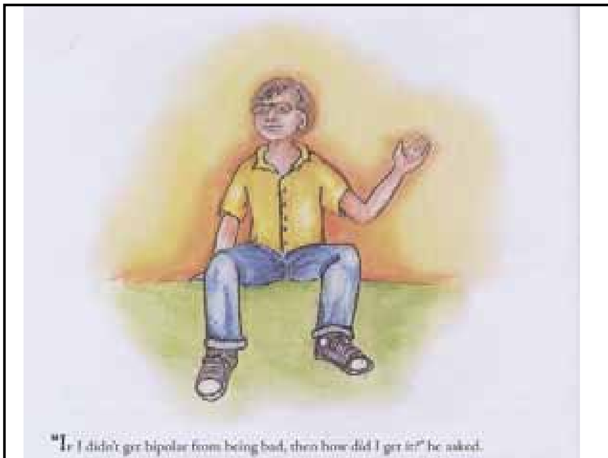




"BRANDON" Dr. Samuel said. "I want to tell you something." Brandon sat close to his mother careful not to hurt his bears' broken arm. "You have bipolar disorder," the doctor said.

"Bi….what?" asked Brandon as he watched his feet swishing back and forth through the air.

"Bipolar disorder," repeated Dr. Samuel. "You see, the way we feel is controlled by chemicals in our brain. In people with bipolar disorder, these chemicals can't do their job right so their feelings get jumbled inside. You might feel wonderfully happy, horribly angry, very excited, terribly sad, or extremely irritated all in the same day. It's very scary and confusing sometimes. It can be so confusing inside that living seems too hard."



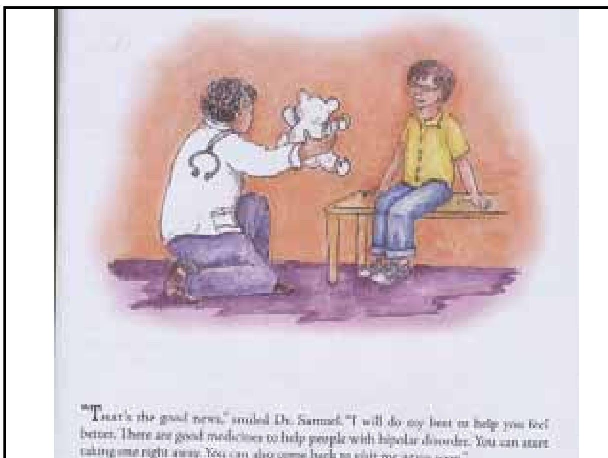
"IF I didn't get bipolar from being bad, then how did I get it?" he asked.

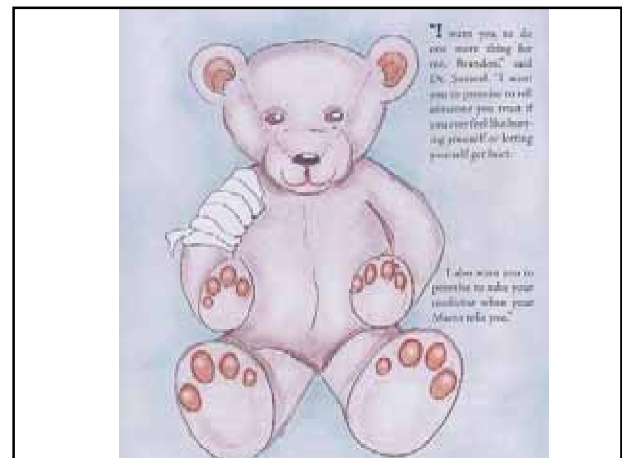
"How did you get your green eyes and your brown hair?" asked Dr. Samuel.

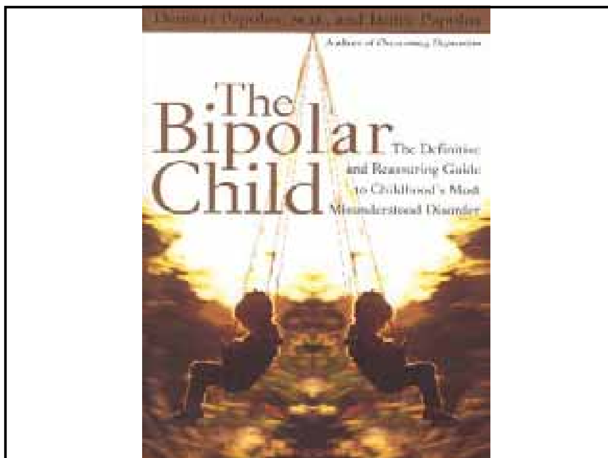
"My Mama has green eyes," Brandon said looking at his mother.

"And your Daddy has brown hair," said his mother as she ran her fingers through his soft hair.

"It's the same with bipolar disorder. You can inherit it. Someone else in your family may have it too. Many other children have also inherited it from their families."







Many of the mothers we interviewed remembered their baby's excessive activity in utero.

1/ While my daughter was in the womb, she kicked so hard and often that I had very little rest… much of the time it felt like she was in a fight - rolling and tumbling around and then, when she was born.. she kept all the other babies up with her screaming.

2/ I too noticed signs that this was an extra-spirited child. In fact, while I was pregnant, I remember saying, "Uh-oh, the baby is angry again." His kicks would last for an hour as I doubled over in pain..

3/ "At 14 weeks the sonographer and obstetrician were unable to get a picture of Ian's face and could not sample the amniotic fluid due to *constant, unpredictable activity*."

P51

Open trial of atypical antipsychotics in preschoolers with bipolar disorder

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Objective: To evaluate the short-term safety and efficacy of atypical neuroleptics in a single-site, prospective, open-label, eight-week study of risperidone and olanzapine monotherapy in preschoolers with bipolar disorder (BPD).

Methods: Risperidone was initiated at an open-label dose of 0.25 mg/day to be increased weekly according to response and