Psychopharm, Regulation and Industry: A Story in Three Chapters

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March 22, 2019

For Dr Lemmens' and Dr Sharpe's class "Mental Health and the Law"

But first, “mental health and the law”: What’s at stake here?

- 1. The diagnoses – are they sound? Are they credible in court?
- 2. The treatments – are they safe and effective? Grounds here for legal action?
- 3. The regulators – impartial or corruptible?

So there are lots of “systemic” issues here, aside from the psychiatric status of a given individual.

Let’s take a look.

The interplay among law, psychiatry and psychopharmacology is a big story.

Let's simplify: We'll tell it in three chapters. This slide starts us off in 1949, when "psychopharmaceuticals" were non-existent, and the only psychoactive agents were the barbiturates and the amphetamines.

FIGURE 2
One of a series of photograph from Peterson's textbook depicting a model sales call. The caption beneath this image reads, 'Select an "across-the-corner" position at the desk'.

Source: Peterson (1949: 271–73) courtesy of McGraw-Hill Inc. and Eli Lilly and Co.

Then in the “golden age” of 1950s the major drug classes of modern psychopharm were developed.

Lithium (1949)

Chlorpromazine (Thorazine, Largactyl), 1952

The monoamine oxidase inhibitors – MAOIs (iproniazid, Marsilid, marketed in 1951 for TB, for depression 1957)

Meprobamate (Miltown) 1955 – the first blockbuster

The first tricyclic antidepressant (imipramine, Tofranil), 1957

The first benzodiazepine (Librium), 1960

Note: that I have not used “drug class” names – eg “antipsychotics,” “antidepressants” because these are overly restrictive. Most effective drugs affect a number of functions in mood and cognition.

(The Sea View TB sanatorium story in 1952, where the clinical efficacy of Marsilid in depression was discovered.)

Abbildung 19: Eine Schwester wiegt ein sehr glückliche Tuberkulose-Patientin, die im Staten Island Hospital zwei Monate lang Marsilid erhalten hat (Fotografiert am 23.02.1952 von Frank Jurkoski ®corbisimages)

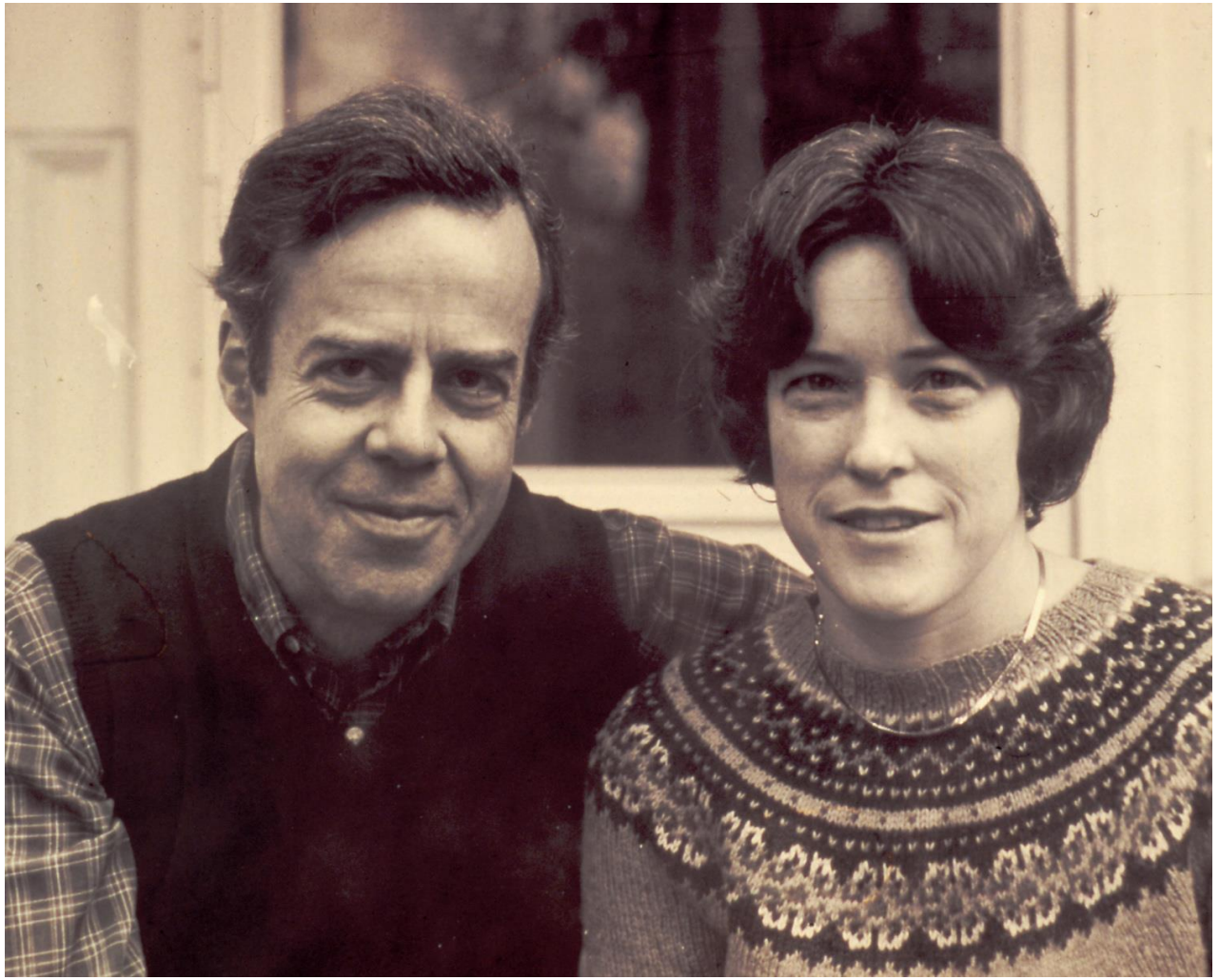
Some of these new drugs *are* specific for certain diseases – although not necessarily for just that disease.

One consequence: We needed a new edition of the DSM-II (1968) to give us appropriate disease-specific diagnoses. Doctors require a specific disease to prescribe a specific medication for -- was the idea.

- Here “endogenous depression” (undoubtedly melancholia) – Spain, 1940s

- DSM-II was kind of vague about depression. Can’t we do better?

So in 1974 the American Psychiatric Association convoked a Task Force to design a new *Manual*.



It was under the leadership of this man.

Who is this man? (with his wife, Janet Williams)

Robert Spitzer

In 1974 Spitzer's Task Force set to work to devise a whole new nosology.

What an adventure!

So many new diseases to design!

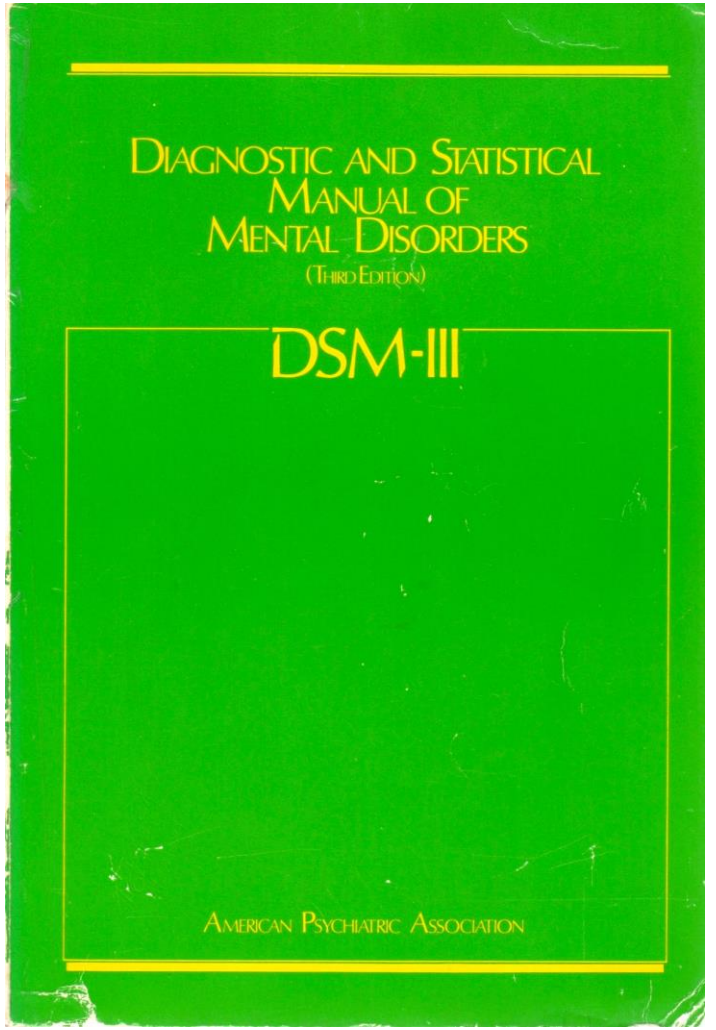
Major depression

ADHD

PTSD

And much more.

DSM-III came out in 1980.



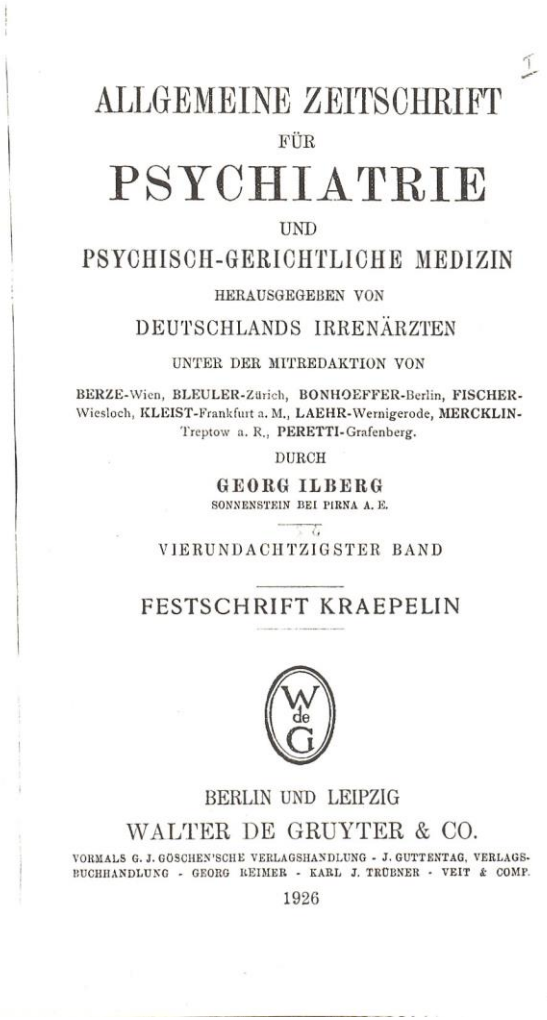
Now, there were some problems.

One problem was that the Task Force seemed unaware that there was a psychiatric tradition of nosology (disease classification) going back two centuries. [Here is Emil Kraepelin]

It was conceivable that in that amount of experience, some useful disease conceptions might have evolved, comparable to TCM (Traditional Chinese Medicine, which had two millennia to sort out helpful from unhelpful medications).

Yet the monoglot Task Force had no insight into this at all and thought they would devise a nosology from scratch – “Hey, let’s just sit down . . . “

Kraepelin



ALLGEMEINE ZEITSCHRIFT

FÜR

PSYCHIATRIE

UND

PSYCHISCH-GERICHTLICHE MEDIZIN

HERAUSGEGEBEN VON

DEUTSCHLANDS IRRENÄRZTEN

UNTER DER MITREDAKTION VON

BERZE-Wien, BLEULER-Zürich, BONHOEFFER-Berlin, FISCHER-Wiesloch, KLEIST-Frankfurt a. M., LAEHR-Wernigerode, MERCKLIN-Treptow a. R., PERETTI-Grafenberg.

DURCH

GEORG ILBERG

SONNENSTEIN BEI PIRNA A. E.

VIERUNDACHTZIGSTER BAND

FESTSCHRIFT KRAEPELIN

BERLIN UND LEIPZIG

WALTER DE GRUYTER & CO.

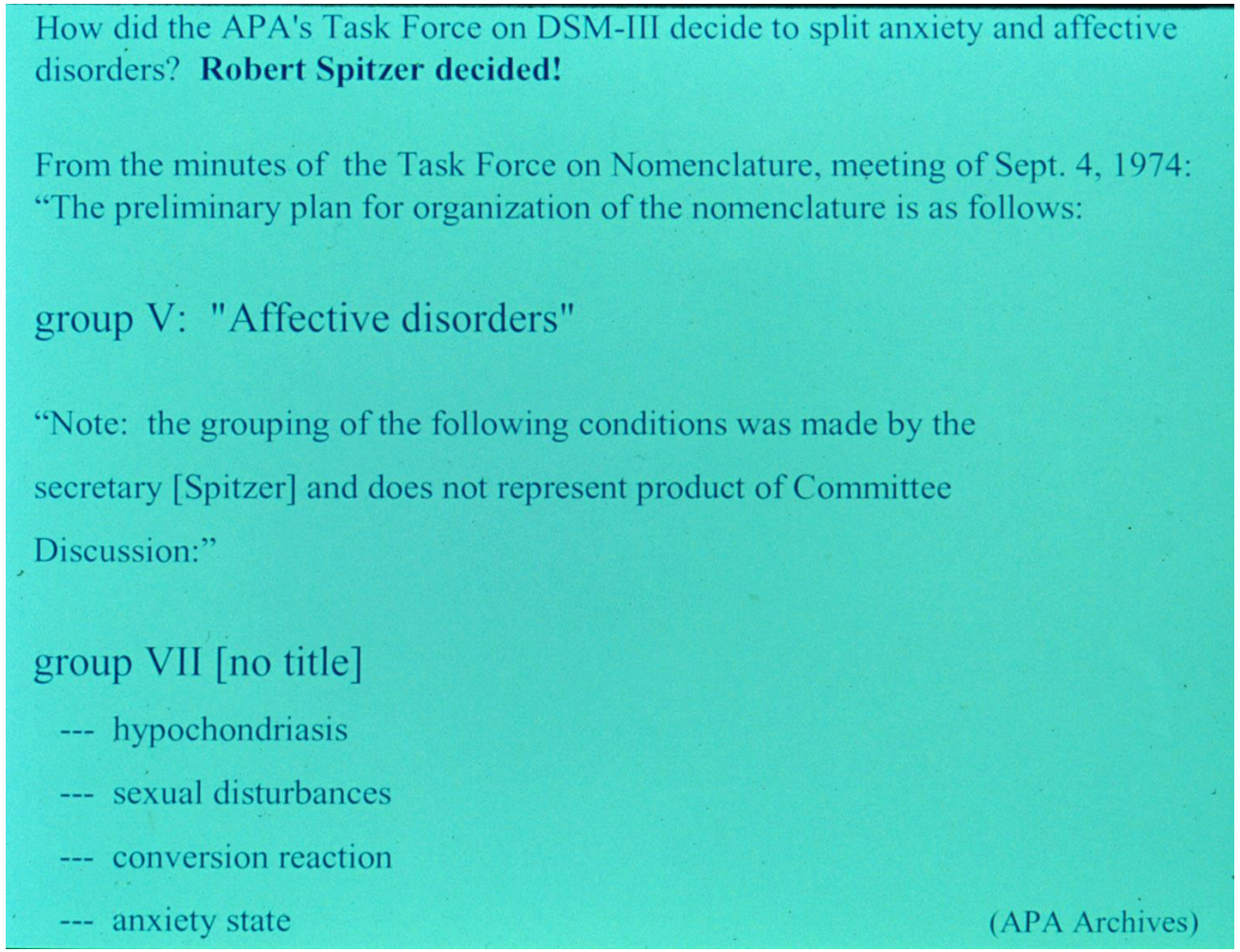
VORMALS G. J. GÖSCHEN'SCHE VERLAGSHANDLUNG - J. GUTTENTAG, VERLAGS-BUCHHANDLUNG - GEORG REIMER - KARL J. TRÜBNER - VEIT & COMP.

1926

As a result, the Task Force made some questionable decisions.

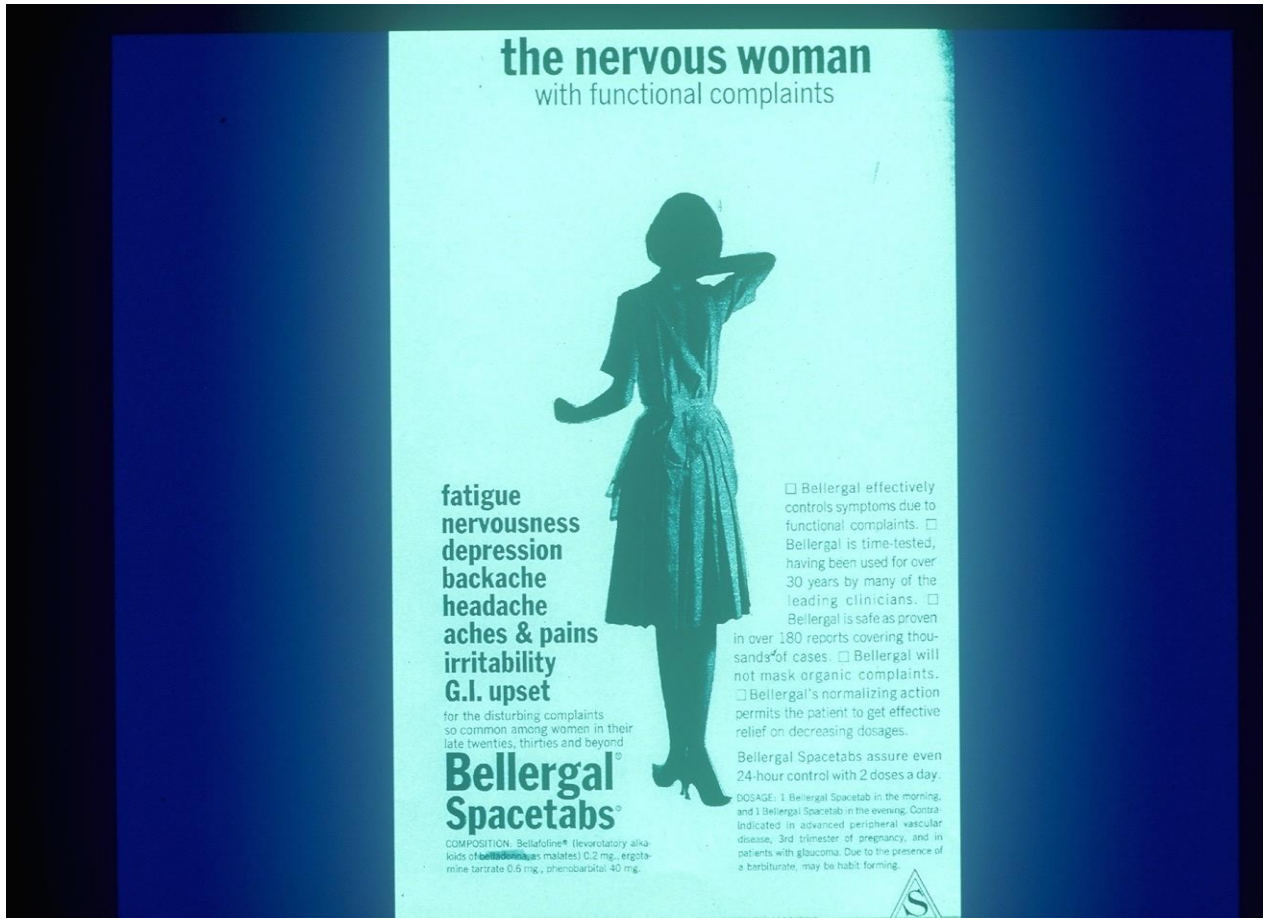
For example, splitting up anxiety and depression, which clinically often co-occur.

(Mixed anxiety-depression is, in fact, the commonest form of either illness.)

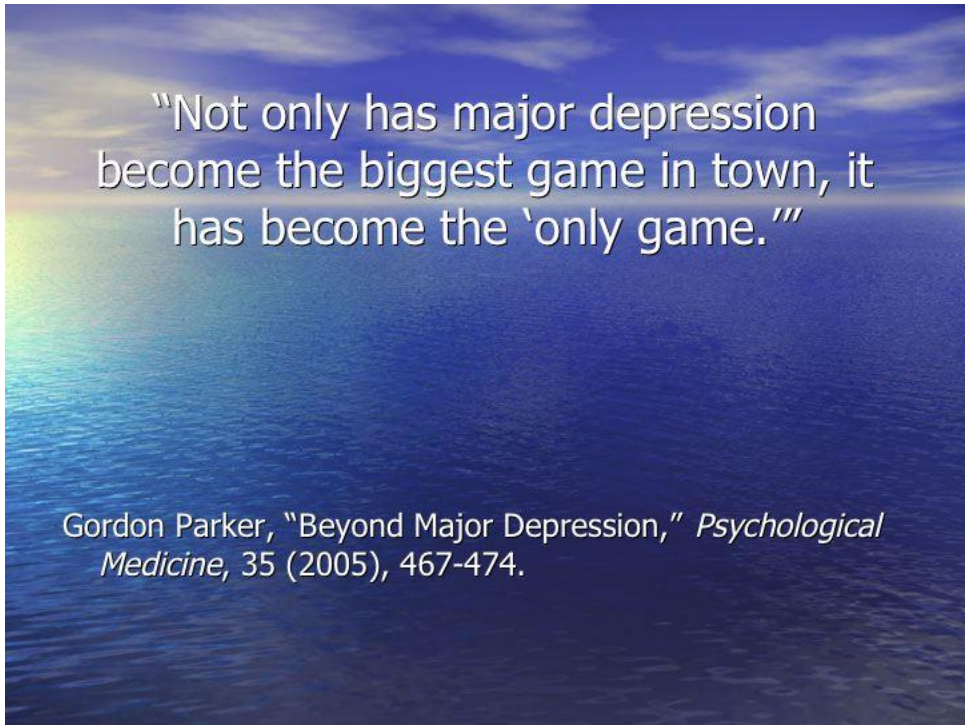


But the most questionable decision of all . . .

- Was to merge psychiatry's two (or three) depressions into the single diagnosis: "major depression."
- Consider: psychiatry had always had two depressions, which were in fact different diseases, not just differences in severity:
- (1) **Melancholia** (profound anhedonia, inability to feel anything or else deep sadness), psychomotor slowing). Also called "endogenous depression."
- (2) **Neurasthenic "depression"** Quotes around depression because the patients are not necessarily sad. They have anxiety, insomnia, fatigue, somatic symptoms, etc). Also called "nerves" or "nervous disease." Or "reactive depression."
- Here: nerves



So we ended up with “major depression.”



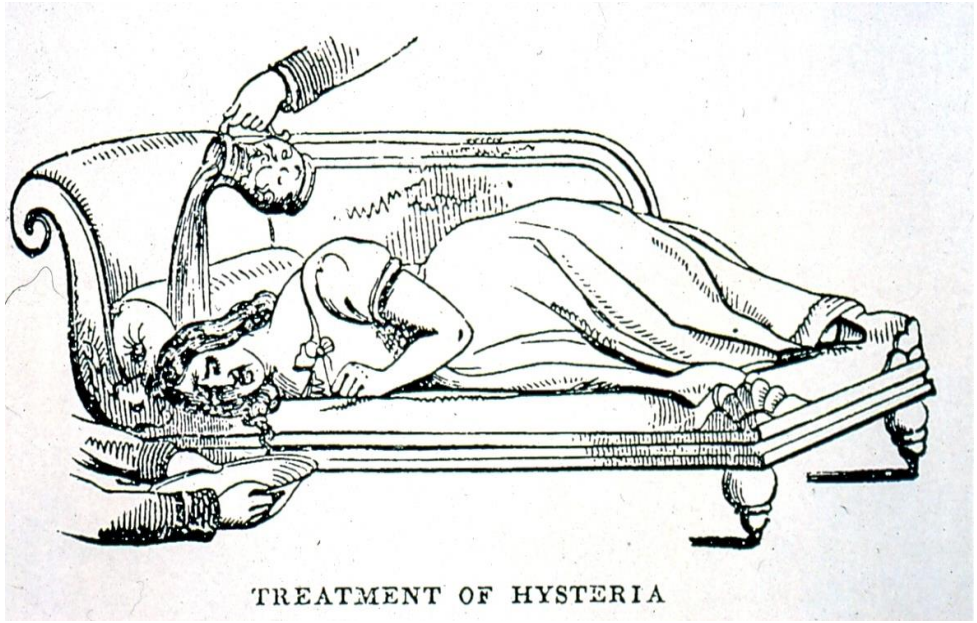
And these two former depressions had separate treatments.

- For melancholia: opium, TCAs, convulsive therapy
- For neurasthenic depression: just about anything; latterly, meprobamate, benzodiazepines
- So this differential diagnosis, that might have led to differential prescribing, was *lost*.

Now, one more thing about diagnosis . . .

Some of the other DSM categories cause uneasiness too: schizophrenia, bipolar disorder, autism. These all have the same status in psychiatry today that "hysteria" once had. Very popular, but that doesn't mean they exist in nature.

We'll come back to this.



TREATMENT OF HYSTERIA

So this is the end of chapter 1: DSM-III inserts vast confusion into nosology and diagnosis.

Chapter Two

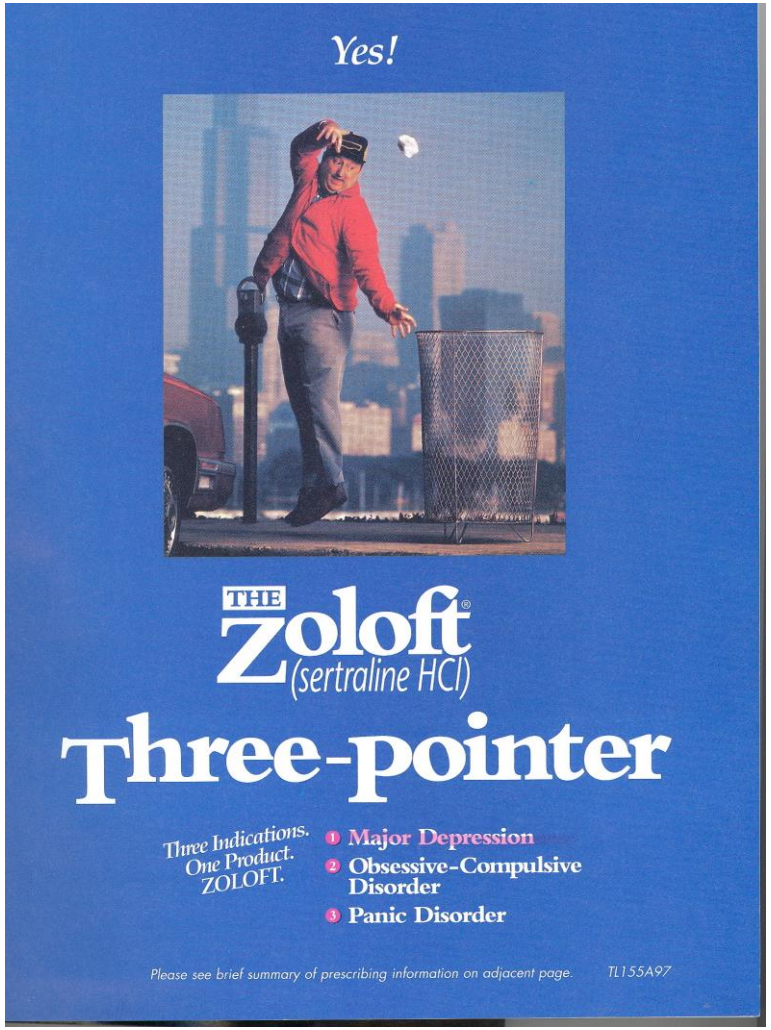
- The Development of the SSRI “antidepressants.” The drug class that swallowed psychiatry.

Pharma had nothing to do with the drafting of DSM-III.

But the new Manual was a great gift to them, because it created these huge, biological-sounding disease entities.

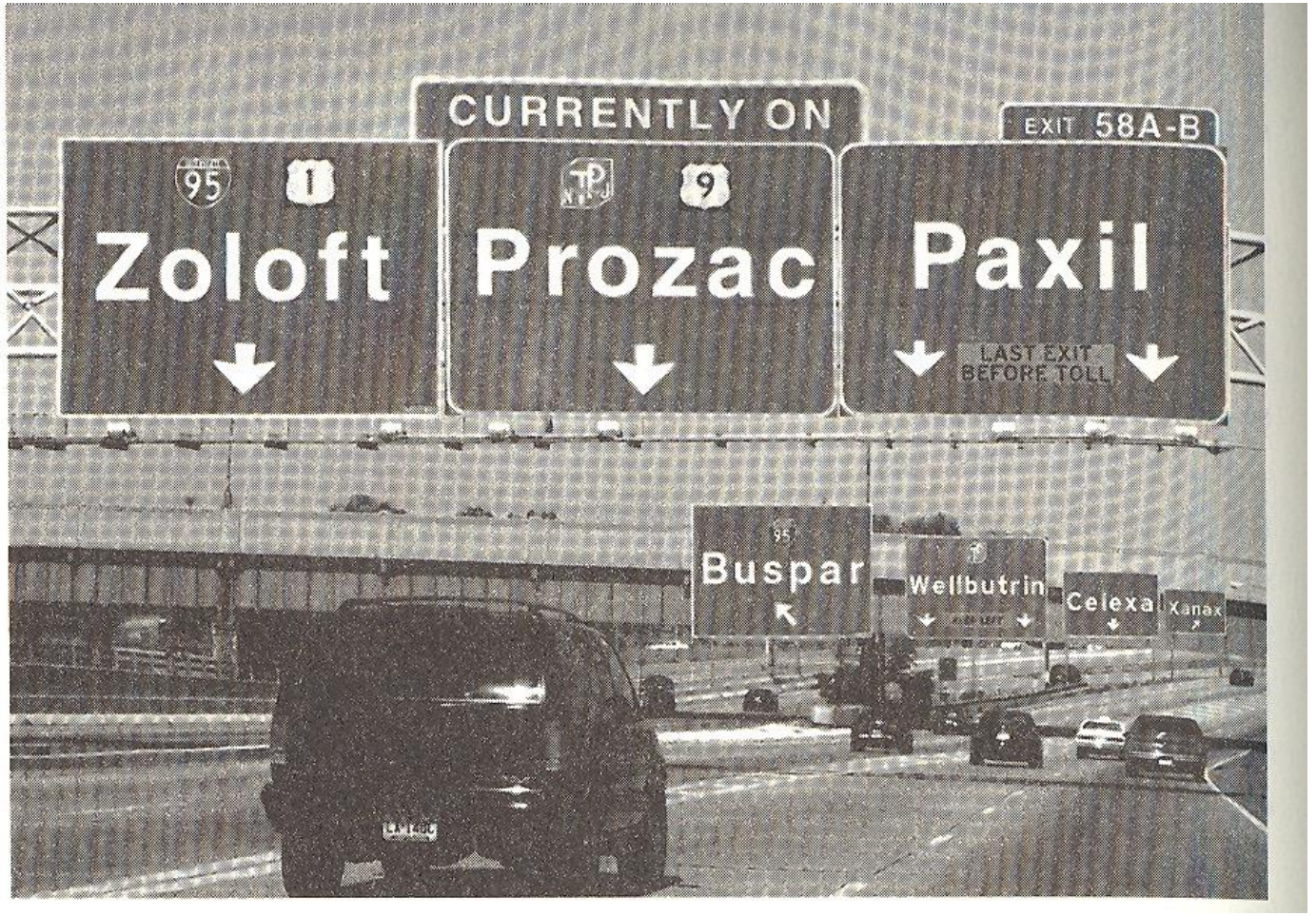
Some previous psychiatric diagnoses did not sound very “biological”: “depressive neurosis”: what’s the neurochemical basis of that? (It was a favored psychoanalytic diagnosis.)

But major depression: There’s a single big diagnosis we can work with. And we’ve discovered all kinds of anomalies in serotonin and norepinephrine metabolism in MDD. It was a diagnosis that screamed out for pharmacotherapy.



Prozac (fluoxetine) was the first SSRI “antidepressant”

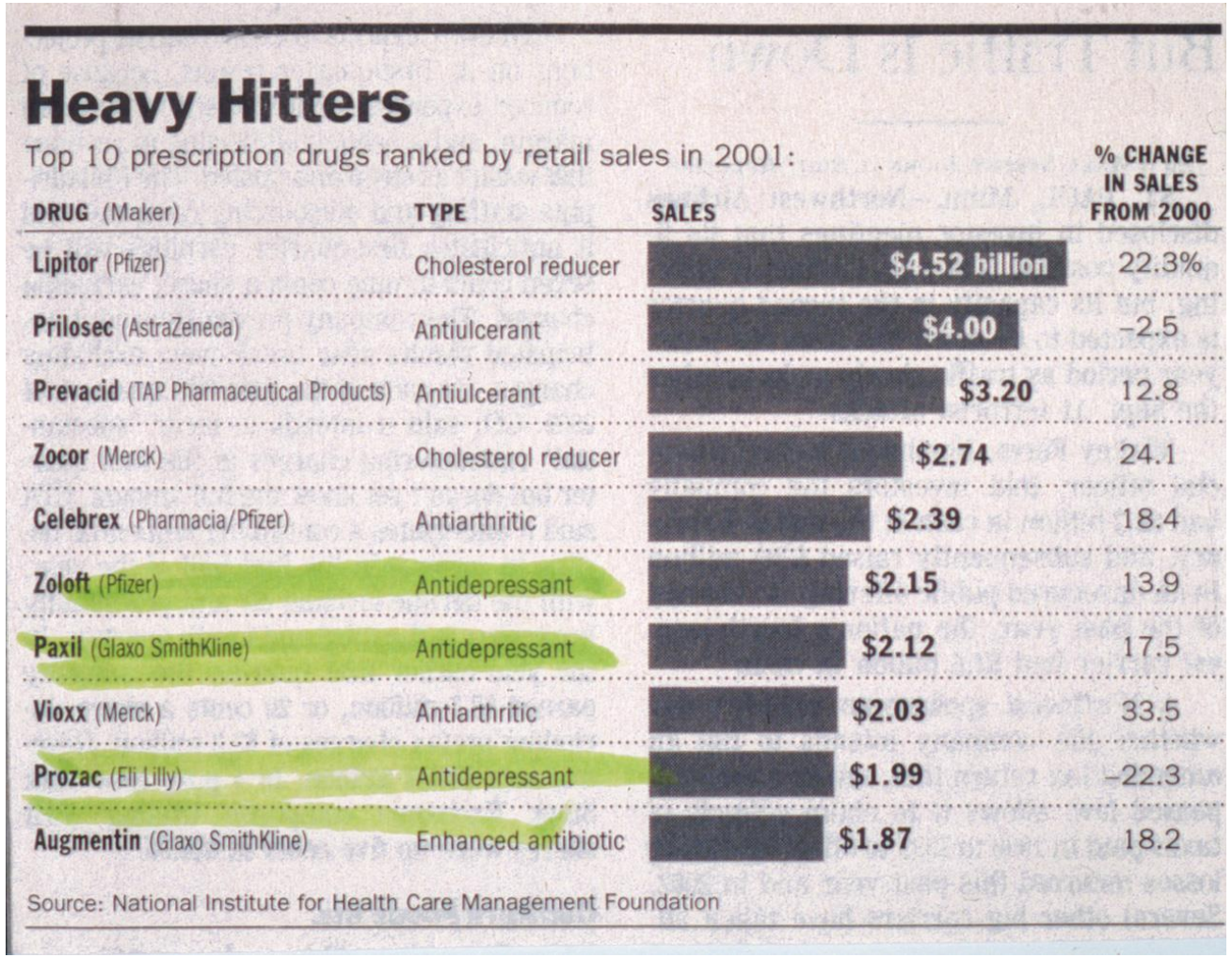
Marketed by Eli Lilly in December 1987.



The SSRIs fit major depression like a hand in glove.

We have a single depression; we have a single clinical entity – the SSRIs – that treats all depressions.

The sky was the limit. The sales climbed into the billions of dollars.



Heavy Hitters

Top 10 prescription drugs ranked by retail sales in 2001:

DRUG (Maker)	TYPE	SALES	% CHANGE IN SALES FROM 2000
Lipitor (Pfizer)	Cholesterol reducer	$4.52 billion	22.3%
Prilosec (AstraZeneca)	Antiulcerant	$4.00	–2.5
Prevacid (TAP Pharmaceutical Products)	Antiulcerant	$3.20	12.8
Zocor (Merck)	Cholesterol reducer	$2.74	24.1
Celebrex (Pharmacia/Pfizer)	Antiarthritic	$2.39	18.4
Zoloft (Pfizer)	Antidepressant	$2.15	13.9
Paxil (Glaxo SmithKline)	Antidepressant	$2.12	17.5
Vioxx (Merck)	Antiarthritic	$2.03	33.5
Prozac (Eli Lilly)	Antidepressant	$1.99	–22.3
Augmentin (Glaxo SmithKline)	Enhanced antibiotic	$1.87	18.2

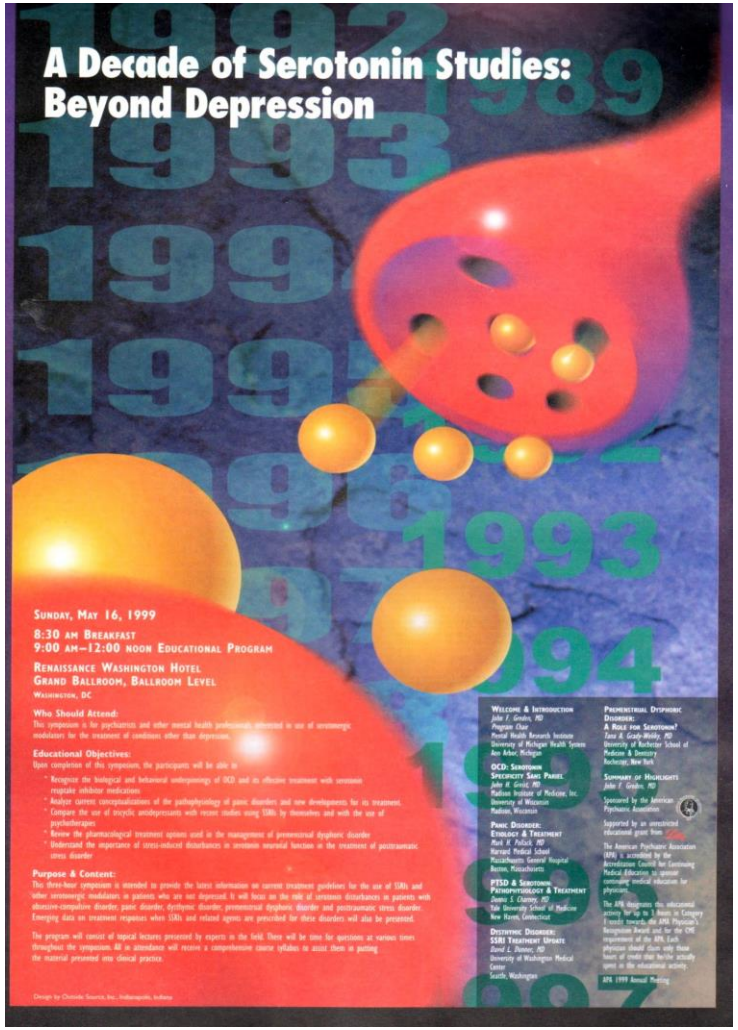
Source: National Institute for Health Care Management Foundation

And the biological narrative was irresistible.

"You're suffering from a 'chemical imbalance' in your brain. Our drug will restore your serotonin levels."

Who could resist such images! Physicians were as susceptible as patients.

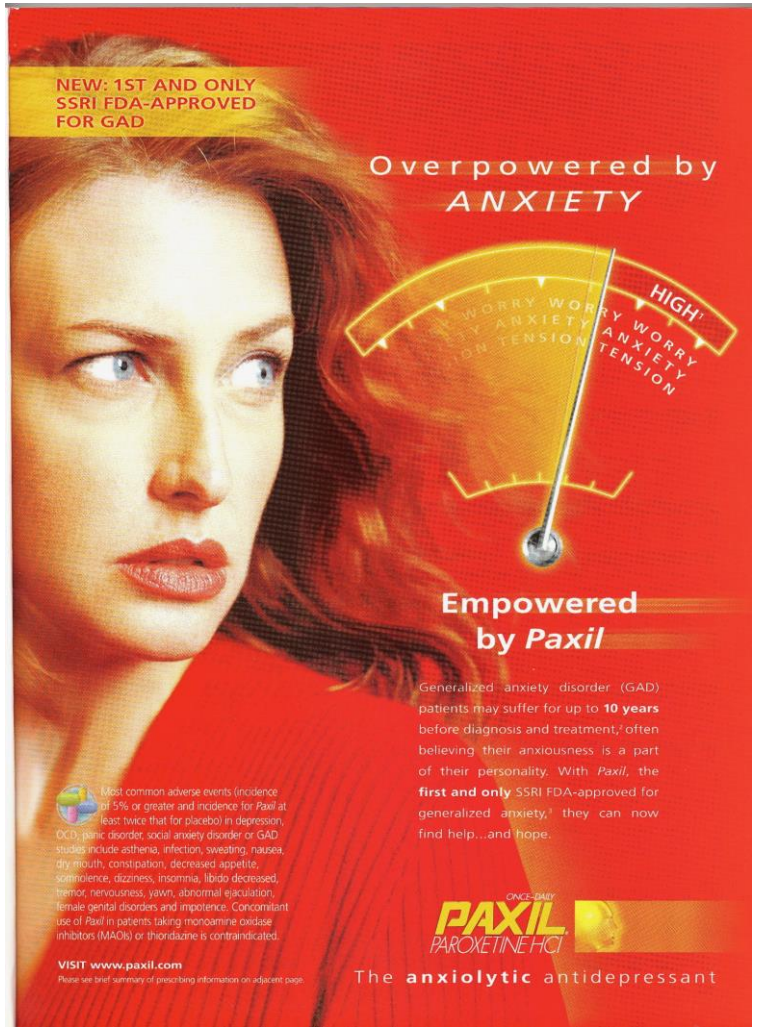
This "chemical imbalance" story is a marketing trope. There is no scientific evidence of a shortage of any neurotransmitter in "depression" – although this trope is still used in marketing.



Bitter commercial rivalries led to a steady expansion of indications for the SSRIs.

Anxiety, PTSD, “pediatric depression,” the list went on and on.

The SSRIs started to look like panaceas, “good for everything”!



The SSRIs took over the field of psychiatric prescription.

The older, often effective drugs were simply forgotten; residents stopped learning about them.

--- The MAOIs: gone

---The TCAs: going (“too many side effects”)

---Lithium: widely *not* taught to the residents.

---the opioids and psychotogens: Out of the question! “Addictive, you know.” (But, Doctor, just try getting your patients off Paxil.)

---ECT, sort of making a comeback, but the stigma is intense.

‘Depressing, isn’t it?’

We could do this same story for the “second generation antipsychotics”

The “SGAs”. Also called “atypical antipsychotics.” Much less popular than the SSRIs, but, still, widely prescribed for indications other than “schizophrenia.”

Great for “pediatric bipolar disorder”!

But I won’t today, because the point has been made. But we can get into it in the discussion, if you like.

Chapter 3

Where are the regulators in all this?

FDA

- Two observations:
- ---Their statistical assessors are very sharp and do a highly professional job on the numbers (although everyone is hypnotized by p-values and “significance”).
- ---However, the leadership is inclined to leniency with Pharma (with good reason from the viewpoint of post-FDA employment).

FDA – the leadership

Robert Temple, director of the Office of Drug Evaluation of the FDA. (pictured)

Tom Laughren, director of the Division of Psychiatry Products

So, these are the two crucial gatekeepers.

In fairness to FDA, they were not minions of Pharma but (try to) protect the public health.

- **March 3, 2000:** A Janssen internal document: "record of FDA contact." Janssen Research Foundation had sought FDA meeting to inquire about pediatric exclusivity and about conduct disorder "as an indication" for Risperdal. Re conduct disorder: FDA is very skeptical: "Their main concern [said the memo] is that Risperdal or any other product would be used as a chemical straight jacket." We can move ahead to conduct-disorder trials, but even if they are positive, FDA would want a meeting of the Psychopharmacologic Drugs Advisory Committee. So, this is a tough, public-health stance for the FDA.

- (from Janssen internal correspondence discovered at litigation)

Huge litigation over “misbranding” of the SSRIs

- The companies had wanted to expand the markets, especially to childhood and adolescence. So did the makers of the ”second-generation antipsychotics.” The FDA opposed these expansions because, either there had been no trials for “pediatric depression.” Or the trials had been negative.

FDA view at approval: SSRI's don't work very well.

- The SSRI's lack of effectiveness was long an open secret. At a meeting of the Psychopharmacologic Drugs Advisory Committee on April 8, 2009, Robert Temple, director of the Office of Drug Evaluation, had this to say about the "antidepressants": "People have been remarking on how small the [treatment] effect of all the antidepressants [is]; it's only 2 or 3 HAMD points and stuff, and that's absolutely true. Tom's [Laughren]been accumulating this stuff over years. Fifty percent of trials can't show anything, like their [Forest Labs] escitalopram study."
- Source: FDA, Center for Drug Evaluation and Research, Psychopharmacologic Drugs Advisory Committee Meeting, Apr 8, 2009, transcript, 223.
- Interestingly, Laughren would soon leave the FDA to begin consulting for Forest.

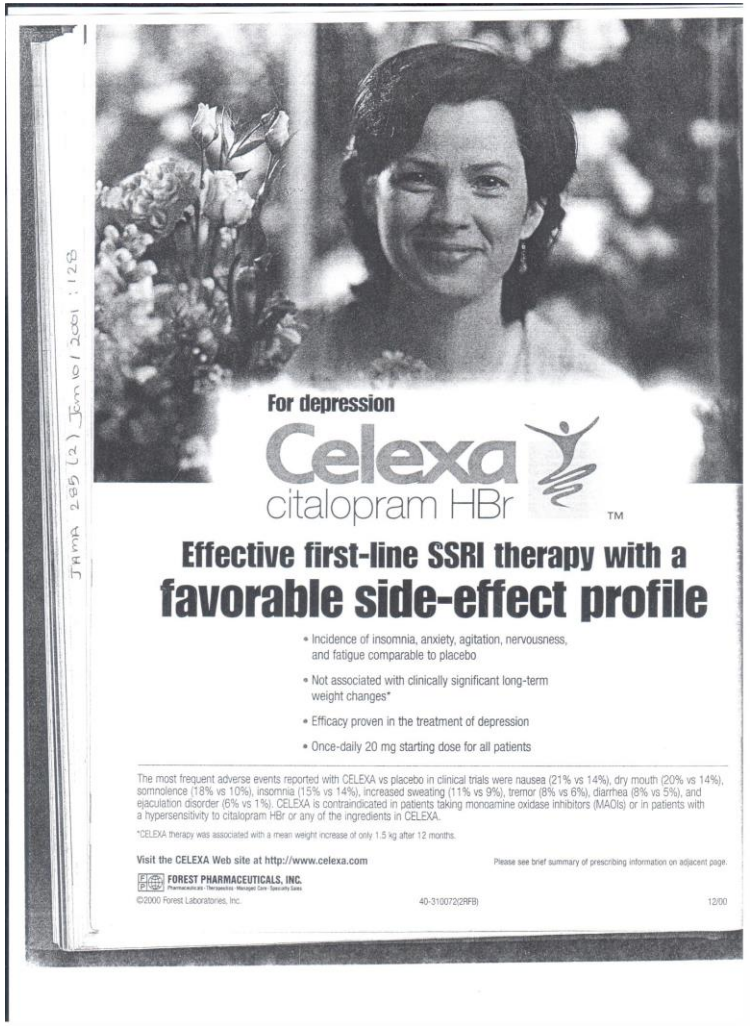
Lots of litigation surrounding these agents: Citalopram = Celexa
Escitalopram = Lexapro

2012. Laughren leaves FDA, becomes a Forest “consultant.”

Jan 27, 2017: Laughren deposition, re FDA approval of Lexapro: says that "These two studies, Study 18 for Celexa and Study 32 for Lexapro, were sufficient as a source of evidence of the effectiveness of Lexapro in adolescents." (393)

Ad from 2001

Forest also used results of study 18 (CIT-MD-18) to support a child depression application for Lexapro.

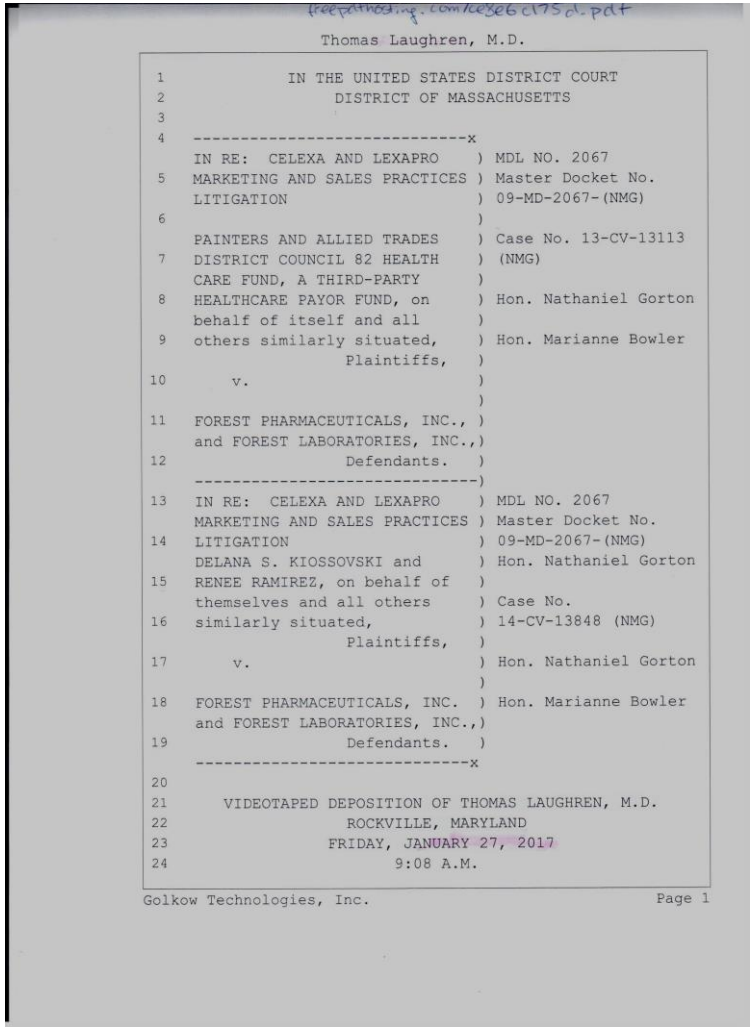


Now, it's 2017

Forest is being sued by the Department of Justice for falsely claiming that Celexa is effective in pediatric depression ("misbranding").

It was Laughren who, while at FDA, pushed through this highly profitable indication.

Here Laughren is giving a deposition.



freepatents.com/case6cv75d.pdf

Thomas Laughren, M.D.

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

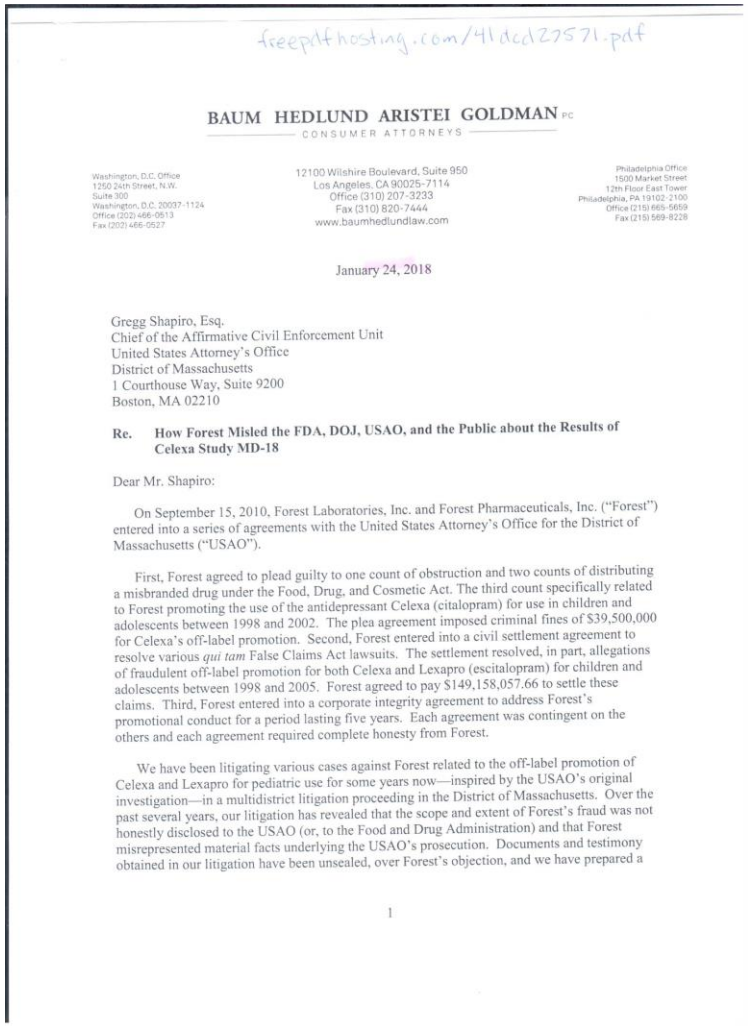
IN RE: CELEXA AND LEXAPRO MARKETING AND SALES PRACTICES LITIGATION	MDL NO. 2067 Master Docket No. 09-MD-2067-(NMG)
PAINTERS AND ALLIED TRADES DISTRICT COUNCIL 82 HEALTH CARE FUND, A THIRD-PARTY HEALTHCARE PAYOR FUND, on behalf of itself and all others similarly situated, Plaintiffs, v. FOREST PHARMACEUTICALS, INC., and FOREST LABORATORIES, INC., Defendants.	Case No. 13-CV-13113 (NMG) Hon. Nathaniel Gorton Hon. Marianne Bowler
IN RE: CELEXA AND LEXAPRO MARKETING AND SALES PRACTICES LITIGATION	MDL NO. 2067 Master Docket No. 09-MD-2067-(NMG)
DELANA S. KIOSSOVSKI and RENEE RAMIREZ, on behalf of themselves and all others similarly situated, Plaintiffs, v. FOREST PHARMACEUTICALS, INC. and FOREST LABORATORIES, INC., Defendants.	Hon. Nathaniel Gorton Case No. 14-CV-13848 (NMG) Hon. Nathaniel Gorton Hon. Marianne Bowler

VIDEOTAPED DEPOSITION OF THOMAS LAUGHREN, M.D.
ROCKVILLE, MARYLAND
FRIDAY, JANUARY 27, 2017
9:08 A.M.

Golkow Technologies, Inc. Page 1

A lawfirm named Baum Hedlund is representing the plaintiffs.

And here is part of a brief that Baum Hedlund filed in 2018. . . Asking that the DOJ reopen the case on MD-18 (Celexa) in light of new information.



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January 24, 2018

Gregg Shapiro, Esq.
Chief of the Affirmative Civil Enforcement Unit
United States Attorney's Office
District of Massachusetts
1 Courthouse Way, Suite 9200
Boston, MA 02210

Re. How Forest Misled the FDA, DOJ, USAO, and the Public about the Results of Celexa Study MD-18

Dear Mr. Shapiro:

On September 15, 2010, Forest Laboratories, Inc. and Forest Pharmaceuticals, Inc. ("Forest") entered into a series of agreements with the United States Attorney's Office for the District of Massachusetts ("USAO").

First, Forest agreed to plead guilty to one count of obstruction and two counts of distributing a misbranded drug under the Food, Drug, and Cosmetic Act. The third count specifically related to Forest promoting the use of the antidepressant Celexa (citalopram) for use in children and adolescents between 1998 and 2002. The plea agreement imposed criminal fines of $39,500,000 for Celexa's off-label promotion. Second, Forest entered into a civil settlement agreement to resolve various *qui tam* False Claims Act lawsuits. The settlement resolved, in part, allegations of fraudulent off-label promotion for both Celexa and Lexapro (escitalopram) for children and adolescents between 1998 and 2005. Forest agreed to pay $149,158,057.66 to settle these claims. Third, Forest entered into a corporate integrity agreement to address Forest's promotional conduct for a period lasting five years. Each agreement was contingent on the others and each agreement required complete honesty from Forest.

We have been litigating various cases against Forest related to the off-label promotion of Celexa and Lexapro for pediatric use for some years now—inspired by the USAO's original investigation—in a multidistrict litigation proceeding in the District of Massachusetts. Over the past several years, our litigation has revealed that the scope and extent of Forest's fraud was not honestly disclosed to the USAO (or, to the Food and Drug Administration) and that Forest misrepresented material facts underlying the USAO's prosecution. Documents and testimony obtained in our litigation have been unsealed, over Forest's objection, and we have prepared a

And here Baum Hedlund attacks Laughren, formerly of the FDA

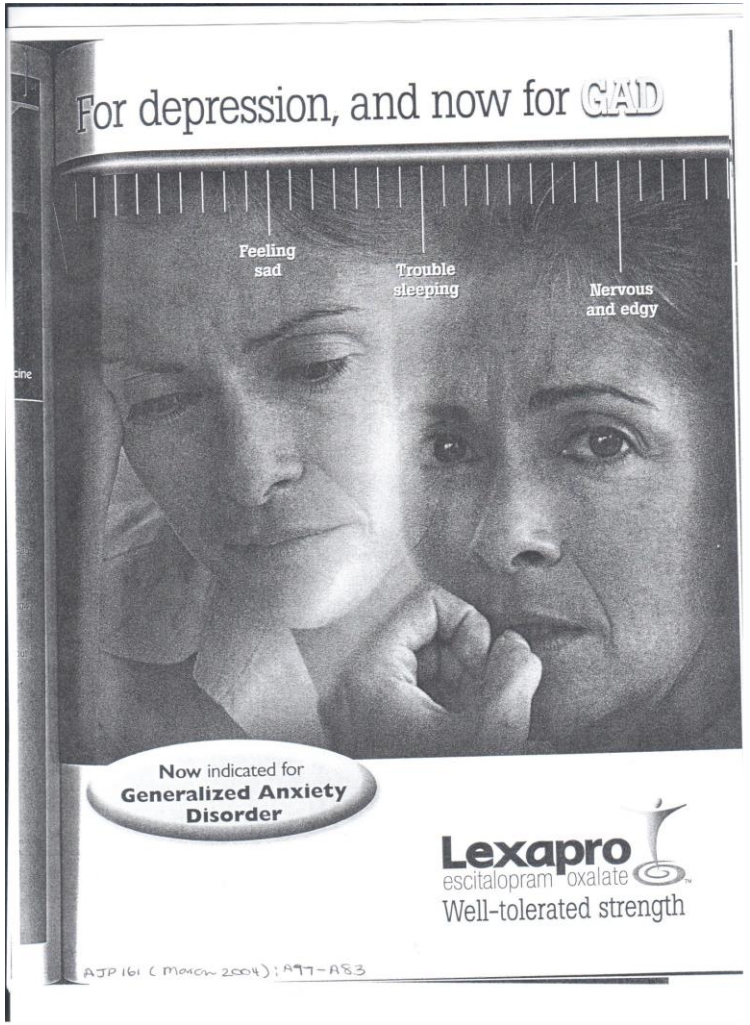
2013 Depo. T. Laughren at 301:20-302:2 (emphasis added). Indeed, Forest and Dr. Heydorn both agree that MD-18, with the unblinded patients excluded, is negative. Exh. 12, 2016 Depo. of S. Closter (Forest's Rule 30(b)(6) Corporate Representative) at 294:10-295:20 ("***If they were removed from the study, I understand that the result would have been negative.***" (emphasis added)); Exh. 11, 2016 Depo. of W. Heydorn at 87:11-87:14 (same). Dr. Laughren's "close enough" opinion is an after-the-fact attempt to justify his conclusion that MD-18 was positive—conclusion that formed the basis of *his* approval of Lexapro for use in adolescents in 2009. To admit that the study would be negative while excluding the unblinded patients would force him to concede that he made a mistake in approving Lexapro for use in adolescents.

What can we conclude from the Citalopram/Lexapro case?

1. FDA can be gamed (the details involve these 9 unrandomized patients included in the randomized group and whose presence made the study all of a sudden “significant.”)

2. The civil servants of the FDA can’t wait to get to the trough

3. Lexapro and Citalopram became indicated for pediatric depression almost certainly erroneously – because, in my view, there is very little “pediatric depression,” – I don’t believe in the diagnosis -- and because the SSRIs are ineffective in it, in any event.



Now, there is an important point about statistics that I am going to make in a minute.

There have been important whistle-blowers before me

Although they might not have expressed the same conclusions that I reach.

Here is one (Jureidini).

International Journal of Risk & Safety in Medicine 28 (2016) 33–43
DOI 10.3233/JRS-160671
IOS Press

The citalopram CIT-MD-18 pediatric depression trial: Deconstruction of medical ghostwriting, data mischaracterisation and academic malfeasance

Jon N. Jureidini[a], Jay D. Amsterdam[b,*] and Leemon B. McHenry[c]
[a]*Critical and Ethical Mental Health Research Group, University of Adelaide, Adelaide, Australia*
[b]*Depression Research Unit, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[c]*Department of Philosophy, California State University, Northridge, CA, USA*

Received 5 October 2015
Accepted 7 January 2016

Abstract.
OBJECTIVE: Deconstruction of a ghostwritten report of a randomized, double-blind, placebo-controlled efficacy and safety trial of citalopram in depressed children and adolescents conducted in the United States.
METHODS: Approximately 750 documents from the *Celexa and Lexapro Marketing and Sales Practices Litigation*: Master Docket 09-MD-2067-(NMG) were deconstructed.
RESULTS: The published article contained efficacy and safety data inconsistent with the protocol criteria. Procedural deviations went unreported imparting statistical significance to the primary outcome, and an implausible effect size was claimed; positive *post hoc* measures were introduced and negative secondary outcomes were not reported; and adverse events were misleadingly analysed. Manuscript drafts were prepared by company employees and outside ghostwriters with academic researchers solicited as 'authors'.

Here is another

Lemmens

Health Law
The Journal of Things We Like (Lots)
https://health.jotwell.com

Restoring the Integrity of the Pharmaceutical Science Record: Two Tales of Transparency

Author : Trudo Lemmens

Date : July 14, 2016

- Jon N. Jureidini, Jay D. Amsterdam & Leemon B. McHenry, The Citalopram CIT-MD-18 Pediatric Depression on Trial: Deconstruction of Medical Ghostwriting, Data Mischaracterisation and Academic Malfeasance, 28 **Int'l J. Risk & Safety Med.** 33 (2016)
- Joanna Le Noury et al., Restoring Study 329: Efficacy and Harms of Paroxetine and Imipramine in Treatment of Major Depression in Adolescence, 351 **Brit. Med. J.** 4320 (2015)

Inappropriate prescription and overconsumption of pharmaceuticals is one of the most pressing public health concerns in North America. Aggressive pharmaceutical promotion practices are widely recognized as a major contributing factor. Two recent medical journal articles provide further evidence of serious problems with the scientific record that has become an intrinsic part of pharmaceutical marketing. They document each in their own way the corruption of scientific practices in which academic scientists appear to play a significant role, but also indicate how the scientific community and civil society can help correct the record and expose misconduct. The papers further illustrate how legal tools can enable them to do so. They both affirm the importance of transparency, which many in the medical and health policy community increasingly support as essential to restore confidence in the science surrounding pharmaceuticals.

Jon N. Jureidini, Jay D. Amsterdam, and Leemon B. McHenry's paper in the International Journal of Risk and Safety in Medicine is a case study of how the pharmaceutical company Foster used a scientific publication to boost prescription of its blockbuster anti-depressant citalopram. A paper by Joanna Le Noury and colleagues in the British Medical Journal is the first publication produced as part of an innovative initiative by the scientific community aimed at correcting the scientific record on a host of pharmaceutical products. The study involves a reanalysis of the raw data of a Smithkline Beecham (now GSK)-sponsored published study on the efficacy of paroxetine and imipramine for the treatment of depression in adolescents.

There had been a lot of issues in Forest's citalopram (Celexa) trial

Ghosting, etc. But let's come back to these 9 patients who hadn't been randomized and yet were placed on the drug. If we keep these 9 patients in the sample in the trial, the drug works. If we remove them, the drug doesn't work? Is that right?

No. This is numerology. It fetishizes "significance" and ignores clinical effectiveness.

Now, here is real, clinical observation of effectiveness (non-)

“Significance” vs “strength of association”

- “Significance” does not measure effectiveness.
- The whole kerfuffle over the non-randomized nine patients who somehow got included in the randomized sample strikes me as an example of fetishizing numbers in establishing effectiveness. If we don’t know, on the basis of observations and open studies whether the thing works, it probably doesn’t work, or at least not well.
- This whole dance around “significance” is a kind of Kabuki theater: It doesn’t have much real-world meaning, but we dance through it pro forma for the sake of registration.

Somehow, in this festival of numbers . . .

. . . Clinical effectiveness (NNT) has been left at the wayside. This is also called "strength of effect."

You never see NNT in any of the trial literature.

"Significance," expressed as a p-value, means the probability that the result was not a chance result. A .05 measure of probability means that 19 times out of 20 the result is probably a true result – not the effect of randomness. But it doesn't tell you how *strong* that result is. NNT does.

- **Strength of Effect**: In these studies, the investigator defines the change in the outcome measure that will define *response* and *remission* in advance. There are two ways to express the results – Odds Ratio and Number Needed to Treat, both calculated from the same things – the percentages of *response* or *remission* compared between placebo and drug. So if 5% respond to placebo and 25% respond to the drug, the Odds Ratio and Number Needed to Treat are:

$$OR = \frac{\frac{0.25}{1-0.25}}{\frac{0.05}{1-0.05}} = 6.333 \qquad NNT = \frac{1}{(0.25-0.05)} = 5$$

Obviously, the higher the OR, the better the response, and the lower the NNT the better the response. The

So, what's the outcome of the story? How does the drama end?

- We can say of the three acts:
- 1. An exciting new academic field is developing at the intersection of diagnosis, Pharma and regulation
- 2. So far, the bad guys are winning. The good guys have had to found their own journal in order to get published.
- 3. Of the various components at this intersection, the most interesting – from my viewpoint – is diagnosis. Because it's the most difficult to tackle (what *are* the real diagnoses?), and it's where the conventional wisdom is most entrenched.

So, major depression, schizophrenia, bipolar disorder . . .

Do they exist? These are the big questions.

And if they are artifacts, what *are* the real diseases in psychiatry? The Spanish diagnosis in 1949 was “anxious melancholia.” That’s not in DSM. But why not?

These big questions have little to do with p-values and “significance.”

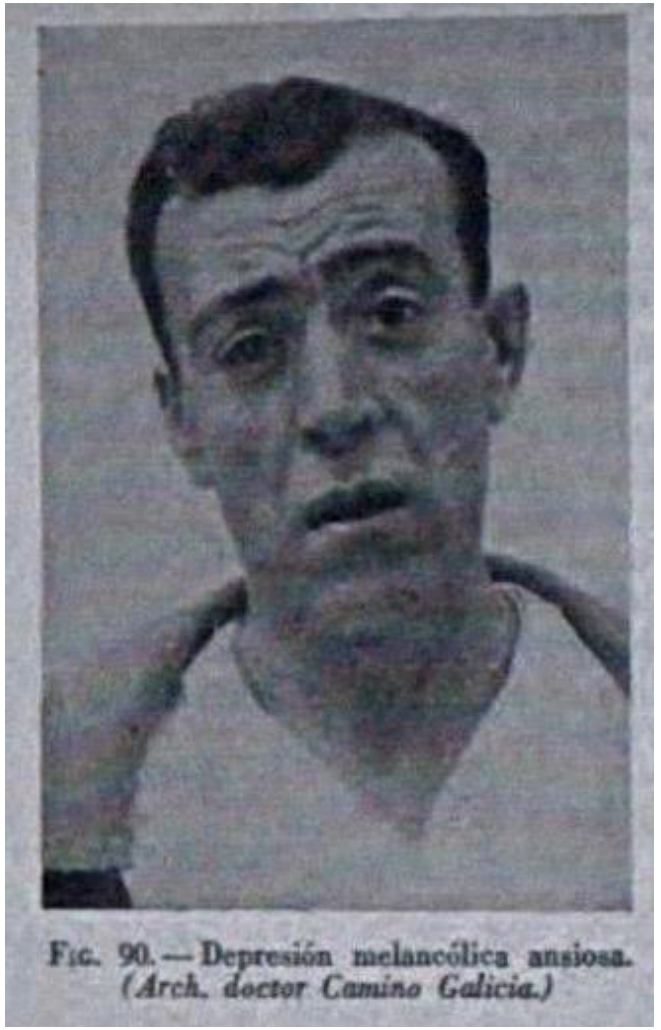


Fig. 90. — Depresión melancólica ansiosa. (*Arch. doctor Camino Galicia.*)

Your turn now.

Thanks!