A Journalist's Dilemma:

How to Separate Marketing Propaganda From Scientific Fact

Robert Whitaker
September 2014

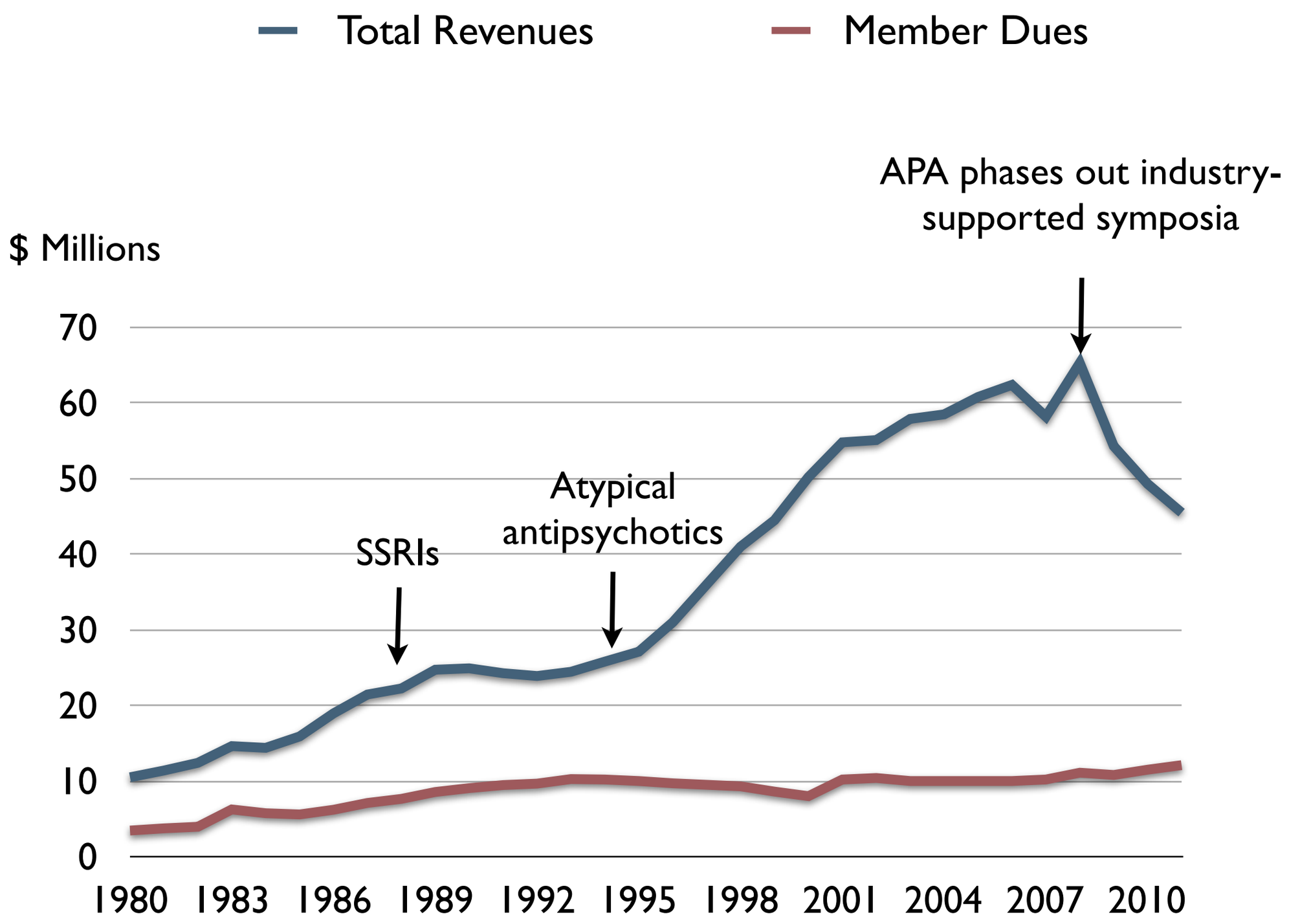
Financial Influences on Psychiatry Since DSM III (1980)

- Pharmaceutical influence on American Psychiatric Association

- Pharmaceutical influence on academic psychiatry and community psychiatry

- Guild influences

APA's Annual Revenues, 1980-2011



Source: APA's annual financial reports, 1980 to 1011.

Pharmaceutical Payments to Academic Psychiatrists in U.S.

• Charles Nemeroff: From 2000 to 2007, while chair of psychiatry department at Emory Medical School, he earned $2.8 million as a speaker and consultant for pharmaceutical companies.

• Frederick Goodwin: The former director of the National Institute of Mental Health was paid $1.2 million from 2000 to 2008 by GlaxoSmithKline.

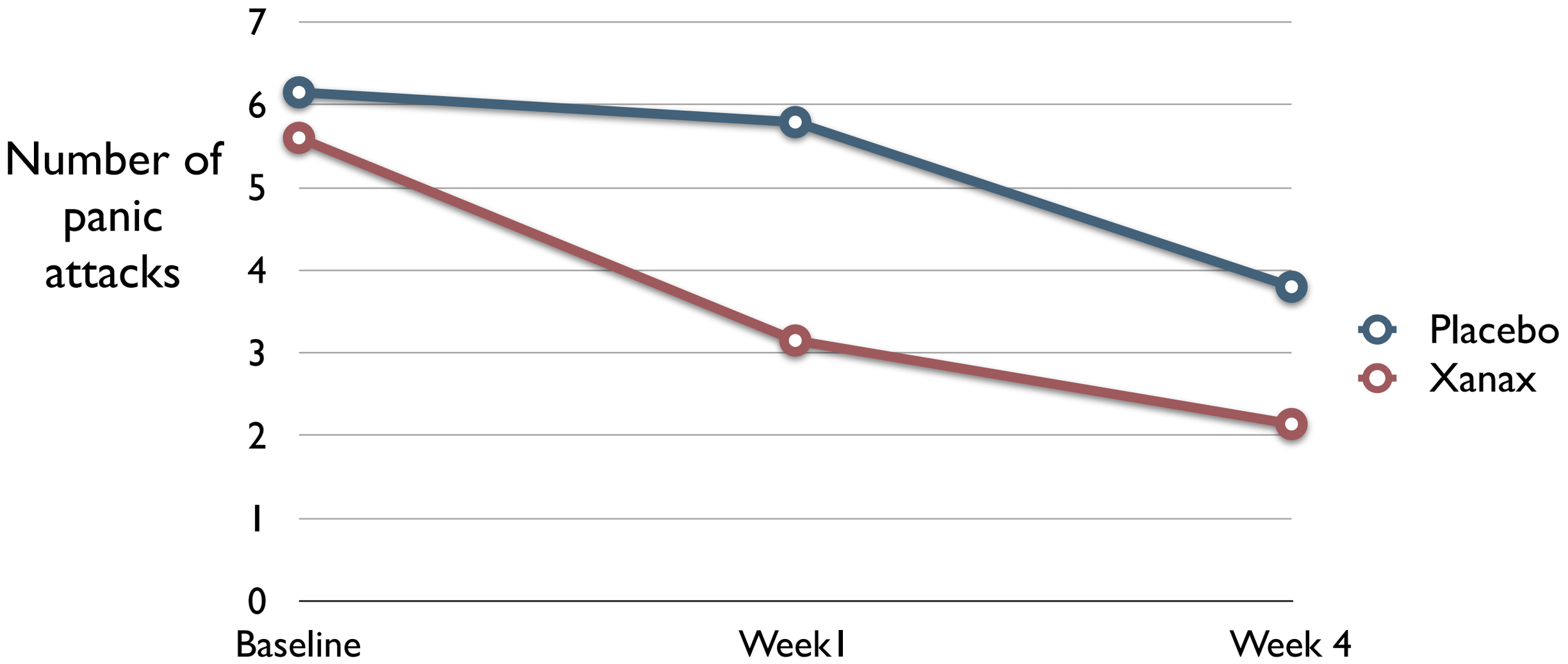
• Joseph Biederman: Professor of psychiatry at Harvard Medical School, he received $1.6 million from Janssen between 2000 and 2007.

•Karen Wagner: Director of child psychiatry at University of Texas, she received more than $160,000 from GlaxoSmithKline from 2000 to 2005.

• Melissa DelBello: Association professor of psychiatry at University of Cincinnati, she received $418,000 from AstraZeneca from 2003 to 2007.

The Xanax Reports

This was the story summarized in the medical journals



Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988):413-22.

The Conclusion That Was Drawn

"Alprazolam (Xanax) was found to be effective and well-tolerated."

Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988):413-22.

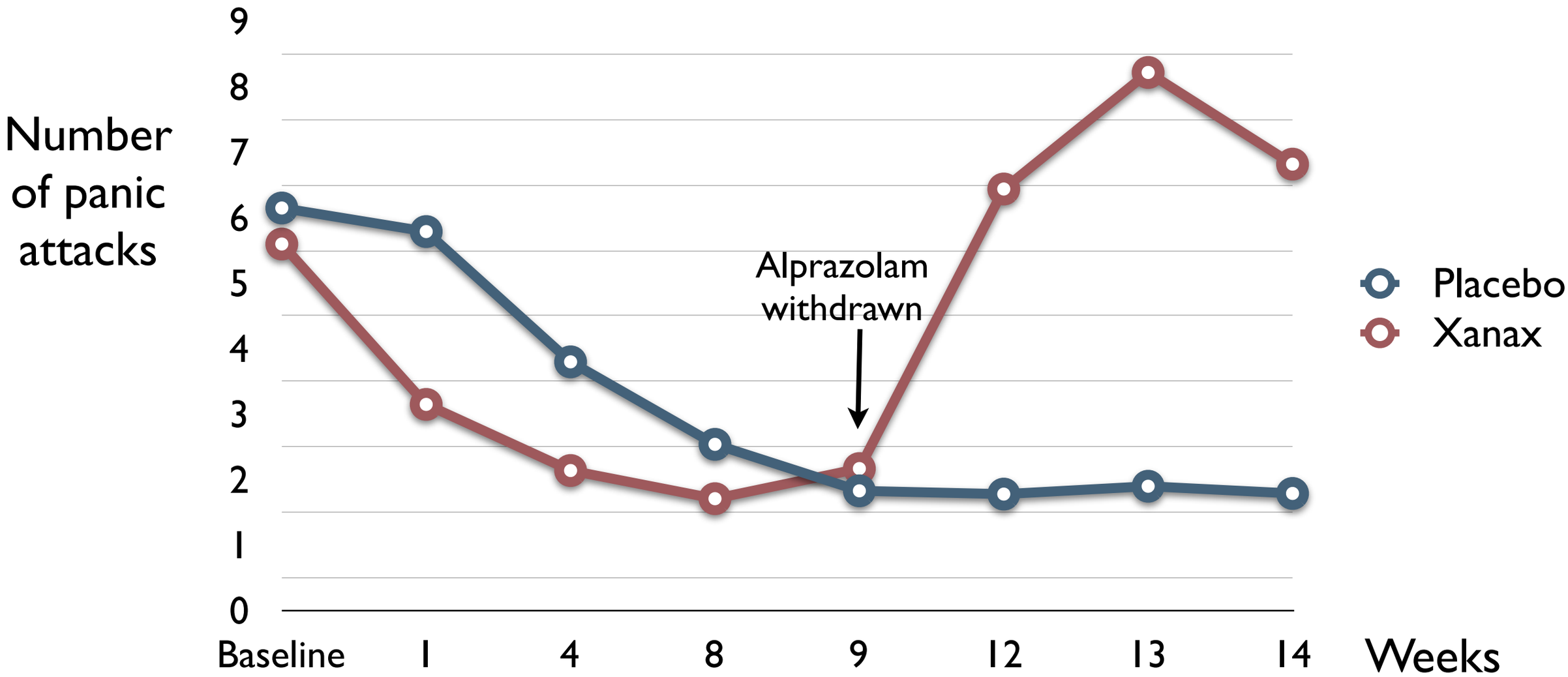
American Psychiatry Helps Market Xanax

- Robert Pasnau, former head of the American Psychiatric Association (APA), sends a glossy brochure on the "Consequences of Anxiety" to APA members, an "educational" effort paid for by Upjohn.

- Shervert Frazier and Gerald Klerman, prominent leaders within the APA, pen a "Dear Doctor" letter that Upjohn included in the promotional letter sent to doctors about Xanax.

- Upjohn gives $1.5 million to APA so that it could mount an educational campaign informing the public that panic disorder was "underrecognized and undertreated."

Now For the Rest of The Story



In Upjohn's study, patients were treated with the drug or placebo for eight weeks. Then this treatment was slowly withdrawn (weeks 9 through 12), and during the last two weeks patients did not receive any treatment. Source: C. Ballenger, "Alprazolam in panic disorder and agoraphobia," *Archives of General Psychiatry* 45 (1988):413-22. Also, C. Pecknold. "Alprazolam in panic disorder and agoraphobia." *Archives of General Psychiatry* 45 (1988):429-36.

Why This is Important for Patients

- Benzodiazepines are understood to be addictive, and thus not recommended for long-term use.

- As such, withdrawal from a benzodiazepine after daily use for four to six weeks is the recommended form of care.

- In this study, withdrawn patients ended up much worse than the placebo patients, and even worse than they had been at baseline.

- 44% of the aplrazolam patients were unable to get off the drug, and thus could be seen as having become "addicted" to it. Long-term use of benzodiazepines is known to be associated with poor outcomes (cognitive, emotional, and physical.)

The Challenge for Journalists

The 14-week data can be found in the published articles, but not in the abstracts. The journalist has to find this data on his or her own.

Promoting Prozac

• After the FDA approved Prozac in 1987, the NIMH launched a Depression Awareness Recognition and Treatment campaign, which was funded in part by pharmaceutical companies. The campaign's primary message was that depressive disorders were "unrecognized, untreated, and undertreated," and that it was vital that people seek out medical help. "Left untreated," the NIMH now informed the public, "depression may be a fatal disease."

• The public was told that antidepressants were highly effective. "Recovery rates with these medications have been shown to be in the range of 70% to 80% in comparison with 20% to 40% for placebo," the NIMH stated.

Prozac in the Press

- "A Wonder Drug for Depression." -- *Newsweek*

- "One of the best antidepressants ever designed." -- *New York Times*

- Depression is "caused by a chemical imbalance in the brain," which Prozac helps correct. -- *Sixty Minutes*

- "Today depression can be treated—quickly and effectively—in seven cases out of ten. If a second round of treatment is required, the cure rate jumps to 90%." -- *Time*

The Clinical Trials of Prozac Submitted to the FDA

- Eli Lilly presented data from five clinical studies to the FDA.

- In the trials, investigators were allowed to prescribe benzodiazepines to control agitation frequently seen in the Prozac-exposed group, and patients were also allowed to take a sedative to help them sleep at night.

- This concurrent use of other psychiatric medications, admitted Eli Lilly's Dorothy Dobbs in a later legal case, was "scientifically bad," since it would "confound the results," and "interfere with the analysis of both safety and efficacy."

- The FDA's reviewers also noted, in its review of the trial data, that Eli Lilly had engaged in "large-scale underreporting" of the harm that fluoxetine could cause.

The FDA's Review of Prozac

- Two of the five clinical studies did not show a statistically significant benefit for the drug.

- For a third to be seen as positive, the data had to be parsed in a certain way.

- One of the remaining two studies compared fluoxetine to imipramine. The FDA concluded that the data showed that "imipramine was clearly more effective than placebo, whereas fluoxetine was less consistently better than placebo."

- When the outcomes from all five studies were pooled, the improvement in HAM-D scores for the fluoxetine patients was only one point more than for the placebo patients, which is a clinically meaningless difference.

The Challenge for Journalists

The real results could not be found in the scientific articles that were originally published. They could only be found in the FDA's review of the trial data. There is a need to read those reviews when writing about newly approved psychiatric medications, which today are available online.

The NIMH's STAR*D Trial

- The largest antidepressant trial ever conducted (4,041 patients).

- Funded by the NIMH at a cost of $35 million. It took six years to conduct.

- As it was conducted to study "real-world" strategies for helping people recover and stay well, with a one-year followup, it was expected to produce results that would have "substantial public health and scientific significance."

- Design: If patients didn't respond to a first antidepressant, they were switched to a second drug, and so on, through four treatment steps.

Announced Results

NIMH: "Over the course of all four treatment levels, almost 70% of those who did not withdraw from the study became symptom free."

Current Psychiatry Reports: "With all steps included, almost 70% of participants who remained in the study experienced remission. Patients and clinicians are encouraged not to give up."

Source: NIMH press release. "Questions and answers about the NIMH sequenced treatment alternatives to relieve depression (STAR*D) study--all medication levels." November 2006. D. Warden, "The STAR*D Project Results." *Current Psychiatry Reports* 9 (2007):449-459.

Deconstructing STAR*D: How the 70% Success Rate Was Calculated

- **Study Dropouts Counted as Responders:** The 70% figure was a theoretical remission rate, based on the premise that if the study dropouts had stayed in trial through all four treatment steps, they would have remitted at same rate as those who remained in the trial.

- **Rating Scales Were Switched:** According to the protocol, the Hamilton Rating Scale was to be used to measure symptoms. The researchers were also testing a second scale, the QIDS-SR, in order to guide clinical decisions at each visit. The protocol stated that the QIDS-SR would not be used to report research results. However, in their published articles, when the STAR*D investigators calculated the 70% remission rate, they used the QIDs-SR data, which added 200 patients to the remitted group.

• **Ineligible Patients Were Enrolled:** The investigators enrolled 607 patients who had a baseline Hamilton score less than 14, and thus, according to the protocol, weren't depressed enough to be in the trial. Yet these ineligible patients were included when calculating the remission rate.

Re-Calculating Remission Rates According to the Protocol

Only 1,192 of the 3,110 patients who began the study with a Hamilton score greater than 14 remitted (38%). The remaining 62% either failed to remit or dropped out. This is the real remission rate, as defined by the protocol. No newspaper has ever reported this fact.

Source: Pigott, E. "Efficacy and effectiveness of antidepressants." *Psychother Psychosom* 79 (2010):267-79.

Long-Term Stay Well Rates

There were 1518 patients who entered the follow-up phase (one year) in remission.

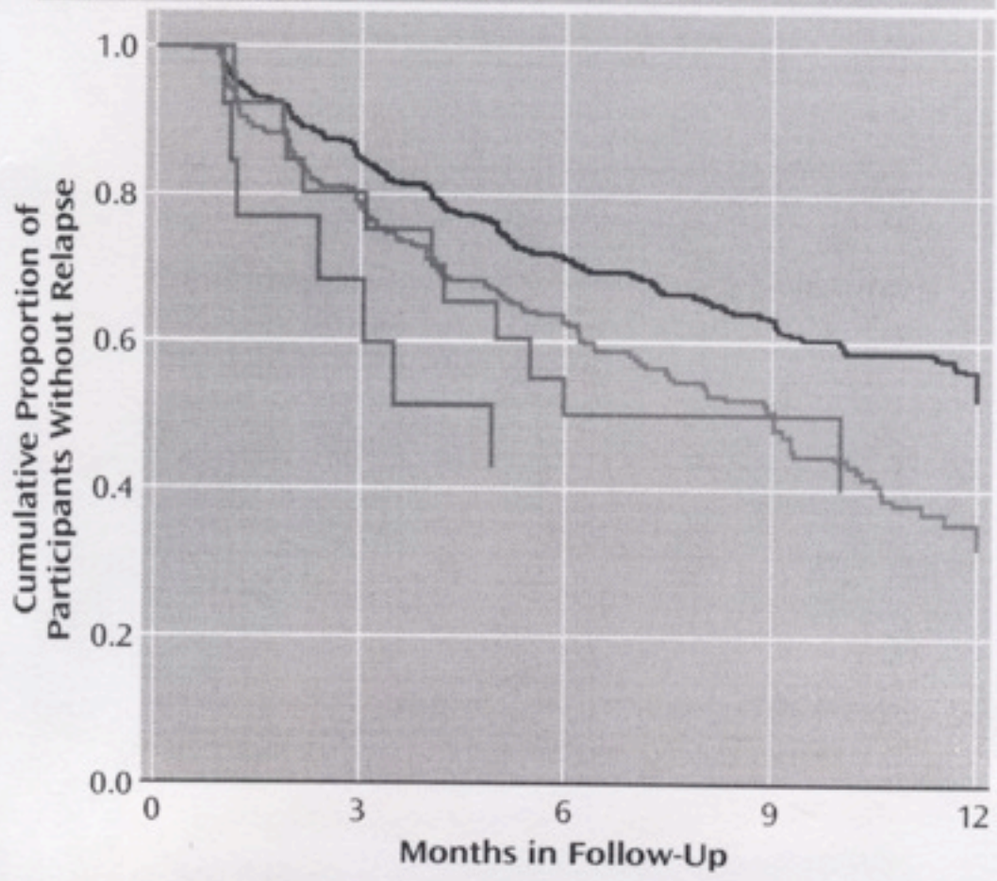
Although the researchers only briefly discussed the one-year results, their discussion suggested that 950 patients--or 63%--had remained well throughout the year.

STAR*D Long-Term Results

How many patients remitted and then stayed well and in the trial during the followup?

FIGURE 3. Relapse During Follow-Up Phase by Number of Acute Treatment Steps for STAR*D Participants Who Entered Follow-Up Phase in Remission[a]

Step 1 N=1,085	628	431	290	84
Step 2 N= 383	199	133	79	20
Step 3 N= 35	16	11	8	2
Step 4 N= 15	8	5	5	2
Total N=1,518	851	580	382	108



[a] Significant overall difference among steps (χ^2=23, df=3, p<0.0001). Significant post-hoc comparisons with Bonferroni corrections revealed significant differences between steps 1 and 2.

The Actual One-Year Results

Of the 4,041 patients who entered the trial, 108 remitted and then stayed well and in the trial throughout the one-year followup. That is a documented stay well-rate of 3%.

The researchers calculated the higher stay-well rate by counting those who dropped out during the maintenance year while still in remission as non-relapsers.

This meant that someone who dropped out after one month, but was in remission at that last visit, would be counted as never having relapsed during the one-year followup.

Source: Pigott, E. "Efficacy and effectiveness of antidepressants." *Psychother Psychosom* 79 (2010):267-79.

The Challenge for Journalists

If you read the published studies very closely, you can see something wasn't right with how the data was being presented. But it wasn't until a psychologist obtained the *protocol* via a freedom of information request that you could see how the investigators had manipulated the data to hide the poor results for patients treated with antidepressants.

The NIMH Mounts a Study to Assess Long-term Outcomes

• Known as the Multisite Multimodal Treatment Study of Children With ADHD

• Hailed as the "first major clinical trial" that the NIMH had ever conducted of "a childhood mental disorder."

• At outset, the investigators wrote that "the long-term efficacy of stimulant medication has not been demonstrated for *any* domain of child functioning."

• Diagnosed children were randomized to one of four treatment groups: medication alone, behavioral therapy, medication plus behavioral therapy, or routine community care.

14-Month Results from NIMH's MTA Study

At end of 14 months, "carefully crafted medication management" had proven to be superior to behavioral treatment in terms of reducing core ADHD symptoms. There was a hint that medicated children also did better on reading tests.

Conclusion: "Since ADHD is now regarded by most experts as a chronic disorder, ongoing treatment often seems necessary."

This is the finding that was widely reported in the media.

Source: The MTA Cooperative Group, "A 14-month randomized cliniical trial of treatment strategies for attention-deficit/ hyperactivity disorder," *Archives of General Psychiatry* 56 (1999):1073-86.

Three-Year Results from NIMH's MTA Study

At the end of 36 months, "medication use was a significant marker not of beneficial outcome, but of deterioration. That is, participants using medication in the 24-to-36 month period actually showed increased symptomatology during that interval relative to those not taking medication." Medicated children were also slightly smaller, and had higher delinquency scores.

This information, which was not in the abstract, has never been reported in an American newspaper.

Source: Jensen, "A 3-year follow-up of the NIMH MTA study," *J Amer Academy of Child & Adolescent Psychiatry* 46 (200&):989-1002.

Six-Year Results from MTA Study

At end of six years, medication use was "associated with worse hyperactivity-impulsivity and oppositional defiant disorder symptoms," and with greater "overall functional impairment."

This information, which was not in the abstract, has never been reported in an American newspaper.

Source: Molina, "MTA at 8 years," *J Amer Academy of Child & Adolescent Psychiatry 48 (2009):*484-500.

MTA Study Conclusion, Reported in U.K. by Psychologist

"We had thought that children medicated longer would have better outcomes. That didn't happen to be the case. There were no beneficial effects, none. In the short term, [medication] will help the child behave better, in the long run it won't. And that information should be made very clear to parents."

--MTA Investigator William Pelham, University at Buffalo

U.Daily Telegraph, "ADHD drugs could stunt growth," Nov. 12, 2007.

What Parents in U.S. Are Told

ADHD Parents Medication Guide,
American Academy of Child and Adolescent Psychiatry

"To help families make important decisions about treatment, the National Institute of Mental Health began a large treatment study in 1992 called the Multimodal Treatment Study of Children with ADHD (Or the MTA study.) Data from this 14-month study showed that stimulant medication is most effective in treating the symptoms of ADHD, as long as it is administered in doses adjusted for each child to give the best response—either alone or in combination with behavioral therapy. This is especially true when the medication dosage is regularly monitored and adjusted for each child."

American Academy of Child & Adolescent Psychiatry and American Psychiatric Association. "ADHD Parents Medication Guide." Revised July 2013.

The Challenge for Journalists

You can find the three-year and six year results in the published articles if you read them very carefully. You can not find them in the abstracts.

The TADS Study

- Design: 439 youth ages 12 to 17 years old were randomized to placebo, fluoxetine (Prozac), cognitive behavior therapy (CBT), or a combination of CBT plus fluoxetine.

- After 12 weeks, all youth could choose one of the three active treatments (fluoxetine, CBT, or CBT plus fluoxetine), or no treatment at at all. They were then followed for another 24 weeks.

- Societal context: This study is conducted after the Food and Drug Administration has reported that SSRIs double the risk of suicidal ideation in children and adolescents, a risk that required a "black box warning" on the drug insert.

Findings Published in Abstract on Final Account of Suicide Risks in Trial

There was "no difference in [suicidal] event timing for patients receiving medication versus those not on medication," the researchers wrote. There was "no evidence of medication-induced behavioral activation as a precursor" to a suicide attempt.

Source.: B. Vitiello. "Suicidal events in the treatment for adolescents with depression study (TADS)." *J Clin Psychiatry* 70 (2009):741-7.

The Real Suicide Data from The TADS Study

- Seventeen of the 18 youth who attempted suicide during the 36 weeks were on fluoxetine at the time of their attempt. No patient on placebo during the 36-week trial had a suicide attempt. The only non-drug suicide attempt during the trial occurred in the CBT-alone group at week five.

- There were 26 other "suicidal events" in the study (preparation for suicidal behavior or suicidal ideation.) Nineteen of the 26 events occurred in patients on fluoxetine. Three occurred in patients on placebo, and five in the CBT-alone group. (Thus, in total, 36 of 44 suicidal events occurred in youth on fluoxetine.)

Source.: B. Vitiello. "Suicidal events in the treatment for adolescents with depression study (TADS)." *J Clin Psychiatry* 70 (2009):741-7.

How The Suicide Data Was Obscured

During the 12-to-36 week period, many in the group initially randomized to placebo or CBT alone took fluoxetine, and it was then, after going on the drug, that they became suicidal or attempted suicide. But those events were still chalked up to the "placebo" or "CBT alone" group, making it seem that the events had occurred in a non-medicated group."

The Challenge for Journalists

You can find the data reporting the real suicide events in a chart in the May 2009 article. That chart, when read closely, provided information on when the suicidal events in the "placebo" group and "CBT alone" group occurred, and whether the youth had started fluoxetine prior to the suicidal event.

Long-term Studies: Have You Heard of these Results?

• 1990: In a large, national depression study, the 18-month stay-well rate was highest for those treated with psychotherapy (30%), and lowest for those treated with an antidepressant (19%.) (NIMH).

•1992: Schizophrenia outcomes were found to be much better in two poor countries, India and Nigeria, where only 16% of patients are regularly maintained on antipsychotics, than in the United States and six other rich countries, where continual drug usage is the standard of care. (World Health Organization.)

•1995: In a six-year study of 547 depressed patients, those who were treated for the disorder were seven times more likely to become incapacitated than those who weren't, and three times more likely to suffer a "cessation" of their "principal social role." (NIMH.)

- 1998: Antipsychotic drugs cause morphological changes in the brain that are associated with a worsening of psychotic symptoms. (University of Pennsylvania.)

- 1998: In a World Health Organization study of the merits of screening for depression, those diagnosed and treated with psychiatric medications fared worst over a one-year period than those who weren't exposed to either antidepressants or benzodiazepines. Those treated with antidepressants had the worst outcomes. (WHO)

- 2001: In a study of 1,281 Canadians who went on short-term disability for depression, 19 percent of those who took an antidepressant ended up on long-term disability, versus 9 percent of those who didn't take the medication. (Canadian investigators.)

- 2005: In a five-year study of 9,508 depressed patients, those who took an antidepressant were, on average, symptomatic 19 weeks a year, versus 11 weeks for those who didn't take any medication. (University of Calgary)

• 2007: In an NIMH funded study, 40 percent of schizophrenia patients off medication recovered over the long term (15 years), versus 5 percent of the medicated patients. Those off antipsychotics were much less likely to be symptomatic at the 10-year and 15-year followups. (Harrow, University of Illinois.)

•2012: In that same NIMH-funded study of long-term schizophrenia outcomes, investigators reported that at the end of 20 years, those who had stayed on antipsychotics throughout the study had more psychotic episodes, much greater anxiety, worse cognitive function, and were much less likely to be employed than those who got off the medications.

The Challenge for Journalists Covering Psychiatry

• Findings reported in the abstracts of published articles may not reflect actual trial data.

• In their discussions, the investigators may obscure or hide poor results for medicated patients.

• Published articles of clinical trials may present misleading, or incomplete picture of data submitted to FDA.

• Findings from long-term studies may not be publicized by the NIMH or the American Psychiatric Association because of the poor outcomes for the medicated patients.

• Psychiatrists conducting the trials are not going to point out the poor results for medicated patients in interviews with journalists.