While there’s more to say about the Sertraline study mentioned in the last post, specifically about the article version published in 1995, I think I’ll first mention the remaining data available in the N.D.A. that was approved in 1991. Recall the F.D.A. reviewer’s comment:

"The second study mentioned in the N.D.A. Report was a double blind trial with an active comparator [Amitriptyline]. Here’s what the Baum Hedlund Lawsuit [Laura A. Plumlee et. al. v. Pfizer] had to say:"

Pfizer submitted its new drug application ["NDA"] to the FDA in 1990. As part of the application, six placebo controlled trials were presented to the FDA. Of the six clinical trials, four showed that Zoloft was no more effective than placebo in treating depression and two indicated that Zoloft had slight positive impact on depression. The two studies that showed that Zoloft was more effective than placebo in treating depression, however, were severely flawed.

In the second trial that supposedly demonstrated efficacy, researchers enrolled 448 patients in a double-blind trial and divided the patients into three groups—patients taking Zoloft at doses between 50-200mg, patients taking a different antidepressant, and patients taking placebo. Much like the first “efficacy-establishing” clinical study, approximately 43% of people in the Zoloft treatment groups quit, 18% because of side effects, 9% because of a lack of efficacy, and 16% for other reasons. Of the remaining patients, the researchers tracked HAM-D scale changes over eight weeks. The trial’s data indicated that there was no clinically significant difference between Zoloft for the first six weeks of treatment, and that in weeks 7 and 8, a person taking Zoloft had a HAM-D scale improvement of about 3.5 points above those taking placebo. This was, again, a very small treatment effect, especially when one considers the serious potential side-effects attendant to Zoloft.

By this time, they’d learned to go up on the dose slowly (to keep the drop-out rate from soaring?). So there was a gradual dose titration for the first three weeks [mean maintenance doses, Sertraline 145 mg/day, Amitriptyline 108 mg/day]:

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Sertraline</th>
<th>Amitriptyline</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received Double-Dosed</td>
<td>149</td>
<td>149</td>
<td>130</td>
<td>428</td>
</tr>
<tr>
<td>Received at Least 1 Dose Double-Dosed Weekly But Not an Efficacy</td>
<td>5</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>All Patient Group</td>
<td>142</td>
<td>142</td>
<td>141</td>
<td>425</td>
</tr>
<tr>
<td>Completed Study</td>
<td>86</td>
<td>86</td>
<td>94</td>
<td>266</td>
</tr>
<tr>
<td>Total Premature Termination</td>
<td>63</td>
<td>63</td>
<td>56</td>
<td>180</td>
</tr>
<tr>
<td>Drug Related</td>
<td>25</td>
<td>28</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Side Effects</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Laboratory Abnormalities</td>
<td>13</td>
<td>6</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Lack of Efficacy</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Maximum Improvement</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Not Drug Related</td>
<td>18</td>
<td>29</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Patient Requested</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Intermittent Illness</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

"Refused further treatments, discontinued for personal reasons, noncompliance, did not return."
Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression.

by Reimherr FW, Chouinard G, Cohn CK, Cole JO, Itil TM, LaPierre YD, Masco HL, and Mendels J.


A double-blind, placebo- and amitriptyline-controlled comparison study was performed to evaluate the antidepressant efficacy of sertraline, a specific serotonin uptake inhibitor. Patients with DSM-III-defined major depression randomly received either sertraline \( N = 149 \), amitriptyline \( N = 149 \), or placebo \( N = 150 \) once daily for the 8-week study period. The mean final daily medication dose for the all-patients group was 145 mg and 104 mg for the sertraline- and amitriptyline-treatment groups, respectively. As measured by the Hamilton Rating Scale for Depression and the Clinical Global Impressions Scale, both the sertraline and amitriptyline treatment groups showed a significantly greater improvement from baseline \( p \leq .001 \) than the placebo group. The sertraline group had a higher proportion of gastrointestinal complaints and male sexual dysfunction than either the amitriptyline or the placebo group. The amitriptyline group showed a higher proportion of anticholinergic and sedative side effects and dizziness compared with patients who received either sertraline or placebo.

While I have no access to the full published article on this study, the F.D.A. N.D.A. information on this Trial is more convincing than the first one. I can't argue that a 3.5-point difference in HAM-D isn't much to write home about, but by F.D.A. standards, this appears to be a significant study.

There was a third supportive Clinical Trial reported in the F.D.A. N.D.A. It was a Pfizer conducted study looking at Sertraline in preventing relapse. Patients took Sertraline [open-label] for 8 weeks. Responders were then randomized [Placebo, Sertraline] and followed for 44 weeks. The Baum Hedlund Lawsuit didn’t mention it; the F.D.A. reviewer didn’t know what to say about it; and I’m similarly afflicted – who knows? Here’s the reason for the confusion – their flow chart:

Antidepressant efficacy of sertraline: a double-blind, placebo- and amitriptyline-controlled, multicenter comparison study in outpatients with major depression.

by Reimherr FW, Chouinard G, Cohn CK, Cole JO, Itil TM, LaPierre YD, Masco HL, and Mendels J.

Frankly, this was one of those studies you wish wasn’t there. There’s something a bit off at every level, but you can neither refute nor confirm its results. Here’s what the F.D.A. reviewer reported:

It was published twice:

**Sertraline in the prevention of depression.**
by Doogan DP and Caillard V
Department of Clinical Research, Pfizer Ltd, Sandwich, Kent.

A group of 480 patients, aged 19-78 with an HRSD score of at least 17 and who met DSM-III criteria for major depressive disorder were studied. Patients were given placebo for a one-week single-blind run-in period, after which sertraline was administered for eight weeks. This was followed by 44 weeks in which patients received sertraline or placebo on a double-blind, randomised basis. Patients were assessed periodically using the 17-item HRSD and the Clinical Global Impression scales. During the entire double-blind period 24 [13.0%] sertraline patients relapsed compared with 48 [45.7%] placebo patients [P<0.001]. The protective effect of sertraline was maintained throughout the 44 weeks. The study provides evidence that sertraline prevents relapse of the index episode of depression as well as recurrence of further episodes and has few side-effects.

There are several problems with these analyses. First, the use of the DLP analysis is questionable since so many patients terminated early in the trial and because there was a disproportionate number of placebo patients in this group. That is, there were 73 percent of the sertraline patients and 57 percent of placebo patients remaining at 20 weeks and 58 percent of the sertraline group and 50 percent of the placebo group at the completion of the trial (week 44). Another problem was the use of different criteria for relapse categories raising the issue of data conditioned analyses.

Several additional analyses were done. In the sertraline double-blind group, 17 [4%] were dropped for inadequate response. The corresponding number of dropouts on placebo was 46 [4%]. An examination of the data appeared to indicate that a higher proportion of placebo than sertraline dropouts occurred in the first eight weeks of the double-blind trial. Results of a life table analysis of time to discontinuation for dropouts for lack of efficacy confirmed this difference.

Conclusion. This study demonstrated that the continuation of sertraline beyond the initial eight week open trial decreased the incidence of depressive relapse and the number of dropouts for lack of clinical effect in comparison with placebo. This difference occurred during the first eight weeks of the 44-week double-blind segment. There were problems with the protocol in that it lacked detailed information concerning critical variables, patient inclusion/exclusion criteria and dosing requirements.

**The influence of different relapse criteria on the assessment of long-term efficacy of sertraline.**
by Montgomery SA, Doogan DP, and Burnside R

The treatment of depression with antidepressant agents must be continued beyond the acute phase, until the response is complete. The precise length of this continuation phase is still debated, but most authors estimate that it should last for between 4-6 months after apparent recovery. If antidepressants are withdrawn sooner, the original depression will return [relapse] in a proportion of patients. Relapse rates on placebo are high, whether patients are first-time or recurrent depressives. Most depressions are recurrent and long-term treatment therefore ensures that the changes of a new episode of illness developing are reduced. The importance of this aspect of efficacy is recognized and new antidepressants are being tested in long-term prophylactic studies. A long-term efficacy study has shown that sertraline was significantly more effective than placebo in preventing both relapse and recurrence.

There were just too many drop-outs and the response criteria were too fuzzy to really know what to do with it. The Pfizer authors concluded that it confirmed relapse prevention by Zoloft. I classify it as "whatever."

So here’s what they had. I must add, parenthetically, that, as always, I was impressed with the quality of the report from the F.D.A. reviewer. The reviewers are
tasked with summarizing and evaluating the submitted information for the actual "approvers", and they are regularly thorough. Here's what they had:

<table>
<thead>
<tr>
<th>Placebo Controlled Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>protocol 103</td>
</tr>
<tr>
<td>protocol 101</td>
</tr>
<tr>
<td>protocol 310</td>
</tr>
<tr>
<td>protocol 104</td>
</tr>
<tr>
<td>protocol 315</td>
</tr>
<tr>
<td>protocol 320</td>
</tr>
</tbody>
</table>

So this report went to the approval group, and what we know is that they approved Zoloft in November 1991. But the Baum Hedlund complaint has some actual information about how that came to be from discovery documents collected in the process of filing their suit. I don’t have those documents, but there’s a lot from them in the Laura A. Plumlee et. al. v. Pfizer complaint. That’s where we’re headed next...

zoloft: the approval I...

This is a lot for a blog post. I’ve tried to only show the essence of things, but it’s still a lot of words and some confusing tables. There are a number of sources: a recent lawsuit, a twenty-five year old FDA drug approval, and an eighteen year old journal article. While a lot of the information is old, the issues raised are as much on the front burner today as they should have been in the past. So while the post is dense, I think the information adds important details and underscores why the AllTrials campaign is an essential ingredient in any chance we have for effective Clinical Trial reform. I have no dog in this hunt that relates to the lawsuit itself – that’s for the courts. But it’s through discovery in suits like this that we gain valuable documentation of the story behind what we’ve previously been able to see as physicians, observers, and patients. As is apparent from my title [zoloft: the approval I…], there’s more coming...

A week and a half ago, I mentioned a suit filed against Pfizer [a wide net…] with an unique complaint. The complaint essentially said that Zoloft was marketed and labeled as an effective Antidepressant but that was untrue:

1. Zoloft’s drug label. between 1991 to the present, was misleading or deceptive because it did not contain material information about Zoloft’s efficacy, to wit, the drug label failed to provide information about the majority of clinical trials demonstrating that Zoloft was no more effective than placebo in treating depression and specify the marginal benefit to treating depression observed in the two clinical trials purporting to show Zoloft’s efficacy;
2. Pfizer intentionally, deliberately, or recklessly created and distributed Zoloft’s misleading drug label with regard to its efficacy description for depression.

I found that intriguing, and read the whole complaint [Laura A. Plumlee et. al. v. Pfizer]. After reading this…

Pfizer submitted its new drug application ["NDA"] to the FDA in 1990. As part of the application, six placebo controlled trials were presented to the FDA. Of the six clinical trials, four showed that Zoloft was no more effective than placebo in treating depression and two indicated that Zoloft had slight positive impact on depression. The two studies that showed that Zoloft was more effective than placebo in treating depression, however, were severely flawed.

In the first trial that supposedly demonstrated efficacy, researchers enrolled 369 patients in a double-blind trial to test the efficacy of Zoloft at 50mg, 100mg, and 200mg against placebo. Within the treatment groups, i.e., those taking Zoloft and not placebo, about 50% of the patients quit before the trial was completed-22% because of side-effects, 18% because it was not effective, and 10% for unexplained reasons. This large drop-out rate reduced the available patient population to 191. Of the remaining 50%, i.e., the population that did not quit Zoloft, the trial tracked patient changes in depression based on the Hamilton Rating Scale for Depression ["HAM-D"] over the course of six weeks. The HAM-D scale is a multiple item questionnaire used to measure a person’s perception of depression. It is usually composed of 17-29 questions where the patient rates specific areas on a 0-5 point scale. A person’s HAM-D scale rating can be anywhere between 0-70 depending on the scale used. The trial revealed that there was only a slight improvement in those taking Zoloft than those taking placebo. During the first four weeks of treatment, the study did not show any statistically significant difference on the patient’s HAM-D scale between those taking Zoloft and those taking a placebo. Then, during weeks 5 and 6, the data showed that there was a slight statistically significant difference for the 50mg treatment group, although there was no significance in the...
The study showed that, on average, a person taking Zoloft had a HAM-D scale improvement of about 2.3 points above those taking placebo after six weeks, which, depending on the scale being used, means that Zoloft, with its many documented adverse side effects, appeared to be better than placebo by 1-5% after six weeks. This is an extremely small treatment effect and it was not associated with dosage.

I went to the FDA site looking for that original N.D.A. [New Drug Approval]. It wasn’t there, so I submitted an F.O.I.A. [Freedom of Information Act] request and the disk arrived Friday [I’ll admit that I thought the suit might be exaggerating]. Here’s some text from the N.D.A. Report [submitted April 13, 1988, and approved September 30, 1991]:

5.1 Efficacy Data

5.1.1 Overview of Efficacy Data

The clinical trials to evaluate the efficacy of sertraline were carried out primarily in adult and geriatric patients whose diagnosis corresponded most closely to the DSM-III category of major depression.

In the HAM, there were 15 clinical trials. Including six placebo-controlled trials, two active-controlled trials, four long-term continuation trials, and three uncontrolled trials. The two active-controlled studies included only elderly patients while the remainder included adults with a wide age range. The duration of the studies ranged from 4 weeks to 2 years. Two of the placebo-controlled trials were in hospitalized patients while the remainder included depressed outpatients.

5.1.2 Studies Providing Primary Evidence of Effectiveness

There were six placebo-controlled trials evaluating sertraline in major depression, four of which were double-blind and one in patients of the four open trials, the fixed-dose trial and one of the dose titration trials indicated sertraline was more effective than placebo in the treatment of major depression. A second dose titration study did not show sertraline superior to placebo. The fourth open trial, a "sleepless" trial, provided suggestive evidence for a continuation effect of sertraline. The two open trials followed fixed-dose designs and no difference between sertraline and placebo were detected.

This is from the fixed dose trial they mentioned – a table showing the drop-out rates and reasons for dropping out:

<table>
<thead>
<tr>
<th>Number of Subjects (Percent)</th>
<th>Sertraline 50mg</th>
<th>Sertraline 100mg</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled Double-Bind</td>
<td>95</td>
<td>92</td>
<td>91</td>
<td>169</td>
</tr>
<tr>
<td>Received at least one dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>double-blind trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no on-dose rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patient Group</td>
<td>95</td>
<td>92</td>
<td>91</td>
<td>169</td>
</tr>
<tr>
<td>Completed Study</td>
<td>59(62)</td>
<td>47(51)</td>
<td>59(62)</td>
<td>166(19)</td>
</tr>
<tr>
<td>Total Premature Terminations</td>
<td>56(58)</td>
<td>46(49)</td>
<td>55(57)</td>
<td>158(18)</td>
</tr>
</tbody>
</table>

And this is the HAM-D data table with my graph made from that table:
Sertraline safety and efficacy in major depression: a double-blind fixed-dose comparison with placebo.

by Fabre LF, Abuzzahab FS, Amin M, Claghorn JL, Mendels J, Patel WM, Dubé S, and Small JG.


In a 6-week, randomized, double-blind, multicenter trial, sertraline 50 mg, 100 mg, or 200 mg, or placebo, was administered once daily to 369 patients with DSM-III-defined major depression. Efficacy variables included changes from baseline scores for total Hamilton Rating Scale for Depression [HAMD], HAMD Bech Depression Cluster, Clinical Global Impressions [CGI] Severity, CGI Improvement, and Profile of Mood States Depression/Dejection Factor. For the evaluable-patients analysis, all sertraline groups showed significantly [p < 0.05 or better] greater improvements in all efficacy variables except one when compared with the placebo group. For the all-patients analysis, all efficacy variables in the 50 mg group were statistically significantly [p < 0.05] better than placebo. Side effects increased with increasing dosage but were usually mild and well tolerated. The results of this study show that sertraline 50 mg once daily is as effective as higher dosages for the treatment of major depression with fewer side effects and therapy discontinuations.

And here are the versions of the drop-out table and HAM-D graphs in the published version:

When you look at my HAM-D graph and the one in the published paper, it’s kind of hard to imagine they’re from the same study. And then when you read the F.D.A. reviewer’s comment about a dose response curve...

... and compare it to the published article’s version, "Side effects increased with increasing dosage but were usually mild and well tolerated. The results of this study show that sertraline 50 mg once daily is as effective as higher dosages for the treatment of major depression with fewer side effects and therapy discontinuations.

" How did they do that?

The answer is in the table’s footnote and the graph’s parentheses. It’s the phrase "evaluable patients." The published paper mentions "evaluable patients" sixteen times. This is the most pertinent instance:

A total of 178 patients [48%] discontinued prematurely from this study (Table 2). Side effects and lack of efficacy were the most frequently cited reasons for discontinuation. The number of patients in each group who discontinued because of side effects prior to study day 11 and who were thus excluded from the evaluable-patients efficacy analysis was 4 [4%] in the sertraline 50 mg/day group, 10 [11%] in the 100 mg/day group, 23 [25%] in the 200 mg/day group, and 2 [2%] in the placebo group.

The version we have from the F.D.A. N.D.A. is not the primary data and is suspect itself because of the ubiquitous L.O.C.F. correction factor [Last Observation Carried Forward]. The justification for using it is the assumption that drop-outs are random and equal among groups. That is clearly not the case here [see either version of the tables above or the comments about that first eleven days]. The validity of throwing out the first eleven days and basing conclusions on "evaluable patients" in the published study is only justifiable if you want to monkey with the results, as is the averaging ["Sertraline Combined"]. What they gained is obvious. They brought the
The results of this study show that sertraline 50 mg once daily is as effective as higher dosages for the treatment of major depression...

There’s plenty more to be gleaned from these documents, but I’m going to take a break. This is enough to show the extent of the jury-rigging of a Clinical Trial report from twenty-five years ago, the dawn of time for the era of new psychopharmacology in psychiatry. To be honest, today, the South is in a deep freeze. It was 19° in the sun on my front porch the last time I looked, and the little gas heater in my office is no competition for the roaring fire in the living room [and, the next episode of Helen Mirren’s Prime Suspect is singing from NetFlix]. I’ll have to say that I didn’t expect this much sleight of hand that long ago, but it is what it is as they say. And what it is is really bad. Much more later...

to buy or not to buy, that is the question...

We think about it more now than we used to, but it still hasn’t thoroughly sunk in – the USA is just a country in a world of many countries. And from a medical perspective, the real overarching organization is the WHO established by the United Nations. One of its functions is to maintain the International Classification of Diseases [ICD]. The United States is treaty bound to use the ICD to report diseases to its public health database – vital for health policy decisions around the world. For obvious reasons, the ICD is also the standard used for other reporting – Medicare, Medicaid, third party carriers, CDC, etc.

The International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] is the official system used in the United States to classify and assign codes to health conditions and related information. The use of standardized codes improves consistency among physicians in recording patient symptoms and diagnoses.

The ICD-9-CM contains a list of alphanumeric codes which correspond to diagnoses and procedures recorded in conjunction with hospital care in the United States. For example, a patient with acute appendicitis will be assigned a code of 540. This code may be entered onto a patient’s electronic medical record and used for diagnostic, billing and reporting purposes. Related information also classified and codified in the system includes symptoms, patient complaints, causes of injury, and mental disorders.


Of course, we have to be a bit special, so the official disease classification is the ICD-9-CM [The International Classification of Diseases, Ninth Revision, Clinical
Modification] a subset for America. While there’s currently an ICD-10, the US version [ICD-10-CM] won’t be in use until 2015 if even then. Because the ICD-11 is in preparation, due out in 2015-2016, it’s possible we’ll just skip ahead to it. The only thing that matters to we mortals is that the ICD-10 and coming ICD-11 use a different coding scheme than the ICD-9 and ICD-9-CM, so all the codes are different even if the diagnoses have been kept the same. That’s the major reason that we haven’t made the changeover. Every computer system will need redoing, a massive and expensive task. These weighty matters are beyond my further elucidating powers [or patience], but I’m pretty sure I’ve got that part right.

The Diagnostic and Statistical Manual [DSM] is a creation of the American Psychiatric Association. It came to life in 1952 as a simple code-book with terse definitions [DSM] revised in 1968 [DSM-II]. The creation of the DSM-III in 1980 was something very different. It was written as a textbook with defined diagnostic criteria for each disorder. It was still a code-book and the codes were from the ICD, but it was treated as much more. It was adopted everywhere, or so it seemed. But what was official were the codes. The definitions were simply what the APA Task Force said they were.

Which brings us to now, with the DSM-IV [1994] as the widely used standard in mental health. The American Psychiatric Association is suggesting that we buy their DSM-5, due out in May this year. Well, it’s going to have the same diagnostic codes as the DSM-IV – the ICD-9-CM codes. And when they finally change-over to the ICD-10-CM or the ICD-11, the DSM-5 will have to change too. So the DSM-5 is the official code-book for the APA. But that has about the same meaning as Papa John’s Pizza is the official pizza of the super-bowl [which is no meaning at all]. Eating Dominos is allowed. The reason to buy the DSM-5 is for the words in between the codes, not for anything that has to do with your practice or official reporting to third party carriers [or anywhere else]. It’s the textbook part that’s for sale, not the codes. You’ve already got them in your DSM-IV or on the Internet, and when they change ICDs in a few years, they’ll be widely available [a “how-to...”]

While there’s much talk of a boycott which sounds like it’s some kind of active process that requires sacrifice, it’s more like holding on to your iPhone 4 instead of racing out for the iPhone 5 because you don’t care for the new features or are on a budget, or using Windows XP [as I do] instead of buying Windows 7.0 [or 8.0]. So if you want the new textbook according to the DSM-5 Task Force with their changes, buy it. Otherwise, follow the simple instructions of Zen Master Basho at the top of this post. The grass will continue to grow...

the road behind: paradigms that needed ending...

Posted on Thursday 14 February 2013

We shall drink no wine before its time...

Orson Wells

The DSM-III/DSM-IIIR/DSM-IV series had given the third party carriers, policy makers, and pharmaceutical industry what they wanted – an objective diagnostic system in psychiatry. In some ways, it was trivial because there’s so much more to a given person’s mental illness than signs and symptoms. In other ways, it was
A Warning Sign on the Road to DSM-V: Beware of Its Unintended Consequences

Psychiatric Times
By Allen Frances, MD
June 26, 2009

...The DSM-V goal to effect a “paradigm shift” in psychiatric diagnosis is absurdly premature. Simply stated, descriptive psychiatric diagnosis does not now need and cannot support a paradigm shift. There can be no dramatic improvements in psychiatric diagnosis until we make a fundamental leap in our understanding of what causes mental disorders. The incredible recent advances in neuroscience, molecular biology, and brain imaging that have taught us so much about normal brain functioning are still not relevant to the clinical practicalities of everyday psychiatric diagnosis. The clearest evidence supporting this disappointing fact is that not even 1 biological test is ready for inclusion in the criteria sets for DSM-V...

So long as psychiatric diagnosis is stuck at its current descriptive level, there is little to be gained and much to be lost in frequently and arbitrarily changing the system. Descriptive diagnosis should remain fairly stable until, disorder by disorder, we gradually attain a more fundamental and explanatory understanding of causality. Indeed, there has been only 1 paradigm shift in psychiatric diagnosis in the past 100 years—the DSM-III introduction in 1980 of operational criteria sets and the multiaxial system. With these methodological advances, DSM-III rescued psychiatric diagnosis from unreliability and the oblivion of irrelevancy. In the subsequent evolution of descriptive diagnosis, DSM-III-R and DSM-IV were really no more than footnotes to DSM-III and, at best, DSM-V could only hope to join them in making a modest contribution. Descriptive diagnosis is simply not equipped to carry us much farther than it already has. The real paradigm shift will require an increase in our knowledge—not just a “rearrangement of the furniture” of the various descriptive possibilities.

Part of the exaggerated claim of a paradigm shift in DSM-V is based on the suggestion that it will be introducing dimensional ratings and that this will increase the precision of diagnosis. I am a big fan of dimensional diagnosis and wrote a paper promoting its use as early as 1982. Naturally, I had hoped to expand the role of dimensional diagnosis in DSM-IV but came to realize that busy clinicians do not have the time, training, or inclination to use dimensional ratings. Indeed, the dimensional components already built into the DSM system (ie, severity ratings of mild, moderate, and severe for every disorder and the Axis V Global Assessment of Functioning scale) are very often ignored. Including an ad hoc, untested, and complex dimensional system in an official nomenclature is premature and will likely lead to similar neglect and confusion...

In the four years since that warning, much of the contentious debate has centered on specific changes made in the DSM-5, as it came to be called. But I thought I’d go back to the beginning because some of what matters has gotten lost. There was no general outcry among clinicians about the DSM-IV in place since 1994. It was a code-book with its glitches, but it worked okay. The outcry was from the psychopharmacologists and neuroscientists who could not get their drugs onto the system. They blamed the system rather than considering that their science was not yet advanced enough for that kind of direct clinical application. Not their fault, but hardly a reason to be jury-rigging clinical medicine to fit their needs. If I had said as a psychoanalyst that the DSM-IV didn’t fit my understanding of patients, I’d have been run out of town on a rail, much like what happened when the 1968 DSM-II Task Force added some psychoanalytic theory to several of the categories [and have been vilified to the grave]. What Dr. Frances was warning them about was making that same mistake – that and overly complexifying a code-book with an elaborate dimensional system. The response less than a week later:

Setting the Record Straight: A Response to Frances Commentary on DSM-V

Psychiatric Times
By Alan F. Schatzberg, James H. Scully Jr, David J. Kuper, Darrel A. Regier
July 1, 2009

Dr Schatzberg is President of the American Psychiatric Association.
Dr Scull is Medical Director, CEO, of the American Psychiatric Association.
Dr Kuper is Chair, DSM-V Task Force
Dr Regier is Vice Chair, DSM-V Task Force

...The DSM-III categorical diagnoses with operational criteria were a major advance for our field, but they are now holding us back because the system has not kept up with current thinking. Clinicians complain that the current DSM-IV system poorly reflects the clinical realities of their patients. Researchers are skeptical that the existing DSM categories represent a valid basis for scientific investigations, and accumulating evidence supports this skepticism. Science has advanced, treatments have advanced, and clinical practice has advanced since Dr. Frances’ work on DSM-IV. The DSM will become irrelevant if it does not change to reflect these advances.

If the clinicians were complaining, they were doing it quietly. I hadn’t heard them. The researchers may have been complaining, but the NIMH had already begun setting up a system for them to research around on to their hearts content [RDoC]. Those responding to Dr. Frances were the big guns, and they not only ignored his warning, they attacked – a broadside ad hominem attack at that:
Finally, Dr. Frances opened his commentary with the statement, “We should begin with full disclosure.” It is unfortunate that Dr. Frances failed to take this statement to heart when he did not disclose his continued financial interests in several publications based on DSM-IV. Only with this information could the reader make a full assessment of his critiques of a new and different DSM-V. Both Dr. Frances and Dr. Spitzer have more than a personal “pride of authorship” interest in preserving the DSM-IV and its related case book and study products. Both continue to receive royalties on DSM-IV associated products. The fact that Dr. Frances was informed at the APA Annual Meeting last month that subsequent editions of his DSM-IV associated products would cease when the new edition is finalized, should be considered when evaluating his critique and its timing.

Dr. Frances shook off the attack and carried on with his DSM-5 in Distress blog which mainly focused on some of the more outlandish new disorders and their expansion of old ones. In that year, 2009, Dr. Schatzberg, then APA president, was investigated for COI violations by the US Senate [Senator Grassley] and soon stepped down as Chairman of Psychiatry at Stanford. Dr. Scully has retired this year shortly after the DSM-5 was approved.

Both of the two main topics from Dr. Frances’ initial criticism above – the paradigm shift to a biological basis for the DSM-5 and their complex dimensional system – were totally abandoned along the way [for the reasons he foretold]. In addition, also along the way, the APA DSM-5 Task Force has managed to alienate almost every one of the non-medical mental health professions by looking at mental illness through the monocular lens of a subset of psychiatrist neuroscientists.

While I obviously agree with Dr. Frances’ perspective and did when he first started talking about it in 2009, the thing about the road behind that bothers me is not just their inappropriate insertion of the biological agenda into the DSM-5 revision, it’s what they didn’t do. As I’ve gone through the Clinical Trial literature over the last twenty-five years, it’s abundantly clear that the imprecision of the DSM-III+ has made a mess of the drug trials that underlie our psychopharmacology literature, particularly in depression. In practice, the majority of antidepressant prescriptions are written based simply on a patient’s report, “I’m depressed,” not on a careful evaluation. Worse, even in situations where a patient is thoroughly examined, the existing category of Major Depressive Disorder is so broad and overly-inclusive that the best cohort possible is still unacceptably heterogeneous.

In adults, it includes Melancholic Depression, the depressive affect of people with personality disorders, situational depressions, the culturally deprived, the traumatized, etc. etc. In kids, it’s worse. I’ve never personally seen a depressed adolescent that didn’t have an apparent reason to be depressed – and it’s usually a reason that needed to be addressed. We all know that Major Depressive Disorder was a political creation [as historian Ed Shorter puts it], and yet nobody took it on as an area in need of the intense study it deserves. I sure don’t blame just psychiatry for the depression problem, though we certainly have played our role. Both the third party carriers [insurance] and the pharmaceutical industry have a major part in the depression game – both driven by money, not mental health. But it’s ours to fix, and I don’t even think the DSM-5 Task Force looked at it. They kvetch about the problem of not being able to map their drugs or their neuroscience findings on clinical diagnoses, but matching anything with that category is like matching long words with a bowl of soggy alphabet soup. That’s the loudest example, but there are many others.

With all the talk about the misguided things the DSM-5 did try to do, there are two central things it didn’t do. It didn’t revise the categories that begged for revision like Major Depressive Disorder. And it didn’t set an over-riding agenda to address the widespread problem of industry driven interference and rampant over-use of medication. If anything, it promoted them under the guise of early intervention. The DSM-5 could have been a vehicle for change that focused attention on some paradigms that needed ending – conflicting interests and tolerance of scientific corruption...

the road ahead...

Posted on Wednesday 13 February 2013
An aspect rarely commented on is that the DSM-5 leaders didn’t seem enthusiastic about the basic principles of the earlier revisions. In A Research Agenda for DSM-V, they said:

Questions have been raised by many critics that the DSM’s descriptive approach may have outlived its usefulness and is in fact potentially misleading. Although there is a large body of research that indicates a neurobiological basis for most mental disorders, the DSM definitions are virtually devoid of biology. Instead, DSM-IV definitions are based on clusters of symptoms and characteristics of clinical course.

Later, when they announced that they were abandoning their attempt to put the DSM-5 in a neurobiological framework, they said [Neuroscience, Clinical Evidence, and the Future of Psychiatric Classification in DSM-5]:

We realized from our Research Agenda conference series that we would not be able to accomplish by DSM-5’s deadline all of the things we set out to and, in fact, that portions of that agenda related to advances in neuroscience were already being addressed in other arenas. A logical extension of those discussions, as detailed in our Research Agenda articles, is the Research Domain Criteria (RDoC) initiative recently launched by the National Institute of Mental Health (NIMH). A commentary by Insel and colleagues introduced readers to the working principles behind the RDoC, whose proposed reclassification of mental disorders for research purposes is predicated on a neuroscience-based framework that can contribute to a nosology in which disorders are grouped by underlying pathophysiological similarities rather than phenomenological observations. This NIMH objective is consistent with our research planning conferences and conclusions, which underscored our commitment to examining evidence from neurobiology and assessing the readiness of proposed revisions for DSM-5.

They seem to be taking some credit for the RDoC, which was actually an independent NIMH creation. But my reading is that their failure to meet their neurobiological goal was a major disappointment and it remained the shiny object of the future – the paradigm shift they longed for.

But there was another paradigm shift in the wings. There is a reasonably large symptom overlap among the various psychiatric syndromes disorders. In addition, they had difficulty mapping neuroscience findings or functional impairment onto the disorders. So they came up with the idea of a “cross-cutting” or a “dimensional” system to replace the not much used Axial system of the DSM-III/DSM-IV manual. This is going to be a short paragraph because I never really got it [nor did anyone else]. It was too complex for most of the mortals using the manual and was dropped in the approval process. I mention it because it was another attempt to escape the confines of the descriptive principles underlying the earlier revisions.

They wanted to do something different – move psychiatry towards a biological classification, add other dimensions, innovate, add-on preventive medicine principles. And there are lots of ways to interpret their drive for a major change in the diagnostic system in mental health. The most obvious is their impatience with neuroscience research. By the time they started, we had twenty years of venerating Robins and Guze, the Feighner criteria, and the neoKraepelinian Tenets. You’d have to have been in a deep coma not to know that psychiatry has become hardly so neutral as the DSM-III/DSM-IV diagnostic system implied – it has become a biomedical specialty, but its biologic underpinnings are tenuous. No matter how many times and ways one writes “exciting recent advances in neuroscience…”, the absence of biomarkers and proven biological pathophysiology or etiology is painfully obvious. They are way behind schedule.

Another explanation for the zeal to change things might possibly have been an attempt to keep psychiatry honest. It’s hard to imagine that the DSM-5 leaders [Kupfer, Regier, and Scully] didn’t know about the widespread alliances between the pharmaceutical companies and some of the more prolific academic psychiatrists and chairmen, and about the shady science filling our journals. It occurs to me that there might have been some wish to put psychiatry on a more solid biological carriage
than the speculative and jury-rigged fare that was frequently haunting our journals. Just a thought that maybe they were trying to prevent the shaming that escalated during their tenure in spite of their efforts. Maybe they saw what was coming.

My own bias covers the third possibility. In my view, psychiatry has traditionally been at its best when it has focused on the caretaking aspect of *doctoring*, and most of its foibles have historically come with the overzealous forays into medical therapeutics. I’m not anti-therapeutics, but our story says we should walk very softly. But I think mine is an idiosyncratic view. I don’t mind that psychiatry lives on the edge of medicine and I don’t feel envy about the solidity of science in medicine proper. But I’m acutely aware that for most of my colleagues, the drive to sit firmly among their medical peers is strong – and envy is one of the more powerful motivators on the planet. So my take is that one of the drivers of the DSM-5 is medical/therapeutic envy run amok.

Whatever the origins, the DSM-5 Task Force was hell-bent to do something *new* – put the DSM-5 on a solid biological footing, add a new cross-cutting dimensional axis, be innovative, or add a dose of early detection and treatment – and came up short on every count. But worse, they were remarkably inattentive to everything *old*. The two biggest categories, MDD and GAD [also most in need of attention] were untouched except for the silliness with the bereavement exclusion. This was not a *revision*. It was something else. They just didn’t get around to doing their assigned task, and the poor performance of MDD and GAD in the field trials bears testimony.

So it has gone to press accompanied by all its ancillary books all with their exorbitant price-tags to find its place in history. Reading Dr. Sabshin’s book, *Changing American Psychiatry: A Personal Perspective*, it’s clear that the “Aw Shucks” myth about the DSM-III’s place in making a paradigm shift is silly – it was planned to do exactly what it did. I don’t know who thought that they could bring off another paradigm shift with the DSM-5, but they badly miscalculated. While they were having thirteen expert conferences between 2004 and 2008 making their plans, a lot was happening. Allen Jones blew the whistle on TMAP. Dr. Nemeroff and others were recurrently busted for undeclared conflicts of interest. Suits against PHARMA grew in number and success, producing internal documents that were incriminating, revealing widespread ghost-writing and PHARMA influence on our literature and practice. There was a lot more attention to the exaggerated claims of efficacy and downplaying of adverse effects. And the black box warning made its way to every Antidepressant label – potential suicidality in kids. By the time of Senator Grassley’s investigation of academic psychiatrists in 2008, the climate was changing at a rapid pace. Then the pipeline dried up. Both previous DSM gurus, Dr. Spitzer and Dr. Frances began to ask, “what’s going on?” And people like me and you also began to wake up and ask, “what’s going on?” But the DSM-5 leaders were in a bunker, meeting in something pretty close to secret conclave. Behind schedule, they cancelled plans for a second checkup round of field trials. As things progressed, they had to admit that the grand plan of basing the DSM-5 on neurobiology wasn’t going to work – the science just wasn’t there. By this time, they’d released an early draft and the reaction was uniformly negative. Dr. Frances was writing a blog in *Psychology Today* essentially pleading with them to change their course [DSM-5 in Distress], joined by an impressive list of other organizations.

And so I’m afraid that the future of the DSM-5 is already written in its past. It’s an anachronism before it goes on sale – a testimony to a goal of change that was not just premature or even speculative, but out of touch with the story it was part of. The DSM has been a standard for all of the mental health professions, but the DSM-5 Task Force decided to push an agenda that was only pertinent to a particular subset of psychiatrists. And that agenda was not to give our mental health community its best diagnostic system for the road ahead in a rapidly changing environment. And they didn’t…
The diagnosis of Major Depressive Disorder is less precise to my mind so I haven’t posted some summary slide. But notice that in the graph on the right, black is for the Bipolar Phenotype and the open bar is using the standard of [Bipolar + Recurrent Unipolar Depression + Suicide] and it approaches 100% in monozygotic [identical] twins. The study below is a meta-analysis of the studies in Major Depressive
Overview of the Genetics of Major Depressive Disorder

Falk W. Lohoff


Abstract: Major depressive disorder (MDD) is a common psychiatric illness with high levels of morbidity and mortality. Despite intensive research during the past several decades, the neurobiological basis and pathophysiology of depressive disorders remain unknown. Genetic factors play important roles in the development of MDD, as indicated by family, twin, and adoption studies, and may reveal important information about disease mechanisms. This article describes recent developments in the field of psychiatric genetics, with a focus on MDD. Early twin studies, linkage studies, and association studies are discussed. Recent findings from genome-wide association studies are reviewed and future directions discussed. Despite all efforts, thus far, no single genetic variation has been identified to increase the risk of depression substantially. Genetic variants are expected to have only small effects on overall disease risk, and multiple genetic factors in conjunction with environmental factors are likely necessary for the development of MDD. Future large-scale studies are needed to dissect this complex phenotype and to identify pathways involved in the etiology of MDD.

Major depressive disorder (MDD) is a common psychiatric illness with high levels of morbidity and mortality. It is estimated that 10% to 15% of the general population will experience clinical depression during their lifetime [1], and 5% of men and 9% of women will experience a depressive disorder in a given year, according to the World Health Organization [2]. Genetic factors play important roles in the development of MDD, as indicated by family, twin, and adoption studies. Early twin studies suggested heritability of 40% to 50%, and family studies indicate a twofold to threefold increase in lifetime risk of developing MDD among first-degree relatives. This degree of familial aggregation, coupled with the high heritability from twin studies, generated optimism that molecular genetic techniques would reveal genes of substantial influence on MDD risk. Unfortunately, gene localization and identification has been a slow, labor-intensive process. Genetic investigators have encountered similar frustrations with other common complex traits [eg, asthma, hypertension, and diabetes mellitus].

The major impediments to mood disorder gene localization and identification are as follows: [1] no single gene is necessary and sufficient for MDD; [2] each susceptibility gene contributes a small fraction of the total genetic risk; and [3] complex genetic heterogeneity, meaning that multiple partially overlapping sets of susceptibility genes [which interact with the environment] can predispose individuals to similar syndromes that are indistinguishable on clinical grounds.

The field of psychiatric genetics in general has been disappointing given that the initial hope to find common gene variants of large effect in the pathogenesis of mental illnesses has been unsuccessful. In most psychiatric illnesses, the phenotype seems too complex, with the patient cohort too small, and no findings have been consistently replicated. This is also the case for MDDs. In addition, the phenotypic effects of genetic variants identified to date are weak, with ORs of 1.0 to 1.2. The picture is further complicated when comparing the magnitude of the impact of gene variation on disease susceptibility with the impact of lifestyle and environmental factors, which is likely to be large. Despite these obstacles, the field of psychiatric genetics is rapidly growing, and several new technological advances [eg, whole-genome sequencing] will be soon available for large-scale studies. It is important to remember that genetic information will only provide additional information on one aspect of the complex and personal history of psychiatric patients. It is the sum of inside and outside factors that contributes and influences mental pathology and well-being.

Why is this here? Two reasons:

1. DSM-5. Throughout the months of watching the DSM-5 implode, I’ve wondered the same thing over and over. In 2002, the future leaders of the DSM-V Task Force published a book, A Research Agenda for DSM-V, that said in the introduction:

   The descriptive approach adopted by the DSM allowed for the development of a classification system that met the field’s need for a common language, without being mired in ideological hypotheses about the causes of psychiatric illness. Questions have been raised by many critics that the DSM’s descriptive approach may have outweighed its usefulness and is in fact potentially misleading. Although there is a growing body of research that indicates a neurobiological basis for most mental disorders, the DSM definitions are virtually devoid of biology. Instead, DSM-IV definitions are based on clusters of symptoms and characteristics of clinical courses.

   It is our goal to translate basic and clinical neuroscience research relating brain structure, brain function, and behavior into a classification of psychiatric disorders based on etiology and pathophysiology.

While it’s not my main point here, I don’t personally think that "there is a large body of research that indicates a neurobiological basis for most mental disorders. But I sure don’t question that the body psychiatric believes that and has for some time. My preoccupation has been "What made the DSM-V [DSM-5] Task Force leaders think that they could come out of the closet and declare that the DSM-5 would aim to be based on 'etiology and pathophysiology'? They didn’t have anything to back up that statement. I recall the party line back in 1980 was that etiology would be added when it was known. It sure wasn’t known in 2002. And they didn’t say they would classify some psychiatric disorders by adding neurobiological data, they said "a classification of psychiatric disorders based on etiology and pathophysiology" was the goal. They stepped way out of the closet. They hedged their bets by saying such a classification might be in the far distant future, but they were pretty sure that was the future. They also thought the
“descriptive approach may have outlived its usefulness” e.g. they had already given up on the DSM-III, DSM-III-R, DSM-IV solution and were headed for greater things.

A Research Agenda for DSM-V had an army of contributors, so it must have been in production around the time the Human Genome Project was finally bearing fruit. I think that the coming of the technology of the Human Genome Project was the thing that made them think that they could get away with finally saying that psychiatry = medicine = biology, a twenty year old dream. No more equivocating, Robins and Guze, neoKraepelinian tenets, and John Feighner set free! They had the runs in families data; they were going to finally see the genetic code and find the offending genes; and they had ten years for it to happen. It was in the bag!

I doubt that in 2000, anyone had any idea how the the cracking of the human genome wasn’t going to be the end of something, but rather a new beginning. And I think this statement above – “The field of psychiatric genetics in general has been disappointing given that the initial hope to find common gene variants of large effect in the pathogenesis of mental illnesses has been unsuccessful” – is why the DSM-5 went so far off track. They thought there would be enough in the genetic findings to validate their biologizing psychiatry formally. At least that’s my guess. Bad call! They were in too big a hurry. They hadn’t planned on “The picture is further complicated when comparing the magnitude of the impact of gene variation on disease susceptibility with the impact of lifestyle and environmental factors, which is likely to be large.”

2. Translational Science: “Translational science is a cross disciplinary, scientific research that is motivated by the need for practical applications that help people. The term is used mostly in the health sciences and refers to real-time translation of bench science, conducted only in a lab, to bedside clinical practice or dissemination to population-based community interventions.” While it sounds good, it’s a racket. Make your research sound practical, and you’ll get funded. $35 M for STAR*D is one of the reasons I don’t like it. Genetic research like this is an example:

Common Genetic Variation and Antidepressant Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Genome-Wide Pharmacogenetic Studies
by the GENDEP Investigators, MARS investigators, and STAR*D Investigators

Objective: Indirect evidence suggests that common genetic variation contributes to individual differences in antidepressant efficacy among individuals with major depressive disorder, but previous studies may have been underpowered to detect these effects.

Method: A meta-analysis was performed on data from three genome-wide pharmacogenetic studies – the Genome-Based Therapeutic Drugs for Depression (GENDEP) project, the Munich Antidepressant Response Signature (MARS) project, and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study – which included 2,256 individuals of Northern European descent with major depressive disorder, and antidepressant treatment outcomes were prospectively collected. After imputation, 1.2 million single-nucleotide polymorphisms were tested, capturing common variation for association with symptomatic improvement and remission after up to 12 weeks of antidepressant treatment.

Results: No individual association met a genome-wide threshold for statistical significance in the primary analyses. A polygenic score derived from a meta-analysis of GENDEP and MARS participants accounted for up to approximately 1.2% of the variance in outcomes in STAR*D, suggesting a weakly concordant signal distributed over many polymorphisms. An analysis restricted to 1,354 individuals treated with citalopram [STAR*D] or escitalopram [GENDEP] identified an intergenic region on chromosome 5 associated with early improvement after 2 weeks of treatment.

Conclusions: Despite increased statistical power accorded by meta-analysis, the authors identified no reliable predictors of antidepressant treatment outcome, although they did identify modest, direct evidence that common genetic variation contributes to individual differences in antidepressant response.

If we can’t yet identify the genetics in diseased like Schizophrenia, Manic Depressive Illness, or Major Depressive Disorder, I doubt we’re going to find the genetics in speculative hypotheses like this endless talk of personalized medicine. It’s not just this meta-analysis that I’m talking about, it’s that the NIMH has already wasted our research money on STAR*D, CO-MED, IMPACT, following this same goal of trying to find a way to get more out the antidepressants than they have to give. Now, even with this current meta-analysis coming up empty handed, we’re still funding these same investigators for EMBARC – yet another Translational Science program to predict response to antidepressant medications based on genetic profiles. In my view, we’re not there yet, but because these projects have been pitched as practical (Translational), they get funded over and over in various incarnations. EMBARC is going to come out just like STAR*D, CO-MED, and IMPACT – lost in translation.

I find genetics research fascinating just like the rest of us. But we’re not yet ready for Translational Research. Now that we can actually measure the genetic code, it’s a time to divert our precious research money to the basic scientists, not opportunistic clinical scientists who know how to write translational grants, but not enough about
the basics to have much chance of success. They don’t yet even know the right questions to ask. Like the DSM-5 Task Force and much of the Translational Research, being in too big a hurry for breakthroughs usually backfires…

words to be later eaten…

Posted on Friday 8 February 2013

I started to list all the links to the bruhaha brewing over the AllTrials petition, but decided to summarize instead. There’s much posturing around the Alltrials petition, and all parties have behaved in an exemplary fashion [except for the other guys]. That’s it, the whole summary – meaning that the games have begun. Meanwhile, there are 28,000+ signatures on the petition and Ben Goldacre’s Bad Pharma was released three days ago. Here’s one comment for flavoring:

PhRMA Statement on Clinical Trials and Bad Pharma

WASHINGTON, D.C. [February 4, 2013] Pharmaceutical Research and Manufacturers of America (PhRMA) Executive Vice President Josie Martin issued the following statement today:

Dr. Ben Goldacre’s book Bad Pharma provides a one-sided and factually questionable view of the clinical trial process led by the innovative biopharmaceutical sector. The book ignores that the current clinical trial system, which is essential to the development of new medicines that save and improve lives, is scientifically rigorous, tightly regulated and working well. “The book’s unfounded and sensational claims may attract attention, but they do not advance biomedical science or patient health. Based on cherry-picked examples and incomplete stories, the accusations leave countless unanswered questions that could threaten public health and the development of future medicines. Criticizing the research process without acknowledging the vigorous oversight and broad commitment to safe and ethical conduct is a disservice to the tens of thousands of scientists exploring new medicines and the millions of patients hoping for cures…

The demands by Dr. Goldacre and the British Medical Journal (BMJ) to release patient-level clinical trial data are irresponsible with potentially harmful consequences for future medicine development. The recommendations would jeopardize patient privacy and could serve as a deterrent to individuals considering participation in trials. It would also encourage second-guessing of the regulatory approval process, which would be disastrous for patients. The FDA has the most advanced and rigorous review process for potential new medicines and it is continuously improving its regulatory and scientific capabilities.

Why so snappy? Here’s a paragraph from the introduction to Bad Pharma:

Drugs are tested by the people who manufacture them, in poorly designed trials, on hopelessly small numbers of weird, unrepresentative patients, and analysed using techniques which are flawed by design, so such a way that they exaggerate the benefits of treatments. Unsurprisingly, these trials tend to produce results that favour the manufacturer. When trials throw up results that companies don’t like, they are perfectly entitled to hide them from doctors and patients, so we only ever see a distorted picture of any drug’s true effects. Regulators see most of the trial data, but only from early on in a drug’s life, and even then they don’t give this data to doctors or patients, or even to other parts of government. This distorted evidence is then communicated and applied in a distorted fashion. In their forty years of practice after leaving medical school, doctors hear about what works through ad hoc oral traditions, from sales reps, colleagues or journals. But those colleagues can be in the pay of drug companies – often undisclosed – and the journals are too. And so are the patient groups. And finally, academic papers, which everyone thinks of as objective, are often covertly planned and written by people who work directly for the companies, without disclosure. Sometimes whole academic journals are even owned outright by one drug company. Aside from all this, for several of the most important and enduring problems in medicine, we have no idea what the best treatment is, because it’s not in anyone’s financial interest to conduct any trials at all. These are ongoing problems, and although people have claimed to fix many of them, for the most part they have failed; so all these problems persist, but worse than ever, because now people can pretend that everything is fine after all.

That’s why.

Ben Goldacre has been writing about these matters for quite a while, but it appears that his widely viewed TED Talks have skyrocketed him into a position of leadership. He has that combination of qualities that are tailor-made for
the job: he’s intelligent and knowledgeable; he’s iconoclastic; and he’s something of a court jester. Throughout the history of drama, role of truthsay often falls to the royal fool, or an innocent child [the emperor’s new clothes], or the Greek Chorus – some unlikely character perceived as an “outsider” – someone free from the constraints and protocols of convention. The 1960s were ushered in by the Merry Pranksters and sustained by Abbie Hoffman and the Yippies.

And he’s being helped along by PhRMA, or at least by whoever wrote the pompous statement above. One actually wonders who it was written to, their members perhaps? The whole statement goes on to spell out the process and the number of hoops the pharmaceutical industry has to go through to get a drug approved, but spends no time on the fact that the system doesn’t work – form without function as they say. And PhRMA ends with a bit of business-ese:

There are currently over 5,000 new medicines in the pipeline, 70 percent of which are potential first-in-class medicines that could provide exciting new approaches to treating diseases for patients. Personalized medicines and drugs for rare diseases account for a growing share of the research being conducted by the biopharmaceutical sector. Clinical trials are critical to fulfilling the promise of this robust pipeline. Our sector and other stakeholders in the trials process welcome a constructive dialogue and are focused on protecting the privacy and safety of study participants, overcoming barriers to greater participation and discovery. Debating the self-serving claims of Dr. Goldacre does nothing to advance patient health.

My bias in these affairs is a matter of almost daily public record, but it’s hard for me to imagine that the kind of rhetoric in this PhRMA statement will work anymore. Recall the PHARMA fraud settlement graphs reported by Public Citizen in September [a sad tale...].

I doubt that snippiness like “Debating the self-serving claims of Dr. Goldacre does nothing to advance patient health.” will carry the day in the face of this kind of evidence...

my therapist, my psychiatrist, my plan, my meds...

Posted on Thursday 7 February 2013

I don’t usually do this – republish someone else’s complete blog post. I try to pull out the parts I want to say something about or emphasize, then link the source in case you want to read the whole thing. But I could find nothing I wanted to take out of this post by Dr. Healy [I reformatted it for space and I think his original is much easier to read]. I just thought every word needed emphasis:

Prozac and SSRIs: Twenty-fifth Anniversary
Dr. David Healy
06 Feb 2013

One Prescription for Every Man, Woman and Child
Prozac was approved in 1987 in the US, and launched in early 1988, followed by a clutch of other SSRIs. Twenty-five years later, we now have one prescription for an antidepressant for
I came at this from a different angle from Dr. Healy. In my early thirties, I had made a mid-course correction in my career as an Internist and retrained in psychiatry – interested in psychotherapy. For me, the nodal point in that second career was the publication of the DSM-III in 1980. At the time, I was in psychoanalytic training and directing a psychiatric residency. By the time Prozac came out, I had either left or been extruded from academia [actually both] and was starting my private practice. The coming of Prozac was just a blip on the radar screen already covered with other bogies. In contrast, Dr. Healy was a young and upcoming biological psychiatrists who caught on to the toxicity of the drug early on and pursued it when most others were denying it. So our perspectives were very different. When Prozac came, I was in a practice with like-minded colleagues, involved in the analytic institute and an academic program at our college. I had no connection with the Psychiatry Department though I was on the clinical faculty.

When Dr. Healy says that "Twenty-five years ago, no one could have imagined that..." he is completely correct. But from my perspective, twenty-five years ago I couldn’t even imagine what had already happened in psychiatry and was once again personally making another mid-course correction. The part of Dr. Healy’s post that I relate to the most is The Dead Doctor Sketch. I had come to psychiatry from Internal Medicine because I realized that many of the people I saw were primarily in need of help with their lives and matters mental, and I had become dissatisfied with just dealing with the physical part. When psychiatry medicalized in the early 1980s, it went off and left me and the whole reason I was there in the first place. So the way I see it, Prozac didn’t cause the things he mentions. It was the drug the newly revised psychiatry had been waiting for – a biological messiah fulfilling the prophecy of the neoKraepelinitans, and it was followed by a series of latter-day saints.
I n The Dead Doctor Sketch, Dr. Healy mentions CBT – Cognitive Behavior Therapy. Aaron Beck, its founder, was dissatisfied with the psychoanalysis of his training and came up with a therapy based on his observation that depressed people think depressively, dream depressively, and live depressively. He proposed seeing their depressive cognition as a behavior and applying the principles of behavioral therapy to their depressive cognition, and later to other cognitive styles. He was right about that kind of thinking and had some measurable success in changing it. Now, everyone is a cognitive behavior therapist, primarily because it is sanctioned as an “evidence-based” therapy. What Dr. Healy says is exactly right. Mental Health practitioners send their clients to psychiatrists for “meds” and then do counseling of various kinds. For all the talk about CBT, I haven’t run into many people who actually do formal CBT. I’m sure they’re out there, but I think it’s more something fresh graduates do until they find a style of their own. But no matter what they end up doing, they sure send their clients for “meds,” and the psychiatrists sure prescribe them. In the US, there’s a third party involved – the insurance carrier. So patients now talk about a number of things: my therapist, my psychiatrist, and my plan – the latter being a major ingredient. All three forces point to the fourth thing – my meds. I couldn’t have imagined that set-up twenty-five years ago either.

Among the many points Dr. Healy makes in this post, none is more insightful than this:

A good generalist, who knows your circumstances, relationships, difficulties at work and the community from which you come, can spot when aches and numbness stem from strain or tension – they see you rather than bits of you. Prozac has killed Generalism. It did so by focusing attention on mood in the way neurologists hyper-focus on nerves.

While I would quibble that it wasn’t only Prozac that killed Generalism, there’s little question that Prozac was an essential link in the tragedy that Dr. Healy so eloquently lays on the table…

Mickey @ 12:26 PM

6 Comments

foxhole conversions…

Posted on Wednesday 6 February 2013

GSK statement of support for AllTrials campaign for clinical data transparency

AllTrials
Feb 6, 2013

We are pleased to sign up to the AllTrials campaign for clinical trial transparency and support its call for the registration of clinical trials and the disclosure of clinical trial results and clinical study reports. At GSK, we are committed to being transparent with our clinical trial data to help advance scientific understanding and inform medical judgment. We already publicly disclose a significant amount of information about our clinical trials. We register and post summary information about each trial we begin and share the results of all our clinical trials – whether positive or negative – on a website accessible to all. Today this website includes almost 5,000 clinical trial result summaries and receives an average of almost 11,000 visitors each month. We have also previously committed to seek publication of the results of all of our clinical trials that evaluate our medicines to peer-reviewed scientific journals.

Expanding on this, we have committed to make CSRs publicly available through our clinical trials register. From now, we will publish CSRs for all of our medicines once they have been approved or discontinued from development and the results have been published. This is to allow for the data to be first reviewed by regulators and the scientific community. Patient data in the CSRs and their appendices will be removed to ensure patient confidentiality is maintained.

In addition, while there are practical challenges, we also intend to publish CSRs for clinical outcomes trials for all approved medicines dating back to the formation of GSK. This will require retrieval and examination of each historic CSR to remove confidential patient information. Given the significant volume of studies involved, we will put in a dedicated team to conduct this work which we expect to complete over a number of years. Posting will take place in a step-wise manner, with priority given to CSRs for its most commonly prescribed medicines. Separately, we are also working to develop a system where researchers will be able request access to detailed anonymised patient level data that sit behind the results of our clinical trials to enable additional scientific inquiry and analyses to help further scientific knowledge.

Press coverage:

Reuters: GSK promises to publish detailed drug trial data
The Guardian: GlaxoSmithKline to publish clinical trial data
The Independent: GSK to publish clinical trial data for drugs
The Times (UK): Victory for The Times as drug firm vows to publish drug test data

Foxhole conversions are better than no conversions at all, I always say. Why, I’ll bet they’ll be thinking about suggesting Paxil Study 329 and Paxil Study 352 should be retracted from the literature soon. Unlike? If you told me this time last year that GSK would sign a petition calling for full data transparency in Clinical Trials, I’d have recommended a full competency evaluation at your earliest convenience…

[see Glaxo Clashes With PhRMA Over Data Disclosure, on Pharmalot]
Because Zoloft is FDA approved as a treatment for obsessive-compulsive disorder (OCD) – and Lexapro is not, it's reasonable to regard Zoloft as a medically-favorable treatment choice relative to Lexapro for this condition, on the basis of its FDA approval. Although Zoloft may be a medically-favorable treatment choice relative to Lexapro for obsessive-compulsive disorder, it's unclear as to whether there are differences between these medications in efficacy among patients with OCD.