

From Evidence-based Medicine to Marketing-based Medicine: Evidence from Internal Industry Documents

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Abstract While much excitement has been generated surrounding evidence-based medicine, internal documents from the pharmaceutical industry suggest that the publicly available evidence base may not accurately represent the underlying data regarding its products. The industry and its associated medical communication firms state that publications in the medical literature primarily serve marketing interests. Suppression and spinning of negative data and ghostwriting have emerged as tools to help manage medical journal publications to best suit product sales, while disease mongering and market segmentation of physicians are also used to efficiently maximize profits. We propose that while evidence-based medicine is a noble ideal, marketing-based medicine is the current reality.

Keywords Evidence-based medicine · Marketing · Marketing-based medicine · Pharmaceutical industry · Olanzapine · Quetiapine

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The larger issue is how do we face the outside world when they begin to criticize us for suppressing data...

AstraZeneca publications manager in internal email 6 Dec 1999.

According to conventional wisdom, we are firmly grounded in evidence-based medicine (EBM). While many forms of data, such as clinical experience, case studies, and uncontrolled trials can provide useful information regarding patient care, the randomized controlled trial (RCT) reigns supreme. As RCTs allow the direct comparison of drug and placebo or of various compounds to one another, their rigor exceeds that of other forms of research (Sackett et al. 1996). As more and more RCTs are published in medical journals, we gain a better understanding of what works best. Interventions that fail to demonstrate adequate efficacy and safety lose first line status and are discarded over time. Patients, of course, benefit immensely from this meticulous scientific evaluation process, as they can rest assured that they are receiving treatments that show the greatest benefit and least risk. So the story goes. However, one could argue that rather than EBM, we are actually now entrenched in *marketing-based medicine* (MBM), in which science has largely been taken captive in the name of increasing profits for pharmaceutical firms. The case for MBM is based on several factors, each of which influences the knowledge and practice of medicine, including: suppression and spinning of

negative data, ghostwriting, disease mongering, market segmentation of physicians, and failure of regulatory authorities and peer-reviewed journals (despite increasing efforts) to police what, in the words of Marcia Angell, former chief-editor of the *New England Journal of Medicine*, is a “broken system” (Angell 2008, 1069).

Richard Smith, former chief-editor of the *British Medical Journal*, in a paper titled “Medical journals are an extension of the marketing arm of pharmaceutical companies” described the many and sophisticated ways in which drug trial data can be manipulated. He said it took “almost a quarter of a century editing for the *BMJ* to wake up to what was happening” (Smith 2005, e138). Such manipulation was indeed difficult to discern in the past, but the release of internal pharmaceutical industry documents has shed light on how marketing has come to trump science (e.g., Applbaum 2008; Steinman et al. 2004).

These documents have been released by courts where pharmaceutical companies have been subject to litigation from class action plaintiffs and government prosecutors. They allow for close examination of many practices that are not typically widely publicized. Indeed, although many internal industry documents are legally available on the internet, there are as yet few publications in the biomedical literature based primarily on internal industry sources. These internal documents, as well as material drawn from other sources, provide insight into the intersection between marketing and science within the pharmaceutical industry. While the documents examined in this paper reflect our specialties in mental health, the manipulation of drug trial data they expose are clearly not limited to only this field, as evidenced by situations involving medications for osteoporosis (Washburn 2005) or non-steroidal anti-inflammatory agents (Ross et al. 2008; Smith 2006).

Science as Marketing

Especially given the current focus on using evidence-based treatments, it comes as no surprise that the pharmaceutical industry values scientific data that demonstrate efficacy and/or safety of their products. These data are particularly valuable when translated into articles in high impact peer-reviewed journals. A pharmaceutical industry trade publication emphasized

this point. It mentioned that a good publication plan “targets such information toward highly reputable, peer-reviewed journals (which are today viewed as the single most trusted source of information by US physicians, over that of continuing medical education, thus enhancing its scientific imprimatur, while building relationships with the journals and their readership)” (Scarpuzza undated). Similarly, one memo from Pfizer asked “What is the purpose of publication?” and responded with “High quality and timely publications optimize our ability to sell Zoloft [the antidepressant sertraline] most effectively” (Clary 2000). The same document makes it clear that the data from sponsored drug trials belongs to the company and the “purpose of data is to support, directly or indirectly, marketing of our product” (see Fig. 1).

PeerView is a company that provides various services to the pharmaceutical industry, including “... products that support publication strategy and other commercialization processes for our pharmaceutical and biotech clients”. The CEO of PeerView stated that “...most pharma and biotech companies recognize the significant impact that the clear and consistent publication of results will have on subsequent commercialization efforts” (Villaruel 2007, 2). An Eli Lilly internal document refers to new strategic planning for the branding of its antipsychotic drug olanzapine (Zyprexa). The document states under “strategic imperatives,” that a goal is to “develop scientific research and publication plan that enhances credibility of the new brand positioning and enables the achievement of the ideal positioning” (Eli Lilly 2001a). To help meet this goal, it is mentioned that the company should “mine existing data to generate and publish findings that support the reasons to believe the brand promise” (Eli Lilly 2001a).

Data “Ownership” and Transfer

- Pfizer-sponsored studies belong to Pfizer, not to any individual
- Purpose of data is to support, directly or indirectly, marketing of our product
 - Through use in label enhancements, sNDA filings
 - Through publications for field force use
 - Through publications that can be utilized to support off-label data dissemination
- Therefore commercial marketing/medical need to be involved in all data dissemination efforts

Fig. 1 Excerpt from document regarding marketing of sertraline (Pfizer)

Science is clearly related to marketing goals, which of course is not necessarily problematic. If a product is supported by good data, then few would find it unethical to disseminate such information. But what if the science is *not* supportive; what if a drug does not demonstrate efficacy or is dangerous? What if a study's results do not jive with the brand promise?

Suppressing and Spinning Negative Data

While drugs still enjoy patent protection, pharmaceutical companies typically provide the lion's share of the funding to investigate their products. Journal articles that tout the positive features of a drug help to keep product moving from pharmacy shelves. The data which form the backbone of these articles is controlled by the sponsor. It is well-known that studies funded by a drug manufacturer are much more likely to yield positive results than studies of the same drug conducted by researchers not tied to the sponsor (Lexchin et al. 2003). One main reason for this finding is that drug manufacturers are under no obligation to publish negative results. Indeed, if the primary goal of publicly traded drug firms is to maximize return to shareholders, it makes no sense at all to publish results that cast a drug in a negative light.

Quetiapine: Internal vs. Published Data

AstraZeneca's antipsychotic drug quetiapine (Seroquel) is one of a class of drugs known as atypical antipsychotics or second-generation antipsychotics. In 2000, data comparing quetiapine to haloperidol, an older, generic antipsychotic, were presented at the annual convention of the American Psychiatric Association. In a press release, the author of the presentation stated: "I hope that our findings help physicians better understand the dramatic benefits of newer medications like Seroquel, because, if they do, we may be able to help ensure patients receive these medications first" (Olson 2009). The presentation, in line with the press release, shows that quetiapine possessed a statistically significant advantage over haloperidol in inducing treatment response among patients with schizophrenia. These data were based on a meta-analysis of four studies that compared quetiapine and haloperidol. However, documents released by the company during

litigation suggest a quite different story. The results of research comparing the two compounds are found in an AstraZeneca document, in which it was concluded that quetiapine possessed *weaker* efficacy than haloperidol (AstraZeneca 2000; see Fig. 2). The company document was produced in March 2000, two months prior to the rosy presentation of quetiapine's efficacy. An email regarding this data, from a publications manager at AstraZeneca, stated in part: "The data don't look good. In fact, I don't know how we can get a paper out of this" (Tumas 2000; see Fig. 3). The lead researcher on the 2000 paper, when queried recently by a journalist regarding the claim that quetiapine is "significantly superior" to haloperidol, conceded that the claim was indeed an exaggeration yet maintained that the data analysis was accurate (Olson 2009).

AstraZeneca also commissioned a comparative trial known as Study 15. In this trial, patients in partial to full remission of schizophrenia were randomly assigned to receive either haloperidol or quetiapine. At the end of the one-year trial, patients receiving haloperidol fared better in terms of symptom ratings and had significantly fewer psychotic relapses relative to patients on quetiapine. These negative results were not published. Rather, as stated in an internal email, "cherry picking" occurred (Tumas 1999; see Fig. 4). On some measures of cognitive functioning, quetiapine significantly outperformed haloperidol, which was the basis for a publication (Velligan et al. 2002). The abstract included the statement: "Treatment with quetiapine at higher doses relative to haloperidol appears to have a positive impact on important domains of cognitive performance that have been found to predict role function and community outcomes in patients with schizophrenia" (239). While the paper suggested the likelihood of better community outcomes, it failed to mention the increased risk of psychotic relapse and the relatively poorer scores on symptom measures compared to haloperidol. In an internal email two other "buried trials" are mentioned, in addition to a third trial that was pending potential suppression at the time of the message (Tumas 1999).

Antidepressants: Internal vs. Published Data

Such tactics are not unique to any individual company; they are quite plainly widespread. Indeed,

Fig. 2 AstraZeneca internal meta-analysis of quetiapine vs. competitors/placebo

The following table is an attempt to simplify the claims that could be obtained from these results. A ✓ is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or using LVCF. A ✗ marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel.

Table 1

Comparator	Category						
	Anxiety	Total BPRS	Factor I	Factor V	Hostility	Hostility Cluster	Mood Cluster
Placebo	✓	✓	✓	✓	✓	✓	✓
Haloperidol	-	✗	-	✗	-	✗	-
Chlorpromazine	-	-	-	-	-	-	-
Risperidone	✗	✗	✗	✗	-	✗	✗
Other typicals	-	✗	-	✗	-	✗	-

one investigator calls data suppression “the dirty little secret” of medical research (Dawdy 2008). The researcher, Erick Turner, led a team which compared published trials of antidepressants versus their unpublished counterparts. Pharmaceutical firms must submit their clinical trial data to the Food and Drug Administration (FDA) as part of their application for approval for marketing the drugs in the United States. Turner’s team examined the publication status of trials submitted to the FDA for all antidepressants approved by the agency from 1987 through 2004 (Turner et al. 2008a). They found that 97% of the trials in which the FDA review found a positive outcome were then published in a journal. Some trials yielded a “questionable” outcome, in which the data on the primary outcome was negative but some secondary measures found the drug was efficacious. Half of the trials in which the FDA review found a “questionable” outcome were published and half were not. Of the “questionable outcome” trials that were published in a medical journal, all were written up as if the results

were positive. Only one-third of studies finding negative results were published, and over half of those were published claiming that the study actually found positive outcomes.

How can a trial go from showing questionable or no efficacy to a definitive statement of efficacy? Various publications did the following: failing to report data from all participants (those who dropped out due to lack of efficacy or adverse events were excluded), reporting data from only one site of a multisite trial, reporting data for something called an “efficacy subset,” which is an apparent euphemism for scrubbing inconvenient data from the dataset, and by switching primary outcomes post hoc (Turner et al. 2008b). For each of the 12 antidepressants, at least one trial was unpublished or at least one trial was published with conclusions conflicting with FDA review of the data. Thus, one cannot blame one or two “bad apples,” as it appears data suppression is part of the industry’s standard operating procedure.

Fig. 3 AstraZeneca email regarding meta-analysis of Seroquel vs. competitors/placebo

From: Tamas John JA
Sent: Thursday, March 23, 2000 10:05 AM
To: Goldstein Jeffrey JM; Murray Michael MF
Subject: FW: Meta Analyses
Importance: High

Jeff and Mike,

Here's the analyses that I got from Emma. I've also attached a message that I sent to her yesterday asking for clarification.

The data don't look good. In fact, I don't know how we can get a paper out of this.

My guess is that we all (including Schulz) saw the good stuff, ie the meta analyses of responder rates that showed we were superior to placebo and haloperidol, and then thought that further analyses would be supportive and that a paper was in order. What seems to be the case is that we were highlighting the only good stuff and that our own analysis support the "view out there" that we are less effective than haloperidol and our competitors.

Once you have a chance to digest this, let's get together (or teleconference) and discuss where to go from here. We need to do this quickly, because Schulz needs to get a draft ready for APA and he needs any additional analyses we can give him well before then.

Thanks.

Fig. 4 AstraZeneca email regarding “cherry picking” and “suppressing data”

From: Tamas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding “cherry picking” of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

Along the same line, data were selectively published regarding antidepressant use among children and adolescents (Whittington et al. 2004). One notable example is a study (known as Study 329) comparing paroxetine (a serotonin-reuptake inhibitor antidepressant, manufactured by Smith Kline Beecham (SKB) which is now GlaxoSmithKline (GSK) under the brand name Paxil), imipramine (an older, tricyclic antidepressant), and placebo in the treatment of adolescent depression. Study 329, sponsored by SKB/GSK, was published in 2001 with a clear message stated in the abstract: “paroxetine is generally well tolerated and effective for major depression in children” (Keller et al. 2001, 762). However, the trial data indicated that the drug was neither efficacious nor particularly safe.

How did this come about? During litigation, GSK released documents concerning the study, which were then compared with the published version. The study protocol and its revisions named two primary outcome measures but both failed to demonstrate a significant advantage over placebo at study endpoint. The original study protocol also had six secondary measures, all of which likewise failed to show efficacy. In the published version of the study, four of eight measures were reported as positive (rather than zero of eight)—all were on measures not called for in the study protocol or revisions, a classic case of data fishing.

The study publication referred to six of 93 paroxetine participants compared to one of 87

placebo participants experiencing “emotional lability,” (a term used to describe “suicidal ideation/gestures”). An internal company report of side effects of paroxetine yields more—eight participants experienced suicidal gestures or deliberate self-harm and seven cases of hostility on paroxetine compared to zero on placebo. An earlier draft of the results stated that “worsening depression, emotional lability, and hostility were considered related or possibly related to treatment,” yet the published version claims that only one case of headache was considered related to paroxetine. Thus, a drug failed to demonstrate efficacy on all eight pre-specified primary and secondary efficacy measures, is related to more treatment-emergent suicidal gestures and hostility, and yet is claimed in a peer-reviewed journal to be safe and effective (Jureidini et al. 2008).

Internal discussion about whether the company should even publish the study included an email that read: “originally we had planned to do extensive media relations surrounding this study until we actually viewed the results. Essentially the study did not really show Paxil was effective in treating adolescent depression, which is not something we want to publicize” (White 2001). Nonetheless, the study was published and, in an internal document distributed to all company representatives selling paroxetine, was labelled a “cutting-edge landmark study” demonstrating “REMARKABLE” efficacy and safety for the drug (Hawkins 2001).

Ghostwriting

Publications provide important information regarding drug safety and efficacy. These articles are probably most influential when they are perceived as independent from the drug company. A physician may view an article with a corporate authorship line as biased yet view the same article as more credible if independent academic authors were listed as contributors. However, academics are often busy with research obligations, speaking engagements, teaching, administrative duties, clinical work and other tasks and some are not particularly skilled at writing. Ghostwriting overcomes these limitations. A pharmaceutical firm may design a paper in-house or contract with a medical education and communication company (MECC) to write a manuscript.

Writing Firms

One example is Sunvalley Communication (<http://sunvalleycommunication.com>). Their website describes several important services (Hofland undated). They produce papers closely linked with “brand strategies” and also create a publication strategy to “align with marketing strategy” and “tweak” their message to best suit the publication and target audience. This firm also offers to compose papers for researchers and graduate students based on an outline provided by the researcher—and its involvement can be “strictly confidential” (Sunvalley Communication undated). Another company, Dianthus Medical, receives “key messages” from pharmaceutical clients and writes a manuscript outline, which they recommend receives approval from all authors who will be listed on the paper. They then write the first draft of the paper, “ensuring that your message is communicated in the most effective way,” then pass it along for the client’s approval. Revisions are made and the paper prepared for submission to the journal (Dianthus Medical undated). This company lists such pharmaceutical giants as AstraZeneca, GlaxoSmithKline, Lilly, and Wyeth among its clients. Sunvalley and Dianthus are but two of many such companies; descriptions of similar firms have been provided elsewhere (Sismondo 2007).

The process is relatively simple: A ghostwriter includes messages to maximize the marketing power of the publication while one or more “honorary” academic authors lend their names, titles, and purported

independence to the paper (Moffat and Elliott 2007). While the audience may look suspiciously on a paper with an all-corporate authorship line, the presence of an academic author lends the air of independence and prestige, making the article appear more credible. The academic authors may review an outline or draft, but typically perform little writing. For example, an internal Eli Lilly document discusses “drafting a full feature for review” by an influential author or perhaps having the author develop the article after reviewing the outline provided by the company or its associated writing firm (Eli Lilly undated-a).

Ghostwriting in the Antidepressant Literature

The prevalence of ghostwriting is obviously hard to determine. A few studies have suggested that approximately 10% of papers are ghostwritten, but these are based upon self-report surveys, which likely under-report the incidence of such behaviour (Flanagin et al. 1998; Mowatt et al. 2002).

Through litigation, one research team gained access to documents regarding the antidepressant sertraline (Zoloft)—remember that according to its manufacturer, publications were primarily meant to maximize sales of this drug. A MECC named Current Medical Directions (CMD) contracted with Pfizer to produce 85 publications regarding the drug. According to one analysis, between 18% and 40% of articles on sertraline from 1998–2000 were managed by CMD (Sismondo 2007). The majority of the CMD articles featured academic authors—one author appeared in 12 such publications. In addition, the articles managed by CMD appeared in significantly higher-impact journals compared to non-CMD articles on sertraline. One document from CMD lists a number of sertraline publications in various stages of completion—several contain notes such as “Author TBD”—indicating that while a medical writing firm was completing (or had completed) the paper, a so-called “author” had yet to lend his or her name to the piece. Other notes include such comments as “outline sent to Pfizer for approval” (Current Medical Directions 1999).

Researchers who investigated the CMD-affiliated articles made the crucial point that traditional science relies on authors having access to the underlying raw data that forms the basis of publications (Healy and Cattell 2003). However, publications written by drug

firms or MECCs are often based on proprietary data belonging to the drug firm. If an academic author cannot vouch for the underlying data and did not write the paper, then how can he or she be anything other than window dressing for a marketing device wrapped in scientific packaging? Healy and Cattell (2003) note that a case of completed suicide and several cases of suicidal ideation were not reported in the CMD-authored pieces. The first draft of the paper from Study 329, which clearly overstated benefits and understated risks, was also written by a MECC (McHenry and Jureidini 2008). The lead author of the study said that he only reviewed data tables, not the raw data (BBC 2007). Thus, honorary academic authors are not just padding their vitae, they are also potentially harming public health when they fail to carefully review data presented in studies on which their names appear as authors.

While honorary authors are typically affiliated with universities, non-academic clinicians are also sometimes utilized to author papers in an unconventional manner. GlaxoSmithKline used such a program to promote its antidepressant paroxetine (Paxil). The plan, which used the interesting acronym “CASPPER—Case Study Publications for Peer Review” had the following main goal: “Publications of such articles will benefit the sales force by expanding the database of published data to support Paxil” (SmithKlineBeecham undated). If a physician mentioned a success with paroxetine, sales representatives were to encourage the physician to write a case study. Sales reps were instructed to acknowledge the importance of the physician’s time and offer to save precious time through the contracted editorial staff, who could assist with everything from literature searches to editing the paper. It seems that physicians had relatively little leeway regarding their papers—one excerpt from a company document stated that the editorial team would “work closely with contributing physicians to ensure rapid dissemination of consistent data and messages”. It is likely that data inconsistent with the company’s marketing was not part of the publication plan. At least five journals reportedly published papers produced through CASPPER (Edwards 2009a).

Placebo-controlled trials often include a placebo wash-out phase, in which all participants initially receive placebo prior to some participants then switching to the drug under investigation. For example, a study may use a 3-week period of

placebo washout, followed by 8 weeks of patients receiving either drug or placebo. It should be obvious that the comparison of efficacy and safety between drug and placebo should begin during the fourth week, when half of the participants have started receiving active medication. Yet some manufacturers of antidepressants counted suicidal behaviour in the placebo wash-out phase against placebo in their comparisons of drug to placebo. Comparing suicidal acts on 11 weeks on placebo to 8 weeks on a drug helped to drive up apparent rates of suicidal behaviour on placebo, which made the drugs appear safe in comparison. Indeed, an article was published in 1995 allegedly showing that paroxetine reduces suicidality. The academic author admitted that he had not seen the actual raw data; rather, he had been provided data tables by the manufacturer, which he then helped to convert into an article (Glennmullen 2007). However, the data in the article included suicide attempts which occurred during the placebo washout phase, though this was not stated in the manuscript. GSK has since posted its own analysis online, in which it notes an increased risk of suicidal behaviour among patients taking paroxetine relative to placebo (GlaxoSmithKline undated). Nearly anyone reading a journal article will assume that the named authors had access to raw data rather than misleading data tables provided by a drug firm. While not technically ghost authorship, the manner in which the data were translated into final form is clearly outside of the norms of science.

Investigator-initiated Trials and Opinion Leaders

Further evidence on the extent that companies, rather than honorary authors, own and manage drug trial data comes from an internal AstraZeneca email from the “Global Brand Manager—Seroquel” (quetiapine) to the “SEROQUEL GLOBAL BRAND TEAM” dated “8/7/2003” on the subject “IIT benchmarking report” (Hagger 2003). IIT stands for “Investigator-initiated trials” where an academic or clinician from outside the company is sourced as author of the trial. This email refers to a “series of interviews carried out with internal AZ staff who were known to have worked for competitor companies before as well as a number of KOL [key opinion leader] investigators from the UK, Italy, Germany

and Spain.” The email lists “key messages emerging from the report:

- ...Lilly run a large and highly effective IIT program...They offer significant financial support but want control of the data in return. They are able to spin the same data in many different ways through an effective publications team. Negative data usually remains well hidden.
- Janssen have a well organized IIT plan...no IIT data is allowed to be published without going through Janssen for approval, and communication is controlled by Janssen. High expectations are set on investigators who publish favourable results but they are well rewarded for their involvement. They seem less concerned than Lilly about negative data reaching the public domain.
- BMS IIT program is growing very fast in launched markets...most proposals are modified by BMS. Strategic focus is unlicensed indications...

Recommendations...for AstraZeneca...publications should be more creative spinning the data, aka Lilly...”

In fact an Eli Lilly document on “influencing key players” in a passage headed “Investigator-Initiated Trials, Relationship Building, and External Authorship”, states:

Given our current business needs, it is important that funds spent on IITs predominantly support the brand strategy. The review process should consider whether they are on strategy, as well as looking at whether they fill current gaps in our scientific data (Eli Lilly [undated-b](#)).

KOLs with the right message can be very valuable to a company. An August 2002 email reporting on a Janssen-sponsored dinner presentation on metabolic side-effects of atypical antipsychotics in which a speaker “consistently implicated (Zyprexa) as a likely cause of type 2 diabetes or cardiac problems via weight gain” noted “I think if I were with J [Janssen], I’d be throwing some cash at this chap to get his message more widely known” (Eli Lilly [2002a](#)). The Eli Lilly “Key Player Playbook” ranks contracted academic experts as “Guild and Executive level Thought leaders” who “are well respected and acknowledged by their peers...influence the thinking and treatment practices of their peers...and are

typically in the academic setting and treat a minimal number of patients, if any...and serve on academic advisory boards, providing feedback to the Zyprexa Product and Brand Team” (Eli Lilly [undated-b](#)). Next in rank are “Consultant Thought Leaders...who are a critical component of successful DTP (direct to physician i.e. sales rep) interventions and stimulate the physicians at both the regional and the local level”. A September 2000 letter from a psychiatrist who was “one of our (Eli Lilly) speakers” on off-label use of olanzapine by primary care physicians suggested the local thought leader understood his role very well:

...Once the ground is extensively plowed with good credible clinical information, not limited by the GPP [Good Promotional Practice] guidelines that restrict information to schizophrenia and acute mania, then (perhaps) turning the sales force loose may be appropriate. I believe one of my strengths is in taking scientific information and placing it in a clear, clinically useful format...Lilly could use someone with a strong clinical background but with strong marketing instincts to assist them on this one (Eli Lilly [2000a](#)).

Safety: Science or Marketing?

Weight gain, hyperglycaemia and precipitation of diabetes have been major concerns in the side effect profiles of atypical antipsychotic medications. Internal company documents from Eli Lilly and AstraZeneca have a significant focus on the marketing management of these side effects.

Olanzapine: Managing Perceptions of Side Effects

The transcript of a speech by the olanzapine (Zyprexa) Brand Manager stated: “For Zyprexa, weight gain is the ultimate topic to handle with skill. Take this opportunity to tell the truth, to fight fire with facts and to put this manageable side effect in perspective. Keep it simple, so that you don’t overwhelm the doctor with data” (Bandick [2001](#)). Industry documents, read as a whole, give a strong impression that ensuring adverse events “not overwhelm the doctor” means telling the doctor the bare minimum about them.

Eli Lilly had been aware that “forty percent [on olanzapine] gained $\geq 7\%$ body weight” (the FDA’s level of “significant concern” for weight gain) from at least an early trial—the HGAJ study—reported in minutes of a meeting with the US schizophrenia advisory panel in December 1995 (Eli Lilly 1995). The company received a letter of reprimand from the FDA in November 1996 reminding that “the information on weight gain was indeed included in the approved labelling, but as an adverse event, not a therapeutic benefit” (Feather 1996). An internal email among senior science executives in Eli Lilly dated 24 November 1999, “subject: Olanzapine-associated Weight Changes (OWC)” noted that, “...OWC has been and continues to be a top priority for the Zyprexa Product Team”. The email went on to state: “Olanzapine is viewed to have more associated weight gain than risperidone, seroquel, and traditional neuroleptics (Fact: the order of weight gain among antipsychotics is: Clozapine>olanzapine>seroquel>risperidone>traditional neuroleptics)”. The email noted “Physicians want more data” but also, “Blanket detailing will be damaging since many physicians do not see OWC as an issue” (Breier 1999).

Despite this early recognition that olanzapine caused more weight gain than other antipsychotics apart from clozapine, the marketing message for sales visits and CME became the “comparable rates” or “class side effect” message—olanzapine was no different than other atypical antipsychotic agents in inducing weight gain or diabetes (Eli Lilly undated-c; Eli Lilly 2000b; see Figs. 5 and 6). A September 2001 hyperglycaemia/ diabetes resource guide for sales reps states:

What do we mean by “neutralizing” physicians’ concerns about hyperglycemia and how do we

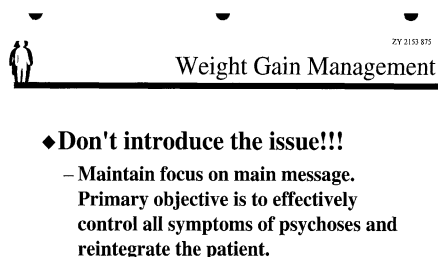


Fig. 5 Eli Lilly instructions to sales reps regarding weight gain issue

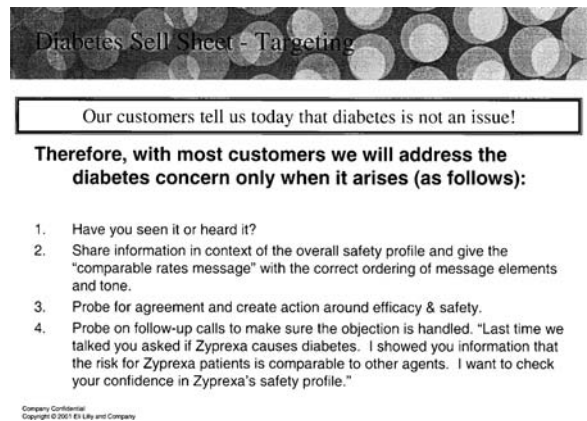


Fig. 6 Olanzapine diabetes sell sheet excerpt

go about this? By neutralizing we mean leveling the playing field, setting the record straight with the “comparable rates” message (Eli Lilly 2001b).

Documents reveal Eli Lilly wanted to keep weight gain and diabetes as separate issues that were not linked. An undated review of “Olanzapine core safety and efficacy beliefs” stated: “A causal link between Olanzapine therapy and diabetes has not been established” (Eli Lilly undated-d). However, the same document also noted: “A potential reason for this is that most of our studies were not designed (especially given the relatively short duration of these studies) to study a link between Olanzapine therapy and Diabetes”. Documents reveal the company was in receipt of letters from psychiatrists describing anecdotal reports of high rates of hyperglycaemia and diabetes from olanzapine, such as a letter dated 17 November 1999 stating: “we have had eight patients out of possibly 35 on Zyprexa show up with high blood sugars...we certainly have never seen this with Haldol, Navane, Risperdal, and others to this extend [sic]” (Ventura County Behavioral Health Department 1999). An early report of data on adverse events from placebo-controlled trials of olanzapine stated in larger font than the rest of the document:

As of September 30, 1999, olanzapine-treated patients ($N=4,234$) who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Random glucose levels ≥ 160 mg/dL but < 200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 2% of

patients. Of these patients, the random elevated glucose levels were found to be transient in 44% while they continued to receive olanzapine. Random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 1% of patients. Of these patients, the random elevated glucose levels were found to be transient in 26% of them while they continued to receive olanzapine (Eli Lilly [undated-e](#)).

In other words, despite the short-term nature of most of these trials, 3% of patients were exhibiting possible new onset hyperglycaemia or diabetes and a proportion of them reverted to normal when olanzapine was withdrawn. The fact that hyperglycaemia was reversible at least if caught early was not appreciated by one Eli Lilly company psychiatrist, who responded in an October 2002 email: “But, surely we want patients to stay on OLZ long-term, so the reversibility of the event is not an advantage?” (Williamson 2002).

An internal email dated “12/01/98” on “Subject: Re: Wishing/Goldstein articles” stated:

I do have concerns regarding making any connections between olanzapine-induced weight gain and hyperglycemia. Therefore, in my opinion, I would not include your following statement: “Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes” (Kinon 1998).

By September 2000 Eli Lilly’s own market research revealed that many more physicians (81%) associated “increased risk of diabetes with...Zyprexa” than with other agents—Clozaril (56%), Risperdal (16%), Haldol (11%), Mellaril (11%), Seroquel (7%), Tercian (4%) (Phoenix International Research 2000). An internal email to 15 company scientists and executives from October 2000 on “Subject: meeting with endocrinologic consultants” noted “at least the vocal” endocrinologists were disputing the company’s “finding that relative risk was not higher than comparative drugs” and “reinforced (the writer’s) impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic” (Baker 2000). A reply email revealed a growing debate within the company “that unless we come clean on this...issue that Zyprexa leads to diabetes...it could get much more serious than we might anticipate” and urged

“gaining the ear of senior leadership and articulating this finding” (Brodie 2000).

Nonetheless the company still held to the marketing strategy of “comparable rates” and a December 2000 “diabetes situation analysis” on “Market Research on ‘message’” reported the “comparable rates” message “appears to be generally believable, makes ‘em think but not all MDs change their basic premise” (Eli Lilly 2000b). The message to the sales reps was still the same in a September 2001 hyperglycaemia/diabetes resource guide:

Market research has shown that ALL of our competitors are talking about a supposed link between hyperglycemia/diabetes and ZYPREXA. This is one of the biggest issues we face in the marketplace. The exciting thing is that we have more data than ever to back up our story of “comparable rates of hyperglycemia and diabetes across psychotropic agents.” It is critical to our success that we share this information with physicians (Eli Lilly 2001b).

Internal documents addressed to sales reps mostly refer to physicians, pharmacists and other health professionals as “customers”. The September 2001 resource guide went on to note: “For tough customers, the use of the Hyperglycemia Sell Sheet followed by the Study Comparison Insert increased the believability of the ‘comparable rates’ message” and concluded: “Customers require lots of repetition for message recall and true behaviour change”. Slides from 2001, to be used in sales rep training reflected that minimizing discussion of hyperglycaemia/diabetes where possible was company sales strategy (Eli Lilly 2001b; see Figs. 6 and 7).

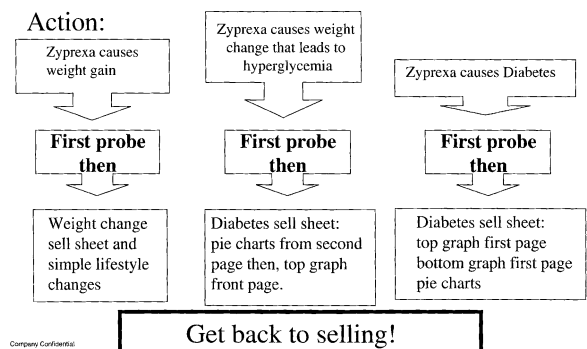


Fig. 7 Excerpt from olanzapine sales representative training material

A series of emails in March and April 2002 reveal that Eli Lilly was extremely keen to avoid regulatory product information label changes “to not use Zyprexa in patients with diabetes or a history of diabetes” and “contain a warning statement that some patients may experience a marked increase in blood glucose during Zyprexa administration” as proposed by Japanese regulators (Cavazzoni 2002a, b; Kerr 2002). A verbatim statement was drafted on the issue that “Lilly’s fundamental position regarding incidence of hyperglycemia and/or diabetes across antipsychotic class continues to be ‘comparable rates’” and further that “Lilly stands by its science, and is exploring several options to correct this regulatory injustice”. But the issue persisted and by November 2002 an email on the Japanese label issue stated: “What is the strategy regarding diabetes? Are we trying to show through retrospective studies that it isn’t that big of a problem? I understand that we are trying to neutralize the issue, but how are we trying to do that?” (Aubuchon 2002). On 15 September 2003 Eli Lilly “received letter from FDA requesting inclusion of warning regarding hyperglycemia and diabetes in labeling” for the US market (Eli Lilly undated-f).

By January 2004 the Eli Lilly “Weight Task Force” suggested “A major change in tone and approach is required (empathic with conviction) to restore confidence...weight gain will no longer be handled as an objection. Instead weight gain will be discussed up front, integrated into the brand promise” (Eli Lilly 2004). Nonetheless a December 2003 PowerPoint presentation for the sales reps concerning “managing weight gain and diabetes concerns” suggested a less empathic approach (Eli Lilly 2003; see Fig. 8).

**We will select tactics for each strategy
that offer us best chance of success
and execute the *%#&*1 out of them**

Lilly

Answers That Matter.

Fig. 8 Excerpt from olanzapine sales rep training for managing customer (physician) concerns regarding weight gain and diabetes

Quetiapine: Managing Side Effects

In a somewhat similar manner, data regarding weight gain on quetiapine were managed by AstraZeneca. One internal document, titled “Seroquel Speakers Slide Kit” from March 2001, was apparently utilized to educate physicians regarding the safety and efficacy of the drug (AstraZeneca 2001). One slide makes the claim, in bold, that “Long-term Seroquel has neutral effect on weight,” while another stated “Seroquel—weight neutral at all doses”. Several other slides make similar claims. These slides were based on studies examining the drug in the treatment of schizophrenia. Another set of slides, included in a 2003 email, were said to “represent a core detail flow” to “support our current position for Seroquel in the treatment of schizophrenia”. One slide stated that: “Seroquel, unlike some other antipsychotics, is not associated with meaningful weight gain” (AstraZeneca 2003).

Yet in July 2008, an internal analysis of quetiapine studies in schizophrenia conducted from 1993 to 1999 concluded that “the incidence rate in adult patients with weight gain $\geq 7\%$ in all trials was 18.2%” and that in placebo-controlled trials, the relative risk of clinically significant weight gain was 2.5 (Alam and Jeffries 2008). The document noted that “the results of the analysis show that long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia”. However, a journal publication in 2000, with a lead AstraZeneca author, concluded that based on data from clinical trials with patients with schizophrenia, quetiapine had a neutral effect on weight (Brecher et al. 2000). A physician practicing EBM may have examined this study and concluded that quetiapine was weight-neutral when the internal data indicated that weight gain was a common side effect of the drug.¹

Despite marketing claims to the contrary, employees at AstraZeneca were concerned about quetiapine-induced weight gain as early as 1997. In one email, written regarding an apparently fluke study associating quetiapine with weight loss, an employee noted that “we

¹ One of the authors (PP) prescribed quetiapine to several patients due to its promotion as weight-neutral (based on publicly available EBM at the time) and was quite surprised when some patients experienced significant weight gain.

must not get too carried away with weight loss when we know the rest of our data appears to point in the other direction” (Hough 1999). In another email, a company physician who worked with quetiapine noted that trial results consistently found that, over time, weight gain “doesn’t stop...the slope just appears to change” (Arvanitis 1997). A brief synopsis of several relevant documents on the topic of quetiapine and weight gain is available online (Edwards 2009b).

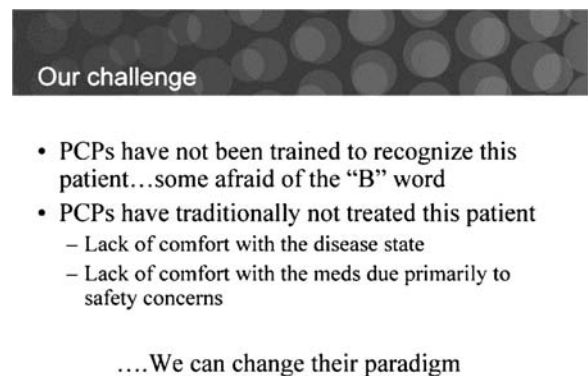
Disease Mongering

“Disease mongering” refers to the practice of expanding the recognised boundaries of a disease entity to encompass subclinical, borderline and normal range symptoms in order to increase prescriptions and sales for a drug or therapy (Moynihan et al. 2002). Internal industry documents concerning Eli Lilly’s atypical antipsychotic olanzapine (Zyprexa) suggest the company saw the potential to increase sales not only by gaining indication for the management of all phases of bipolar disorder, but for utilizing marketing tactics that expanded the boundaries of the illness itself.

Eli Lilly’s original “lifepan” document for olanzapine in 1994 described the marketing profile for olanzapine as the “safer clozapine”; the market was to be schizophrenia and there was no mention of bipolar disorder (Eli Lilly 1994). However the company’s patent on its bestselling antidepressant fluoxetine (Prozac) was due to expire in August 2001. Slides from a PowerPoint presentation at a meeting of the “Zyprexa Product Team”, 25 July 2001, stated “The company is betting the farm on Zyprexa. The ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve *world class commercialization of Zyprexa*” (Eli Lilly 2001c, italics in original). Graphs and text in the “Zyprexa Product Team summary” from 1997 referring to “Global Zyprexa Bipolar Forecast” indicated sales projections for the year 2000 would increase more than fourfold if Zyprexa could be viewed as a “Depakote-like...MOOD-STABILIZER” rather than a “Risperdal-like...Antipsychotic” (Tollefson 1997). A slide titled “Bipolar Vision of Product Evolution” stated: “To be a leader in the bipolar market, Zyprexa will need to be viewed as a *true mood stabilizer*. A *true mood stabilizer* will work in acute manic

episodes without inducing depression, acute depression without inducing mania, and protect the patient from future episodes of mania or depression”. These are noble aims but the same document indicated the company did not yet have the data to support such a goal.

An internal company PowerPoint presentation on “Zyprexa PCP [Primary Care Physician] Vision” stated that a goal was to “Expand our market by redefining how primary care physicians identify, diagnose and treat complicated mood disorders (i.e. Bipolar Disorder)” (Eli Lilly 2002b). A slide featured in Fig. 9 shows that the move into primary care was recognized as a challenge. Physicians in primary care did not typically treat bipolar disorder and used antipsychotic medications infrequently, partially due to safety concerns. The company, however, aimed to “change their paradigm”. Part of this marketing campaign was to broaden the concept of bipolar disorder to include “complicated mood,” comprised of some combination of anxiety, disruptive sleep, irritability, and mood swings (Spielmans 2009). This new type of patient was a source of “untapped growth potential” for the drug. Additionally, fictional patient vignettes were created for sales reps that highlighted possible bipolar disorder or “complicated mood” in cases of relatively minor mood instability that did not meet current diagnostic manual (DSM-IV, ICD-10) criteria for bipolar disorder I diagnosis. These vignettes were to be used in sales visits to help physicians identify patients who might suffer from “complicated mood” symptoms. To handle objections from physicians who indicated they did not treat schizophrenia or bipolar disorder, a script read:



Our challenge

- PCPs have not been trained to recognize this patient...some afraid of the “B” word
- PCPs have traditionally not treated this patient
 - Lack of comfort with the disease state
 - Lack of comfort with the meds due primarily to safety concerns

....We can change their paradigm

Fig. 9 Eli Lilly slide regarding perceptions of primary care physicians toward bipolar disorder

“Doctor, would you agree that you see patients who present with symptoms of mood, thought, and behavioural disorders who are not responding to your satisfaction” (Eli Lilly [undated-g](#)). Thus, physicians who worked with exceedingly few patients who met diagnostic criteria for olanzapine’s indications were encouraged to simply look for patients who had *symptoms* as opposed to the full-blown disorder in question.

These documents, with reference to changing and expanding the diagnostic paradigm for bipolar disorder, are of great topical interest in the context of the current controversy over the boundaries of bipolar disorder (Paris 2009). Despite valid concerns of late diagnosis of bipolar disorder (Berk et al. 2006), there is evidence of overdiagnosis of bipolar disorder in recent years in adults (Goldberg et al. 2008; Zimmerman et al. 2008) and children (Carlson 2009; Healy and Le Noury 2007; Moreno et al. 2007). It seems quite likely that pharmaceutical marketing is related to the increasing rate of bipolar diagnoses (Zimmerman et al. 2008; Healy 2006; Healy and Le Noury 2007).

Market Segmentation

The lengthy Eli Lilly document titled “Key Player Playbook” provides insight into how marketing messages are tailored specifically to certain characteristics of a physician. Physicians were broken into five segments: Rule Bound, High Flyer, Skeptical Experimenters, Selective Majority, and Systematic Conservatives (Eli Lilly [undated-a](#)). At the time the document was written, olanzapine marketing was focused on High Flyers and Rule Bounds.

High Flyers were described as physicians who were defined by the statement “I eagerly seek out new ways to treat my patients (first to adopt new medicines)”. These were the physicians on the cutting edge of medicine. Other descriptions of this segment of physicians were as follows:

- “Not bound by rules, guidelines, or system...”
- “Treat based on symptoms, not formal diagnosis”
- “Will push the envelope with off-label doses and indications...”

Based on this profile, olanzapine marketers were encouraged to utilize a few specific tactics to sell the drug. It was noted that High Flyers like to receive

“pharmaceutical company sponsored programs and tools in ‘fun’ environments”. They were also noted as being highly responsive to discussions with sales reps, likely because High Flyers viewed reps as “providing the source of latest information”. It was also noted that they might like to become part of a forum/club, presumably formed by the company, to “reinforce NS [neuroscience] leadership in a social way”. A skeptic might note that this technique could be taking advantage of a certain vanity believed to exist in the High Flyers, who would appreciate their “leadership” being recognized by a drug company.

To sell the exact same drug to a different group, the “Rule Bounds,” a much different approach was recommended. While the High Flyers did not play by the rules, Rule Bounds were described as follows:

- “I follow the rules when treating my patients; if you don’t follow the rules, you’ll pay for it later”
- “Diagnosis clearly determined for treatment”
- “Wait to use medication when well established in the system”

Rule Bounds were to be reassured that they were following treatment guidelines. It was advised that Rule Bounds should be placed with physicians who could discuss “what everyone is doing”. It seems likely that the other physicians would be carefully selected by Lilly to make sure to describe olanzapine as the drug that “everyone” is prescribing, thus catering to the tendency of Rule Bound physicians to use “well-established” medications. Another document cited the company’s “superior recruiting capabilities so the right doctors go to the right programs,” then referencing both sales rep visits and “peer-to-peer” marketing, where physicians would market the drug to their peers (Eli Lilly 2002c).

The other types of physicians (Skeptical Experimenters, Selective Majority, and Systematic Conservatives) were perceived as less likely to respond to marketing than Rule Bounds and High Flyers. Thus, marketing resources were targeted toward the most easily influenced physicians, enabling Eli Lilly to achieve a greater return on its marketing investment.

Potential Remedies

MBM likely leads to poorer outcomes and increased costs. The time is ripe to reform how data from

pharmaceutical trials are disseminated. Clearly, better access to raw data is needed. Clinical trial registries have not solved the problem; even among trials which appear in such registries, selective reporting of outcomes is common (Mathieu et al. 2009). Editors, peer reviewers, and readers of trial results should check online registry entries to verify whether the data in a published clinical trial match the results and protocol in the registry. In addition, public access to regulatory agency reports would also be useful, as there is often a notable discrepancy between data received by regulatory agencies and data published in medical journals (e.g., Turner et al. 2008a). Public access to both trial protocols and results would greatly increase transparency and allow physicians and consumers to better assess the validity of clinical trial results (Chan 2008).

More radical methods have also been proposed. A former editor of *BMJ*, Richard Smith, suggests that journals should cease the publication of clinical trials. Rather, trial protocols and results could be published in some form of online registry. Journal articles would then discuss the validity of these trials. This may seem like an odd solution, but there is in fact little evidence that peer review is linked with notably better reporting of trial results (Jefferson et al. 2007). Reprints of trials with ostensibly positive results are often disseminated to prescribers, a marketing strategy that one large biomedical journal publisher calls “invaluable for direct marketing, exhibitions/seminars, sales campaigns, and for mailing new product information to physicians” (Elsevier 2007). Further, reprints generate revenue for journals; thus, Smith claims that editors may feel pressured to publish trials that could make profits for the journal’s publisher regardless of the trial’s quality (Smith 2005). Indeed, Smith estimated that one especially profitable reprint used to market the now disgraced painkiller rofecoxib generated about \$450,000 for the publisher (Smith 2006). Such conflicts of interest could be eliminated if journals no longer published clinical trials. However, it seems unlikely that publishers would want to reduce their profitability by simply giving up publication of clinical trials. These reforms may seem drastic, but if we are truly interested in providing the most safe and effective treatments to patients, then the actual scientific evidence regarding treatments must be made publicly available.

Conclusion

Internal industry documents allow a glimpse into the shadowy world of MBM, where data serve the needs of marketing and inconvenient data are often recast as positive or buried entirely. If, on the other hand, we are to fulfil the worthy ambitions of EBM, all data collected in clinical trials would be easily accessible. Journal articles would accurately represent the underlying data and individual contributors to a study would be given credit for their role in conducting research. Marketing efforts would contain accurate information. However, in the current world of MBM, journal articles are an overly positive representation of safety and efficacy, articles are often prepared by drug marketers (whose influence is hidden by honorary authors), marketing efforts contain misleading information about both diseases and treatments, and physicians are partitioned into market segments in order to best persuade them to believe various marketing pitches. Until such issues are resolved, particularly those regarding widespread access to accurate data, any great enthusiasm for so-called evidence-based medicine should be viewed with scepticism.

Limitations

The industry argues in court that subpoenaed documents are taken out of context. This should be considered by readers of the above excerpts. A fuller picture is available from reading the many documents released and posted on the internet (e.g., <http://www.furiouseasons.com/zyprexadocs.html>, <http://www.furiouseasons.com/zip/seroqueldocs.zip>, www.healthyskepticism.org/documents/Antipsychotics.php). However, having read through hundreds of such documents the authors found little to contradict and much to support the conclusions proffered here.

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References

- Alam, E.S.K., and L. Jeffries. 2008. Discussion document: Seroquel/Seroquel XR and weight gain. AstraZeneca document available from authors.
- Angell, M. 2008. Industry-sponsored clinical research: A broken system. *Journal of the American Medical Association* 300: 1069–1071.
- Appelbaum, K. 2008. Where supply meets demand: Comorbidity and channel stabilization in the creation of a psychopharmaceutical blockbuster. Paper presented at the Rethinking Economic Anthropology conference, January, in London, UK. Available: http://www.rethinkingeconomies.org.uk/web/d/doc_62.pdf (Accessed March 10, 2008).
- Arvanitis, L. 1997. Weight gain (email). Retrieved March 3 2009 from <http://www.furiousseasons.com/zip/seroqueldocs.zip>.
- AstraZeneca. 2000. Seroquel (quetiapine) commercial support team technical document (TD004): BPRS meta-analysis. Retrieved March 3, 2009, from <http://www.furiousseasons.com/zip/seroqueldocs.zip>.
- AstraZeneca. 2001. Seroquel (quetiapine) speakers slide kit. AstraZeneca document available from authors.
- AstraZeneca. 2003. Untitled. Retrieved March 3, 2009, from <http://www.furiousseasons.com/zip/seroqueldocs.zip>.
- Aubuchon, N.W. 2002. Re: Request (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY201381347.pdf>.
- Baker, R.W. 2000. Meeting with endocrinologic consultants (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100378053.pdf>.
- Bandick, M. 2001. Zyprexa primary care presentation. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100041630.pdf>.
- BBC. 2007. Panorama: Secrets of the drugs trials. Retrieved March 30, 2007, from <http://news.bbc.co.uk/2/hi/programmes/panorama/6317137.stm>.
- Berk, M., L. Berk, K. Moss, S. Dodd, and G.S. Malhi. 2006. Diagnosing bipolar disorder: How can we do it better? *Medical Journal of Australia* 184: 459–462.
- Brecher, M., I.W. Rak, K. Melvin, and A.M. Jones. 2000. The long-term effect of quetiapine (Seroquel) monotherapy on weight in patients with schizophrenia. *International Journal of Psychiatry in Clinical Practice* 4: 287–291.
- Breier, A. 1999. Olanzapine-associated weight changes (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY1%20%2000008867.pdf>.
- Brodie, T.M. 2000. Re: Meeting with endocrinologic consultants (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100378054.pdf>.
- Carlson, G.A. 2009. Treating the childhood bipolar controversy: A tale of two children. *American Journal of Psychiatry* 166: 18–24.
- Cavazzoni, P. 2002a. Re: ZYP: Diabetic coma and neuroleptic malignant syndrome (case no. 200201953) (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY201797499.pdf>.
- Cavazzoni, P. 2002b. MHLW PI (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY200388811.pdf>.
- Chan, A.-W. 2008. Bias, spin, and misreporting: Time for full access to trial protocols and results. *PLoS Medicine* 5: e230.
- Clary, C. 2000. Zolof: PSC update. Pfizer document available from authors.
- Current Medical Directions. 1999. Worldwide publications status update. Retrieved May 27, 2007, from <http://healyprozac.com/GhostlyData/zolofpublications.htm>.
- Dawdy, P. 2008, April 2. Bitter pill. *Willamette Week*. Available at: <http://wweek.com/editorial/3421/10752/>.
- Dianthus Medical. Undated. Untitled. Retrieved September 21, 2009, from <http://dianthus.co.uk/our-services/medical-writing/medical-communications/manuscripts-for-publication>.
- Edwards, J. 2009a. CASPERR was GSK's friendly ghostwriting program on Paxil. Retrieved September 18, 2009, from <http://industry.bnet.com/pharma/10003807/cassper-was-gsk-friendly-ghostwriting-program-on-paxil/>.
- Edwards, J. 2009b. Email: AstraZeneca knew in 1997 that Seroquel caused weight gain. Retrieved March 5, 2009, from <http://industry.bnet.com/pharma/10001228/e-mail-astrazeneca-knew-in-1997-that-seroquel-caused-weight-gain/>.
- Eli Lilly. 1994. Olanzapine lifeplan. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100035541.pdf>.
- Eli Lilly. 1995. The third United States schizophrenia advisory panel meeting. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100426128.pdf>.
- Eli Lilly. 2000a. Note from one of our speakers about Zyprexa and primary care. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100629260.pdf>.
- Eli Lilly. 2000b. Untitled. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100175585.pdf>.
- Eli Lilly. 2001a. Global positioning strategic imperatives and tactical directions: Final report. Retrieved September 1, 2009, from <http://zyprexalitigationdocuments.com/%5Cdocuments%5CConfidentiality-Challenge%5Cdocs-challenged-in-10-3-list%5C56-ZY71561134.pdf>.
- Eli Lilly. 2001b. Hyperglycemia/diabetes data on demand resource guide. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY202417638.pdf>.
- Eli Lilly. 2001c. Zyprexa product team off-site. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY201548768.pdf>.
- Eli Lilly. 2002a. Janssen meeting feedback—Chris Fear. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY200399435.pdf>.
- Eli Lilly. 2002b. Managed care—June 2002. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY200083405.pdf>.
- Eli Lilly. 2002c. Zyprexa (olanzapine) brand council III: Zyprexa US 2003–2004 marketing and business. Retrieved September 2, 2009, from <http://zyprexalitigationdocuments.com/%5Cdocuments%5CConfidentiality-Challenge%5Cdocs-challenged-in-10-3-list%5C123-ZY203452219.pdf>.

- Eli Lilly. 2003. CSF # 1 review. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY200506745.pdf>.
- Eli Lilly. 2004. Weight task force. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY200523684.pdf>.
- Eli Lilly. Undated-a. Medical press: Pre-launch feature outline. Retrieved August 20, 2009, from <http://zyprealitigationdocuments.com/%5Cdocuments%5CConfidentiality-Challenge%5CDocs-challenged-in-10-3-list%5C145-ZY200187608-7614.pdf>.
- Eli Lilly. Undated-b. Key player playbook. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100174816.pdf>.
- Eli Lilly. Undated-c. Weight gain management marketing verbatims. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100040198.pdf>.
- Eli Lilly. Undated-d. Olanzapine core medical efficacy and safety beliefs. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100592565.pdf>.
- Eli Lilly. Undated-e. Adverse reactions. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100379985.pdf>.
- Eli Lilly. Undated-f. Regulatory activity. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100386523.pdf>.
- Eli Lilly. Undated-g. Zyprexa retail implementation guide. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100040668.pdf>.
- Elsevier. 2007. Pharma solutions: The preferred medical publishing partner for healthcare worldwide. Document available from author.
- Feather, K.R. 1996. Re: NDA#20–592. Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100074131.pdf>.
- Flanagin, A., L.A. Carey, P.B. Fontanarosa, S.G. Phillips, B.P. Pace, G.D. Lundberg, et al. 1998. Prevalence of articles with honorary authors and ghost authors in peer-reviewed medical journals. *Journal of the American Medical Association* 280: 222–224.
- GlaxoSmithKline. Undated. *Effect of Paxil CR tablets and Paxil tablets on suicidal ideation and behavior in adults*. Retrieved May 10, 2009, from <http://www.gsk.com/media/paroxetine/Paxil-CR-and-Paxil-Adult-Suicide.pdf>.
- Glenmullen, J. 2007. Untitled. Retrieved March 13, 2008, from <http://finance.senate.gov/press/Gpress/2008/prg061208a.pdf>.
- Goldberg, J.F., J.L. Gamo, A.M. Callahan, D.L. Kearns, B. Kerner, and S.H. Ackerman. 2008. Overdiagnosis of bipolar disorder among substance use disorder inpatients with mood instability. *Journal of Clinical Psychiatry* 69: 1751–1757.
- Hagger, S. 2003. IIT benchmarking report (email). Retrieved September 2, 2009, from <http://www.healthyskepticism.org/documents/documents/IIT-Seroquel.pdf>.
- Hawkins, Z. 2001. To all sales representatives selling Paxil (memo). Retrieved August 10, 2009, from <http://www.healthyskepticism.org/documents/documents/20010816Hawkinstoreps.pdf>.
- Healy, D. 2006. The latest mania: Selling bipolar disorder. *PLoS Medicine* 3: e185.
- Healy, D., and D. Cattell. 2003. Interface between authorship, industry and science in the domain of therapeutics. *British Journal of Psychiatry* 183: 22–27.
- Healy, D., and J. Le Noury. 2007. Pediatric bipolar disorder: An object of study in the creation of an illness. *International Journal of Risk & Safety in Medicine* 19: 209–221.
- Hofland, P. Undated. Optimizing brand success through effective publication planning & management. Retrieved September 21, 2009, from http://sunvalleycommunication.com/Documents/Optimizing%20Publication%20Planning%20Introduction_va.ppt.
- Hough, N. 1999. Re: ECNP abstract ‘weight gain & diabetes management’ (email). Retrieved March 3, 2009, from <http://www.furiouseasons.com/zip/seroqueldocs.zip>.
- Jefferson T., M. Rudin, S. Brodney Folse, F. Davidoff. 2007. Editorial peer review for improving the quality of reports of biomedical studies. *Cochrane Database of Systematic Reviews* 2.
- Jureidini, J.N., L.B. McHenry, and P.R. Mansfield. 2008. Clinical trials and drug promotion: Selective reporting of study 329. *International Journal of Risk & Safety in Medicine* 20: 73–81.
- Keller, M.B., N.D. Ryan, M. Strober, R.G. Klein, S.P. Kutcher, B. Birmaher, et al. 2001. Efficacy of paroxetine in the treatment of adolescent major depression: A randomized, controlled trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 40: 762–772.
- Kerr, J.G. 2002. Re: Japan: Glucose—teleconference review (email). Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY200388761.pdf>.
- Kinon, B. 1998. Re: Wishing/Goldstein articles (email). Retrieved February 15, 2007, from <http://www.furiouseasons.com/zyprexa%20documents/ZY100095495.pdf>.
- Lexchin, J., L.A. Bero, B. Djulbegovic, and O. Clark. 2003. Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *British Medical Journal* 326: 1167–1170.
- Mathieu, S., I. Boutron, D. Moher, D.G. Altman, and P. Ravaud. 2009. Comparison of registered and published primary outcomes in randomized controlled trials. *Journal of the American Medical Association* 302: 977–984.
- McHenry, L.B., and J.N. Jureidini. 2008. Industry-sponsored ghostwriting in clinical trial reporting: A case study. *Accountability in Research* 15: 152–167.
- Moffat, B., and C. Elliott. 2007. Ghost marketing: pharmaceutical companies and ghostwritten journal articles. *Perspectives in Biology and Medicine* 50: 18–31.
- Moreno, C., G. Laje, C. Blanco, H. Jiang, A.B. Schmidt, and M. Olfson. 2007. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Archives of General Psychiatry* 64: 1032–1039.
- Mowatt, G., L. Shirran, J.M. Grimshaw, D. Rennie, A. Flanagin, V. Yank, et al. 2002. Prevalence of honorary and ghost authorship in Cochrane reviews. *Journal of the American Medical Association* 287: 2769–2771.
- Moynihan, R., I. Heath, and D. Henry. 2002. Selling sickness: The pharmaceutical industry and disease mongering. *British Medical Journal* 324: 886–891.
- Olson, J. 2009. U doctor scrutinized over drug research. *St. Paul Pioneer Press*. 18 March.

- Paris, J. 2009. The bipolar spectrum: A critical perspective. *Harvard Review of Psychiatry* 17: 206–213.
- Phoenix International Research. 2000. Awareness of diabetes in association with antipsychotics. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY100375967.pdf>.
- Ross, J.S., K.P. Hill, D.S. Egilman, and H.M. Krumholz. 2008. Guest authorship and ghostwriting in publications related to rofecoxib: A case study of industry documents from rofecoxib litigation. *Journal of the American Medical Association* 299: 1800–1812.
- Sackett, D.L., W.M.C. Rosenberg, J.A.M. Gray, R.B. Haynes, and W.S. Richardson. 1996. Evidence based medicine: What it is and what it isn't. *British Medical Journal* 312: 71–72.
- Scarpuzza, J. Undated. *Scientific publications build brand success*. Retrieved September 23, 2009, from <http://www.ngpharma.com/article/Scientific-Publications-Build-Brand-Success/>.
- Sismondo, S. 2007. Ghost management: How much of the medical literature is shaped behind the scenes by the pharmaceutical industry? *PLoS Medicine* 4: e286.
- Smith, R. 2005. Medical journals are an extension of the marketing arm of pharmaceutical companies. *PLoS Medicine* 2: e138.
- Smith, R. 2006. Lapses at the New England Journal of Medicine. *Journal of the Royal Society of Medicine* 99: 380–382.
- SmithKlineBeecham. Undated. CASPERR: Case study publications for peer review. Unpublished manuscript.
- Spielmann, G.I. 2009. The promotion of olanzapine in primary care: An examination of internal industry documents. *Social Science & Medicine* 69: 14–20.
- Steinman, M.A., L.A. Bero, M.M. Chren, and C.S. Landefeld. 2004. Narrative review: The promotion of gabapentin: an analysis of internal industry documents. *Annals of Internal Medicine* 145: 284–293.
- Sunvalley Communication. Undated. *Writing and editorial services*. Retrieved September 21, 2009, from <http://sunvalleycommunication.com/writingandeditorial.aspx>.
- Tollefson, G.D. 1997. Zyprexa product team 4 column summary. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY200270343.pdf>.
- Tumas, J. 1999. Re: 2 EPS abstracts for APA. Retrieved February 29, 2009, from <http://www.furiousseasons.com/zip/seroqueldocs.zip>.
- Tumas, J. 2000. FW: Meta analyses (email). Retrieved February 28, 2009, from <http://www.furiousseasons.com/zip/seroqueldocs.zip>.
- Turner, E.H., A.M. Matthews, E. Linardatos, R.A. Tell, and R. Rosenthal. 2008a. Selective publication of antidepressant trials and its influence on apparent efficacy. *New England Journal of Medicine* 358: 252–260.
- Turner, E.H., A.M. Matthews, E. Linardatos, R.A. Tell, and R. Rosenthal. 2008b. *Supplement to: Selective publication of antidepressant trials and its influence on apparent efficacy*. Retrieved January 19, 2008, from <http://content.nejm.org/cgi/data/358/3/252/DC1/1>.
- Velligan, D.I., J. Newcomer, J. Pultz, J. Csernansky, A.L. Hoff, R. Mahurin, et al. 2002. Does cognitive function improve with quetiapine in comparison to haloperidol? *Schizophrenia Research* 53: 239–248.
- Ventura County Behavioral Health Department. 1999. Untitled. Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY201016928.pdf>.
- Villaruel, E.P. 2007. March Master plan: The making of a successful publication strategy. *PharmaVOICE*, 1–5.
- Washburn, J. 2005. Rent-a-researcher. *Slate*. Retrieved February 10, 2007 from: <http://www.slate.com/id/2133061/>.
- White, H. 2001. RE: Publication date for Paroxetine Adolescent Depression Study (email). Document available from authors.
- Whittington, C.J., T. Kendall, P. Fonagy, D. Cottrell, A. Cotgrove, and E. Boddington. 2004. Selective serotonin reuptake inhibitors in childhood depression: Systematic review of published versus unpublished data. *Lancet* 363: 1341–1345.
- Williamson, D. 2002. Re: Clinical summary update (email). Retrieved February 15, 2007, from <http://www.furiousseasons.com/zyprexa%20documents/ZY200540696.pdf>.
- Zimmerman, M., C.J. Ruggero, I. Chelminski, and D. Young. 2008. Is bipolar disorder overdiagnosed? *Journal of Clinical Psychiatry* 69: 935–940.