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The promotion of olanzapine in primary care: An examination of internal industry documents

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ABSTRACT

Media reports have discussed how olanzapine was marketed off-label for dementia, subsyndromal bipolar disorder, and dementia. Much of this marketing occurred in primary care settings. However, these reports have provided few details. In legal proceedings, Lilly disclosed internal documents that detail the strategies utilized to market olanzapine. The current paper addresses the marketing of olanzapine in detail based upon a review of these documents. All 358 documents released by Lilly are publicly available online. Documents were utilized for this review if they were relevant to the marketing of olanzapine in primary care settings in the United States. It was found that olanzapine was marketed off-label in primary care settings for relatively mild symptoms that were framed as bipolar disorder and schizophrenia. A key strategy in this campaign was the use of hypothetical patient profiles in detailing visits, most of which clearly failed to meet diagnostic criteria for any recognized mental disorder. Evidence emerged that olanzapine was also marketed off-label as a treatment for dementia.

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Olanzapine (Zyprexa®) is an atypical antipsychotic agent that is currently Federal Drug Administration (FDA)-approved for the acute and long-term treatment of bipolar I disorder and schizophrenia as well as agitation associated with these conditions. A media report alleged that olanzapine was promoted off-label as a treatment for dementia and that sales representatives were instructed to market olanzapine as a treatment for symptoms of schizophrenia and bipolar disorder, even if patients did not necessarily meet the full diagnostic criteria for either condition (Berenson, 2006). Likewise, there has been further discussion of the off-label marketing of olanzapine for dementia (Siegel, 2006). Reports have suggested that off-label marketing of olanzapine occurred in primary care settings (Goldstein, 2007). Lilly originally denied allegations of off-label marketing (Berenson, 2006; Goldstein, 2007) but in January 2009, as part of a global settlement with the United States to resolve criminal and civil allegations that it promoted Zyprexa for uses not approved by the FDA, Lilly agreed to plead guilty to a misdemeanor criminal charge of misbranding (Eli Lilly, 2009; United States Department of Justice, 2009). Lilly specifically admitted that between September 1999 and 31 March 2001 it promoted Zyprexa in elderly populations as treatment for dementia, including Alzheimer's dementia. Furthermore, the company has agreed to a monetary settlement of \$1.415 billion,

including a criminal fine of \$515 million, subject to the guilty plea being accepted by the U.S. District Court. This is the largest individual corporate criminal fine in US history (United States Department of Justice, 2009). John Lechleiter, chief executive officer of Lilly, said in a press release that "we deeply regret the past actions covered by this misdemeanor plea" (Eli Lilly, 2009). In October 2008, Lilly also settled olanzapine marketing-related claims brought by 33 states for \$62 million (Berenson, 2008).

Olanzapine use has been linked to significant weight gain (Bogenschutz & Nurnberg, 2004; Robinson et al., 2006; Strassnig, Miewald, Keshavan, & Ganglui, 2007; Thase et al., 2007) and increased onset of diabetes (Gianfrancesco, Wang, & Nasrallah, 2006; Guo et al., 2006; Guo et al., 2007; Lambert, Cunningham, Miller, Dalack, & Hur, 2006). Thus, promotion of olanzapine may have led to serious health consequences. It is certainly possible that some patients taking olanzapine for an off-label condition received some symptomatic relief. However, a meta-analysis indicated that olanzapine showed no benefit versus placebo in treating symptoms of dementia (Schneider, Dagerman, & Insel, 2006). At present, there is no evidence from controlled clinical trials available regarding the efficacy of olanzapine in treating relatively mild nervous symptoms such as those for which olanzapine was marketed.

While reports have described various details of marketing practices in primary care (Berenson, 2006; Goldstein, 2007), an in-depth analysis of the topic has not appeared in the media and no

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peer-reviewed article has addressed the latest revelations surrounding olanzapine's marketing. This paper presents findings from internal Lilly documents which were disclosed by Lilly in legal proceedings but which are now publicly available online. The paper will describe Lilly's high expectations for olanzapine and how olanzapine was marketed in primary care using broadened definitions of bipolar disorder and schizophrenia. In addition, evidence will be discussed regarding the marketing of olanzapine as a treatment for both dementia and "schizophrenia lite," as will details of the main methods used to market the drug, primarily focusing on the promotion of olanzapine to primary care physicians.

Method

Documents

Documents pertaining to Lilly's marketing of olanzapine as well as side effects of the medication were obtained via subpoena, and were expected to remain under seal. However, the documents were leaked to a New York Times reporter (Alex Berenson), who wrote several pieces based upon the documents (Berenson, 2006; Berenson, 2007a; Berenson, 2007b; Berenson, 2007c). Though there has been controversy surrounding the disclosure of the documents outside the litigation (Demer, 2007), the US District Court refused to grant injunctions to prevent five named websites from publishing the documents. Furthermore, the judge in the case stated that "no website is enjoined from disseminating documents." (Zyprexa Litigation et al., 2007, pg. 71). The documents are available at <http://www.furiouseasons.com/zyprexadocs.html>.

Search strategy

The entire set of documents was reviewed by the present author. The majority of the documents were related to health concerns, particularly hyperglycemia and/or diabetes. Of the 358 documents, 67 were relevant to the present focus on marketing in primary care and these are the focus of this paper (of the remainder, 50 related to marketing, but focused on health concerns rather than primary care, and the remaining 241 documents were unrelated to marketing). Documents ranged in dates from 1995 to 2004 and included a variety of memoranda, reports, email messages, and other documents.

Interpretation

The documents were reviewed using the principles of grounded theory in which no *a priori* hypothesis was tested; rather, observations were made and theory generated from the obtained documents (Glaser & Strauss, 1967). The documents were highly consistent in their portrayal of tactics used to market olanzapine in primary care settings. As each document relevant to marketing in primary care was reviewed, the author compiled notes about the key points contained within the document. These notes were grouped into several different categories (primary care, marketing, dementia, bipolar, etc.). After review of the initial set of notes, the author compiled a more abbreviated set of notes and checked the original documents to ensure they were cited accurately. From both sets of notes and the set of accompanying documents, the current paper was compiled. The author maintains full responsibility for the data extraction and interpretation of the referenced internal industry documents.

Findings

Expectations for olanzapine

Lilly clearly had high sales expectations for olanzapine. According to a 1997 document, olanzapine "is a profound corporate opportunity" and was intended to be "the world's number one neuroscience pharmaceutical in history" (Tollefson, 1997). In 2001, a document describing a Zyprexa Product Team meeting stated, "The company is betting the farm on Zyprexa...the ability of Eli Lilly to remain independent...depends solely on our ability to achieve world class commercialization of Zyprexa [emphases in original]." The same document stated, "If we succeed, Zyprexa will be the most successful pharmaceutical product ever...we will have made history" (Eli Lilly, 2001a). Olanzapine sales were expected to reach \$6 billion by 2006 and nearly \$8 billion by 2010 (Eli Lilly, 2004). Indeed, sales have been robust, with global olanzapine sales ranking among the top eight drugs in sales each year from 2000 to 2007, ranking fourth among all drugs in 2002 (Eli Lilly, 2004, pg. 9) at about \$4 billion, and leveling off at about \$4.7–\$5.0 billion annually since 2003 (IMS Health, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007). In order to help reach these impressive sales goals, olanzapine was marketed not only toward psychiatrists but toward primary care physicians (e.g., Bandick, 2000a; Eli Lilly, 2000), an effort that met with some success. Though constituting a relatively small fraction of overall sales, it was estimated in 2002 that olanzapine sales in primary care would total about \$368 million in 2003 (Eli Lilly, 2002a, pg. 6). Further sales figures for olanzapine in primary care were unavailable from the documents.

Primary care: bipolar/complicated mood

As early as 1995 (Eli Lilly, 1995, pg. 43), Lilly discussed seeking approval for olanzapine as a treatment for bipolar disorder. Shortly after its March 2000 FDA approval as a short-term treatment for bipolar disorder, Lilly began a promotional initiative, dubbed Viva Zyprexa (Eli Lilly, 2000; later retitled Zyprexa Limitless (Eli Lilly, 2002b) that aimed to increase the use of olanzapine in primary care settings. About 59,000 primary care physicians (PCPs) in the US were labeled as "key targets" of this program, which launched in approximately October 2000 (Bandick, 2000a, pg. 1). According to the brand manager for Zyprexa, Mike Bandick, "[olanzapine's] potential in this arena is virtually untapped" (pg. 1). In multiple documents, the marketing message for olanzapine in primary care was stated clearly: "Zyprexa: The safe, proven solution in mood, thought, and behavior disorders" (Bandick, 2000a, pg. 1; Eli Lilly, 2000, pg. 6). Additionally, the marketing strategy was designed to "fit within the brand vision of broad spectrum efficacy" (Bandick, 2000a, pg. 1), though olanzapine was only FDA-approved for the treatment of bipolar manic and mixed episodes and for schizophrenia when the primary care marketing campaign began. Bandick further stated that the intention of Viva Zyprexa was to "redefine the way PCPs treat mood, thought, and behavioral disturbances" (Bandick, 2000b, pg. 12) and another document stated that a main component of the primary care marketing message was to "focus on symptoms and behaviors found in mood, thought, and behavioral disturbances" (Eli Lilly, 2000, pg. 9, emphasis in original). In a similar vein, olanzapine was rebranded as a "broad spectrum psychotropic" in the primary care campaign (Eli Lilly, 2001b, pg. 9).

The promotion of olanzapine in primary care was associated with some concerns at Lilly, including that "Zyprexa's primary indications – schizophrenia and bipolar – are not viewed as PCP-treated conditions, so there's not a specific indication for Lilly reps to promote in the PCP segment" and that most PCPs write very few

antipsychotic and mood stabilizer prescriptions (Bandick, 2000a, pg. 1). The promotion of Zyprexa in the primary care setting included the use of hypothetical patient profiles as well as positioning olanzapine “as the next incremental step in the PCP’s expanding clinical orbit: e.g., SSRI’s → 2nd generation [antidepressants] → safe gentle psychotropics” (Bandick, 2000a, pg. 1). Using a similar analogy, it was stated: “just as Prozac revolutionized the treatment of depression in the late 80s and throughout the 90s, so too will Zyprexa forever change the way primary care physicians view and treat bipolar disorder” (Eli Lilly, 2002b, pg. 3).

It was clear that olanzapine was not to be marketed in primary care as a treatment for severe bipolar disorder (bipolar I), as these patients are generally referred to psychiatrists by primary care physicians. In the June 2002 Primary Care Sales Force Resource Guide (Eli Lilly, 2002b), the prevalence of bipolar disorder is estimated to be as high as 6%, an estimate much higher than epidemiological lifetime prevalence estimates for bipolar I, which range from about 1% to 3%; only estimates that include “subthreshold” cases of bipolar disorder have found a 6% lifetime prevalence rate (Grant et al., 2005; Judd & Akiskal, 2003; Weissman et al., 1996). Rather than limiting representatives to discussing clear-cut cases of bipolar I (for which olanzapine was FDA-indicated) olanzapine was instead marketed as a treatment for “complicated mood,” a cluster of symptoms that seems related to a notably less severe variety of bipolar disorder. For example, a script in the 2002 Primary Care Sales Force Resource Guide, stated: “Doctor, you treat patients who present with complicated mood symptoms. Many of these patients are struggling to gain control of symptoms like anxiety, irritability, disruptive sleep, and mood swings...” (Eli Lilly, 2002b, pg. 5). In addition, a visual aid to be used by representatives’ lists anxiety, irritability, disturbed sleep, and mood swings as the core components of complicated mood (Eli Lilly, 2002b, pg. 6). According to the DSM-IV, anxiety is not a symptom of bipolar disorder and it is unclear to what extent disturbed sleep maps onto the DSM-IV criterion of decreased need for sleep for bipolar disorder. The use of mood swings as a descriptor is likewise unclear, and it is likely that many more people would endorse having “mood swings” than would actually meet the DSM-IV criteria for shifting between clinically significant episodes of mania and depression.

The “complicated mood patient” was said to relate to “untapped growth potential” for the use of olanzapine in primary care settings (Eli Lilly, undated-a, pg. 3). As touched on related above, under the “PCP Vision” of olanzapine, it was stated that the plan was to “expand our market by redefining how primary care physicians identify, diagnose, and treat complicated mood disorders (i.e., bipolar disorder) (Eli Lilly, 2002d, pg. 2).” In June 2002, it was written, regarding complicated mood, “we’ve only scratched the surface of a market with tremendous upside” (Eli Lilly, 2002d, pg. 5). Sales representatives were instructed to handle primary care physician concerns that they do not treat bipolar or schizophrenia as follows: “Make sure the PCP recognizes the type of patient we are talking about today, not the psychotic or severely ill patient, but the complicated mood patient who has symptoms of irritability, anxiety, poor sleep and mood swings” (Eli Lilly, undated-b, pg. 1). Such symptoms do not appear to meet DSM-IV criteria for bipolar I disorder.

A Lilly market researcher suggested that bipolar disorder tends to lead primary care physicians to think of acutely manic patients, “less so the hypomanic or less severely ill patient, which tend to be the patients presenting most often in their offices (Porat, 2002, pg. 3).” The same market researcher suggested that sales representatives “help [primary care physicians] recognize the ‘mushy middle’ patients they are already treating... (Porat, 2002, pg. 7).” It was also suggested that patients on “the low to middle end” of bipolar severity, who were “higher functioning” receive olanzapine treatment via their primary care physicians (Porat, 2002, pg. 11).

Patient profiles: bipolar spectrum

Olanzapine was marketed in the primary care setting based largely upon the presentation of scripted patient profiles (Eli Lilly, 2001b). A total of 10 different profiles were discussed in the obtained documents. The majority of these patients fall into the bipolar spectrum, defined quite loosely.

A hypothetical patient named Donna was featured in a handful of documents (Eli Lilly, 2002b; Eli Lilly, undated-b, undated-c; Eli Lilly, 2001c). The “goal and focus [was] on creating a market [for olanzapine]” with her case (Eli Lilly, 2001c, pg. 2). She was described as “a single mom in her mid-30s, appearing in your office in drab clothing and appearing somewhat ill at ease. Her chief complaint is, ‘I feel so anxious and irritable lately.’ Today, she says she’s been sleeping more than usual and has trouble concentrating at work and at home. However, several appointments earlier, she was talkative, elated, and reported little need for sleep.”

Under the heading “Create Action”, a script read, “I would like you to get a patient like Donna started today. I will be back in a week to follow up” (Eli Lilly, 2002b, pg. 8). In another document, a more detailed description of Donna is provided. She was described as exhibiting the four “core symptoms [of complicated mood, including] mood swings, irritability, sleep disturbances and anxiety, as well as other symptoms including a lack of concentration, mood lability and increased energy, depressed mood, loss of interest, and agitation.” The symptoms were described as occurring simultaneously, “hence her mixed [i.e., mixed episode] presentation” (Eli Lilly, undated-c, pg. 1).

The hypothetical patient named Mark “is a middle-aged male brought in by his wife. He appears agitated and disheveled. His wife says that he is irritable and causing problems at home but he believes he is fine.” It is further mentioned that he has had “periods” where he needed little sleep and had “significantly increased energy.” Further, his “anger and mood swings are causing trouble at work” (Eli Lilly, 2002b, pg. 9). In another document, his symptoms were said to be indicative of a manic episode (Eli Lilly, undated-c, pg. 1).

An undated document titled “PCP Discussion Guide,” focused on “using olanzapine for patients with complicated mood symptoms.” Three patients (Ashley, Andrea, and Cindy) were described. Ashley was described as having insomnia, irritability, distractibility, and racing thoughts. She also “has a tendency to be over-talkative.” (Eli Lilly, undated-d, pg. 4). DSM-IV criteria for bipolar I disorder require significant impairment in social or occupational functioning, psychotic features, or hospitalization to prevent harm to self or others; no such impairment is noted in Ashley’s case.

Andrea, another hypothetical case, was described as suffering from a variety of depressive symptoms. After taking an antidepressant for 10 days, her behavior became “increasingly irritable, restless, anxious, hyperverbal, and [she] experiences great difficulty sleeping (pg. 7).” She was then labeled as manic and treated successfully with olanzapine.

The case named Cindy suffered from a variety of depressive symptoms as well as distractibility, irritability, inability to sit still, and racing thoughts. After taking an antidepressant, she became “very anxious, agitated and hyperactive, with pressured speech and racing thoughts (pg. 12).” After taking olanzapine, she “reports significant improvement” within one week (pg. 12).

The scenarios of Cindy, Andrea, and Ashley were not discussed directly in further documents, though one document (Eli Lilly, 2002c) referred to “three good complicated mood case summaries”, (pg. 2). It may well be that this is a reference to the aforementioned three cases as it also mentioned an email attachment partially titled “PCP DiscGd”, which coincides with the document titled “PCP Discussion Guide” (Eli Lilly, undated-d) that described

the three cases. The “PCP Discussion Guide” further stated that “I would highly suggest we direct reps to utilize” the three cases in marketing (pg. 1). However, it is unclear to what extent these cases were utilized to promote olanzapine in the primary care setting.

Another mood-related patient profile, Michael, was included in a document titled “Olanzapine Primary Care Q3 Implementation Guide”, dated June 2001 (Eli Lilly, 2001b). Michael was described as “highly functional” but “prone to mood swings” and as having switched from “down, unmotivated, detached” to “wired, irritable, and anxious...hasn’t been sleeping much.” His wife was concerned about his “recent spending habits and erratic behavior” (pg. 12).

In addition, one other patient profile, David, was described very briefly in one document. Though it appears that David represented a patient with bipolar disorder, he was later replaced by Michael, perhaps because market research (Eli Lilly, 2001b) labeled David as a “strike out” (Eli Lilly, 2001d, pg. 8). Based upon the description of their symptoms, the cases described above do not appear to reference clear-cut cases of bipolar I disorder.

Dementia

As early as 1996, Lilly sought to collect data for an FDA indication for “psychosis in Alzheimer’s” (Eli Lilly, 1995, pg. 43) and, in a Zyprexa Product Team document from 1997, “dementia with psychosis” was listed in the highest priority group for olanzapine under “disease state prioritization” (Tollefson, 1997, pg. 18). In 1999, a document that focused on primary care physicians stated that “Dementia should be first message” (Eli Lilly, 1999, pg. 1); the same document added that some physicians “might prescribe outside of label” (pg. 2). Further, in 2001, the Integrated Product Plan for olanzapine stated that the drug would remain the “bestselling psychotropic drug in history” by treating people suffering from “schizophrenia, bipolar disorder, and dementia” (Eli Lilly, 2001e, pg. 5). Documents provided various timelines for expected FDA approval in dementia, though olanzapine never received FDA approval for the population with dementia (Bandick, 2000b; Eli Lilly, 2001e). Lilly appears to have stopped pursuing FDA approval for dementia in 2003 (Eli Lilly, 2003; Eli Lilly, 2004). Indeed, olanzapine carries a label warning (along with other atypical antipsychotics) that the drug is related to an increased risk of death when taken by elderly patients with dementia-related psychoses.

Zyprexa brand manager, Mike Bandick stated that donepezil (a cholinesterase inhibitor popularly used in dementia) belongs to a “companion” class of medication, a drug “we augment rather than replace” (Bandick, 2000b, pg. 23). Further, it is mentioned that the marketing of olanzapine in long-term care settings (where dementia is quite common) may have adversely impacted olanzapine sales in bipolar and schizophrenia markets (Eli Lilly, 2002f, pg. 1).

Patient profile: dementia

In a manner similar to bipolar disorder/complicated mood, documents detailed the marketing of dementia to primary care physicians through the use of a hypothetical patient profile, described as follows:

Martha is a widow who lives independently and has been your patient for some time. She is becoming more complicated to manage, and you note increasing agitation. Her sleep is disturbed; she dozes during the day and is up most of the night. Her family has shared their concerns with you, saying “She thinks we’re trying to take advantage of her.” Martha’s family doesn’t want to send her to a nursing home, but her agitation and confusion must be addressed. Your goals of treatment for Martha may include reducing her behavioral

disturbances without impairing her cognitive functioning (Eli Lilly, 2001b, pg. 11).

The script went on to ask, “Do you see patients like Martha? What medication(s) do you prescribe in treating her behavioral disturbances?” (2001b, pg. 11)

According to a media report (Berenson, 2006), a Lilly spokesperson indicated that the Martha profile was utilized to reference a patient with untreated schizophrenia; however, Martha’s case seems more consistent with mild dementia rather than schizophrenia that has remained undetected for decades. Olanzapine is typically utilized in doses of at least 10–15 mg daily for schizophrenia (Crespo-Facorro et al., 2006; Kinon et al., 2006; Takahashi, Kamata, Yoshida, Ishigooka, & Higuchi, 2006), yet sales material suggested that patients like Martha receive doses in the 2.5 mg–5 mg range (Eli Lilly, 2001b), a range typical of what was utilized in olanzapine trials for dementia (De Deyn et al., 2004; Schneider, Dagerman, et al., 2006; Schneider, Tariot, et al., 2006). In addition, although Lilly claimed that they intended Martha’s profile to represent a patient with schizophrenia, an internal email stated that the diagnosis of Martha was “dementia” (Dobbs, 2000, pg. 1), followed by a comment that “we are getting a little grief from some of our docs about promoting Zyprexa for dementia” (pg. 1). Several psychiatrists have disagreed with the assessment of Martha’s case as one of schizophrenia, noting that schizophrenia “could not be confused with mild dementia” (Berenson, 2006).

Schizophrenia

It is likely that few primary care physicians treat schizophrenia on a regular basis. However, the primary care marketing campaign placed significant emphasis on symptoms of “thought disturbances,” including discussion of disorganized thinking, as well as poor attention, poor judgment and lack of insight (Eli Lilly, undated-e). Olanzapine was specifically marketed for “mood, thought, and behavior disorders” in an “intentionally broad and vague” manner, “providing latitude to frame the discussion around symptoms and behaviors rather than specific indications” (Bandick, 2000a, pg. 1). While schizophrenia is not treated frequently by PCPs, one document mentioned the idea of treating schizophrenia or “schizophrenia lite” in primary care (Eli Lilly, 2001d, pg. 7).

Patient profiles: schizophrenia

The profile named Kelly was purportedly designed to represent a patient with some form of psychotic disorder. Kelly was described as becoming more “socially isolated and fearful. Her personal hygiene is starting to decline and she is difficult to draw out...[her family says] ‘she thinks people are talking about her behind her back’”. The description of Kelly does not appear to place her into any recognized DSM-IV disorder category. She is described earlier in the document as struggling with “mild to moderate psychosis.” Kelly replaced a profile named Christine (Eli Lilly, 2001b) that was listed as a patient with “schizophrenia lite” (Eli Lilly, 2001d). A detailed description of Christine was not located in the archive. Kelly’s case replaced that of Christine because Kelly seemed “more treatable” in a primary care setting, while Christine seemed “defiant” (Eli Lilly, 2001b).

Discussion

Starting in 2000, a sizable campaign was launched to increase olanzapine prescriptions in primary care. Materials utilized by sales representatives in primary care contained a high prevalence estimate for bipolar I disorder, as one document suggested that the

prevalence of bipolar disorder was 6% (Eli Lilly, 2002b), yet the prevalence for bipolar I disorder has been estimated as much less frequent (Grant et al., 2005; Judd & Akiskal, 2003; Weissman et al., 1996). In addition, as suggested above, hypothetical cases used various diagnostic criteria that were overly inclusive, and presented scenarios of several patients who did not seem to meet criteria for bipolar I disorder or schizophrenia. Based upon review of several documents, it appears that sales representatives were instructed to market olanzapine as a treatment for patients well outside of its indicated uses (Eli Lilly, 2001b, 2002b; Eli Lilly, undated-b, undated-d; Porat, 2002). In addition, there is evidence that Lilly promoted olanzapine off-label for dementia (Dobbs, 2000; Eli Lilly, 2001b; Hobson, 2001), and marketed olanzapine as a long-term treatment for bipolar disorder in advance of its FDA approval for the condition (Eli Lilly, 2002b; Eli Lilly, 2002e).

The relatively mild symptoms marketed by Lilly as components of “complicated mood” (anxiety, irritability, disturbed sleep, and mood swings) are ill-defined and, to some extent, are likely to be experienced by a large number of people. Labeling this constellation of ill-defined and likely common symptoms as indicative of a mental condition is suggestive of ‘disease mongering’ a term referencing the effort of pharmaceutical companies to broaden the market by convincing patients (and physicians) that a large number of people are suffering from a (usually relatively mild) illness which would benefit from pharmaceutical intervention (Moynihan & Cassels, 2005). In trade journals, pharmaceutical industry insiders have plainly stated that expanding the market for their products via “condition branding” (an industry term analogous to ‘disease mongering’) is a highly useful tool in the marketing arsenal (Angelmar, Angelmar, & Kane, 2007). Indeed, the current corpus of internal documents hints that, in addition to marketing olanzapine, sales representatives were also marketing the *expanded boundaries* of bipolar disorder. No longer was bipolar disorder a relatively uncommon condition relegated to treatment by psychiatrists, it was to be marketed as a common illness with a broad spectrum of severity that warranted treatment in primary care. Despite an expanded treatment market, there is a paucity of controlled clinical trial data regarding the benefits and risks of treating adults with mild symptoms of bipolar disorder/complicated mood with ‘mood stabilizers’ or atypical antipsychotics such as olanzapine (Healy, 2006).

One document stated that Lilly was committed to position olanzapine as a “broad spectrum psychotropic to differentiate it from other antipsychotics...” (Eli Lilly, 2001b). Such a focus on product differentiation is sensible in a crowded marketplace of atypical antipsychotic medications. Indeed, product differentiation is a key component of modern-day marketing, with products from cola to toilet cleaners to antidepressants marketed on the basis of their ostensible uniqueness, often in spite of their high degree of similarity to competing products (Applbaum, 2004). Lilly also emphasized product differentiation when marketing its antidepressant duloxetine as a treatment for patients with depression who also suffer from physical pain, as research indicated that entering this niche market would differentiate duloxetine from its competition (Ofek, 2007). As part of the marketing strategy for duloxetine, hypothetical patient profiles tailored to the perceived market were created, though it is unclear to what extent the patient profiles were used in detailing visits (Ofek, 2007). This niche strategy appears to have been successful, as duloxetine sales exceeded \$2 billion in 2007. Indeed, Lilly expects duloxetine sales to overtake those of its current bestseller, olanzapine, in 2008 (Lopatto, 2008). Despite the successful marketing of duloxetine, a recent meta-analysis concluded that the drug yielded little to no benefit over placebo in treating pain symptoms in depression (Spielmans, 2008), though Lilly claims duloxetine is indeed effective at treating such symptoms (Silverman, 2008).

It appears that olanzapine’s marketing in primary care can be viewed as a similar attempt to market a drug for a new niche – “Just as Prozac revolutionized the treatment of depression in the late 80s and throughout the 90s, so too will Zyprexa forever change the way primary care physicians view and treat bipolar disorder” (Eli Lilly, 2002b, pg. 3). Carving out new niches and expanding a drug’s uses to a wide range of medical conditions (defined loosely) is a common tactic. In a pharmaceutical trade publication, it was written that “indication expansion is also tried and tested in the psychotropic field, where diagnostic distinctions can be blurred...(Hisey, 2004, para. 22).” The expansion of somewhat fuzzy boundaries of mental illness makes perfect sense in a highly competitive market in which various pharmaceutical companies are attempting to maximize sales. Such expanded definitions open the gates to more people qualifying as mentally ill, for which they might receive treatment with “broad spectrum psychotropics” that purportedly work to alleviate a wide variety of symptoms. Part of such market expansion occurs by marketing to primary care physicians, who have access to a wide base of patients. Indeed, it is interesting to note that Lilly’s most famous product, fluoxetine (Prozac), was successful largely because it vastly expanded the depression treatment market into primary care settings (Eaton & Xu, 2005).

As described in the paper and elsewhere (e.g., Antonuccio, Danton, & McClanahan, 2003; Healy, 2004), pharmaceutical companies utilize many methods to market their products. It is not entirely clear why patient profiles were seemingly utilized quite frequently in the marketing of olanzapine in primary care, though one document pointed out that the profiles would aid physicians in recognizing symptoms and in “early identification of relevant patient types” (Eli Lilly, undated-e, pg. 1).

Given that olanzapine was estimated to hit over \$350 million in primary care sales in 2003, it appears that a reasonably large number of patients in primary care received olanzapine prescriptions. As the primary care marketing campaign seemed focused primarily on cases suffering from relatively mild mental distress (e.g., “complicated mood”), many patients who were prescribed olanzapine via primary care may have been prescribed treatment that lacked a supporting evidence base. Several studies have linked olanzapine to weight gain (Bogenschutz & Nurnberg, 2004; Robinson et al., 2006; Strassnig et al., 2007; Thase et al., 2007) and to onset of diabetes (Gianfancesco et al., 2006; Guo et al., 2006; Guo et al., 2007; Lambert et al., 2006), and it is possible that olanzapine may increase risk for cardiovascular disease (Newcomer & Haupt, 2006). Indeed, the olanzapine label was updated in October 2007 to reflect an increased risk of hyperglycemia, hyperlipidemia, and weight gain. Thus, it is quite possible that some patients received a treatment of questionable efficacy that resulted in adverse health effects, though the current documents do not clarify to what extent such health consequences may have occurred.

This study has a number of limitations, the most obvious of which is the reliance on the present set of documents. Though their authenticity has not been challenged, it is certainly possible that the documents may have been taken out of context and that further internal documents related to olanzapine’s promotion would paint a different picture of how the drug was marketed. However, this seems unlikely given that the documents obtained were quite consistent in their descriptions of the marketing of the compound.

The documents were reviewed by one author, so it is possible that different reviewers may come to different conclusions. As all the internal documents are accessible by the public online (Anonymous, 2007; Dawdy, 2007), they can be easily examined by anyone who wishes to check the veracity of the current author’s claims. The source material was also somewhat dated, in that documents reviewed dated from 1995 to 2004. Practices regarding the marketing of olanzapine that have occurred since 2004 are thus unknown.

Given that regulations surrounding off-label marketing are somewhat murky and controversial (Hall & Berlin, 2006; Kahan & Shapiro, 2003; O'Reilly & Dalal, 2003), and that the present author is not an attorney, this paper makes no claims as to the legality of any of the practices utilized in the promotion of olanzapine.

The current examination of Lilly's marketing of olanzapine in primary care adds to a small but burgeoning literature on the intersection between pharmaceutical companies and the boundaries of medical conditions (e.g., Healy, 2006, Moynihan & Cassels, 2005; Woloshin & Schwartz, 2006) and off-label marketing (Steinman, Bero, Chren, & Landefeld, 2006). Future researchers should seek to examine the impact of such marketing tactics, taking ideas from guidelines offered previously (Moynihan & Henry, 2006). From a social science perspective, these internal industry documents are a rare find. Documents from the present archive detailing how Lilly handled issues with potential health concerns related to olanzapine will likely be of interest to social scientists, as the documents seem to involve a potentially interesting intersection of marketing, health, and public relations concerns.

A physician affiliated with the FDA wrote that regulation of off-label marketing in the pharmaceutical industry is needed in order to prevent "harm to patients from unstudied uses that actually lead to bad results, or that are merely ineffective" and that insufficiently regulated off-label drug marketing "could ultimately erode the efficacy standard" (Woodcock, 1997, pg. 6). In the wake of revelations regarding olanzapine's off-label marketing, it may behoove regulatory agencies to attend more closely to such practices.

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