MEASURING THE IMPACT OF BREAKTHROUGH CLINICAL DATA AND RELATED PUBLICITY ON PHYSICIAN PRACTICE PATTERNS IN THE UNITED STATES.

by

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Abstract

Physicians are constantly being exposed to new evidence that may effect how they practice medicine. While they read medical journals that contain peer-reviewed publications and attend scientific meetings at which results are presented, quite often they learn of new medical developments through the general consumer media. This paper summarizes the results of two case studies evaluating the impact of new clinical data and related media events on physician prescribing behavior within two different therapeutic classes: antipsychotics, used to treat psychosis, and female contraceptives. The analysis included a time-series analysis of total prescriptions (TRx) and market share (% of TRx) in the timeframe pre- and post- publication of landmark clinical data and surrounding media events.

Results from these case studies suggest that the communication of landmark clinical data had a significant influence on physician prescribing behavior within both therapeutic classes. Although more rigorous statistical analysis would be required to definitively prove a correlation, in both case studies – antipsychotics and contraceptives – physicians appear to be more influenced by media communication of new data than by the publication of the CATIE study results (antipsychotics) and the FDA's advisory on updated labeling for the contraceptive patch Ortho Evra (contraceptives), respectively.

Introduction

The objective of this paper is to evaluate the impact of media events on physician prescribing behavior for two therapeutic categories: antipsychotics and contraceptives. In this analysis, the media events selected focused on the publication of landmark clinical trial results (antipsychotics) and new safety information for a marketed contraceptive. There are several ways in which physicians are exposed to new evidence. They may read medical journals, attend scientific meetings at which results are presented, or hear about this information through the media. This analysis will aim to gauge changes in physician prescribing behavior over time in response to publicity surrounding major medical events, each covered widely in the media.

Utilizing a proprietary prescription database, which captures nearly half of all prescription activity in the US, two time-series analyses were performed. The first analysis (Case Study 1) is conducted on the antipsychotic market to evaluate an effect on antipsychotics, which are primarily prescribed by psychiatrists. The second analysis (Case Study 2) examines the effect on contraceptive prescribing by ob/gyns.

Case Study 1 – Antipsychotics

Introduction

Although the pharmaceutical industry has conducted a significant number of studies in the treatment of major psychiatric illnesses, the majority of these studies: have been designed to evaluate a single product, are short-term in duration (i.e., 8 to 12 weeks), and may not reflect all schizophrenia patients due to study inclusion/exclusion criteria. Understanding the need for long-term, objective comparative data in a broad population of schizophrenia patients, in January 2001, the National Institute of Mental Health (NIMH) initiated a study of a first-generation antipsychotic, perphenazine, vs. several newer second-generation antipsychotics.[1] At that time, the relative effectiveness

of these second-generation atypical antipsychotics as compared with that of older antipsychotics was incompletely addressed, although newer agents were (and still are) used far more readily due to the more favorable side effect profile.[1] This study was one of four trials funded over a six year period by the mental-health division of the National Institutes of Health to produce reliable scientific data regarding the differences between drugs and treatment strategies for the major psychiatric illnesses.[2]

The CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness) Schizophrenia Study (Comparative Effectiveness of Antipsychotic Medications in Patients with Schizophrenia) was a comparator study of the newer atypical antipsychotics (olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon)) with each other and with the first-generation antipsychotic perphenazine. Led by Jeffrey Lieberman of Columbia University and director of the New York State Psychiatric Institute, the study involved 1,493 schizophrenic patients at 57 US medical centers randomized to 18 months of treatment.[1] The specific aims of the study were 1. to determine the long-term effectiveness and tolerability (all-cause treatment discontinuation) of the newer atypical antipsychotics, relative to each other, 2. to determine the long-term effectiveness and tolerability of the newer atypical antipsychotics relative to a conventional antipsychotic (perphenazine), 3. to determine, among patients who fail treatment with an initially assigned newer atypical antipsychotic due to lack of efficacy, the long-term effectiveness and tolerability of the other newer atypical antipsychotics, relative to clozapine, and 4. to determine, among patients who discontinue treatment with an initially assigned newer atypical antipsychotic due to treatment intolerance, the long-term effectiveness and tolerability of the other newer atypical antipsychotics, relative to ziprasidone.[3]

Published in the September 22, 2005 issue of the New England Journal of Medicine, results from the CATIE study, published widely in the media, found that the newer, more expensive atypical antipsychotics are no more effective and no safer than an older, less expensive medication (perphenazine (Trilafon)) that many physicians no longer use. The most striking finding was that 74% of patients discontinued their assigned study medication, due to lack of efficacy and/or adverse side effects, and switched to another before 18 months (1061 of the 1432 patients who received at least one dose)[1]. According to Thomas Insel, director of NIMH: "The study has vital public health implications. It is the largest, longest and most comprehensive, independent trial ever done to examine existing therapies for this disease."

Recognizing the importance of the CATIE study to physician treatment of schizophrenia, in this analysis the effect of the study findings on physician prescribing habits was evaluated. Because of the significant amount of negative publicity that surfaced during the course of the CATIE study in mid-2003 regarding weight gain associated with the second generation antipsychotics, particularly Zyprexa, concerns abounded that focusing solely on changes following publication of the CATIE study results would be incomplete. As a result, the analysis was broadened to look at the impact on prescribing over the entire five-year time frame so as to evaluate the effect of these Zyprexa-related media events on prescribing habits.

Methods

To investigate the impact of clinical findings during and following the CATIE study, the key media communications surrounding the study initiation, interim publicity, and results dissemination were identified, and, once complete, the impact of this information on use of antipsychotic therapies from January 2002 to December 2005 was evaluated. A time series analysis was set-up in order to gauge any effect.

Although the CATIE study was initiated in January 2001, January 2002 was chosen as a starting point for the analysis due to limitations in availability of retail prescription data. December 2005 was selected as the end date because it was not only the most recent month of data, but also captures the publicity surrounding publication of the final study results in September 2005.

Retail pharmacy prescription data for the antipsychotic schizophrenia treatments Zyprexa (oral), Seroquel, Risperdal (oral), Geodon (oral), and perphenazine were obtained from Verispan, a joint venture between Quintiles and McKesson. The Verispan data captures more than 1.4 billion patient-centric prescriptions per year, nearly half of all prescription activity in the US, and is a proprietary service of Quintiles, Inc. [4] Total prescriptions (TRx) and market share (% of TRx) was obtained from January 2002 through December 2005. Risperdal Consta, Zyprexa Zydis, and the Geodon IM injectable formulations of these drugs were not included in this prescription data as they are not typically dispensed through retail pharmacy and thus, capture through the Verispan data is incomplete. However, this should not affect the analysis as an examination of the TRx for the non-oral formulations show that they are a small fraction of the overall TRx for these antipsychotics.

To identify media communications surrounding the study, an Internet search in Google from January 2001 to March 2006 using the following terms was conducted (see Attachment A):

- Dr. Jeffrey Lieberman + CATIE
- Effectiveness of Antipsychotic Drugs in Patients

Understanding the importance of communications regarding weight gain associated with Zyprexa use, a supplemental search was conducted using the terms

"weight gain" + "Zyprexa" (see Attachment B). Articles or references to articles contained within the following formats were excluded:

- Personal blogs (articles from "periodical type" blogs were included)
- Listings of ongoing clinical trials (unless preliminary results were mentioned as a part of the listing)
- Listings of the article and/or abstract itself
- Listings of ongoing litigation
- Speaking engagement announcements where the article is referenced
- Articles not written in English

Results

Communication of Efficacy and Safety Data for Antipsychotics

The analysis of media events identified seven major communications that could potentially influence physician-prescribing behavior:

- *Increased Prevalence of Diabetes Among Patients Receiving Antipsychotic Drugs*, May 30, 2003
- *Weight Gain is Potential Problem in Patients Switched from Risperidal to Zyprexa*, October 16, 2003
- *Zyprexa Efficacy Questionable*, November 25, 2003
- *Zyprexa Class Action Lawsuit Announced*, April 19, 2004
- *The Next Phase in Psychiatry: Largest Ever Studies on Drugs for Depression, Schizophrenia Could Transform Treatment*, July 27, 2005
- *Study Shows Older, Cheaper Drug is Effective as Newer Antipsychotic Meds*, September 2005
- *Study Finds Little Advantage In New Schizophrenia Drugs*, September 20, 2005

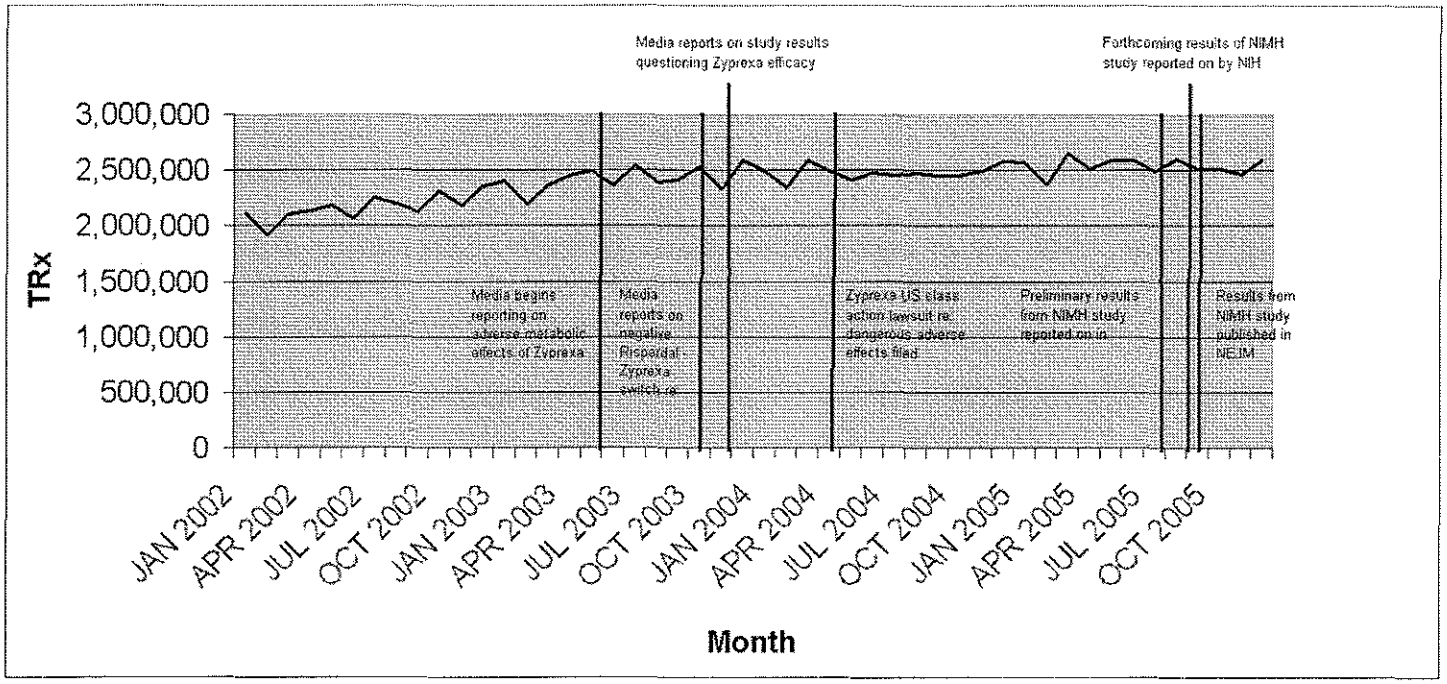
As can be seen from the list of communications above, outside of the press surrounding the CATIE study, the major data being published was related to the impact of antipsychotics on weight/diabetes. The evidence linking the atypical products, and in particular Zyprexa, to the metabolic side effect began in May 2003 with reports related to a significantly higher rate of diabetes among patients receiving antipsychotics.[5] In October 2003, Zyprexa was specifically and prominently targeted for its induction of significant increases in body mass index weight gain in patients taking it.[6] Soon thereafter, media reports began appearing linking Zyprexa to other serious side effects

including altered lipid profile, hyperglycemia, pancreatitis, ketoacidosis, and diabetic coma. In November 2003, the results of a study *sponsored by Eli Lilly & Co.* revealed that its very own Zyprexa may not be a much more effective treatment than older and cheaper schizophrenic medications.[7] Finally, in April 2004, the filing of the first nationwide (US) Zyprexa class action lawsuit was announced against Eli Lilly & Co.[8]

Prescription Data

Figure 1 presents total prescriptions (TRx) from January 2002 to December 2005, inclusive, for all antipsychotics (antipsychotic prescription data was not available for calendar year 2001 when the CATIE study began enrollment) graphed concurrently with the timing of the 7 key data communications outlined above. As can be seen in Figure 1, there has been a leveling off of prescriptions for antipsychotics in the early 2003 to late 2005 timeframe, which suggests that much of the change in volume across agents observed during this timeframe is really a shift in prescribing behavior among products rather than an expansion in the market size. It is interesting to note that the plateau in market growth occurred around the time that negative data was communicated on weight gain associated with atypical antipsychotics, and in particular, with Zyprexa, one of the leading products at the time.

Figure 1 - Antipsychotic TRx January 2002 to December 2005

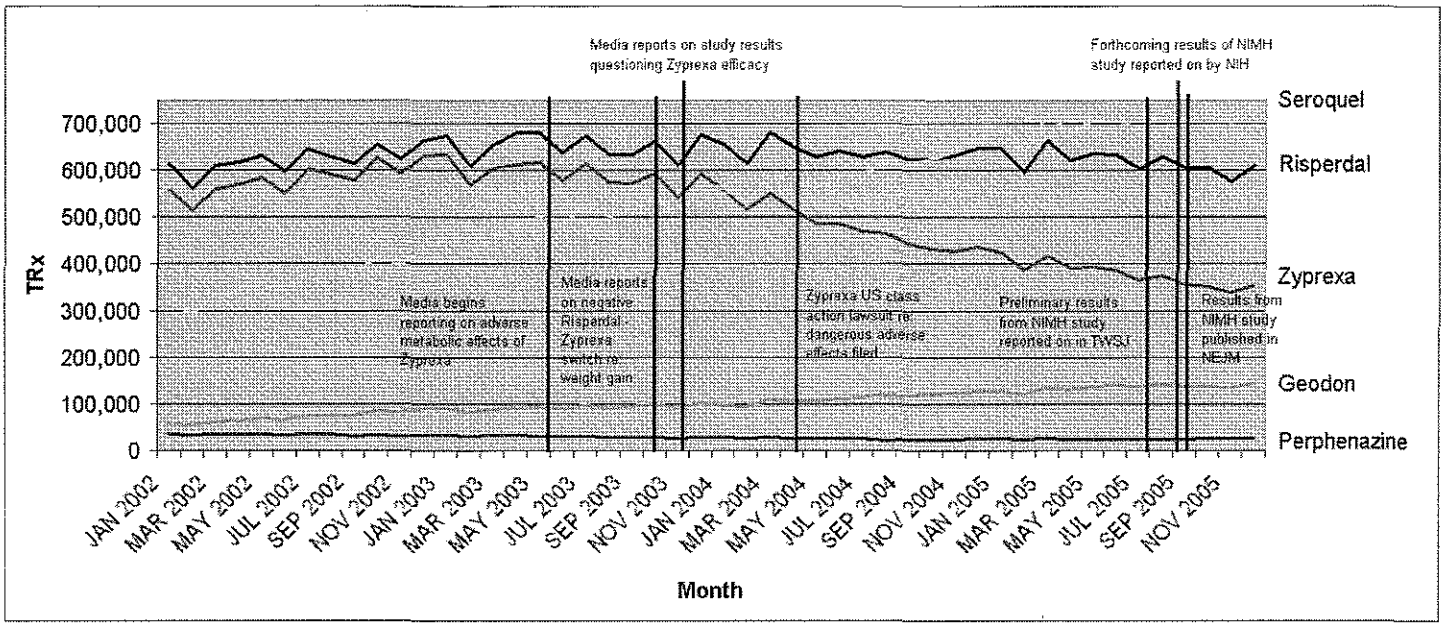


Source: Verispan VONA, Antipsychotics, Feb 2006

Figure 2 presents total prescriptions (TRx) from January 2002 to December 2005, inclusive, for each individual antipsychotic.* As can be seen in Figure 2, there is a significant downward trend of TRx for Zyprexa and a counter-balancing upward trend of TRx for Seroquel. The TRx trending for the other three antipsychotics in relation to Zyprexa and Seroquel, by and large, stayed the same. Because the total market (as displayed in Figure 1) was stable over this timeframe, the data suggest that physicians primarily shifted prescribing amongst the two antipsychotics Zyprexa and Seroquel. Although more months of data will need to be observed to completely characterize the impact of the CATIE study, there does not seem to be a significant shift in the prescribing trends based on reporting of study results.

* Please note that the monthly fluctuations in TRx that can be seen for the individual antipsychotics are normal and are caused by a varying number of working days in any given month (e.g., length of the month, holidays).

Figure 2 – Individual Antipsychotic TRx January 2002 to December 2005



Source: Verispan VONA, Antipsychotics, Feb 2006

Figure 3 presents similar data for the individual antipsychotics represented as percent market share at each of the seven major media communications time points. What can be seen from this graphic is a significant shift in market share between Zyprexa and Seroquel. In January 2002, Zyprexa was second to Risperdal in market share with a 15.1% margin separating it from Seroquel, the third highest prescribed antipsychotic. By September 2005, Zyprexa's market share had fallen and it became the third highest prescribed antipsychotic, supplanted by the surging Seroquel. A 19.3% margin in favor of Seroquel now separated Zyprexa and Seroquel. In total, Zyprexa experienced a 34.4% loss in market share to Seroquel during this time period.

Figure 3 – Antipsychotic Market Share (% of TRx) for Each of the Major Media Communications Time Points

Product Brand	JAN 2002	MAY 2003	OCT 2003	NOV 2003	APR 2004	JUL 2005	SEP 2005	DEC 2005
RISPERDAL	29.1%	27.4%	26.0%	25.9%	25.7%	23.8%	23.7%	23.6%
ZYPREXA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SEROQUEL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GEODON ORAL	2.7%	3.8%	3.9%	4.0%	4.3%	5.5%	5.5%	5.6%
PERPHENAZINE	1.7%	1.3%	1.2%	1.1%	1.1%	1.0%	1.0%	1.0%

Source: Verispan VONA, Antipsychotics, Feb 2006

Discussion

The results of this analysis demonstrate a significant shift in prescribing behavior away from Zyprexa that appears to be well correlated with the timing of negative press regarding the associated weight gain. While all other antipsychotics benefited from this shift away from Zyprexa by either increasing prescriptions (Abilify, Geodon) or stemming a downward trend (Risperdal), Seroquel prescribing increased the most substantially over the time period. We suspect that the shift to Seroquel was largely based on the combination of a more favorable side effect profile coupled with an aggressive clinical program to expand product indications/uses.[9]

Despite all of the negative press regarding atypical antipsychotics, perphenazine experienced a slight loss in market share of approximately 1% which suggests that the neurological side effects associated with first generation antipsychotics (e.g., extrapyramidal signs and tardive dyskinesia) are sufficiently common and problematic that physicians did not shift behavior away from the atypical agents upon publication of evidence associating weight gain with the second generation agents or the equivalent efficacy data demonstrated with agents other than Zyprexa in the CATIE study.[10]

One limitation of this analysis was that Verispan data was not available until January 2002, one year after the initiation of the CATIE study. Although this analysis

could not parallel the conduct of the CATIE study, the analysis of the communication literature suggests that there were no substantial media events that occurred between January 2001 and January 2002 that would likely have had an effect on prescribing.

Another limitation of this analysis is the lack of longer-term data following the publication of the CATIE study results in September 2005. Although the data is limited, the trend information exhibited in the few months post September 2005 is suggestive of a continuation of stabile TRx volume through December 2005. It is difficult to discern, however, whether the share of individual products has continued on previous trends or, perhaps, whether there is a modest stabilization in the shift in share between Zyprexa and the other second-generation products.

As a follow-up to this analysis, it would be interesting to track further market behavior in the wake of the release of the CATIE study results as psychiatrists anticipate the release of the next round of results, scheduled for 2006. This follow-up analysis should start with Verispan prescription data from January 2006 once it becomes available. The publishing of the CATIE study results on September 22, 2005 included only top-line analysis of the data. Perhaps psychiatrists are eagerly awaiting the publication of subsequent analyses from this landmark study before actually implementing changes in their patient care and prescribing habits.

Conclusion

The analysis presented in this paper demonstrates the potential for clinical data to impact physician prescribing behavior. In this case, however, the information suggests that the more significant change in antipsychotic market prescribing behavior was brought on by media events surrounding the adverse side effects associated with top-selling atypical antipsychotics in 2003 rather than the release of study results from the CATIE Schizophrenia Study in September 2005.

References

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[2] Abboud, L. (July 27, 2005). The Next Phase in Psychiatry: Largest Ever Studies on Drugs for Depression, Schizophrenia Could Transform Treatment. The Wall Street Journal.

[3] CATIE (Clinical Antipsychotic Trials in Intervention Effectiveness). National Institute of Mental Health. Website.

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Case Study 2 – Contraceptives

Introduction

Clinical trials conducted in support of a New Drug Application are primarily randomized controlled trials conducted in narrowly defined patient populations as directed by regulatory requirements. The result of the stringent inclusion/exclusion criteria, limited size and diversity of the patient population being studied, combined with the short duration of Phase III studies limits the amount of data available on a drug's safety profile.[1] As a result, many serious safety issues only come to light after the product has been approved and used more widely both in terms of patient exposures and demographics. Two recent, highly publicized instances of unanticipated side effects ultimately resulting in product withdrawal include Merck's Vioxx and Biogen/Elan's Tysabri. Many other products have not been withdrawn, but rather have been the subject of Dear Doctor letters and Black Box Warnings; Ortho Evra is one such example of this type of product.

Ortho Evra, a product of Johnson & Johnson subsidiary Ortho-McNeil Pharmaceutical, was approved in November 20, 2001 as a once-a-week contraceptive patch for women. It was and still is the first transdermal hormonal patch to be approved, as well as the first non-invasive form of birth control that, when used correctly, is 99% effective. The Ortho Evra patch is worn for seven days releasing the hormones progesterone and estrogen directly into the blood before being replaced, for three weeks. The fourth week is treatment free, as with oral contraceptives.[2]

Deemed a "wonder drug" when it was launched with much fanfare and glitzy advertising in March 2002, Ortho Evra was touted as the most revolutionary drug after the oral contraceptive pill. In 2004, Ortho Evra prescriptions totaled more than 9.9 million with sales topping $411 million.[3] However, an Associated Press investigation

published in July 2005 reported that women on the Ortho Evra patch were three times more likely to die or be injured by a blood clot than women on the pill. The AP used the Freedom of Information Act to obtain adverse drug reaction reports for Ortho Evra from the Food and Drug administration (FDA) and reportedly found that out of the 23 cases in which death was the outcome, physicians reviewing the cases found 17 that appeared to be blood-clot-related, including 12 cases from 2004. The first fatality publicly blamed on Ortho Evra came in April 2005, when an autopsy found a blood clot had moved into the victim's lung and the medical examiner ruled that the clot was a side effect of the contraceptive patch that she was currently taking. FDA records show that 17 patch users between the ages of 17 and 30 years of age have suffered fatal heart attacks, blood clots, and possible strokes since August 2002.[4]

The initial merits of Ortho Evra were its mechanism of action whereby hormones are absorbed directly into the bloodstream, avoiding metabolism through the digestive system. Although this mechanism of action was initially considered to contribute to increased efficacy, it may ultimately have been Ortho Evra's downfall from a safety perspective due to prolonged exposure to a high dose of estrogen in the circulatory system. In comparison, oral contraception is taken orally and enters the digestive tract first, with 50% of the estrogen being eradicated through the digestive system within a few hours of taking the pill.[5]

On November 10, 2005, the FDA announced and Ortho McNeil confirmed the approval of updated labeling for Ortho Evra, warning healthcare providers and consumers about the increased risk. The move was a result of the FDA's review of two sponsor-funded studies directly comparing the levels of estrogen in users of Ortho Evra with those using a typical oral contraceptive. The analysis showed that women who use Ortho Evra might be exposed to 60% more estrogen than those using a typical birth control pill,

which contains 35 micrograms of estrogen. Higher levels of estrogen may put some women at increased risk for getting blood clots.[6] In the same announcement, the FDA indicated that Ortho McNeil is currently conducting studies to evaluate the risks of developing serious blood clots in women using Ortho Evra versus the risks caused by traditional birth control pills.

The FDA, however, does not know if women using Ortho Evra are at a higher risk for serious side effects than if they are using a traditional birth control pill. There is currently no epidemiological data available to determine whether safety and efficacy with the transdermal route of administration would be different than with the oral route. As a result of this predicament and in addition to the fact that the safety of medications delivered by the mechanism of transdermal patches seemingly present common problems, on March 2, 2006 the FDA announced that it would launch an "exhaustive review" regarding the safety of medicated patches, including Ortho Evra.[7]

In the wake of the FDA and Ortho-McNeil press releases and the FDA advisory, The Wall Street Journal (WSJ) reported on November 22, 2005 that there have been several reports of physicians and other healthcare providers curtailing or suspending the prescribing of Ortho Evra to patients. The WSJ reported that some physicians and health care providers "don't want to take any chances" with Ortho Evra and are no longer offering new prescriptions. Others are advising their patients who currently are using Ortho Evra to switch to another form of birth control. [7]

To examine the impact of the FDA's action as well as publicity from the general press, this analysis examines prescribing habits over a four-year period, starting two months after Ortho Evra's 2001 regulatory approval and continuing through January 2006, following communication of safety concerns.

Methods

The approach to investigating the impact of widespread publicity regarding the safety of Ortho Evra consisted of two activities: 1) identification of the key communications surrounding safety concerns with Ortho Evra and, 2) time series analysis of TRx data for Ortho Evra in isolation, and in comparison to three other oral contraceptive launch brands during the January 2002 to January 2006 timeframe – Yasmin (pill), Ortho Tri-Cyclen Lo (pill), and Seasonale (pill). By selecting another Johnson & Johnson product, Ortho Tri-Cyclen Lo, as one of the comparison brands, we are also able to examine the impact on Ortho Evra independent of promotional resources.

January 2002 was chosen as a starting point for the analysis since 2002 is the year that Ortho Evra sales began, with product launch occurring two months after this date. January 2006 was selected as the end date because it was the most recent month of data available.

Total prescriptions (TRx) and market share (% of TRx) were obtained from January 2002 through January 2006 for the four contraceptive products of interest. Generic and "branded" generic contraceptives were not included in this analysis in order to eliminate confusion surrounding the conversion of patients from the brand name product to generic products. By including only branded products, the analysis focuses solely on products being actively promoted by sales representatives to support market share growth.

To identify media communications surrounding Ortho Evra, an Internet search was conducted in Google to identify media events in the November 2001 to March 2006 timeframe using the terms "Ortho Evra" (see Attachment C). Articles or references to articles contained within the following formats were excluded:

- Personal blogs (articles from "periodical type" blogs were included)

- Listings of ongoing litigation
- Articles not written in English

Results

Publicity on Safety of Ortho Evra

The analysis of media events identified eight major communications that could potentially influence physician-prescribing behavior:

- *Birth-control patch may have higher risk*, July 16, 2005
- *FDA Updates Labeling for Ortho Evra Contraceptive Patch; New Prescribing Information Announced For Ortho Evra® Birth Control Patch*, November 10, 2005
- *Birth Control Patch Users Warned*, November 11, 2005
- *Some Doctors Stop Prescribing Ortho Evra Birth Control Patch After FDA Warning, Wall Street Journal Report*, November 22, 2005
- *Results Of Two Epidemiological Studies Provide Important New Clinical Information About The Safety Of ORTHO EVRA®*, February 16, 2006
- *Birth-Control Patch Users Risk Blood Clots*, February 17, 2006
- *Clot Risk for Birth-Control Patch Is Found to Be Double That of Pill*, February 18, 2006
- *Warning issued for Ortho Evra birth control patch*, February 21, 2006

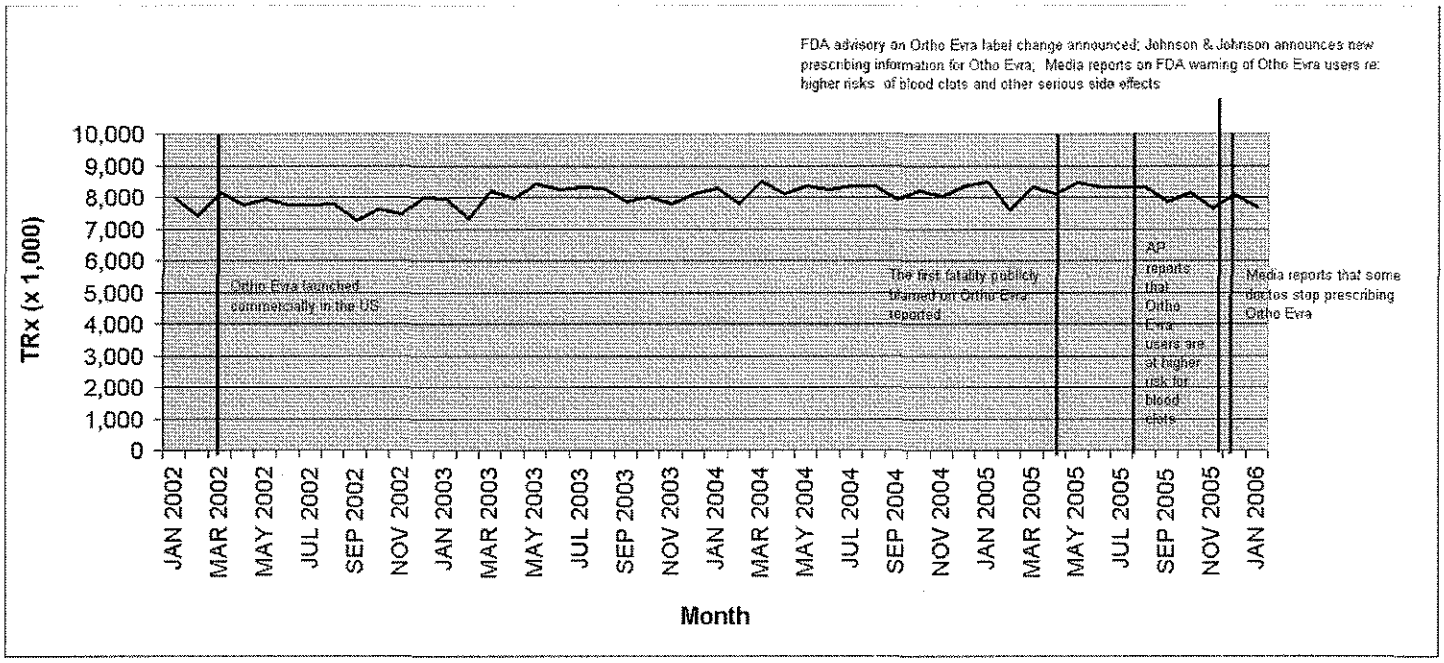
As can be seen from the dates of the communications listed above, reporting on the safety issues regarding Ortho Evra were still very much unfolding at the time that this paper was written. The Associated Press article on Ortho Evra users being at higher risks of blood clots in July 2005 was the first major media report found regarding the Ortho Evra safety concerns. This article was based on FDA adverse drug reaction reports for Ortho Evra obtained by the AP through the Freedom of Information Act. The AP focused on data from 2004, when Ortho Evra's popularity was at its peak. Starting in November 2005 with the FDA advisory on the Ortho Evra label change and continuing through the present day with the FDA's announcement that they will be reviewing the safety of all types of medicated patches, including Ortho Evra, the publicity regarding this issue has been very prominent and widespread in the popular press.

Prescription Data

Figure 1 presents total prescriptions (TRx) from January 2002 to January 2006, inclusive, for all female contraceptives, excluding condoms, graphed concurrently with the timing of four of the eight key data communications listed above. Since the most current month of Verispan data available for this analysis was January 2006, four of the eight communications listed above post-January 2006 could not be graphed. Additionally, although it was not identified as a standalone communication in the Internet search for this analysis, a time point for the first fatality publicly blamed on Ortho Evra that was reported, April 2005, has been added to Figures 1 and 2 as the event was referred to in one of the identified communications. A time point for the commercial launch of Ortho Evra in March 2002 has been added to Figures 1 and 2 as a reference.

As can be seen in Figure 1, TRx for contraceptives has been steady at around 8,000,000 prescriptions per year for the 2002 to early 2006 timeframe, which suggests that much of the change in volume across agents observed during this timeframe is really a shift in prescribing behavior among products rather than an expansion in the market size.

Figure 1 - Contraceptives TRx January 2002 to January 2006



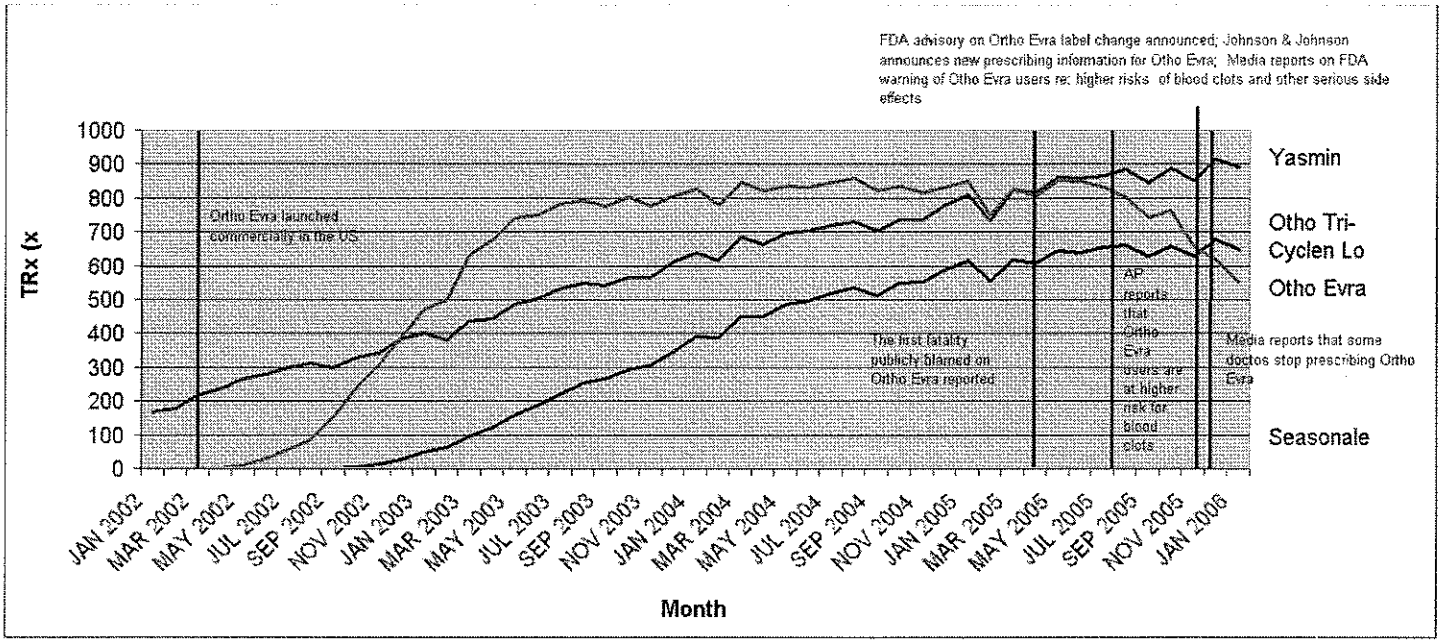
Source: Verispan VONA, Contraceptives, Feb 2006

Figure 2 presents total prescriptions (TRx) from January 2002 to January 2006, inclusive, for the four contraceptive products commercially launched between 2001 and 2003: Yasmin, Ortho Tri-Cyclen Lo, Ortho Evra, and Seasonale. As can be seen in Figure 2, there is a significant downward trend of TRx for Ortho Evra post-May 2005, one month after the first fatality publicly blamed on Ortho Evra was reported. This downward trend continued and even increased in rate through January 2006. Noticeably, the TRx trending for Ortho Tri Cyclen Lo and Yasmin in relation to Ortho Evra basically stayed the same. Both products continued their steady upward trends in TRx post-launch and it can be noted that these trends are very similar to one another and both represent a standard TRx growth rate for a newly marketed contraceptive. Ortho Evra, on the other hand, experienced an explosive growth rate between its launch in March 2002 through August 2004, when it was at the height of its popularity. This non-standard trend in TRx growth rate is most likely a result of the aggressive marketing campaign initiated by

Johnson & Johnson that accompanied the product's launch as well as the popularity stemming from the novelty of a contraceptive patch, the first and still only one of its kind.

The downward trending of Ortho Evra TRx post-May 2005 through January 2006 and the lack of accelerated growth of the Ortho Tri Cyclen Lo and Yasmin growth rate in response indicates that consumers were not switching to either one of these products but rather to other older, generic contraceptive methods with more robust longitudinal safety data. Further investigation on this point is warranted in order to draw any definitive conclusions regarding specific products that may have benefited from the Ortho Evra decline. Retail pharmacy data post-January 2006 needs to be observed in order to more fully characterize the impact of the publicity regarding Ortho Evra; including mapping the four remaining media communications that were unable to be graphed due to data constraints. However, as can be seen from Figure 2, Ortho Evra TRx began trending downward in May 2005 and increased in rate of decline in October 2005, continuing through the data cut-off in January 2006. Since this pattern of decline has been in motion now for over nine months, and it is likely that the additional communications mentioned previously will only continue to sustain or perhaps accelerate further this trend, one can safely conclude that there does seem to be a significant shift in the prescribing trend of Ortho Evra based on this publicity regarding safety concerns.

Figure 2 – Individual Contraceptives TRx January 2002 to January 2006



Source: Verispan VONA, Contraceptives, Feb 2006

Figure 3 presents similar data for the four contraceptive products represented as percent share between each of the four products. What can be seen from this graphic is a significant decline in share for Ortho Evra. In May 2005, Ortho Evra was ranked second to Yasmin by a small margin. It was separated by a 9.5% margin from the other Johnson & Johnson launch brand, Ortho Tri Cyclen Lo, which was ranked number 3 of 4 of the branded products at the time. By the end of January 2006, Ortho Evra had fallen to number 3 behind number 2 ranked Ortho Tri Cyclen Lo, separated by a 4% margin. Ortho Evra lost a total of 10 percentage points in share compared to the other three products over this nine-month period.

Figure 3 – Contraceptives Share (% of TRx) May 2005 to January 2006

Product Brand	MAY 2005	JUN 2005	JUL 2005	AUG 2005	SEPT 2005	OCT 2005	NOV 2005	DEC 2005	JAN 2006
YASMIN	35.5%	35.6%	35.8%	36.5%	37.0%	37.2%	38.5%	40.0%	41.1%
ORTHO TRI CYCLEN LO	26.5%	26.4%	27.0%	27.3%	27.5%	27.7%	28.4%	29.6%	29.9%
ORTHO EVRA	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SEASONALE	3.0%	2.9%	2.8%	3.0%	3.0%	3.1%	3.3%	3.3%	3.5%

Source: Verispan VONA, Contraceptives, Feb 2006

Discussion

The results of this analysis demonstrate a significant shift in prescribing behavior away from Ortho Evra that appears to be well correlated with the timing of negative press regarding its safety. While the other three contraceptive products do not appear to have benefited directly from this shift in prescribing activity, it is likely that other older, generic birth control methods with more comprehensive safety data have benefited with slight increases in market share.

The trend information exhibited in the wake of the reporting in April 2005 of the first fatality publicly blamed on Ortho Evra is suggestive of a significant shift in prescribing activity, which is continuing at the present time. One limitation of this analysis was that Verispan data was not available after January 2006, which is when half of the identified communications that could potentially influence physician-prescribing behavior were released. However, as Figure 2 demonstrates the downward trend in TRx for Ortho Evra was set in motion eight months prior to the data cut-off for this analysis, in May 2005. So, there was substantial data available from which to base this conclusion. As a follow-up to this analysis, it would be interesting to track further the continuing behavior in TRx for these four contraceptive products in the months post-January 2006 to assess the impact of the FDA's review of medicated patches, reported on in March 2006,

as well as the continuing publicity regarding the safety concerns of Ortho Evra, released seemingly on a daily basis.

Conclusion

The analysis of contraceptives presented in this case study demonstrates the potential for publicity surrounding safety concerns of a marketed product to impact physician prescribing behavior. The information suggests a significant shift in physician prescribing behavior in response to negative publicity regarding the safety of Ortho Evra. However, as was demonstrated in the first case study, the information suggests that the more significant change in contraceptive prescribing behavior was brought on by the initial media event in July 2005 surrounding the increased risk of blood clots for users of Ortho Evra, rather than the FDA and Ortho-McNeil press releases and the FDA advisory released in November 2005.

References

[1] Stephenson M.D., H. (2005). Strategic Research: A Practical Handbook for Phase IIB and Phase IV Clinical Studies. Durham, NC: Quintiles Transnational.
[2] http://www.orthoevra.com/html/pevr/home.jsp
[3] Steven DiJoseph, "Transdermal Patches: An Innovative Drug Delivery System That Has Raised Serious Safety Concerns," Newsinferno.com, March 6, 2006.
[4] Martha Mendoza, "Birth Control Patch May Have Higher Risk," The Associated Press, July 16, 2005.
[5] http://www.contraceptiononline.org/slides/slide01.cfm?q=mechanism+of+action&pg=0
[6] "FDA Updates Labeling for Ortho Evra Contraceptive Patch," FDA News, http://www.fda.gov/bbs/topics/news/2005/NEW01262.html
[7] Henry J. Kaiser Family Foundation, "FDA Will Review Safety of Medicated Patches, Including Ortho Evra," kaisernetwork.org, March 7, 2006.

Conclusion

The analyses presented in this paper have demonstrated that physician-prescribing behavior for both antipsychotics and contraceptives, two therapeutic categories with very different prescribing bases, was influenced by media events but not the events that were initially targeted in each analysis; the publication of the CATIE study results and the FDA's advisory on updated labeling for Ortho Evra. In both case studies, the impact on physician-prescribing behavior was pre-empted by earlier mass media events regarding adverse side effects associated with top-selling atypical antipsychotics, specifically Zyprexa, and the increased risk of blood clots for users of Ortho Evra. Nevertheless, both analyses demonstrate that the media, in one form or another has the capability of permeating physician practice as demonstrated by physicians within both of these therapeutic classes.

Attachment A

Log of NIMH Schizophrenia Study-Related Media Events during the Time Period January 2001 – March 2006

Search Text	Article	Author	Date
"Dr. Jeffrey Lieberman + CATIE"	The Next Phase in Psychiatry: Largest Ever Studies on Drugs for Depression, Schizophrenia Could Transform Treatment	The Wall Street Journal	7/27/05
Link:	http://www.paxilprogress.org/forums/showthread.php?t=12839 (alternate link to free copy of article)		
"Dr. Jeffrey Lieberman + CATIE"	CATIE Study - New Schizophrenia Treatment Standards Coming	Schizophrenia Daily News Blog	7/27/05
Link:	http://www.schizophrenia.com/sznews/archives/002172.html		
"Dr. Jeffrey Lieberman + CATIE"	Next Phase in Psychiatry? Or, NIMH Effort to Rescue Bad Drugs - WSJ	Alliance for Human Research Protection	7/29/05
Link:	http://www.ahrp.org/infomail/05/07/29a.php		
"Dr. Jeffrey Lieberman + CATIE"	Study Shows Older, Cheaper Drug is Effective as Newer Antipsychotic Meds	National Institutes of Health	9/2005
Link:	http://www.nih.gov/news/radio/sep2005/09252005catie.htm		
"Effectiveness of Antipsychotic Drugs in Patients"	NIMH study to guide treatment choices for schizophrenia	Medical News Today	9/10/05
Link:	http://www.medicalnewstoday.com/medicalnews.php?newsid=30861		
"Effectiveness of Antipsychotic Drugs in Patients"	Study finds old, new schizophrenia drugs about equal	Science Blog	9/19/05
Link:	http://www.scienceblog.com/cms/study_finds_old_new_schizophrenia_drugs_about_equal_8936		
"Effectiveness of	Zyprexa Edges Four Other Agents With Modest Benefit for Schizophrenia	Medpage Today	9/19/05

Antipsychotic Drugs in Patients"			
Link:	http://www.medpagetoday.com/Psychiatry/GeneralPsychiatry/tb/1758		
"Dr. Jeffrey Lieberman + CATIE"	Landmark UNC-led schizophrenia study finds older drug comparably effective to newer drugs	The University of North Carolina at Chapel Hill	9/19/05
Link:	http://www.unc.edu/news/archives/sep05/catie091905.htm		
"Dr. Jeffrey Lieberman + CATIE"	Schizophrenia Drugs Still Fall Short Newer ones not much more effective than older medicines, a new study finds.	Healthfinder	9/19/05
Link:	http://www.healthfinder.gov/news/newsstory.asp?docID=528062		
"Dr. Jeffrey Lieberman + CATIE"	Study finds no best schizophrenia drug	The Arizona Republic	9/19/05
Link:	http://www.azcentral.com/health/wellness/articles/0919sch-CR.html		
"Dr. Jeffrey Lieberman + CATIE"	Differences seen in anti-psychotic drugs	Monsters and Critics	9/19/05
Link:	http://news.monstersandcritics.com/health/article_1049163.php/Differences_seen_in_anti-psychotic_drugs		
"Effectiveness of Antipsychotic Drugs in Patients"	Are Anti-psychotic Medications All the Same?	Dare to Dream	9/19/05
Link:	http://dej.us/mt/archives/mental_health_treatment/antipsychotic_medication/		
"Effectiveness of Antipsychotic Drugs in Patients"	NIMH study to guide treatment choices for schizophrenia	EurekAlert	9/19/05
Link:	http://www.eurekalert.org/pub_releases/2005-09/niom-nst091905.php		
"Effectiveness of Antipsychotic Drugs in Patients"	CATIE Results - Perphenazine almost as good as newer drugs	Schizophrenia Daily News Blog	9/20/05

Link:	http://www.schizophrenia.com/sznews/archives/002424.html		
"Effectiveness of Antipsychotic Drugs in Patients"	DON'T BE A BIG PHARMA VICTIM - USE COMMON SENSE	Dr. Carolyn Dean, MD, ND and Elissa Meininger	9/20/05
Link:	http://www.newswithviews.com/Dean/carolyn16.htm		
"Dr. Jeffrey Lieberman + CATIE"	Study Finds Little Advantage In New Schizophrenia Drugs	The New York Times	9/20/05
Link:	http://psychrights.org/Articles/NYTimesAtypicalsnobetter.html		
"Effectiveness of Antipsychotic Drugs in Patients"	Antipsychotics - Newer Is Not Always Better	Clinical Cases and Images - Blog	9/20/05
Link:	http://casesblog.blogspot.com/2005/09/antipsychotics-newer-is-not-always.html		
"Dr. Jeffrey Lieberman + CATIE"	Tough Choices in Treating Schizophrenia	National Public Radio	9/20/05
Link:	http://www.npr.org/templates/story/story.php?storyId=4855599		
"Dr. Jeffrey Lieberman + CATIE"	Old schizophrenia drugs as good as new	myDNA	9/20/05
Link:	http://www.mydna.com/resources/meds/resources/news/200509/news_20050920_schrx.html		
"Effectiveness of Antipsychotic Drugs in Patients"	STUDY FINDS LITTLE ADVANTAGE IN NEW SCHIZOPHRENIA DRUGS	National Center for Policy Analysis	9/21/05
Link:	http://www.ncpa.org/newdpd/dpdarticle.php?article_id=2277		
"Effectiveness of Antipsychotic Drugs in Patients"	Meds Alert: Old schizophrenia drug stands up to new ones	Science News Online	9/24/05
Link:	http://www.sciencenews.org/articles/20050924/fob1ref.asp		
"Dr. Jeffrey	NIMH study to guide treatment choices for schizophrenia	PsychLinks Online	9/27/05

Lieberman + CATIE"		Psychology Forum	
Link:	http://www.psychlinks.ca/phpbb/viewtopic.php?t=3029&		
"Effectiveness of Antipsychotic Drugs in Patients"	National Institute of Mental Health Study Compares Treatments for Schizophrenia	CAREMARK – Trends Rx – Drug Pipeline and News	9/30/05
Link:	http://www.caremark.com/portal/asset/Pipeline-September30.pdf		
"Dr. Jeffrey Lieberman + CATIE"	Differences Seen In Anti Psychotic Drugs	Applesforhealth.com	9/30/05
Link:	http://www.applesforhealth.com/MentalHealth/dsapd7.html		
"Effectiveness of Antipsychotic Drugs in Patients"	APA Says CATIE Schizophrenia Study Argues for Full Range of Treatment Options	PedsCare Children's Mental Health Initiatives	10/2005
Link:	http://www.aap.org/commpeds/dochs/mentalhealth/MH-OCT2005.pdf		
"Effectiveness of Antipsychotic Drugs in Patients"	Most patients taking second-generation (atypical) antipsychotic drugs discontinued their treatment because of inefficacy or intolerable side effects, or for other reasons	Wonca Online	10/4/05
Link:	http://www.globalfamilydoctor.com/search/GFDSearch.asp?itemNum=4647		
"Effectiveness of Antipsychotic Drugs in Patients"	Top Abstracts in Schizophrenia 10/06/2005	Doctor's Guide	10/6/05
Link:	http://www.docguide.com/news/content.nsf/news/34ED8BD7D55E8EC385257093000C5314		
"Effectiveness of Antipsychotic Drugs in Patients"	CATIE Comes To Surprising Conclusions	Schizophrenia Research Forum	10/16/05
Link:	http://www.schizophreniaforum.org/new/detail.asp?id=1198		
"Effectiveness of Antipsychotic Drugs in Patients"	Comments on Paper and Primary News *Comments by mostly MDs on the study paper via the article listed above.	Schizophrenia Research Forum	10/18/05

Link:	http://www.schizophreniaforum.org/pap/annotation.asp?powID=59284		
"Effectiveness of Antipsychotic Drugs in Patients"	Government Antipsychotic Study Finds No Clear Winner in `Horse Race'	Psychiatric News	10/21/05
Link:	http://pn.psychiatryonline.org/cgi/content/full/40/20/1		
"Effectiveness of Antipsychotic Drugs in Patients"	Antipsychotics in the elderly: Reducing risks of stroke and death	Current Psychiatry Online	11/2005
Link:	http://www.currentpsychiatry.com/article_pages.asp?AID=2825&UID=		
"Effectiveness of Antipsychotic Drugs in Patients"	Little Difference Found in Schizophrenia Drugs	Caring and Sharing	11/2005
Link:	http://www.namiphoenix.org/SchizophreniaDrugs.html		
"Effectiveness of Antipsychotic Drugs in Patients"	Effectiveness of antipsychotic drugs for chronic schizophrenia investigated	NewsRx	11/7/05
Link:	http://www.newsrx.com/issue_article/5W/2005-11-07/1107200533313335W.html		
"Effectiveness of Antipsychotic Drugs in Patients"	Top Abstracts in Schizophrenia 11/17/2005	Doctor's Guide	11/17/05
Link:	http://www.docguide.com/news/content.nsf/news/745A6736C255DC2C852570BD00116AB4		
"Effectiveness of Antipsychotic Drugs in Patients"	National Council Response to CATIE Study on Antipsychotics	National Council for Community Behavioral Healthcare	2005
Link:	http://www.nccbh.org/WHO/INDUSTRY/CATIE.HTM		
"Effectiveness of Antipsychotic Drugs in Patients"	Prescribing Review - Drugs Used in Mental Health	NHS Prescription Pricing Authority	UNK
Link:	http://www.ppa.org.uk/news/pact-092005.htm		
"Effectiveness of	Report on the Escalating International	Citizens Commission on	UNK

Antipsychotic Drugs in Patients"	Warnings on Psychiatric Drugs	Human Rights (EClub)	
Link:	http://www.campaignfortruth.com/Eclub/241005/CTM%20-%20ADHD%20drugs%20don't%20work.htm		
"Effectiveness of Antipsychotic Drugs in Patients"	Report on the Escalating International Warnings on Psychiatric Drugs	Citizens Commission on Human Rights International	UNK
Link:	http://h11.protectedsite.net/files/8011/drug_report.pdf		
"Effectiveness of Antipsychotic Drugs in Patients"	Newer antipsychotics similar to older agents (CATIE)	InfoPOEMs – The Clinical Awareness System	UNK
Link:	http://www.infopoems.com/infopoems/showPOEM.cfm?ID=71105		
"Dr. Jeffrey Lieberman + CATIE"	Lost In Translation: What We Really Learned From CATIE	Psychiatric News	1/6/06
Link:	http://pn.psychiatryonline.org/cgi/content/full/41/1/20		
"Dr. Jeffrey Lieberman + CATIE"	Dr. Lieberman and Colleagues Reply	American Journal of Psychiatry	3/2/06
Link:	http://ajp.psychiatryonline.org/cgi/content/full/163/3/555-a		
"Dr. Jeffrey Lieberman + CATIE"	The CATIE Study	American Journal of Psychiatry	3/10/06
Link:	http://ajp.psychiatryonline.org/cgi/content/full/163/3/554		

ARTICLES OR REFERENCE TO ARTICLES CONTAINED WITHIN THE FOLLOWING FORMATS WERE EXCLUDED: personal blogs (articles from "periodical type" blogs were included), listings of ongoing clinical trials (**unless** preliminary results were mentioned as a part of the listing), listings of the article and/or abstract itself, listings of ongoing litigation, speaking engagement announcements where the article is referenced, articles in non-English languages.

Attachment B

Log of Media Events Related to Zyprexa and Weight Gain during the Time Period January 2001 – March 2006

Search Text	Article	Author	Date
"Weight Gain + Zyprexa"	Increased Prevalence of Diabetes Among Patients Receiving Antipsychotic Drugs	HealthyPlace.com	5/20/03
Link:	http://www.healthyplace.com/Communities/Thought_Disorders/schizo/news/diabetes_antipsychotics.asp		
"Weight Gain + Zyprexa"	Most Atypical Antipsychotics Tied to Increase in Diabetes	HealthyPlace.com	8/22/03
Link:	http://www.healthyplace.com/Communities/Thought_Disorders/schizo/news/diabetes_antipsychotics_2.asp		
"Weight Gain + Zyprexa"	FDA Seeks Diabetes Warning on All Antipsychotic Drugs	HealthyPlace.com	9/18/03
Link:	http://www.healthyplace.com/Communities/Thought_Disorders/schizo/news/diabetes_antipsychotics_3.asp		
"Weight Gain + Zyprexa"	Weight Gain is Potential Problem in Patients Switched from Risperidal to Zyprexa	HealthyPlace.com	10/16/03
Link:	http://www.healthyplace.com/Communities/Thought_Disorders/schizo/news/weight_gain_antipsychotics_2.asp		
"Weight Gain + Zyprexa"	Atypical Antipsychotic Drugs Linked to Diabetes	HealthyPlace.com	11/3/03
Link:	http://www.healthyplace.com/Communities/Thought_Disorders/schizo/news/diabetes_antipsychotics_4.asp		
"Weight Gain + Zyprexa"	Zyprexa Efficacy Questionable	Online Lawyer Source	11/25/03
Link:	http://www.onlinelawyersource.com/news/zyprexa.html		
"Weight Gain + Zyprexa"	Eli Lilly and Co. Shares Fall Following Zyprexa Study	Online Lawyer Source	11/26/03
Link:	http://www.onlinelawyersource.com/news/zyprexa2.html		
"Weight Gain + Zyprexa"	Antipsychotic Drugs Raise Diabetes Risk	HealthyPlace.com	1/27/04
Link:	http://www.healthyplace.com/Communities/Thought_Disorders/schizo/news/diabetes_antipsychotics_5.asp		
"Weight Gain +	Diabetes Risk Increased by Antipsychotic Drugs	Online Lawyer Source	1/28/04

Zyprexa"			
Link:	http://www.onlinelawyersource.com/news/zyprexa4.html		
"Weight Gain + Zyprexa"	Elderly Warned of Off-Label Zyprexa Use	Online Lawyer Source	2/10/04
Link:	http://www.onlinelawyersource.com/news/zyprexa5.html		
"Weight Gain + Zyprexa"	Zyprexa Lawsuits Filed Due to Serious Cases of Diabetes and Pancreatitis	Online Lawyer Source	3/19/04
Link:	http://www.onlinelawyersource.com/news/zyprexa-diabetes.html		
"Weight Gain + Zyprexa"	Zyprexa Class Action Lawsuit Announced	Online Lawyer Source	4/19/04
Link:	http://www.onlinelawyersource.com/news/zyprexa-lawsuit.html		
"Weight Gain + Zyprexa"	Nationwide Zyprexa class action lawsuit filed	Defective Drugs Adrugrecall.com	5/21/04
Link:	http://www.adrugrecall.com/newsletter/jun04/zyprexa.html		
"Weight Gain + Zyprexa"	Zyprexa Sales Hurting Because of Safety Concerns	Online Lawyer Source	7/8/04
Link:	http://www.onlinelawyersource.com/news/zyprexa-safety.html		
"Weight Gain + Zyprexa"	Eli Lilly Sued for Its Zyprexa Drug	Online Lawyer Source	7/31/04
Link:	http://www.onlinelawyersource.com/news/zyprexa-claim.html		
"Weight Gain + Zyprexa"	Antipsychotics linked to serious adulthood diseases	Defective Drugs Adrugrecall.com	10/25/04
Link:	http://www.adrugrecall.com/newsletter/nov04/zyprexa-safety.html		
"Weight Gain + Zyprexa"	Eli Lilly using legal tactic to stall Zyprexa lawsuits	Online Lawyer Source	11/7/04
Link:	http://www.onlinelawyersource.com/news/zyprexa-legal.html		
"Weight Gain + Zyprexa"	Zyprexa lawsuit on behalf of Canadians filed	Defective Drugs Adrugrecall.com	2/5/05
Link:	http://www.adrugrecall.com/news/zyprexa-lawsuit.html		
"Weight Gain +	Zyprexa warning issued	Defective Drugs	4/11/05

Zyprexa"		Adrugrecall.com	
Link:	http://www.adrugrecall.com/news/zyprexa-warning.html		
"Weight Gain + Zyprexa"	Elderly patients warned of Zyprexa risks	Defective Drugs Adrugrecall.com	4/12/05
Link:	http://www.adrugrecall.com/news/zyprexa-elderly.html		
"Weight Gain + Zyprexa"	Zyprexa linked with Diabetes	National Alliance for the Mentally Ill – Santa Cruz County	10/14/05
Link:	http://www.namiscc.org/News/2003/Summer/ZyprexaLinkToDiabetes.htm		
"Weight Gain + Zyprexa"	Zyprexa Weight Gain: Medical Information	Monheit Law	UNK
Link:	http://www.monheit.com/zyprexa/medical.shtml		
"Weight Gain + Zyprexa"	Zyprexa Weight Gain	Online Lawyer Source	UNK
Link:	http://www.onlinelawyersource.com/zyprexa/weight.html		
"Weight Gain + Zyprexa"	The Side Effects of Zyprexa May Be Deadly	Class Action America Online	UNK
Link:	http://www.classactionamerica.com/Current-Cases/zyprexa-side-effects.asp		
"Weight Gain + Zyprexa"	Zyprexa Warning	Defective Drugs Adrugrecall.com	UNK
Link:	http://www.adrugrecall.com/zyprexa/warning.html		
"Weight Gain + Zyprexa"	Zyprexa Medicaid Gravy Train Derailed	OpEdNews.com	2/21/06
Link:	http://www.opednews.com/articles/genera_evelyn_p_060221_zyprexa_medicaid_gra.htm		

ARTICLES OR REFERENCE TO ARTICLES CONTAINED WITHIN THE FOLLOWING FORMATS WERE EXCLUDED:
personal blogs (articles from "periodical type" blogs were included) and articles in non-English languages.

Attachment C

Log of Media Events Related to Ortho Evra during the Time Period January 2002 - March 2006

Search Text	Article	Author	Date
Ortho Evra	FDA Approves First Hormonal Contraceptive Skin Patch	Food and Drug Administration	11/20/01
Link:	http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01119.html		
Ortho Evra	First Birth Control Patch, ORTHO EVRA™ (norelgestromin/ethinyl estradiol transdermal system) Now Available by Prescription	Johnson & Johnson	4/30/02
Link:	http://www.jnj.com/news/jnj_news/20020430_1425.htm		
Ortho Evra	Birth-control patch may have higher risk	Associated Press (reported by The Boston Globe)	7/16/05
Link:	http://www.boston.com/yourlife/health/women/articles/2005/07/16/birth_control_patch_may_have_higher_risk/?page=full		
Ortho Evra	FDA Updates Labeling for Ortho Evra Contraceptive Patch (Press Release)	Food and Drug Administration	11/10/05
Link:	http://www.fda.gov/bbs/topics/news/2005/NEW01262.html		
Ortho Evra	New Prescribing Information Announced For Ortho Evra® Birth Control Patch	Johnson & Johnson	11/10/05
Link:	http://www.jnj.com/news/jnj_news/20051111_091549.htm		
Ortho Evra	FDA Issues Warning Against J&J's Ortha Evra Birth Control Patch	kaisernetwork.org.	11/11/05
Link:	http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=33664		
Ortho Evra	New Birth Control Patch Warning	Associated Press (reported by NBC News 11)	11/11/05
Link:	http://www.11alive.com/news/health/health_article.aspx?storyid=71799		
Ortho Evra	Do Not Use the Ortho Evra Birth Control Patch	Public Citizen	11/11/05
Link:	http://www.citizen.org/pressroom/release.cfm?ID=2081		
Ortho Evra	Birth Control Patch Users Warned	CBS News	11/11/05
Link:	http://www.cbsnews.com/stories/2005/11/11/earlyshow/health/health_news/main1037611.shtml		

Ortho Evra	Some Doctors Stop Prescribing Ortho Evra Birth Control Patch After FDA Warning, Wall Street Journal Reports	kaisernetwork.org.	11/22/05
Link:	http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=33884		
Ortho Evra	Results Of Two Epidemiological Studies Provide Important New Clinical Information About The Safety Of ORTHO EVRA®	Johnson & Johnson	2/16/06
Link:	http://www.jnj.com/news/jnj_news/20060217_093331.htm		
Ortho Evra	Birth-Control Patch Users Risk Blood Clots	Washington Post	2/16/06
Link:	http://www.washingtonpost.com/wp-dyn/content/article/2006/02/17/AR2006021700011.html		
Ortho Evra	Evidence on Ortho Evra Patch Thrombosis Risk Is Contradictory	Medpage today	2/17/06
Link:	http://www.medpagetoday.com/ProductAlert/Prescriptions/tb/2697		
Ortho Evra	Manufacturer Releases Conflicting Studies Concerning Birth Control Patch Users' Risk of Developing Blood Clots	kaisernetwork.org.	2/17/06
Link:	http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=35473		
Ortho Evra	Birth-Control Patch Users Risk Blood Clots	Associated Press (reported by ABC News)	2/17/06
Link:	http://abcnews.go.com/Health/wireStory?id=1630203		
Ortho Evra	Birth-control patch linked to blood clots	Chicago Tribune	2/17/06
Link:	http://www.chicagotribune.com/news/nationworld/chi-0602170115feb17,1,6644359.story?coll=chi-newsnationworld-hed		
Ortho Evra	Study: Clot risk doubles with birth control patch	Chicago Sun-Times	2/17/06
Link:	http://www.suntimes.com/output/health/cst-nws-patch17.html		
Ortho Evra	Birth Control Patch: How Dangerous Is It?	ABC Naws	2/17/06
Link:	http://abcnews.go.com/Health/story?id=1631709&page=1		
Ortho Evra	Birth-Control Patch May Boost Risk of Blood Clots	Forbes	2/17/06
Link:	http://www.forbes.com/lifestyle/health/feeds/hscout/2006/02/17/hscout531096.html		
Ortho Evra	Study links birth control patch to clots	Newark Star Ledger, NJ	2/17/06
Link:	http://www.nj.com/business/ledger/index.ssf?/base/business-0/1140241877241540.xml&coll=1		
Ortho Evra	FDA: More study needed on birth control patch risk	ABC News	2/17/06
Link:	http://abcnews.go.com/US/wireStory?id=1632130		
Ortho Evra	J&J unit says mixed blood-clot risk on birth-control patch	CBS MarketWatch	2/17/06
Link:	http://www.marketwatch.com/News/Story/Story.aspx?guid=%7B05699A8E%2D5EF6%2D4293%2D926E%2D0E185DB5B130		

	%7D&siteid=google&keyword=		
Ortho Evra	Birth Control Patch May Up Clot Risk	WebMD	2/17/06
Link:	http://www.webmd.com/content/article/118/113151.htm		
Ortho Evra	Clot risk may rise for women on patch	Houston Chronicle	2/17/06
Link:	http://www.chron.com/disp/story.mpl/health/3668392.html		
Ortho Evra	Clot Risk for Birth-Control Patch Is Found to Be Double That of Pill	The New York Times	2/18/06
Link:	http://select.nytimes.com/gst/abstract.html?res=F50D13F83B5A0C7B8DDDAB0894DE404482		
Ortho Evra	Clot of Trouble	New York Post	2/18/06
Link:	http://www.nypost.com/news/nationalnews/60101.htm		
Ortho Evra	FDA Official Calls Results of Ortho Evra Birth Control Patch Studies 'Preliminary'; No Regulatory Action Expected	kaisernetwork.org.	2/21/06
Link:	http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=35514		
Ortho Evra	Warning issued for Ortho Evra birth control patch	CNN	2/21/06
Link:	http://www.cnn.com/HEALTH/library/DI/00047.html		
Ortho Evra	FDA to look into safety of medicated patches	The State, SC	3/6/06
Link:	http://www.thestate.com/mld/thestate/news/nation/14035435.htm		
Ortho Evra	FDA Will Review Safety of Medicated Patches, Including Ortho Evra	kaisernetwork.org.	3/7/06
Link:	http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=35820		
Ortho Evra	FDA Will Review Safety Of Medicated Patches, Including Ortho Evra	Medical News Today	3/9/06
Link:	http://www.medicalnewstoday.com/medicalnews.php?newsid=39066&nfid=rssfeeds		

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personal blogs (articles from "periodical type" blogs were included), listings of ongoing litigation, and articles in non-English languages.