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Examining The Effect Of Fda Approval Of Risperdal For Pediatric Use On Prescribing Trends From 2005-2008

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Antipsychotic Drug Prescribing Trends in Pediatric Populations

Examining the Effect of FDA Approval of Risperdal for Pediatric Use on Prescribing Trends from 2005-2008

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Abstract:

Prior to the 1990s, antipsychotic prescribing to children and adolescents was uncommon, given the scarcity of safety data and the high risk of developing extrapyramidal side effects. The emergence of second generation antipsychotics, changes in the epidemiology of pediatric mental health disorders, and expansion of antipsychotic drug use have facilitated the uptake of pediatric prescribing. The speed at which these drugs are being taken up by this vulnerable population is a concern. From 2002 to 2008, antipsychotic use in pediatric patients increased by 65% from 2.9 million to 4.8 million prescriptions.[1] Until 2006, all atypical antipsychotic prescribing was off-label, as these drugs were not approved by the FDA for use among children and adolescents. Using national retail prescription data of children and adolescents ages 0-17 obtained from IMS Health covering the years 2005-2008, the effect of the 2006 and 2007 FDA approvals of Risperdal for specific pediatric use was examined using segmented interrupted time-series regressions. The analysis reveals that the FDA approvals had a statistically significant level effect but no trend effect on Risperdal prescribing. In addition, there was a stronger level effect observed among non-mental health specialists compared to psychiatrists and other mental health specialists. The results of this study suggest that FDA pediatric approvals have an important role in legitimizing and facilitating prescribing, as there are some physicians who are reluctant to weigh the risks and benefits independently through off-label prescribing.

[1] Chai, G., Mehta, H., Moeny, D., & Governale, L. (2010). *Atypical Antipsychotic Drug Use in the US Outpatient Pediatric Population.* FDA. Silver Spring: Office of Surveillance and Epidemiology.

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I. Background

Introduction

Over the past two decades, the use of antipsychotic prescriptions has changed from treating adults with severe psychotic disorders to treating a wider range of disorders for a more diverse population. This change in prescribing has led to exponential increases in overall utilization and expenditure. As a result, spending on antipsychotic prescriptions is roughly $13.1 billion annually, exceeded only by lipid regulators, proton pumps, and antidepressants. Within the Medicaid program, antipsychotics have become the most costly drug class, accounting for more than 15% of overall drug spending. (Crystal, Olfson, Huang, Pincus, & Gerhard, 2009) Given these trends, it is becoming increasingly important to consider the appropriateness and possible consequences of antipsychotic prescribing to this new diverse population that now includes young children and adolescents. It is also equally important to ask who is being prescribed these antipsychotics, by whom, and for what reasons.

The origins of Antipsychotics

Antipsychotics (also referred to as *neuroleptics*) are a class of drugs used primarily to manage psychotic symptoms such as hallucinations, delusions, and disorganized thinking and behavior. (Ivanov & Charney, 2008) The first antipsychotic drug chlorpromazine (marketed under the name Thorazine) originated from Paul Erhlich's early work researching the antimalarial effects of phenothiazine derivatives in the late 1800s. First introduced in the late 1950s, the widespread use of chlorpromazine drastically reduced psychiatric inpatient populations and stimulated the search for other phenothiazine

derivatives. Between 1954 and 1975, 15 antipsychotic drugs were introduced in the United States. These included haloperidol, thioridazine, thiothixene, loxapine, and trifluoperazine. Despite their clinical benefit, these first generation antipsychotics were observed to have relatively high risks of extrapyramidal symptoms (adverse neurological responses) that include parkinsonism, dystonias, akathisia, and tardive dyskensia. (Shen, 1999) Given the severity and intrusion of these side effects, these first generation antipsychotics were only prescribed to adults with severe psychotic disorders in cases where the benefits clearly outweighed the risk of extrapyramidal symptoms.

Beginning in the 1990s, a new drug, clozapine was introduced. Unlike previous antipsychotic drugs, this particular drug was not only effective in reducing symptoms associated with schizophrenia, but carried with it a lower risk of inducing extrapyramidal symptoms. As a result, clozapine was labeled as an "atypical" antipsychotic; as it disproved the assumption that extrapyramidal symptoms couldn't be disentangled from the efficacy of the first generation antipsychotics. In addition, clozapine showed an increase in efficacy for negative symptoms of schizophrenia, an increase in efficacy for treatment-refractory patients, as well as a lower likelihood of raising serum prolactin levels. (Shen, 1999) The actual pharmacological difference is that the primary mechanism for first generation antipsychotics is mediated through the dopamine D2 receptor blockade, whereas "atypical" antipsychotics (also known as second generation antipsychotics) use mixed dopamine receptors. (Surja, Tamas, & El-Mallakh, 2006) The success of clozapine led to the development of several other similar antipsychotic drugs that include risperidone in 1994 (marketed as Risperdal), olanzapine in 1996 (marketed as Zyprexa), quetiapine in 1997 (marketed as Seroquel), ziprasidone in 2001 (marketed as Geodon), aripiprazole in 2002 (marketed as Abilify), and paliperidone in 2006 (marketed as Invega). (drugs@FDA.gov)

The emergence of these "atypical" antipsychotics has had a tremendous influence in broadening the use of antipsychotic prescriptions, primarily through off-label use. The reduction of extrapyramidal symptoms associated with these second generation antipsychotics has facilitated the expansion of their use for a wider variety of clinical indications and for a more diverse population including children and adolescents. Although off-label prescribing is common practice, it is a concern for antipsychotic prescribing, as this class of drugs still carries with it substantial risk. Despite its perceived clinical advantage and safety, antipsychotic drug use has been associated with metabolic and developmental side-effects among children and adolescents. Without substantial long-term safety data, the use of these drugs should be more closely monitored. (Crystal, Olfson, Huang, Pincus, & Gerhard, 2009)

Pediatric Mental Health and Use of Antipsychotics

As the use of antipsychotics have broadened, use among children and adolescents has increased nearly two-fold over the past decade. (America's State of Mind, 2011) Schizophrenia, bipolar disorder, attention deficit disorders, and autism have been the leading indications associated with the use of "atypical" antipsychotic prescriptions. (Chai, Mehta, Moeny, & Governale, 2010) Changes in the identification of pediatric psychotic disorders and the expansion of use in non-psychotic disorders that include ADHD and autism have driven the uptake of these drugs among children and adolescents. (Ivanov & Charney, 2008)

The diagnostic criteria for disorders such as schizophrenia and bipolar disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) are based on clinical presentations in adult populations, making it difficult to extrapolate a definitive

diagnosis for a child or adolescent. Without a clear understanding of the psychopathology of these psychotic disorders, clinicians have been reluctant in the past to diagnose children and adolescents with these disorders, especially given the stigma and prognosis implications attached to them. However, pediatric schizophrenia and bipolar disorder have become increasingly accepted diagnoses as more and more individuals are diagnosed with these conditions and retrospective studies provide validation and support. Furthermore, the diagnostic criterion for these psychotic disorders has evolved with subsequent revisions of the DSM. (Ivanov & Charney, 2008) As the inclusion criterion has broadened and the diagnoses have become legitimized, a larger subset of the population has been captured with these disorders. Over the last ten years, there has been a 40-fold increase in the diagnosis of bipolar disorder among children and adolescents. (Moreno C. , Laje, Blanco, Olfson, Jiang, & Schmidt, 2007)

Psychotropic drug use has become increasingly common in managing autism spectrum disorders. Otherwise referred to as ASD, autism spectrum disorders are a collection of neuro-developmental disorders that are characterized by social and communication deficits in addition to repetitive behavior. It has been estimated that between 30-60% of children and adolescents with ASD use at least one psychotropic medication. (Mandell, Morales, Marcus, Stahmer, Doshi, & Polsky, 2008) Antipsychotics have become accepted practices to treat irritability, aggression, and self-injury associated with ASD. Studies have found that haloperidol is effective in improving behavioral symptoms in children with autism. However the high risk of extrapyramidal side effects has limited its use to only the most severe and treatment resistant cases. Atypical antipsychotics are much more commonly used, given their reduced risk of extrapyramidal side effects. Antipsychotics are also being used to treat hyperactivity and stereotyped

behavior associated with autistic disorders, despite lack of clinical efficacy data. (Posey, Stigler, Erickson, & McDougle, 2008) Although antipsychotic prescriptions such as risperidone have been proven to be effective in reducing these behavioral symptoms, it is unclear whether or not these drugs actually improve the social and communication impairments characteristic of autism. Therefore it is necessary to consider the possibility that these drugs are simply mitigating side effects, as opposed to addressing the core problems.

Antipsychotics are also being prescribed to children and adolescents with ADHD, as they have been shown to be effective in reducing aggression. A study looking at Medicaid enrollees in the state of Tennessee found that 46% of antipsychotics prescribed were for ADHD as a primary diagnosis. (Cooper, Fuchs, Arbogast, & Ray, 2004) In a national study by the Office of Surveillance and Epidemiology at the FDA found that in 2009, the third leading indication associated with the use of atypical antipsychotics among children and adolescents was for attention deficit disorders. (Chai et al., 2010) The increase in the percentage of antipsychotic prescribing for ADHD is a growing concern, as prescribing this class of drugs to treat non-psychotic conditions remains controversial. Further complicating the trend in ADHD prescribing, is the high co-morbidity between ADHD and pediatric bipolar. Some physicians have questioned the safety and efficacy of stimulants in the treatment of children and adolescents with co-morbid ADHD/bipolar disorder. There has been concern over whether or not long-term stimulant use induces mania and psychosis. Given the complexity of differentiating between ADHD and bipolar, as well as the lack of substantial knowledge about the efficacy and safety of prescribing combinations of stimulants and antipsychotics (also referred to as poly-pharmacy), prescribing should be done cautiously. (Moreno C. , Laje, Blanco, Jiang, Schmidt, & Olfson, 2007)

Adverse Effects Associated with Pediatric Antipsychotic Use

Despite their clinical effectiveness in treating schizophrenia and bipolar disorder, as well as managing aggression in non-psychotic disorders, antipsychotics still carry with them substantial risk of side effects. Although atypical antipsychotics now represent the majority of antipsychotic prescriptions, these second generation antipsychotics are not risk free. Children are more likely than adults to develop extrapyramidal side effects with risperidone and olanzapine. In addition, children are at a higher risk of developing withdrawal dyskinesia associated with the discontinuation of an atypical antipsychotic drug. (Ivanov & Charney, 2008)

Atypical antipsychotic use has also been associated in elevating levels of serum prolactin, which can develop into hyperprolactinemia. Evidence suggests that this effect is most pronounced in adolescents. Hyperprolactinemia can lead to hypogonadism (low estrogen in females and low testosterone in males), galatctorrhea, decreased libido, erectile dysfunction, osteoporosis, and possible delay in puberty. (Wudarsky, Nicolson, & Hamburger, 1999) There is currently no research on the long-term effects of these impairments on cognitive and physical development.

The metabolic risk associated with atypical antipsychotic use has been the most concerning side effect. In an eight-week trial, participants prescribed risperidone gained an average of 8 pounds, while participants prescribed olanzapine gained 13 pounds. The tendency to promote excessive weight gain has become the focus of ongoing pediatric trials, as obesity poses serious health implications. Weight gain for example is associated with elevated triglycerides and total cholesterol, as well as with metabolic syndrome and diabetes mellitus. Metabolic syndrome is characterized with abdominal obesity, dyslipidemia, glucose intolerance, and hypertension. (Ivanov & Charney, 2008) This

concern over metabolic effects was demonstrated when the FDA did not follow the Pediatric Advisory Committee's controversial recommendation to approve Geodon (ziprasidone) in 2009, as clinical trial data emerged revealing significant weight gain associated with pediatric use. (drugs@FDA.gov)

Prescribing Discrepancies

Differential prescribing patterns of antipsychotic drugs to children and adolescents raises concern over safety and access to proper mental health services. According to an analysis of Medicaid and private insurance claims data, children and adolescents covered by Medicaid were four times more likely to receive an antipsychotic medication in 2004 than those individuals with private insurance. ((Crystal, Olfson, Huang, Pincus, & Gerhard, 2009) In addition there has been concern over higher rates of antipsychotic prescribing among foster kids. A 2011 study found that foster kids were more likely to receive overlapping antipsychotic prescriptions and for longer durations than other kids enrolled in Medicaid. In addition, black foster children were more likely than white children to be prescribed multiple antipsychotic drugs. (dosReis, Yoon, Rubin, Riddle, Noll, & Rothbard, 2011) Higher utilization among these vulnerable populations raises the question whether or not these children and adolescents are accurately being diagnosed and receiving the appropriate mental health care. Most importantly, are these individuals being placed at a higher risk, as antipsychotics have become a cost-effective and short-term solution to mitigate larger systemic problems?

FDA Regulatory Activity

In an effort to address insufficient pediatric data on dosing, safety, and efficacy, the FDA has used both a "carrot and stick" approach. In 1997, the Congress passed Section

505A of the US Food and Drug Administration Modernization Act, providing an additional 6 months of patent protection or marketing exclusivity extension, in return for performing studies specified by the FDA. The incentive program, also referred to as the Pediatric Exclusivity Provision was renewed in 2002 and in 2007 as part of the Best Pharmaceutical Children's Act (BPCA). In addition to using the "carrot" approach to encourage more pediatric trials, the 2003 Pediatric Research Equity Act granted the FDA the authority to require studies in children for a new drug likely to be used in pediatric populations. As a result of these two approaches, the availability of pediatric data has substantially increased, leading to over 100 labeling changes. (Vanchieri, Stith Buter, & Knutsen, 2008)

With the availability of more pediatric clinical trial data, the FDA approved the use of risperidone in children and adolescents ages 5-16 for the treatment of autistic disorder on October 6, 2006. This was the first pediatric approval for an atypical antipsychotic. Prior to this approval, only haloperidol and thioridazine (both first generation antipsychotics) were approved for children and adolescents. The following is a timeline of the current pediatric approvals of atypical antipsychotics:

Risperdal (risperidone)

October 6, 2006:	Autistic disorder in children and adolescents ages 5-16
August 22, 2007:	Schizophrenia in adolescents ages 13-17
	Short term treatment of manic or mixed episodes of bipolar disorder in children and adolescents ages 10-17.

Abilify (aripiprazole)

November 29, 2007	Schizophrenia in adolescents ages 13-17
February 27, 2008	Short term treatment of manic or mixed episodes of bipolar disorder in children and adolescents ages 10-17.
November 19, 2009	Autistic disorder in children and adolescents ages 6-17

Seroquel (quetiapine)

December 2009	Schizophrenia in adolescents ages 13-17
	Short term treatment of manic or mixed episodes of bipolar disorder in children and adolescents ages 10-17.

Zyprexa (olanzapine)

December 4 , 2009 : Schizophrenia in adolescents ages 13-17
Short term treatment of manic or mixed episodes of bipolar disorder in children and adolescents ages 10-17.

FDA regulatory activity on already approved drugs can have a profound as well as differential impact on the uptake and discontinuation of a drug. (Gibbons, Brown, Hur, Bhaumik, Erkens, & Herings, 2007) (Olfson, Marcus, & Druss, 2008) (Busch & Barry, 2009) The FDA can positively impact utilization through new approvals and labeling changes, and negatively impact utilization through the use of black-box warnings and advisories.

The majority of research that has primarily concentrated on the effect of warnings and restrictions as opposed to approvals or labeling changes provides strong evidence for the influence of FDA regulatory activity. The 2003 black-box warning on antidepressants regarding increased risk of suicidal behavior among pediatric patients resulted in a decrease in antidepressant use, demonstrating the influence of the FDA in conveying information. In 2005, the FDA issued an advisory and a subsequent black-box warning on the risk of atypical antipsychotic use among elderly patients with dementia. According to a study using office-based physician data, mentions of atypical antipsychotics fell 2% overall and 19% among those with dementia in the year following the advisories. (Dorsey, Rabbani, Gallagher, Conti, & Alexander, 2010) The decrease in atypical antipsychotic drug use, especially among elderly dementia patients provide further support that FDA regulatory activity is closely watched and has a profound impact on drug prescribing trends. Given the strong response to both the black-box warnings that were issued for pediatric antidepressant use and the warnings issued for elderly dementia patients, there is reason to believe that physicians and patients are reactive to FDA regulatory activity.

Objective

Although there have been several reports on the trends in antipsychotic prescribing among children and adolescents, there have been no studies looking into how these trends have been affected by the pediatric FDA approvals that began in 2006. Although drugs can be prescribed off-label, having an approval for a specific indication or population not only allows a drug to be marketed for a specific indication, but conveys a sense of safety by condoning and legitimizing its use. Given the complexity of pediatric mental health disorders and the known safety risks associated with atypical antipsychotics, it is likely that physicians might be hesitant to prescribe off-label. Therefore there it is hypothesized that these approvals have contributed to the increase in pediatric antipsychotic prescribing primarily among non-mental health specialists. This study will examine these assumptions and fill the gaps in the literature on the effects of FDA regulatory activity on pediatric prescribing trends.

II. Methods

To examine the effect of expanding FDA approvals to pediatric populations, this study focuses on the prescribing trends of Risperdal (risperidone) among children and adolescents ages 0-17 with respect to overall antipsychotic prescribing. Using an interrupted time series design, this study looked at the individual and combined effect of the 2006 and 2007 FDA pediatric approval for the treatment of autism for individuals ages 5-17, Schizophrenia for individuals ages 13-17, and bipolar disorder for individuals ages 10-17. A segmented regression analysis of interrupted time series data is the strongest, quasi-experimental design, as it can examine the immediate and long-term effects of the FDA approvals on Risperdal prescribing. (Wagner et al., 2002)

Data

Longitudinal data from IMS Health was used to look at antipsychotic prescribing from 2005 to 2008. The data set includes retail pharmacy prescriptions data for a representative sample of children and adolescents ages 0-17 who filled an antipsychotic prescription during the time period. This data set represents more than 60% of all annual retail prescriptions filled in the US. Each prescription record contains a unique patient identifier, data about the patient (date of birth and sex), the name of the drug, the dose, the dispense date, the geographic location of where the prescription was written, a unique physician id number, and payment type (i.e. private insurance or cash). This data set was merged using the unique physician id numbers with a data set containing demographic information on the providers that included specialty, age, and sex.

For the analysis, the raw data was collapsed to generate monthly counts of Risperdal as well as all antipsychotic prescriptions written by each physician to create the outcome variable. Two indicator variables were created for two FDA approval dates, as well as two interaction terms between the interventions and time. Month indicator variables were created to account for time effects and indicator variables for physician specialties were created to stratify the analysis.

Model Specifications

To examine the changes in Risperdal prescribing with respect to the two FDA pediatric approvals in 2006 and in 2007, several segmented regression models were built analyzing provider-month counts of Risperdal. For the first set of analyses, each intervention was tested independently and then jointly. Each of the segmented regression models were fitted using Poisson regression to model the mean number of Risperdal

prescriptions written by each unique provider, offsetting for the total number of antipsychotics prescribed per month with robust standard errors clustered around unique physicians. Although there was no evidence of over dispersion, the segmented regression models were also fitted using a negative binomial regression model as a robustness check. In addition, since Rispderal was so commonly prescribed among clinicians, there was no need to run a zero-inflated Poisson model.

Model 1a:

$$\log\left(\frac{y_t}{vol}\right) = \beta_0 + \beta_1 * time_t + \beta_2 * intervention1_t + \beta_3 * time\ afer\ intervention1_t + e_t$$

Model 2a:

$$\log\left(\frac{y_t}{vol}\right) = \beta_0 + \beta_1 * time_t + \beta_2 * intervention2_t + \beta_3 * time\ afer\ intervention2_t + e_t$$

Model 3a:

$$\log\left(\frac{y_t}{vol}\right) = \beta_0 + \beta_1 * time_t + \beta_2 * intervention1_t + \beta_3 * time\ afer\ intervention1_t + \beta_4 * intervention2_t + \beta_5 * time\ afer\ intervention2_t + month\ dummies + e_t$$

Where:

- For each of the regressions, the average provider-month counts of Risperdal prescriptions were modeled, offsetting for the average provider-month counts of total antipsychotic prescriptions
- $\boldsymbol{time_t}$ is measured in t months beginning from January 2005
- $\boldsymbol{intervention1_t}$ is an indicator variable where a value of 1 represents a prescription that was written after the first approval date (October 2006)
- $\boldsymbol{time\ afer\ intervention1_t}$ is an interaction between time measured in months and the first intervention dummy variable
- $\boldsymbol{intervention2_t}$ is a dummy variable where a value of 1 represents a prescription that was written after the second approval date (November 2007)
- $\boldsymbol{time\ afer\ intervention2_t}$is an interaction between time measured in months and the second intervention dummy variable.

For the second set of analyses, 11 indicator variables to control for monthly time effects were added to the model. April was chosen as the reference month since this month reflects average prescribing.

Finally, to examine the differential effects due to physician specialty, the combined models were analyzed by stratifying by pediatricians versus non-pediatricians and mental health specialists versus non-mental health specialists. The mental health specialists consisted of psychiatrists, child psychiatrists, neurologists, and child neurologists. These models were run with and without the month indicator variables.

To interpret the results of the interrupted time-series analyses, the pre- and post-intervention slopes were plotted using the method of recycled predictions. This process involved coding observations for each time period with a zero if they were before the intervention or a 1 if they occurred after the intervention. (Liao, 1994) STATA version 11.2 was used to generate the predicated values as well as to run all of the statistical analyses.

III. Results

In each of the regressions, there were 1,494,366 observations representing the monthly prescription counts of 140, 838 unique providers who wrote a least one antipsychotic prescription to a child or adolescent ages 0-17 from 2005-2008. To highlight the breakdown by specialty, 18.53% specialized in Family Medicine, 17.78% in Pediatrics, 14.66% in Psychiatry, and 7.51% in Internal Medicine. (Refer to Figure 1.2 and Table 1.3) These unique providers prescribed a combined total of 1, 025, 773 prescriptions for Risperdal in 2005, 1,245,078 in 2006, 1,337,050 in 2007, and 1,408,423 in 2008. (Refer for Figure 1.1) In addition, total antipsychotic prescribing volume was 2,335,727 in 2005, 2,910,539 in 2006, 3,097,803 in 2007, and 3,296,260 in 2008. (Refer to Table 1.1) Looking

at total Risperdal prescribing by month, there appears to be seasonal trends, as evidenced by the dip in the number of Risperdal prescriptions written in March. (Refer to Figure 1.1)

Looking at the regressions modeling each of the interventions separately show a statistically significant effect of the FDA approvals on Risperdal prescribing. The October 2006 approval had a positive immediate effect on the level of Risperdal prescribing by shifting up the percent of Risperdal prescribing by 1.31% points (refer to figure 2.1b). In addition, there was a positive effect on the trend of Risperdal prescribing as the post-intervention slope increased. The November 2007 approval also had an immediate effect on the level of Risperdal prescribing by shifting up the percent of Risperdal prescribing by 1.04% points (refer to figure 2.2b). However the effect on trend was negative, as the post-intervention slope decreased.

Although modeling the effects of each approval separately provides useful insight into the short term effects of each approval, it is more accurate to model the approvals in a combined model, especially since there is less than a year between the two interventions. The results of the combined model show a positive effect on the level of Risperdal prescribing by shifting up the percent of Risperdal prescribing by 2.44% points (refer to figure 2.3b). In addition, the slope following the two FDA approvals remained the same as the pre-intervention slope. Therefore the overall long-term effect of the FDA approvals had a positive effect on the level of Risperdal prescribing, but did not have any effect on the rate at which Risperdal lost market share from 2005-2008. In other words, the net effect of the approvals provided an additional 24.4 months of market share that would have otherwise would have naturally decayed due to loss of patent life, market competition, and loss of novelty. This estimate was calculated using the pre-intervention slope to solve for the number of months it would have taken for Risperdal to lose 2.44% points of market share.

Stratifying the analyses by mental health specialists and non-mental health specialists suggest that the FDA approvals had a differential impact on physician prescribing by specialty. As hypothesized, there was a greater effect on non-mental health specialists as the level of Risperdal prescribing shifted up 3.56% points versus 2.01% points among specialists (refer to Figures 4.1b and 4.2b). In addition, stratifying the analysis by Pediatricians and non-Pediatricians found that the level of Risperdal prescribing shifted up by 4.02% points among Pediatricians versus 2.25% points among non-Pediatricians (Refer to Figures 3.1b and 3.2b). Figure 5 in the appendix shows a comparison of these stratified regressions in terms of the number of months of market share gained as a result of the FDA approvals. It is clear from the histogram that Pediatricians were affected the most.

IV. Discussion

Limitations

Although the FDA labeling change had a statistically significant impact on Risperdal prescribing trends, there are several factors that may have dampened the effects. First, there is substantial evidence to suggest that the trend in the uptake of antipsychotic drugs among children and adolescents began prior to the FDA labeling changes in 2006. In the past decade, there have been several federal lawsuits against the leading antipsychotic drug manufacturers under the False Claims Act for deceptive practices as well as several state and individual class action law suits alleging off-label marketing. In 2009, Pfizer paid $2.3 billion to settle allegations of illegally marketing Geodon, while Eli Lilly paid $1.4 billion to settle lawsuits against Zyprexa. In addition, Johnson and Johnson has paid $743 million to settle lawsuits alleging fraud and illegal marketing practices to pediatric and elderly populations from 1999 to 2006. (Field, 2010) The effect of FDA labeling changes may

have also been dampened by changes in the market for atypical antipsychotic drugs. During this period, Invega, a similar atypical antipsychotic was introduced. In addition to competition from this new drug, pediatric approvals for Zyprexa (olanzapine), Seroquel (quetiapine), and Abilify (aripiprazole) may have also affected Risperdal prescribing trends. Alternatively, insurance coverage could have dampened the effect of FDA labeling changes. Use of two and three-tier cost structures to steer consumers and physicians to choose either lower cost or preferred drugs using price incentives may have impeded drug choice. However this is highly unlikely, as there were no generic alternatives available prior to 2008.

Further interference in detecting the effect of the FDA labeling changes could be due to the fact that Risperdal went off patent in October, 2008. Firms typically reduce their allocation of marketing expenditures to drugs that are approaching the end of their patent life. Although Risperdal did gain pediatric approval, the new labeling change might not have been as heavily promoted since its patent was nearing expiration. Therefore the market share of Risperdal was already in decline due to competition from newer and more heavily promoted drugs. In addition, if resources were not allocated to detailing and DTCA, knowledge of the labeling changes to include pediatric populations would have been diffused more slowly through FDA press releases, popular media, journals, and word of mouth.

This study did not look at prescribing changes with respect to indication. It would have been useful to look at whether the FDA approvals had differential effects based on indication. This would have allowed us to see whether or not physicians were closely following FDA prescribing guidelines or merely interpreting the approvals as a broad approval for pediatric use. In addition, by not looking at indications, this study is not able

to determine whether or not the FDA approvals have facilitated the off-label prescribing of antipsychotics for ADHD.

Lastly, this study focuses solely on Risperdal prescribing, rather than all 4 of the antipsychotics that were approved for pediatric use. Looking the effects on these other antipsychotics could have provided further evidence to strengthen the Risperdal findings. In addition, this study focused on the effect of expanding antipsychotic labels. Therefore the results of this study may not be applicable to other classes of drugs. It is very likely that psychotropic drug prescribing patterns differ from other drug classes.

Implications

The results of this study clearly suggest that FDA labeling changes to include pediatric populations had a significant impact on prescribing. Prior to the pediatric FDA approval of Risperdal for autism, schizophrenia, bipolar disorder, all prescribing was off-label. Given the complexity and difficulties in diagnosing pediatric mood disorders as well as the risk of known and unknown adverse effects, it is reasonable to assume that physicians without specific mental health training as compared to psychiatrists might have been reluctant or less likely to prescribe antipsychotics to children and adolescents prior to the approvals. The results of this study are consistent with this hypothesis and suggest that physicians, especially those without specific mental health training rely heavily on the FDA for guidance regarding safe and appropriate prescribing. Therefore it is extremely important that pediatric approvals be made carefully, as they have the potential to have a strong influence on utilization and prescribing trends.

For the pharmaceutical industry, the results of this study provide compelling evidence to the value of conducting pediatric trials and thereby gaining drug approval for

pediatric populations. The combined effect of the Risperdal approvals for pediatric use resulted in shifting the market share of Risperdal prescribing by 2.44% points which is the equivalent to retaining 24.4 months of market share. More broadly, the uptake in Risperdal in response to the FDA approvals in 2006 and 2007 reflects the influence of an approval conveying safety and legitimacy.

Although this study only examined the impact of the FDA approval of Risperdal for pediatric use, the increase in utilization and expenditure on antipsychotic drugs is most likely attributable in large part to these approvals. Therefore future studies should focus on assessing the magnitude of the effect of FDA approvals on the increase in expenditures on antipsychotic drugs.

Conclusion

Using retail prescription pharmacy data, an interrupted time-series analysis was used to look at the prescribing trends of Risperdal before and after the FDA approval for pediatric use in 2006 and 2006. Given the results of this study that suggest FDA approvals have a significant effect on the level of prescribing but no significant effect on trend, it is extremely important to continue studying the effects of these approvals to determine whether this response has been harmful or beneficial. Given the discrepancy in antipsychotic prescribing and the increasing off-label use for ADHD, there is suspicion to believe that FDA approvals may be broadly interpreted as legitimizing use among children and adolescents for all indications rather than for their specific approval. This study provides the first assessment of the effect of the FDA approval of antipsychotic drugs for pediatric use and as well as a foundation for future studies.

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Table 1: Descriptive Statistics

Table 1.1 Annual Risperdal Prescribing

Year	Risperdal	All	Percent Risperdal
2005	1,025,773	2,335,727	43.92%
2006	1,245,078	2,910,539	42.78%
2007	1,337,050	3,097,803	43.16%
2008	1,408,423	3,296,260	42.73%

Table 1.2 Physician Specialties

Specialty	Count	Percent
Family Medicine	26,098	18.53%
Pediatrician	25,046	17.78%
Psychiatrist	20,652	14.66%
Internal Medicine	10,579	7.51%
Nurse Practitioner	9,574	6.80%
Family Practice	6,993	4.97%
Child Psychiatrist	5,631	4.00%
Physician Assistant	4,415	3.13%
Emergency Room	4,163	2.96%
Other	27,687	19.66%
Total	140,838	100.00%

Table 2
Individual and Combined Regression Models
(Number of Observations foe each Regression= 1,494,366)

	Model 1a	Model 2a	Model 3b	Model 1b	Model 2b	Model 3b
intercept (B0)	-0.792634***	-0.813151***	-0.792634***	-0.795609***	-0.808780***	-0.796043***
month (B1)	-0.003364*** (.996642)	-0.001355*** (.998646)	-0.003364*** (.996642)	-0.002503*** (.997450)	-0.001132*** (.998868)	-0.002458*** (.997545)
intervention1 (B2)	-0.016017** (.984110)		-0.069021*** (.933307)	-0.0209906 (.979228)		-0.078243*** (.924739)
t_aftr_intr1 (B3)	0.002299*** (1.00230)		0.004071*** (1.00408)	0.001957*** (1.001959)		0.003855*** (1.003863)
intervention2 (B4)		0.081631*** (1.08506)	0.130135*** (1.138982)		0.06461*** (1.066744)	0.126845*** (1.135241)
t_aftr_intr2 (B5)		-0.001549*** (.998646)	-0.003611*** (.996396)		-0.001103*** (.998897)	-0.003601*** (.996406)
jan (B6)				0.011627*** (1.011695)	0.011364*** (1.011429)	0.011840*** (1.011910)
feb (B7)				0.007554*** (1.007583)	0.007300*** (1.007327)	0.007625*** (1.007654)
mar (B8)				0.035308*** (1.035939)	0.036129*** (1.036789)	0.035486*** (1.036123)
may (B9)				-0.004004*** (.996004)	-0.003918*** (.996090)	-0.004044*** (.995964)
jun (B10)				-0.014656*** (.985451)	-0.014555*** (.985550)	-0.014781*** (.985328)
jul (B11)				-0.020231*** (.979973)	-0.019926*** (.980271)	-0.020421*** (.979787)
aug (B12)				-0.016392*** (.983742)	-0.015958*** (.984169)	-0.016688*** (.983451)
sep (B13)				-0.020007*** (.980192)	-0.026765*** (.973590)	-0.022312*** (.977935)
oct (B14)				-0.018840*** (.981336)	-0.025524*** (.974799)	-0.020409*** (.979798)
nov (B15)				-0.022931*** (.977330)	-0.023632*** (.976644)	-0.020392*** (.979815)
dec (B16)				-0.029057*** (.971361)	-0.028866*** (.971547)	-0.025987*** (.974348)

Incidence Rate Ratios are reported in parentheses
Asterisk denote statistical significance as follows:
$***\ \boldsymbol{p-value} \leq .\mathbf{01}, \quad **\ .\mathbf{01} < p-value \leq .05, \quad *\ 0.05 < p-value \leq 0.1\mathbf{0}$

Table 3
Pediatricians vs. Non-Pediatricians

	Pediatricians (n=284,100)	Pediatricians (n=284,100)	Non-Pediatricians (n=1,210,266)	Non-Pediatricians (n=1,210,266)
intercept (B0)	-0.450248***	-0.446746***	-0.824682***	-0.828795***
month (B1)	-0.0013218** (.9987)	-0.0010239* (0.9990)	-0.0037959*** (.9962)	-0.002806*** (.9972)
intervention1 (B2)	-0.114285*** (.8920)	-0.102244*** (.9028)	-0.0587775*** (.9429)	-0.069481*** (.9329)
t_aftr_intr1 (B3)	0.0055165*** (1.0055)	0.0048781*** (1.0049)	0.0036995*** (1.0037)	0.0034884*** (1.0035)
intervention2 (B4)	0.1626727*** (1.1767)	0.1468148*** (1.1581)	0.1251542*** (1.1333)	0.1231821*** (1.1311)
t_aftr_intr2 (B5)	-0.004901*** (.9951)	-0.004318*** (.9957)	-0.003407*** (.9966)	-0.003447*** (.9967)
jan (B6)		0.0006263 (1.0006)		0.0112047*** (1.0113)
feb (B7)		0.0023173 (1.0023)		0.0070959*** (1.0071)
mar (B8)		-0.004673 (.9953)		0.0437541*** (1.0447)
may (B9)		-0.0017373 (.9983)		-0.004315*** (.9957)
jun (B10)		-0.009228*** (.9908)		-0.015184*** (.9849)
jul (B11)		-0.011524*** (.9885)		-0.021774*** (.9785)
aug (B12)		-0.0054505 (.9946)		-0.019240*** (.9809)
sep (B13)		-0.014428*** (.9857)		-0.024247*** (.9760)
oct (B14)		-0.014348*** (.9858)		-0.021297*** (.9789)
nov (B15)		-0.014325*** (.9858)		-0.021647*** (.9786)
dec (B16)		-0.016638*** (.9835)		-0.027156*** (.9732)

Incidence Rate Ratios are reported in parentheses
Asterisk denote statistical significance as follows:
$***\ \boldsymbol{p-value \leq .01}$, $**\ \boldsymbol{.01 < p-value \leq .05}$, $*\ \boldsymbol{0.05 < p-value \leq 0.10}$

Table 4
Mental Health Specialist vs. Non-Mental Health Specialists

	Specialist (n=654,216)	Specialist (n=654,216)	Non-Specialist (n=840,150)	Non-Specialist (n=840,150)
intercept (B0)	-0.839572***	-0.843264***	-0.642437***	-0.645151***
month (B1)	-0.003664*** (.9963)	-0.002678*** (0.9973)	-0.0029700*** (.9970)	-0.002226*** (.9978)
intervetion1 (B2)	-0.049850*** (.9514)	-0.065297*** (.9368)	-0.1121815*** (.8939)	-0.097553*** (.9071)
t_aftr_intr1 (B3)	0.003308*** (1.0033)	0.03275*** (1.0033)	0.005636*** (1.0057)	0.004629*** (1.0046)
intervention2 (B4)	0.123704*** (1.1317)	0.125359*** (1.1336)	0.161353*** (1.1751)	0.140181*** (1.1505)
t_aftr_intr2 (B5)	-0.003392*** (.9966)	-003587*** (.9964)	-0.004559*** (.9954)	-0.003786*** (.9962)
jan (B6)		0.011234*** (1.0113)		.009524*** (1.0096)
feb (B7)		0.007004*** (1.0070)		0.007379*** (1.0074)
mar (B8)		-0.043129*** (1.0441)		0.022909*** (1.0232)
may (B9)		-0.005505*** (.9945)		0.000531 (1.0005)
jun (B10)		-0.016184*** (.9839)		-0.009117*** (.9909)
jul (B11)		-0.023108*** (.9772)		-0.013115*** (.9870)
aug (B12)		-0.020384*** (.9798)		-0.008770*** (.9913)
sep (B13)		-0.023869*** (.9764)		-021223*** (.9790)
oct (B14)		-0.020714*** (.9754)		-0.021819*** (.9784)
nov (B15)		-0.0216923*** (9785)		-0.018400*** (.9818)
dec (B16)		-0.026751*** (.9736)		-0.025538*** (.9748)

Incidence Rate Ratios are reported in parentheses
Asterisk denote statistical significance as follows:
$***\ \boldsymbol{p-value} \leq .\mathbf{01}, \quad **\ .\mathbf{01} < p-value \leq .05, \quad *\ 0.05 < p-value \leq 0.1\mathbf{0}$

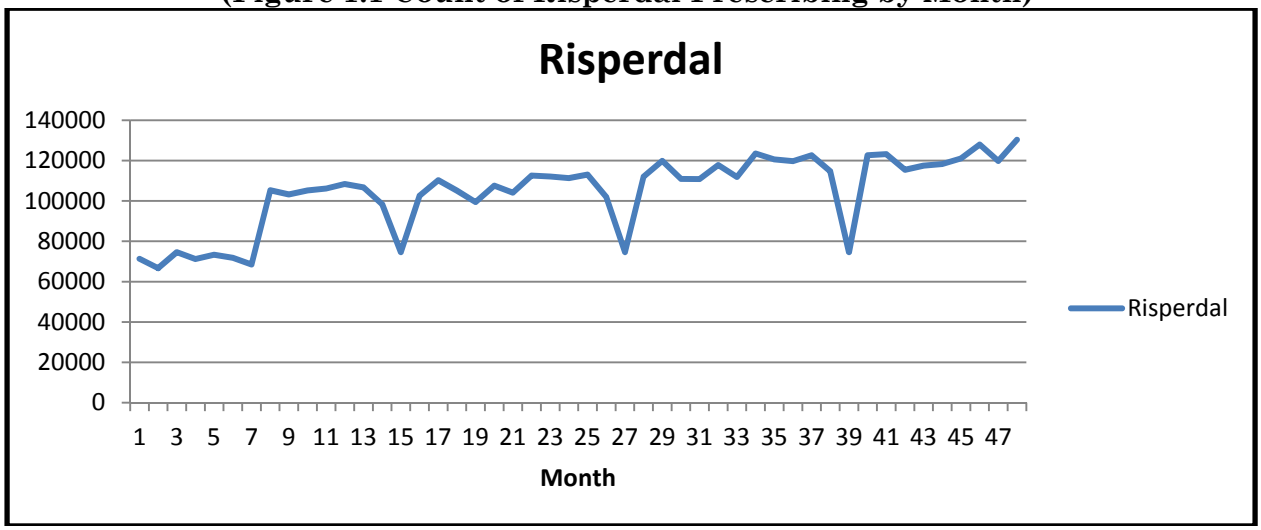
Table 5
Negative Binomial Regression Model

	Poisson Regression Model (n=1,494,366)	Negative Binomial Regression (n=1,494,366
intercept (B0)	-0.796043***	-.760243***
month (B1)	-0.002458*** (.997545)	-.002220*** (.997782)
intervention1 (B2)	-0.078243*** (.924739)	-.089367*** (.914510)
t_aftr_intr1 (B3)	0.003855*** (1.003863)	.004087*** (1.004095)
intervention2 (B4)	0.126845*** (1.135241)	.131239*** (1.140240)
t_aftr_intr2 (B5)	-0.003601*** (.996406)	-.003767*** (.996240)
Jan (B6)	0.011840*** (1.011910)	.013827*** (1.013923)
Feb (B7)	0.007625*** (1.007654)	.007312*** (1.007339)
Mar (B8)	0.035486*** (1.036123)	.0330077*** (1.033630)
May (B9)	-0.004044*** (.995964)	-.003999*** (.996010)
Jun (B10)	-0.014781*** (.985328)	-.014364*** (.985739)
Jul (B11)	-0.020421*** (.979787)	-.020330*** (.979876)
Aug (B12)	-0.016688*** (.983451)	-.0159996*** (.984131)
Sep (B13)	-0.022312*** (.977935)	-.020720*** (.979494)
Oct (B14)	-0.020409*** (.979798)	-.019926*** (.980271)
Nov (B15)	-0.020392*** (.979815)	-.019708*** (.980485)
Dec (B16)	-0.025987*** (.974348)	-.024816*** (.975490)

Incidence Rate Ratios are reported in parentheses
Asterisk denote statistical significance as follows:
$***\ \boldsymbol{p-value \leq .01}, \quad **\ .01 < p-value \leq .05, \quad *\ 0.05 < p-value \leq 0.10$

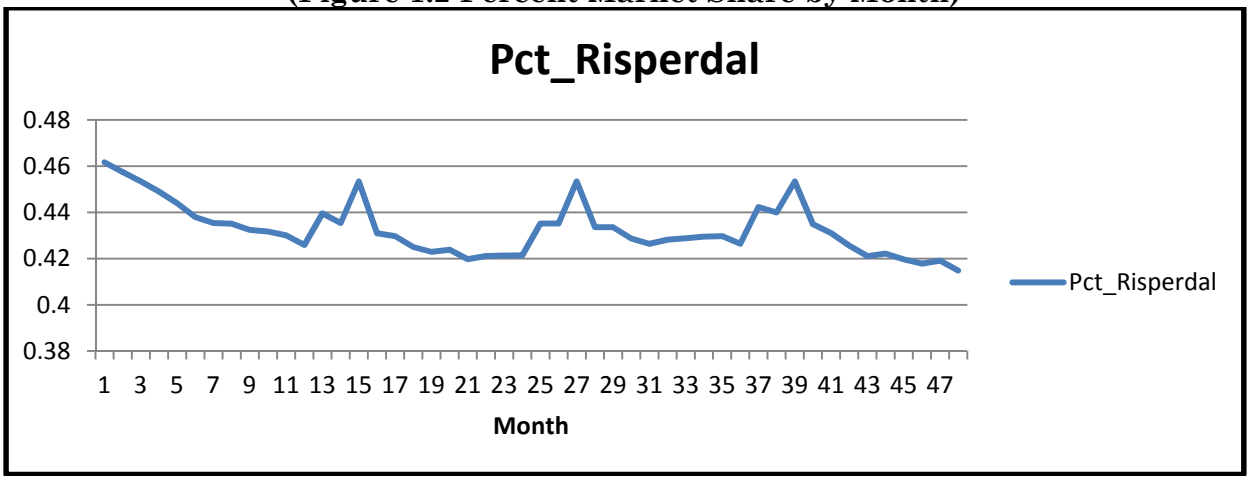
Figure 1 Descriptive Statistics

(Figure 1.1 Count of Risperdal Prescribing by Month)



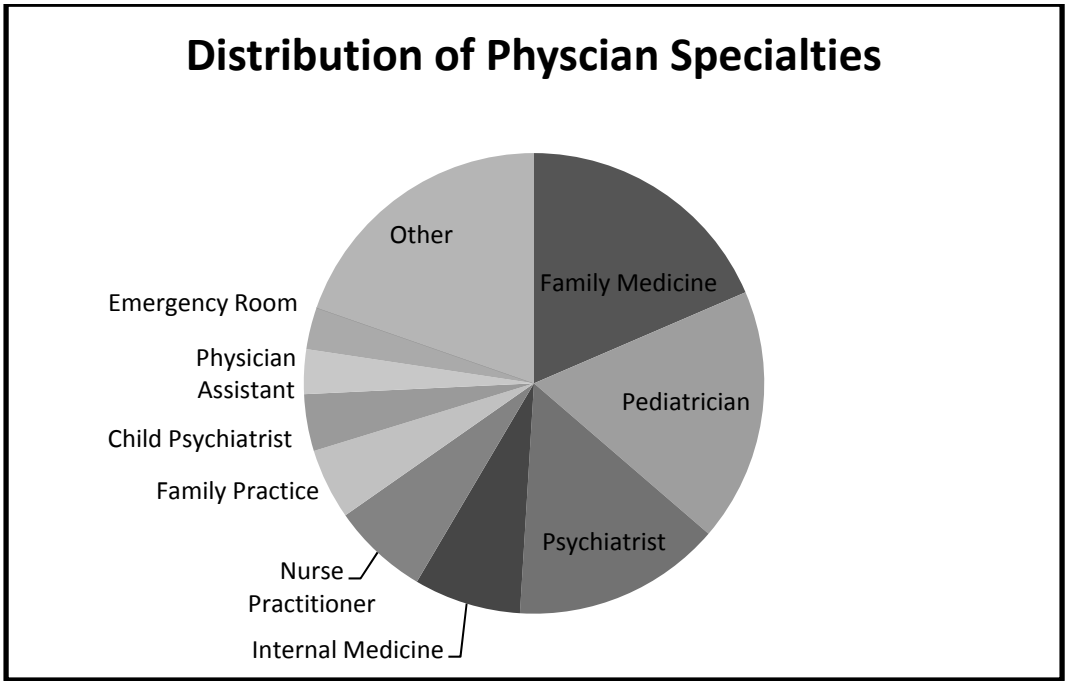
The raw counts by month show an increase in the total number of Risperdal prescriptions from 2005-2008. The obvious cyclical trends indicate the need to control for seasonal effects.

(Figure 1.2 Percent Market Share by Month)



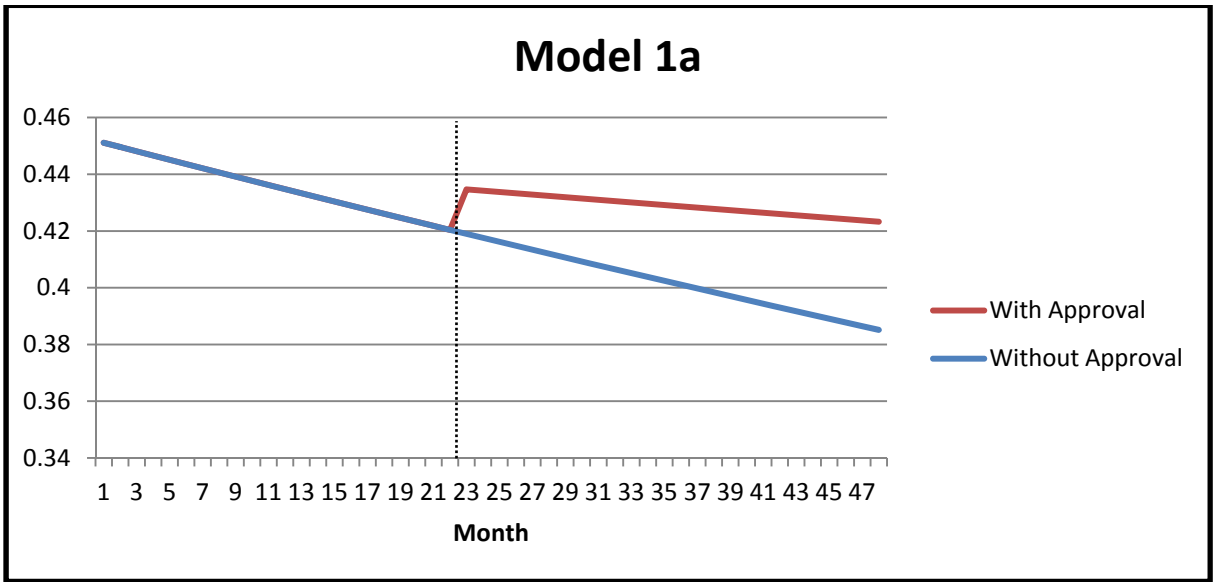
There appears to be a decrease in the market share of Risperdal from 2005-2008. The cyclical pattern seems to suggest that there is a distinct season effect in Risperdal prescribing compared to all other antipsychotic prescribing.

(Figure 1.3 Physician Specialties)



Individual and Combined Regression Models

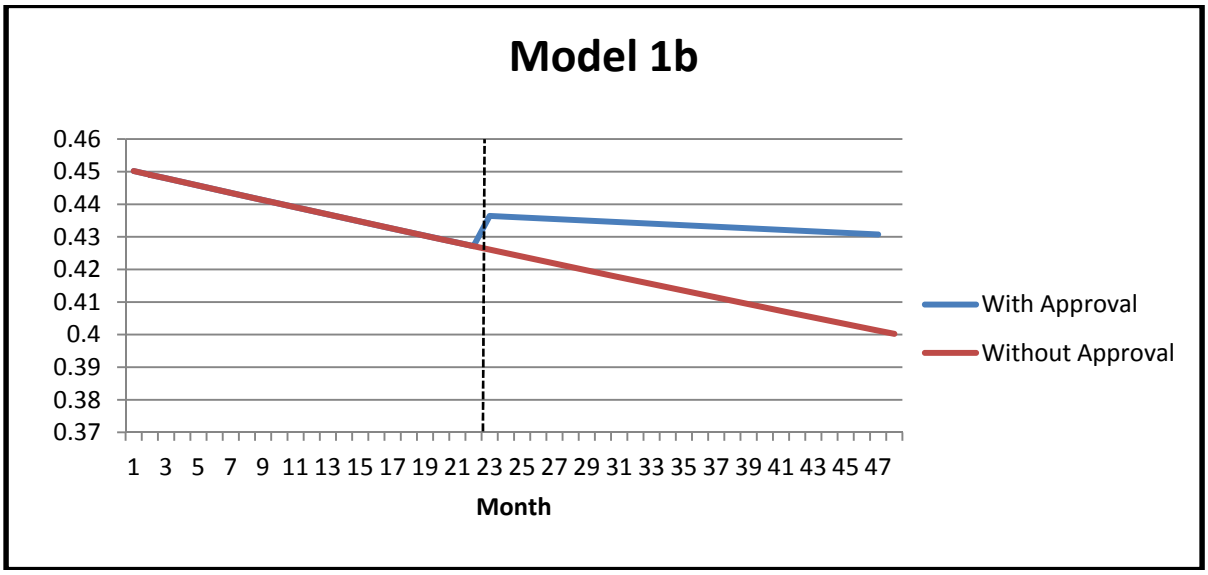
Figure 2.1a October 2006 Approval



Difference at Month 23: 1.57%

Dashed line refers to the intervention (October 2006 FDA approval)

Figure 2.1b October 2006 Approval with month dummies

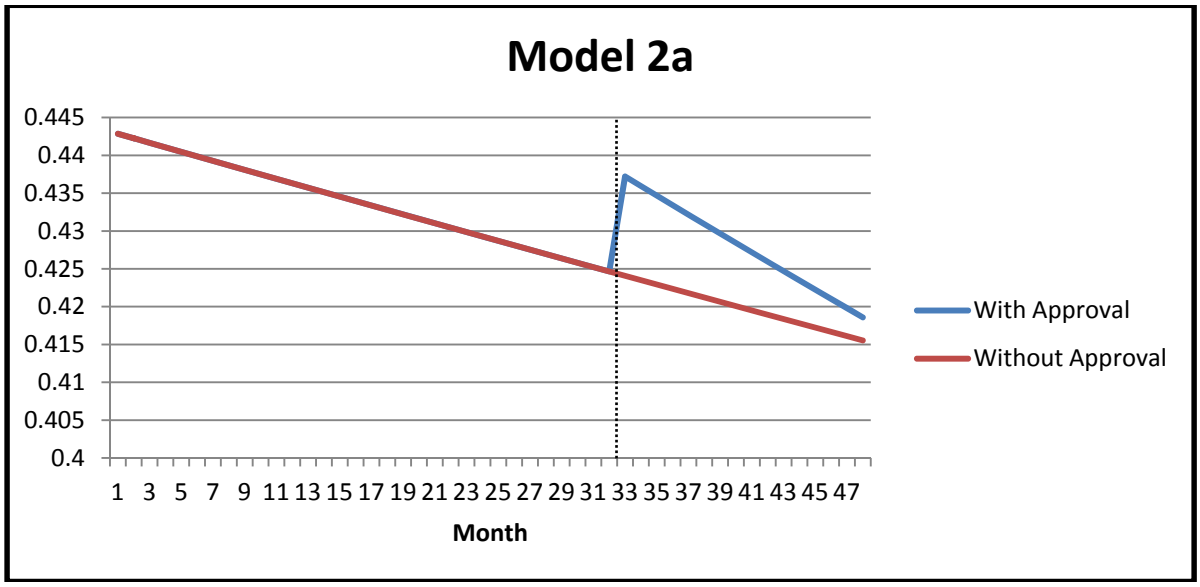


Difference at Month 23: 1.04%

Dashed line refers to the intervention (October 2006 FDA approval)

Individual and Combined Regression Models

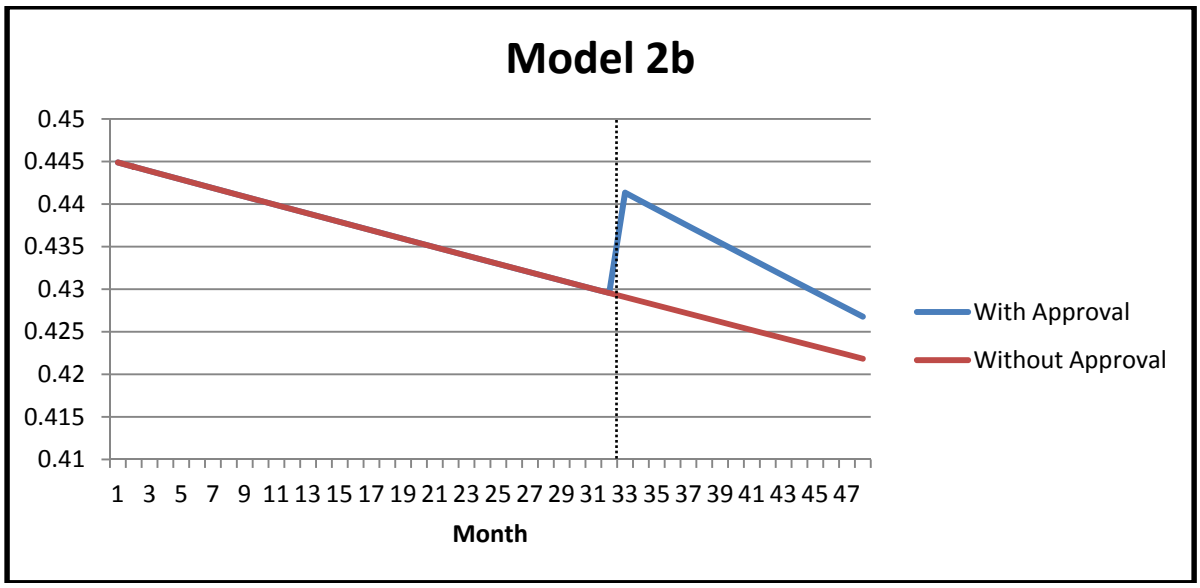
Figure 2.2a November 2007 Approval



Difference at Month 32: 1.31%

Dashed line refers to the intervention (November 2007 FDA approval)

Figure 2.2b November 2007 Approval with month dummies

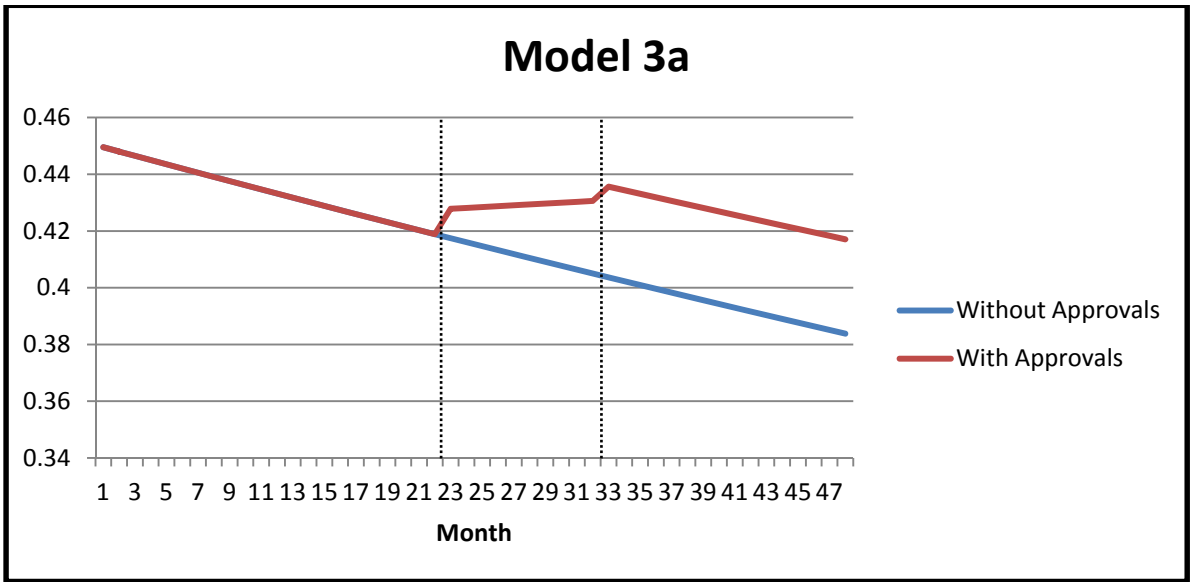


Difference at Month 32: 1.23%

Dashed line refers to the intervention (November 2007 FDA approval)

Individual and Combined Regression Models

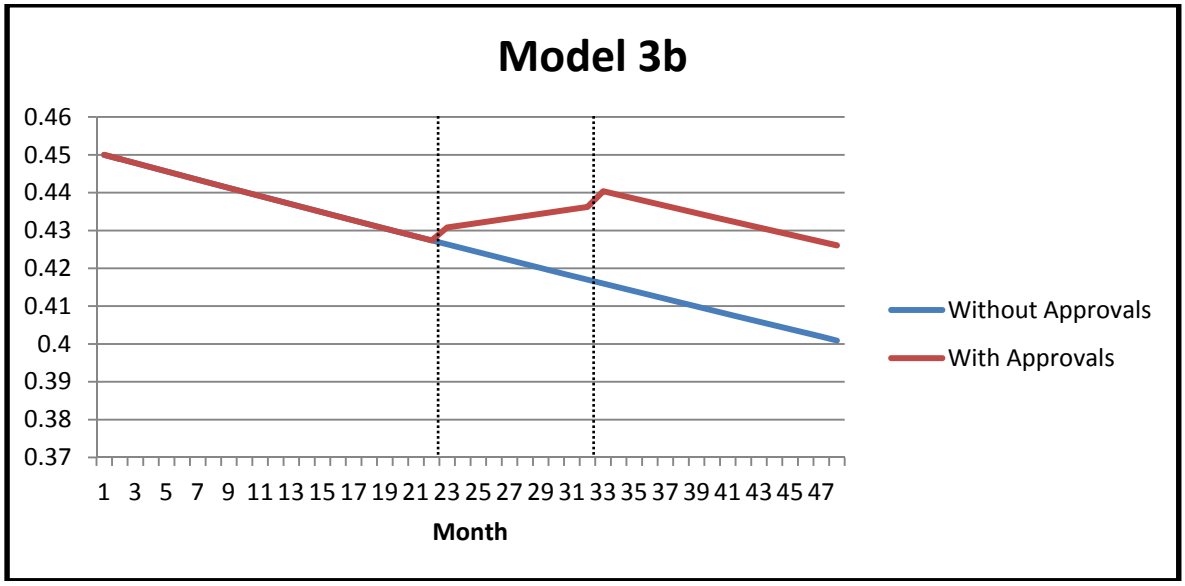
Figure 2.3a Combined Model



Difference at Month 32: 3.20%

Dashed lines refer to the interventions (FDA approvals)

Figure 2.3b Combined Model with month dummies

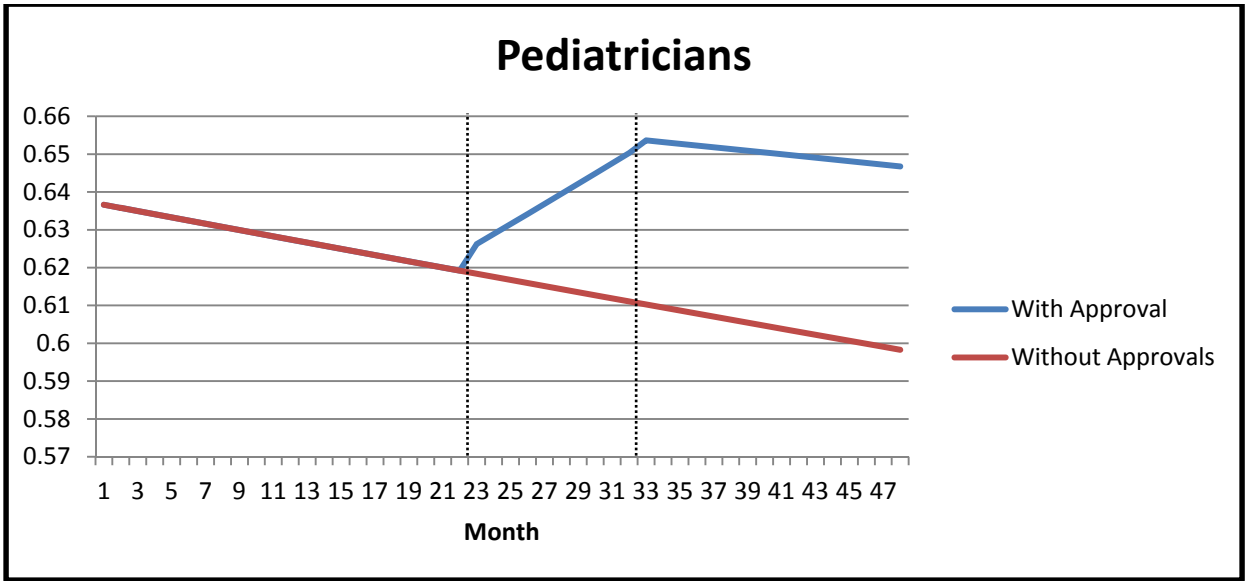


Difference at Month 32: 2.44%

Dashed lines refer to the interventions (FDA approvals)

Pediatricians vs. Non-Pediatricians

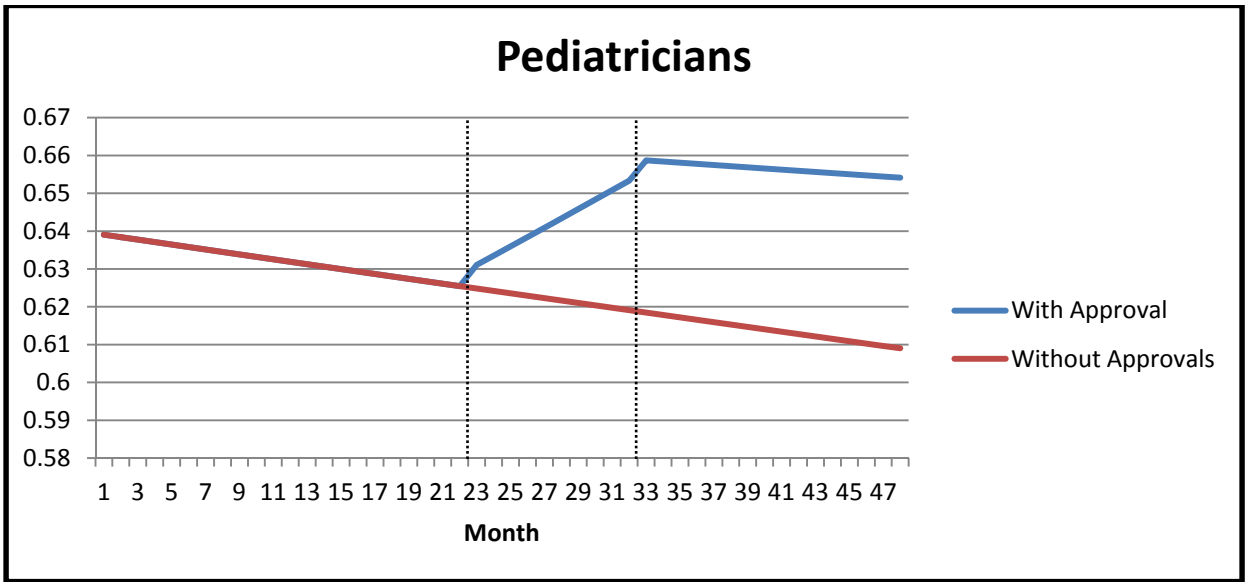
(Figure 3.1a Pediatricians)



Difference at Month 32: 4.34%

Dashed lines refer to the interventions (FDA approvals)

(Figure 3.1b Pediatricians with month dummies)

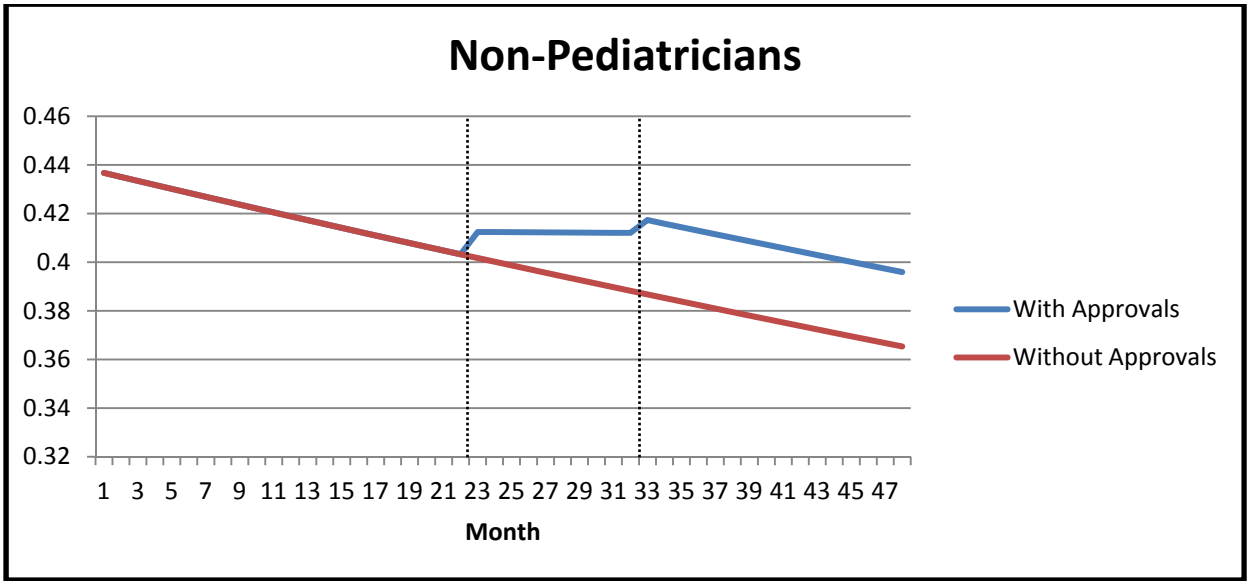


Difference at Month 32: 4.02%

Dashed lines refer to the interventions (FDA approvals)

Pediatricians vs. Non-Pediatricians

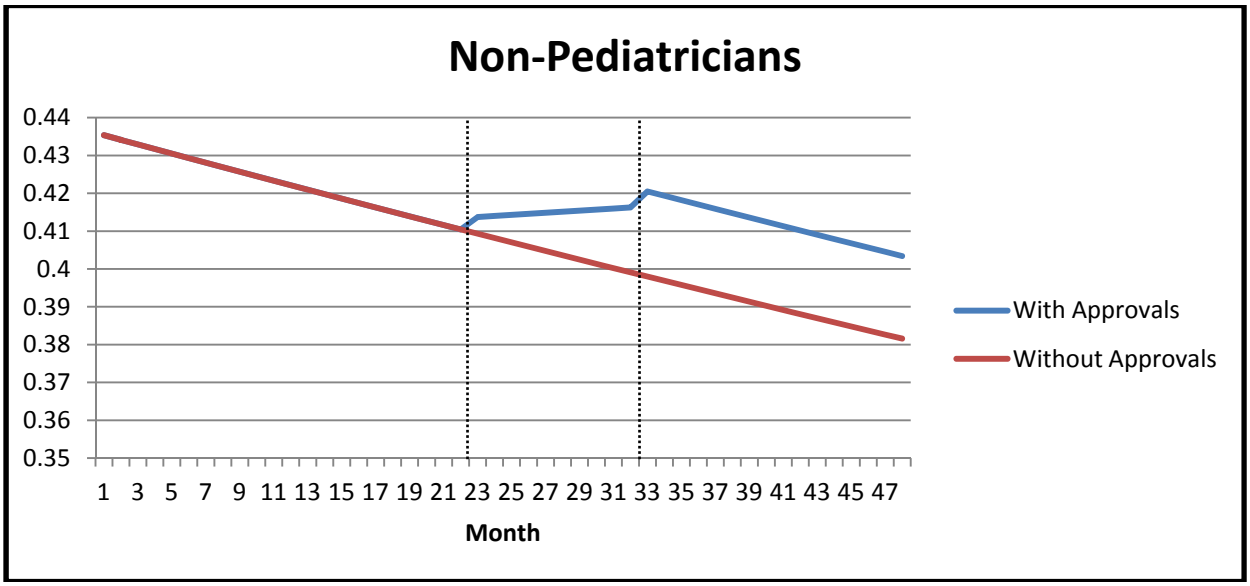
(Figure 3.2a Non-Pediatricians)



Difference at Month 32: 3.06%

Dashed lines refer to the interventions (FDA approvals)

(Figure 3.2b Non-Pediatricians with month dummies)

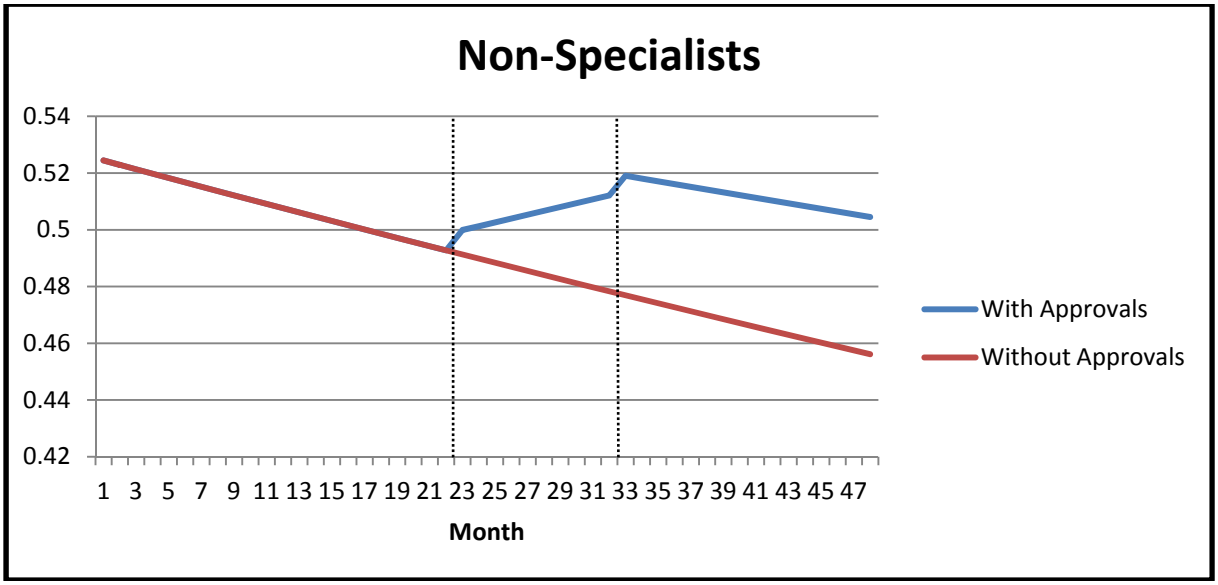


Difference at Month 32: 2.25%

Dashed lines refer to the interventions (FDA approvals)

Mental Health Specialists

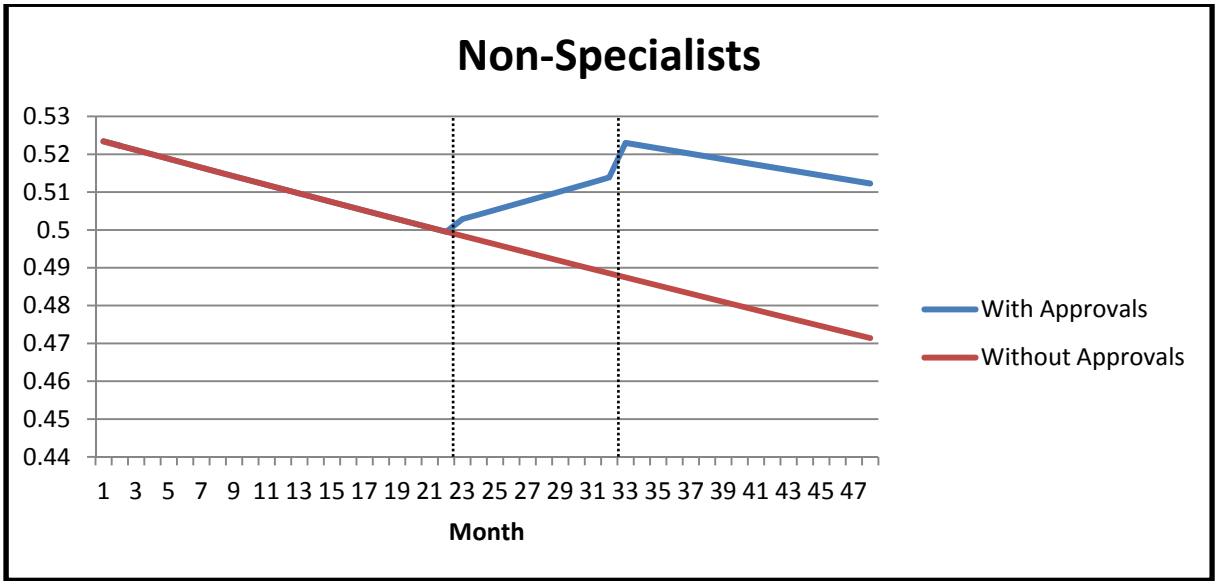
(Figure 4.1a: Non-Mental Health Specialists)



Difference at Month 32: 4.22%

Dashed lines refer to the interventions (FDA approvals)

(Figure 4.1b: Non-Mental Health Specialists with month dummies)

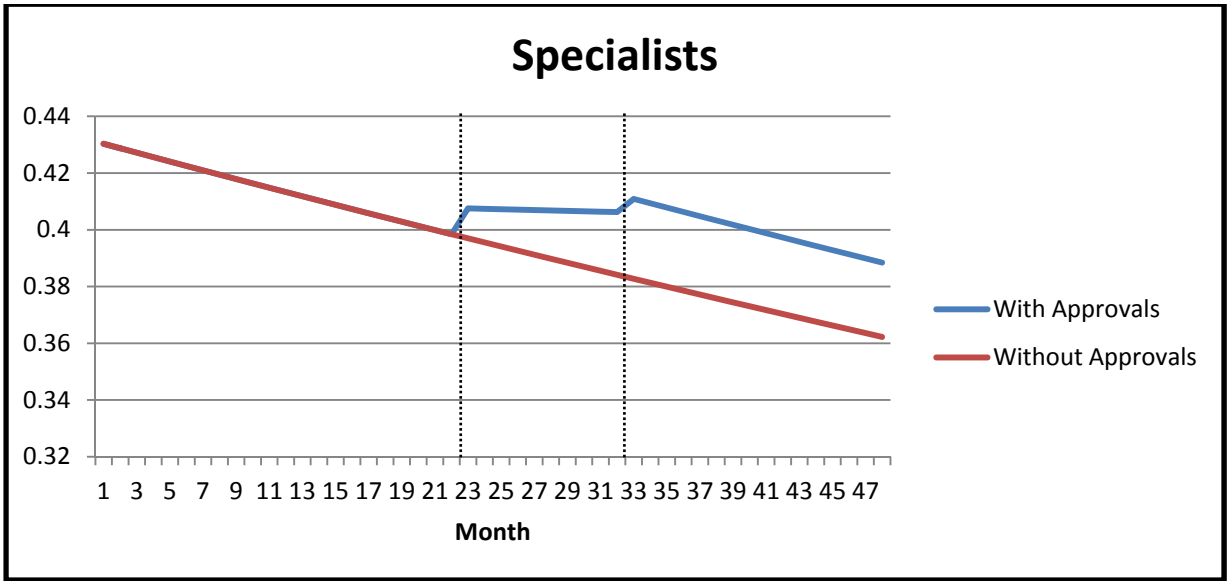


Difference at Month 32: 3.56%

Dashed lines refer to the interventions (FDA approvals)

Mental Health Specialists

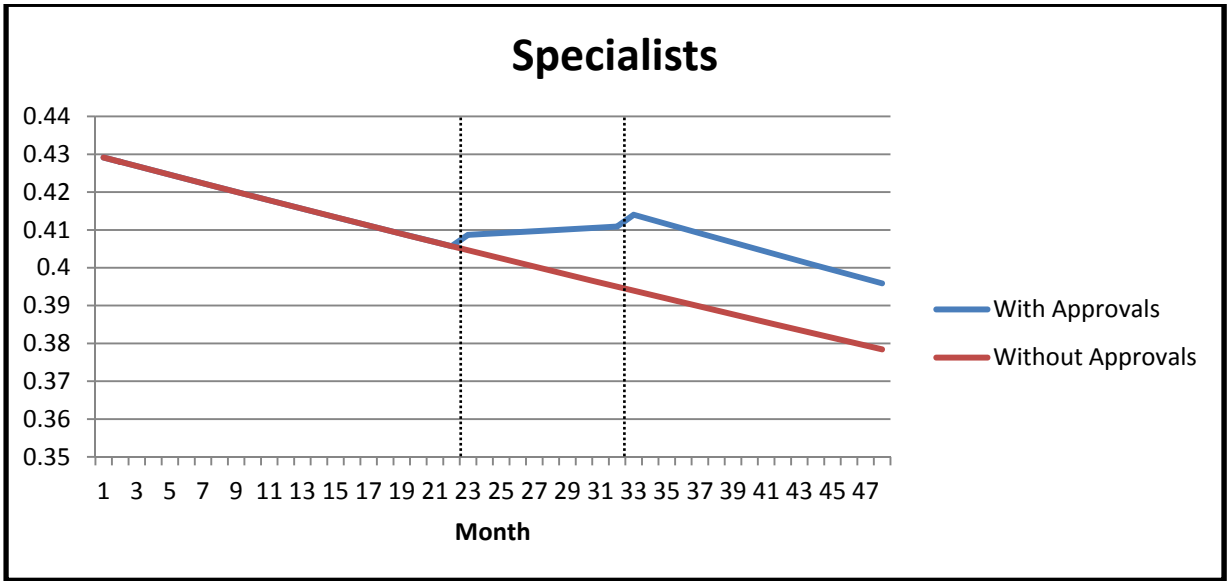
(Figure 4.2a: Mental Health Specialists with month dummies)



Difference at Month 32: 2.82%

Dashed lines refer to the interventions (FDA approvals)

(Figure 4.2b: Mental Health Specialists with month dummies)



Difference at Month 32: 2.01%

Dashed lines refer to the interventions (FDA approvals)

Figure 5: Effect of the Combined FDA Approvals