Changes in Long-acting β-agonist Utilization After the FDA's 2010 Drug Safety Communication

Citation	Hartung, D. M., Middleton, L., Markwardt, S., Williamson, K., & Ketchum, K. (2015). Changes in Long-acting β-agonist Utilization After the FDA's 2010 Drug Safety Communication. Clinical Therapeutics, 37(1), 114-123. doi:10.1016/j.clinthera.2014.10.025
DOI	10.1016/j.clinthera.2014.10.025
Publisher	Elsevier
Version	Accepted Manuscript
Terms of Use	http://cdss.library.oregonstate.edu/sa-termsofuse

Title: Changes in Long-acting Beta Agonist Utilization Following the FDA's 2010 Drug Safety Communication

Abstract

Purpose: In February 2010, the US Food and Drug Administration (FDA) issued new recommendations for the safe use of long-acting beta agonists (LABA) in those with asthma. The objective of this study was to determine the impact of the FDA's 2010 LABA advisory on LABA utilization.

Methods: Using administrative data from the state of Oregon Medicaid program we performed an interrupted time series regression to evaluate changes in the trend in new LABA prescriptions before and after the FDA's 2010 advisory. Trends in incident fills were examined among those with and without an asthma diagnosis code, prior respiratory controller medication use, and by age.

Findings: Of the 8646 study patients, 53% had a diagnosis of asthma, 21% of patients had no respiratory diagnosis, and 32% did not use a respiratory controller medication in the recent past. The trend in new LABA prescriptions declined by 0.09 new starts per 10,000 patients per month (95% confidence interval [CI] -0.19 to -0.01) following the FDA's advisory. Among those with a diagnosis of asthma, there was an immediate drop of 0.48 (95% CI -0.93 to -0.03) and a 0.10 (95% CI -0.13 to -0.06) decline in the monthly rate of new starts per 10,000 patients. Immediately following the FDA's advisory we observed a statistically significant 4.7% increase (95% CI 0.8% to 8.7%) in the proportion of new LABA starts with history of previous respiratory controller medication use. Utilization of LABAs did not change in those without a diagnosis of asthma.

Implications: The FDA's 2010 advisory was associated with modest reductions in LABA utilization overall and in ways highlighted in their recommendations.

Key Words: United States Food and Drug Administration, Utilization, adrenergic beta2-agonists, Medicaid

Introduction[a]

Controversy surrounding long-acting beta agonists (LABAs) use has persisted since salmeterol was originally approved by the US Food and Drug Administration (FDA) in 1994.[1,2] Concerns about the association between salmeterol and the risk for serious asthma-related events were first noted in 1993 with publication of the Serevent National Surveillance study.[3] The FDA-mandated Salmeterol Multicenter Asthma Research Trial (SMART) corroborated these findings suggesting a small but significant increase in asthma-related deaths and life threatening events, particular among African Americans, in those randomized to salmeterol.[4] Following early termination of SMART, FDA issued their initial black box warning for salmeterol in 2003. During the past decade, this warning has been revised several times and expanded to the entire class.[5,6]

Over this same period, meta-analytic reviews of SMART and other accumulated safety data have flourished along with varying interpretations of their significance.[6] Despite the ongoing safety debate, use and expenditures for LABAs have soared. Between 2002 and 2009, the number of prescriptions dispensed for medications containing a LABA increased from 15.6 to 21.7 million.[7] In 2012, nearly $5 billion dollars was spent on fluticasone/salmeterol (Advair™), making it the fourth largest drug market in the US behind Nexium™, Abilify™, and Crestor™.[7] There is growing evidence that certain aspects of LABA prescribing appear to be sub-optimal. Although LABA monotherapy, which has been strongly discouraged by the FDA and in clinical practice guidelines, is uncommon,[8] nearly 70% of asthma patients with a new prescription for a combination LABA/inhaled corticosteroid (ICS) have no previous history of

[a] Abbreviations: long-acting beta agonists (LABA), US Food and Drug Administration (FDA), Salmeterol Multicenter Asthma Research Trial (SMART), International Classification of Disease 9th Revision (ICD9), chronic obstructive pulmonary disease (COPD), National Asthma Education and Prevention Program's Expert Panel Report-3 (EPR-3)

controller use.[9-13] Also, LABA use in patients without a diagnosis of either asthma or chronic obstructive pulmonary disease (COPD) is considerable.[14-16] Despite the revised warnings and extensive publicity, the existing literature demonstrates overall LABA utilization has been largely unaffected, and in fact grown substantially over the last decade..[10-12]

On February 19, 2010, following extensive advisory committee deliberation, the FDA announced revised recommendations on the use of LABAs and further modified the LABA black box warnings. The revised recommendations include the following: (1) an emphasized contraindication to LABA monotherapy without another asthma controller medication; (2) using LABAs long-term only in patients whose asthma cannot be adequately controlled on other asthma controller medications; (3) using LABAs for the shortest duration of time required to achieve asthma control and then discontinuing; and, (4) using fixed dose combination LABAs in pediatric and adolescent patients to ensure compliance to both medications. Manufacturers of LABA products were required to change package inserts, medication labels and patient medication guides.

The FDA's LABA recommendations and black box revisions of 2010 are the most prescriptive to date, yet controversy still remains about the relative benefits and safety of these agents.[6,17,18] Utilization studies of previous FDA action have yielded mixed results, so it is unclear if clinicians have modified their prescribing habits to better conform to the most recent FDA communication.[10-12,19] The objective of this study was to examine changes in LABA use and appropriateness in a state Medicaid program following the FDA's 2010 drug safety communication.

Methods

Patient Population

This study employed a retrospective interrupted time series design to evaluate longitudinal changes in incident (new) LABA prescriptions before and after the FDA's 2010 LABA advisory. Using state of Oregon administrative pharmacy and medical claims data we identified monthly rolling cohorts of incident LABA users from January 2008 to December 2012. Patients were included if they had a new prescription claim for a single source LABA or fixed dose LABA/ICS combination product with no LABA claims in the six months prior; this was defined as their index claim. LABA products included salmeterol xinafoate (Serevent Diskus™, GlaxoSmithKline); formoterol fumarate inhalational powder (Foradil Aerolizer™, Merck); arformoterol tartrate (Brovana™, Sonovion); and indacaterol inhalation powder (Arcapta Neohaler™, Novartis). Combination LABA/ICS products included fluticasone proprionate and salmeterol inhalational powder (Advair HFA™, Advair Diskus™, GlaxoSmithKline); budesonide and formoterol fumarate dehydrate inhalational aerosol (Symbicort™, AstraZeneca); and mometasone furoate and formoterol fumarate dehydrate inhalational aerosol (Dulera™, Merck). In order to assess baseline patient characteristics, only patients with 6 months of enrollment prior to their index claim were included. Baseline patient characteristics were assessed using pharmacy and medical claims data six months prior to each patient's index claim. Data from this period were used to summarize age in years as of the index date, sex, and race. Using International Classification of Disease 9th Revision (ICD9) codes we quantified whether patients had diagnoses of asthma (ICD9 493.x), chronic obstructive pulmonary disease (COPD) (ICD9 4912x, 492.xx, 496xx, 5064x, 5181x, 5182x), both, or neither. We also determined if the patient had previous asthma or COPD controller medications (Supplemental Table A) in the three months prior to their index claim. We used an expansive

definition of controller medication that included most inhaled respiratory agents with the exception of short acting beta-agonists.

We excluded patients with fee-for-service Medicaid because of a prior authorization restricting LABA that took effect during the study period.[20] Patients were also excluded if they had dual Medicare Medicaid enrollment because of the potential for missing Medicare data. Because the first six months of data were used to establish eligibility and define baseline characteristics, the actual study period ran from July 2008 to December 2012 (54 months).

Analysis

We analyzed monthly trends and changes in incident LABA use before and after the FDA's LABA advisory on February 18, 2010 using segmented regression analyses.[21] The general form of our segmented regression model was $Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * FDA\ Advisory_t + \beta_3 * time\ after\ advisory + e_t$. The dependent variable (Y_t) was the number of new LABA starts per 10,000 Medicaid enrollees per month. *Time* was a continuous variable from 1 to 54 indicating time in months from the beginning of study period. *FDA advisory* was a dummy variable set at 0 if the month was before the FDA's advisory (July 2008 to January 2010; 19 months) and 1 if the month was after the FDA's advisory (March 2010 to December 2012; 34 months). The time point in February 2010 (month 20) was censored because the advisory was issued in the middle of the month. *Time after advisory* was a continuous variable indicating the number of months after the FDA's advisory; this variable was set at 0 if before the FDA's advisory. The β_0 estimates the number of new LABA starts per 10,000 patients at time 0 (intercept); β_1 estimates the change in new LABA starts over time (*baseline trend)* before the FDA advisory; β_2 estimates the immediate change in new LABA starts (*level change)* occurring between January 2010 (month 19) and March 2010 (month 21); and β_3 estimates the change in trend over time

(*trend change)* of new LABA starts after the FDA advisory. Using the multivariate delta procedure described by Zhang et al.,[22] we derived absolute changes in new starts for the final period of the time series (month 54, December 2012) by comparing the post-FDA advisory estimate to an estimate assuming a continuation of the baseline trend. Predications were generated only for those models with significant changes in trend over time. All regressions were performed using PROC AUTOREG within SAS version 9.3 (SAS Institute, Cary, NC). Autocorrelation between error terms was assessed using the Durbin-Watson test statistic. If significant autocorrelation was detected ($p<.05$), we adjusted the models with autocorrelation terms selected using a stepwise approach that first fit a model with higher order autocorrelation terms. The least non-significant term was then dropped and the reduced model was successively re-fit until all remaining autocorrelation terms were significant ($p<.05$).

Several models were fit to describe changes in LABA starts overall, if the patient had a baseline diagnosis of asthma alone (excluding those with no diagnosis and those with a co-occurring COPD diagnosis), and by age (less than 18 years of age). Additionally, as a measure of potential appropriateness, we analyzed changes in the proportion new starts with previous use of a respiratory controller medication. Finally, to minimize the possibility that observed LABA trends reflected larger asthma controller use, we analyzed an identically constructed cohort of new users of other asthma controller medications in those with a diagnosis of asthma. This study was approved by the Oregon Health & Science University Institutional Review Board and data use agreements with the Oregon Health Authority were obtained.

Results

Between July 2008 and December 2012, 8646 patients started using a LABA containing product and met our eligibility criteria. As summarized in Table 1, new LABA users during this period were predominately females and over 18 years of age. Only 12% of the study sample were twelve years of age or younger. The most commonly prescribed LABA during this period was combination fluticasone/salmeterol. Nearly two-thirds of patients had a diagnosis of asthma, and 53% had a diagnosis of asthma without a concurrent diagnosis code for COPD. One in five patients had no respiratory diagnosis prior to initiating a LABA. Only 32% of patients initiating a LABA had a history of previous respiratory controller use. This was similar in those with only a diagnosis of asthma.

Table 2 summarizes estimates from the segmented regression analyses of the trend in new starts of LABA from July 2008 through December 2012. As shown in Figure 1, following the FDA's advisory in 2010 incident LABA prescriptions declined significantly each month by 0.09 prescriptions per 10,000 patients (95% confidence interval [CI] -1.19 to -0.01; $p<0.05$). Assuming a continuation of the baseline trend, this decline would be expected to result in a 3.16 (95% CI -4.09 to -2.22) reduction in new starts per 10,000 patients by December 2012. There was no significant change immediately following the FDA's advisory. Examining LABA utilization by baseline diagnoses (Figure 2), we found a similar decline in trend of 0.1 new starts per 10,000 patients (95% CI -0.13 to -0.06; $p<0.001$) among those with an asthma diagnosis, but no significant changes in those without. Additionally, among those with an asthma diagnosis there was an immediate drop of 0.48 new starts per 10,000 patients (95% CI -0.93 to -0.03; $p<0.05$) following the FDA advisory. By the end of 2012, this decline would be predicted to result in a reduction of 3.76 (95% CI -4.09 to -3.43) new starts per 10,000 patients. The trend in

utilization was significantly reduced in both those less than 18 years of age and among those 18 and older.

During the same period, new starts of other asthma controller agents in those with an asthma diagnosis also declined in trend, but this change was not statistically significant.

Finally, as shown in Figure 3, there was statistically significant 4.7% immediate increase (95% CI 0.8% to 8.7%; $p<0.05$) in the proportion of incident users with a recent history of respiratory controller medication use. Significant changes in the overall trend were not observed. Consequently, the model does not predict an increase (or decrease) in the proportion of new LABA starts with a history of respiratory controller medication beyond the immediate 4.7% change. However, the trend in prior controller medication use is non-significantly reversed from negative in the pre-period to positive in the post-period.

Discussion

In this study we observed modest, but significant changes in LABA utilization following the 2010 FDA drug safety communication. Specifically, there were significant declines in trend overall and among those with a diagnosis of asthma – a subgroup specifically addressed in the FDA's Advisory. Additionally, we observed a significant jump in the proportion patients starting a LABA for the first time with a recent history of some other respiratory controller medication. While the overall decline in trend appears modest, extrapolation out to the last month of the time series results in a cumulative one-third reduction in new starts relative to predicted utilization. Although the FDA's advisory and the clinical data only pertain to treatment of asthma, it is conceivable that treatment of COPD or other conditions may also have been impacted. Because of the anticipated limited number of patients with a diagnosis of COPD

in Medicaid, we combined those with any COPD diagnosis with no respiratory diagnosis to evaluate spillover effect. We found no evidence suggesting prescribing behavior changed for patients without a diagnosis of asthma, for whom the FDA's advisory do not apply.

Our data suggest a trend towards further conformity to both the revised FDA label and practice guidelines. Specifically, we observed an increase in the proportion of new users who have used a respiratory controller medication immediately prior to starting a LABA. Despite this, the proportion of new users with previous controller remains below 50%. Although speculative, the decline in use among those with an asthma diagnosis may indicate increasing reluctance of prescribers to begin LABA therapy given ongoing safety concerns.[23] There were significant declines in trend for both those less than and 18 years or older.

Previous investigations of the FDA's LABA labeling changes have generated equivocal or ambiguous findings. Using a commercial health insurance dataset, Stockl and colleagues found that the FDA's 2005 advisory had no impact on the likelihood of being prescribed an asthma controller medication prior to starting a LABA, a recommendation added in the black box warning.[12] Similar conclusions were reached by two other studies examining quarterly trends in use of fluticasone/salmeterol combination inhaler as initial therapy for both adults and children before and after the FDA's 2005 communication.[10,11] In these and other studies, the proportion of patients prescribed an asthma controller agent prior to initiating LABA therapy ranged from 30% to 40%, similar to what we observed.[8,9,24] Another study by Zhou and colleagues found that the rate of single-ingredient LABA has declined significantly between 2003 and 2011, with growing use of other asthma controller medications concurrent with single-agent LABAs.[19]

Our findings may contrast with previous studies because of how the FDA advisory was

formulated. In a recent systematic review assessing how FDA drug risk communication affects utilization and outcomes, Dusetzina and colleagues found considerable heterogeneity in measured responses.[25] Synthesized results suggest that FDA advisories offering specific guidance may be more effective than general risk communications. This may explain why the 2010 advisory appears to have produced changes in prescribing behavior while previous studies of the 2005 label changes were largely unheeded, with the exception of single-agent LABA use. In situations where FDA advisories are issued targeting a specific subpopulation, such as with the use of LABAs, studies have found some evidence of spillover onto non-targeted populations.[26,27] The FDA's LABA risk communication is directed towards those with asthma and not COPD. Our data show the impact on prescribing was largely confined to those with a diagnosis of asthma, although COPD is relatively uncommon in a younger Medicaid population.

We note several limitations of this study. First, our data were derived from one state Medicaid program of modest size. Although Medicaid is the largest provider of healthcare for low income children and adolescents who are disproportionately affected by asthma, trends in Oregon may not reflect utilization in other states.[28,29] Replication of findings in larger, more diverse, populations would be helpful. Second, interrupted time series with control group is the strongest quasi-experimental research design.[30] Our analysis lacks a control group, precluding true counterfactual comparisons. It is unlikely that prescribing data acquired from a non-US source would be an adequate control because the influence of FDA communication has been shown to impact utilization in other countries.[31] However, causality is strengthened because the decline in new starts was confined to LABAs, as opposed to other asthma controller. Third, inferences from time series data may be confounded by secular change in behavior unrelated to the intervention under study. In 2012 GlaxoSmithKline agreed to a civil settlement for off-label

use of salmeterol/fluticasone (Advair™), the most commonly prescribed LABA.[32] The US Department of Justice alleges that through 2010 GlaxoSmithKline promoted Advair™ for milder forms of asthma and other indications not approved by the FDA.[33] It is unclear if cessation of promotional activities also impacted utilization of LABAs during the study period. There were no other policies or trends in utilization that may have acted to confound this analysis. Finally, our study uses paid pharmacy claims as an indicator of changes in prescribing. Along with the many limitations associated with using administrative data, it is also important to recognize that during this period salmeterol/fluticasone was heavily promoted and sampled. As such, patients we have characterized as news users of a LABA may in fact be past users of sampled medication who are merely filling their first prescription through a pharmacy. The extent and impact of this phenomenon are unclear.

In summary, we observed a modest decline in the trend of new LABA starts following the FDA's 2010 recommendations. New LABA starts were significantly reduced over time among those with a diagnosis of asthma but largely unchanged in those without. Finally, we observed a significant increase in the proportion of new user with a previous history of respiratory controller use – an indicator of possible inappropriate use. In addition to the limitations noted above, other questions remain. Several of the FDA's 2010 recommendations have caused concern among clinicians because they are somewhat inconsistent with existing treatment guidelines and evidence.[17,34] For example, FDA now recommends LABAs be discontinued after asthma control is achieved, however the most recent National Asthma Education and Prevention Program's Expert Panel Report-3 (EPR-3) guidelines recommend step down consideration only after at least three months of therapy. Updated labeling also state LABAs should not be added in patients who can be adequately controlled on low or medium

doses of an ICS, a recommendation that some feel is at odds with the clinical evidence.[35] In patients who remain symptomatic on low-dose ICS, EPR-3 guidelines acknowledge the additional benefits of LABA step up on lung function and symptom control, but in deference to LABA safety concerns, considers medium dose ICS escalation or LABA addition as equally acceptable options.[13] It is unclear how these complex clinical decisions are being made in light of potentially conflicting recommendations. The FDA has mandated the conduct of five additional randomized controlled trials by LABA manufacturers to further clarify the benefits and harms of adding LABAs compared to continued ICS treatment.[36] Results from these trials, expected in 2017, will likely prompt further modifications to product labeling for LABAs.

Acknowledgments

Financial disclosures: This study was unfunded. During the course of this study, DM was funded through the Oregon Comparative Effectiveness Research K12 Program, grant number 1K12HS019456 (PI JMG) from the Agency for Healthcare Research and Quality.

Prior Presentations: 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management; August 25-28, 2013; Montréal, Canada

Conflicts of Interest: No authors have any conflicts of interest

References

1. Chan CM, Shorr AF. Black clouds and black boxes: comment on "Long-acting beta2-agonist step-off in patients with controlled asthma". Arch Intern Med 2012;172:1375-6.

2. Aaronson DW. The "black box" warning and allergy drugs. The Journal of allergy and clinical immunology 2006;117:40-4.

3. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993;306:1034-7.

4. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26.

5. Briefing Information for the March 10-11, 2010 Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Committee. US Food and Drug Administration. (Accessed at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PulmonaryAllergyDrugsAdvisoryCommittee/UCM202701.pdf (Accessed 8/30/2013).)

6. Sears MR. The FDA-mandated trial of safety of long-acting beta-agonists in asthma: finality or futility? Thorax 2013;68:195-8.

7. IMS. Top-Line Market Data. (Accessed at http://www.imshealth.com/portal/site/ims/menuitem.5ad1c081663fdf9b41d84b903208c22a/?vgnextoid=fbc65890d33ee210VgnVCM10000071812ca2RCRD.)

8. Wasilevich EA, Clark SJ, Cohn LM, Dombkowski KJ. Long-acting beta-agonist monotherapy among children and adults with asthma. Am J Manag Care 2011;17:e91-5.

9. Kaplan S, Zhou EH, Iyasu S. Characterization of long-acting beta(2)-adrenergic agonists utilization in asthma patients. The Journal of asthma : official journal of the Association for the Care of Asthma 2012;49:1079-85.

10. Friedman H, Wilcox T, Reardon G, Crespi S, Yawn BP. A retrospective study of the use of fluticasone propionate/salmeterol combination as initial asthma controller therapy in a commercially insured population. Clin Ther 2008;30:1908-17.

11. Friedman HS, Eid NS, Crespi S, Wilcox TK, Reardon G. Retrospective claims study of fluticasone propionate/salmeterol fixed-dose combination use as initial asthma controller therapy in children despite guideline recommendations. Clin Ther 2009;31:1056-63.

12. Stockl KM, Le L, Harada AS, Zhang S. Use of controller medications in patients initiated on a long-acting beta2-adrenergic agonist before and after safety alerts. Am J Health Syst Pharm 2008;65:1533-8.

13. National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma—full report 2007; 2007.

14. Drug Use Evaluation: LongActing Beta Agonist (LABA). Oregon State University College of Pharmacy - Drug Use Research and Management, 2006. (Accessed at http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/laba.pdf.)

15. Combination Long-Acting Beta-Agonist Inhaled Corticosteroid: Summary of Clinical Evidence and Drug Utilization Evaluation. 2010. (Accessed at http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/laba_ics_due.pdf (Accessed 09/1/2013).)

16. Helm ME, Vargas PA, Jones SM. Advair prescribing patterns in a state medicaid and child health insurance program. In: American Academy of Allergy, Asthma, and Immunology Annual Meeting. San Diego, California; 2007.

17. Lemanske RF, Jr., Busse WW. The US Food and Drug Administration and long-acting beta2-agonists: the importance of striking the right balance between risks and benefits of therapy? The Journal of allergy and clinical immunology 2010;126:449-52.

18. Szefler SJ, Busse WW. The long-acting beta-adrenergic agonist controversy in asthma: troublesome times! The Journal of allergy and clinical immunology 2012;130:1256-9.

19. Zhou EH, Kang EM, Seymour S, Iyasu S. Long-acting beta-adrenergic agonist dispensings in pediatric and adolescent asthma patients, 2003-2011. In: 29th International Conference on Pharmacoepidemiology & Therapeutic Risk Management. Montreal, Canada; 2013.

20. Policy Evaluation: Step Therapy Prior Authorization of Combination Inhaled Corticosteroid / Long-Acting Beta-Agonists. 2012. (Accessed at http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/evaluations/articles/2012_05_31_ICS_LABA%20_Pol_Eval.pdf (accessed 9/4/2013).)

21. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. Journal of clinical pharmacy and therapeutics 2002;27:299-309.

22. Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol 2009;62:143-8.

23. Karpel JP, Peters JI, Szema AM, Smith B, Anderson PJ. Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting beta-agonists. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2009;103:304-10.

24. Ye X, Gutierrez B, Zarotsky V, Nelson M, Blanchette CM. Appropriate use of inhaled corticosteroid and long-acting beta(2)-adrenergic agonist combination therapy among asthma patients in a US commercially insured population. Curr Med Res Opin 2009;25:2251-8.

25. Dusetzina SB, Higashi AS, Dorsey ER, et al. Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review. Med Care 2012;50:466-78.

26. Olfson M, Marcus SC, Druss BG. EFfects of food and drug administration warnings on antidepressant use in a national sample. Archives of General Psychiatry 2008;65:94-01.

27. Valuck RJ, Libby AM, Orton HD, Morrato EH, Allen R, Baldessarini RJ. Spillover effects on treatment of adult depression in primary care after FDA advisory on risk of pediatric suicidality with SSRIs. The American journal of psychiatry 2007;164:1198-205.

28. Medicaid: A Primer; 2013.

29. Clement LT, Jones CA, Cole J. Health disparities in the United States: childhood asthma. The American journal of the medical sciences 2008;335:260-5.

30. Shadish WR, Cook TD, Campbell DT. Experimental and quasi-experimental designs for generalized causal inference. Boston: Houghton Mifflin; 2001.

31. Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifiro G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. British journal of clinical pharmacology 2013;75:861-8.

32. Thomas K, Schmidt MS. Glaxo Agrees to Pay $3 Billion in Fraud Settlement. New York Times 2012 July 2, 2012.

33. Whalen J. Glaxo Tries to Shake Marketing Questions on Advair WSJ 2012 July 6, 2012.

34. Rodrigo GJ, Castro-Rodríguez JA. Safety of long-acting β agonists for the treatment of asthma: clearing the air. Thorax 2012;67:342-9.

35. Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev 2010:CD005533.

36. Chowdhury BA, Seymour SM, Levenson MS. Assessing the Safety of Adding LABAs to Inhaled Corticosteroids for Treating Asthma. New England Journal of Medicine 2011;364:2473-5.

Figure Legends:

Figure 1: New long-acting beta agonist starts per 10,000 enrollees per month

Figure 2: New long-acting beta agonist starts per 10,000 enrollees per month in those with and without a diagnosis of asthma. Cross represent new LABA starts in those with an asthma only diagnosis. Grey boxes represent new LABA starts in those without an asthma only diagnosis.

Figure 3: Proportion of new long-acting beta agonist starts with a recent history of respiratory controller medication use