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Using PROC GENMOD to Investigate Drug Interactions: Beta Blockers and Beta Agonists and Their Association with Hospital Admissions

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ABSTRACT

Every year, more than half a million adverse reactions to drugs are reported to the FDA. This paper is a real-world, large-scale review of beta blockers and beta agonist usage. We use New York City public hospitals' records to investigate whether interactions of beta blockers and beta agonists are associated with increased hospital inpatient admissions, a common indicator of health care quality. PROC GENMOD in SAS® provides a variety of count data models, including Poisson regression and Negative Binomial regression. During clinical trials, many patients are excluded by strict selection criteria. This includes young patients, older patients, and patients with history of multiple illnesses. These patients tend to have higher hospital inpatient admission rates. These patients may be prescribed FDA-approved drugs in combinations they could not have received as part of the clinical trials. We examine whether untested uses of beta blockers and beta agonists are associated with changes in admission rates.

INTRODUCTION

In 2010, 750,000 adverse reactions to drugs were reported to the Food and Drug Administration (FDA); more than half the affected individuals suffered from serious medical outcomes including death [1,2]. While clinical trials conducted during drug development assess drug safety in addition to drug efficacy, a drug shown to be safe in a clinical trial may still not be safe in the real world [3], especially since all of the drug's interactions with other drugs may not be fully investigated during clinical trials. Clinical trials typically exclude patients for whom an adverse effect of the tested drug is anticipated: asthma patients are typically excluded from trials of beta blockers; patients with malignant dysrhythmias controlled by beta blockers are often excluded from trials of beta agonists. In reality, drugs are often prescribed to patients in ways that were not part of the original clinical trial. This phenomenon was evident when researchers who mined FDA records of adverse drug events found that "certain pairs of drugs, when used together, caused side effects not associated with either drug alone" [4]. In this paper, we define "non clinical trial use" as drugs being used in combinations that were not examined during clinical trials.

Beta blockers and beta agonists are among the most widely prescribed medications in New York City's public hospitals. Theoretically, administering beta agonists and beta antagonists at the same time could exacerbate the conditions for which the drugs were originally prescribed, but these combinations are often used with the hope that partial beta1 selectivity will somehow improve lung function without adverse cardiac effect. We define beta blocker and beta agonist "non clinical trial use" as using beta blockers and beta agonists at the same time or using more than one drug of the same class at the same time.

OBJECTIVE

We wish to identify factors associated with hospital inpatient admissions of patients using beta blockers and beta agonists, and investigate if patients on beta blocker and beta agonist "non clinical trial use" are more likely to be admitted. Hospital inpatient admission is an indicator commonly used to evaluate the quality of care provided by a hospital. Other medical outcomes that can be studied include length of hospital stay, death, emergency room admissions, clinic admissions, and 30-day readmission, an increasingly prominent measure of hospital care quality due to its use by the Centers of Medicare and Medicaid Services (CMS) to determine Medicare reimbursements.

METHODS

Data for this report was abstracted from an ongoing effort in New York City's public hospitals to reduce costs and hospital admissions. That clinical effort addresses individual patients; only summary data are reported in this paper.

COUNT MODELS

Patients come to hospitals through various avenues: some patients visit emergency rooms and are subsequently discharged; some patients visit clinics and are subsequently discharged; the rest of the patients are admitted as

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inpatients. Hospital inpatient admissions are a type of count data and can be modeled using Poisson regression, a generalized linear model with the logarithm function as the link function. This model assumes that the outcome variable follows a Poisson distribution. In SAS®, Poisson regression can be done using PROC GENMOD.

Figure 1 describes the mathematical formulation and SAS® code for Poisson regression:

Let y_i be the number of hospital visits for patient i, and let $x_{1i}, \ldots, x_{pi}$ be the explanatory variables for patient i, then the model formulation is:

$$y_i \sim \text{Poisson}(\mu_i) \quad \text{i.e.} \quad P(y_i) = \frac{e^{-\mu_i}\mu_i^{y_i}}{y_i!}$$
$$\text{where } E(y_i) = \mu_i \text{ and } Var(y_i) = \mu_i$$
$$\log(\mu_i) = a + b_1 x_{1i} + \ldots + b_p x_{pi} \quad \text{or equivalently} \quad \mu_i = e^{a+b_1 x_{1i}+\ldots+b_p x_{pi}}$$

```
PROC GENMOD data = mydata;
    model y = x1 x2 / type3 dist=poisson;
run;
```

Figure 1. Mathematical formulation and SAS® code for Poisson regression

Because the Poisson distribution has equal mean and variance, if hospital inpatient admissions follow a Poisson distribution, the variance of hospital inpatient admissions should not differ greatly from mean hospital inpatient admissions. If this is not the case, the Poisson regression is said to be over-dispersed, in which case we can either adjust for over-dispersion or use other count models that are able to handle over-dispersion such as Negative Binomial regression [5]. In SAS®, Negative Binomial regression can be done using PROC GENMOD.

Figure 2 describes the mathematical formulation and SAS® code for Negative Binomial regression:

Let y_i be the number of hospital visits for patient i, and let $x_{1i}, \ldots, x_{pi}$ be the explanatory variables for patient i, then the model formulation is:

$$y_i \sim \text{Negative Binomial}(\mu_i, k) \quad \text{i.e.} \quad P(y_i) = \frac{\Gamma(y_i+k)}{\Gamma(k)\Gamma(y_i+1)}\left(\frac{k}{\mu_i+k}\right)^k\left(\frac{\mu_i}{\mu_i+k}\right)^{y_i}$$
$$\text{where } E(y_i) = \mu_i \text{ and } Var(y_i) = \mu_i + \frac{\mu_i^2}{k}$$
$$\log(\mu_i) = a + b_1 x_{1i} + \ldots + b_p x_{pi} \quad \text{or equivalently} \quad \mu_i = e^{a+b_1 x_{1i}+\ldots+b_p x_{pi}}$$

```
PROC GENMOD data = mydata;
    model y = x1 x2 / type3 dist=negbin;
run;
```

Figure 2. Mathematical formulation and SAS® code for Negative Binomial regression

ZERO-TRUNCATED COUNT MODELS

Modeling hospital visits is slightly different from modeling hospital inpatient admissions. Since individuals who do not visit hospitals do not appear in hospital records, the number of hospital visits is zero-truncated. However, basic Poisson regression and Negative Binomial regression predict non-zero probabilities of zero counts. In order to model hospital visits correctly, we have to use zero-truncated count models. In SAS®, this can be done using PROC FMM and PROC NLMIXED.

Figure 3 describes the mathematical formulation for zero-truncated Poisson regression:

Let y_i be the number of hospital visits for patient i, and let $x_{1i}, \ldots, x_{pi}$ be the explanatory variables for patient i, then the model formulation is:

$$y_i \sim \text{Poisson}(\mu_i) \text{ provided } y_i > 0 \quad \text{i.e.} \quad P(y_i) = \frac{e^{-\mu_i}\mu_i^{y_i}}{y_i!(1-e^{-\mu_i})}$$
$$\text{where } E(y_i) = \mu_i \text{ and } Var(y_i) = \mu_i$$
$$\log(\mu_i) = a + b_1 x_{1i} + \ldots + b_p x_{pi} \quad \text{or equivalently} \quad \mu_i = e^{a+b_1 x_{1i}+\ldots+b_p x_{pi}}$$

Figure 3. Mathematical formulation for zero-truncated Poisson regression

Figure 4 describes the mathematical formulation and SAS® code for zero-truncated Negative Binomial regression:

Let y_i be the number of hospital visits for patient i, and let $x_{1i}, \ldots, x_{pi}$ be the explanatory variables for patient i, then the model formulation is:

$$y_i \sim \text{Negative Binomial}(\mu_i, k) \text{ provided } y_i > 0$$

$$\text{i.e. } P(y_i) = \frac{\Gamma(y_i + k)}{\Gamma(k)\Gamma(y_i + 1)} \left(\frac{k}{\mu_i + k}\right)^k \left(\frac{\mu_i}{\mu_i + k}\right)^{y_i} \frac{1}{1 - \left(\frac{k}{\mu_i + k}\right)^k}$$

$$\text{where } E(y_i) = \mu_i \text{ and } Var(y_i) = \mu_i + \frac{\mu_i^2}{k}$$

$$\log(\mu_i) = a + b_1 x_{1i} + \ldots + b_p x_{pi} \quad \text{or equivalently} \quad \mu_i = e^{a + b_1 x_{1i} + \ldots + b_p x_{pi}}$$

Figure 4. Mathematical formulation for zero-truncated Negative Binomial regression

ZERO-INFLATED COUNT MODELS

On the other hand, if count data has an "excess" number of zeros, zero-inflated count models can be used. In SAS®, this can be done using PROC GENMOD.

DATA

The data comes from the New York City Health and Hospitals Corporation (HHC). HHC operates New York City's public hospitals. This data set of 317,084 patients from all 11 acute care hospitals, 2 long term hospitals, 2 nursing facilities and 6 treatment centers in New York City extends over approximately 4 years (January 2008 to October 2012). Each patient in the data was using at least one beta agonist or beta blocker in this time period.

We provide descriptive statistics for all three kinds of patients: patients who visit emergency rooms and are subsequently discharged, patients who visit our clinics and are subsequently discharged, and patients are admitted as inpatients. The focus of our study is to model hospital inpatient admissions, hence the outcome variable is the number of inpatient admissions for each patient during this time period.

The explanatory variables include indicator variables for whether the patient was on beta blocker and beta agonist "non clinical trial use" in this time period. We define beta blocker and beta agonist "non clinical trial use" as using beta blockers and beta agonists at the same time or using more than one drug of the same class (long-acting beta agonist, short-acting beta agonist, or beta blocker) at the same time. This information is obtained by comparing, for each patient, the starting and ending dates of all drugs prescriptions. Other explanatory variables are patient medical history for diseases thought to be exacerbated or alleviated by beta blocker or beta agonist use, and patient demographics (gender, race, and age). The latter is important because old or young people are often excluded from clinical trials.

Data on hospital visits and medical diagnoses were obtained from hospital billing databases. Data on medications prescribed came from clinical data warehouses. A description of how the data was cleaned and merged, including challenges faced, can be found in the Discussion section of this paper.

RESULTS

DRUGS AND DRUG INTERACTIONS

From Table 1, most patients use short-acting beta agonists or beta blockers; fewer use long-acting beta agonists.

Combination	Number of Patients	Percentage
One or more beta blocker	141,568	44.64%
One or more short-acting beta agonist	196,041	61.83%
One or more long-acting beta agonist	27,829	8.78%

Table 1. Patients on each drug

From Table 2, close to 6% of patients use short and long-acting beta agonists at the same time.

Combination	Number of Patients	Percentage
Short and long-acting beta agonists	18,630	5.88%

Table 2. Patients using short and long-acting beta agonists at the same time

From Table 3, using beta blockers and beta agonists at the same time is more common than the other "non clinical trial" combinations.

Combination	Number of Patients	Percentage
Beta blocker(s) and beta agonist(s)	10,490	3.31%
More than one beta blocker	3,159	1%
More than one short-acting beta agonist	1,158	0.37%
More than one long-acting beta agonist	125	0.04%

Table 3. Patients on beta blocker and beta agonist "non clinical trial use"

DRUG INTERACTIONS AND THEIR ASSOCIATION WITH VARIOUS MEDICAL OUTCOMES

To test if there is any association between drug interactions and death, we use the Chi-Square test for independence or Fisher's Exact Test. To test if total hospital visits, inpatient admissions, clinic visits, and emergency room visits differ by drug interactions, we use the Wilcoxon signed-rank test since count data is not normally distributed.

From Table 4, patients using short and long-acting beta agonists at the same time have significantly different death outcomes compared to patients not using short and long-acting beta agonists at the same time.

Combination	Patient on this combination of drugs?	Died?		Chi-Square Test P-Value	Fisher Exact Test P-Value
		No	Yes		
Short and long-acting beta agonists	No	297,738	716	0.0003	7.964E-05
	Yes	18,610	20		

Table 4. Deaths of patients who are and are not using short and long-acting beta agonists at the same time

From Table 5, patients using beta blockers and beta agonists at the same time have significantly different death outcomes compared to patients not using beta blockers and beta agonists at the same time. However, this is not the case for patients using more than one drug of the same class at the same time.

Combination	Patient on this combination of drugs?	Died?		Chi-Square Test P-Value	Fisher Exact Test P-Value
		No	Yes		
Beta blocker(s) and beta agonist(s)	No	305,894	700	0.0162	0.0225
	Yes	10,454	36		
More than one beta blocker	No	313,196	729	0.9017	1
	Yes	3,152	7		
More than one short-acting beta agonist	No	315,190	736	0.1001*	0.1227
	Yes	1,158	0*		
More than one long-acting beta agonist	No	316,223	736	0.5896*	1
	Yes	125	0*		

Table 5. Deaths by beta blocker and beta agonist "non clinical trial use"

* Fisher's Exact test is recommended over Chi-Square test when cells have low counts.

From Table 6, patients using short and long-acting beta agonists at the same time have significantly different mean visits compared to patients not using short and long-acting beta agonists at the same time.

Combination	Patient on this combination of drugs?	Inpatient Admissions	Emergency Room Visits	Clinic Visits	Total Visits
		Wilcoxon P-Value			
Short and long-acting beta agonists	No	<0.0001	<0.0001	<0.0001	<0.0001
	Yes				

Table 6. Hospital visits of patients who are and are not using short and long-acting beta agonists at the same time

From Table 7, patients on beta blockers and beta agonists at the same time have significantly different mean visits compared to patients not on beta blockers and beta agonists at the same time. This holds for patients using more than one drug of the same class at the same time, with one exception - emergency room visits for patients using

more than one beta blocker at the same time are not significantly different from patients not using more than one beta blocker at the same time.

Combination	Patient on this combination of drugs?	Inpatient Admissions	Emergency Room Visits	Clinic Visits	Total Visits
		Wilcoxon P-Value			
Beta blocker(s) and beta agonist(s)	No	<0.0001	<0.0001	<0.0001	<0.0001
	Yes				
More than one beta blocker	No	<0.0001	0.8213	<0.0001	<0.0001
	Yes				
More than one short-acting beta agonist	No	0.0826	<0.0001	<0.0001	<0.0001
	Yes				
More than one long-acting beta agonist	No	<0.0001	<0.0001	<0.0001	<0.0001
	Yes				

Table 7. Hospital visits by beta blocker and beta agonist "non clinical trial use"

DRUG INTERACTIONS AND INPATIENT ADMISSIONS

From Table 8, inpatient admission distributions of patients using short and long-acting beta agonists at the same time have higher mean and variance compared to that of patients not using short and long-acting beta agonists at the same time. From Figure 5, a higher proportion of patients not using short and long-acting beta agonists at the same time are never admitted as inpatients.

Combination	Patient on this combination of drugs?	Inpatient Admissions	
		Mean	Standard Deviation
Short and long-acting beta agonists	No	0.82	1.82
	Yes	1.64	3.35

Table 8. Inpatient admissions of patients who are and are not using short and long-acting beta agonists at the same time

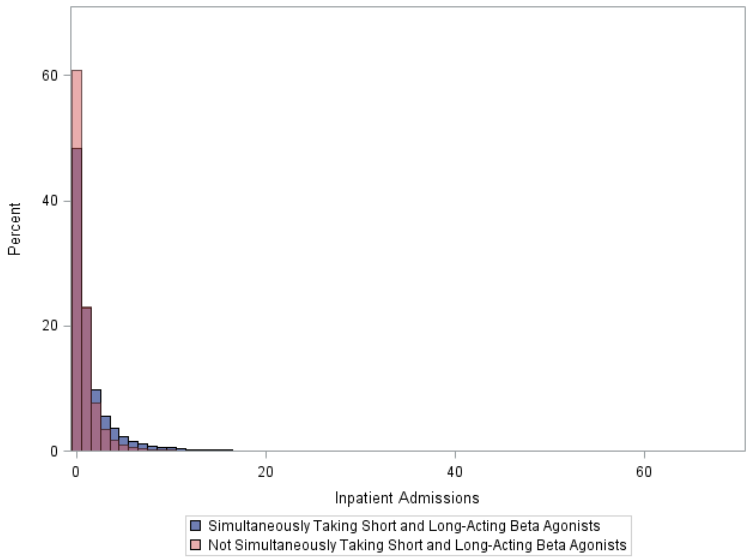

Figure 5. Inpatient admissions of patients who are and are not using short and long-acting beta agonists at the same time

From Table 9, inpatient admission distributions of patients on beta blocker and beta agonist "non clinical trial use" have higher mean and variance compared to that of patients not on beta blocker and beta agonist "non clinical trial use". We also see this in Figure 6 where the distribution of hospital inpatient admissions for patients on beta blocker and beta agonist "non clinical trial use" is more long-tailed, especially for patients using more than one long-acting beta agonist at the same time, where several patients have as many as 50 inpatient admissions.

Combination	Patient on this combination of drugs?	Inpatient Admissions	
		Mean	Standard Deviation
Beta blocker(s) and beta agonist(s)	No	0.81	1.83
	Yes	2.52	3.84
More than one beta blocker	No	0.85	1.92
	Yes	2.30	4.03
More than one short-acting beta agonist	No	0.86	1.95
	Yes	1.31	3.55
More than one long-acting beta agonist	No	0.86	1.95
	Yes	3.78	6.52

Table 9. Inpatient admissions summary statistics of patients on and not on beta blocker and beta agonist "non clinical trial use"

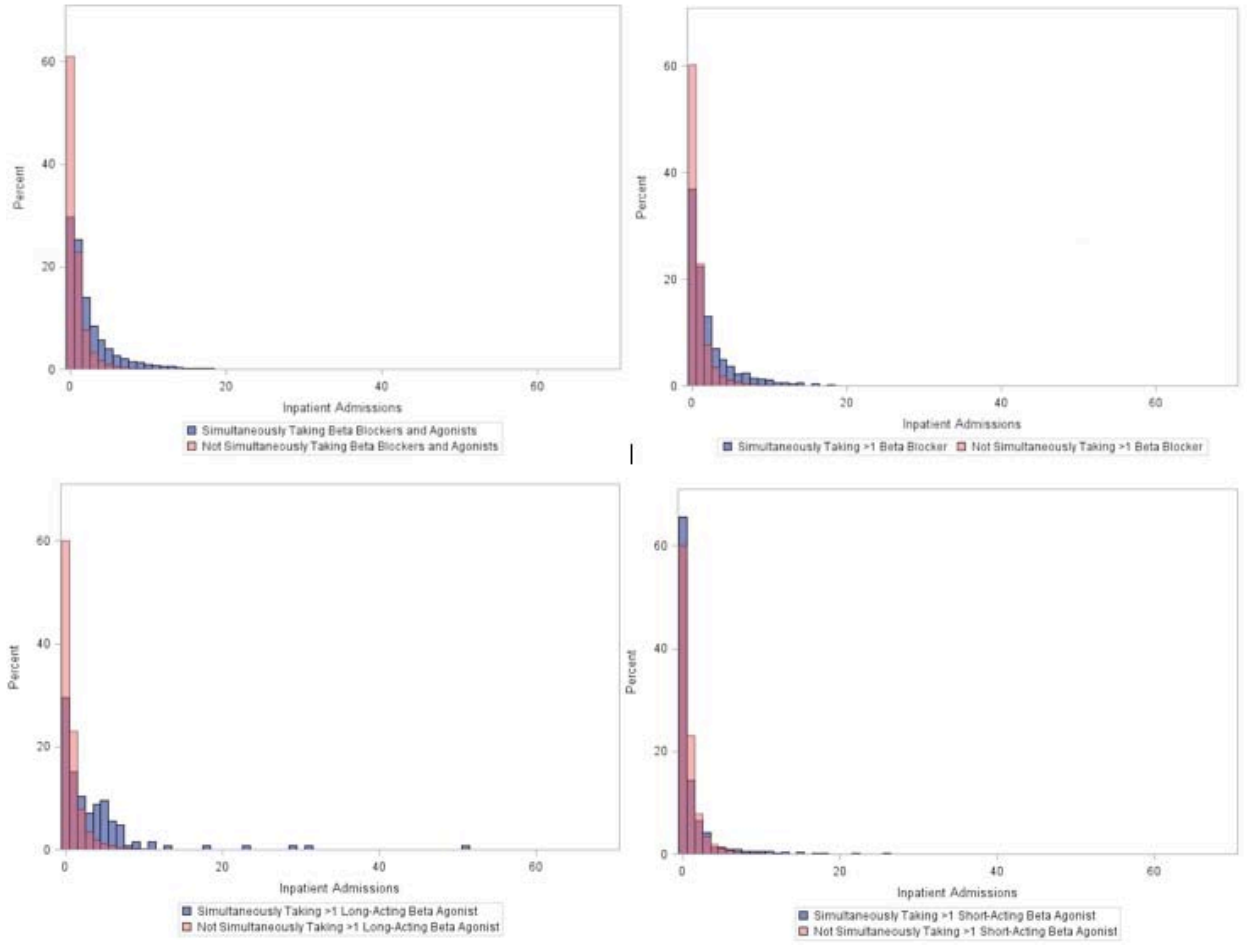

Figure 6. Inpatient admissions histogram of patients on and not on beta blocker and beta agonist "non clinical trial use"

REGRESSION MODELS

We start with a Poisson regression for hospital inpatient admissions with all explanatory variables. After several rounds of model selection, we settled on a model with variables that fit the data well and are medically meaningful. SAS® output is presented in the Appendices section of this paper. The coefficient of the indicator variable for a patient being on more than one long-acting beta agonist is 0.4909. In order to interpret this coefficient, we first take it

to the power of the natural exponential, i.e. exp(0.4909), and obtain 1.63. This is known as the incidence rate ratio; similar to the odds ratio, it can be interpreted as patients on more than one long-acting beta agonist tend to be admitted at a rate that is 63% higher than patients not on more than one long-acting beta agonist, holding all other explanatory variables constant. The incidence rate ratios for being on more than one short-acting beta agonist, being on more than one beta blocker, and being on beta blockers and beta agonists at the same time, are 1.34, 1.43, and 1.12 respectively. Besides these indicator variables for whether the patient was on beta blocker and beta agonist "non clinical trial use", we included indicator variables for gender, race, age, and medical history. The intercept term represents the base category of non-black females between 5 and 64 years old with no medical history of asthma, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), acute myocardial infarction (AMI), pneumonia, psychiatric illness, headache, or hypertension. The intercept term is -1.8049, which means patients in this base category have expected inpatient admissions of exp(-1.8049) = 0.16. The coefficients for the indicator variables for age less than 4 and age greater than 65 are all positive, signifying that extremely young and old patients tend to have higher admission rates. The coefficients for all medical history indicators are positive, with hypertension having the largest incidence rate ratio of 2.46 followed by pneumonia with an incidence rate ratio of 2.37; as expected, patients with a history of these diseases tend to be admitted to the hospital more often.

Although all the explanatory variables are statistically significant, the Poisson model does not fit that well, with the model deviance being quite high. Moreover, the scaled Pearson chi-square of 2 tells us that the variance of hospital inpatient admissions is roughly twice its mean, hence mild over-dispersion is present.

Negative Binomial regression is a type of count model that can better handle over-dispersion. SAS® output is presented in the Appendices section of this paper. This model showed a significant improvement in model fit compared to the previous model, with the model deviance being low enough to pass the deviance goodness-of-fit test. All coefficients are still statistically significant and the scaled Pearson Chi-Square value is now 1.3, a decrease from before. By and large, the relationships between the explanatory variables and hospital inpatient admissions remain the same as described above. The indicator variables for "non clinical drug use" now have even larger coefficients, which means their presence increases the hospital inpatient admission rate even more than before. Indeed, the incidence rate ratio for patients on more than one long-acting beta agonist has spiked from 1.63 to 2.3, signifying that patients on more than one long-acting beta agonist tend to be admitted as inpatients at a rate that is more than double that of patients not on more than one long-acting beta agonist, holding all other explanatory variables constant. Many of the coefficients for medical history indicators have similar large spikes, with the incidence rate ratios for CAD, pneumonia, psychiatric illness, and hypertension all above 2.

DISCUSSION

REGRESSION RESULTS

During clinical trials, patients are often excluded for various reasons. Some of these reasons are: increased potential liability (e.g. pregnant patients), more problems with consent (e.g. children, mentally handicapped), theoretical increased susceptibility to side effects (e.g. asthmatics and beta blockers), potential interaction with other medication (e.g. giving a beta agonist to a patient using a beta blocker), the presence of confounding conditions that would make analysis difficult (e.g. giving a second beta blocker to patient still using a different beta blocker), or any situation which might make it difficult to show that the drug is efficacious – the goal of the study. For whatever reason, some of our real life patients were using beta selective drugs in ways that were not tested clinically. As best we can, we statistically adjust for confounding conditions, such as the presence of relevant diseases and then look for residual effects of the "non clinical trial" drug combinations.

DATA CLEANING

Hospital records offer up their own set of challenges. We dealt with some using the following SAS® programming techniques:

- Hospitals store different types of records in different databases. We pulled wanted information from all relevant databases and merge the different data sets together. This was done using the MERGE statement in the data step. Initial non-matches were identified using the (IN=xxx) options and iterative matching was done using other identifiers. In Point 3 below, we describe in greater detail the 10-step merging system we used on 7 pieces of patient identifying information.
- Some data are organized as one record per patient, some as one record per admission, and some as one record per event. We used SAS data step coding, including the use of multiple arrays to flatten hierarchical data, to transform a patient's multiple hospital inpatient admissions records into one record with information on all the patient's drug prescriptions and diagnoses.
- We tracked patients accurately across different hospitals to accurately count all patients' drug prescriptions, as a patient could have a valid prescription filled at a hospital different from the hospital where he or she first obtained

the prescription. Different hospitals, even those within the same system such as New York City's public hospitals, typically have different ways of identifying patients. To track patients across different hospitals, we developed a 10-step system involving 7 pieces of patient identifying information, including facility-specific medical record number, social security number, birth date, last name, first name, and gender, used in different combinations in different steps, prioritizing information less prone to typos by hospital clerks.

- New York City's public hospitals, the largest municipal healthcare system in the US, serves a large number of patients, hence SAS macro programming is essential to avoid repeatedly typing in the same lines of code to import and clean this immense data set for analysis.

CONCLUSION

Very rarely are a drug's possible interactions with all other drugs fully investigated during clinical trials. The FDA's adverse drug event reporting system attempts to monitor the performance of drugs in the real world. This study demonstrates that we can also mine hospital records and other drug prescription records to detect negative drug interactions. Using count models such as Poisson regression and Negative Binomial provided by PROC GENMOD in SAS®, we investigated if patients on beta blocker and beta agonist "non clinical trial use" are more likely to be admitted to the hospital. A Negative Binomial model better fit our data as it was able to handle over-dispersion. We found that patients on beta blocker and beta agonist "non clinical trial use", extremely young patients, older patients, and patients with history of illnesses such as hypertension, CAD, and pneumonia tend to have higher hospital inpatient admission rates. For future work, other medical outcomes that can be studied include length of hospital stay, death, and 30-day readmission. More explanatory variables can also be used to augment the models to provide an even clearer picture of the mechanisms behind hospital inpatient admissions.

REFERENCES

1. U.S. Food and Drug Administration. "FDA AERS Reports Received and Reports Entered into AERS by Year". 31 December 2010. Accessed 15 November 2012. < http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm>
2. U.S. Food and Drug Administration. "FDA AERS Patient Outcomes by Year". 31 December 2010. Accessed 15 November 2012. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070461.htm
3. Ledford, Heidi. "Drug data reveal sneaky side effects". Nature News. 14 March 2012. Accessed 15 November 2012. < http://www.nature.com/news/drug-data-reveal-sneaky-side-effects-1.10220>
4. Tatonetti, Nicholas P., J. C. Denny, S. N. Murphy, G. H. Fernald, G. Krishnan, V. Castro, P. Yue, P. S. Tsau, I. Kohane, D. M. Roden, R. B. Altman. "Detecting Drug Interactions From Adverse-Event Reports: Interactions Between Paroxetine and Pravastatin Increases Blood Glucose Levels". Clinical Pharmacology & Therapeutics. 2011.
5. Liu, WenSui, Jimmy Cela. "Count Data Models in SAS". Online Proceedings of SAS Global Forum. 2008.

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APPENDICES

REGRESSION COEFFICIENTS

Poisson Regression

Variable	Estimate	Exp(Estimate)	Standard Error	P-Value
Intercept	-1.8049	0.16	0.0064	<.0001
Beta blocker(s) and beta agonist(s)	0.1114	1.12	0.0071	<.0001
More than one beta blocker	0.3595	1.43	0.0259	<.0001
More than one short-acting beta agonist	0.2926	1.34	0.0461	<.0001
More than one long-acting beta agonist	0.4909	1.63	0.0121	<.0001
Gender – Male	0.1301	1.14	0.0039	<.0001
Race – Black	0.1151	1.12	0.0039	<.0001
Age – 4 or younger	0.0295	1.03	0.0197	0.1343
Age – 65 to 80 years old	0.0592	1.06	0.0049	<.0001
Age – 81 or older	0.2439	1.28	0.0062	<.0001
Medical history – asthma	0.2607	1.30	0.0044	<.0001
Medical history – COPD	0.3928	1.48	0.0061	<.0001
Medical history – CAD	0.6661	1.95	0.0047	<.0001
Medical history – AMI	0.2309	1.26	0.0070	<.0001
Medical history – pneumonia	0.8632	2.37	0.0046	<.0001
Medical history – psychiatric illness	0.8395	2.32	0.0041	<.0001
Medical history – headache	0.5985	1.82	0.0080	<.0001
Medical history – hypertension	0.9014	2.46	0.0056	<.0001

Negative Binomial Regression

Variable	Estimate	Exp(Estimate)	Standard Error	P-Value
Intercept	-1.9371	0.14	0.0088	<.0001
Beta blocker(s) and beta agonist(s)	0.1429	1.15	0.0125	<.0001
More than one beta blocker	0.3655	1.44	0.0215	<.0001
More than one short-acting beta agonist	0.2956	1.34	0.0432	<.0001
More than one long-acting beta agonist	0.8335	2.30	0.0993	<.0001
Gender – Male	0.1379	1.15	0.0056	<.0001
Race – Black	0.1225	1.13	0.0055	<.0001
Age – 4 or younger	0.0659	1.07	0.0231	0.0043
Age – 65 to 80 years old	0.0954	1.10	0.0073	<.0001
Age – 81 or older	0.3427	1.41	0.0098	<.0001
Medical history – asthma	0.2642	1.30	0.0065	<.0001
Medical history – COPD	0.4179	1.52	0.0109	<.0001
Medical history – CAD	0.7477	2.11	0.0073	<.0001
Medical history – AMI	0.2876	1.33	0.0127	<.0001
Medical history – pneumonia	0.9807	2.67	0.0075	<.0001
Medical history – psychiatric illness	0.9445	2.57	0.0056	<.0001
Medical history – headache	0.6461	1.91	0.0145	<.0001
Medical history – hypertension	0.9053	2.47	0.0073	<.0001

DRUGS

Short-Acting Beta Agonists

albuterol, ventolin, airomir, Proventil, salbutamol, asmasal, buventol, inspiryl, salamol, salbulin, ventodisk, aerolin

bambuterol, bambec

isoetherine, bronkosol, bronkometer

isoproterenol, isuprel

levalbuterol, xopenex

metaproterenol, alupent, metaprel, prometa

pirbuterol, maxair

terbutaline, breathaire, brethine, bricanyl

tornalate, bitolerol

fenoterol, berotec

Long-Acting Beta Agonists

Formoterol, foradil, oxis

salmeterol, serevent

Beta Blockers (Including Non-Selective, Cardio Selective, and Alpha-Beta Blockers)

propranolol

sotalol

timolol

pindolol

levobunolol

nadolol

metipranolol

atenolol

acebutolol

metoprolol

bisoprolol

esmolol

betaxolol

nebivolol

labetalol

carvedilol