



A CROSS-SECTIONAL STUDY OF GERIATRIC LABELING FOR HIGH IMPACT MEDICATIONS USED BY OLDER AMERICANS

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Abbreviations definition

ADEs = Adverse Drugs Events

AOU = Assessment of Underutilization

AOR = Adjusted Odds Ratio

BLA = Biologics License Application

CBER = Center for Biologics Evaluation and Research

CDER = Center for Drug Evaluation and Research

CFR = Code of Federal Regulations

CMS = Centers for Medicare/Medicaid Services

CNS = Central Nervous System

CVS = Cardiovascular System

ED = Emergency Department

Endo = Endocrine

FDA = Food and Drug Administration

FR = Federal Register

FORTA = Fit fOR The Aged

Hema = Hematology

HIMs = High Impact Medications

HRMs = High Risk Medications

IMS = Institute for Healthcare Informatics

NDA = New Drug Application

OR= Odds Ratio

Pk = Pharmacokinetics

USDHHS = United States Department of Health and Human Services

Abstract

Background

This study assessed the availability of geriatric information in labeling for FDA-approved drug products most frequently used by Medicare Part D beneficiaries and designated by the Centers for Medicare & Medicaid Services (CMS) to be high risk medications for older adults.

Methods

Drugs@FDA, our database, served as the primary tool for the research. We used the most current (2017) approved labeling to analyze 30 prescription drugs that meet our operational definition of High Impact Medications (HIMs) for older adults. The prevalence of geriatric information was assessed in the relevant drug labels using descriptive statistics (e.g., frequency and percentage). Examining the number and percentage of drug labels as well as any of specific information of interest (e.g., efficacy, safety, dosing recommendations, etc.). The data were then stratified by year of approval, year of milestone labeling regulation dates (1998 and 2007), and drug class. Fisher's exact test was utilized to assess the independence between the year of approval and the geriatric drug labeling information, considering years of milestone labeling regulation (1998); a p-value of < 0.05 was considered statistically significant.

Results

At the end of our analysis analyses, we realized that out of the 30 HIM labels, 17% (n=5) had the information of interest (geriatric dosing, efficacy, and safety) and 83% (n=25) did not have all the labeling information of interest. Of the 30 labels we reviewed, the odds of the presence of the geriatric information in the labeling of HIMs approved after 1998, is about one-third the odds of occurrence of the geriatric information in the labeling of HIMs passed before 1998.

Conclusion

All in all, the geriatric information content of the High Impact Medication labels we examined has not significantly changed since 1998.

Introduction

Populations across the globe are aging at an exponential rate and the increase poses a greater challenge to resource-constrained communities. Based on the Population Reference Bureau, the number of Americans ages 65 and older is projected to double from about 46 million today to over 98 million by 2060¹. Therefore, issues that affect geriatric populations may generate public health crises if they are not effectively controlled. Moreover, the extensive medication use in geriatric populations is accompanied by an increase in occurrence of adverse drug events (ADEs).

The geriatric ADE rate depends on whether the geriatric subpopulation is outpatient, inpatient, institutionalized, or post-hospital discharge. In a cohort study of outpatient Medicare enrollees aged ≥ 65 years², the overall rate of ADEs was about 5% per year³; 38% of these ADEs were severe. The nursing home population ADE rate ranged from 1.9 - 9.8% per month. During hospitalization, 14.6-31.9% of older adults' experience ADEs⁴.

The labeling of a drug is the most reliable source for safe drug utilization. To appropriately use medications, patients and their caregivers including healthcare providers need reliable information. Therefore, optimizing drug labeling is among the most effective approaches to promote the safe use of medications by older adults. Since 1990, FDA has instituted a variety of provisions to improve geriatric drug safety to ensure that the public has adequate information for appropriate drug use for older adults (Federal Register, Geriatric Labeling Final Rule, 1997)⁵. On November 1, 1990, FDA published in the Federal Register (55 FR 46134) an amendment to the prescription drug regulations to include a "Geriatric Use" subsection to the "Precautions" section of drug labeling. On August 27, 1997, FDA published the final rule (62 FR 45313) which required drugs approved before August 27, 1998, to submit a supplement with a *Geriatric Use* subsection. Moreover, marketing applications (e.g., NDAs, BLAs) filed after August 27, 1998, were to include a *Geriatric Use* subsection in the proposed labeling (Federal Register, Geriatric Labeling Final Rule, 1997)⁶. On January 24, 2006, FDA updated its labeling content and format regulations (71

FR 3922), by establishing a *Geriatric Use* subsection in the USE IN SPECIFIC POPULATIONS section; making drug labeling for geriatric use a priority. Also, CMS has designated certain drugs as high impact for geriatric populations; a high impact drug is a drug that is among the most frequently used medications by Medicare Part D beneficiaries; therefore, are an important subset of drugs valuable for effective geriatric drug safety monitoring.

Despite the numerous efforts at the federal level to reduce ADEs in the US (National Action Plan for Adverse Event Prevention)⁷, there has not been any significant reduction in medication use including HRMs in geriatric populations⁸. In fact, ADE rates seem to be increasing among US geriatric populations. Shehab *et al.* (2016) reported that the population rate of older Americans visiting EDs for ADEs rose from 5.2 per 1000 in 2005-2006 to 9.7 per 1000 in 2013-2014⁹. Reasons for the increase are likely multifactorial. While the increasing average number of medications used per older adult may be contributing to the rise in ADEs, adequacy of geriatric information in drug labeling is not fully explored. For ADEs risk minimization, especially through preventable ADEs such as medication errors, availability of labeling information is critical, especially for HIMs.

In this study, we assessed the availability of geriatric information in the labeling for HIMs for geriatric populations. The knowledge generated from this study has the potential use by public health and regulatory agencies such as FDA, CMS, CDC, and Administration for Community Living (ACL) since enhancing geriatric drug labeling is likely to increase drug safety for older Americans.

Methods

Experimental design: A Cross-sectional study

Using the most current (2017) approved labeling in Drugs@FDA, 30 prescription drugs that meet our operational definition of HIMs for older adults were analyzed. The following information was extracted: The initial year of drug approval, the presence or absence of dosing recommendations, efficacy, and safety, including warning and precautions information specific to geriatric populations. If none of the information of interest is included in the labeling, an assignment of “absent” was given. If the information is included in the labeling, an assignment of “present” was given only if the labeling states that older adults were evaluated in clinical studies and there were no differences in pharmacokinetics and pharmacodynamics (i.e., efficacy and safety) between them and young adults (18-64 years of age).

Statistical Analysis Plan:

We assessed the prevalence of geriatric information in the relevant drug labels using descriptive statistics (e.g., frequency and percentage). Specifically, we examined the number and percentage of drug labels as well as any of specific information of interest (e.g., efficacy, safety, dosing recommendations, etc.). The data were then stratified by year of approval, year of milestone labeling regulation dates (1998 and 2007), and drug class. Finally, we used Fisher's exact test to assess the independence between the year of approval and the geriatric drug labeling information, considering years of milestone labeling regulation (1998); a p-value of < 0.05 was considered statistically significant.

Results

Of the 30 HIM labels, as shown in Figure 1, 30% (n=9) were cardiovascular drugs, 27% (n=8) antilipid drugs, 20% central nervous system drugs, 13% (n=6) endocrine drugs, 7% (n=2) hematologic drugs, and 3% (n=1) drugs for treating pain. Table 1 shows that 83% (n=25) of all the HIM drug labels reviewed had information on geriatric dosing, efficacy or safety and 17%

(n=5) did not have any of the three categories of information of interest. Conversely, only 17% (n=5) of all the HIM drug labels had all the information of interest (geriatric dosing, efficacy, and safety) and 83% (n=25) did not have all the information of interest simultaneously in the labeling.

Figure 2 shows the percentages of the presence of geriatric information (dosing or efficacy or safety) in labeling by approval year. Before 1998, 92.3% of the drugs had geriatric information in the labeling as against 76.5% after 1998. On the other hand, before 2007, 88.5% of the drugs had geriatric information, but after 2007, only 50% of the drugs had geriatric information in the labeling. As displayed in Figure 3, when the analysis is limited to only geriatric efficacy and safety data, the presence of the information by drug class was endocrine – 100%, antilipid- 62.5%, cardiovascular- 55.6%, central nervous system drugs - 33.3%. None of the labels for hematologic and pain drugs we reviewed had both geriatric efficacy and safety data in the same label.

Of the 30 labels we reviewed, the odds of presence of the geriatric information in the labeling of HIMs approved after 1998 is about one-third the odds of presence of the geriatric information in the labeling of HIMs approved before 1998 (Odds ratio=0.27), the difference in presence of information was, however, not statistically significant ($p=0.35$).

Discussion

This cross-sectional study reveals relevant information useful to healthcare providers, geriatric patients and anyone interested in the efficacy and safety of most drugs prescribed to elders as High Impacts. For our study, the geriatric dosing or efficacy or safety information in the labeling of the drugs is equally essential. One of our study strength relies on the fact that we focused on HIMs drugs. Most of the labels we reviewed (83%) did have geriatric dosing, efficacy or safety information in the labeling of the drug. Conversely, we found that only less than one-fifth (17%) had all the crucial information present in the labeling of the drug. This is very important, especially when it comes to drug prescription to geriatric patients. Absence of information necessary for safe and appropriate use of the drug increase the risk for occurrence of ADEs. Hinshaw identified that

about more than 1/3 geriatric relevant new molecular entities lacked sufficient information in the manufacturer's FDA-approved labeling to be prescribed to geriatric patients¹⁰; From Hinshaw's study, the information gap extends to new molecular entities, which further increases risk for ADEs in the geriatric population.

Among the drugs we studied, the three most frequent drug classes were cardiovascular agents, antilipid and central nervous system agents. These drug classes reflect the high frequency of geriatric diseases associated with cardiovascular, lipid and the central nervous systems. It is essential to point out that, of the top three drug classes, the central nervous system drugs had prevalence of about 30% of the presence of both geriatric efficacy and safety information in the drug labeling. If this finding persist after review of a larger sample of HIM labels, then CNS drugs may be a priority drug class for drug developers to focus on to inclusion of geriatric information in the relevant labeling.

The lack of a statistically significant change in the presence of information in HIMs labeling since 1998 is of concern, particularly if this finding is confirmed after a review of a larger sample of labels. A potential explanation of such a finding may be the continued absence of data from older adults due to persistence of their limited inclusion in drug development programs.

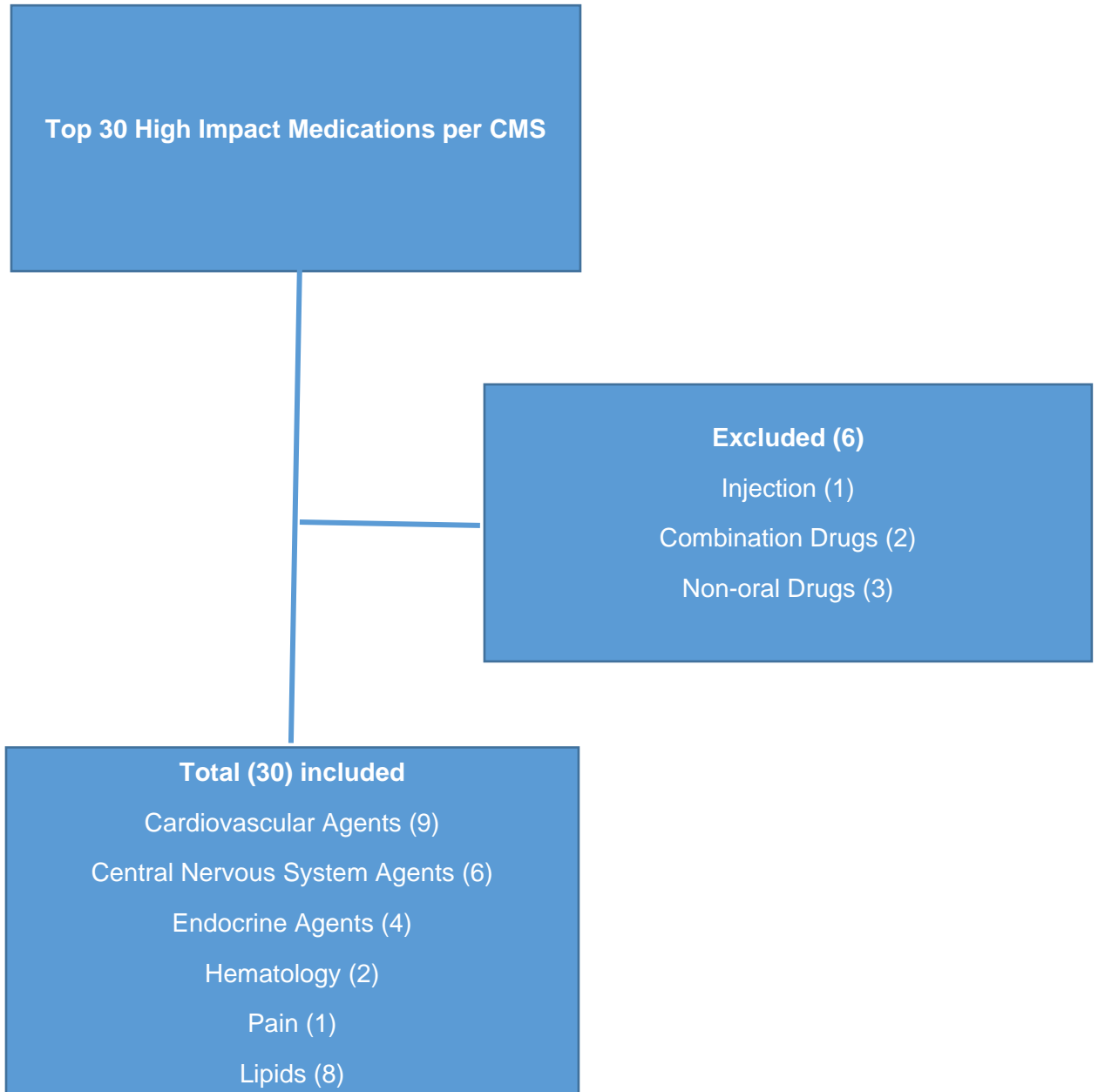
This study's strength is the fact that, we focused on HIMs drugs in a vulnerable population. The primary limitation for our study is the sample size of the number of labels reviewed. Future studies should include a larger sample size of drug labels, especially HIMs in the class of drugs used to treat hematology, endocrine and pain conditions. Nevertheless, this study provides preliminary insights into geriatric drug labeling especially those that are constantly/frequently prescribed to geriatric patients.

Conclusion

The geriatric information content of the High Impact Medication labels we examined has not significantly changed since 1998. Additionally, CNS drugs may be a high priority drug class for inclusion of geriatric efficacy and safety information in the relevant labeling. For the past two

decades, the labeling of the drugs has not improved especially the most essential section of a drug label for geriatric patients: *Geriatric Use* subsection in the USE IN SPECIFIC POPULATIONS section.

Schema of the HIMs



Top 30 HIMs selected

Brand	Generic	Class
PLAVIX	Clopidogrel bisulfate	Cardiovascular
LEXAPRO	ESCITALOPRAM OXALATE	Central Nervous System
CYMBALTA	DULOXETINE HCL	Central Nervous System
JANUVIA	SITAGLIPTIN PHOSPHATE	Endocrine
ACTOS	PIOGLITAZONE HCL	Endocrine
XARELTO	RIVAROXABAN	Hematology
ABILIFY	ARIPIRAZOLE	Central Nervous System
ZYPREXA	OLANZAPINE	Central Nervous System
OXYCONTIN	Oxycodone HCL	Pain
PRADAXA	DABIGATRAN ETEXILATE MESYLATE	Hematology
ONGLYZA	SAXAGLIPTIN HCL	Endocrine
SEROQUEL XR	QUETIAPINE FUMARATE	Central Nervous System
RISPERDAL CONSTA	Risperdone Microspheres	Central Nervous System
ZOCOR	Simvastatin	Lipid
PRINIVIL	Lisinopril	Cardiovascular
NORVASC	Amlodipine Besylate	Cardiovascular
LIPITOR	Atorvastatin Calcium	Lipid
COZAAR	Losartan Potassium	Cardiovascular
TOPROLOL XL	Metoprolol succinate	Cardiovascular
PRAVACHOL	Pravastatin Sodium	Lipid
CRESTOR	Rosuvastatin Calcium	Lipid
DIOVAN	Valsartan	Cardiovascular
ZETIA	VALSARTAN	Lipid
TRICOR	Fenofibrate Nanocrystallized	Lipid
BYSTOLIC	Nebivolol HCL	Cardiovascular
BENICAR	Olmesartan Medoxomil	Cardiovascular
NIASPAN	Niacin	Lipid
WELCHOL	Colesevelam HCL	Lipid
RANEXA	Ranolazine	Cardiovascular
LANTUS	Insulin Glargine	Endocrine

Presence of geriatric dosing or efficacy or safety information in the labeling	83% of the drugs DO (n=25)
	17% of the drugs do NOT (n=5)
Presence of geriatric dosing and efficacy and safety information in the labeling.	17% of the drugs DO (n=5)
	83% of the drugs do NOT (n=25)

Table 1: Geriatric Drug Labeling information of all the 30 High Impact Medications.

Figure1: Pie Chart of HIM Drug Class

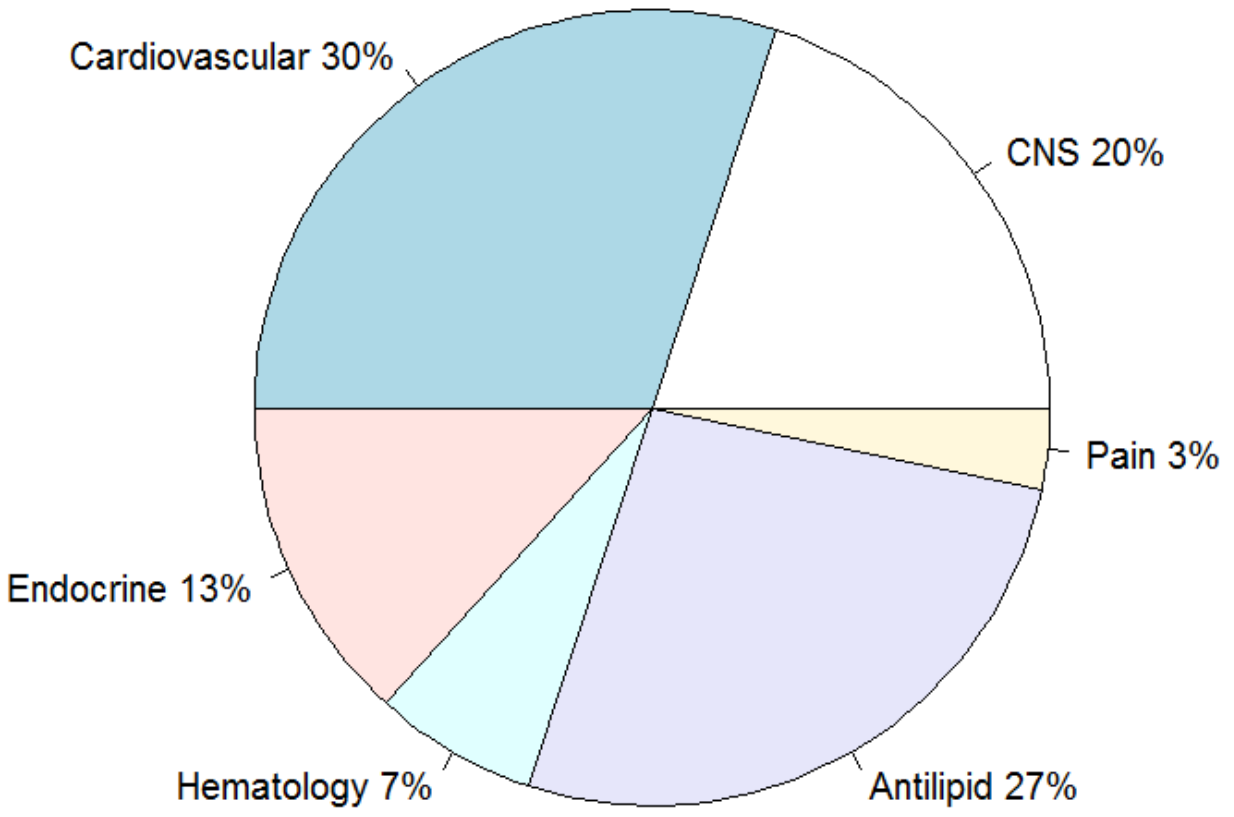


Figure 2: Percentage of Presence of Geriatric Information by Approval Year

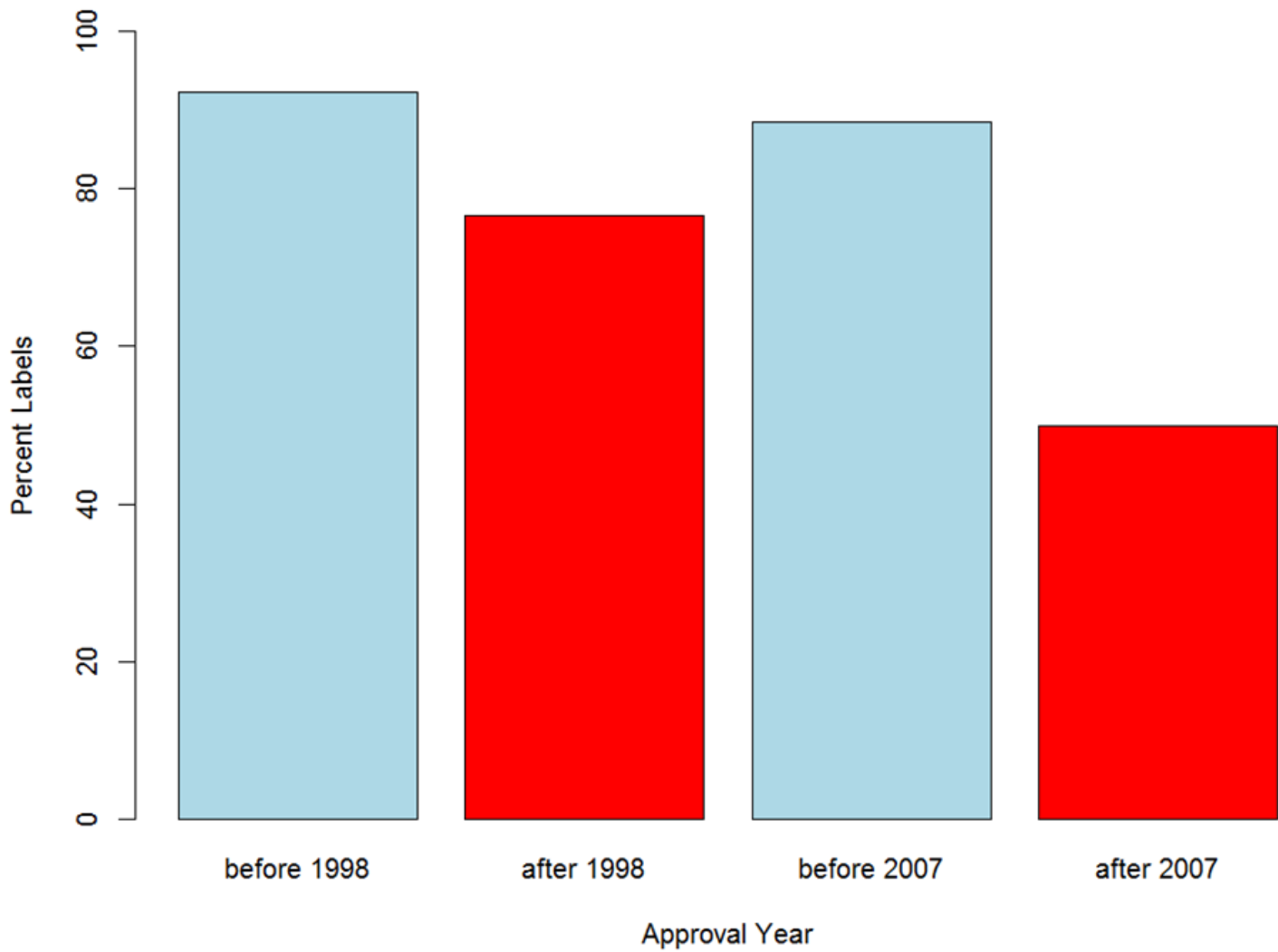
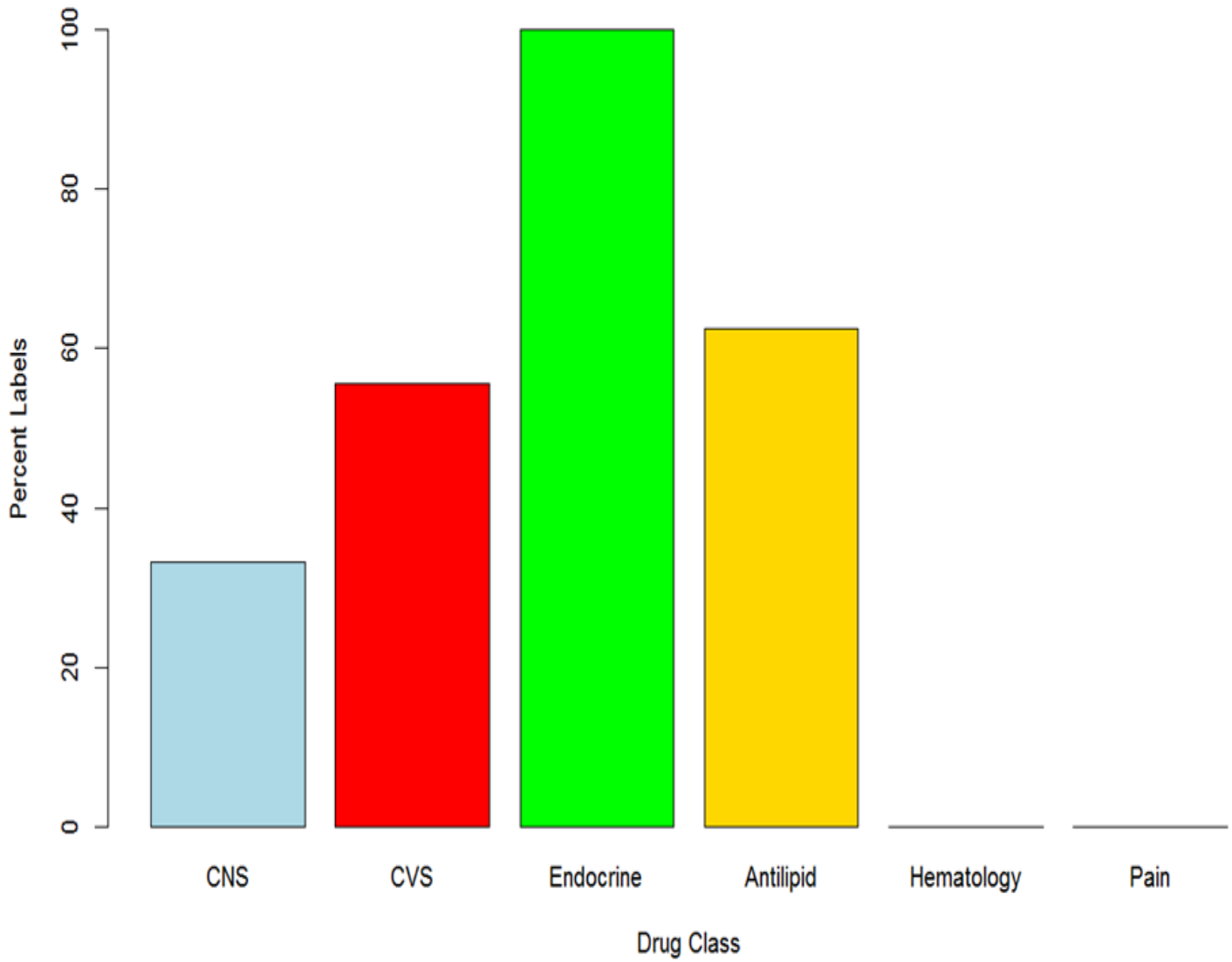


Figure 3: Percentage of Presence of Both Geriatric Efficacy and Safety Information by Drug Class



References:

- 1- Mather, M. (2016): The Population Reference Bureau report, "Aging in the United States." <http://www.prb.org/Publications/Media-Guides/2016/aging-unitedstates-fact-sheet> (Accessed 11/19/2017).
- 2- Gurwitz JH, Field TS, Judge J, Rochon P, Harrold LR, Cadoret C, Lee M, White K, LaPrino J, Erramuspe-Mainard J, DeFlorio M, Gavendo L, Auger J, Bates DW (2005): The incidence of adverse drug events in two large academic long-term care facilities. *Am J Med.*; 118(3):251-8.
- 3- Gray SL, Sager M, Lestico MR, Jalaluddin M (1998): Adverse drug events in hospitalized elderly; *J Gerontol A Biol Sci Med Sci.* 1998 Jan;53(1):M59-63.
- 4- Page RL and Ruscin JM (2006): The risk of adverse drug events and hospital-related morbidity and mortality among older adults with potentially inappropriate medication use. *The American Journal of Geriatric Pharmacotherapy*; 4 (4): 297-305.
- 5- Federal Register, Geriatric Labeling Final Rule: <https://www.gpo.gov/fdsys/pkg/FR-1997-08-27/pdf/97-22701.pdf> (Accessed 11/29/2017).
- 6- Federal Register, Geriatric Labeling Final Rule: <https://www.gpo.gov/fdsys/pkg/FR-1997-08-27/pdf/97-22701.pdf> (Accessed 11/29/2017).
- 7- Stevenson DG, Dusetzina SB, O'Malley AJ, Mitchell SL, Zarowitz BJ, Chernew ME, Newhouse JP, Huskamp HA (2004): High-risk medication use by nursing home residents.
- 8- Qato DM and Trivedi AN (2013): Receipt of high risk medications among elderly enrollees in Medicare Advantage plans. *J Gen Intern Med.*;28(4):546-53.
- 9- Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS (2016): US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA.* 22;316(20):2115-2125.
- 10- Hinshaw, T., Kapusnik-Uner, J., Zarowitz, B., & Matuszewski, K. (2013, September). Identifying Knowledge Gaps in the Labeling of Medications for Geriatric Patients. Retrieved February 02, 2018, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828932/>.

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