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### Influence Of Medicare Formulary Restrictions On Evidence-Based Prescribing Practices

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Influence of Medicare Formulary Restrictions on Evidence-Based  
Prescribing Practices

A Thesis Submitted to the Yale University School of Medicine in Partial  
Fulfillment of the Requirements for the Degree of Doctor of Medicine

By

Aishwarya Vijay

2020

## **Abstract**

Controlling the cost of prescription drugs is integral to improving health outcomes, and patient access and adherence to treatment. While prescription drugs can often provide essential therapeutic benefit, previous studies have suggested that inappropriate prescription drug use is a principal cause of adverse drug events as well as abuse and diversion of drugs. Thus, balancing the benefits and harms to promote appropriate prescription drug use is an essential component of healthcare delivery in the United States. There are multiple ways appropriate prescription drug use is promoted. Black-box warnings and drug labeling controlled by the FDA as well as guidelines released by the CDC, such as the 2013 guidelines released during the opioid epidemic, aim to promote appropriate prescription at a population level. At a patient-level, drug formularies have multiple strategies in place to promote safe and cost-effective prescribing of individual medications.

The Center for Medicare & Medicaid Services (CMS) makes use of prescription drug formularies that are used for the coverage of around 17% of the US population. These formularies have uniformly adopted utilization management strategies, such as quantity limits, prior authorization, and step therapy, in order to promote safe, evidence-based and cost-effective prescribing. These strategies are in place to impact drug prescription rates as well as to incentivize use of biological or therapeutically interchangeable generics over brand-name drugs. Thus far, the implementation of utilization management strategies for commonly prescribed drugs has not been thoroughly studied.

This study presents three main analyses conducted and published in the peer reviewed literature during my time in medical school. The first characterized the change in opioid prescription versus non-opioid analgesics in both the outpatient and emergency room setting in

the context of the 2013 CDC guidelines encouraging prescription on non-opioid analgesic alternatives. We found that overall rates of pain medication prescribing were high and that opioid pain medication prescription increased in the outpatient setting only, whereas non-opioid pain medication prescribing increased in both the outpatient and ED settings, an area that has not been previously reported or well-investigated.

The second study characterized how Medicare formulary restrictions were applied to opioid “potentiators”, which are commonly used in conjunction with opioids and increase patients’ risk of adverse events. We found that from 2013-2017, Medicare prescription drug plan formularies had relatively unchanged rates of benzodiazepine, non-benzodiazepine sedative-hypnotic, and gabapentinoid coverage with small increases in use of quantity limits, and that more than a quarter of formularies provided unrestrictive coverage of these potentially unsafe opioid potentiators in 2017.

The third and final study herein presents a more global analysis of whether Medicare used formulary restrictions to promote prescription of therapeutically interchangeable generics over the top 100-grossing brand-name drugs in light of the 2020 CMS plans for an indication-based formulary design. We showed that a substantial portion of CMS formularies provided similarly restrictive coverage of brand-name drugs and their therapeutically interchangeable generics, including the same tier placement or utilization management, thereby missing opportunities to incentivize prescribing of less costly generics.

Overall, the results of this comprehensive study on safe and cost-effective drug prescription showed that while current formulary design includes opportunities to reduce costly and potentially unsafe prescribing, the impact of these tools is sub-optimal. These results highlight the need for both physician and patient education on the utility of the formulary

restriction strategies. On a larger scale, it suggests that these strategies alone may not be sufficient to reduce over-prescription of potentially unsafe drugs like opioid potentiators, or to incentivize prescription of cost-saving generics over brand-name drugs. The Center for Medicare & Medicaid Services (CMS) has proposed an indication-based formulary design starting in 2020, allowing Medicare Advantage and Part D prescription drug plans to cover drugs only for select indications, which could increase formulary negotiating power and secure more competitive pricing. This might be the change needed in order to ensure continued patient access to affordable and safe prescription drugs.

### **Acknowledgements**

This thesis is the product of 3.5 years of research conducted as a medical student at Yale. When I first started at Yale Medical School, I had just finished a global health project in Malaysia working with marginalized prisoner and transgender populations. While there, I came to realize that societal and financial barriers to care are important factors in determining health outcomes, sometimes far more than the actual clinical encounter. I wanted to conduct research that effected change at a larger, more structural level, research that would affect patients across different ages, gender, ethnicity and ideology. This body of work addresses issues in prescribing practices at a nationwide, policy level in order to promote cost-effective, evidence-based access to drugs for all patients. I hope it will have a part in changing the way we prescribe medicine as a medical community. I also aim to use it to inform my own clinical practice during and after residency and fellowship training.

I would like to thank Dr. Joseph Ross for his role as both my thesis advisor and mentor during the entirety of medical school. I am grateful for your time, advice and thoughts over these past four years. I would also like to thank Dr. Sanket Dhruva, who has acted not only a research mentor and collaborator but also as an invaluable source of career and life advice. I am eternally grateful for the generous funding the Yale School of Medicine has provided through the years to enable me to devote my time to this work. Finally, I would like to thank my parents, my sister, Varsha, and my fiancé, Steen, for their constant support of my pursuits.

### **Publication Note**

All research presented in this thesis was conducted during my time as a Yale medical student. The analyses presented have been published as cited below, in addition to a publication on off-label prescription that has not been presented in this thesis.

Vijay A, Gupta R, Liu P, Dhruva SS, Shah ND, Ross JS. Medicare Formulary Coverage of Brand-Name Drugs and Therapeutically Interchangeable Generics. *Journal of general internal medicine*. 2019 Oct 17;1-3.

Vijay A, Ross JS, Shah ND, Jeffery MM, Dhruva SS. Medicare Formulary Coverage and Restrictions for Opioid Potentiators from 2013 to 2017. *Journal of general internal medicine*. 2019 Apr 15;34(4):518-20.

Vijay A, Rhee TG, Ross JS. US prescribing trends of fentanyl, opioids, and other pain medications in outpatient and emergency department visits from 2006 to 2015. *Preventive medicine*. 2019 Jun 1;123:123-9.

Vijay A, Becker JE, Ross JS. Patterns and predictors of off-label prescription of psychiatric drugs. *PloS one*. 2018 Jul 19;13(7):e0198363.

## **1. INTRODUCTION**

### **1.1 Safe and Cost-Effective Prescribing**

Access to safe, cost-effective prescription drugs is integral to increasing patient adherence, improving patient health outcomes and ultimately decreasing all-cause medical costs<sup>1,2</sup>. Previous studies have suggested that inappropriate prescription drug use is a principal cause of adverse drug events (ADEs), which in turn can lead to additional physician visits, hospitalizations, injury, deterioration of body functioning, and death<sup>3</sup>. Inappropriate prescription drug use on the patient side can also lead to addiction, diversion and overdose deaths<sup>4</sup>. Thus, balancing harms and benefits of prescription drug use by incentivizing appropriate prescription is paramount in ensuring positive health outcomes across a broad range of patient populations.

At a population level, safe drug prescribing is controlled by the Food and Drug administration (FDA) through labeling and black box warnings, as well as through CDC guidelines<sup>5</sup>. Cost-effective drug prescription can be promoted in part through the incentivization of generic drugs over brand-name equivalents<sup>6</sup>. At a patient level, there have been various strategies adopted: requiring communication between pharmacist and physician at time of dispensation, requiring prescription drug monitoring programs to be in place for high-risk medications, and utilization management strategies incorporated within drug formulary policies<sup>4,7,8</sup>.

Utilization management strategies, in theory, act to control costs of expensive branded drugs as well as prevent over-prescription of potentially unsafe drugs. These strategies include tiering of formularies (drugs are divided into “tiers,” with the first tier typically representing generics at the lowest level of patient cost-sharing, and a higher tier requiring higher patient cost-

sharing), prior authorization (requiring physicians to obtain approval from the health plan before prescription for coverage) and quantity limits (limiting the amount of drug a patient can receive over a given amount of time) <sup>9</sup>. A case study of opioid coverage among a private insurer showed that implementing these restriction strategies lead to a 15% decrease in opioid prescribing, suggesting that these methods can be used for their intended effect <sup>10</sup>. Another study on rosiglitazone, which has a black box warning on increased risk of myocardial ischemia, showed that there was reduced rosiglitazone prescribing associated with Medicaid plans that implemented formulary restrictions compared with plans without formulary restrictions, although overall, these restrictions were underutilized <sup>11</sup>.

## **1.2 Controlling Prescription with Restriction Strategies – Effective or Not?**

Studying the impact of formulary management on drug prescription is a new and emerging field, still understudied. Previous studies have often focused on a specific therapeutic drug class, from anti-thrombotics to antihyperglycemic agents, or specific FDA labeling, such as black box warnings. By and large, the results of these studies show a) that many drugs of concern remain relatively unrestricted, b) that the restrictions had little impact on how providers managed treatment regimens, and c) that for many drugs, brand-name and generics are treated very similarly. All of this taken together suggests sub-optimal utilization or relative ineffectiveness of the formulary management strategies despite pilot studies. Furthermore, even in cases where formulary restrictions were shown to decrease prescription of targeted drugs, there was less consensus on whether this actually affected patient costs and health outcomes <sup>12</sup>. Table 1 shows results from these past studies.



**Table 1. Past Studies Examining Impact of Formulary Management Strategies on Drug Prescription**

Author	Title	Year	Therapeutic Area Studied	Main Finding
Liang et. al	Medicare formulary coverage for top-selling biologics	2009	Top 20 Biologics from 2006-2009	<ul style="list-style-type: none"> <li>- Cost-sharing and utilization management of top-selling biologics increased from 2006-2009, thus decreasing access</li> </ul>
Samuels et. al.	Medicare Formulary Coverage Restrictions for Prescription Opioids, 2006 to 2015	2017	Short and long-acting opioids (except methadone)	<ul style="list-style-type: none"> <li>- Increasing use of quantity limits and, to a lesser extent, prior authorization on opioid medications from 2006-2015</li> <li>- Overall, high rates of unrestrictive coverage persisted for many opioids, especially at high doses,</li> </ul>
Dhruva et. al.	Association between FDA black box warnings and Medicare formulary coverage changes	2017	Nine drugs that received black-box warning from 2013-2017	<ul style="list-style-type: none"> <li>- Medicare formularies became more restrictive for half of the drugs</li> <li>- A substantial proportion of formularies remained unrestrictive</li> </ul>
Shaw et al.	Coverage of Novel	2018	144 novel therapeutic	<ul style="list-style-type: none"> <li>- Most novel agents were</li> </ul>

	Therapeutic Agents by Medicare Prescription Drug Plans Following FDA Approval		agents approved by the FD between 2006-2012	covered, but access was often restricted through prior authorization or step therapy and was dependent on plan choice
Alghamdi et. al.	Analysis of formulary coverage and cost of biologic disease modifying anti-rheumatic drugs in Medicare Part D	2018	Biologic DMARDS	<ul style="list-style-type: none"> <li>- Majority of formularies placed restrictions on the utilization of biologic DMARDS.</li> <li>- Biologic DMARDS were increasingly placed in higher specialty tiers that required high cost-sharing payments.</li> </ul>
Roberto et. al.	Impact of Formulary Restrictions on Medication Intensification in Diabetes Treatment	2018	Second-Line Anti-hyperglycemics	<ul style="list-style-type: none"> <li>- Formulary restrictions had no statistically significant impact on selection of and days' supply of second-line anti-hyperglycemics</li> </ul>
Dayoub et. al.	Evolution of Medicare Formulary Coverage Changes for Antithrombotic Therapies After Guideline Updates	2019	Anti-thrombotics (DOACs and warfarin)	<ul style="list-style-type: none"> <li>- Formularies are providing increased restrictiveness (higher tiering) with increasing DOAC coverage</li> </ul>

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### 1.3 Opioid Prescriptions – A Changing Landscape

The United States is currently facing an opioid epidemic, which began in the mid-1990s with increased pharmaceutical marketing, as well as promotion by both hospital accrediting bodies and official medical societies<sup>13</sup>. Emergency department (ED) visits for opioid overdoses rose 30% across the country from July 2016 through September 2017<sup>14,15</sup>. Opioid-related deaths were five times higher in 2016 than 1999<sup>15</sup>. In response, the Centers for Disease Control and Prevention (CDC) issued guidelines in 2013 encouraging the replacement of opioid medications with non-opioid alternatives to treat chronic pain<sup>16</sup>. Despite such efforts, opioid-related harms have been rising nationwide.

While a study of nationwide opioid prescriptions from 2002-2013 suggested that opioid prescriptions began to decline prior to the 2013 CDC guideline announcement<sup>17</sup>, the response to these guidelines has not been very well studied. Samuels et al. demonstrated that prescription of opioids through CMS formularies remained relatively unrestricted, especially at high doses and for the particular medications that have higher rates of overdose deaths<sup>18</sup>. Partly as a result of these findings combined with the 2013 CDC guidelines, Medicare recently proposed formulary changes to restrict opioid availability based on maximum daily dosage and initial fill quantity.<sup>19</sup>

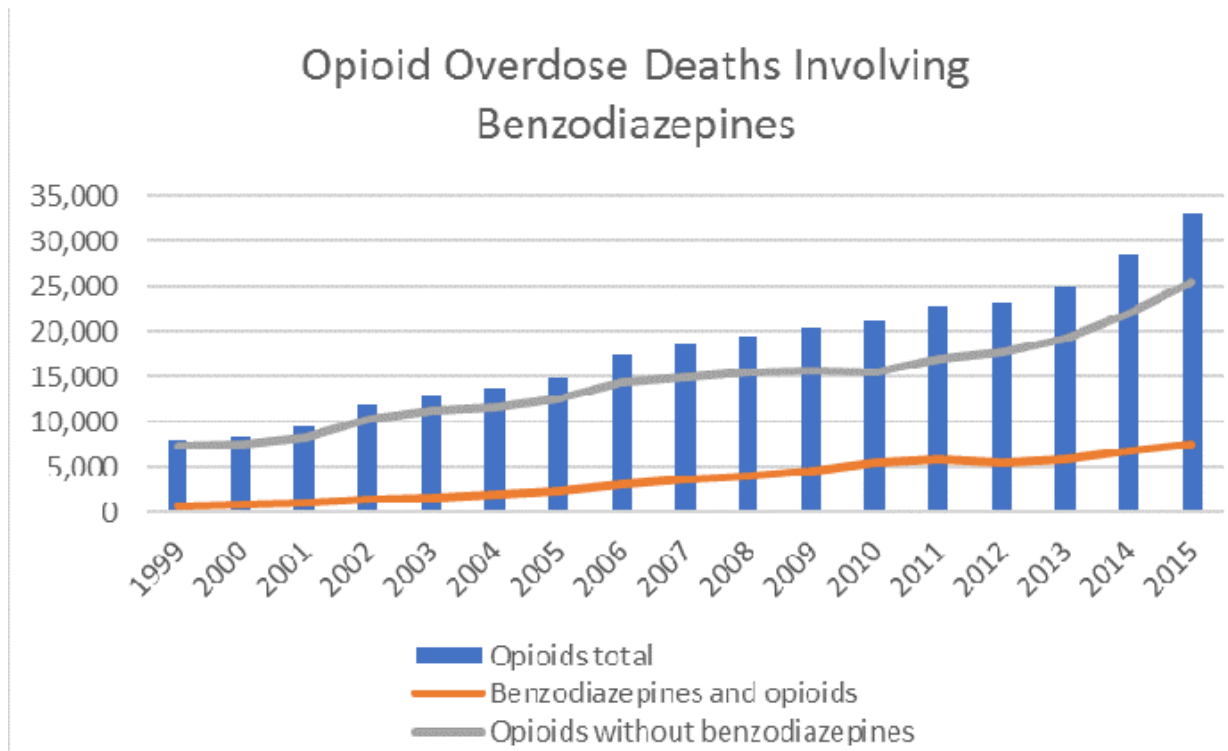
In order to fully understand the impact of these findings and characterize the relationship between formulary restriction and nationwide prescription rates, it was necessary to examine the nationwide changes in opioid prescribing rates versus non-opioid analgesic prescriptions after the 2013 CDC guidelines were announced, especially in an outpatient setting where formulary restrictions are quite relevant to patient access to medication. The objective of the first study was

thus to investigate and compare current prescribing rates of opioid medications, including fentanyl, and of non-opioid medications in the outpatient and emergency department settings using a nationally-representative sample.

#### **1.4 Opioid potentiators – a new epidemic**

A currently under-recognized but important concern concurrent to the opioid epidemic is the over-prescription of “opioid potentiator” drug classes: benzodiazepines, non-benzodiazepine sedative-hypnotics, and gabapentinoids.<sup>20, 21</sup> These drugs have risks when used on their own; benzodiazepines, in particular, have the second highest overdose death rate after opioids.<sup>22</sup> In addition, they increase the risk of an adverse event when taken with opioids. Figure 1, taken from the CDC, graphically shows the role of opioid and opioid potentiator co-prescription within the umbrella of the opioid epidemic.

**Figure 1. Opioid Overdose Deaths Involving Benzodiazepines (source: CDC, Multiple Cause of Death 2009-2015).**



Unfortunately, it appears there has been little effort to decrease prescribing of these potentially dangerous drugs. Between 1996 and 2013, the number of adults who filled a benzodiazepine prescription increased by 67%, and the quantity of benzodiazepines obtained more than tripled.<sup>23</sup> While the MMA excluded benzodiazepines in 2006 because of multiple reported adverse effects in the elderly, they eventually gained coverage in 2014 under Part D for any medically accepted indication<sup>24, 25</sup>. A recent study indicates that subsequent to a 2016 CDC guideline release recommending avoidance of concurrent opioid and benzodiazepines use, the intensity of benzodiazepine prescription has not reduced and the rate of co-prescribing only decreased by a small amount<sup>26</sup>.

Overuse of the non-benzodiazepine sedative hypnotics is associated with increased mortality and adverse outcomes such as fractures, falls and cognitive impairment.<sup>27</sup> Nonetheless, more than 50% of patients within hospitals may receive these medications, which are sometimes

continued after discharge.<sup>28</sup> Gabapentinoids have also seen a surge in prescribing in recent years for a broad range of pain diagnoses. In a recent study of a Medicaid managed care population, 95% of gabapentin prescribing was for off-label indications.<sup>29</sup>

Despite evidence that these medications are being increasingly prescribed and can have devastating effects, especially in combination with opioids, examination of how Medicare controls coverage of opioid potentiators had not been previously characterized. The aim of the second study was to characterize Medicare formulary coverage and restriction of benzodiazepines, non-benzodiazepine sedative-hypnotics, and gabapentinoids from 2013-2017.

### **1.5 Therapeutic Exchange – Incentivizing Generic over Brand Drug Prescription to Reduce Patient Costs**

U.S. prescription drug sales, excluding physician administered drugs, accounted for nearly 10% of total healthcare spending in 2017<sup>30</sup>. Given that generic drugs are generally less expensive than brand-name drugs for patients, and that these lower out-of-pocket costs can improve patient adherence, preferential prescription of generic drugs over brand-name is one important target in improving health outcomes<sup>1</sup>. While generic substitution is critical to curtailing prescription drug spending, a previous study has shown that 72% of current formularies favor pricier, branded drugs over bioequivalent generics in at least one therapeutic area<sup>31</sup>.

It is apparent that the incentivization of generic prescribing through formulary restriction is not uniform across drug classes. The issue is further complicated in that not all brand-name drugs have an approved bioequivalent generic. However, for many drugs, therapeutically interchangeable generics are available, offering potential cost savings if substituted. Therapeutic

interchangeables are drugs within the same class, with similar clinical effect and safety profile, but with a different chemical composition of the drug of interest <sup>32</sup>- for brand-name drugs without an approved generic bioequivalent, a TE can usually be substituted. In fact, one study estimated that between 2010 and 2012, \$73 billion could have been saved by TE substitution for the most commonly prescribed medication classes <sup>33</sup>.

The Center for Medicare & Medicaid Services (CMS) has proposed an indication-based formulary design starting in 2020 <sup>34</sup>, allowing Medicare Advantage and Part D prescription drug plans to cover brand-name drugs only for select indications. This could potentially increase formulary negotiating power and secure more competitive pricing. The indication-based formulary design also defines a role of the therapeutic interchangeable, as the formulary must ensure coverage with a therapeutic interchangeable of any indication not covered by the corresponding brand-name drug. With the new formulary design in the horizon, the third study aimed to understand if and how 2016 Medicare prescription drug plan formularies incentivize selection of brand-name drugs without bioequivalent generics compared to their corresponding therapeutically interchangeable generic drugs through tier placement and utilization management strategies.

## **2. STATEMENT OF PURPOSE**

The purpose of this thesis is to describe three published studies that systematically characterize the relationship between CMS formulary regulations and a) safe and evidence-based prescribing, using opioids and opioid potentiators as a case study, b) cost-effective prescribing using therapeutic exchanges across a broad, nationally representative drug sample.

### **Study 1: U.S. Prescribing Trends of Opioids, Fentanyl and Other Pain Medications in Outpatient and Emergency Department Visits from 2006-2015:**

Examination of national opioid versus non-opioid analgesic prescription rates before and after release of CDC guidelines encouraging prescription of non-opioid analgesics.

### **Study 2: Medicare Formulary Coverage and Restrictions for Opioid Potentiators from 2013-2017:**

Characterization of CMS formulary coverage, including utilization management strategies, of opioid potentiators such as benzodiazepines, non-benzodiazepine sedative hypnotics and gabapentinoids.

### **Study 3: Medicare Formulary Coverage of Brand-Name Drugs with Available FDA-Approved Therapeutically Interchangeable Generics**

Characterization of how 2016 Medicare prescription drug plan formularies incentivize selection of top 100-grossing brand-name drugs without bioequivalent generics compared to their corresponding therapeutically interchangeable generic drugs through tier placement and utilization management strategies.

Medicare files provide a broad and impactful perspective on key components of health care in the United States. Medicare is the largest national insurer, accounting for 29% of United States' total prescription drug spending and covering 17% of the nation's patient population. Thus, it has a strong impact on nationwide drug demand. In fact, Medicare coverage policies often drive private insurance coverage decisions<sup>9</sup>. Finally, Medicare primarily provides prescription drug coverage to an older adult population (>65 yo) vulnerable because of the need for more medications combined with limited or fixed incomes<sup>3</sup>. Therefore, findings on the



impact of Medicare formulary restrictions on prescription drug policy are fairly nationally representative and especially impactful regarding safe and affordable access to prescription drugs.

### **3. STUDY 1 – METHODS AND RESULTS**

#### **3.1 U.S. Prescribing Trends of Opioids, Fentanyl and Other Pain Medications in Outpatient and Emergency Department Visits from 2006-2015**

##### Data Source

We used 2006-2015 data from the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS), which provide nationally representative samples of office-based outpatient visits and emergency department visits, respectively ([https://www.cdc.gov/nchs/ahcd/ahcd\\_questionnaires.htm](https://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm)). NAMCS and NHAMCS both sample non-federally employed physicians who are primarily engaged in direct patient care – the sampling design utilizes a stratified two-stage sample, with physicians selected in the first stage and visits in the second stage. The data provide an analytic base that serves as an important tracking tool on ambulatory and emergency care utilization regarding national trends, medication use, and practice patterns in the US. Samples included 390,538 visits in NAMCS and 305,570 visits in NHAMCS.

##### Drug Sample

To characterize pain medication prescribing, we examined the first eight medications listed for all outpatient and ED visits, ensuring consistency across all survey years. We constructed three indicator variables using generic names of medications: fentanyl products (i.e., fentanyl and droperidol-fentanyl), all opioid products other than fentanyl (including analogues), and all other non-opioid pain medications. Opioid products other than fentanyl consisted of the

following medications: codeine, meperidine, methadone, alfentanil, hydromorphone, morphine, oxycodone, pentazocine, propoxyphene, sufentanil, opium, levorphanol, oxymorphone, butorphanol, nalbuphine, buprenorphine, hydrocodone, dihydrocodeine, remifentanil, tapentadol, and their combined products. Other non-opioid pain medications are nonsteroidal anti-inflammatory drugs (NSAIDs), non-analgesics, and other drugs (i.e., acetaminophen, aspirin, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, phenylbutazone, piroxicam, tolmetin, tramadol, gabapentin, and pregabalin).

### Demographics

We included a number of patient demographic and clinical covariates provided during visits. Demographic variables included: age (<19, 19-44, 45-64, or  $\geq 65$ ), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), primary source of payment (private, Medicare, Medicaid, or other). Medicare is a federal program that provides health coverage for US adults over the age of 65, and Medicaid is a state and federal program that provides health coverage for low-income individuals and families. Clinical variables included visit diagnosis and physician specialty. Both NAMCS and NHAMCS collect up to three visit diagnoses for each sampled visit using the *International Classification of Diseases, 9th edition, Clinical Modification* (ICD-9-CM) diagnostic codes. We categorized visit diagnosis into three groups: cancer-related pain diagnoses, non-cancer related pain diagnoses, and no pain-related diagnosis. For physician specialty, we distinguished between generalists (i.e., general/family practice, internal medicine, pediatrics, and obstetrics and gynecology) vs. other in NAMCS. In NHAMCS, we distinguished clinical specialty by clinical degree (i.e., MD vs. other). We also reported number of visits in the past 12 months (0, 1-2, 3-5, or  $\geq 6$ ), number of chronic conditions (0-1 or  $\geq 2$ ), and number of concomitant medications (0-5 or  $\geq 6$ ) prescribed in NAMCS datasets.

## Statistical Analysis

We determined the proportion of visits for which any pain medication was prescribed and examined associations with selected characteristics (e.g., age, sex, race/ethnicity, clinical comorbidities, concomitant medication use, and physician specialty), using Bonferroni-adjusted bivariate analyses. Next, we determined the proportion of visits for which any pain medication was prescribed across survey years, overall and for each pain medication class, also stratifying overall analyses by selected patient and visit characteristics. We used Chi-Square analysis to compare rates in 2006-2007 and 2014-2015. All analyses were conducted using Stata MP/6-Core version 15.1 (College Station, TX), accounting for the complex survey design and sampling weights.

### **3.2 U.S. Prescribing Trends of Opioids, Fentanyl and Other Pain Medications in Outpatient and Emergency Department Visits from 2006-2015**

#### Selected characteristics of the study subjects

Between 2006 and 2015, 66,987 (17.4%) of 390,538 office-based outpatient visits (nationally-representative of 961 million visits) and 134,953 (45.0%) of 305,570 ED visits (nationally-representative of 130 million visits) listed a pain medication prescription (**Table 2**). 56.3% of office-based outpatient visits were to primary care physicians, and of these visits, 18.3% involved a prescription for a pain medication. Among office-based outpatient visits, pain medication prescription was highest among patients aged 45-64, non-Hispanic Black patients, patients with Medicare coverage, patients receiving care from primary care physicians, and patients receiving care for a pain-related diagnosis (all p-values < 0.001). Among ED visits, pain medication prescription was highest among patients aged 19-44, males, Hispanic patients,

patients with private insurance, patients receiving care from MDs, and patients receiving care for a pain-related diagnosis (all p-values < 0.001).

**Table 2. Selected characteristics (weighted %) of visits in which pain medications were prescribed, 2006-2015 NAMCS and NHAMCS.**

	NAMCS			NHAMCS		
	Total (column %)	Pain medication prescription (row %)	P-value <sup>†</sup>	Total (column %)	Pain medication prescription (row %)	P-value <sup>†</sup>
Sample size						
Unweighted sample	390,538	66,987		305,570	134,953	
Weighted visits	961,261,3	167,349,60		130,155,3	58,568,338	
Age						
<19	18.9	9.6		24.1	40.0	
19-44	24.1	17.3	<0.001	39.0	51.9	<0.001
45-64	29.7	21.8		21.7	47.8	
≥65	27.3	18.1		15.2	31.1	
Gender						
Female	58.5	17.6	0.045	54.9	43.6	<0.001
Male	41.5	17.1		45.1	46.1	
Race/ethnicity						
Non-Hispanic White	71.8	17.5	<0.001	59.7	44.9	0.001
Non-Hispanic Black	10.3	19.0		22.5	44.8	
Hispanic	12.5	16.9		14.6	46.3	
Other <sup>a)</sup>	5.3	14.1		3.2	43.3	
Primary source of payment						
Private	53.7	15.3	<0.001	32.6	47.8	<0.001
Medicare	25.9	20.1		18.7	35.5	
Medicaid	12.5	17.7		28.8	45.3	
Other	7.9	21.6		19.9	50.0	
Physician specialty						
Generalists <sup>b)</sup>	56.3	18.3	<0.001	-	-	-
Other <sup>c)</sup>	43.7	16.3		-	-	
Clinician specialty						
MDs	-	-	-	90.1	45.8	<0.001
Other <sup>d)</sup>	-	-		9.9	39.6	
Repeat of visits in the past 12 months						
0 visit	6.9	12.4	<0.001	-	-	-
1-2 visits	36.4	15.7		-	-	
3-5 visits	31.2	18.3		-	-	
6+ visits	25.4	21.2		-	-	
Chronic conditions <sup>e)</sup>						
<2	68.2	14.7	<0.001	-	-	-
≥2	31.8	23.8		-	-	
Concomitant medications prescribed						
<6	83.9	13.0	<0.001	-	-	-
≥6	16.1	37.7		-	-	
Visit diagnosis						
Cancer-related <sup>f)</sup>	4.7	14.9	<0.001	0.6	46.5	<0.001

Other pain-related <sup>g)</sup>	5.0	43.8	13.0	60.6
No indication	90.3	16.1	86.5	42.7

Note: † compares proportion differences by any pain prescription using a weight-corrected, Bonferroni-adjusted chi-squared statistic. a) includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups; b) includes general/family practice, internal medicine, pediatrics, and obstetrics and gynecology; c) includes psychiatry, general surgery, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; d) includes physician assistants (PAs) and nurse practitioners (NPs); e) was based 14 chronic conditions (yes/no) collected by the NAMCS (e.g., arthritis, congestive heart failure, and diabetes); f) was based on ICD-9-CM diagnostic codes 140-239, 338.3X; and g) was based on ICD-9-CM codes 338.XX, 350.1X-350.2X, 354.4X, 355.71, 379.91, 388.7X, 719.4X, 724.1X-724.2X, 729.1X, 780.96, 786.5X, 789.XX.

### National prescribing trends of opioids and other pain medications

The proportion of all outpatient visits in which any pain medication was prescribed increased significantly from 15.0% in 2006-2007 to 20.5% in 2014-2015 ( $p<0.001$ ). Among ED visits, the proportion did not change significantly, ranging from 44.2% in 2006-2007 to 44.5% in 2014-2015 ( $p=0.72$ ) (**Table 3**).

Non-opioid pain medication prescription increased in both settings, from 9.2% to 12.6% ( $p<0.001$ ) in the outpatient setting and from 26.3% to 29.2% ( $p=0.001$ ) in the ED setting in 2006-2007 and 2014-2015, respectively.

**Table 3. Pain medication prescribing trends, 2006-2015 NAMCS and NHAMCS.**

	Years (%)					2006-2007 vs. 2014-2015, <i>P</i> -value
	2006-2007	2008-2009	2010-2011	2012-2013	2014-2015	
<b>NAMCS</b>						
Visits in which any pain medication prescribed	15.0%	16.4%	17.4%	18.0%	20.5%	<0.001
Visits in which any pain medication from the specific class prescribed						
Opioid and combined products <sup>†</sup>	5.9%	6.8%	7.1%	7.6%	8.1%	<0.001
Non-analgesics, NSAIDs, tylenol, tramadol, and non-opioid combined products <sup>‡</sup>	10.4%	11.3%	12.1%	12.8%	14.9%	<0.001
<b>NHAMCS</b>						

Visits in which any pain medication prescribed	44.2%	45.6%	46.8%	44.0%	44.5%	0.719
Visits in which any pain medication from the specific class prescribed						
Opioid and combined products <sup>†</sup>	25.1%	25.7%	27.0%	24.2%	21.9%	0.001
Non-analgesics, NSAIDs, tylenol, tramadol, and non-opioid combined products <sup>‡</sup>	26.4%	27.7%	28.2%	27.2%	29.6%	<0.001

Note: <sup>†</sup>codeine, meperidine, methadone, alfentanil, hydromorphone, morphine, oxycodone, pentazocine, propoxyphene, sufentanil, opium, levorphanol, oxymorphone, butorphanol, nalbuphine, buprenorphine, hydrocodone, dihydrocodeine, remifentanil, tapentadol, and their combined products; <sup>‡</sup>includes gabapentin and pregabalin for non-analgesics, and NSAIDs include acetaminophen, aspirin, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, phenylbutazone, piroxicam, tolmetin, and tramadol.

### Factors of prescribing any pain medication

There were several patient factors predictive of higher rates of prescribing of any pain medication among both outpatient and ED visits (**Table 4**). Among outpatient visits, pain medication prescription was highest among visits by patients aged 45-64 years, increasing significantly over time to 25.6% in 2014-2015 ( $p<0.001$ ), and among visits by patients with Medicare, increasing significantly over time to 24.2% in 2014-2015 ( $p<0.001$ ). In contrast, among ED visits, pain medication prescription was lowest among visits by patients with Medicare insurance, but increased significantly over time to 36.4% in 2014-2015 ( $p=0.003$ ).

**Table 4. Stratified analysis of pain medication prescribing trends by key patient and visit characteristics, 2006-2015 NAMCS and NHAMCS.**

	Years (%)					2006-2007 vs. 2014-2015, P-value
	2006-2007	2008-2009	2010-2011	2012-2013	2014-2015	
<b>NAMCS</b>						
Visit diagnosis						
Cancer-related*	11.9%	14.3%	16.0%	15.2%	16.4%	0.037
Other pain-related <sup>†</sup>	43.4%	43.6%	43.3%	44.2%	44.1%	0.846
No indication	13.9%	15.1%	16.0%	16.5%	19.1%	<0.001
Physician specialty						
Generalist <sup>‡</sup>	16.3%	17.7%	17.8%	18.4%	21.6%	<0.001
Other <sup>§</sup>	13.1%	14.4%	16.8%	17.6%	19.2%	<0.001
Age						
<19	9.4%	10.1%	10.1%	8.4%	10.0%	0.504
19-44	15.7%	15.5%	17.6%	18.7%	19.5%	0.001

45-64	18.8%	20.3%	21.7%	22.5%	25.6%	<0.001
≥65	14.6%	17.0%	18.2%	19.0%	21.4%	<0.001
Gender						
Female	15.0%	16.9%	17.6%	18.1%	20.6%	<0.001
Male	14.9%	15.5%	17.1%	18.0%	20.2%	<0.001
Race/ethnicity						
Non-Hispanic White	15.1%	16.7%	17.5%	17.9%	20.8%	<0.001
Non-Hispanic Black	15.6%	16.7%	19.8%	19.6%	22.9%	<0.001
Hispanic	14.5%	15.1%	16.6%	18.9%	19.5%	0.003
Other <sup>ll</sup>	13.4%	14.1%	12.7%	15.0%	15.3%	0.331
Primary source of payment						
Private	13.5%	14.8%	15.2%	15.7%	17.8%	<0.001
Medicare	15.8%	19.1%	19.8%	20.9%	24.2%	<0.001
Medicaid	16.6%	15.9%	19.0%	17.3%	19.5%	0.055
Other	19.1%	19.5%	22.6%	23.9%	22.8%	0.168

### NHAMCS

Visit diagnosis						
Cancer-related*	41.0%	46.2%	46.8%	47.8%	49.3%	0.074
Other pain-related <sup>†</sup>	57.9%	62.2%	63.2%	60.0%	59.3%	0.262
No indication	42.5%	43.3%	44.3%	41.3%	41.9%	0.548
Clinician specialty						
MDs	45.4%	46.8%	47.5%	44.7%	44.8%	0.580
Other <sup>ll</sup>	35.5%	36.5%	43.5%	37.7%	42.5%	<0.001
Age						
<19	39.6%	41.9%	41.2%	39.0%	38.2%	0.350
19-44	51.4%	52.9%	54.2%	50.0%	51.1%	0.785
45-64	45.5%	47.5%	49.9%	47.4%	48.6%	0.024
≥65	30.1%	30.1%	31.9%	31.1%	32.1%	0.118
Gender						
Female	45.2%	46.7%	48.0%	44.9%	45.8%	0.570
Male	42.9%	44.2%	45.4%	42.6%	42.9%	0.955
Race/ethnicity						
Non-Hispanic White	44.6%	45.3%	46.5%	43.6%	44.2%	0.646
Non-Hispanic Black	43.1%	46.1%	46.8%	43.7%	44.1%	0.561
Hispanic	44.2%	46.4%	48.5%	45.8%	46.2%	0.157
Other <sup>ll</sup>	42.4%	43.5%	45.6%	40.3%	44.6%	0.395
Primary source of payment						
Private	48.2%	48.2%	49.5%	46.1%	46.8%	0.253
Medicare	32.6%	35.1%	37.0%	35.3%	36.4%	0.003
Medicaid	43.0%	46.8%	46.7%	44.7%	45.3%	0.067
Other	48.5%	51.0%	52.1%	49.3%	48.3%	0.839

Note: \*was based on ICD-9-CM diagnostic codes 140-239, 338.3X; <sup>†</sup>was based on ICD-9-CM codes 338.XX, 350.1X-350.2X, 354.4X, 355.71, 379.91, 388.7X, 719.4X, 724.1X-724.2X, 729.1X, 780.96, 786.5X, 789.XX; <sup>‡</sup>includes general/family practice, internal medicine, pediatrics, and obstetrics and gynecology; <sup>§</sup>includes psychiatry, general surgery, orthopedic surgery, cardiovascular diseases, dermatology, urology, neurology, ophthalmology, otolaryngology, and others; <sup>ll</sup>includes Asians, American Indian/Alaska Natives (AIANs), Native Hawaiian or Other Pacific Islanders (NHOPI), or 2+ reported racial/ethnic groups; and <sup>lll</sup>includes physician assistants (PAs) and nurse practitioners (NPs).

## **4. STUDY 2 – METHODS AND RESULTS**

### **4.1 Medicare Formulary Coverage and Restrictions for Opioid Potentiators from 2013-2017**

#### **Data Source**

We used 2013, 2015, and 2017 Medicare Prescription Drug Formulary Files, which include data on all Medicare Advantage and Stand-alone Part D formularies. This data was gathered from the CMS Prescription Drug Plan Formulary and Pharmacy Network Files. The following variables for each plan were collected for each opioid potentiator: coverage, prior authorization, specialty tier, quantity limit amount, and step therapy.

#### **Drug Sample**

We identified all benzodiazepines, non-benzodiazepine sedative-hypnotics, and gabapentinoids available in oral formulations. Benzodiazepines studied included alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, oxazepam, quazepam, temazepam, and triazolam. Non-benzodiazepine sedative-hypnotics included doxepin, zaleplon, zolpidem. Gabapentinoids included gabapentin, gabapentin enacarbil, and pregabalin.

We characterized median formulary coverage of the lowest dose of the generic version of each drug, or the brand-name version when generics were unavailable. We focused on generics since they are used more commonly than the bioequivalent brand-name version, and on the lowest dose because higher doses can be created from lower doses. We excluded two brand-name drugs (Rozerem and Lunesta) that became available as a generic between 2013 and 2017, as generic availability impacts brand-name formulary coverage.



## Statistical Analysis

For each drug in each year, we determined the proportion of formularies not providing coverage; providing restrictive coverage using one or more utilization management strategy (quantity limit, prior authorization, or step therapy); or providing unrestrictive coverage (no utilization management). We summarized median coverage across all drugs in all three years. Analyses were conducted in R Studio version 3.2.3.

### **4.2 Medicare Formulary Coverage and Restrictions for Opioid Potentiators from 2013-2017**

#### Formulary Restrictions on Opioid Potentiators

There were 12 benzodiazepines, 3 non-benzodiazepine sedative-hypnotics and 3 gabapentinoids eligible for study. The median proportion of formularies not providing coverage across all drugs was 21.8% (interquartile range [IQR], 0.3-64.8%) in 2013, 14.4% (IQR, 0.0-66.3%) in 2015, and 17.6% (IQR, 0.0-68.7%) in 2017 (**Table 5**). The median proportion of formularies providing restrictive coverage was 63.3% (IQR, 49.6-69.4%) in 2013, 70.1% (IQR, 65.8-81.2%) in 2015, and 66.8% (IQR, 54.4-77.9%) in 2017, with the largest growth in use of quantity limits, a smaller increase in prior authorization, and infrequent use of step therapy. The median proportion of formularies providing unrestrictive coverage in the 3 years was 33.3% (IQR, 27.1-43.7%), 27.0% (IQR, 16.3-32.2%), and 27.9% (IQR, 18.0-41.6%), respectively. In 2017, 47.9% of formularies provided unrestrictive coverage of at least 1 benzodiazepine, 39.9% of at least 1 non-benzodiazepine sedative-hypnotic, and 67.2% of at least 1 gabapentinoid.

**Table 5. Median Medicare Prescription Drug Plan Formulary Coverage and Use of Utilization Management Strategies for Benzodiazepines, Non-benzodiazepine Sedative-hypnotics, and Gabapentinoids<sup>a</sup>, 2013-2017**

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Median Formulary Coverage (Interquartile Range), %

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	2013 formularies (n=314)	2015 formularies (n=389)	2017 formularies (n=378)
No coverage	21.8 (0.3-64.8)	14.4 (0.0-66.3)	17.6 (0.0– 68.7)
Restrictive coverage	63.3 (49.6-69.4)	70.1 (65.8-81.2)	66.8 (54.4-77.9)
Imposes a quantity limit	44.8 (34.6-54.8)	58.7 (39.1-68.4)	59.8 (41.5–70.0)
Requires prior authorization	16.4 (11.8-23.5)	31.9 (17.2-38.8)	21.0 (14.0-39.0)
Requires step therapy	0 (0-0)	0.0 (0.0-2.7)	0 (0-0.8)
Coverage with no restrictions	33.3 (27.1-43.7)	27.0 (16.3-32.2)	27.9 (18.0– 41.6)

<sup>a</sup>12 benzodiazepines, 3 non-benzodiazepine sedative-hypnotics, and 3 gabapentinoids were included

### Medicare Coverage of Individual Opioid Potentiators

Medicare coverage in 2017 of each drug varied (**Table 6**). Quazepam and gabapentin enacarbil were not covered by any plan. Lorazepam, diazepam, clonazepam, doxepin, pregabalin, and gabapentin were covered by all. Among benzodiazepines, hypnotics (estazolam, flurazepam and triazolam) had lower rates of coverage, whereas anxiolytics (alprazolam, diazepam, and lorazepam) had higher rates, albeit usually with restrictions.

**Table 6. Medicare Prescription Drug Plan Formulary Coverage and Use of Utilization Management for Individual Benzodiazepines, Non-benzodiazepine Sedative-hypnotics, and Gabapentinoids, 2017 Second Quarter**

Formulary Coverage <sup>a</sup>	No coverage (%)	Unrestrictive coverage (%)	Restrictive coverage <sup>a</sup> (%)	Imposes a quantity limit (%)	Requires prior authorization (%)	Requires step therapy (%)
<b>Benzodiazepines</b>						
Alprazolam	11.9	21.9	67.1	75.7	7.5	0
Chlordiazepoxide	48.9	37.6	13.5	57.4	17.7	0
Clonazepam	0	28.8	71.2	62.2	22.5	2.1
Clorazepate	0	27.2	72.8	63.8	37.0	0
Diazepam	0	19.6	80.4	72.0	39.7	0
Estazolam	59.4	33.6	7.0	55.9	23.4	0
Flurazepam	56.9	38.2	4.9	45.2	17.9	0
Lorazepam	0	17.5	82.5	74.6	19.6	0
Oxazepam	33.9	28.6	37.5	34.6	28.3	0
Quazepam <sup>b</sup>	100					
Temazepam	45.2	22.8	32.0	63.8	58.5	0
Triazolam	60.3	36.5	3.2	53.3	13.3	0
<b>Non-Benzodiazepine Sedative-Hypnotics</b>						
Doxepin	0	39.4	60.6	0	57.1	3.4

Zaleplon	23.3	3.8	72.9	78.6	54.8	10.0
Zolpidem	4.5	1.4	94.1	84.5	65.4	8.3
<b>Gabapentinoids</b>						
Gabapentin	0	59.8	40.2	40.2	0	0
Gabapentin enacarbil <sup>b</sup>	100					
Pregabalin	0	28.6	71.8	64.0	16.1	1.1

<sup>a</sup> Restrictive coverage defined as use of one or more utilization management strategy: quantity limit, prior authorization requirement, and step therapy requirement. <sup>b</sup> Drug was not covered by any formulary over the study period

## **5. STUDY 3 – METHODS AND RESULTS**

### **5.1 Medicare Formulary Coverage of Brand-Name Drugs with Available FDA-Approved Therapeutically Interchangeable Generics**

#### Data Source

We used June 2016 CMS Prescription Drug Plan Formulary Files, inclusive of 374 Medicare Advantage and stand-alone Part D formularies. This data was gathered from the CMS Prescription Drug Plan Formulary and Pharmacy Network Files. The following variables for each plan were collected for each brand-name drug: coverage, prior authorization, specialty tier, quantity limit amount, and step therapy.

#### Drug Sample

We included the top 100 non-biologic drugs as measured by total retail sales in 2016<sup>35</sup>. We included all brand-name drugs without an FDA-approved bioequivalent generic as of June 2016, but with at least one therapeutically interchangeable generic. Regulatory data, including status of generic approval, for all of the brand-name drugs were collected from the Drug@FDA database. For this study, therapeutically interchangeable generics were determined using the U.S. Pharmacopeia Medicare Model Guidelines or based on prior studies<sup>33, 36</sup>.

## Statistical Analysis

For each brand-name drug and their corresponding therapeutically interchangeable generic(s), we compared tier placement and utilization management. Tier placement broadly determines beneficiary out-of-pocket costs, the lowest of which are for drugs in tier 1 and 6; tier 1 generally includes preferred medications and tier 6, when present, includes “select-care” generics. Utilization management encompasses three separate strategies to limit prescribing: step therapy, prior authorization and quantity limits, which were used to calculate a restrictiveness score based on the number of strategies used. For both estimates, for each formulary, the brand-name drug was compared to the therapeutically interchangeable generic available at the lowest tier or with the least restrictive utilization management; this information was used to calculate percentages across all covering formularies, which were summarized as medians for all drugs that met our study’s inclusion criteria. All statistical analyses were performed using R Studio version 3.2.5.

### **5.2 Medicare Formulary Coverage of Brand-Name Drugs with Available FDA-Approved Therapeutically Interchangeable Generics**

Results as described in the following sections are shown in **Table 7**.

#### Coverage of Drug Sample

There were 24 brand-name drugs that met the inclusion criteria, for which there was a median of 3.0 (range: 1-9) therapeutically interchangeable generic drugs. At least one Medicare formulary covered both the brand-name and corresponding therapeutically interchangeable generic for 23 drugs (95.8%; ranolazine was not covered by any formulary), although the median proportion of formularies providing no brand-name drug coverage was 42.4% (IQR, 2.5-71.5).

### Examining Tiering of Brand-Name versus Therapeutic Interchangeables

The median proportion of formularies that placed therapeutically interchangeable generics in a lower tier than the corresponding brand-name drug was 86.0% (IQR, 85.5-90.3). For 17 of 23 (73.9%) brand-name drugs, more than 10% of formularies placed the brand-name and therapeutically interchangeable generic on the same tier.

### Formulary Restrictions on Brand-Name versus Therapeutic Interchangeables

For 10 (43.5%) brand-name drugs, 50% or more of formularies did not use any utilization management restrictions, whereas for 14 (60.9%), more than 10% of formularies had equivalent utilization management restrictiveness scores for brand-name and their corresponding therapeutically interchangeable drugs.

**Table 7.** Medicare Prescription Drug Plan Formulary Coverage of the Top 100 Brand-Name Drugs in 2016 without a Bioequivalent Generic but with a Therapeutically Interchangeable Generic, including Tier Placement and Utilization Management.

Drug Class	Brand-Name Drug	No Brand Coverage (%)	Tier Placement			Utilization Management <sup>h</sup>				
			Generic <sup>a</sup> Favored (%)	Equal Treatment (%)	Brand Favored (%)	Strategies Applied to Brand			Strategies Not Applied to Brand	
						Generic <sup>a</sup> Favored (%)	Equal Treatment (%)	Brand Favored (%)	Equal Treatment (%)	Brand Favored (%)
Statins <sup>b</sup>	Pitavastatin	66.3	92.1	7.9	0	37.3	23.8	0	38.9	0
	Rosuvastatin	74.9	94.7	5.3	0	37.2	48.9	0	11.7	2.2
Low molecular-weight heparin <sup>c</sup>	Dalteparin	54.5	54.7	45.3	0	8.2	40.6	0	39.4	11.8
Direct oral anti-coagulant <sup>d</sup>	Apixaban	22.5	85.5	14.5	0	51.4	0	0	48.6	0
	Dabigatran	1.9	85.8	14.2	0	53.1	0	0	46.9	0
	Edoxaban	81.3	95.7	4.3	0	42.9	0	0	57.1	0
	Rivaroxaban	0.5	86.0	14.0	0	43.0	0	0	57.0	0

P2Y12 receptor antagonists <sup>e</sup>	Prasugrel	13.6	88.5	11.5	0	15.8	24.8	0	58.4	1.0
	Ticagrelor	2.7	86.8	13.2	0	6.9	21.4	0	68.9	2.8
Beta-adrenergic blocking agents <sup>f</sup>	Carvedilol CR <sup>f</sup>	70.6	94.5	5.5	0	41.8	0	0	58.2	0
	Nebivolol <sup>g</sup>	33.7	87.5	12.5	0	17.7	0	0	82.3	0
Angiotensin II receptor antagonists <sup>h</sup>	Azilsartan	74.3	92.7	7.3	0	33.3	10.4	0	56.3	0
	Olmesartan	47.6	92.9	7.1	0	26.0	16.9	0	56.6	0.5
Anti-anginal	Ranolazine <sup>i</sup>	100								
Gabapentinoid	Pregabalin <sup>j</sup>	0	85.8	14.2	0	42.8	29.7	0	19.7	7.8
SGLT-2 inhibitor	Dapagliflozin <sup>k</sup>	55.6	85.5	13.3	1.2	33.7	57.2	0	8.4	0.7
Stimulant	Lisdexamfetamine <sup>l</sup>	76.5	87.5	12.5	0	15.9	40.9	0	35.2	8.0
Anti-psychotic	Lurasidone <sup>m</sup>	0	85.8	14.2	0	67.3	23.3	0	9.4	0
Smoking cessation	Varenicline <sup>n</sup>	0	83.7	16.0	0.3	59.3	9.1	0	23.3	8.3
PDE-5 inhibitor	Tadalafil <sup>o</sup>	83.2	84.1	15.9	0	19.0	81.0	0	0	0
Beta-adrenergic agent	Mirabegron <sup>p</sup>	11.8	85.5	14.2	0.3	47.9	8.4	0	42.7	1.0

Calcimimetic	Cinacalcet <sup>q</sup>	0	56.7	18.7	24.6	22.2	22.2	7.5	28.6	19.5
Immuno-modulatory	Teriflunomide <sup>r</sup>	43.9	78.1	17.6	4.3	87.1	11.5	0	0.8	0.6
Amino-salicylate	Mesalamine <sup>s</sup>	40.9	86.4	13.6	0	26.2	0	0	73.8	0
<b>Overall Median (Interquartile Range)</b>		42.4 (2.5-71.5)	86.0 (85.5-90.3)	14.0 (9.7-14.8)	0 (0-0)	37.2 (20.6-45.5)	16.9 (0-27.3)	0 (0-0)	42.7 (21.5-71.5)	3.2 (0.5-5.2)

<sup>a</sup> Generic refers to therapeutically interchangeable generic equivalent

<sup>b</sup> Therapeutically interchangeable generic drugs for pitavastatin and rosuvastatin were atorvastatin, simvastatin, lovastatin, pravastatin, fluvastatin

<sup>c</sup> Therapeutically interchangeable generic drugs for dalteparin were enoxaparin and fondaparinux

<sup>d</sup> Therapeutically interchangeable generic drug for direct oral anti-coagulants (apixaban, dabigatran, edoxaban and rivaroxaban) was warfarin

<sup>e</sup> Therapeutically interchangeable generic drug for prasugrel and ticagrelor was clopidogrel

<sup>f</sup> Therapeutically interchangeable generic drugs for carvedilol CR were atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol succinate, nadolol, propranolol

<sup>g</sup> Therapeutically interchangeable generic drugs for nebivolol were atenolol, betaxolol, bisoprolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, nadolol, propranolol

<sup>h</sup> Therapeutically interchangeable generic drugs for azilsartan and olmesartan were valsartan, candesartan, eprosartan, irbesartan, losartan, telmisartan

<sup>i</sup> Therapeutically interchangeable generic drugs for ranolazine were isosorbide dinitrate, isosorbide mononitrate, amlodipine, nicardipine, nifedipine, felodipine

<sup>j</sup> Therapeutically interchangeable generic drug for pregabalin was gabapentin

<sup>k</sup> Therapeutically interchangeable generic drugs for sodium-glucose co-transporter 2 (SLGT2) inhibitor dapagliflozin were glipizide, glyburide, glimepiride

<sup>l</sup> Therapeutically interchangeable generic drugs for lisdexamfetamine were methylphenidate, dextroamphetamine

<sup>m</sup> Therapeutically interchangeable generic drugs for lurasidone were aripiprazole, olanzapine, quetiapine, ziprasidone, risperidone, clozapine

<sup>n</sup> Therapeutically interchangeable generic drug for varenicline was bupropion

<sup>o</sup> Therapeutically interchangeable generic drugs for phosphodiesterase-5 (PDE-5) inhibitor tadalafil were sildenafil, vardenafil

<sup>p</sup> Therapeutically interchangeable generic drugs for mirabegron were oxybutynin, tolterodine, darifenacin

<sup>q</sup> Therapeutically interchangeable generic drug for cinacalcet was paricalcitol

<sup>r</sup> Therapeutically interchangeable generic drug for teriflunomide was leflunomide

<sup>s</sup> Therapeutically interchangeable generic drug for mesalamine was sulfasalazine

<sup>h</sup> Utilization management strategies include: 1) step therapy, which requires using a lower-cost drug before a more expensive drug can be used, 2) prior authorization, which requires that a prescription medication meet specific criteria before it can be approved by the health plan for coverage, and 3) quantity limits, which control the amount of drug that can be filled at a given time



## **6. DISCUSSION**

### **6.1 Study Findings and Context**

This study provides both a focused and systematic overview of the relationship between CMS formulary regulations and evidence-based, cost-effective prescribing through three analyses. The first study was an examination of national opioid versus non-opioid analgesic prescription rates before and after release of CDC guidelines encouraging prescription of non-opioid analgesics, and the second was a characterization of CMS formulary coverage, including utilization management strategies, of opioid potentiators such as benzodiazepines, non-benzodiazepine sedative hypnotics and gabapentinoids in light of increasing morbidity from co-prescription of opioids and opioid potentiators. Finally, the third study examined how 2016 Medicare prescription drug plan formularies incentivize selection of top 100-grossing brand-name drugs without bioequivalent generics compared to their corresponding therapeutically interchangeable generic drugs through tier placement and utilization management strategies, in anticipation of the 2020 CMS proposal for an indication-based formulary.

### **6.2 Impact of 2013 CMS Cautionary Opioid Guidelines on Rate of Opioid Prescription**

In this study of pain medication prescribing in a nationally representative sample of outpatient and ED visits from 2006-2015, overall rates of pain medication prescribing were high, with a prescription provided among approximately one in five outpatient visits and nearly one in two ED visits. Over this period, we found increased opioid pain medication prescribing in the outpatient setting, rising to nearly one in twelve visits. Finally, reassuringly, there was an increase in non-opioid pain medication prescribing in both the outpatient and ED settings, an area that has not been previously reported or well-investigated.

The prescription of opioids increased in the outpatient setting. Chronic non-cancer-related pain is a common presentation in primary care, and the difficulties of determining when to prescribe opioids, and for how long, has been acknowledged in multiple studies <sup>37, 38</sup>. In primary care, there have been numerous efforts to encourage appropriate opioid prescribing, including targeted physician education <sup>39</sup>. Requiring patients to have a structured care system comprising of periodic visits dedicated to monitoring and discussion of their current opioid medications has been shown to reduce opioid prescriptions <sup>40</sup>. Ongoing education for patients who are currently struggling with opioid dependence is especially important, as patients who have experienced a non-fatal overdose are at high risk of fatal opioid overdose throughout this period <sup>41</sup>. A multicomponent system involving a nurse care manager, electronic registry, data-driven academic detailing (face-to-face education of prescribers by trained health care professionals in order to improve evidence-based prescribing of targeted drugs), and clinical decision support (such as care reminders, up-to-date guidelines, recommendations, and databases that can provide information relevant to particular patients) has been shown to improve adherence to opioid-prescribing guidelines <sup>42, 43</sup>. Nonetheless, our results show that there was a steady increase in opioid prescribing across the ten years period, suggesting the need for implementing effective interventions such as those described above, and developing still others, that attempt to reduce opioid prescribing for chronic pain in the primary care setting.

The increase in non-opioid pain medication prescribing in both outpatient and emergency room settings is reassuring. Many reports have linked increased opioid prescribing to increased opioid-related deaths <sup>17, 44</sup>. Previous reports on pain medication, specifically in the ED, reported an increase in opioid prescribing and no change in non-opioid prescribing from 2001-2010 <sup>45</sup>. Our results showed the opposite, with an increase in non-opioid prescription. Our results

suggests a response by ED providers to replace opioid treatments with non-opioid NSAIDs for patients presenting with pain disorder starting in 2010<sup>16</sup>. Likewise, multiple studies in the primary care setting have shown the benefit of choosing non-opioid therapies for chronic pain. Our results show that outpatient physicians are starting to use evidence-based guidelines for managing chronic pain<sup>46,47</sup>.

### **6.3 Opioid Potentiators: Are Formulary Regulations Being Used to Control Unsafe Prescribing?**

From 2013-2017, Medicare prescription drug plan formularies had relatively unchanged rates of benzodiazepine, non-benzodiazepine sedative-hypnotic, and gabapentinoid coverage with small increases in use of quantity limits. More than a quarter of formularies provided unrestrictive coverage of these potentially unsafe opioid potentiators in 2017, and approximately 20% of formularies provided unrestrictive coverage of alprazolam and lorazepam, the two most commonly prescribed benzodiazepines. Furthermore, despite concern about the potential for prescription abuse, gabapentin was covered without restrictions by almost 60% of formularies.

As CMS formulary coverage is a representation of national prescribing patterns, this study suggests that utilization management strategies are being sub-optimally implemented to restrict prescribing of opioid potentiators, similar to prescribing of opioids themselves as reported in the paper by Samuels et al.<sup>18</sup> The CMS overutilization monitoring system currently flags co-prescription of benzodiazepines and opioids, and CMS has proposed flagging co-prescription of other potentiator drugs with opioids.<sup>19</sup> Although we could not examine co-restriction of opioids and opioid potentiators using Medicare formulary data, our findings suggest opportunity for greater use of utilization management strategies to reduce use of these potentially unsafe medications.

## **6.4 Treatment of Therapeutic Equivalents by CMS Formularies**

In 2016, more than 85% of Medicare prescription drug plan formularies incentivized use of therapeutically interchangeable generic drugs over brand-name drugs through tier placement and utilization management. However, a substantial portion of formularies (80%) provided similarly restrictive coverage of some brand-name drugs and their therapeutically interchangeable generics, including the same tier placement or utilization management, thereby missing opportunities to incentivize prescribing of less costly generics. Furthermore, in 52% of the drug study sample, there were multiple formularies that used more restrictive utilization management strategies on therapeutic equivalents compared to branded drugs. While our study focused on therapeutically interchangeable generic drug coverage, our findings align with a study showing that while most 2016 Part D formularies incentivized bioequivalent generic drugs, there were formularies offering more favorable placement for brand-name drugs <sup>48</sup>.

Our findings can inform the proposed 2020 indication-based formulary design, suggesting that restricted coverage of brand-name drugs and favored coverage of their therapeutically interchangeable generics might further incentivize use of generic drugs and potentially reduce both Medicare and beneficiary spending.

## **6.5 Implications of Findings**

Restricting formulary coverage for prescription drugs is a strategy to increase safe and cost-effective prescribing for a large portion of the US patient population. Using opioids as a case study, our initial findings showed that opioid prescription has increased in the outpatient setting even in light of 2013 CDC guidelines encouraging prescription of non-opioid analgesics. These results correlate with the Samuels et al. paper noting unrestricted formulary coverage of

high-dose opioids <sup>18</sup>, suggesting that formulary restrictions may be a good measure with which to monitor prescription practices of potentially unsafe drugs. Our findings concerning unrestricted coverage of multiple opioid potentiators suggests that while CMS utilization management strategies are in place, they are being underutilized, leading to a concern that the restriction strategies alone are not promoting safe prescribing. In this case, it may be time to further strengthen the CMS overutilization system by adding a new measure that monitors concurrent opioid and opioid potentiator use and limits the supply of both medications for the first prescription filled for acute pain <sup>49</sup>.

The final study examined how formularies incentivize prescribing of therapeutic interchangeable generics over their corresponding high-grossing brand-name drugs across a breadth of therapeutic areas. The findings are concerning in that favorable or even equal formulary placement of branded drugs compared to therapeutically interchangeable generics incentivizes use of more expensive brand-name products and can lead to higher out-of-pocket costs for Medicare beneficiaries and higher expenditures for the Part D program.

## **6.6 Implications for Future Formulary Regulation and Structure**

Perhaps the most direct and straightforward option to encourage safe and cost-effective prescribing is for Medicare to prohibit giving branded products or certain classes of drugs more favorable formulary placement than generic products or preferred alternative classes. This has been suggested in previous work <sup>31</sup>— however, it may limit choices in cases where the branded drug has a differential effect or cases where the benefit of a potentially harmful class of drugs outweighs the potentially harmful side effects. Furthermore, treatment of generic drugs versus branded drugs in the CMS formulary is complicated by the policy of volume-based rebates. Currently, prescription drug plans earn some of their profits through rebates and other price

concessions paid by pharmaceutical manufacturers in exchange for inclusion on certain tiers of the formulary<sup>50</sup>. As a result, generic drugs are often placed in a higher tier or treated more restrictively, if not left off of the formulary entirely. Thus, it might be necessary to also change the incentive structure of Part D plans.

Another solution is on the horizon in the form of a proposed indication-based formulary for all participating CMS prescription drug plans. This would by definition limit use of brand-name drugs to only certain indications, leaving much more opportunity for providers to utilize therapeutically interchangeable generics, especially in the relatively common occurrence of there being no bioequivalent generic available. Unfortunately, the issue of generic drug substitution is complex and often poorly understood by physicians, even where bioequivalents are concerned<sup>51</sup>.<sup>52</sup> Therapeutically interchangeable generics are even more contentious, as direct evidence to support equivalence is often lacking and FDA regulatory guidelines are somewhat ambiguous<sup>53</sup>.<sup>54</sup> Further work to establish guidelines for therapeutic exchange across multiple therapeutic areas will be necessary in order for the proposed formulary structural changes to have meaningful impact.

## **7. LIMITATIONS**

There are important limitations to consider in this study. For the first analysis, both NAMCS and NHAMCS limit the number of medications that are listed as prescribed during each visit. For patient visits where more than eight medications were prescribed, fentanyl or other opioid prescriptions, and especially NSAIDs (which are not consistently prescribed as they are available over the counter), may have not been captured, potentially underestimating pain medication prescribing. Second, NHAMCS only captures ED visits and does not include visits to hospital-based outpatient clinics, which limits the generalizability of our findings. Third,

NAMCS and NHAMCS are representative of a nationwide physician sample but likely underestimate physician prescriptions. Of note, change in clinical practice often occurs more slowly and the CDC guidelines release in 2013 may not have been dispersed and implemented fully in our research sample that runs from 2006-2015.

For the second analysis, we were unable to examine co-restriction of opioids and opioid potentiators using Medicare formulary data. Finally for the third analysis using CMS formulary data, Medicare prescription drug formulary data are not linked to beneficiary spending data, limiting our understanding of the actual patient out-of-pocket costs of brand-name and therapeutically interchangeable generic drugs.

## **8. CONCLUSION**

Controlling the cost of prescription drugs is integral to improving both patient access and adherence to treatment. The Center for Medicare & Medicaid Services (CMS) formularies, which cover around 17% of the US population, have uniformly adopted utilization management strategies, such as quantity limits, prior authorization, and step therapy, in order to promote safe, evidence-based and cost-effective prescribing. These strategies are in place to impact drug prescription rates as well as to incentivize use of biological or therapeutically interchangeable generics over brand-name drugs. Thus far, the implementation of utilization management strategies for commonly prescribed drugs has not been thoroughly studied.

This study presents three main analyses. The first showed that there has been an increase in outpatient opioid prescribing that correlates with the lack of formulary restriction of high-dose opioids shown previously. Our second study reported a similar lack of formulary restriction for

opioid potentiators such as benzodiazepines, non-benzodiazepine sedative-hypnotics and gabapentinoids. Finally, our third study showed that therapeutically interchangeable generics are not less restricted than their corresponding brand-name drugs across formularies. Overall, while formulary restrictions are in place, they are often underutilized in promoting safe and cost-effective prescribing.

The results of this comprehensive study on safe and cost-effective drug prescription strategies suggest that these strategies alone may not be sufficient to reduce over-prescription of potentially unsafe drugs like opioid potentiators, or to incentivize prescription of cost-saving generics over brand-name drugs. The CMS overutilization monitoring system should be updated to not only monitor, but also actively restrict prescription of potentially harmful drugs or drug combinations. The Center for Medicare & Medicaid Services (CMS) has proposed an indication-based formulary design starting in 2020, allowing Medicare Advantage and Part D prescription drug plans to cover drugs only for select indications, which could increase formulary negotiating power and secure more competitive pricing. With these changes, CMS can ensure continued patient access to affordable and safe prescription drugs.

## **9. REFERENCES**

1. Chernew ME, Shah MR, Wagh A, Rosenberg SN, Juster IA, Rosen AB, Sokol MC, Yu-Isenberg K and Fendrick AM. Impact of decreasing copayments on medication adherence within a disease management environment. *Health Affairs*. 2008;27:103-112.
2. Sokol MC, McGuigan KA, Verbrugge RR and Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care*. 2005:521-530.



3. Fu AZ, Liu GG and Christensen DB. Inappropriate medication use and health outcomes in the elderly. *Journal of the American Geriatrics Society*. 2004;52:1934-1939.
4. Twillman RK, Kirch R and Gilson A. Efforts to control prescription drug abuse: Why clinicians should be concerned and take action as essential advocates for rational policy. *CA Cancer J Clin*. 2014;64:369-376.
5. Meyer RJ. FDA “black box” labeling. *Annals of emergency medicine*. 2003;41:559-560.
6. Kanter J and Feldman R. Understanding the Incentivizing Biosimilars. *Hastings LJ*. 2012;64:57.
7. Phillips J. Prescription drug abuse: problem, policies, and implications. *Nurs Outlook*. 2013;61:78-84.
8. Solotke MT, Ross JS, Shah ND, Karaca-Mandic P and Dhruva SS. Medicare Prescription Drug Plan Formulary Restrictions After Postmarket FDA Black Box Warnings. *Journal of managed care & specialty pharmacy*. 2019;25:1201-1217.
9. Liang S-Y, Haas JS and Phillips KA. Medicare formulary coverage for top-selling biologics. *Nature biotechnology*. 2009;27:1082.
10. García MC. Declines in Opioid prescribing after a private insurer policy change—Massachusetts, 2011–2015. *MMWR Morbidity and mortality weekly report*. 2016;65.
11. Ross JS, Jackevicius C, Krumholz HM, Ridgeway J, Montori VM, Alexander GC, Zerzan J, Fan J and Shah ND. State Medicaid programs did not make use of prior authorization to promote safer prescribing after rosiglitazone warning. *Health Affairs*. 2012;31:188-198.
12. Roberto P, Michael Ciarametaro M and Dubois R. Impact of Formulary Restrictions on Medication Intensification in Diabetes Treatment. *The American journal of managed care*. 2018;24:239-246.

13. Kolodny A, Courtwright DT, Hwang CS, Kreiner P, Eadie JL, Clark TW and Alexander GC. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015;36:559-574.
14. Centers for Disease Control and Prevention. Opioid Overdoses Treated in Emergency Departments. 2018;2018.
15. Centers for Disease Control and Prevention. Drug Overdose Death Data. 2017;2018.
16. Dowell D, Haegerich TM and Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016. Accessed: September 7, 2018;315:1624-1645.
17. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B and Green JL. Trends in opioid analgesic abuse and mortality in the United States. *N Engl J Med*. 2015;372:241-248.
18. Samuels EA, Ross JS and Dhruva SS. Medicare formulary coverage restrictions for prescription opioids, 2006 to 2015. *Ann Intern Med*. 2017;167:895-896.
19. Centers for Medicare and Medicaid Services. 2019 Medicare Advantage and Part D Advance Notice Part II and Draft Call Letter.  
<https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2018-Fact-sheets-items/2018-02-01.html>. 2018. Accessed: October 19, 2018.
20. National Institutes of Health. Benzodiazepines and Opioids.  
<https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids>. 2018. Accessed: October 19, 2018.
21. Gomes T, Greaves S, van den Brink W, Antoniou T, Mamdani MM, Paterson JM, Martins D and Juurlink DN. Pregabalin and the Risk for Opioid-Related Death: A Nested Case–Control Study. *Ann Intern Med*. 2018.

22. National Institutes of Health. Overdose Death Rates. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>. 2018. Accessed: October 19, 2018.
23. Bachhuber MA, Hennessy S, Cunningham CO and Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. *Am J Public Health*. 2016;106:686-688.
24. NCOA. Medicare Part D Drug Plans: What They Must, May, and Cannot Cover. <https://www.ncoa.org/wp-content/uploads/part-d-drug-coverage-rules.pdf>. 2017.
25. Ong MK, Xu H, Zhang L, Azocar F and Ettner SL. Effect of medicare part D benzodiazepine exclusion on psychotropic use in benzodiazepine users. *J Am Geriatr Soc*. 2012;60:1292-1297.
26. Jeffery MM, Hooten WM, Jena AB, Ross JS, Shah ND and Karaca-Mandic P. Rates of Physician Coprescribing of Opioids and Benzodiazepines After the Release of the Centers for Disease Control and Prevention Guidelines in 2016. *JAMA network open*. 2019;2:e198325-e198325.
27. Lembke A, Papac J and Humphreys K. Our Other Prescription Drug Problem. *N Engl J Med*. 2018;378:693-695.
28. Dolan C, Omer S, Glynn D, Corcoran M and McCarthy G. Benzodiazepine and Z-drug prescribing for elderly people in a general hospital: a complete audit cycle. *Ir J Psychol Med*. 2012;29:128-131.
29. Hamer AM, Haxby DG, McFarland BH and Ketchum K. Gabapentin use in a managed Medicaid population. *J Manag Care Pharm*. 2002;8:266-271.
30. Kamal R, Cox C and McDermott D. What are the recent and forecasted trends in prescription drug spending? 2019. Accessed: August 5, 2019.

31. Socal MP, Bai G and Anderson GF. Favorable Formulary Placement of Branded Drugs in Medicare Prescription Drug Plans When Generics Are Available. *JAMA internal medicine*. 2019.
32. Euen BJ and Fadda HM. Community pharmacists' understanding and perceptions of FDA therapeutic equivalence standards. *Research in Social and Administrative Pharmacy*. 2019;15:77-83.
33. Johansen ME and Richardson C. Estimation of Potential Savings Through Therapeutic Substitution. *JAMA internal medicine*. 2016;176:769-75.
34. Centers for Medicaid and Medicare Services. Indication-Based Formulary Design Beginning in Contract Year (CY) 2020 2018. Accessed: August 5, 2019.
35. Sedelmeier G and Sedelmeier J. Top 200 Drugs by Worldwide Sales 2016. *Chimia (Aarau)*. 2017;71:730.
36. Lanthier M, Miller KL, Nardinelli C and Woodcock J. An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals, 1987-2011. *Health Aff (Millwood)*. 2013;32:1433-9.
37. Harle CA, Bauer SE, Hoang HQ, Cook RL, Hurley RW and Fillingim RB. Decision support for chronic pain care: how do primary care physicians decide when to prescribe opioids? a qualitative study. *BMC Fam Pract*. 2015;16:48.
38. Jamison RN, Kerry Anne Sheehan B, Elizabeth Scanlan N and Ross EL. Beliefs and attitudes about opioid prescribing and chronic pain management: survey of primary care providers. *Journal of opioid management*. 2014;10:375-382.
39. Leece P, Buchman DZ, Hamilton M, Timmings C, Shantharam Y, Moore J and Furlan AD. Improving opioid safety practices in primary care: protocol for the development and

evaluation of a multifaceted, theory-informed pilot intervention for healthcare providers. *BMJ open*. 2017;7:e013244.

40. McCann KS, Barker S, Cousins R, Franks A, McDaniel C, Petraney S and Riley E. Structured Management of Chronic Nonmalignant Pain with Opioids in a Rural Primary Care Office. *The Journal of the American Board of Family Medicine*. 2018;31:57-63.
41. Olfson M, Wall M, Wang S, Crystal S and Blanco C. Risks of fatal opioid overdose during the first year following nonfatal overdose. *Drug Alcohol Depend*. 2018;190:112-119.
42. Liebschutz JM, Xuan Z, Shanahan CW, LaRochelle M, Keosaian J, Beers D, Guara G, O'connor K, Alford DP and Parker V. Improving adherence to long-term opioid therapy guidelines to reduce opioid misuse in primary care: a cluster-randomized clinical trial. *JAMA internal medicine*. 2017;177:1265-1272.
43. Cushman PA. The primary care provider experience in an intervention to improve adherence to opioid prescribing guidelines. 2017;2018.
44. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA and Blow FC. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011;305:1315-1321.
45. Mazer-Amirshahi M, Mullins PM, Rasooly I, den Anker J and Pines JM. Rising opioid prescribing in adult US emergency department visits: 2001–2010. *Acad Emerg Med*. 2014;21:236-243.
46. Schneiderhan J, Clauw D and Schwenk TL. Primary care of patients with chronic pain. *JAMA*. 2017;317:2367-2368.
47. Renthal W. Seeking balance between pain relief and safety: CDC issues new opioid-prescribing guidelines. *JAMA neurology*. 2016;73:513-514.

48. Socal MP, Bai G and Anderson GF. Favorable Formulary Placement of Branded Drugs in Medicare Prescription Drug Plans When Generics Are Available. *JAMA Intern Med.* 2019;179:832-833.
49. Rubin R. CMS to Improve Drug Programs and Opioid Overuse Oversight. *Jama.* 2018;319:1189-1189.
50. Seeley E and Kesselheim AS. Pharmacy Benefit Managers: Practices, Controversies, and What Lies Ahead. *Issue brief (Commonwealth Fund).* 2019;2019:1-11.
51. Wilner AN. Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy & behavior.* 2004;5:995-998.
52. Al-Jazairi AS, Blhareth S, Eqtefan IS and Al-Suwayeh SA. Brand and generic medications: are they interchangeable? *Annals of Saudi medicine.* 2008;28:33-41.
53. Duerden MG and Hughes DA. Generic and therapeutic substitutions in the UK: are they a good thing? *British journal of clinical pharmacology.* 2010;70:335-341.
54. Meredith PA. Potential concerns about generic substitution: bioequivalence versus therapeutic equivalence of different amlodipine salt forms. *Current medical research and opinion.* 2009;25:2179-2189.