EVIDENCE OF BIAS AGAINST ADOPTION OF ANTI-OBESITY PHARMACOTHERAPIES

A Thesis

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of Medical Sciences

in Partial Fulfillment of the Requirements for the Degree of

Master of Science

by

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ABSTRACT

Background

Approximately half of adults in the U.S. fit the criteria for use of anti-obesity pharmacotherapy, but only 2% of those receive such treatment. This is in sharp contrast to the 8.4% of adults diagnosed with diabetes, with 86% of those receiving anti-diabetes pharmacotherapy. In 2012-2014, the first medications in 13 years were FDA approved for long-term management of obesity. In 2013-2014, the newest class of anti-diabetes pharmacotherapy, subtype 2 sodium-glucose transport protein inhibitors (SGLT2s), were FDA approved.

Methods

A retrospective analysis of extracted data from the IMS Health National Prescription Audit™ and Xponent™ assessed adoption rates of anti-obesity pharmacotherapies and SGLT2s using univariate linear regressions. Volumes of new and continuing prescriptions were compared using ratio analyses. Prescriber groups were compared by descriptive proportions according to prescription volumes, medical specialty, geographic region, and prescriber-drug overlap.

Results

The entire anti-diabetes market was 15 times the entire anti-obesity market. The anti-obesity market share was: 74.0% phentermine and 18.6% new anti-obesity pharmacotherapies. The mean increase in prescriptions per month were: 25,259 for SGLT2s (95% CI 23,133-27,383 p<.0001), 5,154 for new

anti-obesity pharmacotherapies (95% CI 4,800-5,507 p<.0001), and 2,718 for phentermine (95% CI 1,345-4,089 p=0.0003). Medical specialties prescribing the majority of the analysis medications were Family Medicine/General Practice and Internal Medicine. Endocrinology had the highest prevalence of prescribers of any sub-specialty.

Conclusions

The adoption rate of SGLT2s was nearly exponential, while the adoption rate of new anti-obesity pharmacotherapies was linear. Considering the relative prevalence of obesity to diabetes and that obesity is a major cause of diabetes, these results are paradoxical and suggest biases against the prescribing of anti-obesity pharmacotherapies. The under-prescribing of anti-obesity pharmacotherapies is widely acknowledged, but this is the first prescription data to demonstrate its extent in the U.S.

BIOGRAPHICAL SKETCH

In 2006, Catherine Elizabeth Thomas obtained her Bachelor of Science degree in Nutritional Sciences from the Pennsylvania State University. In 2007, she began working for her mentor, Louis J. Aronne, MD.

To my children, God willing, for whom I hope I have become a good example.

ACKNOWLEDGEMENTS

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I would especially thank Michael Chen, MBA, who generously facilitated this project from its inception. The completion of this project is thanks to the excellent statistical support of Elizabeth A. Mauer, MS and Paul Christos, DrPH, MS. I would not be the researcher or the person I have become without the mentorship of Louis J. Aronne, MD, FACP, FTOS, DABOM and Alpana P. Shukla, MD, MRCP. A very special thank you to George Thomas, Jr., MD for giving me the strength and clinical insight needed to cross the finish line.

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CHAPTER ONE
BACKGROUND

In the United States, more than two thirds (69%) of adults are overweight, more than one third have obesity (35%), and 6.4% have extreme obesity.[1] Obesity is a major risk factor for a constellation of diseases including type 2 diabetes and cardiovascular disease.[2] Anti-obesity pharmacotherapy is indicated as an adjunct to reduced-calorie diet and increased physical activity in adults with a body mass index ≥30 or ≥27 kg/m^2 with hypertension, type 2 diabetes, or dyslipidemia. Just under half (46%) of adults in the U.S. fit the criteria for use of anti-obesity pharmacotherapy, but only 2% of those receive such treatment.[3,4] This is in sharp contrast to the 8.4% of adults in the U.S. diagnosed with diabetes[5], with 86% of those receiving anti-diabetes pharmacotherapy[6] (Figure1).

Figure 1. Obesity and diabetes prevalence and pharmacotherapy utilization.

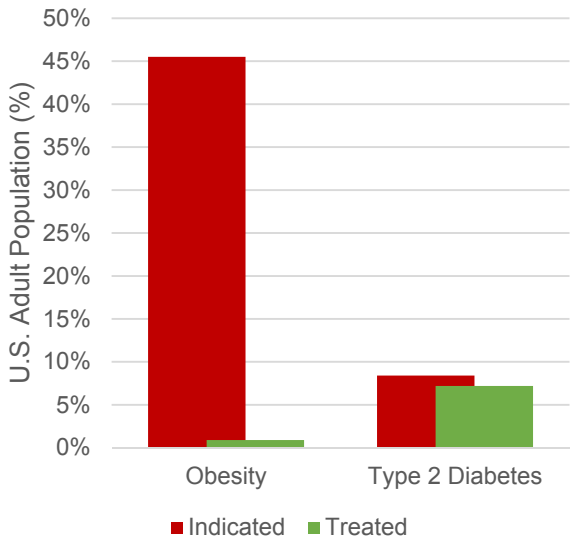

Figure 1. Prevalence of obesity and diabetes in the U.S. adult population and pharmacotherapy utilization of anti-obesity pharmacotherapies and anti-diabetes pharmacotherapies.

It has taken the past 20 years for the world's leading public health and medical bodies to recognize obesity as a disease. In 1995, the Institute of Medicine recognized obesity as a disease and recommended use of pharmacotherapy in treatment of the disease.[7] In 1997, the World Health Organization followed suit[8], continuing with the National Institutes of Health in 1998[9] and in 2000[10], the American College of Physicians in 2005[11], the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinologists (ACE) in 2012[12], and the American Medical Association in 2013[13]. In June 2013, the American Heart Association, the American College of Cardiology, and The Obesity Society issued joint guidelines for the management of overweight and obesity in adults.[14] In February 2015, The Endocrine Society issued clinical practice guidelines on the pharmacological management of obesity.[15] The declaration by each body included the recommendation of using anti-obesity pharmacotherapy as an adjunct to behavioral management in appropriate individuals.

The most commonly prescribed anti-obesity pharmacotherapies in the U.S. are: phentermine, naltrexone + bupropion, lorcaserin, and topiramate + phentermine. Phentermine was FDA-approved in 1959 for short-term treatment of obesity (3 months). Topiramate + phentermine and lorcaserin were FDA-approved in 2012 and naltrexone + bupropion in 2014. Topiramate + phentermine, lorcaserin, and naltrexone + bupropion (new anti-obesity pharmacotherapies) were the first medications in 13 years to receive FDA approval for long-term management of obesity in adults. The newest class of anti-diabetes pharmacotherapy, subtype 2

sodium-glucose transport protein inhibitors (SGLT2s), served as comparators in this analysis due to their similarly timed commercial availability as the new anti-obesity pharmacotherapies and their mid-range placement in the AACE/ACE Glycemic Control Algorithm.[16] The SGLT2s include: canagliflozin, dapagliflozin, and empagliflozin and were FDA-approved to treat adults with type 2 diabetes mellitus in 2013 and 2014.

CHAPTER TWO
MATERIALS AND METHODS

This study was approved, with the requirement of informed consent waived, by the Weill Cornell Medical College Institutional Review Board. This is a retrospective analysis, 2012-2015, of deidentified extracted data from the IMS Health National Prescription Audit™ and Xponent™ databases. IMS Health is the industry standard source of national prescription activity for all pharmaceutical products in the U.S. The National Prescription Audit™ is a database of all dispensed prescription information from 38,939 pharmacies (retail, long-term care, and mail service) across the U.S., which represents 70% of the dispensed outpatient prescription volume in the U.S.[17] The uncaptured prescription volume is projected to 100% by proprietary IMS Health methodologies. Xponent™ contains demographic and dispensed prescription information for U.S. prescribers. Prescriber demographic information is obtained by IMS Health from the American Medical Association's Physician Professional Data, which are based on clinician self-selected responses.

Wholesale acquisition costs for each medication were obtained from the Wolters Kluwer Clinical Drug Information application, Medi-Span Price Rx™. Wholesale acquisition costs are the manufacturer's list price for their drug to wholesalers or direct purchasers in the U.S.

Total numbers of active physicians, active physicians per specialty, and active physicians per state were obtained from the Association of American Medical Colleges' *2014 Physician Specialty Data Book*[18] and *State Physician Workforce Data Book 2013*[19]. Both publications source their data from the same source as

IMS Health, the American Medical Association's Physician Masterfile, which is informed by the American Medical Association's Census of Physicians and National Graduate Medical Education Census.

For this analysis, medical specialties in Xponent™ were grouped according to the groupings defined in the Association of American Medical Colleges' publications (e.g. Endocrinology, Diabetes & Metabolism and Diabetes were group together as Endocrinology). Prescriber specialties were further grouped into physicians and non-physicians (e.g. nurse practitioner, physician assistant, chiropractor, dentist, podiatrist). The continental states were grouped into regions according to the U.S. Census Bureau. Alaska and Hawaii were grouped into the Pacific Region.

This analysis assessed the adoption rate of anti-obesity pharmacotherapies and SGLT2s by evaluating the change in mean prescriptions per month over the analysis period using univariate linear regressions. National volumes of dispensed prescriptions were described according to frequency over time. Volumes of new and continuing prescriptions were compared using ratio analyses. Prescriber groups were compared by descriptive proportions according to prescription volumes, medical specialty, geographic region, and prescriber-drug overlap.

CHAPTER THREE
RESULTS

As of August 2015, the entire anti-diabetes pharmacotherapy market, excluding insulin, was 15 times the entire anti-obesity pharmacotherapy market. SGLT2s comprised 4.9% of the anti-diabetes pharmacotherapy market, which was equivalent to three-quarters of the entire anti-obesity pharmacotherapy market (Figure 2).

Figure 2. Dispensed volumes of anti-obesity and anti-diabetes pharmacotherapies and SGLT2s.

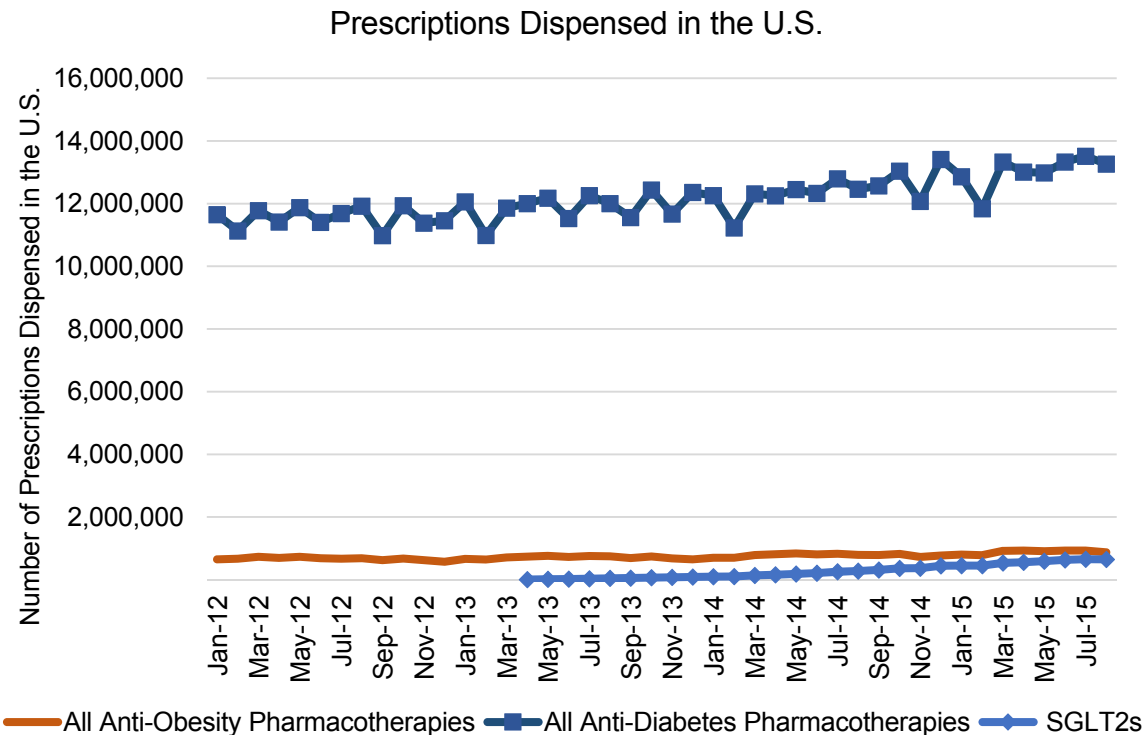

Figure 2. Volume of prescriptions of all anti-obesity pharmacotherapies, all anti-diabetes pharmacotherapies (excluding insulin), and SGLT2s dispensed in the U.S., 2012-2015.

The anti-obesity pharmacotherapy market share was: 74.0% phentermine and 18.6% new anti-obesity pharmacotherapies (Figure 3). The mean increase in

prescriptions per month were: 25,259 for SGLT2s (95% CI 23,133-27,383 p<.0001), 5,154 for new anti-obesity pharmacotherapies (95% CI 4,800-5,507 p<.0001), and 2,718 for phentermine (95% CI 1,345-4,089 p=0.0003) (Figure 3, Table 1). For each new prescription dispensed there were 5.4 continuing prescriptions dispensed for phentermine, 4.6 for SGLT2s, and 1.4 for new anti-obesity pharmacotherapies.

Figure 3. Dispensed volumes of phentermine, new anti-obesity pharmacotherapies, and SGLT2s.

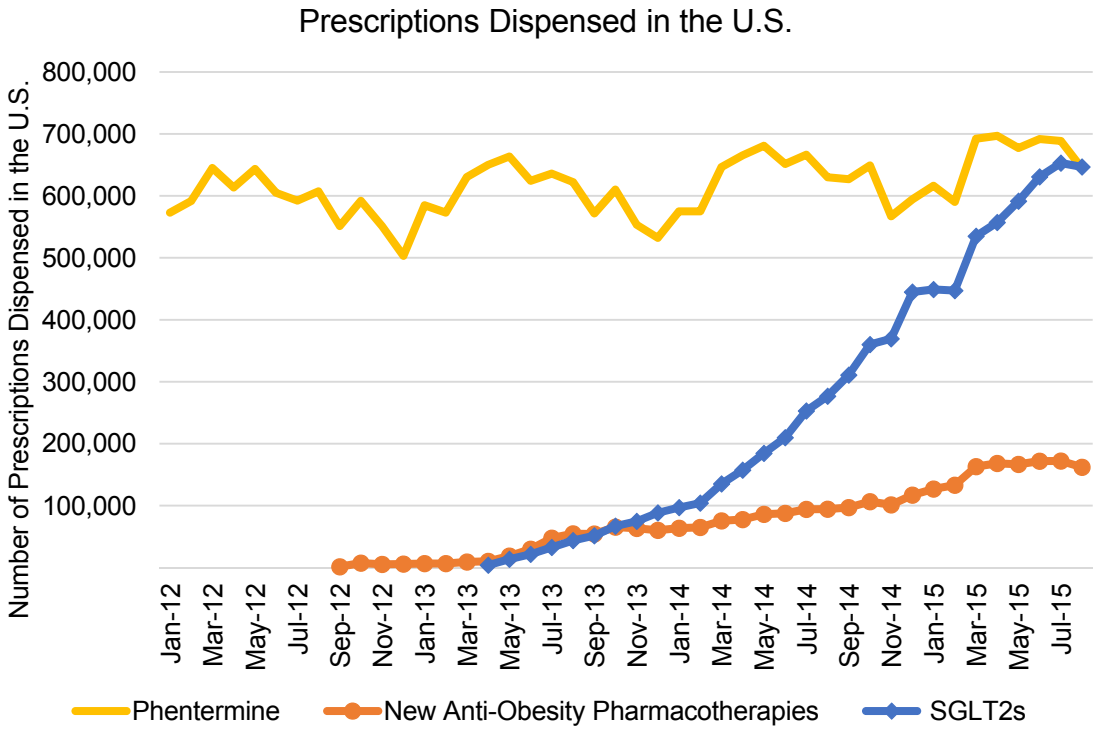

Figure 3. Volume of prescriptions of phentermine, new anti-obesity pharmacotherapies, and SGLT2s dispensed in the U.S, 2012-2015.

Table 1. Output from separate univariate linear regressions by drug category to estimate mean change in prescriptions per month, as presented in Figure 3.

		Estimate	Std. Error	95% CI	t value	Pr(>|t|)
SGLT2s	Intercept	-109,595.00	17,788.00	(-146,093.58, -73,097.20)	-6.16	
	Month	25,259.00	1,036.00	(23,133.65, 27,383.66)	24.39	<.0001
New Anti-Obesity	Intercept	-18,225.60	3,689.90	(-25,724.34, -10,726.84)	-4.94	
	Month	5,153.90	173.90	(4,800.51, 5,507.37)	29.64	<.0001
Phentermine	Intercept	568,472.80	14,325.70	(539,359.45, 597,586.08)	39.68	
	Month	2,717.60	675.20	(1,345.47, 4,089.79)	4.03	0.0003

Of the 900,000 prescribers in the IMS Health Xponent™ database, from 2012 to 2015, 173,882 (19%) prescribed phentermine, 104,612 (12%) prescribed a new anti-obesity pharmacotherapy, and 102,002 (11%) prescribed an SGLT2. Of the 829,962 active physicians in the U.S., 129,414 (16%) prescribed phentermine, 79,624 (10%) prescribed a new anti-obesity pharmacotherapy, and 70,898 (9%) prescribed an SGLT2 (Table 2). The top eight most frequent prescribing medical specialties of each drug group represent: 62% of prescribers and 75% of prescriptions of phentermine, 69% of prescribers and 81% of prescriptions of new anti-obesity pharmacotherapies, and 66% of prescribers and 80% of prescriptions of SGLT2s (Table 2).

Table 2. Prescriber groups compared by descriptive proportions according to prescription volumes, medical specialty, geographic region, and prescriber-drug overlap. Prescriber-Drug Overlap represents the percentage of prescribers of the column drug category who also prescribed the row drug category.

2012-2015	Phentermine			New Anti-Obesity Pharmacotherapies			SGLT2s		
Group	A	B	C	A	B	C	A	B	C
Prescribers in Xponent™	19	100	100	12	100	100	11	100	100
Active Physicians in U.S.	16	74	81	10	76	86	9	70	83
Primary Specialty									
Family Medicine/General Practice	48	30	42	32	34	34	32	34	33
Internal Medicine	27	18	19	21	22	27	22	24	25
Endocrinology	37	1	2	47	3	13	64	4	22
Obstetrics/Gynecology	25	6	7	12	5	4			
Psychiatry	10	2	1	4	2	1			
Emergency Medicine	8	2	1	2	1	<1	2	1	<1
General Surgery	11	2	2	4	1	1			
Cardiovascular Diseases				7	1	1	5	1	<1
Internal Medicine/Pediatrics							14	1	<1
Geriatric Medicine							13	1	<1
Pediatrics	4	1	1						
Nephrology							4	<1	<1
Unavailable		2	<1		2	<1		10	3
Physicians by Region									
South	20	43	46	13	44	46	11	42	41
Midwest	16	22	16	10	21	16	9	22	16
West	14	20	10	8	17	11	6	16	13
Northeast	10	14	7	7	17	12	7	19	12
Pacific	12	1	<1	7	<1	<1	8	1	<1
Unavailable		<1	<1		<1	<1		<1	<1
Prescriber-Drug Overlap									
Phentermine					69			57	
New Anti-Obesity Pharmacotherapies		41						51	
SGLT2s		33			50				

Legend
A: % of group who prescribed drug(s)= drug prescribers from group / active physicians in group
B: % of drug prescribers from group= drug prescribers from group / all prescribers of drug(s)
C: % of drug Rxs in U.S. from group= drug prescriptions from group / all prescriptions of drug(s)
Specialties reported represent the top 8 most frequent prescribing specialties per drug category.

The Medicine sub-specialty with the highest prevalence of prescribers of all drug categories is Endocrinology (n=6,519), with 37% (n=2,388) having prescribed phentermine, 47% (n=3,040) having prescribed a new anti-obesity pharmacotherapy, and 64% (n=4,180) having prescribed an SGLT2 (Table 2,

Figure 4). Further, endocrinologists prescribed the new anti-obesity pharmacotherapies and SGLT2s at a higher rate than any other specialty. In Table 2, the differential between columns B and C indicate if specialties are prescribing at rates relative to their proportions or if they are exceeding it. The significant differentials of this type are: Family Medicine/General Practice with phentermine (by 12%), Internal Medicine with new anti-obesity pharmacotherapies (by 5%), and Endocrinology with new anti-obesity pharmacotherapies (by 10%) and with SGLT2s (by 18%).

Figure 4. Prevalence of physicians, by medical specialty, prescribing phentermine, new anti-obesity pharmacotherapies, and SGLT2s.

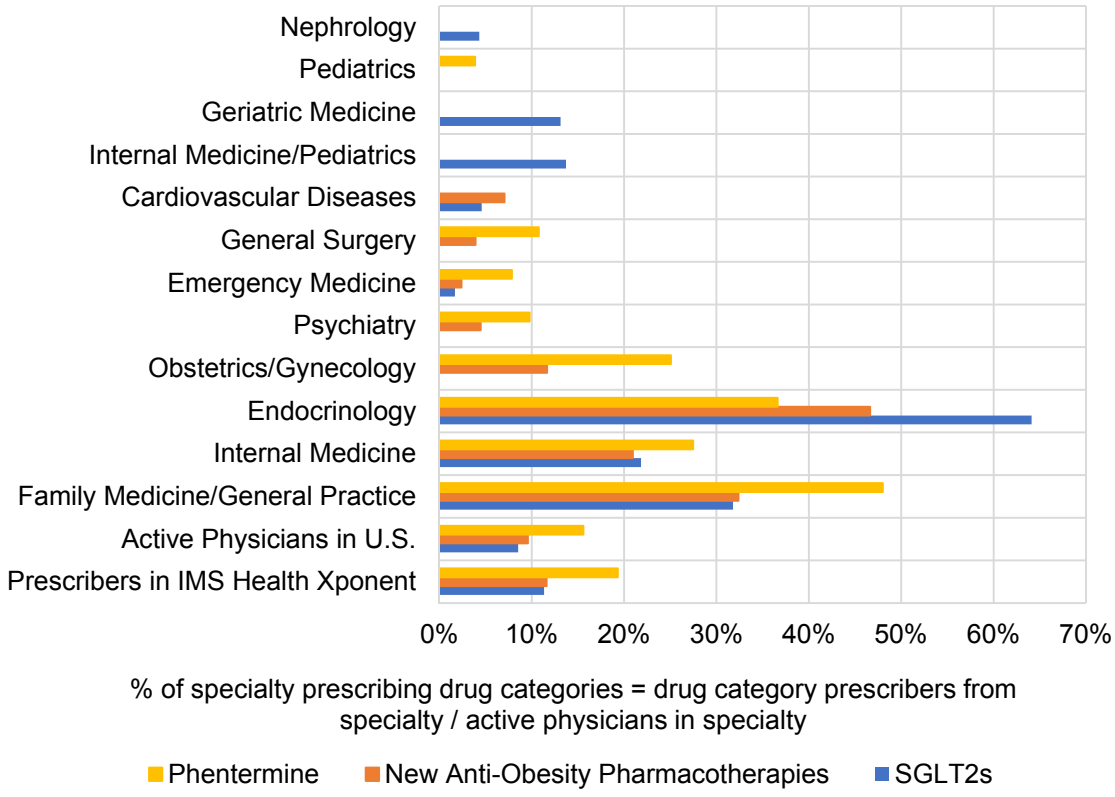

Figure 4. Prevalence of physicians, by medical specialty, prescribing phentermine, new anti-obesity pharmacotherapies, and SGLT2s in the U.S, 2012-2015.

Medical specialties prescribing the majority of each of the anti-obesity pharmacotherapies and the SGLT2s were Family Medicine/General Practice and Internal Medicine (Table 2, Figures 5, 6, 7). The top medical specialties common to all three drug categories are: Family Medicine/General Practice, Internal Medicine, Endocrinology, and Emergency Medicine. The top medical specialties common to the anti-obesity drug categories, but not SGLT2s are: Obstetrics/Gynecology, Psychiatry, and General Surgery. The top medical specialties prescribing SGTL2s, but neither anti-obesity drug category are: Internal Medicine/Pediatrics, Geriatric Medicine, and Nephrology. The Cardiovascular Diseases specialty is common among the top medical specialties prescribing new anti-obesity pharmacotherapies and SGLT2s, but not phentermine. Pediatrics is among the top medical specialties prescribing phentermine, but neither of the other drug categories.

Figure 5. Percent of phentermine prescribers and prescriptions by specialty.

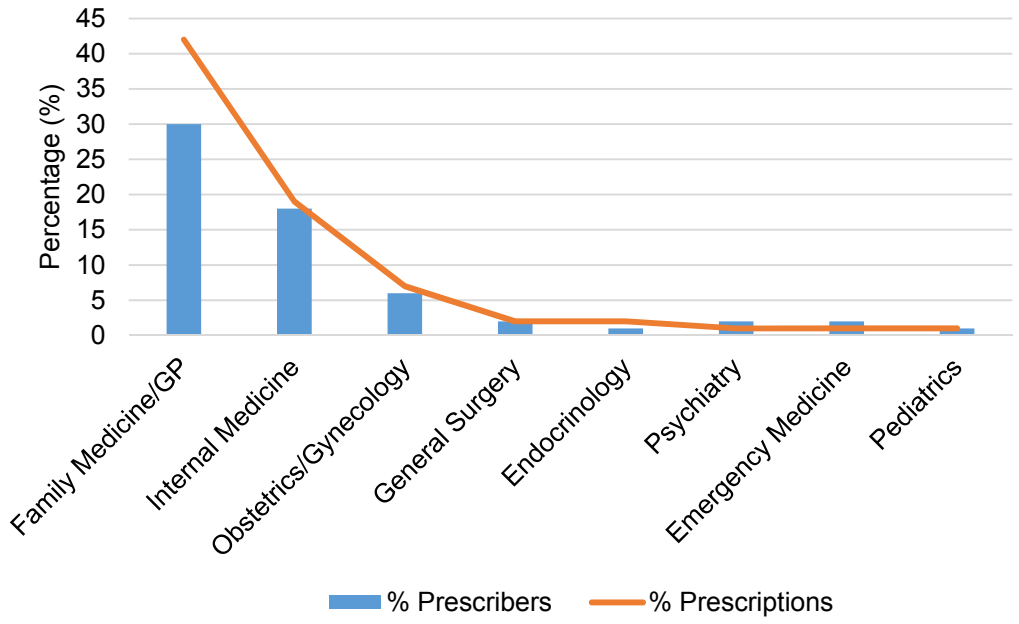

Figure 5. Percent of phentermine prescribers and prescriptions by specialty in the U.S, 2012-2015.

Figure 6. Percent of new anti-obesity pharmacotherapy prescribers and prescriptions by specialty.

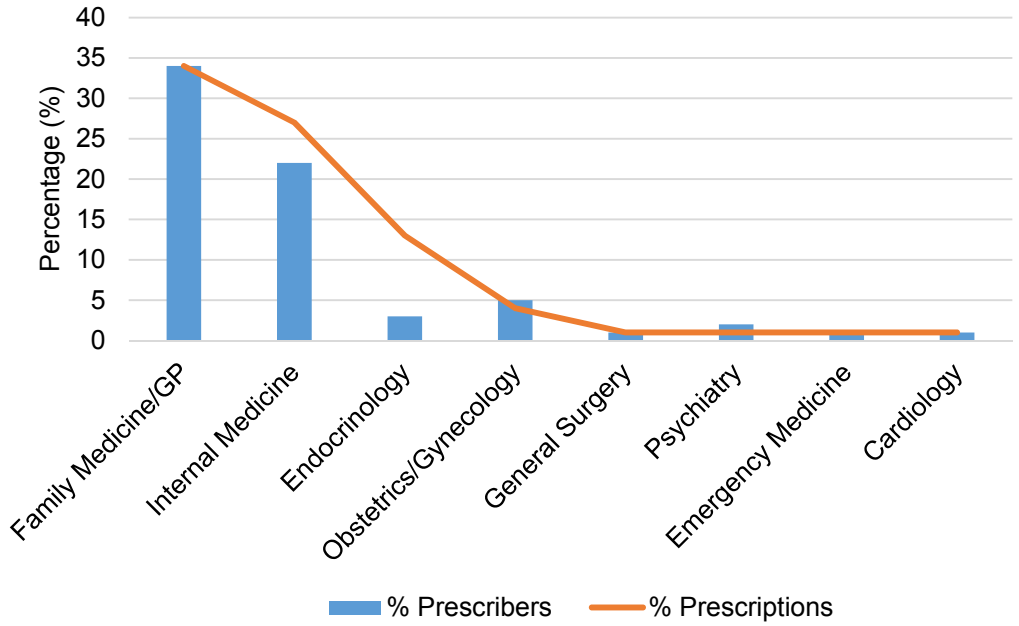

Figure 6. Percent of new anti-obesity pharmacotherapy prescribers and prescriptions by specialty in the U.S, 2012-2015.

Figure 7. Percent of SGLT2 prescribers and prescriptions by specialty.

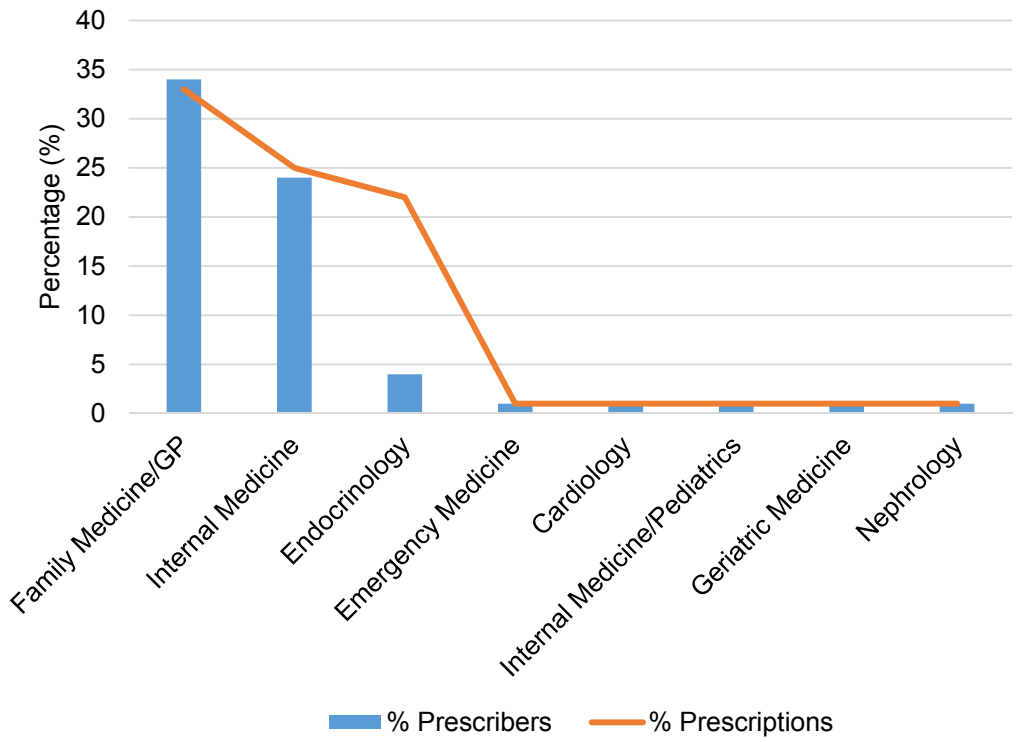

Figure 7. Percent of SGLT2 prescribers and prescriptions by specialty in the U.S, 2012-2015.

The geographic region with the highest: prevalence of physician prescribers (Table 2, Figure 8), percent of physician prescribers, and percent of dispensed prescriptions in each drug category is the South, followed by the Midwest (Table 2, Figures 9, 10, 11).

Figure 8. Prevalence of physicians, by region, prescribing phentermine, new anti-obesity pharmacotherapies, and SGLT2s.

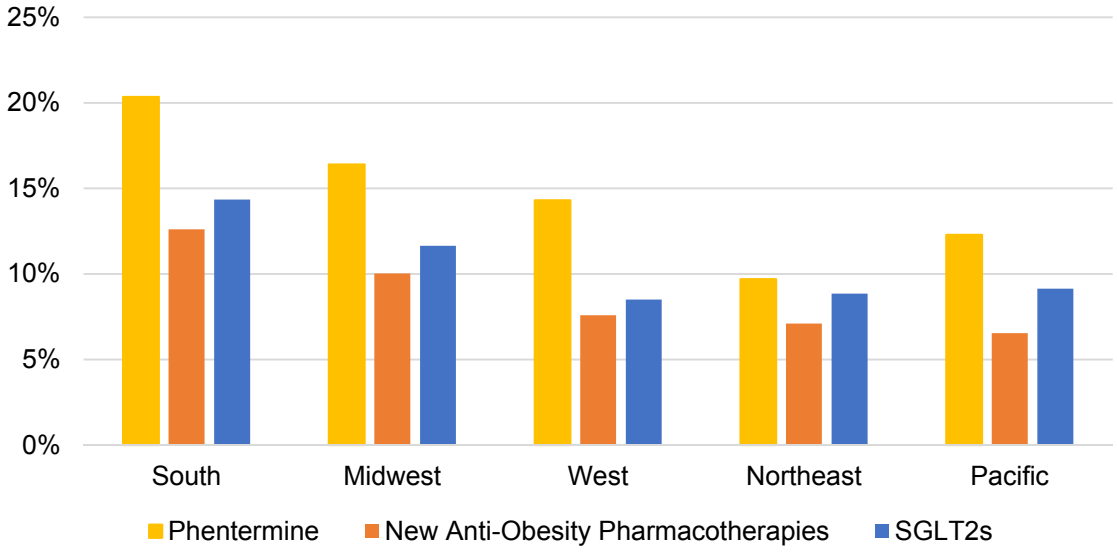

Figure 8. Prevalence of physicians, by region, prescribing phentermine, new anti-obesity pharmacotherapies, and SGLT2s in the U.S, 2012-2015.

Figure 9. Percent of phentermine prescribers and prescriptions by region.

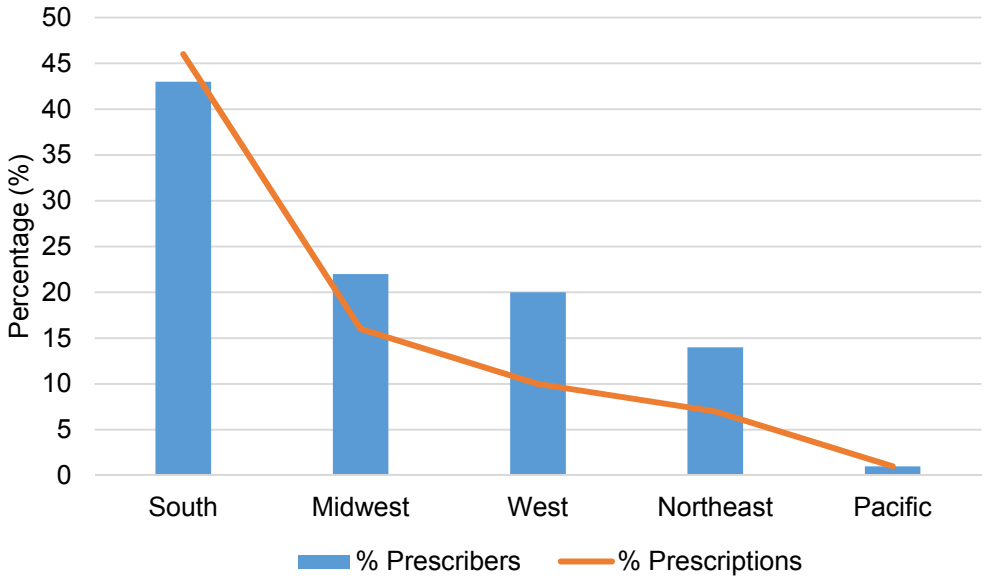

Figure 9. Percent of phentermine prescribers and prescriptions by region in the U.S, 2012-2015.

Figure 10. Percent of new anti-obesity pharmacotherapy prescribers and prescriptions by region.

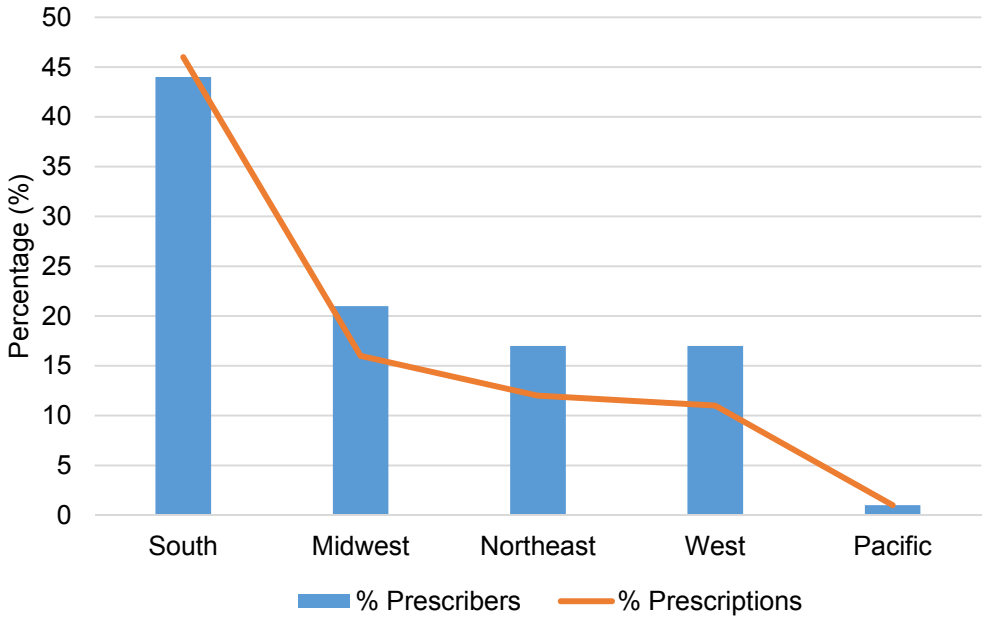

Figure 10. Percent of new anti-obesity pharmacotherapy prescribers and prescriptions by region in the U.S, 2012-2015.

Figure 11. Percent of SGLT2 prescribers and prescriptions by region.

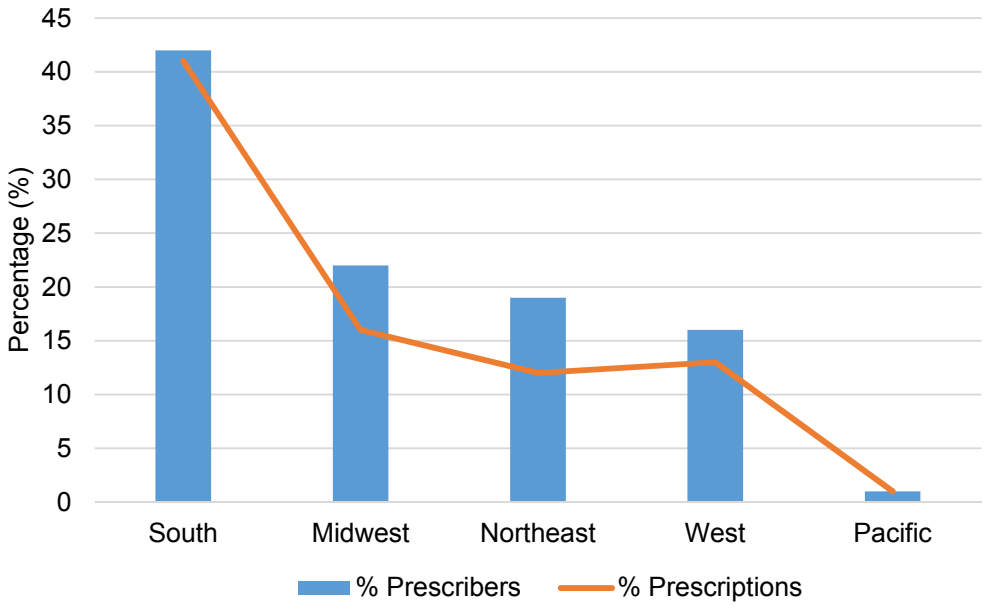

Figure 11. Percent of SGLT2 prescribers and prescriptions by region in the U.S, 2012-2015.

The highest percentage of overlap-prescribing are of new anti-obesity pharmacotherapy prescribers: 69% have also prescribed phentermine, while 41% of phentermine prescribers have also prescribed a new anti-obesity pharmacotherapy. Of SGTL2 prescribers, 57% have also prescribed phentermine, while the inverse represents the lowest percentage overlap: 33% of phentermine prescribers have prescribed an SGLT2. Fifty percent of prescribers of a new anti-obesity pharmacotherapy have prescribed an SGLT2, while 51% of prescribers of an SGLT2 have prescribed a new anti-obesity pharmacotherapy (Table 2).

The wholesale acquisition costs of a 30-day supply of the new anti-obesity pharmacotherapies are $199.50, with the exception of the two lower dose strengths of topiramate + phentermine, which are $170.65 and $165.20. The average wholesale acquisition cost of generic phentermine is $37.14. The wholesale acquisition costs of the SGLT2s range from $342.82 to $342.94.

CHAPTER FOUR
DISCUSSION

The adoption rate of SGLT2s was nearly exponential, while the adoption rate of new anti-obesity pharmacotherapies was linear. Echoing the findings of Xia Y, *et al*., the geographic distribution of dispensed anti-obesity pharmacotherapies[4] and SGLT2s match the geographic prevalence of obesity[20] and diabetes[21]. The specialties that are expected to treat obesity and diabetes (Family Medicine/General Practice, Internal Medicine, and Endocrinology) are the top prescribing medical specialties. That endocrinologists prescribe the new anti-obesity pharmacotherapies and SGLT2s in the highest proportion of any Medicine sub-specialty reflects that they are operating within their area of expertise. Endocrinologists; however, only comprise 0.8% of active physicians in the U.S., which is not sufficient to significantly impact the obesity epidemic. The similar proportions and types of prescribers across the drug categories indicate that there is an awareness among prescribers of anti-obesity pharmacotherapies and a comfort with using them. The disparity in prescription volumes and in the ratio of new prescriptions to continuing prescriptions between anti-obesity and anti-diabetes pharmacotherapies indicate that there are barriers to anti-obesity pharmacotherapy initiation and perseverance. This is likely the result of multiple factors stemming from the retarded recognition of obesity as a disease by leading public health and medical bodies. An analysis of the National Ambulatory Medical Care Survey and the Behavioral Risk Factor Surveillance System indicated that less than half of adults with obesity are being advised to lose weight by healthcare professionals.[22] Cited barriers include physician,

patient, and medical system factors: lack of reimbursement, limited time during office visits, lack of training in counseling, competing demands, low confidence in the ability to treat and change patient behaviors, limited resources, the perception that patients are not motivated, and a paucity of proven and effective interventions to treat obesity.[22]

Prescribers and patients likely have a reduced sense of urgency to treat obesity compared to diseases such as diabetes. They may also have a higher threshold for initiating anti-obesity pharmacotherapy than the guidelines recommend. Barriers to perseverance may include a lower threshold to capitulation, i.e. not taking into consideration the chronic progressive nature of obesity, as compared to the clinical approach with diseases such as diabetes and hypertension where, it is standard practice for patients to continue on long-term polypharmacy regimens despite many remaining at sub-optimal targets. The disparate study drug discontinuation rates in clinical trials of anti-obesity pharmacotherapies (33% for phentermine[23], 38% for topiramate + phentermine[24], 44% for lorcaserin[25], 46% for naltrexone + bupropion[26]) and SGLT2s (12% for canagliflozin[27], 14% for dapagliflozin[28], 9% for empagliflozin[29]) demonstrate this phenomenon. The most common reasons for discontinuation were: non-compliance, lost to follow up, lack of efficacy, and adverse events.

Effectiveness expectations for anti-obesity pharmacotherapy by patients and physicians may be at the cosmetic level and not at the clinically meaningful level, which is considered ≥5% weight loss.[13] For a drug to receive FDA-approval for the management of obesity, it must meet at least one of the following efficacy

criteria: 1) ≥5% difference in mean 1-year weight loss between active-treated and placebo groups or 2) ≥35% subjects in the active-treated group lose ≥5% of body weight after 1 year. In clinical trials, mean bodyweight change observed in those completing the trials hover just above the clinically meaningful threshold: -7% after 6 months with phentermine[23]; -10% on the low dose and -12% on the high dose after 1 year with topiramate + phentermine[24]; -8% after 1 year with lorcaserin[25]; and -8% after 1 year with naltrexone + bupropion[26]. Comparatively, the mean 6-month glycated hemoglobin (HbA1c) reductions and bodyweight changes observed in the SGLT2 clinical trials were: -1.16% Hba1c and -3.3% bodyweight with canagliflozin[27], -0.89% HbA1c and -4.3% bodyweight with dapagliflozin[28], -0.78% HbA1c and -2.48% bodyweight with empagliflozin[29]. Achieving 5-10% weight loss is associated with an increased likelihood of achieving a -0.5% reduction in HbA1c in overweight adults with type 2 diabetes (odds ratio 3.52).[30] The efficacy on glycemic control in overweight adults with type 2 diabetes has been studied as a secondary endpoint in clinical trials of two of the anti-obesity pharmacotherapies. In those who completed the trials, HbA1c reductions and bodyweight changes observed were: -1.1% HbA1c and -5.8% bodyweight after 1 year with lorcaserin[31] and -0.4% HbA1c and -9.0% bodyweight after 2 years with topiramate + phentermine[32].

The notion of physicians avoiding all available medications for treatment of a disease because of a perceived lack of effectiveness is seemingly unique to this field. In other disease areas, such as dyslipidemia or psychiatry, first and second

generation medications were extensively prescribed until improved third and fourth generation medications became available.

In a cohort study of adults with obesity, patients were presented with weight loss interventions and thoroughly explained the risks, benefits, and efficacy evidence of each. A choice of one intervention was available to each patient at a cost of $5 or $10 per month. Based on the information presented, the patients chose an intervention in the following proportions: topiramate + phentermine 31%, meal replacements 27%, recreation center membership 22%, clinic-based weight loss program 10%, Weight Watchers 6%, none 3%, phentermine 1%. The highest percentage of subjects chose topiramate + phentermine, which was the intervention that was presented with the highest efficacy. These results indicate that when the time is taken to explain the evidence base of all available treatments and when the costs are relatively leveled, patients will chose a pharmacotherapy option.[33]

An analysis of the National Health and Nutrition Examination Survey (NHANES) reported that the weight loss strategy most associated with a self-reported bodyweight loss of ≥10% in the prior year, among adults with obesity, was anti-obesity pharmacotherapy (odds ratio 2.05). Yet, the analysis also indicated that anti-obesity pharmacotherapy was reported as the least utilized weight loss strategy (3.5%) among adults with obesity who had attempted to lose weight in the prior year.[34]

To bridge the gap between obesity clinical guidelines and current physician practice, the American Board of Obesity Medicine was established in 2011 with

board certification and maintenance examinations. Consequently, obesity medicine clinical fellowships, preparatory to the certification examination, are being established at academic medical centers throughout the U.S. As of 2015, 1,182 physicians have been certified as Diplomates of the American Board of Obesity Medicine, making it the fastest growing Medicine sub-specialty in the U.S.[35] The majority of Diplomates are from the following medical specialties: Surgery, Pediatrics, Obstetrics-Gynecology, Internal Medicine, Family Medicine, and Endocrinology.[35] The number of certificates issued in 2014 was equivalent to those issued the same year for Infectious Disease, and more than those issued, for Endocrinology, Rheumatology, or Geriatric Medicine, as examples.[36] Cost is another barrier to anti-obesity pharmacotherapy initiation and perseverance. While new anti-obesity pharmacotherapy wholesale acquisition costs are somewhat lower than that of SGLT2s, the lack of insurance coverage makes anti-obesity pharmacotherapy far less affordable for most Americans. Anti-obesity pharmacotherapies are either excluded from insurance formularies, thus limiting to those with the means of self-pay, or require prior authorization[4], thus requiring significantly more physician and office staff time to prescribe. This is in contrast to SGLT2s, which are included in insurance formularies and, depending on the plan, are categorized as low as Tier 1, i.e. having the lowest copay available. As of 2013, only 14 state Medicaid programs provided coverage for at least one anti-obesity pharmacotherapy and all required prior authorization. Anti-obesity pharmacotherapy is not included in the Medicare Part D formulary[4]. From survey results of 9,000 adults in the U.S., 84% reported not having

insurance coverage for anti-obesity pharmacotherapy, which was even reported when their employers offered employee wellness programs that targeted BMI.[37] The fact that phentermine, which was FDA-approved in 1959 for short-term use and with little clinical trial data, remains the most frequently prescribed anti-obesity pharmacotherapy, by a large margin, is likely due to its low cost and its familiarity among patients and prescribers. Phentermine's high proportion of continuing prescriptions to new prescriptions indicates that it is often being prescribed off-label, i.e. for longer than 3 months.[15] Ironically, the very low continuing prescription to new prescription ratio of new anti-obesity pharmacotherapies, which are approved for long-term use, indicate that they are being used for the short-term. The cyclical nadirs in the volume of dispensed phentermine prescriptions occurring each December, followed immediately by a dramatic uptick, are likely explained by the New Year's Resolution phenomenon, indicating that phentermine prescribing, and ostensibly all anti-obesity pharmacotherapy prescribing, is patient driven.

This analysis captures the early-phase adoption and prescribing patterns of the first medications in 13 years to receive FDA approval for long-term management of obesity. Considering the relative prevalence of obesity to diabetes and that obesity is a major cause of diabetes, these results are paradoxical, suggest biases against the prescribing of anti-obesity pharmacotherapies, and highlight an unmet need. The under-prescribing of anti-obesity pharmacotherapies is widely acknowledged, but this is the first prescription data to demonstrate its extent in the U.S.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014 Feb 26;311(8):806-14. doi: 10.1001/jama.2014.732.

2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005 Apr 16-22;365(9468):1415-28.

3. Samaranayake NR, Ong KL, Leung RY, Cheung BM. Management of obesity in the NHANES, 2007-2008. *Ann Epidemiol*. 2012 May;22(5):349-53.

4. Xia Y, Kelton CM, Guo JJ, Bian B, Heaton PC. Treatment of obesity: Pharmacotherapy trends in the United States from 1999 to 2010. *Obesity* (Silver Spring). 2015 Aug;23(8):1721-8. doi: 10.1002/oby.21136.

5. National Center for Health Statistics. *Health, United States, 2014*. Centers for Disease Control and Prevention, 2009-2012 National Health Interview Survey. 2015 May: 165.

6. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. 2010-2012 National Health Interview Survey; 2014: 5.

7. Institute of Medicine. *Weighing the Options: Criteria for Evaluating Weight-Management Programs*. Washington, DC: National Academy of Sciences Press; 1995.

8. World Health Organization. *Obesity: Preventing and managing the Global Epidemic - Report of a WHO Consultation on Obesity*, 3-5 June 1997, Geneva, WHO/NUT/NCD/98.1

9. National Institutes of Health. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report*. 1998 Sep; NIH Publication 98-4083

10. National Institutes of Health. *Practical Guide to the Identification, Evaluation and Treatment of Overweight and Obesity in Adults*. 2000 Oct; NIH Publication 00-4084.

11. Snow V, Barry P, Fitterman N, Qaseem A, Weiss K, Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Pharmacologic and Surgical Management of Obesity in Primary Care: A Clinical Practice Guideline from the American College of Physicians. *Ann Intern Med*. 2005;142:525-531. doi:10.7326/0003-4819-142-7-200504050-00011

12. Gonzalez-Campoy JM, *et al*. Clinical practice guidelines for healthy eating for the prevention and treatment of metabolic and endocrine diseases in adults: cosponsored by the American Association of Clinical Endocrinologists/the American College of Endocrinology and the Obesity Society. *Endocr Pract*. 2013 Sep-Oct;19 Suppl 3:1-82. doi: 10.4158/EP13155.GL.

13. American Medical Association. Policy H-440.842. Recognition of Obesity as a Disease; 2013.

14. Jensen MD, *et al*. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014 Jun 24;129(25 Suppl 2):S102-38. doi: 10.1161/01.cir.0000437739.71477.ee

15. Apovian CM, Aronne LJ, Bessesen DH, McDonnell ME, Murad MH, Pagotto U, Ryan DH, Still CD; Endocrine Society. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015 Feb;100(2):342-62. doi: 10.1210/jc.2014-3415.

16. American Association of Clinical Endocrinologists. AACE Comprehensive Diabetes Management Algorithm - *Endocr Pract*. 2013; 19:327-336.

17. IMS Institute for Healthcare Informatics. *HSRN Data Brief: National Prescription Audit*. Collegeville, PA: IMS Health; 2011.

18. Association of American Medical Colleges Center for Workforce Studies. *2014 Physician Specialty Data Book*. Washington, D.C.: Association of American Medical Colleges; November 2014.

19. Association of American Medical Colleges Center for Workforce Studies. *2013 State Physician Workforce Data Book*. Washington, D.C.: Association of American Medical Colleges; November 2013.

20. National Center for Chronic Disease Prevention and Health Promotion. Division of Nutrition, Physical Activity, and Obesity Data, Trends and Maps. Centers for Disease Control and Prevention website. www.cdc.gov/obesity/data/prevalence-maps.html. Updated September 11, 2015. Accessed October 20, 2015.

21. National Diabetes Surveillance System. Division of Diabetes Translation. Centers for Disease Control and Prevention website. www.cdc.gov/diabetes/statistics/slides/maps_diabetes_trends.pdf. Updated January 2015. Access October 20, 2015.

22. Kushner RF. Tackling obesity: is primary care up to the challenge? *Arch Intern Med*. 2010 Jan 25;170(2):121-3. doi: 10.1001/archinternmed.2009.479.

23. Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity* (Silver Spring). 2013 Nov;21(11):2163-71. doi: 10.1002/oby.20584.

24. Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, Day WW. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011 Apr 16;377(9774):1341-52. doi: 10.1016/S0140-6736(11)60205-5.

25. Aronne L, Shanahan W, Fain R, Glicklich A, Soliman W, Li Y, Smith S. Safety and efficacy of lorcaserin: a combined analysis of the BLOOM and BLOSSOM trials. *Postgrad Med.* 2014 Oct;126(6):7-18. doi: 10.3810/pgm.2014.10.2817.

26. Apovian CM, Aronne L, Rubino D, Still C, Wyatt H, Burns C, Kim D, Dunayevich E; COR-II Study Group. A randomized, phase 3 trial of naltrexone SR/bupropion SR on weight and obesity-related risk factors (COR-II). *Obesity* (Silver Spring). 2013 May;21(5):935-43. doi: 10.1002/oby.20309.

27. Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab.* 2013 Apr;15(4):372-82. doi: 10.1111/dom.12054.

28. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care.* 2010 Oct;33(10):2217-24. doi: 10.2337/dc10-0612.

29. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, Broedl UC; EMPA-REG MONO trial investigators. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013 Nov;1(3):208-19. doi: 10.1016/S2213-8587(13)70084-6.

30. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, Hill JO, Brancati FL, Peters A, Wagenknecht L; Look AHEAD Research

Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*. 2011 Jul;34(7):1481-6. doi: 10.2337/dc10-2415.

31. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Raether B, Anderson CM, Shanahan WR. Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study. *Obesity* (Silver Spring). 2012 July:20(7): 1426–36. doi: 10.1038/oby.2012.66

32. Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr*. 2012 Feb;95(2):297-308. doi: 10.3945/ajcn.111.024927.

33. Bessesen D. Year in Obesity Pharmacotherapy. Keynote lecture at: The Obesity Society Annual Meeting; November 6, 2015; Los Angeles, CA.

34. Nicklas JM, Huskey KW, Davis RB, Wee CC. Successful weight loss among obese U.S. adults. *Am J Prev Med*. 2012 May;42(5):481-5.

35. American Board of Obesity Medicine. Directory of Diplomates. American Board of Obesity Medicine website. http://abom.org/diplomate-search/. Updated March 2, 2015. Accessed October 20, 2015.

36. American Board of Internal Medicine. ABIM Exam Information & Statistics, Number of Candidates Certified. American Board of Internal Medicine website. http://www.abim.org/pdf/data-candidates-certified/Number-Certified-Annually.pdf. Accessed December 10, 2015.

37. Kyle T. Consumers report that health insurance does not often cover obesity treatment, even when wellness programs target BMI. Oral abstract presentation at: The Obesity Society Annual Meeting; November 4, 2015; Los Angeles, CA.