

**Impacts of Pharmaceutical Marketing
on Healthcare in the District of Columbia**

**The High Cost of Highly Promoted Drugs
in the District of Columbia**



**Government of the District of Columbia
Department of Health
Health Regulation and Licensing Administration**

Prepared by
The Milken Institute School of Public Health
The George Washington University

Joy C. Eckert
Adriane Fugh-Berman, MD
Alycia Hogenmiller
Nicholas Mendola
Susan F. Wood, PhD

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I. Introduction

Executive Summary

AccessRx and Open Payments marketing expenditures data and Medicaid Drug Utilization data were analyzed to understand how the expense of highly-marketed drugs impacts the District. We identified the 30 drugs that cost the District's Medicaid program the most in reimbursements, the 30 drugs that were associated with the highest amount of marketing payments, and the 30 drugs associated with most frequent marketing payments.

DC Medicaid reimbursed more than \$172 million for prescription drugs in 2015, and approximately half of that amount was for 30 drugs. The average cost per prescription for these 30 drugs was more than \$2,800. Fourteen of the top 30 drugs are used to treat diabetes or asthma.

In 2015, pharmaceutical and medical device manufacturers reported a total of \$96.1 million for gift, advertising, and aggregate expenses in the District of Columbia to AccessRx and Open Payments. Nine drugs were identified as being both highly marketed and high cost to the District. This report puts into context these drugs that the District is spending the most on and makes recommendations about curbing unnecessary costs.

1. Harvoni (ledipasvir/sofosbuvir)

DC Medicaid spent \$19.7 million on 610 prescriptions for Harvoni, which treats hepatitis C. Harvoni also had the highest marketing payments of all hepatitis drugs. At \$32,263 per month, Harvoni is more expensive than Sovaldi (sofosbuvir), which costs Medicaid \$28,800 per month. The District could save \$2.1 million if less expensive hepatitis drugs were prescribed.

2. Abilify (aripiprazole)

In 2015, Abilify, an antipsychotic drug, cost \$995 per prescription, while generic aripiprazole was available and cost \$546 per prescription. If every prescription for branded, oral Abilify that DC Medicaid reimbursed were switched to generic aripiprazole, DC would have saved almost \$3.5 million in 2015.

3. Latuda (lurasidone)

Medicaid reimbursed a total of \$2 million for Latuda, an antipsychotic drug, placing it on the top 30 list for Medicaid reimbursement. Additionally, it was also on the top 30 list of highest frequency of gifts reported to Open Payments, with 278 gifts. Other antipsychotics are available as generics. Additionally, atypical antipsychotics have been found to be neither more effective nor safer than haloperidol and other older antipsychotics.

4. Levemir (insulin detemir)

Between 2014 and 2015, Medicaid reimbursements for Levemir (insulin detemir) increased from \$1.7 million to \$3.4 million while reimbursements for Lantus (insulin

glargine), a long-acting insulin approved in 2000, decreased from \$6.3 million to \$5.9 million. Levemir has a higher average cost per prescription than Lantus for both regular vials and for injection pens (\$391 v. \$375 per prescription). Prescribers may be switching their patients from Lantus to Levemir, despite no evidence of superiority of one over the other.

5. Januvia (sitagliptin)

Januvia had the highest Medicaid reimbursement and the highest Medicaid prescription count of any oral diabetes medications in 2015.

6. Humira (adalimumab)

In 2015, Medicaid reimbursed \$1.63 million for Humira, used to treat rheumatoid arthritis and other autoimmune diseases. Humira had the third highest total for all gifts reported to Open Payments in 2015. In the District, Humira had the highest total frequency of gifts of the top 30 medications reimbursed by Medicaid; the manufacturers of Humira reported 603 gifts totaling \$201,103.

7. Symbicort (budesonide/formoterol)

Symbicort was the only asthma medication that appeared on all 3 lists: the top 30 medications for total Medicaid reimbursement, highest Open Payments gift value, and highest Open Payments gift frequency. Between 2010 and 2015, DC Medicaid reimbursement for Symbicort increased 3,600% from \$37,114 to \$1.4 million and the prescription count increased by more than 2,600%, from 183 to 5,068 prescriptions.

8. Tecfidera (dimethyl fumarate)

DC Medicaid reimbursement costs and prescription counts for Tecfidera, a drug that treats multiple sclerosis, have increased since its approval in 2013. Reimbursements increased from \$167,507 in 2013, the year it was approved, to \$1.0 million in reimbursements in 2015. The average cost per prescription increased by 30% in two years, from \$4,527 to \$5,845.

9. Xarelto (rivaroxaban)

DC reimbursed nearly a million dollars (\$967,956) for Xarelto, an anticoagulant, in 2015. Xarelto was associated with the highest frequency of gifts in DC reported to Open Payments with 691 gifts and was in the top 15 of total value of gifts reported to Open Payment with \$99,133 in gifts.

A discussion of pharmaceutical marketing strategies for patented drugs are included in this report. Recommendations for cost savings in the District include the use of objective education to promote rational prescribing, using DC's flagship program, the [DC Center for Rational Prescribing](#) (DCRx).

Specific educational recommendations that could help to reduce cost and unnecessary prescribing in the District include expanded use of generic drugs, increasing prescriber awareness about drug costs, educating prescribers about pharmaceutical marketing tactics, and specific education to promote rational prescribing in diabetes, hepatitis, and psychiatry.

Background

The District of Columbia's [AccessRx Act of 2004](#) requires pharmaceutical companies to report marketing expenditures to the District of Columbia Department of Health (DC DOH). The DC DOH has been collecting information on pharmaceutical marketing since 2007 and researchers at the George Washington University Milken Institute School of Public Health analyze this information for DC DOH annually.

The [AccessRx](#) program releases two reports annually. The [Expenditures Report](#) documents annual pharmaceutical marketing expenditures for gifts (to physicians, other healthcare professionals, hospitals, and other organizations), advertising, and the salaries of detailers. The second report, *Impacts of Pharmaceutical Marketing on Healthcare in the District of Columbia*, considers how pharmaceutical marketing may affect health and healthcare in the District of Columbia.

Previous *Impacts* reports include:

- [Diabetes in the District](#) (2016)
- [Reporting Changes and the Effect of Gifts on Prescribing Behavior](#) (2015)
- [Focus on Gifts to Organizations and Influential Physicians](#) (2014)
- [Focus on Use of Antipsychotics in Seniors](#) (2013)
- [Report on the Use of Antipsychotics in Children](#) (2012)

This 2017 *Impacts of Pharmaceutical Marketing on Healthcare in the District of Columbia* report focuses on highly promoted drugs that are costly to the District's Medicaid reimbursement program. This report examines drugs used in several disease states that DC Medicaid is spending the most money on, analyzes promotional expenditures on these drugs, discusses related drugs, and highlights instances where there is potential for saving money and improving care. Drugs associated with the highest Medicaid expenditures, related drugs, and alternatives will be discussed.

AccessRx Data: Unique in the Nation

[AccessRx](#) data provides a wealth of information that no other jurisdiction in the United States can match. The Physician Payments Sunshine Act of 2010 established the national [Open Payments](#) system that requires all pharmaceutical and medical device manufacturers to report payments to physicians and teaching hospitals to the Centers for Medicare and Medicaid Services (CMS).

AccessRx and Open Payments serve similar purposes but capture different sets of data. Open Payments only requires companies to report on gifts given to physicians and teaching hospitals. The DC DOH AccessRx program is more comprehensive, requiring reporting for all other licensed healthcare providers (e.g. nurses, nurse practitioners, physician assistants, and pharmacists), non-teaching hospitals, healthcare staff, and organizations. Only AccessRx picks

up gifts received by nurse-practitioners (NPs), nurse midwives, nurse anesthetists, physician assistants (PAs), podiatrists, and optometrists. The number of prescriptions written by NPs and PAs has more than doubled over the past five years; in 2015, NPs and PAs wrote 676 million of 4.4 billion prescriptions in the U.S. (IMS 2016).

Furthermore, only AccessRx collects information on salaries and other payments for detailers and other personnel (employees and contractors) involved in marketing pharmaceuticals in the District. In DC in 2015, this spending category, called *Aggregate Expenses*, was the largest, with more than \$66 million in detailing expenditures reported. AccessRx also tracks expenditures on local advertising, including District-specific print, television and other advertisements. Another advantage AccessRx has over Open Payments is that AccessRx data go back to 2007, enabling analysis of changes over time. The first full year of Open Payments data is from 2014.

Only AccessRx collects information on salaries for detailers and other personnel involved in marketing pharmaceuticals in the District.

An advantage Open Payments has over AccessRx is that data, including physician names, are publicly available. Payments to physicians and teaching hospitals are searchable online through Open Payments, allowing researchers to track patterns in gifts. Additionally, individual patients can see whether their physicians have accepted gifts from pharmaceutical companies. Although AccessRx reports are publicly available, the names of prescribers, nurses, office staff, technicians, and other people or organizations that receive payments and other gifts are confidential. Company-level expenses on advertising, drugs reps, and other marketing personnel are also confidential. Details are available only to DC DOH.

II. DC Medicaid Program

In 2015, the District of Columbia, along with Massachusetts, has the lowest uninsured rate in the U.S., with 96% of the population insured (KFF 2017). Medicaid, which pays for medical services for low-income individuals and people with disabilities, plays a key role in the delivery of health care in DC, including coverage of prescription medications.

In 2015, approximately a quarter of a million people were enrolled in the DC Medicaid and Children’s Health Insurance Plan and Alliance (CHIP) programs (CMS 2016a). Patients on public insurance, including Medicaid, CHIP, and Medicare, account for two-thirds of all in-patient hospital discharges in DC. In 2014, Medicaid was the primary insurer for half of all patients who visited the emergency department in the District. Additionally, 57% of all primary care utilization in 2014 was for individuals insured by Medicaid and CHIP (Merrill 2016).

Medicaid Drug Utilization Data

For this report, DC Medicaid Drug Utilization Data were analyzed to determine which drugs are the most costly for the District. Note that these data do not include drugs with fewer than 11 prescriptions for a given quarter. CMS stopped disclosing low-volume prescriptions in 2015 because there was a concern that prescribers or patients could be identified.¹ For this reason, our analysis may represent an underestimation of drug costs to Medicaid because some data have been suppressed.

DC Medicaid Drug Expenditures

The District of Columbia Medicaid program reimbursed more than \$172 million for the prescription drug program in 2015. The 30 drugs that DC Medicaid spent the most money on in 2015 are listed in **Table 1**. In total, DC spent \$87 million – approximately half of all DC Medicaid drug reimbursements – on these 30 drugs. The average cost per prescription for these 30 drugs was more than \$2,800.

DC spent \$87 million – approximately half of all DC Medicaid drug reimbursements – on 30 drugs.

¹ A full explanation of which data are not publicly available can be found here: <https://www.medicaid.gov/medicaid/prescription-drugs/state-drug-utilization-data/index.html>

Table 1: Drugs with the Highest DC Medicaid Reimbursement Amounts in 2015

Rank	Brand Name	Generic Name	Total Medicaid Reimbursement	Number of Medicaid Prescriptions	Average Cost per Prescription
1	Harvoni	ledipasvir/sofosbuvir	\$19,680,617	610	\$32,263
2	Abilify*	Aripiprazole	\$8,255,286	8,067	\$1,023
3	Lantus	insulin glargine	\$5,859,982	15,636	\$375
4	Flovent	fluticasone propionate	\$4,806,205	24,900	\$193
5	Viekira Pak	ombitasvir/paritaprevir/ritonavir with dasabuvir	\$4,491,736	157	\$28,610
6	Novolog	insulin aspart	\$3,689,341	9,655	\$382
7	Levemir	insulin detemir	\$3,447,225	8,823	\$391
8	Invega*	paliperidone	\$3,392,204	2,243	\$1,512
9	Advair	fluticasone/salmeterol	\$3,238,609	9,477	\$342
10	Suboxone*	buprenorphine/naloxone	\$2,743,086	6,463	\$424
11	Ventolin	albuterol	\$2,099,305	40,656	\$52
12	Januvia	sitagliptin	\$2,089,907	6,028	\$347
13	Spiriva	tiotropium	\$2,076,681	6,472	\$321
14	Latuda	lurasidone	\$2,043,943	2,417	\$846
15	Nexium*	esomeprazole	\$1,729,295	6,516	\$265
16	ProAir	albuterol	\$1,662,122	28,773	\$58
17	Humira	adalimumab	\$1,631,994	459	\$3,556
18	Lyrica	pregabalin	\$1,579,393	4,837	\$327
19	Symbicort	budesonide/formoterol	\$1,375,963	5,068	\$272
20	-	methylphenidate**	\$1,319,282	7,643	\$173
21	EpiPen	epinephrine	\$1,212,579	2,649	\$458
22	Tecfidera	dimethyl fumarate	\$1,028,741	176	\$5,845
23	Neulasta	pegfilgrastim	\$1,006,184	302	\$3,332
24	Apidra	insulin glulisine	\$989,623	2,434	\$407
25	Xarelto	rivaroxaban	\$967,956	2,936	\$330
26	Janumet	metformin/sitagliptin	\$961,624	2,954	\$326
27	Synagis	palivizumab	\$912,391	392	\$2,328
28	Lovenox*	enoxaparin	\$910,895	1,904	\$478
29	Humalog	insulin lispro	\$857,594	2,693	\$318
30	-	budesonide**	\$826,783	2,157	\$383

*Therapeutic Equivalent Available Generically

**Generic Medication

Fourteen of the top 30 drugs are used to treat diabetes or asthma. Seven drugs are used to treat diabetes, each of which costs more than \$300 per prescription. Diabetes drugs include five insulins: Lantus (insulin glargine), Novolog (insulin aspart), Levemir (insulin detemir), Apidra (insulin glulisine), and Humalog (insulin lispro). Lantus had the fourth highest prescription count among the 30 drugs in **Table 1**, with 15,636 prescriptions. The list also includes two oral versions of the same drug: Januvia (sitagliptin) and Janumet, which combines sitagliptin with metformin, a generic drug.

Another seven drugs are used to treat asthma and chronic obstructive pulmonary disease (COPD). These include two albuterol drugs (Ventolin and ProAir) and five steroid preparations: Flovent (fluticasone propionate), Advair (fluticasone/salmeterol), budesonide (one of only two generic drugs on the list), Symbicort (budesonide/formoterol), and Spiriva (tiotropium). Ventolin had the highest prescription count on our list at 40,656 prescriptions. Ventolin, ProAir, and Flovent were the only drugs on this list with more than 20,000 prescriptions.

Harvoni (ledipasvir/sofosbuvir) and Viekira Pak (ombitasvir/paritaprevir/ritonavir with dasabuvir) both treat hepatitis C and cost more than \$28,000 per prescription.

Xarelto (rivaroxaban) is an oral anticoagulant and Lovenox (enoxaparin) is an injected anticoagulant; both are commonly used to prevent blood clots or stroke. In 2015, Xarelto cost \$330 per prescription; Lovenox cost \$478 per prescription.

Abilify (aripiprazole), Invega (paliperidone), and Latuda (lurasidone) are atypical antipsychotics used to treat schizophrenia. Abilify and Invega each cost more than \$1,000 per prescription.

Suboxone (buprenorphine/naloxone) is used to treat opioid use disorder and has a generic formulation available. Lyrica (pregabalin) is used to treat nerve pain. EpiPen is an epinephrine auto-injector used to treat severe allergic reactions.

Six drugs on the list had fewer than 1,000 prescriptions: Harvoni, Viekira Pak, Humira, Neulasta, Tecfidera, and Synagis. All of these drugs cost more than \$2,000 per prescription. Humira (adalimumab) is a TNF-inhibitor used to treat autoimmune diseases. Tecfidera (dimethyl fumarate) is a treatment for relapsing multiple sclerosis. Neulasta (pegfilgrastim) is used to stimulate levels of white blood cells after cancer treatment. Synagis (palivizumab) is an injection of antibodies to prevent respiratory syncytial virus infection in high-risk infants.

III. Pharmaceutical Marketing Expenditures in DC

Promotion and Prescribing

Pharmaceutical promotion includes advertising to health care providers and to patients using drug rep visits, meals, promotional materials, educational events, and payments to health care providers for speaking or consulting. There are several recognized methods that pharmaceutical companies use to sway prescriber preferences towards targeted drugs. Food gifts tend to be lower in value but are given at a higher frequency because they primarily represent lunches brought to physicians' offices by drug reps. Food and drink are used to enhance relationships between drug sales representatives, prescribers, and medical staff. Food gifts may be used as an unspoken *quid pro quo*; physicians and other prescribers may simply prescribe specific drugs as a favor to sales representatives that they like (Fugh-Berman 2007).

Peer "education" is also an important marketing tool. Respected physicians are paid speaking fees to provide promotional or continuing education talks that support specific marketing messages to their peers (Fugh-Berman 2008). Fees paid to individuals for speaking or consulting often can be substantial.

Pharmaceutical Marketing in 2015

In 2015, pharmaceutical and medical device manufacturers reported a total of \$96.1 million for gift, advertising, and aggregate expenses in the District of Columbia to AccessRx and Open Payments. These expenses were broken down into the following categories: *Aggregate Expenses* (\$66.2 million), *Gift Expenses* (\$24.4 million), and *Advertising Expenses* (\$5.6 million). For more information on pharmaceutical marketing in 2015, check out our report *Pharmaceutical Marketing Expenditures in the District of Columbia, 2015*.

The Federal Open Payments system associates gifts with specific drugs that were promoted during a speaking engagement or discussed during a drug rep visit. **Table 2** lists the drugs associated with the highest *value* of payments in DC in 2015. These payments, which may be for meals served during a sales representative's pitch or speaking and consulting fees paid to "key opinion leaders" (physicians who teach other doctors and sway their prescribing choices), inform us about what drugs are being highly promoted in the District.

Table 3 lists drugs associated with the highest *frequency* of gifts tagged in the Open Payments system. These drugs were associated with the highest number of gifts (usually for food and beverage) in 2015.

Table 2: Drugs Associated with the Highest Value of Marketing Payments in DC Reported to Open Payments in 2015

Rank	Brand Name	Generic Name	Total Value of Payments	FDA Approval Date
1	Northera*	droxidopa	\$250,321	Feb 2014
2	Humira*	adalimumab	\$201,103	Dec 2002
3	Invokana*	canagliflozin	\$168,306	Mar 2013
4	Contrave*	naltrexone HCl/bupropion HCl	\$157,451	Sep 2014
5	Azilect*	rasagiline	\$152,725	May 2006
6	Brilinta*	ticagrelor	\$141,946	Jul 2011
7	Soliris	eculizumab	\$138,063	Mar 2007
8	Myobloc*	rimabotulinumtoxinB	\$132,778	Dec 2000
9	Corlanor*	ivabradine	\$126,194	Apr 2015
10	Prezista	darunavir	\$121,999	Jun 2006
11	Eliquis*	apixaban	\$119,367	Dec 2012
12	Kyprolis	carfilzomib	\$108,581	Jul 2012
13	Thyrogen	thyrotropin alfa	\$101,009	Nov 1998
14	Xarelto*	rivaroxaban	\$99,133	Nov 2011
15	Symbicort*	budesonide/formoterol	\$94,887	Jul 2006
16	Perjeta	pertuzumab	\$83,999	Jun 2012
17	Revlimid	lenalidomide	\$82,777	Dec 2005
18	Sprycel	dasatinib	\$74,033	Jun 2006
19	Botox*	onabotulinumtoxinA	\$73,863	Dec 1991
20	Plegridy	peginterferon beta-1a	\$73,374	Aug 2014
21	Avastin	bevacizumab	\$71,554	Feb 2004
22	Harvoni	ledipasvir/sofosbuvir	\$69,553	Oct 2014
23	Gilenya	fingolimod	\$65,935	Sep 2010
24	Victoza*	liraglutide	\$65,029	Jan 2010
25	Saxenda	liraglutide	\$62,839	Dec2014
26	Daklinza	daclatasvir	\$60,012	Jul 2015
27	Isentress*	raltegravir	\$59,458	Oct 2007
28	Tecfidera	dimethyl fumarate	\$58,496	Mar 2013
29	Abilify*	aripiprazole	\$58,462	Nov 2002
30	Genvoya	cobicistat/elvitegravir/emtricitabine/tenofovir	\$57,902	Nov 2015

*Drugs that appear in both **Table 2** (highest value of marketing payments) and **Table 3** (most frequent marketing payments)

Table 3: Drugs Associated with the Highest Frequency of Marketing Payments in DC Reported to Open Payments in 2015

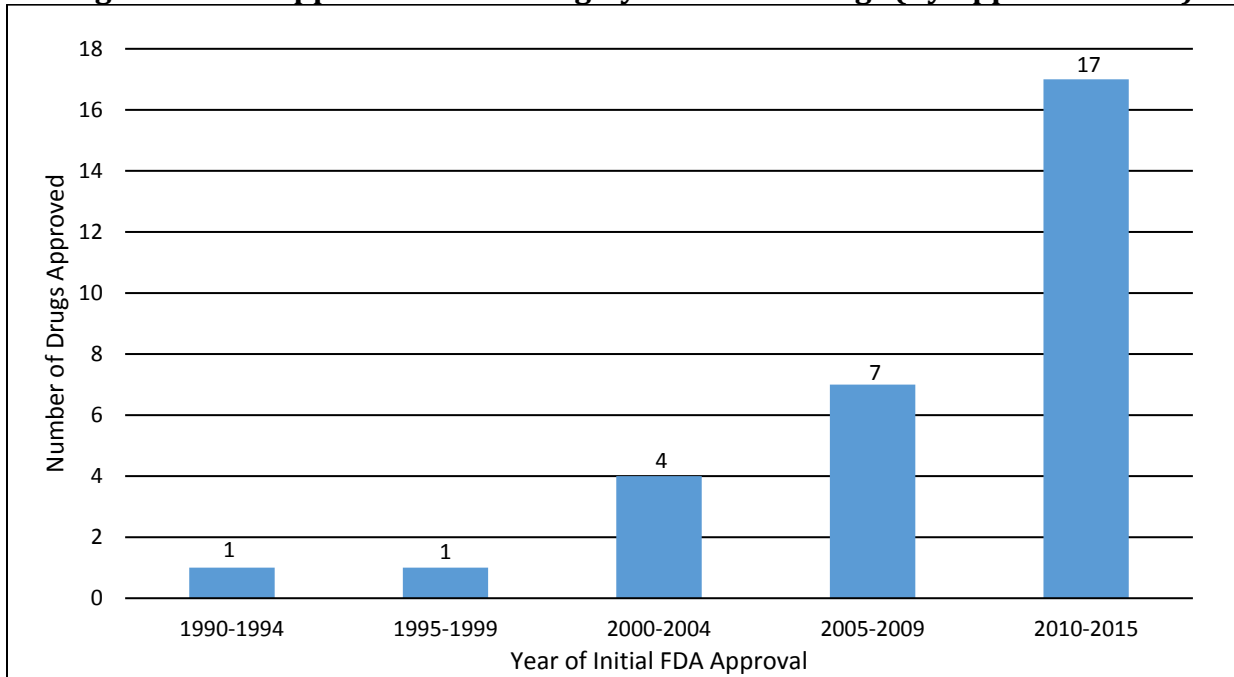
Rank	Brand Name	Generic Name	Count of Payments	FDA Approval Date
1	Xarelto*	rivaroxaban	691	Nov 2011
2	Eliquis*	apixaban	639	Dec 2012
3	Humira*	adalimumab	603	Dec 2002
4	Invokana*	canagliflozin	565	Mar 2013
5	Symbicort*	budesonide/formoterol	526	Jul 2006
6	Savaysa	edoxaban	417	Jan 2015
7	Northera*	droxidopa	377	Feb 2014
8	Toujeo	insulin glargine	357	Feb 2015
9	Contrave*	naltrexone HCl/bupropion HCl	345	Sep 2014
10	Brilinta*	ticagrelor	341	Jul 2011
11	Brintellix†	vortioxetine	338	Sep 2013
12	Corlanor*	ivabradine	334	Apr 2015
13	Farxiga	dapagliflozin	329	Jan 2014
14	Levemir	insulin detemir	315	Jun 2005
15	Stelara	ustekinumab	304	Sep 2009
16	Latuda	lurasidone	278	Oct 2010
17	Botox*	onabotulinumtoxinA	271	Dec 1991
18	Myobloc*	rimabotulinumtoxinB	237	Dec 2000
19	Azilect*	rasagiline	232	May 2006
20	Bydureon	exenatide	232	Jan 2012
21	Victoza*	liraglutide	225	Jan 2010
22	Linzess	linaclotide	221	Aug 2012
23	Abilify*	aripiprazole	219	Nov 2002
24	Triumeq	abacavir/dolutegravir/lamivudine	213	Aug 2014
25	ANORO Elipta	umeclidinium bromide/vilanterol	202	Dec 2013
26	Myrbetriq	mirabegron	202	Jun 2012
27	Prolia	denosumab	194	Jun 2010
28	Isentress*	raltegravir	192	Oct 2007
29	Januvia	sitagliptin	191	Oct 2006
30	Pradaxa	dabigatran	185	Oct 2010

*Drugs that appear in both **Table 2** (highest value of marketing payments) and **Table 3** (most frequent marketing payments)

† In May 2016, the brand name for vortioxetine was changed from Brintellix to Trintellix.

Newer drugs are associated with the highest total gift values (**Figure 1**). Of the top 30 drugs in **Table 2**, 17 were approved between 2010 and 2015, seven between 2005 and 2009, four between 2000 and 2004, and two between 1990 and 1999. Only two older drugs, Thyrogen and Botox, were associated with high gift values. Thyrogen, approved in 1998, and Botox, approved in 1991, remain heavily marketed despite having been available for a longer period of time.

Figure 1: FDA Approval Year for Highly Promoted Drugs (By Approval Count)



Highly Promoted Drugs to Monitor

It bears noting that there is a lag between increased promotion and increased prescribing, so that drugs on which promotional dollars are being spent in one year are likely to result in increased expenditures in following years. High promotional expenditures with low current Medicaid reimbursement can signal increased future expenditures.

Fifteen drugs were associated with both high *values* of gifts (**Table 2**) and also high *frequency* of gifts (**Table 3**). Gifts include payments for meals, promotional talks, or other purposes. The 15 most highly marketed drugs in 2015, with the primary conditions they treat, are ranked below.

- **Northera (droxidopa)** – Dizziness and lightheadedness associated with neurogenic orthostatic hypotension
- **Humira (adalimumab)** – Rheumatoid arthritis
- **Invokana (canagliflozin)** – Diabetes
- **Contrave (naltrexone HCl/bupropion HCl)** – Weight management/obesity
- **Azilect (rasagiline)** – Parkinson’s Disease
- **Brilinta (ticagrelor)** – Acute coronary syndrome
- **Myobloc (rimabotulinumtoxinB)** – Overactive bladder, headaches, cervical dystonia
- **Corlanor (ivabradine)** – Chronic heart failure
- **Eliquis (apixaban)** – Stroke and deep vein thrombosis prevention
- **Xarelto (rivaroxaban)** – Stroke and deep vein thrombosis prevention
- **Symbicort (budesonide/formoterol)** – Asthma and COPD
- **Botox (onabotulinumtoxinA)** – Wrinkles, migraine
- **Victoza (liraglutide)** – Diabetes
- **Isentress (raltegravir)** – HIV antiviral
- **Abilify (aripiprazole)** – Schizophrenia and bipolar disorder

Only three of these 15 drugs – Humira, Xarelto, and Symbicort – had high Medicaid reimbursement rates in 2015. However, the marketing payments spent in 2015 on the other 12 drugs may predict high Medicaid reimbursement costs in subsequent years. This issue will be examined in future reports.

For example, Northera (droxidopa) with the highest total value of marketing payments at \$250,321, is used for orthostatic dizziness, lightheadedness, or the “feeling that you are about to black out”. These symptoms are common. Although Northera is approved only in adult patients with symptomatic neurogenic orthostatic hypotension associated with Parkinson’s disease and other autonomic diseases (Northera 2017), off-label use could occur. It is possible that the amount of marketing dollars spent in 2015 may presage rising prescriptions in subsequent years.

The other fifteen drugs that appear in the list of drugs associated with high *values* for promotion (**Table 2**) were not associated with high *frequency* of gifts. Many of those drugs, including antivirals for hepatitis C or HIV, drugs for multiple sclerosis, and cancer treatments, are usually prescribed by specialists. Often these specialty drugs are promoted more with *Speaking* gifts and talks to specialists rather than drug rep visits to physicians' offices.

IV. Drugs of Interest: High-Cost and Highly Promoted

Nine drugs appeared on the top 30 lists for both Medicaid expenditures (**Table 1**) and Open Payments gifts (**Table 2 or 3**). Drugs with both high Medicaid reimbursements and high marketing payments in DC in 2015 include:

1. Harvoni (ledipasvir/sofosbuvir)
2. Abilify (aripiprazole)
3. Latuda (lurasidone)
4. Levemir (insulin detemir)
5. Januvia (sitagliptin)
6. Humira (adalimumab)
7. Symbicort (budesonide/formoterol)
8. Tecfidera (dimethyl fumarate)
9. Xarelto (rivaroxaban)

The following sections include an analysis of Medicaid spending and promotional spending for these nine drugs. We have also contextualized this information by providing relevant information about related and alternative drugs in the same disease or treatment category, especially if related drugs were highly prescribed, highly promoted, or associated with high amounts of Medicaid reimbursement. Each section highlights key relevant drugs and does not constitute a comprehensive list.

1. Harvoni (ledipasvir/sofosbuvir) (Manufacturer: Gilead Sciences Inc.)

In DC, between 2012 and 2016, there were 16,842 laboratory-reported cases of hepatitis C (including asymptomatic cases and resolved cases) and 1,406 newly diagnosed cases in 2016 (HAHSTA 2017). The Centers for Disease Control (CDC) estimates that there are between 2.7 and 3.9 million people with viral hepatitis C in the U.S. (Viral Hepatitis 2016). About a quarter of people clear the virus on their own (Grebely 2007). For others, hepatitis C infection will progress slowly over decades; progression varies significantly by individual. Approximately 75% to 85% of infected individuals will develop a chronic HCV infection; of those, 60% to 70% develop chronic liver disease and 1% to 5% will die of cirrhosis or liver cancer (Leof 2014).

Direct-acting antivirals (DAAs) are the most effective, but also the most expensive, treatments available for hepatitis C. DAAs on the market include Sovaldi (sofosbuvir), Harvoni (ledipasvir/sofosbuvir), Olysio (simeprevir), Daklinza (daclatasvir), and Viekira Pak (ombitasvir/paritaprevir/ritonavir with dasabuvir). There are currently no generics available for any direct-acting antivirals. Although DAAs are often referred to as “cures” for hepatitis C, there are no long-term data for clinically important outcomes available for DAAs. Relapse rates range from 5% to 28%, depending on HCV genotype, even among fully treated patients (Leof 2014). Additionally, there is a risk of hepatitis B reactivation in patients being treated with DAAs for hepatitis C (FDA Safety Announcement 2016).

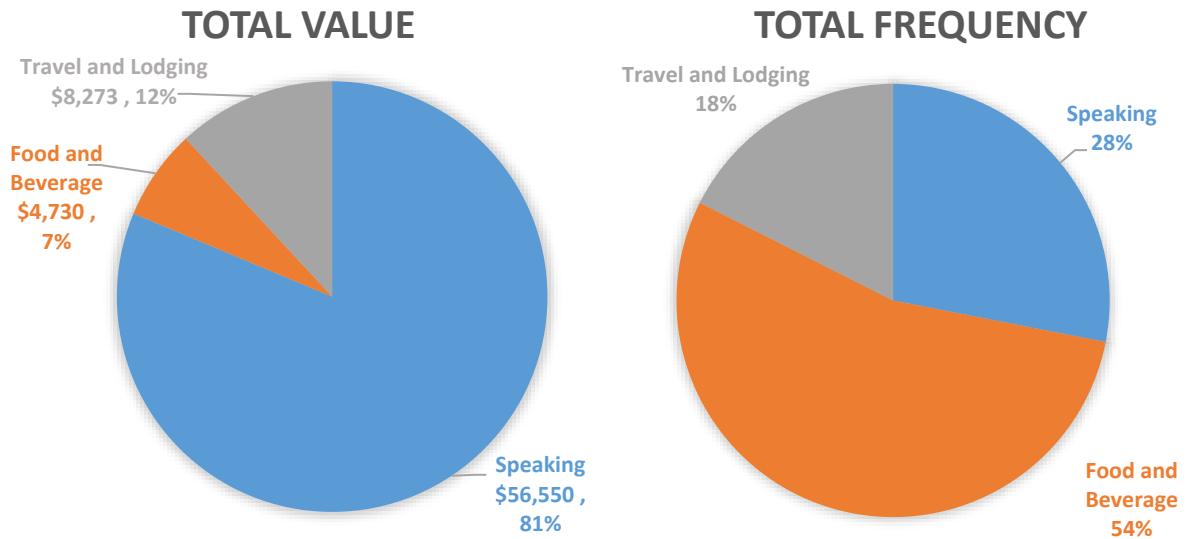
For all hepatitis C drugs, DC Medicaid reimbursed more than \$26.5 million in 2015; \$25 million of this was for DAAs. Two branded hepatitis C drugs, Harvoni and Viekira Pak, cost DC a total of \$24.2 million in total reimbursement in 2015.

Harvoni, a combination of Sovaldi (sofosbuvir) and ledipasvir (a new drug that inhibits the NS5A protein), received FDA approval on October 10, 2014 (Harvoni 2017). Harvoni appears to be effective for HCV genotype 1; evaluation in HCV genotype 3 and 4 is limited (Ledipasvir and sofosbuvir 2015).

Harvoni had the highest DC Medicaid reimbursement of any medication in 2015, with \$19.7 million in total reimbursements for 610 prescriptions, more than double the next highest reimbursed medication. Harvoni was also the most expensive medication on the list at \$32,263 per 30-day prescription; a full 3-month course of treatment costs \$96,789.

In 2015, Harvoni was one of the top 30 marketed drugs in DC. Harvoni had the highest marketing payments of all hepatitis drugs in 2015, with 114 gifts totaling \$69,553 reported to Open Payments. *Speaking* fees represented the largest portion of gifts representing 81% (\$56,550) of total gift value and 28% (32 gifts) of the total gift frequency. *Food and Beverage* accounted for 7% (\$4,730) of the total value of gifts but accounted for the greatest percentage of frequency of gifts at 54% (62 gifts). *Travel and Lodging* accounted for 12% (\$8,273) of total value and 18% (20 gifts) of total number of gifts given.

**Figure 2: Gifts Associated with Harvoni
Nature of Payment**



Other Drugs for Hepatitis C

Sovaldi (sofosbuvir), the first DAA for Hepatitis C to be marketed, was approved on December 6, 2013 for the treatment of hepatitis C genotypes 1, 2, 3, and 4 (Sovaldi 2017). Sovaldi inhibits NS5B RNA-dependent RNA polymerase. DC Medicaid reimbursed for 13 prescriptions of Sovaldi in 2015. Three months of treatment costs \$86,550.

Viekira Pak is a combination of three DAAs (ombitasvir/paritaprevir/ritonavir) and another DAA (dasabuvir) that was approved in 2014 (Viekira Pak 2017). There is no evidence of superiority of this combination over other DAAs for HCV-1 and few data exist for the use of Viekira Pak in HCV-4 (Ombitasvir+paritaprevir+ritonavir 2016). Viekira Pak (ombitasvir/paritaprevir/ritonavir with dasabuvir) and Technivie (ombitasvir/paritaprevir/ritonavir) now carry labeled warnings because they can cause serious, sometimes fatal, liver injury (FDA Safety Announcement 2015). Three months of Viekira Pak costs \$85,830.

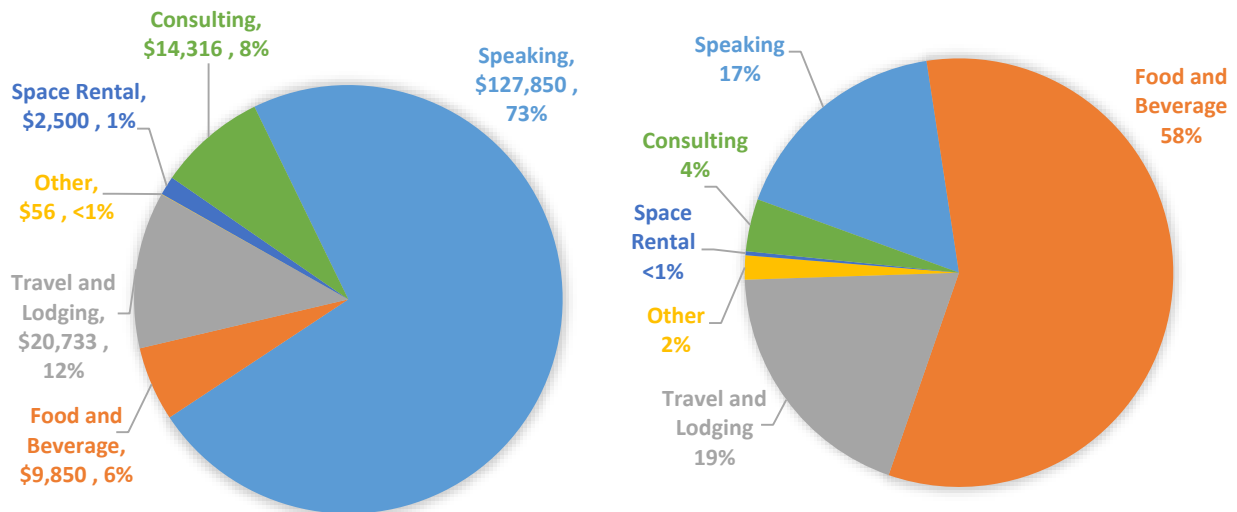
Daklinza (daclatasvir) is approved for use with sofosbuvir to treat hepatitis C virus genotype 3 infection. Three months of treatment with daclatasvir and sofosbuvir costs \$147,000 (Daclatasvir 2015).

Older drugs to treat Hepatitis C include Ribasphere (ribavirin), Intron A (interferon alpha-2), Pegintron (peginterferon alfa-2b), and Pegasys (peginterferon alfa-2a), and protease inhibitors including boceprevir (Victrelis) or telaprevir (Incivek). These inexpensive drugs are effective in some patients; interferon-based regimens have success rates of 40% to 80%, depending on stage of disease, adherence to therapy, genotype, and other medical problems (Leof 2014).

Marketing for All Hepatitis C Drugs

In 2015, promotional payments associated with direct-acting antiviral medications used to treat hepatitis C accounted for 329 associated gifts totaling \$175,305. Almost three quarters (73%) of the total value of gifts given were reported as *Speaking* fees, which accounted for \$127,850. Gifts classified as *Food and Beverage* were the most frequent gifts, comprising 58% (190 gifts) of the total number of gifts associated with a direct-acting antiviral drug. *Speaking* fees accounted for just 17% of total gift frequency.

Figure 3: Gifts Associated with Hepatitis C Treatments*
Nature of Payment



*This chart includes Harvoni, Viekira Pak, Daklinza, and Olysio. Sovaldi was not associated with any gifts reported to Open Payments in DC in 2015.

Harvoni accounted for 40% of the total gift value and 35% of total gift frequency. Viekira Pak accounted for 26% of total gift value and 31% of total gift frequency. Daklinza accounted for 34% of total gift value and 32% of total gift frequency. Olysio accounted for less than 0.1% of total gift value and 6% of total gift frequency. Daklinza was associated with 104 gifts totaling \$60,012, ranking 26th among total gift payments in DC. Viekira Pak was associated with 103 gifts totaling \$45,615, and Olysio was associated with eight gifts totaling \$125. Sovaldi was not associated with any gifts reported to Open Payments in DC in 2015.

2. Abilify (aripiprazole) (Manufacturers: Otsuka Pharmaceuticals Co. and Bristol-Myers Squibb Co.)

Antipsychotics are approved by the FDA for schizophrenia (Christian 2012), which affects 1.1% of the U.S. adult population (Regier 1993); some antipsychotics are also approved for bipolar disorder, which affects 2.6% of the population (Kessler 2005).

Abilify (aripiprazole) is a quinolone antipsychotic medication first approved in 2002 (Abilify 2017). Abilify is currently available as oral tablets or as a long-acting, injectable form called Abilify Maintena, approved in 2013 (Abilify Maintena 2017). Abilify was initially approved for the treatment of schizophrenia in adults and adolescents aged 13 to 17. Abilify has been approved for several additional indications since 2002 including the treatment of bipolar disorder, irritability associated with autistic disorder (also called autism spectrum disorder), Tourette’s Disorder, and as an add-on treatment to depression (Abilify 2017). Generic aripiprazole oral tablets became available in 2015. Abilify Maintena is still under patent.

Abilify was one of the most heavily marketed drugs in the District and also had high Medicaid reimbursement amounts. It was among the top 30 drugs for total Medicaid reimbursement, total Open Payments gift value, and total Open Payments gift frequency in 2015. In 2015, DC Medicaid paid \$8.3 million for 8,067 prescriptions of all forms of Abilify.

The average cost per prescription for all types of Abilify has increased every year, so total reimbursement costs have remained high even though prescriptions have decreased. Between 2010 and 2015, the average cost per prescription of all types of Abilify to Medicaid nearly doubled, from \$551 in 2010 to \$1,023 in 2015 (Table 4).

Table 4: Abilify* DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$8,255,286	8,067	\$1,023
2014	\$9,559,589	10,882	\$878
2013	\$8,156,014	10,618	\$768
2012	\$11,464,802	17,441	\$657
2011	\$8,402,831	14,006	\$600
2010	\$5,732,681	10,401	\$551

*Includes branded oral Abilify and Abilify Maintena

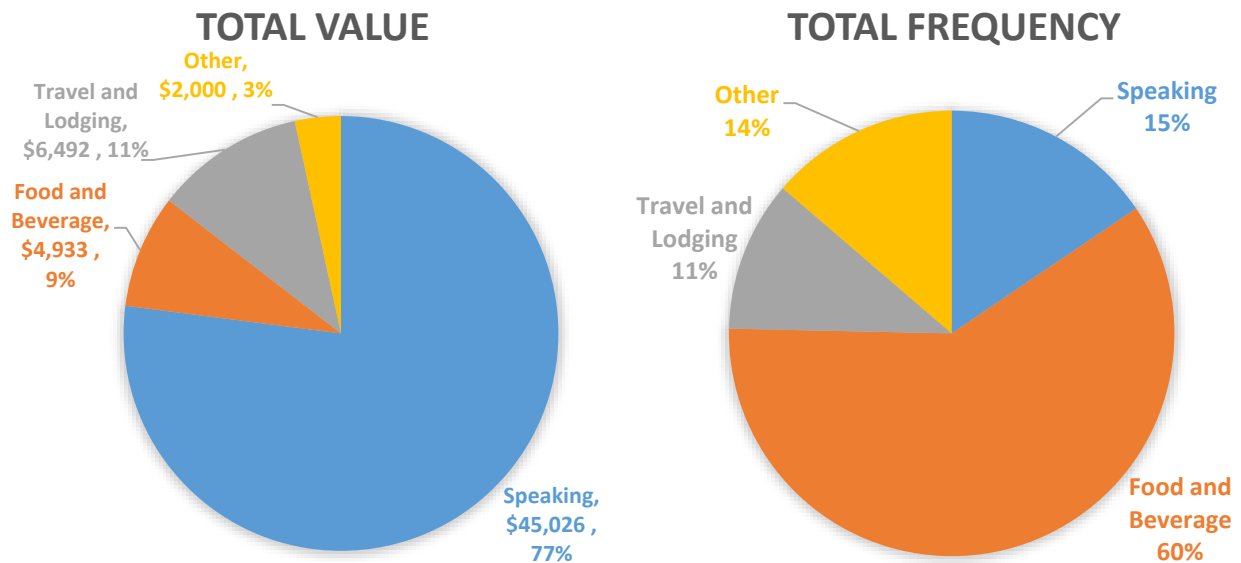
Although most Medicaid costs for Abilify were for the oral tablet rather than the injectable Abilify Maintena, prescriptions and Medicaid reimbursements for Abilify Maintena are increasing. In 2015, Abilify cost \$995 for tablets versus \$1,664 for Abilify Maintena (Table 5).

Table 5: DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription for Abilify and Abilify Maintena

Year	Abilify (branded oral tablet)		Abilify Maintena	
	Total Medicaid Reimbursement (Number of Prescriptions)	Average Cost per Prescription	Total Medicaid Reimbursement (Number of Prescriptions)	Average Cost per Prescription
2015	\$7,688,010 (7,726)	\$995	\$567,276 (341)	\$1,664
2014	\$9,234,934 (10,691)	\$864	\$298,077 (191)	\$1,561
2013	\$8,106,805 (10,585)	\$766	\$49,209 (33)	\$1,491

Gifts to physicians and teaching hospitals associated with Abilify totaled \$58,452 with 219 gifts; Abilify Maintena accounted for 96.5% of gifts. *Speaking* fees accounted for 77% (\$48,026) of the total value and 16% (34 gifts) of the total frequency of gifts. *Food and Beverage* accounted for 9% (\$4,933) of total value of gifts but accounted for the greatest percentage of gifts with 60% (131 gifts) of the total number of gifts given. *Travel and Lodging* accounted for 11% (\$6,942) of total value and 11% (24 gifts) of total frequency of gifts given. *Other* gifts accounted for 14% (\$2,000) of total value and 14% (30 gifts) of the total frequency of gifts given (**Figure 4**).

**Figure 4: Gifts Associated with Abilify*
Nature of Payment**



*Includes branded oral Abilify and Abilify Maintena

3. Latuda (lurasidone) (Manufacturer: Sunovion Pharmaceuticals Inc.)

Latuda (lurasidone) is an atypical antipsychotic initially approved in 2010 for the treatment of schizophrenia in adults (Latuda 2017). In 2013, Latuda was approved for the treatment of bipolar depression, and in 2017, it was approved for the treatment of schizophrenia in adolescents ages 13 to 17 (Mathis 2013, Farchione 2017).

DC Medicaid reimbursement costs and prescription counts for Latuda have increased steeply since 2011. In 2015, Medicaid reimbursed a total of \$2 million for Latuda, placing it on the top 30 list for Medicaid reimbursement. Additionally, it was also on the top 30 list of highest frequency of gifts reported to Open Payments, with 278 gifts. There is no evidence that Latuda is more effective than other antipsychotics (Lurasidone 2011).

Table 6: Latuda DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$2,043,943	2,417	\$846
2014	\$1,187,925	1,524	\$779
2013	\$423,864	651	\$651
2012	\$213,485	410	\$521
2011	\$50,070	83	\$603

The number of prescriptions for Latuda have been increasing. In 2011, there were 83 prescriptions for Latuda; in 2015, there were 2,417 prescriptions. In 2011, the price per prescription for Latuda was \$603; in 2015, the price was \$846 per prescription (**Table 6**).

Gifts associated with Latuda are almost exclusively associated with *Food and Beverage*, which accounted for 99% of gifts; a single gift was classified as *Other*. Promotion for Latuda is unusual because there were no gifts reported for *Speaking*.

Other Antipsychotic Drugs

Invega (paliperidone) was approved by the FDA in 2006 and is used as monotherapy for the treatment of schizophrenia as well as an adjunct therapy for depression and bipolar disorder (Invega 2017). Generic paliperidone was approved by the FDA in 2015.

**Table 7: Invega DC Medicaid Reimbursement and Numbers of Prescriptions
Invega vs. Invega Sustenna**

Year	Invega (oral tablet)		Invega Sustenna	
	Total Medicaid Reimbursement (Number of Prescriptions)	Average Cost per Prescription	Total Medicaid Reimbursement (Number of Prescriptions)	Average Cost per Prescription
2015	\$399,868 (394)	\$1,015	\$2,992,336 (1,849)	\$1,618
2014	\$739,076 (839)	\$881	\$2,748,807 (1,884)	\$1,459
2013	\$635,491 (816)	\$779	\$2,604,584 (1,923)	\$1,354
2012	\$803,071 (1,206)	\$666	\$3,461,402 (2,751)	\$1,258
2011	\$681,378 (1,071)	\$636	\$1,756,442 (1,482)	\$1,185
2010	\$522,718 (995)	\$525	\$349,316 (320)	\$1,092

Seroquel (quetiapine) is an atypical antipsychotic, approved in 1997, used to treat bipolar disorder, bipolar disorder with depressive episodes, and schizophrenia (Seroquel 2017). An extended-release version of Seroquel, Seroquel XR, was released in 2007 (Laughren 2007). Generic quetiapine has been available since 2012.

Table 8: DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription for Seroquel and Seroquel XR

Year	Seroquel (oral tablet)		Seroquel XR	
	Total Medicaid Reimbursement (Number of Prescriptions)	Average Cost per Prescription	Total Medicaid Reimbursement (Number of Prescriptions)	Average Cost per Prescription
2015	n/a*	n/a*	\$817,778 (1,293)	\$632
2014	\$17,629 (93)	\$190	\$979,514 (1,771)	\$553
2013	\$35,803 (151)	\$237	\$909,542 (1,691)	\$538
2012	\$3,934,782 (9,614)	\$409	\$1,337,636 (2,831)	\$472
2011	\$8,063,351 (21,435)	\$376	\$818,898 (1,890)	\$433
2010	\$5,178,326 (14,479)	\$358	\$577,025 (1,536)	\$376

*2015 Medicaid reimbursement data is not publicly available

Haloperidol is an old, generic antipsychotic. Haloperidol and other older, typical antipsychotics are equivalent to or superior in efficacy to atypical antipsychotics (Lieberman 2005, Crossley 2010). AstraZeneca’s own studies showed that quetiapine was inferior to haloperidol in efficacy (Spielmans 2010). Medicaid reimbursed \$139,713 for 3,236 prescriptions of haloperidol, averaging \$43 per prescription in 2015.

4. Levemir (insulin detemir) (Manufacturer: Novo Nordisk Inc.)

Levemir (insulin detemir) is a long-acting insulin approved in 2005 for treating type 1 and type 2 diabetes (Levemir 2015). In 2012, indications were expanded to include treating type 1 diabetes in pregnant women and children aged 2-5. Levemir was in the top 10 for Medicaid reimbursement, totaling \$3.4 million in reimbursement.

There were 315 gifts worth \$5,700 that were associated with Levemir reported to Open Payments. All but one of the gifts associated with Levemir were in the form of *Food and Beverage*.

Medicaid Spending on Insulin Products

In 2015, DC Medicaid spent more than \$15 million on insulin products (**Table 9**). Two long-acting insulins, insulin glargine and insulin detemir, are the most costly insulins; these include Levemir (insulin detemir), Lantus (insulin glargine), and Toujeo (insulin glargine). While insulin is life-sustaining for type 1 diabetics, it is rarely appropriate for type 2 diabetics (Hypoglycemic therapy 2014). Long-acting insulins (active for more than 12 hours) may cost twice as much as the intermediate-acting insulins (active for 8 – 10 hours) and rapid-acting insulins (active for less than one hour). Many diabetics use a combination of products.

In 2015, DC Medicaid spent more than \$15 million on insulin products.

Between 2014 and 2015, Medicaid reimbursements for Lantus (insulin glargine), a long-acting insulin approved in 2000 (Lantus 2015), decreased from \$6.3 million to \$5.9 million while reimbursements for Levemir (insulin detemir) increased from \$1.7 million to \$3.4 million (**Table 9**). Levemir has a higher average cost per prescription than Lantus for both regular vials and for injection pens (\$391 v. \$375 per prescription), but the price difference does not explain the disproportionate expenditures on Levemir. Prescribers may be switching their patients from Lantus to Levemir, despite no evidence of superiority of one over the other. A systematic review comparing Lantus and Levemir for treating type 2 diabetes mellitus in head-to-head studies showed no differences in efficacy or safety (Swinnen 2011).

Table 9: DC Medicaid Reimbursement (Number of Prescriptions) for Insulin Products

Insulin	2010	2011	2012	2013	2014	2015
Lantus	\$1,336,637 (8,696)	\$2,874,878 (17,261)	\$5,763,876 (30,432)	\$5,370,499 (23,132)	\$6,306,260 (20,132)	\$5,859,982 (15,636)
Novolog	\$969,857 (5,567)	\$2,112,226 (10,703)	\$3,825,322 (17,447)	\$3,124,328 (12,024)	\$3,223,267 (10,365)	\$3,689,341 (9,655)
Levemir	\$52,979 (324)	\$72,071 (377)	\$105,052 (548)	\$219,853 (936)	\$1,684,117 (5,162)	\$3,447,225 (8,823)
Apidra	\$971 (5)	\$199 (1)	\$3,793 (19)	\$157,277 (621)	\$715,941 (2,263)	\$989,623 (2,434)
Humalog	\$82,825 (355)	\$137,961 (630)	\$314,012 (1,539)	\$344,509 (1,503)	\$711,220 (2,560)	\$857,594 (2,693)
Novolin	\$298,122 (3,315)	\$448,520 (4,170)	\$655,602 (5,460)	\$479,007 (3,339)	\$366,129 (2,165)	\$257,183 (1,312)
Humulin	\$21,253 (168)	\$62,277 (525)	\$225,348 (1,609)	\$231,245 (1,433)	\$364,056 (2,081)	\$364,093 (1,855)
Totals	\$2,762,644 (18,430)	\$5,708,131 (33,667)	\$10,893,006 (57,054)	\$9,926,719 (42,988)	\$13,370,991 (44,728)	\$15,465,041 (42,408)

Other Insulins

Humalog (insulin lispro) is a rapid-acting insulin analog. It was first approved by the FDA in 1996 as a 50/50 mixture of insulin lispro and insulin lispro protamine (Humalog 2017). Humalog is approved for the treatment of type 1 and type 2 diabetes. In 1999, Humalog 75/25, another mixture of insulin lispro protamine and insulin lispro, was approved by the FDA (FDA For Patients 2017). In 2015, Medicaid reimbursed \$857,594 for Humalog, making it one of the top 30 drugs with the highest amount of Medicaid reimbursement. Humalog was ranked 35th for highest frequency of total gifts reported to Open Payments with 163 gifts. All gifts reported to Open Payments were *Food and Beverage*, with an average gift value of \$15.

Apidra (insulin glusine) is a rapid-acting insulin analog approved by the FDA in 2004 for the improvement of glycemic control in patients with diabetes (Apidra 2015). In 2015, Medicaid reimbursed \$989,623 for Apidra, making it one of the top 30 drugs that had the highest amount of Medicaid reimbursement. In 2015, Apidra was associated with 13 gifts (all for *Food and Beverage*) reported to Open Payments totaling \$273.

Lantus (insulin glargine) is a long-acting insulin analog approved by the FDA in 2000 (Lantus 2015). In 2015, Lantus was associated with \$5.9 million in Medicaid reimbursement, the third most reimbursed medication in DC. Lantus was associated with 28 gifts (all food and beverage) reported to Open Payments totaling \$536.

Toujeo (insulin glargine), a long-acting, concentrated version of insulin glargine, was approved in February 2015 under a 505(b)(2) application (a type of drug application that relies on FDA's finding of safety and effectiveness for a drug approved in the original new drug application) (Guettier 2015, FDA Economics Staff 2016). The Toujeo pen contains 300 units/mL of insulin glargine, compared to 100 units/mL in Lantus (Toujeo 2015). Reimbursement data for Toujeo in 2015 is not available due to low number of prescriptions. Toujeo was associated with 357 gifts to physicians and teaching hospitals reported to Open Payments totaling \$53,507 in gifts. The largest proportion of the total value of gifts was reported as *Speaking* gifts totaling \$32,445. *Speaking* gifts for Toujeo had an average value of \$1,700. However, *Speaking* only accounted for 5% of gifts in terms of total frequency with 19 gifts. *Consulting* represented 20% (\$10,633) of the total value of gifts in DC and 1% (4 gifts) of the total frequency of gifts. The 289 *Food and Beverage* gifts accounted for 4 of 5 gifts associated with Toujeo, although they made up only 14% (\$7,529) of total value. Toujeo was associated with \$2,721 in *Travel and Lodging* payments which accounted for 6% of the total gift frequency.

5. Januvia (sitagliptin) (Manufacturer: Merck Sharp & Dohme Corp.)

Januvia, a DPP-4 inhibitor that was approved in 2006 (Januvia 2017), is among the top 30 medications for both Medicaid reimbursement and total count of gifts in Open Payments. Among oral diabetes medications, Januvia had the highest Medicaid reimbursement and the highest Medicaid prescription count in 2015. Between 2010 and 2015 (**Table 10**), Medicaid reimbursements increased by more than 1,100% and prescription count by more than 660%.

Table 10: Januvia DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$2,089,907	6,028	\$347
2014	\$1,557,121	5,195	\$300
2013	\$947,046	3,596	\$263
2012	\$787,554	3,360	\$234
2011	\$400,436	1,815	\$221
2010	\$163,577	792	\$207

Januvia was associated with 191 gifts to physicians and teaching hospitals worth \$3,159. The makers of Januvia reported no gifts for *Speaking*. More than three fourths (\$2,468) of the total value of gifts were for *Food and Beverage*. The remaining 22% of the value of gifts were for payments categorized as *Other*.

Janumet is a combination treatment that combines Januvia (sitagliptin) with metformin. It was initially approved in 2007 and an extended-release version, Janumet XR, was approved in 2012 (Janumet 2017; Janumet XR 2017). Janumet was among the 30 medications with the highest Medicaid reimbursement, with almost \$1 million in reimbursements in 2015. Reimbursement amounts and prescription counts for Janumet have increased for the last five years, with prescription count increasing 925% and reimbursement increasing more than 1,600% from 2010 to 2015. Janumet (sitagliptin plus metformin) is now less expensive than Januvia (sitagliptin) alone. In 2015, Janumet cost \$326 per prescription, Januvia was \$347 per prescription. Janumet was associated with \$67 in gifts reported to Open Payments, all of which were *Food and Beverage* gifts. Janumet was frequently listed as an additional product that was marketed along with Januvia in gifts reported to Open Payments.

Among oral diabetes medications, Januvia had the highest Medicaid reimbursement and the highest Medicaid prescription count in 2015.

Other Antidiabetic Drugs

Metformin (generic version of Glucophage)

Metformin is a biguanide, originally approved by the FDA in 1994 for type 1 and 2 diabetes. Metformin is an inexpensive, highly effective, generically available drug that is the recommended first-line treatment for type 2 diabetes (Wood 2016). Metformin reduces the amount of glucose produced by the liver, decreases intestinal absorption of glucose, and is not associated with weight gain (Harrigan 2001). Besides being the best treatment for type 2 diabetes, metformin is an effective treatment for pre-diabetics and is an effective adjunct treatment for type 1 diabetes because it increases insulin sensitivity (DeGeeter 2016; Palmer 2016; Lindstrom 2016).

Table 11: Metformin DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$398,207	49,729	\$8
2014	\$452,089	53,293	\$8
2013	\$492,334	49,235	\$10
2012	\$437,447	56,541	\$8
2011	\$231,099	32,880	\$7
2010	\$128,733	14,245	\$9

Prescriptions for metformin have increased by more than 35,000 prescriptions per year from 2010 to 2015, and Medicaid reimbursement has more than tripled during that same time frame (**Table 11**). While metformin was not among the highest reimbursed drugs by Medicaid, it is one of the most commonly prescribed medications in the District of Columbia, with a total of almost 50,000 prescriptions. Metformin is the best drug for treating type 2 diabetes, and its widespread use shows that many prescribers in DC are prescribing rationally.

SGLT-2 Inhibitors (gliflozins)

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, or gliflozins, include Invokana (canagliflozin), Farxiga (dapagliflozin), Invokamet (canagliflozin/metformin), Jardiance (empagliflozin), and Glyxambi (empagliflozin/linagliptin). They are not generally associated with hypoglycemia and have been associated with weight loss. SGLT-2 inhibitors can cause genital and urinary tract infections, kidney failure, and low blood pressure, and may increase bone fracture, hepatitis, cancer, and death rates (Glucose-lowering treatments 2014). In 2015, SGLT-2 inhibitors were associated with \$186,840 in gifts.

GLP-1 Analogs

GLP-1 analogs are injectable medications, including Bydureon (dulaglutide), Victoza (liraglutide), Trulicity (dulaglutide), and Tanzeum (albiglutide). Currently, they are the most expensive treatments for diabetes (Wood 2016). GLP-1 analogs reduce HbA1c by about 1% (Glucose-lowering treatments 2014). In 2015, GLP-1 analogs were associated with \$93,243 in gifts.

Unlike many other medications discussed in this report, GLP-1 analogs did not have gifts classified as *Speaking* account for the largest portion of the total gift values. Instead, *Consulting* (42%) and *Food and Beverage* (30%) accounted for the largest sections for gift values. However, GLP-1 analogs were similar to other medications in terms of gift frequency, with *Food and Beverage* gifts accounting for the vast majority (91%) of the total number of gifts.

A more detailed report on the effect of marketing of diabetes drugs can be found in the AccessRx *Impacts* report on [Diabetes in the District](#), which focuses on pharmaceutical marketing and rising Medicaid expenditures for diabetes treatments in the District (Wood 2016).

6. Humira (adalimumab) (Manufacturer: AbbVie Inc.)

In 2008, an estimated 1.3 million people in the U.S. had rheumatoid arthritis (Helmick 2008). In 2015, an estimated 3 million American adults had inflammatory bowel diseases (Dahlhammer 2015). The prevalence of people with rheumatoid arthritis and inflammatory bowel diseases in DC is not available. Humira (adalimumab), Enbrel (etanercept), and Remicade (infliximab) are monoclonal antibodies that are tumor necrosis factor inhibitors; they are used to treat inflammatory bowel diseases (Crohn’s disease and ulcerative colitis), rheumatoid arthritis, and other serious autoimmune diseases.

Humira was approved in 2002 to treat rheumatoid arthritis. Since then, it has been approved for other indications: psoriatic arthritis, ankylosing spondylitis, hidradenitis suppurativa, non-infectious uveitis in adults, Crohn’s disease in adults and children aged 6 and older, juvenile idiopathic arthritis in children aged 2 and older, moderate to severe ulcerative colitis, and moderate to severe plaque psoriasis (Humira 2017).

In 2015, Medicaid reimbursed \$1.63 million for Humira in 2015, slightly more than the \$1.55 million it reimbursed in 2014. Although Medicaid prescriptions for Humira decreased slightly from 535 prescriptions in 2014 to 459 in 2015, the average cost per prescription increased by \$650, from \$2,900 to \$3,556.

Table 12: Humira DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

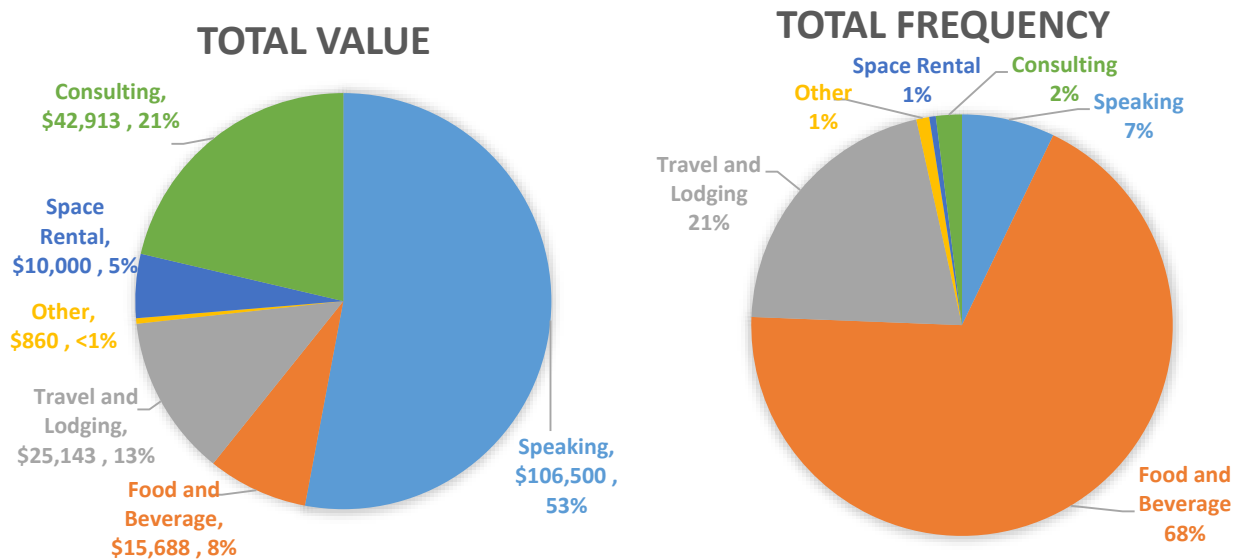
Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$1,631,994	459	\$3,556
2014	\$1,551,819	535	\$2,901
2013	\$824,033	313	\$2,633
2012	\$795,363	337	\$2,360
2011	\$450,190	178	\$2,529
2010	\$360,361	156	\$2,310

Humira had the highest total frequency of gifts of the top 30 medications reimbursed by Medicaid with 603 gifts totaling \$201,103. Humira had the third highest total for all gifts reported to Open Payments.

Humira had the highest total frequency of gifts of the top 30 medications reimbursed by Medicaid with 603 gifts totaling \$201,103.

The total value for the 603 payments associated with Humira given to physicians and teaching hospitals was \$201,103. *Speaking* constituted 53% (\$106,500) of the total value of gifts and 7% (43 gifts) of total number of gifts given. *Consulting* payments consisted of 21% (\$42,913) of the total value of gifts and 2% (12 gifts) of total number of gifts given. *Food and Beverage* gifts accounted for 8% (\$15,688) of the total value of gifts, but constituted 68% (413 gifts) of the total number of gifts given. *Travel and Lodging* accounted for 13% (\$25,143) of the total sum and 21% (126 gifts) of the total number of gifts given. *Space Rental* for teaching hospitals consisted of 5% (\$10,000) of the total value of gifts given and comprised less than 1% (3 gifts) of total number of gifts given. *Other* gifts represented less than 1% of the gifts given.

**Figure 5: Gifts Associated with Humira
Nature of Payment**



A biosimilar of Humira, Amjevita (adalimumab-atto), manufactured by Amgen, was approved by the FDA in September of 2016 (FDA News Release 2016). AbbVie and Amgen agreed to a deal in September of 2017 to allow Amgen to market a biosimilar of Humira; Amjevita (adalimumab-atto) will be available starting January of 2023 (Bell 2017). In August 2017, the FDA approved another biosimilar of Humira, Cyltezo (adalimumab-adbm) by Boehringer Ingelheim. Cyltezo is currently unavailable because of patent litigation between Boehringer Ingelheim and AbbVie Inc. (Boehringer Ingelheim 2017).

Other Tumor Necrosis Factor Inhibitors

Enbrel (etanercept) is approved to treat rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. It was initially approved by the FDA in 1998 (Enbrel 2016). While Enbrel is similar to Humira, it is lower in price, has lower Medicaid reimbursement amounts, and lower prescription counts. In 2015, DC Medicaid reimbursed \$511,277 for 185 prescriptions of Enbrel. This makes Enbrel \$2,764 per prescription. A total of \$6,767 in gifts associated with Enbrel were reported to Open Payments compared to the \$201,103 associated with Humira.

Remicade (infliximab) was approved by the FDA in 1998. It is approved to treat Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis (Remicade 2015). While Remicade is similar to and has many of the same indications as Humira, it has lower Medicaid reimbursement and prescription counts. It is similar in price to Enbrel (etanercept). Unlike Humira and Enbrel, which are injected intramuscularly, Remicade is an intravenous infusion that takes longer to administer. In 2015, DC Medicaid reimbursed \$445,958 for 162 prescriptions of Remicade. In 2015, Remicade was \$2,753 per prescription. In 2015, \$1,895 in marketing gifts related to Remicade was reported to Open Payments for DC.

7. Symbicort (budesonide/formoterol) (Manufacturer: AstraZeneca)

Chronic Obstructive Pulmonary Disease (COPD) includes emphysema and chronic bronchitis. Tobacco smoke is a key risk factor for developing COPD, which is most common among adults aged 65-74 years old (CDC COPD 2017). Nearly 15.7 million Americans, or 6.4% of the population, report having been diagnosed with COPD (Wheaton 2015). Chronic lower respiratory disease, mainly COPD, was the third leading cause of death in the U.S. in 2014 (NCHS 2016).

Asthma is a chronic lung disease associated with repeated occurrences of wheezing, breathlessness, chest tightness, and coughing (CDC Asthma 2017). About 18.4 million adults over the age of 18 and 6.2 million children are affected by asthma in the U.S. In DC, approximately 62,000 people (11.5% of the total population) had asthma in 2014 (CDC 2017). Asthma treatments include chronic medications, which prevent asthma exacerbations, and “rescue” treatments that treat acute attacks. Chronic medications include steroids (budesonide, fluticasone, and others) and long-acting beta agonists, also called LABAs (salmeterol, formoterol, and others). The most common rescue medication is albuterol. Several medications, including Advair and Symbicort, combine a long-acting beta-agonist with a steroid.

Symbicort is a combination of budesonide, a corticosteroid, and formoterol, a long-acting beta agonist. It was initially approved by the FDA in 2006 for managing COPD. Since its initial approval, Symbicort has also been approved for treating asthma in those aged 6 and older (Symbicort 2017).

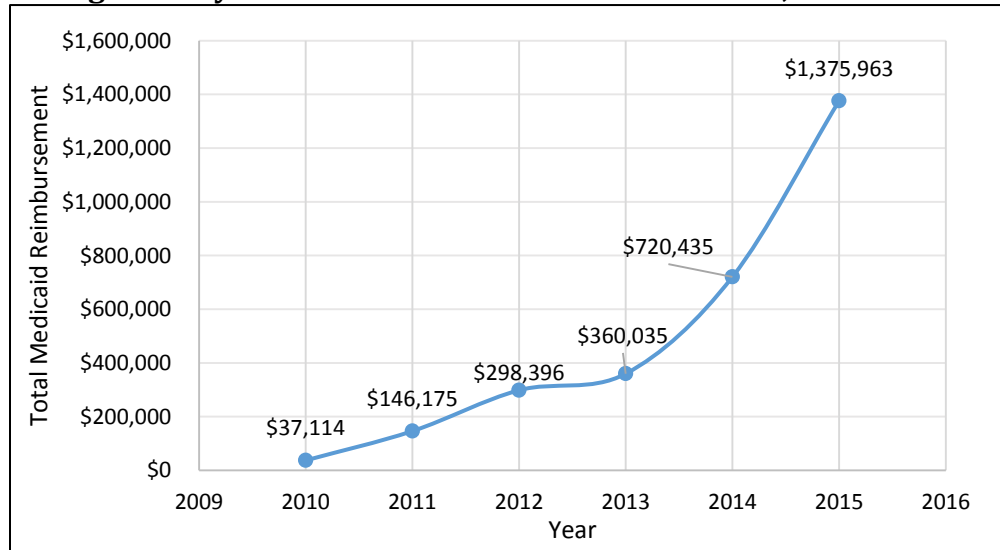
Although Symbicort was not the asthma drug with the highest DC Medicaid reimbursement, it was the only asthma medication that appeared on all 3 lists: top 30 medications for total Medicaid reimbursement, highest Open Payments gift value, and highest Open Payments gift frequency.

Table 13: Symbicort DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$1,375,963	5,068	\$272
2014	\$720,435	2,854	\$252
2013	\$360,035	1,534	\$235
2012	\$298,396	1,377	\$217
2011	\$146,175	716	\$204
2010	\$37,114	183	\$203

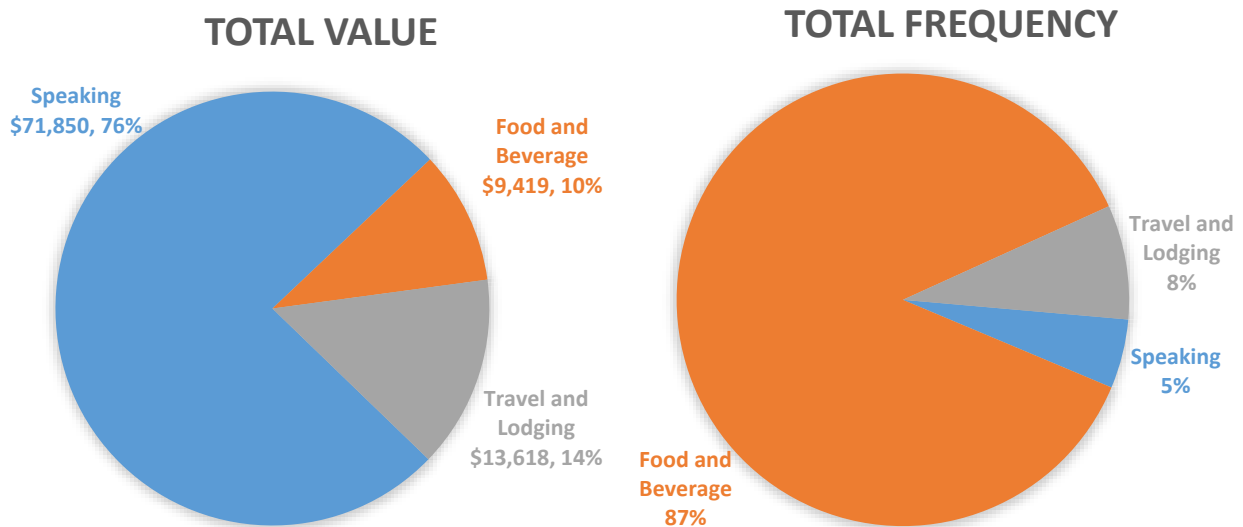
Between 2010 and 2015, DC Medicaid reimbursement for Symbicort increased 3,600% from \$37,114 to \$1.4 million and the prescription count increased by more than 2,600%, from 183 to 5,068 prescriptions.

Figure 6: Symbicort DC Medicaid Reimbursement, 2010-2015



Symbicort was associated with 526 gifts worth \$94,887 reported to Open Payments in 2015. *Speaking* represented 76% of the total value (\$71,850) of gifts associated with Symbicort but only 5% (26 gifts) of the total number of gifts given. *Food and Beverage* gifts accounted for 10% (\$9,419) of the total value but consisted of 87% (457 gifts) of the total number of gifts given. *Travel and Lodging* gifts represented 14% (\$13,618) of the total value and consisted of 8% (43 gifts) of total number of gifts given.

**Figure 7: Gifts Associated with Symbicort
Nature of Payment**



Other Steroidal Drugs for COPD and Asthma

Budesonide (generic version of Entocort, Uceris, Pulmicort)

Budesonide is a generic, inhaled, corticosteroid. Budesonide is available both as an inhaled powder and a liquid for nebulizing (a fine mist delivered by a machine called a nebulizer).

Table 14: Budesonide DC Medicaid Reimbursement and Number of Prescriptions

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$826,783	2,157	\$383
2014	\$1,056,542	2,701	\$391
2013	\$1,191,960	3,137	\$380
2012	\$1,100,709	3,346	\$329
2011	\$727,366	2,332	\$312
2010	\$156,426	585	\$267

Medicaid reimbursement for budesonide rose sharply between 2010 and 2011. Reimbursement was highest in 2013 when there was \$1.2 million in total reimbursement for 3,137 prescriptions. From 2013 to 2015, there was a 30% decrease in total Medicaid reimbursement. It was one of only two generic drugs on the list of top 30 medications for highest Medicaid reimbursement with \$826,783 in reimbursements. While budesonide is generic, it is currently more expensive than Symbicort.

Advair, a combination of fluticasone, a steroid, and salmeterol, a LABA, was originally approved by the FDA in 2000 for the treatment of asthma in those aged 12 and older. Advair HFA is an aerosol inhaler; HFA is a branded propellant and an Advair Diskus is a powder inhaler (Advair HFA 2017, Advair Diskus 2017).

In 2015, DC Medicaid reimbursed \$3.2 million for all versions of Advair. Advair decreased in total Medicaid reimbursement by \$1.3 million from 2014 to 2015. Total prescription counts also decreased from 14,223 prescriptions in 2014 to 9,477 prescriptions in 2015. The Advair Diskus patent expired in 2016 (FDA Orange Book n.d.). A generic fluticasone/salmeterol combination application was submitted in 2016 and the generic product are expected to enter the market in 2017 (Ward 2016; APhA Drug InfoLine 2017).

Advair's manufacturer (GlaxoSmithKline) appears to have stopped promoting Advair as generic competition loomed. It was associated with a trivial number of gifts (13 gifts) totaling \$173 in Open Payments; all gifts were for *Food and Beverage*.

Flovent (fluticasone) is an inhaled steroid used to treat asthma that was approved in 1994. It is manufactured by GlaxoSmithKline. It is currently available as Flovent HFA, an aerosol inhaler, and Flovent Diskus, an inhaled powder (Flovent HFA 2016, Flovent Diskus 2016). A generic fluticasone product is expected to enter the market in 2017 (APhA Drug InfoLine 2017).

From 2010 to 2015, Medicaid reimbursements for Flovent have increased nearly 620%; the number of prescriptions increased 340% in the same time period. In 2015, Flovent had the fourth highest total Medicaid reimbursement among all medications, with \$4.8 million in total reimbursement for 24,900 prescriptions (\$193 per prescription). It was the asthma medication with the highest Medicaid reimbursement total. Flovent was not associated with any gifts that were reported to Open Payments.

Spiriva (tiotropium) is an anticholinergic drug indicated for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease; it was originally approved in 2004. It is manufactured by Boehringer Ingelheim Pharmaceuticals. Spiriva HandiHaler is an inhaled powder; Spiriva Respimat, approved later, is an inhaled aerosol (Spiriva 2015; Spiriva Respimat 2017). The inhaler for Spiriva is also patented, so creating a generic version is more complex than usual (Drug Development Technology n.d.). From 2010 to 2015, total Medicaid reimbursement for Spiriva increased by 219% from \$650,492 to \$2.1 million, and the total prescription count increased by 100% from 3,232 to 6,472 prescriptions.

Spiriva was associated with 87 gifts, mostly for *Food and Beverage*, reported to physicians and teaching hospitals totaling \$3,175. *Food and Beverage* accounted for 63% (\$2,009), *Travel and Lodging* accounted for 37% (\$1,162), and *Other* accounted for <1% (\$4) of total value. For total frequency, *Food and Beverage* accounted for 93% (81 gifts) of gifts, while *Other* accounted for 5% (4 gifts), and *Travel and Lodging* accounted for 2% (2 gifts).

8. Tecfidera (dimethyl fumarate) (Manufacturer: Merck Sharp & Dohme Corp.)

Multiple sclerosis (MS) is a disease affecting the nervous system in which communication between the brain and other parts of the body are disrupted. Symptoms can range from muscle weakness in the extremities, difficulties with coordination and balance, speech impediments, tremors, dizziness, and complete or partial paralysis. Cognitive symptoms including difficulties with concentration, attention, memory, and poor judgment can also occur. The CDC does not require reporting of new cases of multiple sclerosis in the U.S., so prevalence can only be estimated. The National Multiple Sclerosis Foundation estimates between 300,000 and 400,000 people in the United States have multiple sclerosis (Common Questions 2016).

Drug treatments for multiple sclerosis include injectable and oral agents. Injectable treatments include interferons (Avonex, Rebif, Plegridy, Betaseron, Extavia), glatiramer acetate (Copaxone, Glatopa), natalizumab (Tysabri), alemtuzumab (Lemtrada), and mitoxantrone. Oral agents include fingolimod (Gilenya), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera) (Drugs for Multiple Sclerosis 2016).

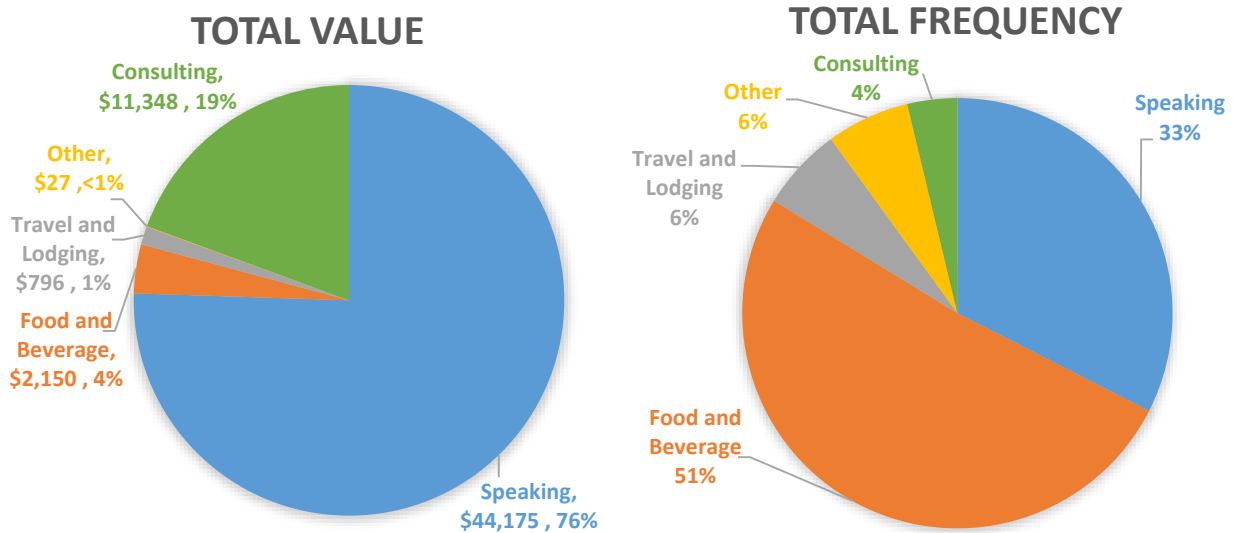
Tecfidera (dimethyl fumarate) is an Nrf2 activator approved in 2013 for the treatment of patients with relapsing forms of multiple sclerosis (Tecfidera 2017). DC Medicaid reimbursement costs and prescription counts for Tecfidera have increased since its approval in 2013, from \$167,507 to \$1.0 million in reimbursements in 2015. The average cost per prescription increased by 30% in two years, from \$4,527 to \$5,845.

Table 15: Tecfidera DC Medicaid Reimbursement, Numbers of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$1,028,741	176	\$5,845
2014	\$657,580	124	\$5,303
2013	\$167,507	37	\$4,527

Tecfidera was associated with 80 gifts that totaled \$58,496. By value, *Speaking* made up the largest portion of spending with \$44,175. *Speaking* only made up a third of gifts by frequency. By frequency, *Food and Beverage* made up the largest portion of gifts with 51%. *Food and Beverage* was associated with \$2,150 in gifts, 4% of the total value of gifts. *Consulting* represented 19% of the total value with \$11,348. *Travel and Lodging* and *Other* each made up 1% or less of the total value of gifts.

**Figure 8: Gifts Associated with Tecfidera
Nature of Payment**



Other Oral Multiple Sclerosis Drugs

Gilenya was approved by the FDA in 2010. It is an oral sphingosine 1-phosphate receptor modulator (Gilenya 2016). DC Medicaid reimbursed 40 prescriptions of Gilenya, costing \$246,949. Both Medicaid reimbursement and prescription count decreased from 2014 to 2015. The average cost per prescription in the same time period increased by 25% from \$4,932 to \$6,174.

Gilenya was associated with 138 gifts to physicians and teaching hospitals, totaling \$65,953. This total amount of gifts placed Gilenya on the top 30 list for highest total gift value. The majority of total gift value (71%) was for gifts related to *Speaking*, which totaled \$46,740. In regards to total gift frequency, *Food and Beverage* gifts accounted for 65% (89 gifts) of total number of gifts given, *Speaking* gifts and *Travel and Lodging* gifts each accounted for 17% (23 and 24 gifts respectively).

Aubagio was approved by the FDA in 2012. It is an oral pyrimidine synthesis inhibitor (Aubagio 2016). Due to a low number of prescriptions, Medicaid reimbursement information for Aubagio in 2015 was not made available by CMS.

Medicaid reimbursed few prescriptions for Aubagio in 2015, but it was associated with 131 gifts to physicians and teaching hospitals totaling \$52,422, which may indicate increased costs in subsequent years. Almost three fourths (72%) of the total value of gifts was reported as *Speaking* gifts totaling \$37,600. *Food and Beverage* accounted for two thirds (66%) of the number of gifts given with 86 gifts. The remaining one third of gifts given consisted of *Travel and Lodging*, *Speaking*, and other categories of gifts.

9. Xarelto (rivaroxaban) (Manufacturer: Janssen Pharmaceuticals)

Oral anticoagulants are used to prevent and treat blood clots. Current oral anticoagulants include Coumadin (warfarin, available as a generic), Xarelto (rivaroxaban), Eliquis (apixaban), Pradaxa (dabigatran), and Savaysa (edoxaban). Injected anticoagulants are used to treat blood clots. Current injected anticoagulants include heparin (generic), Lovenox (enoxaparin, available as a generic) and Arixtra (fondaparinux). Anticoagulants can cause excessive bleeding, so the availability of reversal agents is important. Currently, only Pradaxa (dabigatran) and warfarin have reversal agents. The effects of warfarin can be reversed with phytonadione (vitamin K). Pradaxa can be reversed using Praxbind (idarucizumab).

Xarelto (rivaroxaban) is a factor Xa inhibitor used as an anticoagulant to prevent blood clots. It was first approved in 2011 to prevent deep vein thrombosis in patients undergoing knee or hip surgeries (Xarelto 2017). There is no generic version of Xarelto currently available. Unlike warfarin and Pradaxa, which can be reversed if a patient experiences a bleed, Xarelto is associated with more hemorrhages than other oral anticoagulants (QuarterWatch 2017). Xarelto does not have an approved reversal agent. AndexXa (andexanet alfa), a proposed reversal agent for factor Xa inhibitors, was denied FDA approval in August of 2016. As of August 2017, Portola Pharmaceuticals has resubmitted their application for AndexXa (GlobeNewswire 2017).

Since its approval in 2011, Xarelto has become one of the drugs with the highest DC Medicaid reimbursement costs; in 2015, DC reimbursed nearly a million dollars (\$967,956) for Xarelto. It is heavily marketed in the District, appearing on the list of top 30 drugs for total Medicaid reimbursement, total gift value reported to Open Payments, and total gift count reported to Open Payments. Xarelto was associated with the highest frequency of gifts in DC reported to Open Payments with 691 gifts and was in the top 15 of total value of gifts reported with \$99,133 in gifts.

DC reimbursed nearly a million dollars (\$967,956) for Xarelto in 2015.

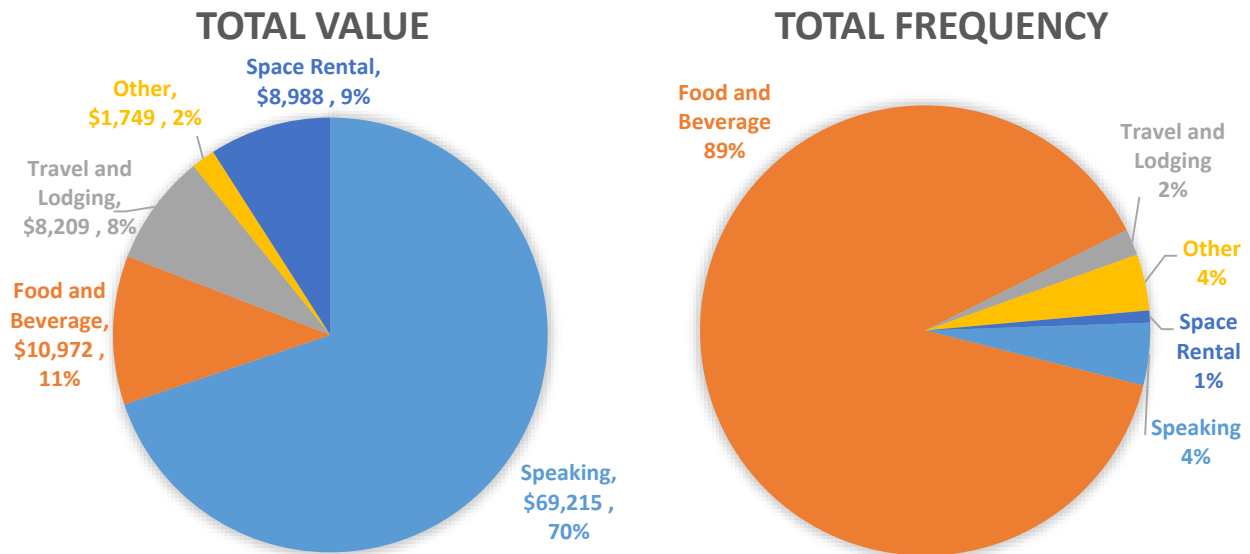
The amount DC Medicaid reimbursed, as well as the number of prescriptions for Xarelto, increased each year since it was approved in 2011 (**Table 16**). The largest increase in total reimbursements and number of prescriptions was between 2013 and 2014, when costs to Medicaid jumped from \$203,354 to \$637,118. The largest percent increase in reimbursements occurred between 2012 and 2013, when costs increased by more than 700% from \$24,987 to \$203,354 in reimbursements.

Table 16: Xarelto DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$967,956	2936	\$330
2014	\$637,118	2249	\$283
2013	\$203,354	737	\$276
2012	\$24,987	101	\$247
2011	\$453	2	\$226

The largest portion of gifts were reported under *Speaking*, which consisted of 70% (\$69,215) of the total value of gifts associated with Xarelto but only represented 5% (31 gifts) of the total gift count. *Food and Beverage* accounted for 11% (\$10,972) of total value of gifts but accounted for the greatest percentage of gifts given at 89% (613 gifts) of the total number of gifts. All other gifts, including *Travel and Lodging*, *Space Rental*, and *Other* accounted for 19% of the total values and less than 10% of the total frequency of gifts.

**Figure 9: Gifts Associated with Xarelto
Nature of Payment**



Other Anticoagulants

Warfarin (generic version of Coumadin)

Coumadin (warfarin) was approved in 1954; generic warfarin has been available since 1997. Warfarin is an old, inexpensive, effective, readily reversible anticoagulant that is a vitamin K antagonist. Its disadvantage is that it requires regular monitoring of the Internationalized Normalized Ratio (INR), a ratio of coagulation tests. Warfarin also interacts with many drugs and patients must keep their intake on vitamin K-containing foods consistent. Its advantage is that it is very inexpensive and is easily and quickly reversed with vitamin K.

Warfarin has lower Medicaid reimbursement than newer anticoagulants, but has a higher prescription count. It has a very low average cost at \$12 per prescription.

Table 17: Warfarin DC Medicaid Reimbursement, Number of Prescriptions, and Average Cost per Prescription

Year	Total Medicaid Reimbursement	Number of Prescriptions	Average Cost per Prescription
2015	\$55,968	4,507	\$12
2014	\$58,781	6,184	\$10
2013	\$57,298	6,463	\$9
2012	\$91,723	9,584	\$10
2011	\$63,051	6,016	\$10
2010	\$58,558	4,033	\$15

Eliquis (apixaban) is a factor Xa inhibitor, initially approved in 2012, indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Eliquis 2016). In 2014, Eliquis received four new indications, including prophylaxis and treatment of deep vein thrombosis. It is manufactured by Bristol-Myers Squibb Co. and Pfizer Inc.

DC Medicaid reimbursement costs and prescription counts have increased each year since Eliquis was approved in 2012. The largest increase in cost was between 2014 and 2015 when reimbursement increased from \$10,125 to \$83,124 and the prescription count increased from 35 to 265 prescriptions.

In 2015, Eliquis had the second highest count of gifts reported to Open Payments, with 639 gifts, behind only Xarelto, which had 691 gifts. Eliquis was associated with 639 gifts totaling \$119,367. The majority of the value of the gifts was for *Speaking*, with \$69,000 (58%). However, the most frequent gifts were for *Food and Beverage*, with 92% (586) of the gifts.

Pradaxa (dabigatran etexilate), first approved by the FDA in 2010, was the first factor Xa inhibitor approved; it is indicated for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Pradaxa 2016). It is manufactured by Boehringer Ingelheim Pharmaceuticals Inc. DC Medicaid reimbursement for Pradaxa decreased between 2012 and 2015 by 39% and the prescription count has decreased from 2012 to 2015 by 57%. Excessive bleeding caused by Pradaxa can be reversed with Praxbind (Praxbind 2015).

Pradaxa appeared in the list of top 30 marketed drugs in DC based on gift frequency with 185 total gifts reported to Open Payments, which totaled \$54,578. Gifts classified as *Speaking* accounted for almost half (49%) of the total value of gifts, totaling \$26,650. *Food and Beverage* gifts accounted for the majority (87%) of total frequency of gifts given.

Savaysa (edoxaban) is a factor Xa inhibitor, approved in 2015, for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (Savaysa 2016). It is manufactured by Daiichi Sankyo Inc. Although Savaysa had no Medicaid reimbursement or prescriptions in 2015, it was in the top 30 for total frequency of Open Payment gifts with 417 gifts and total sum of Open Payment gifts (\$26,969). No current information on reimbursement or prescription number are available. Savaysa is a drug to monitor to see the impact of this marketing.

V. Discussion

It is clear that pharmaceutical marketing affects therapeutic choices in the District as it does in the rest of the country. The District spent \$87 million on 30 drugs, which accounted for about half of all DC Medicaid reimbursements (**Table 1**). While some of these expenses are unavoidable, some expenses are unnecessarily high. The discussion below reviews the cost and quality implications of highly marketed, high-cost medications. This is followed by a discussion of generics and biosimilars and strategies for maintaining sales of branded products.

Direct-Acting Antivirals for Hepatitis C

Hepatitis C drugs are costing the District large sums of money due to both high-need and high-cost medications. DC Medicaid spent \$19.7 million on 610 prescriptions for **Harvoni** and \$4.5 million for 157 prescriptions of **Viekira Pak**. **Harvoni** had the highest marketing payments of all hepatitis drugs in 2015. At \$32,263 per month, **Harvoni** is more expensive than **Sovaldi (sofosbuvir)**, which costs Medicaid \$28,800 per month. Gilead released **Harvoni**, a combination of **Sovaldi** and **ledipasvir**, less than a year after **Sovaldi's** approval.

Promotional expenditures – and prescriptions – appear to have shifted from **Sovaldi** to **Harvoni**. The company appears to have stopped promoting **Sovaldi**, which was not associated with any gifts reported to Open Payments in 2015. Prescriptions followed promotional trends. In 2014, DC Medicaid reimbursed \$6.3 million in prescriptions for **Sovaldi (sofosbuvir)**; this number dropped precipitously to \$374,996 in 2015.

Direct-acting antivirals (DAAs), including **Sovaldi (sofosbuvir)**, **Harvoni (ledipasvir/sofosbuvir)**, **Olysio (simeprevir)**, **Daklinza (daclatasvir)**, **Viekira Pak (ombitasvir/paritaprevir/ritonavir with dasabuvir)** are more effective than older drugs (interferon and ribavirin regimens) for achieving a sustained virologic response, but sustained virologic response is an unvalidated surrogate measure.

The extent to which DAAs prevent liver failure, liver transplants, death, or other clinical endpoints is unclear at this time. A review of 138 randomized clinical trials found that studies of DAAs did not provide adequate data to determine the effect of DAAs on all-cause mortality or hepatitis-related morbidities such as ascites, variceal bleeding, hepato-renal syndrome, hepatic encephalopathy, or hepatocellular carcinoma (Jakobsen 2017). Most studies were short-term and long-term effects cannot be extrapolated from them.

Additionally, all direct-acting HCV drugs received a black box warning from FDA in 2016 because they can cause reactivation of hepatitis B and hepatic failure (FDA Safety Announcement 2016). Needless to say, serious adverse effects and subsequent hospitalizations also incur costs to Medicaid.

Appropriate selection of patients to be treated by DAAs is important. About a quarter of people will clear the virus on their own (Grebely 2007). For those who do not clear the virus, hepatitis C infection usually progresses slowly over decades. Older interferon-based regimens may be appropriate in some patients.

DAAs also vary in price. The difference in price between the most expensive (Harvoni) and least expensive (Sovaldi) DAA for Medicaid is \$3,420 difference per prescription. At 610 **Harvoni** prescriptions, annually the District could save \$2.1 million if less expensive hepatitis drugs like **Sovaldi** were used. Prescribers should be educated on the true benefits and harms of hepatitis drugs.

Antipsychotics

Atypical antipsychotics have been found to be neither more effective nor safer than haloperidol and other older antipsychotics. CATIE, a large, federally-funded comparative effectiveness study, found that older, generically available antipsychotics were equivalent or superior in efficacy to newer, more expensive, antipsychotics (Lieberman 2005). A meta-analysis of 15 randomized controlled trials with 2,522 participants found similar results (Crossley 2010). Additionally, newer antipsychotics are not safer than older drugs. Atypical antipsychotics have also been associated with many adverse events including increased mortality in elders, strokes, cardiac arrhythmias, sudden cardiac death, excessive weight gain, and diabetes (Borkowski 2012). For more information on the promotion of antipsychotics in the District, see the AccessRx *Impacts* reports [Focus on Use of Antipsychotics in Children](#) and [Focus on the Use of Antipsychotics in Seniors](#) (Borkowski 2012, Borkowski 2013).

Abilify (aripiprazole), Invega (paliperidone), and Latuda (lurasidone) are atypical antipsychotics, used to treat schizophrenia. **Abilify** and **Invega** cost more than \$1,000 per prescription. In 2015, the District paid \$3.4 million for 2,243 prescriptions for all forms of **Invega** at \$1,512 per prescription. In 2015, the oral form of **Invega** was associated with \$249 in gifts to physicians and teaching hospitals and accounted for only 394 prescriptions of the total 2,243. Generic **paliperidone** became available in August 2015. There were only 63 prescriptions of generic **paliperidone** paid for by DC Medicaid, accounting for \$59,070 in reimbursement. The average cost per prescription for the generic was \$938.

Promotional efforts appear to have shifted to extended-release, injected forms of **Invega**. Since 2011, more prescriptions have been written for **Invega Sustenna** than immediate-release **Invega**. **Invega Sustenna**, an extended-release injected form of **Invega**, was approved in 2009 (Invega Sustenna 2017). In 2015, 1,849 prescriptions for **Invega Sustenna** were reimbursed by Medicaid. In 2015, **Invega Sustenna** was associated with \$1,610 reported to Open Payments. Another extended-release product, **Invega Trinza**, which lasts three months, was approved in 2015 (Invega Trinza 2017). There were no prescriptions for **Invega Trinza** in DC Medicaid in 2015 but prescriptions can be expected to increase in subsequent years.

Generic **aripiprazole** and **paliperidone** are available and now should be prescribed instead of the branded versions. Generic **quetiapine** and **haloperidol** also should be preferred. Prescribers should be educated about appropriate use of antipsychotics, appropriate use of extended-release forms, the relative benefits and harms of older versus newer antipsychotics, and the reliability of generic drugs. Long-acting forms should be reserved for patients unable to adhere to immediate-release drugs.

Drugs for Diabetes

Seven diabetes drugs are on the top 30 most reimbursed list. These include five insulins: **Lantus (insulin glargine)**, **Levemir (insulin detemir)**, **Novolog (insulin aspart)**, **Apidra (insulin glulisine)**, **Humalog (insulin lispro)**, and two oral drugs, **Januvia (sitagliptin)** and **Janumet (sitagliptin/metformin)**. Medicaid reimbursements for **Lantus** have been decreasing while reimbursements for **Levemir** have increased substantially. **Levemir** is more expensive and has no advantage over **Lantus**.

Although insulin is required for type 1 diabetics, it is rarely appropriate for type 2 diabetics. The number of prescriptions being written for insulins in the District implies that many insulin prescriptions are being written for type 2 diabetics.

Januvia (sitagliptin) and **Janumet (metformin and sitagliptin)** are both on the top-30 list for most Medicaid reimbursement with \$2.1 million and \$961,624 of total Medicaid reimbursement respectively. **Januvia** is also among the top 30 medications in total count of gifts in Open Payments. **Sitagliptin** is not superior to other oral antidiabetic medications (Hypoglycemic therapy 2014). **Januvia** and other gliptins can cause serious allergic reactions, increased risk of infection, kidney dysfunction, and pancreatitis.

The first-line treatment for type 2 diabetics is **metformin**, which costs \$8 per prescription. Many diabetes drug manufacturers are combining metformin with other drugs, which secures new patents. When using multiple drugs to treat a condition, it makes sense to prescribe them separately so that dosage adjustments can be more easily made. Prescribers should be educated to avoid prescribing combination drugs for diabetes, and instead prescribe drugs separately.

Health care providers need to be routinely educated about the harms and benefits of diabetes medications and the appropriate, cost-effective use of insulins and other medications for diabetes. Prescribers should be educated to make more cost-conscious decisions about diabetes medications.

Drugs for Asthma and COPD

Among the top 30 reimbursed by Medicaid, seven drugs are used to treat asthma and chronic obstructive pulmonary disease (COPD). Two **albuterol** drugs, **Ventolin** and **ProAir**, are similar in price; more prescriptions were written for **Ventolin** (40,656 prescriptions at \$52 per prescription), which costs slightly less than **ProAir** (28,773 prescriptions at \$58 per prescription). **Albuterol** is necessary to treat asthma attacks and there is little opportunity for cost savings here.

Steroid preparations, including **Flovent (fluticasone propionate)**, **Advair (fluticasone/salmeterol)**, **budesonide**, and **Symbicort (budesonide/formoterol)**, are used to prevent asthma attacks. **Budesonide** or **fluticasone** are reasonable steroid treatments to use to prevent asthma. **Budesonide** is available as a generic but, oddly, it is more expensive (\$383) than **Advair** (\$342), **Symbicort** (\$272), and **Flovent** (\$193). It is unclear whether cost savings can be implemented with these drugs.

Anticoagulants

Xarelto (rivaroxaban) and **Lovenox (enoxaparin)** are the two anticoagulants on the top-30 most-reimbursed list. The District spent almost a million dollars (\$967,956) on **Xarelto** in 2015. **Xarelto** is heavily marketed in the District. In 2015, **Xarelto** was associated with the highest frequency of gifts in DC reported to Open Payments with 691 gifts and was in the top 15 of total value of gifts reported to Open Payment with \$99,133 in gifts.

Although all oral anticoagulants can precipitate bleeding events, **Xarelto** appears to be the most dangerous anticoagulant. A 2016 analysis of FDA data by the Institute for Safe Medication Practices showed that anticoagulant drugs caused 21,996 serious adverse events (primarily hemorrhages) in the U.S., including 3,018 deaths (QuarterWatch 2017). **Xarelto (rivaroxaban)** was disproportionately represented in these adverse events.

Use of Generics Should Be Expanded

Compared to other jurisdictions, DC has a low generic utilization rate. In 2015, DC's generic utilization rate was 69%, which was the second lowest utilization rate that year after California (67%). The national Medicaid generic drug utilization rate was 81% (CMS 2016b). We have identified several areas in which DC could continue to improve its generic utilization rate to provide for more cost savings.

Generics are therapeutically equivalent to their brand name counterparts. When the FDA approves a generic drug, the generic must contain the same active ingredients as the original drug; be identical in strength, dosage, and route of administration; be bioequivalent; meet the same batch requirements for strength, purity, and quality; and be manufactured under the same strict standards of FDA's good manufacturing practice required for branded drugs.

The FDA uses the same standard for variability between brand and generic drugs as it uses for variability between different batches of branded drugs. A study that examined 2,070 single-dose clinical bioequivalence studies of oral generic medicines approved by the FDA showed that the average difference in absorption into the body between the generic and originator drug was 3.56%. This difference was comparable to acceptable differences between different batches of any drug (Davit 2009). A systematic review and meta-analysis of generic and branded drugs used in cardiovascular disease found that generic and branded drugs were clinically equivalent in 35 out of 38 randomized controlled trials (Kesselheim 2008).

There is no reason to prescribe a brand name drug when a generic drug is available. Widespread generic use would save the system money. The Pharmaceutical Care Management Association (PCMA), a national association of pharmacy benefits managers, estimated cost savings for DC Medicaid at \$6.2 million if generic utilization was increased. PCMA also estimated that DC Medicaid could save another \$649,560 if prescribers utilized lower-cost branded drugs (PCMA 2016). A 2012 Government Accountability Office (GAO) report on generic drug use estimated that if all outpatient prescription drugs available as generics were substituted in place of branded drugs, Medicare could have saved \$900 million in 2007 (U.S. GAO 2012).

Patients are more adherent to generic drugs because they can afford them. In 3-tiered plans, patients who received generics filled 12.6% more prescriptions in the next year than those who received non-preferred branded drugs (Shrank 2006). Prescribing generics will help patients, state Medicaid budgets, and the healthcare system as a whole.

Only two of the 30 drugs with the highest Medicaid reimbursements were generic drugs: **methylphenidate** (the generic name for **Ritalin**), used to treat attention-deficit/hyperactivity disorder [ADHD]) and **budesonide** (an inhaled steroid used to treat asthma and COPD). Five branded drugs accounting for high Medicaid expenditures, including oral tablets of **Abilify (aripiprazole)**, **Nexium (esomeprazole)**, **Suboxone (buprenorphine/naltrexone)**, **Lovenox (enoxaparin)**, and oral tablets of **Invega (paliperidone)** were available as generics during the time of our analysis. Although generics were available for these drugs, prescriptions for branded versions cost the District unnecessary money.

DC also is paying more than necessary for brand name antipsychotic drugs. In 2015, DC Medicaid paid \$8.3 million for 8,067 prescriptions of all forms of **Abilify (aripiprazole)**. Although **aripiprazole** became available as a generic in 2015, only 1,505 prescriptions of **aripiprazole** at \$546 per prescription for a total of \$821,060 were reimbursed that year. In 2015, there was a \$450 cost per prescription difference between **Abilify** and generic **aripiprazole**. If every prescription for branded, oral **Abilify** that DC Medicaid reimbursed in 2015 was switched to the generic **aripiprazole**, DC could have saved close to \$3.5 million.

Almost all of the drugs with the highest Medicaid reimbursements are branded drugs. In 2015, Medicaid reimbursed a total of \$2 million for **Latuda (lurasidone)** despite the fact that there is no evidence that **Latuda** is more effective than other antipsychotics (Lurasidone 2011).

In some cases, uptake of a generic drug has been successful. In 2015, **Seroquel** was \$635 per prescription with 1,293 prescriptions. When generic **quetiapine** was introduced in 2013, prescriptions for branded **Seroquel** dropped to less than 1% of prescriptions written for the previous year. In 2014, there was a \$160 cost difference between tablets of branded **Seroquel** and generic **quetiapine**. By 2015, the average cost per prescription for generic **quetiapine** was \$26; 18,500 prescriptions for generic **quetiapine** were reimbursed in 2015.

Generic **Seroquel** is the most cost-efficient atypical antipsychotic to Medicaid. DC prescribers appear to have made the rational choice to switch to generic **quetiapine**, which is among the 30 most prescribed medications in DC Medicaid.

Biosimilars

Biosimilars are biologic agents that contain active ingredients similar to an already approved biologic agent. The biosimilars approval pathway was created in 2010 as part of the Affordable Care Act to increase competition between biologic agents (FDA 2012). Since its creation, 22% of new FDA drug approvals have been for biosimilars (Hakim 2017). Though there has been an uptake in prescribing and usage of biosimilar drugs, it is unclear how substantial the cost savings will be for patients and the health care system because of various regulatory, legal, and payment hurdles. For example, although there are two approved biosimilars of **Humira**, the current expiration date of **Humira's** patent is 2034 (Koons 2017). In September of 2017, AbbVie and Amgen struck a deal to allow Amgen to market a biosimilar of Humira starting January 2023 (Bell 2017). A biosimilar of **Lantus, Basaglar (insulin glargine)**, manufactured by Eli Lilly, is now available. Unbiased education on the comparative safety and effectiveness biosimilars may be helpful (Chingcuanco 2016).

Evergreening

Pharmaceutical companies regularly extend patent life and battle generic competition by combining two drugs to garner a new patent, or by sequentially releasing different controlled-release preparations.

Extended-Release Drugs

Drug companies release long-acting versions of drugs, sometimes sequentially, in order to extend patent life. When **aripiprazole** became available as a generic in 2015, a branded, long-acting, injectable form, **Abilify Maintena**, had already entered the market. In 2015, **Abilify** cost \$995 for oral tablets, versus \$1,664 for **Abilify Maintena**. The generic version of the oral tablet form of **Abilify, aripiprazole**, cost \$546 per prescription, 45% less than brand name **Abilify**.

Generic **quetiapine**, taken twice daily, is \$26 a prescription, but **Seroquel XR (extended-release quetiapine)**, taken once daily (Seroquel XR 2017), remains under patent and is expensive. The average cost of **Seroquel XR** has increased from \$376 per prescription in 2010 to \$632 in 2015.

Although Medicaid reimbursement and prescription counts for **Seroquel XR** have decreased from their peak in 2012 for **Seroquel XR**, increased costs per prescription have kept Medicaid reimbursements for **Seroquel XR** over \$800,000. Although the average cost per prescription of branded **Seroquel** has decreased by 47% from 2010 to 2014, from 2010 to 2015 the price of **Seroquel XR** increased by 68%.

Invega is a good example of sequential release of extended-release products for patent extension purposes. Once immediate-release and sustained-release oral **paliperidone** became available generically, sequential branded extended-release preparations entered the market. An extended-release injectable form, **Invega Sustenna**, which lasts one month, was approved in 2009, and **Invega Trinza**, which lasts three months, was approved in 2015. Reimbursements for **Invega Sustenna** have exceeded \$2.6 million since 2012. Prescriptions for **Invega Trinza**, approved in 2015, can be expected to rise.

Long-acting injected antipsychotics may be an advantage in some noncompliant patients with schizophrenia, but they are also problematic because their effects cannot be reversed when adverse effects or pregnancy occur. Adverse effects, if they occur, will be maintained or may worsen over an extended time course.

Not every patient needs extended-release antipsychotics. Prescribers should be educated to prescribe generic **quetiapine** twice daily unless there is a compelling reason to use the once-daily or injected form. Prescribers should be educated on the benefits and risks of antipsychotics and appropriate and inappropriate use of extended-release forms.

Fixed-Dose Combinations

Several drugs are fixed-dose combination (FDC) drugs. FDCs include two or more active compounds, which can include branded drugs, generic drugs, over-the-counter drugs, or vitamins. A secondary patent can be obtained on fixed-dose combination drugs, and approvals of combination drugs have increased in the last two decades (Hao 2015).

Between 1980 and 2012, the FDA approved 28 FDCs that contained novel drugs, compared with 117 FDCs that were combinations of drugs already on the market. A change in formulation usually adds 3 years to a patent. It is clear that pharmaceutical companies begin marketing FDC drugs shortly before generic competition for a single drug occurs, thus extending patent and marketing exclusivity protection. Heavy marketing to shift demand from a single drug to an FDC drugs can cost both public and private payers money (Hao 2015).

FDC drugs included in this report include **Harvoni (ledipasvir/sofosbuvir)**, **Viekira Pak (ombitasvir/paritaprevir/ritonavir with dasabuvir)**, **Advair (fluticasone/salmeterol)**, **Janumet (sitagliptin/metformin)**, and **Symbicort (budesonide and formoterol)**

Fixed dose combinations are often more expensive than single drugs and result in decreased flexibility in terms of dosing for individual patients.

VI. Recommendations

Some high-cost drugs are the best drugs; others are not. Highly promoted drugs are often more likely to be prescribed, and highly promoted drugs are likely to be higher cost drugs. There are therapeutic, safety, and cost differences among treatments for various diseases that have financial and public health implications that could be explored in future *Impacts* reports.

Objective education is a cornerstone of rational prescribing. It is important that providers educate themselves through non-industry funded continuing education. DC already has a flagship program, the [DC Center for Rational Prescribing](#) (DCRx), which helps foster rational prescribing and should help reduce unnecessary costs. DCRx provides industry-free, evidence-based modules with free continuing education credit to DC physicians, nurses, physician assistants and pharmacists; providers outside of DC can access the modules for a nominal cost. People who do not need continuing education credit can access all modules without cost. Currently, DCRx has 12 web-based CME modules available on generic drugs, opioids, diabetes, PrEP, medical cannabis, pharmaceutical promotion, and other topics. Promoting DCRx to prescribers is important.

Prescribers should be encouraged to attend conferences that are not sponsored by the pharmaceutical industry to help ensure unbiased information. Prescribers should utilize non-industry sponsored educational materials, such as *Prescribe* (available in English), the *Medical Letter*, or *Pharmacist's Letter*.

Specific recommendations directed at prescribers are identified below. These initiatives will help to reduce cost and unnecessary prescribing in the District.

Specific Educational Efforts

1. Encourage prescribers to use generic and biosimilar products when available.
2. Encourage use of older drugs when there is no evidence of superiority for newer or more expensive drugs.
3. Raise prescriber awareness about drug costs. Encourage prescription of less-expensive drugs when drugs are therapeutically equivalent.
4. Enlist prescribers and pharmacists in choosing more cost-judicious drugs.
5. Educate prescribers about pharmaceutical marketing, patent-extension techniques, and problems associated with fixed-combination and extended-release preparations.
6. Educate prescribers about appropriate diagnosis and treatment of hepatitis C and about the benefits, harms, limitations, and unknowns regarding hepatitis C drugs.
7. Educate prescribers about appropriate use of insulin, oral hypoglycemics, and nonpharmacologic therapies.
8. Educate prescribers about appropriate, cost-judicious use of psychotropic drugs.

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