



APRIL 2016

## Express Scripts 2015 Drug Trend Report **Workers' Compensation**

THE EXPRESS SCRIPTS LAB™

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# Introduction

# 2015 HIGHLIGHTS

## OPIOIDS



-4.9%

Overall spend for opioids, the most expensive therapy class, was **down 4.9%** – the **fifth consecutive annual decrease**. The increased cost per prescription was offset by a decrease in utilization.

## ANTICONVULSANTS AND DERMATOLOGICALS

11.3%  11.7%

Trend was up significantly for both anticonvulsants at **11.3%** and dermatologicals at **11.7%** due to high cost per prescription.

## OVERALL TREND



2.2%

The **low trend of 2.2%** for Workers' Compensation reflects a decrease in utilization, offset by an increase in cost.

## HEPATITIS C



85.1%

Although ranked 11<sup>th</sup> in terms of spend, **the antiviral class increased significantly to 85.1%**, driven primarily by the cost and utilization increases related to specialty medications used to treat hepatitis C.

## COMPOUND MANAGEMENT



-33.7%

Between 2014 and 2015, Express Scripts compound management solutions have yielded a **33.7% decrease in trend**.

# Introduction

Over the past 30 years, Express Scripts researchers, clinicians and product innovators have worked together to leverage the ever-increasing body of data we've collected to understand what drives drug spend and promote evidence-based clinical care. We have used that expertise to gain insights that enable us to identify practical and effective pharmacy solutions for payers and injured workers. Our insights help payers navigate the complexities of state and federal regulations and make decisions about the pharmacy solutions that are both clinically appropriate and effective. Express Scripts currently manages Workers' Compensation prescriptions in all 50 states.

We understand and share payers' goals: to ensure injured workers receive medication needed for treatment of occupational injuries in the most cost-effective, expedient and safe manner to improve patient outcomes.

## What drove trend in 2015?

Overall drug trend for Express Scripts Workers' Compensation clients for 2015 was 2.2%, driven by a 2.6% decrease in utilization and a 4.4% increase in cost per prescription. Six of the top 10 conditions ranked by spend had a negative trend, including compounded medications, which decreased by 33.7%. The impact of new medications on payers' costs was minimal in 2015, as only a few medications with significant costs were brought to market in late 2014 and 2015. Harvoni® (ledipasvir/sofosbuvir), a specialty antiviral medication used to treat hepatitis C, was one of these few high-cost medications, but low use of these medications among injured workers minimized the effect on trend.

Overall drug trend for Express Scripts Workers' Compensation clients for 2015 was **2.2%**, driven by a **2.6% decrease** in utilization and a **4.4% increase** in cost per prescription.

# Opioid medication use

## Challenge

Workers' compensation formularies are developed with clinical appropriateness and association with workplace injuries in mind – injuries that are often accompanied by acute or chronic pain. Defined by the National Institutes of Health as pain lasting more than 12 weeks,<sup>1</sup> chronic pain is estimated to lead to at least \$60 billion in lost productivity annually.<sup>2</sup> When taken as prescribed, opioids (narcotic medications) are effective for managing acute pain following an injury, but there is limited evidence for their effectiveness in chronic noncancer pain. Continued use beyond the acute phase involves both balancing analgesia with risks, and determining whether they are contributing to a clinically meaningful improvement in patient function.

Misuse of prescription medications is a growing problem in the United States. In October 2015, President Barack Obama weighed in on the opioid epidemic, indicating that medication-assisted treatment must be expanded. Injured workers who are treated for pain may develop a dependency on the medications used to treat their injuries, thereby increasing the risk of substance abuse. This is not necessarily due to the underlying pain but because of the reinforcing effects of opioids (e.g., reduced anxiety, and increased feelings of pleasure, boredom and aggression).<sup>3</sup> A study from the National Institute on Drug Abuse reported that approximately 6,600 people newly abused prescription drugs each day in 2010.<sup>4</sup> Individuals who abuse pain medications use more healthcare resources than nonabusers. Guidelines from the American Academy of Neurology suggest that the benefits of prescription opioids in chronic, noncancer conditions, such as headache, fibromyalgia and chronic low-back pain, are outweighed by the risk of death, overdose, addiction or serious side effects.<sup>5</sup> Furthermore, continued opioid use has been associated with poorer outcomes,<sup>6</sup> longer disability<sup>7,8</sup> and higher medical costs<sup>9</sup> among injured workers.<sup>10</sup>

Clear functional improvement and patient engagement in pain-management goals are important considerations in a prescriber's treatment of an injured worker. For prescribers, treating pain is a delicate balance. Undertreating leaves the

patient in pain, yet treatment with opioids may lead to addiction. Although there are several options for treating noncancer-related pain (e.g., nonpharmacologic therapies, oral medications, injections or surgery), oral opioid analgesics are the most widely used.

## Research and clinical

Health officials nationwide have been calling for increases in healthcare, support programs and other care for opioid-drug abusers. Insurance providers can play a role. Recent concerns have emerged around overprescribing controlled narcotic medications, specifically Schedule II and III narcotic pain medications. Innovative tools developed by our Workers' Compensation product and clinical experts, in particular, can address opioid abuse early – before patients progress to misuse.

Express Scripts uses powerful data analysis and reporting resources, including consultative tools and predictive analytics, like the morphine equivalent dose (MED) point-of-sale program, physician outreach programs and patient narcotic education. These resources allow us to flag situations that could indicate abuse or misuse, whether in the actions of physicians, pharmacies or patients. Our Fraud, Waste & Abuse solutions help us identify clinicians who are prescribing many more opioids than their practices would warrant, “pill mill” pharmacies that are filling them and patients who may be seeking drugs by visiting multiple prescribers and pharmacies across a larger-than-expected geographical area.

When we find an outlier – a prescriber, pharmacy or patient behaving in ways we would not expect and that could indicate opioid-drug abuse or misuse – we flag the case for our clients, so they can take appropriate action and determine the most effective intervention. Clients may choose solutions such as implementing patient or prescriber outreach, limiting a patient's opioid prescriptions to a single provider and/or pharmacy, or referring the patient for counseling or more-intensive treatment. Stopping the problem is important. Preventing it from occurring is an even more powerful opportunity. Intervening early in therapy by using cutting-edge predictive analytics is the ideal method for identifying patterns of misuse as early as the initial prescription fill.



# Compounded medication use

## Challenge

A compounded prescription is one that is not available commercially in the strength, dosage form or exact combination needed by the patient. Compounding requires the dispensing pharmacist to mix two or more products with unique National Drug Codes (NDCs) into a final drug product, based on the specific needs of an individual patient. One example is blending a drug that is only commercially formulated as tablets with a syrup base to make a liquid medication for a patient who has trouble swallowing pills.

Each compound is made individually after the prescription has been received at the pharmacy. For workers' compensation patients, many compounded prescriptions consist of pain medications that are incorporated into an ointment or cream base for topical application. Often these compounds contain ingredients that are available in similar doses in a commercially available product. Although many of these compounds contain multiple drugs, there is little evidence in the literature to support their use instead of a commercially available product. And, because of the pharmacist's time, effort and expertise, as well as the choice of the ingredients and compounding base, the associated costs are often much higher for a compounded product than for a commercially available product.

Compounded medications are not considered first line in the Official Disability Guidelines (ODG) for treating occupational injuries,<sup>11</sup> and thus it is important to understand whether there is clear rationale for prescribing, such as to a patient who can't swallow pills, has a drug allergy or has tried over-the-counter or commercially available therapies without success. The issues of safety and high cost associated with compounded medications are concerns for payers.

## Research and clinical

Although Express Scripts research indicates that compounds represent less than 1% of prescription medications dispensed for injured workers, compounded medications continue to remain in the top 10 therapy classes ranked by per-user-per-year (PUPY) cost. An Express Scripts research study published in *The American Journal of Managed Care* found alarming price increases for compounded medications between 2012 and 2013. However, the 2014-2015 negative trend reflects our effective compound strategies. Prior to simply combining drugs that are effective orally for pain in a compound, it is important to know if each of these medications is efficacious topically for a specific condition for a specific patient.

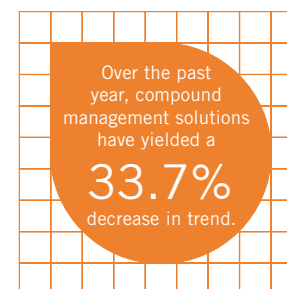
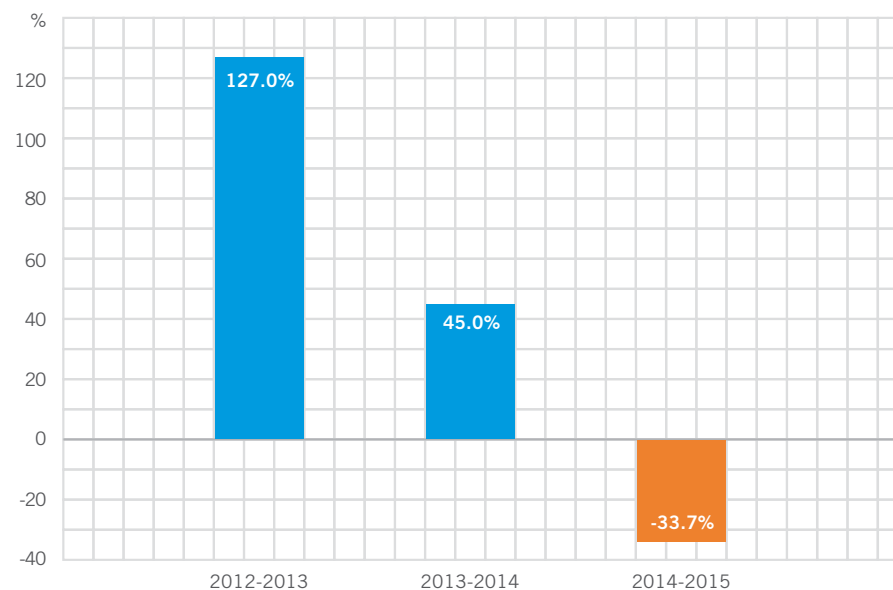


Exhibit 1 illustrates the year-over-year trend rate between 2012 and 2015. As shown, the effect of compounded medications to payer spend is slowing. Compounded medications are not considered first line by workers' compensation treatment guidelines, such as ODG and others, and thus are not on Express Scripts Workers' Compensation formularies. Approval is required prior to filling compounded medications at the pharmacy. This requirement for approval allows the payer to make a decision at the time the prescription is presented. Additional physician and patient outreach communications are available on compounded medications to bring awareness of the associated risks and ensure that they are clinically necessary. Over the last year, Express Scripts compound management solutions have yielded a 33.7% decrease in trend. It is clear that by managing compounded medications, payers can reduce unnecessary costs and waste associated with more than 1,000 clinically unproven ingredients.

In most cases, the practice of pharmacy compounding is regulated by the Board of Pharmacy in the licensure state(s). Traditionally, the state boards have recognized the right to compound by a pharmacist (or physician, depending on the state) for a specific patient upon a prescription from the prescriber who has a relationship with the patient. Following the New England Compounding Center (NECC) outbreak of fungal infections in 2012 and 2013, there has been increased scrutiny by the U.S. Food and Drug Administration (FDA) and state Boards of Pharmacy concerning pharmacy compounding practices. The NECC tragedy was described in a CompPharma white paper<sup>12</sup> on compounding. From a compounding-practice-standard perspective, professional obligations for sterile<sup>13</sup> and nonsterile<sup>14</sup> compounding are outlined in official compendia and include guidance related to the compounder's responsibilities, facilities, equipment, handling of materials, documentation and training of personnel.

#### EXHIBIT 1: PUPY YEAR-OVER-YEAR TREND FOR COMPOUNDED MEDICATIONS

2012-2015





# Physician dispensing

## Challenge

**P**ayers may incur additional costs when medical providers dispense drugs, including injectable and topical medications, directly to injured workers. Although this practice may provide convenience to the injured worker, it has safety risks. Medications dispensed from a physician's office are not subject to the same vital oversight as medications dispensed by a pharmacist in a pharmacy, because point-of-sale safety and drug-utilization review (DUR) edits are bypassed. Using insights gained through our behavioral science research and state policies regulating physician dispensing, Express Scripts developed a solution that can help reduce the impact of physician-dispensed medications. We process physician-dispensed medications against all formularies, prescription history information and state regulations, such as use of originating NDCs when applicable. In addition, when an injured worker receives medications directly from a prescriber, Express Scripts sends the injured worker a letter explaining the safety concerns and highlighting how choosing an in-network pharmacy can help cut down on waste.

## Research and clinical

According to our data, the average cost of a physician-dispensed medication in 2015 was \$166.35, compared to \$105.33 for similar pharmacy-dispensed medications. In the case of omeprazole, the average cost for physician-dispensed medications was \$232.43, compared to \$110.07 for pharmacy-dispensed medication (a difference of \$122.36). Exhibit 2 indicates the top 10 physician-dispensed medications by market share for Express Scripts Workers' Compensation clients. All but one of these medications – which account for nearly half of all physician-dispensed medications – are for pain, inflammation or muscle spasms. And all but one are generic medications that are available through pharmacies.

### EXHIBIT 2: TOP 10 PHYSICIAN-DISPENSED MEDICATIONS BY MARKET SHARE FOR EXPRESS SCRIPTS WORKERS' COMPENSATION CLIENTS

RANKED BY 2015 PERCENTAGE

MEDICATION	CONDITION	PERCENTAGE OF PHYSICIAN-DISPENSED MEDICATION PRESCRIPTIONS
meloxicam	Pain/inflammation	11.2%
nabumetone	Pain/inflammation	10.2%
Māpap® (acetaminophen)	Pain	9.3%
cyclobenzaprine	Muscle spasm	7.3%
tramadol	Pain	4.2%
omeprazole	Heartburn/ulcer disease	3.3%
orphenadrine	Muscle spasm	3.3%
etodolac extended release	Pain/inflammation	2.6%
tramadol extended release	Pain	2.5%
gabapentin	Pain	2.4%

Payers spend **58% more** for physician-dispensed medications than for pharmacy-dispensed medications.

# Network penetration and third-party billers

## Challenge

**M**anaging “out-of-network” bills is an issue all workers’ compensation payers face. Paper bills resulting from prescriptions filled at nonparticipating pharmacies, as well as those processed by third-party billers, cause additional administrative headaches and raise drug costs.

Express Scripts helps mitigate the impact of paper bills through our Paper Bill Conversion program, which saves money for clients by paying the pharmacies or billers on our clients’ behalf. It also provides outreach, when applicable, to ensure that future prescriptions are processed online directly by Express Scripts. The program ensures that all prescriptions, whether submitted electronically or on paper, receive the formulary and DUR safety edits (i.e., for overdosing, adverse drug interactions and other potential drug-related problems) that would have been in place at the point of sale.

## Research and clinical

Third-party billers accounted for 4.7% of all medications processed by Express Scripts for injured workers in 2015. Of all the medications processed through third-party billers, the top five medications account for 40.5% (see Exhibit 3). Hydrocodone/acetaminophen was the medication most frequently processed through a third-party biller. The clinical and societal concerns over the use of such opioid medications further highlight the need to ensure they go through clinical checks and balances, like examination of the cumulative morphine equivalent dose (MED) across all opioid prescriptions for an individual patient.

### EXHIBIT 3: TOP FIVE MEDICATIONS PROCESSED THROUGH THIRD-PARTY BILLERS

RANKED BY 2015 PERCENTAGE

MEDICATION	THERAPY CLASS	PERCENTAGE OF PRESCRIPTIONS PROCESSED BY THIRD-PARTY BILLERS
hydrocodone/acetaminophen	Pain	12.1%
ibuprofen	Pain/inflammation	8.3%
cyclobenzaprine	Muscle spasm	8.2%
tramadol	Pain	6.5%
meloxicam	Pain/inflammation	5.4%
<b>ALL OTHERS</b>		<b>59.5%</b>

**Only 4.7%** of all medications are processed through third-party billers.

# Suboptimal channel use

## Challenge

**W**orkers' compensation prescription-drug costs continue to increase, putting added pressure on carriers and employers in an already difficult economic climate. A major but avoidable factor leading to the increase in pharmacy costs is waste. Defined as the extra amount spent with no incremental gain in health outcomes, waste results when a more expensive medication is dispensed through a more expensive channel than necessary. Waste can be partially attributed to behavior – the active and passive decisions about the pharmacy benefit and medications made by injured workers and prescribers.

The Express Scripts Pharmacy<sup>SM</sup> provides the convenience of home delivery service for injured workers taking long-term medications related to their injuries. The pharmacy leverages state-of-the-art technology that includes multiple checkpoints and sophisticated automation, allowing the dispensing pharmacist to review all medications an injured worker is taking and to avoid dispensing errors.

## Research and clinical

Overall drug trend reflecting cost and utilization of the top 10 medications filled through home delivery shows that they accounted for 25.8% of all home delivery medications. Although several of these medications are not often associated with injuries to workers, some clients (typically municipalities) may design custom formularies that cover conditions such as high blood pressure or high blood cholesterol, due to the nature of the work performed by their employees.

### EXHIBIT 4: TOP 10 MEDICATIONS FILLED THROUGH HOME DELIVERY BY INJURED WORKERS

RANKED BY 2015 PERCENTAGE

MEDICATION	THERAPY CLASS	PERCENTAGE OF PRESCRIPTIONS FILLED THROUGH HOME DELIVERY
gabapentin	Anticonvulsants	5.1%
celecoxib	NSAIDs	3.5%
atorvastatin	High blood cholesterol drugs	3.2%
duloxetine	Antidepressants	2.2%
ibuprofen	NSAIDs	2.2%
meloxicam	NSAIDs	2.1%
cyclobenzaprine	Muscle relaxants	2.0%
lisinopril	High blood pressure/heart disease drugs	1.9%
amlodipine	High blood pressure/heart disease drugs	1.8%
Toprol-XL® (metoprolol succinate)	High blood pressure/heart disease drugs	1.8%
<b>TOP 10 TOTAL</b>		<b>25.8%</b>
<b>ALL OTHER HOME DELIVERY</b>		<b>74.2%</b>

# Therapeutic mix (brand and generic)

## Challenge

Using expensive brand-name prescriptions creates waste when equally effective, lower-cost equivalents are available. There are many reasons why a prescriber might choose branded medications over generic alternatives: because of habit, because of a lack of awareness of new generics or because the necessary dosage is available only as a branded product. Also, injured workers can increase costs by requesting brand-name medications instead of generic equivalents. Unintentionally, drug-mix waste can also be created by workers' compensation payers when they try to limit potential disruption by allowing injured workers to continue expensive prescriptions rather than attempting to move them to more-cost-effective options.

## Research and clinical

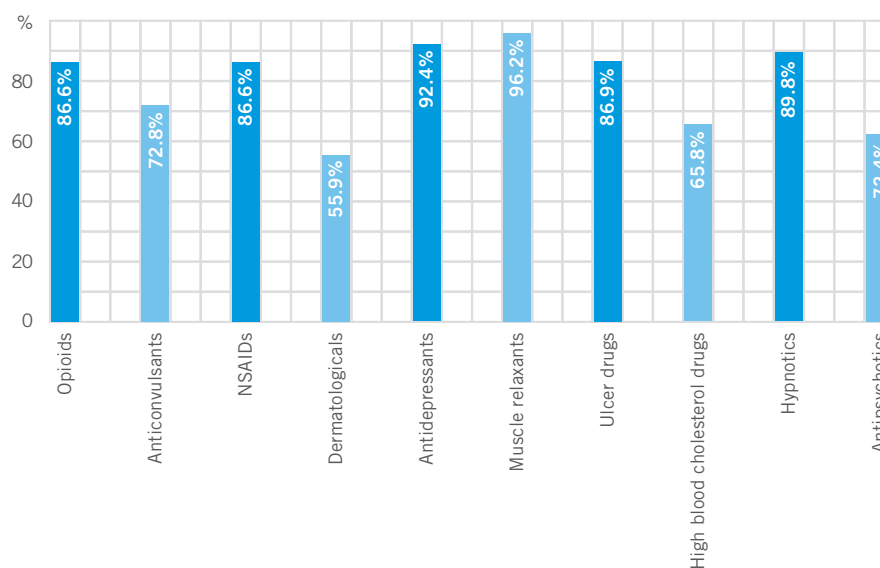
Our exclusive Prescription Price Index reveals that brand price inflation nearly doubled between 2011 and 2015, with the greatest impact seen in more-recent years. Compared to the prices of brand drugs a year earlier, in 2015 brand prices were 16.2% higher. Between 2008 and 2015, brand medications increased in price by 164.3%.

Although the price increases for several generic medications are cause for concern, on the whole, generic prices continue to decline and deliver significant cost savings to payers and patients. Between 2014 and 2015, the price of generic products, on average, decreased 19.9%. While news reports focus on a few outliers, payers should remain confident that use of generics in place of more-expensive brand alternatives, when clinically appropriate, keeps costs down.

The gap between brand inflation and generic deflation increased by 0.6 of a percentage point, to 36.1%, between December 2014 and December 2015. From the base price of \$100.00 set in January 2008, in December 2015 prices for the most commonly used generic medications decreased to \$29.73 (in 2008

**EXHIBIT 5: GENERIC FILL RATES FOR LEADING WORKERS' COMPENSATION THERAPY CLASSES**

2015



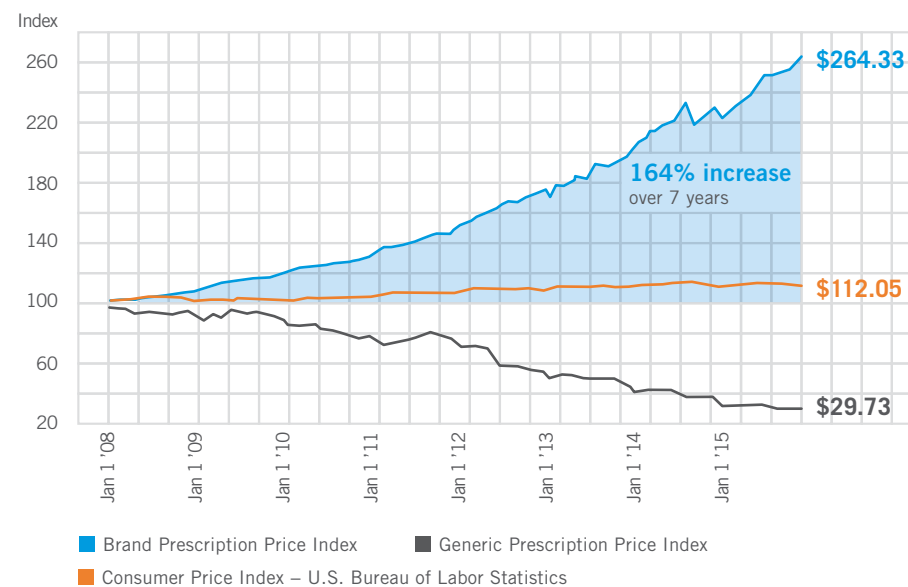
On average, the price of generics **decreased by 19.9%.**

dollars), and prices for the most commonly used brand medications increased to \$264.33 (in 2008 dollars). In contrast, a market basket of commonly used household goods costing \$100.00 in 2008 – as measured by the Bureau of Labor Statistics consumer price index – grew to only \$112.05 (in 2008 dollars) by December 2015.

*Brand price inflation nearly doubled between 2011 and 2015, with the greatest impact seen in more-recent years. On the whole, generic prices continue to decline and deliver significant cost savings to payers and patients.*

## EXHIBIT 6: GAP BETWEEN BRAND INFLATION AND GENERIC DEFLATION

2008-2015



# Specialty medications

**S**pecialty medications, which usually treat relatively small groups of patients with complex, chronic conditions, are typically expensive and they may have special handling requirements. In addition, patients taking specialty medications may need ongoing clinical monitoring and more-intensive assistance from pharmacists or other caregivers. Specialty pharmacies are the optimal dispensing channel for specialty drugs. They offer many services not available at retail pharmacies, including on-staff nurses and pharmacists who are experts in specialty conditions and the treatment of specialty patients. They offer educational resources and patient training on side effects and self-administration of drugs that may not be offered at the counter in a retail pharmacy. Accredo, the Express Scripts specialty pharmacy, which offers some of the most advanced patient services in the industry, has a track record of improving patient adherence and optimizing patient health outcomes.

Although specialty medications represent less than 1% of all medications used by injured workers, their costs have the potential to impact payers significantly. Many occupations have specific risks, such as contracting diseases like HIV and hepatitis C from blood-borne pathogens, resulting from needlesticks or other exposures (healthcare providers and first responders); black lung disease (coal miners); and Lyme disease (outdoor workers/landscapers or park employees). Additionally, some consequential conditions, including postoperative blood clots, osteoarthritis knee pain and even organ failure, are treated with specialty medications.

A closer look at specialty medications for three conditions shows the potential impact of this class on injured workers and payers.

## Hepatitis C

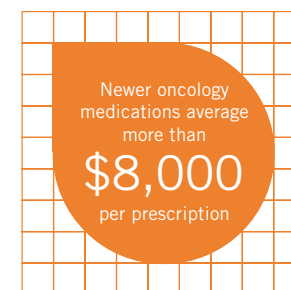
In 2015, Harvoni, an antiviral used to treat hepatitis C, ranked first in the top 10 most expensive medications used by injured workers (see Exhibit 7). Marketplace competition – ignited by Express Scripts – made new hepatitis C therapies more affordable across the U.S. This action made treatment accessible to all patients, not just the sickest. New competitors in this space will continue to bring down prices.

## High blood cholesterol

Although not significant in the workers' compensation population in 2015, Repatha® (evolocumab) and Praluent® (alirocumab) – new cholesterol-lowering drugs known as PCSK9 inhibitors – entered the market in the second half of 2015. These self-injectable medications block a protein that interferes with the liver's ability to clear LDL (“bad”) cholesterol from the bloodstream. They are appropriate for only a small number of patients dealing with very specific, rare forms of high cholesterol that are unresponsive to available statin therapies. The challenge, of course, is that these drugs are priced at more than \$14,000 per year – far greater than the cost for statins. Although the clinical trials for Praluent and Repatha have been successful in getting these drugs approved for lowering LDL cholesterol, little has been proven about their long-term effects of preventing heart attack and stroke – the main reason people are treated for high cholesterol. For both patient safety and payer affordability, it is important to ensure this class of drugs is appropriately managed.

## Cancer

Cancer medications are not usually on workers' compensation formularies, because cancer is not typically considered a work-related condition; consequently those medications require prior authorization. The last decade ushered in an unprecedented number of FDA approvals for oncology medications, including 19 in 2015 alone. These new medications offer oncologists and patients more treatment options and can add months or years of life. They can have positive impacts on patient care but come with hefty price tags – averaging more than \$8,000 per prescription. One of the drugs seen in the Express Scripts Top 10 specialty medications for Workers' Compensation is Gleevec® (imatinib) (see Exhibit 7). Gleevec lost patent protection in February 2016, and generics launched soon after. Although only one generic manufacturer has 180-day exclusivity, generics from multiple manufacturers are expected to be released



in late summer. Express Scripts is directed by payers to cover some oncology medications in rare situations, but drugs like Gleevec would require prior approval to dispensing or payment.

The trend for oncology medications in 2015 was more than 95%, due to growth in utilization (1.9%) and cost (53.6%) of existing products. New drugs accounted for 39.0% of trend. Cancer medication costs continue to represent a significant challenge.

*Specialty accounts for 5.2% of total pharmacy costs and is expected to increase. There are more than 7,000 potential drugs in development, with most aimed at treating categories of oncology and neurologic disorders.*

## Trends

Specialty medications have the potential to increase drug spend significantly because their costs are rising rapidly. Between 2014 and 2015, spend on specialty medications increased 49.5%. New specialty medications offer clinical options for the treatment of occupational injuries and the hope of improved medical outcomes. However, the cost pressures they present prove challenging to payers in the management of these medications.

Eight of the top 10 specialty medications by PUPY spend had at least double-digit increases between 2014 and 2015, and two of those had a triple-digit increase. Only two of the top 10 medications – enoxaparin sodium and Sovaldi® (sofosbuvir) – had decreases in trend. As expected, Harvoni was the top-ranked medication by PUPY spend, reflecting the roughly \$84,000 cost per treatment regimen.

The 49.5% trend for specialty medications was driven by an increase in both the average cost per prescription (38.4%) and utilization (8.1%). In 2015 the average cost per prescription for a specialty medication was \$1,799.02, nearly 10 times that of a typical traditional medication.

### EXHIBIT 7: COMPONENTS AND DRIVERS OF TREND FOR THE TOP 10 WORKERS' COMPENSATION SPECIALTY MEDICATIONS

RANKED BY 2015 PUPY SPEND

MEDICATION	THERAPY CLASS	2015		TREND		
		PUPY SPEND	COST/Rx	TOTAL	UTILIZATION	COST/Rx
Harvoni® (ledipasvir/sofosbuvir)	Antivirals (hepatitis C)	\$16.52	\$31,765.84	6,219.2%	6,142.7%	1.2%
enoxaparin sodium	Anticoagulants	\$4.64	\$714.49	-6.4%	-6.9%	0.5%
Enbrel® (etanercept)	Anti-inflammatories	\$4.33	\$3,324.44	31.4%	9.0%	20.6%
Truvada® (emtricitabine/tenofovir)	Antivirals (HIV)	\$3.60	\$813.89	15.7%	18.2%	-2.2%
Synvisc-One® (hylan G-F 20)	Anti-inflammatories	\$3.52	\$1,098.84	22.7%	21.0%	1.4%
Sovaldi® (sofosbuvir)	Antivirals (hepatitis C)	\$3.19	\$28,185.82	-37.7%	-46.8%	17.2%
Gleevec® (imatinib)	Oncology drugs	\$2.70	\$11,723.43	39.6%	-14.8%	63.9%
Isentress® (raltegravir)	Antivirals (HIV)	\$2.62	\$707.93	19.2%	19.9%	-0.5%
Orenitram® ER (treprostinil)	Pulmonary hypertension drugs	\$1.89	\$11,294.58	312.3%	473.9%	-28.2%
Xolair® (omalizumab)	Asthma and allergy drugs	\$1.71	\$3,499.09	14.4%	2.0%	12.2%

# New drugs

In 2015, new drugs accounted for only 0.5% of the total PUPY spend. Exhibit 8 presents the top five new medications ranked by PUPY spend in 2015. These products are not typically on our Workers' Compensation formularies unless specifically requested by a client. In 2015 the FDA approved more than 50 drugs. Exhibit 9 is a subset list relevant to Workers' Compensation payers.

It is important to note that Movantik® (naloxegol), approved for opioid-induced constipation, is considerably more expensive than other therapies, including over-the-counter medications, for the condition. Many patients respond to these more-traditional therapies, and because this medication requires approval before filling, payers continue to review its medical necessity.

## EXHIBIT 8: TOP FIVE NEW MEDICATIONS IN EXPRESS SCRIPTS WORKERS' COMPENSATION

RANKED BY 2015 PUPY SPEND

MEDICATION	THERAPY CLASS	PUPY SPEND	COST/Rx
Advate™ (antihemophilic factor [recombinant])	Hemophilia drugs	\$1.31	\$56,328.54
Embeda® (morphine/naltrexone)	Pain drugs	\$1.31	\$639.50
Movantik® (naloxegol)	GI conditions/constipation drugs	\$0.94	\$268.80
Viekira Pak® (ombitasvir/paritaprevir/ritonavir; dasabuvir)	Antivirals (hepatitis C) drugs	\$0.39	\$27,829.90
BeneFix™ (coagulation factor IX [recombinant])	Hemophilia drugs	\$0.34	\$72,487.84

## EXHIBIT 9: 2015 BRAND APPROVALS

APPROVAL DATE	BRAND (GENERIC) NAME	PRIMARY INDICATION	PRODUCT UNIQUENESS
Nov. 18, 2015	Narcan™ (naloxone) Nasal Spray	Opioid overdose	Existing product with new dosing form
Nov. 4, 2015	Nucala® (mepolizumab)	Asthma	New mechanism of action
Oct. 23, 2015	Belbuca™ (buprenorphine) buccal film	Pain	Existing product with new dosing form
Oct. 22, 2015	Vivlodex™ (meloxicam) capsules	Osteoarthritis	Existing product with new dosing form
Oct. 2, 2015	MorphaBond™ (morphine) extended-release tablets	Pain	Existing product with new dosing form
Aug. 27, 2015	Repatha™ (evolocumab)	Familial hypercholesterolemia	Similar to existing products
July 24, 2015	Praluent® (alirocumab)	Familial hypercholesterolemia	New mechanism of action
July 24, 2015	Technivie® (ombitasvir/paritaprevir/ritonavir)	Hepatitis C	New combination of existing products
July 24, 2015	Daklinza™ (daclatasvir)	Hepatitis C	New mechanism of action
Jan. 30, 2015	Zohydro® ER (hydrocodone) with abuse deterrents	Pain	Refinement of an existing product



## Highlights

- Narcan® Nasal Spray, the first noninjectable form of naloxone, was approved by the FDA in November 2015. To treat opioid overdoses in emergency situations, the first spray (4mg) should be administered immediately. One spray is given every two to three minutes until the patient recovers consciousness or emergency medical help arrives. Narcan Nasal Spray can be used for both adults and children. It now is available at retail pharmacies across the United States; in some states, a prescription will not be required.
- FDA approved Nucala® (mepolizumab) injection for use as an add-on maintenance treatment for severe eosinophilic asthma.
- In the summer of 2015, two specialty drugs were approved for specific types of hard-to-treat high cholesterol. Praluent and Repatha are the first in a new class of inhibitors – called proprotein convertase subtilisin/kexin type 9, or PCSK9, inhibitors. Praluent was approved to be used once every two weeks for treating patients with heterozygous familial hypercholesterolemia (HeFH) and patients with clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). Repatha is indicated once or twice a month for the same two conditions and also for homozygous familial hypercholesterolemia (HoFH). Both drugs are available in self-injectors, and each is used in tandem with dietary and statin therapies. About 11 million Americans have one of the three indicated conditions, but the use of PCSK9 inhibitors may expand if results from ongoing clinical trials show they reduce heart disease risks.

## Regulatory landscape

**A**cross the United States, 2015 was a busy year of regulatory activity. From Alaska to Florida, state policymakers were proposing legislation and modifying regulations for the workers' compensation industry. Following are some highlights of state and federal pharmacy-related legislation reviewed by the Express Scripts compliance team.

### Formularies

Drug formularies are an important component of pharmacy benefit management strategy for controlling costs in workers' compensation cases. In 2011, Texas implemented a closed formulary which yielded savings and helped control drug costs since implementation. Many other states have adopted or are considering new formularies for workers' compensation. In recent years, these states have proposed legislation and regulations focused on drug formularies and treatment guidelines: Arkansas, California, Delaware, Louisiana, Maine, Montana, Nebraska, Nevada, North Carolina, Ohio, Oklahoma, South Carolina, Tennessee and Texas.

### Pain management

At the federal level, President Obama released a \$1.1 billion initiative in early 2016 to combat opioid misuse and abuse. The topic is nothing new in the workers' compensation industry. Pain medications continue to be among the most costly and most prescribed medications for injured workers. As such, states have continued to consider regulations and policy to further tackle this issue.

### Physician-dispensed medications and compounds

In addition to the fee schedules setting the maximum allowable reimbursements for physician-dispensed and compounded medications, some states have begun to limit what can be dispensed. For example, Kansas requires prior approval for all compounds and physician-dispensed medications, while others have limitations on dispensing based on class of drugs and days' supply.

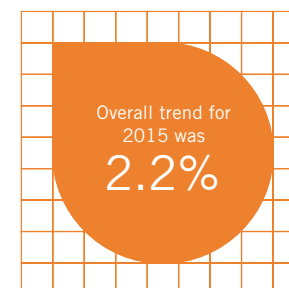


# Trend analysis

# Trend analysis



Overall trend for 2015 was 2.2%, reflecting a 4.4% increase in the average cost per prescription and a 2.6% decrease in PUPY utilization. The top 10 therapy classes accounted for 77.2% of total Workers' Compensation drug spending in 2015. On average, payers spent \$1,590.99 per injured worker for prescription medications in 2015 (see Exhibit 10).



Increases in the average cost per prescription had a significant impact on trend, with substantial increases in dermatologicals (15.8%) and muscle relaxants (10.1%). Less-dramatic increases occurred in the classes of antidepressants and ulcer medications. The cost per prescription for compounded medications was also up by 6.6%, but much less than the 35% increase seen in 2014.

Utilization had a significant moderating impact on trend. The utilization of compounded medications, for example, dropped significantly (38.8%) from 2014 to 2015, while opioids had a 10.9% decrease in utilization. In fact, the only classes in the top 10 that increased in utilization were high blood cholesterol inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticonvulsant medications used for pain and inflammation.

OxyContin® (oxycodone) extended release had the highest PUPY cost, accounting for 6.2% of total Workers' Compensation drug spend (see Exhibit 11). Even though opioids had a 10.9% decrease in utilization, they accounted for 40.1% of the 25 most commonly dispensed medications in 2015.

Lyrica® (pregabalin) and gabapentin, the generic for Neurontin®, are two of the most highly utilized anticonvulsants, typically used for neuropathic pain. Utilization decreased for Lyrica (3.2%), but increased for gabapentin (7.5%). The cost per prescription for Lyrica increased 18.1%, while that for generic gabapentin was essentially flat, resulting in savings for payers.

The utilization of compounded medications dropped significantly (**38.8%**) from 2014 to 2015, while opioids had a **10.9% decrease** in utilization.

The generic for Celebrex®, celecoxib, an NSAID used to treat pain and inflammation, was approved in May of 2014, but the full effect of the generic shift was not seen until 2015. Generic celecoxib is ranked fourth of the top 25 of Workers' Compensation medications according to PUPY spend (see Exhibit 11), with a dramatic increase in utilization and an increase in average cost per prescription of 4.8%. Similarly, the average cost per prescription for brand Celebrex increased 17.1%, but the increase was more than offset by a 91.6% drop in utilization, resulting in a total trend of -90.2% for the brand medication in 2015.

Compounded topical gabapentin (number nine on the top 25 list) decreased in PUPY spend, with overall trend of -15.3%. Although likely prescribed off-label for pain management, the effectiveness of topical gabapentin is questionable. Pain-management guidelines do not consider compounded drugs to be first-line therapy.

In 2015, Harvoni, an antiviral approved for hepatitis C, is in the top 25 for the first time. Discussed in more detail in the section on specialty medications, it warrants further mention due to the significant increase in its utilization. Although not commonly associated with workplace injuries, hepatitis C is relevant to clients with a large population of healthcare workers or first responders at risk for contracting hepatitis C following an occupational exposure.

#### EXHIBIT 10: COMPONENTS AND DRIVERS OF TREND FOR THE TOP 10 WORKERS' COMPENSATION THERAPY CLASSES

RANKED BY 2015 PUPY COST

THERAPY CLASS	COST/Rx		UTILIZATION		NEW DRUGS		OVERALL	
	AVERAGE	TREND	PUPY	TREND	PUPY COST	TREND	PUPY COST	TREND
Opioids	\$154.66	6.4%	2.91	-10.9%	\$1.27	0.27%	\$450.90	-4.9%
Anticonvulsants	\$170.21	8.1%	1.00	3.0%	\$0.00	0.00%	\$170.51	11.3%
NSAIDs	\$102.01	-10.1%	1.38	1.4%	\$0.15	0.10%	\$141.41	-8.7%
Dermatologicals	\$288.42	15.8%	0.39	-3.8%	\$0.34	0.34%	\$112.99	11.7%
Antidepressants	\$120.83	0.3%	0.81	-3.3%	\$0.00	0.00%	\$98.23	-3.0%
Muscle relaxants	\$88.24	10.1%	0.97	-5.6%	\$0.00	0.00%	\$86.01	3.9%
Ulcer drugs	\$129.95	0.2%	0.40	-2.5%	\$0.00	0.00%	\$51.65	-2.3%
High blood cholesterol drugs	\$135.64	6.2%	0.36	16.9%	\$0.03	0.09%	\$48.32	24.2%
Compounded medications	\$1,769.45	8.2%	0.02	-38.8%	\$0.04	0.08%	\$37.08	-33.7%
Antipsychotics	\$443.20	-1.2%	0.07	-4.9%	\$0.14	0.42%	\$32.20	-5.7%
<b>TOP 10 THERAPY CLASSES</b>	<b>\$147.53</b>	<b>2.8%</b>	<b>8.31</b>	<b>-4.4%</b>	<b>\$1.97</b>	<b>0.2%</b>	<b>\$1,229.30</b>	<b>-1.6%</b>
<b>OTHER THERAPY CLASSES</b>	<b>\$118.72</b>	<b>12.3%</b>	<b>3.00</b>	<b>3.0%</b>	<b>\$5.70</b>	<b>1.9%</b>	<b>\$361.69</b>	<b>17.5%</b>
<b>TOTAL</b>	<b>\$139.90</b>	<b>4.4%</b>	<b>11.31</b>	<b>-2.6%</b>	<b>\$7.67</b>	<b>0.5%</b>	<b>\$1,590.99</b>	<b>2.2%</b>

## EXHIBIT 11: TREND COMPONENTS FOR THE TOP 25 WORKERS' COMPENSATION MEDICATIONS

RANKED BY 2015 PUPY SPEND

RANK	MEDICATION	THERAPY CLASS	2015 PUPY SPEND	% OF TOTAL SPEND	PUPY SPEND CHANGE FROM 2014	TREND		
						COST/Rx	UTILIZATION	TOTAL
1	OxyContin® (oxycodone) extended release	Opioids	\$98.39	6.2%	-\$19.65	-1.7%	-15.2%	-16.6%
2	Lyrica® (pregabalin)	Anticonvulsants	\$93.82	5.9%	\$11.76	18.1%	-3.2%	14.3%
3	lidocaine	Dermatologicals	\$50.13	3.2%	\$2.96	7.5%	-1.2%	6.3%
4	celecoxib	NSAIDs	\$47.50	3.0%	\$46.78	4.8%	6168.3%	6,468.5%
5	duloxetine	Antidepressants	\$46.71	2.9%	-\$2.36	-5.6%	0.8%	-4.8%
6	hydrocodone/acetaminophen	Opioids	\$46.58	2.9%	-\$6.55	10.0%	-20.3%	-12.3%
7	gabapentin	Anticonvulsants	\$41.89	2.6%	\$3.00	0.2%	7.5%	7.7%
8	oxycodone/acetaminophen	Opioids	\$36.74	2.3%	\$0.22	-3.4%	4.2%	0.6%
9	gabapentin	Compounded medications	\$22.97	1.4%	-\$4.16	31.7%	-35.7%	-15.3%
10	fentanyl	Opioids	\$22.68	1.4%	-\$2.76	-2.6%	-8.5%	-10.8%
11	Percocet® (oxycodone/acetaminophen)	Opioids	\$21.16	1.3%	\$1.91	16.0%	-5.2%	9.9%
12	oxycodone	Opioids	\$20.27	1.3%	-\$2.05	-10.9%	1.9%	-9.2%
13	morphine ER	Opioids	\$19.09	1.2%	-\$3.71	-10.4%	-6.6%	-16.3%
14	Opana® ER (oxymorphone) extended release	Opioids	\$16.79	1.1%	-\$2.61	5.1%	-17.7%	-13.5%
15	Harvoni® (ledipasvir/sofosbuvir)	Antivirals (hepatitis C)	\$16.52	1.0%	\$16.26	1.2%	6142.7%	6,219.2%
16	Nucynta® ER (tapentadol) extended release	Opioids	\$15.64	1.0%	\$2.78	35.3%	-10.1%	21.6%
17	metaxalone	Muscle relaxants	\$15.33	1.0%	-\$0.89	3.3%	-8.6%	-5.5%
18	omeprazole	Ulcer drugs	\$15.03	0.9%	-\$1.04	-2.5%	-4.1%	-6.5%
19	Flector® (diclofenac epolamine patch)	Dermatologicals	\$15.02	0.9%	-\$0.63	15.2%	-16.7%	-4.0%
20	tizanidine	Muscle relaxants	\$14.65	0.9%	\$0.02	6.3%	-5.8%	0.1%
21	Duexis® (ibuprofen/famotidine)	NSAIDs	\$14.22	0.9%	\$3.96	64.0%	-15.5%	38.7%
22	cyclobenzaprine	Muscle relaxants	\$13.39	0.8%	\$1.58	18.0%	-3.9%	13.4%
23	Amrix™ (cyclobenzaprine ER)	Muscle relaxants	\$12.39	0.8%	\$0.61	11.9%	-6.0%	5.2%
24	atorvastatin	High blood cholesterol drugs	\$12.32	0.8%	\$2.32	-2.8%	26.8%	23.3%
25	meloxicam	NSAIDs	\$12.27	0.8%	\$1.19	-3.0%	14.1%	10.8%

## PUPY COST RANK 1

# Opioids

## Trends

- Opioids continue to be the most expensive and highly utilized class of medications for work-related injuries, accounting for 28.3% of PUPY spend and 25.7% of PUPY utilization.
- Exhibit 11 shows that in 2015 nine of the top 25 Workers' Compensation medications were opioids.
- OxyContin, which had an overall decrease in trend of 16.6%, is the fifth-ranked opioid in terms of utilization. It is ranked first in overall PUPY spend.
- The abuse-deterrent formulations of opioids represent about 2% of opioid prescriptions filled by injured workers in 2015, which is consistent with the numbers in 2014. These formulations include OxyContin, Hysingla® ER (hydrocodone), Zohydro® ER (hydrocodone), Opana® ER (oxymorphone), Embeda® (morphine/naltrexone), Exalgo® (hydromorphone), Nucynta® ER (tapentadol) and Oxaydo® (oxycodone – formerly Oxecta®). With the exceptions of OxyContin and Oxaydo, pricing and utilization trends increased for each of the opioids.

## EXHIBIT 12: TOP FIVE OPIOID MEDICATIONS

RANKED BY 2015 PUPY UTILIZATION

MEDICATION	PUPY UTILIZATION		COST/Rx		
	2014	2015	2014	2015	TREND
hydrocodone/acetaminophen	1.26	1.01	\$42.07	\$46.27	-12.3%
oxycodone/acetaminophen	0.35	0.37	\$104.06	\$100.50	0.6%
tramadol	0.38	0.36	\$31.46	\$31.26	-7.5%
oxycodone	0.24	0.25	\$91.13	\$81.24	-9.2%
OxyContin® (oxycodone) extended release	0.20	0.17	\$584.71	\$574.69	-16.6%

## A closer look

- Hydrocodone/acetaminophen**, a Schedule II controlled substance since Oct. 6, 2014, accounted for **34.6%** of all 2015 Workers' Compensation opioid prescriptions. A 10.0% increase in the average cost per prescription and a 20.3% decrease in PUPY utilization resulted in a trend of -12.3%. Overall utilization decreased 17.5% in 2014, reflecting changes to opioid classification rescheduling.
- New to the market for 2015 was **Hysingla ER**, an abuse deterrent, single-entity, long-acting form of hydrocodone. Released on Nov. 14, 2014, it had an average cost per prescription approaching **\$400**.

By the numbers

-4.9%  
Trend

\$154.66  
Average cost  
per prescription

2.91  
Number of  
prescriptions PUPY

\$450.90  
Cost  
PUPY

## PUPY COST RANK 2

# Anticonvulsants

## Trends

- Anticonvulsants, often used to treat neuropathic pain and other painful conditions such as fibromyalgia, had a trend of 11.3% from 2014 to 2015, driven by an 8.1% increase in the average cost per prescription and a 3.0% increase in PUPY utilization.
- Though not in the top five, utilization of Trokendi XR®, a long-acting form of topiramate, had an increase in spend of 167.0%, comprising a 94.7% increase in utilization and 37.1% increase in cost per prescription. The clinical rationale for prescribing this medication for most workers' compensation pain conditions is uncertain; however, increased utilization of Trokendi XR may be due to its once-a-day dosing profile. Generic topiramate is available, however, including in a once-daily form.
- The 18.1% increase in the average cost per prescription of Lyrica more than offset the 3.2% decrease in utilization. Its increased cost likely reflects the delayed launch of generic pregabalin following litigation by the brand manufacturer. Generics are not expected until after July 2019.

## EXHIBIT 13: TOP FIVE ANTICONVULSANTS

RANKED BY 2015 PUPY UTILIZATION

MEDICATION	PUPY UTILIZATION		COST/Rx		
	2014	2015	2014	2015	TREND
gabapentin	0.49	0.52	\$79.68	\$79.82	7.7%
Lyrica® (pregabalin)	0.25	0.24	\$328.68	\$388.06	14.3%
clonazepam	0.08	0.07	\$23.81	\$24.88	-3.5%
topiramate	0.06	0.06	\$117.88	\$117.09	3.3%
lamotrigine extended release	0.02	0.02	\$103.36	\$96.57	-4.9%

## A closer look

- The top five medications by utilization accounted for more than **77%** of Workers' Compensation anticonvulsant medications in 2015, with the top two (**gabapentin** and **Lyrica**) together accounting for 79.6% of utilization in this class. A likely reason is that anticonvulsant medications have multiple uses, including treating neuropathic and fibromyalgia pain.
- Both **Lamictal™** and its generic, **lamotrigine extended release**, increased in cost between 2014 and 2015, by 29.3% and 5.1%, respectively. They are not considered first line for treatment of

neuropathic pain conditions, though they may have utility for certain pain conditions such as migraine headaches.

- Though **clonazepam** is among the top five anticonvulsants in terms of utilization, it is used less frequently than gabapentin or Lyrica. Clonazepam often is used for its sedating properties or for patients with seizures following occupational injury, rather than being considered first line for management of neuropathic or fibromyalgia pain conditions.

By the numbers

11.3%  
Trend

\$170.21  
Average cost  
per prescription

1.00  
Number of  
prescriptions PUPY

\$170.51  
Cost  
PUPY

## PUPY COST RANK 3

## NSAIDs

## Trends

- Nonsteroidal anti-inflammatory drugs are the second most utilized category of medication for work-related injuries, often used to reduce pain and inflammation. Injured workers may use NSAIDs in oral or topical forms. NSAIDs had a total trend of -8.7% in 2015, resulting from a 10.1% decrease in the average cost per prescription and a 1.4% increase in PUPY utilization.
- Two drugs that include both an NSAID and a gastrointestinal (GI) protectant are Duexis® (ibuprofen/famotidine) and Vimovo® (naproxen/esomeprazole magnesium). Both had decreases in utilization, -15.5% and -19.7%, respectively. Conversely, their average costs per prescription increased significantly – 64.0% for Duexis and 93.8% for Vimovo. The individual drugs in each of these products are available generically. Through programs that address drug mix – step therapy, for example – Express Scripts encourages use of a generic NSAID with a traditional GI protectant first. The success of such programs is demonstrated by the decrease in utilization of the two combination medications.

## EXHIBIT 14: TOP FIVE NSAIDs

RANKED BY 2015 PUPY UTILIZATION

MEDICATION	PUPY UTILIZATION		COST/Rx		
	2014	2015	2014	2015	TREND
ibuprofen	0.39	0.39	\$15.17	\$14.47	-4.6%
meloxicam	0.21	0.24	\$53.45	\$51.87	-3.0%
celecoxib	0.00	0.22	\$202.14	\$211.82	4.8%
naproxen	0.18	0.18	\$23.72	\$22.47	-5.2%
nabumetone	0.06	0.07	\$54.86	\$51.32	-6.5%

## A closer look

- Utilization of brand **Celebrex**, the only cyclooxygenase (COX-2) inhibitor, dropped more than **90%**, as anticipated with the release of its generic, celecoxib, approved in May 2014. For many patients, a traditional NSAID may be a more appropriate choice than a COX-2 drug, depending on the concern for cardiac or renal side effects with the COX-2 drugs balanced against the ulcer risk often associated with traditional NSAIDs. Express Scripts encourages use of a traditional NSAID prior to use of a COX-2 drug with our drug-mix solutions.
- Celecoxib** is now the number-four drug in terms of overall PUPY spend. Its average cost per prescription is almost **four times** that of meloxicam and 13 times that of ibuprofen. The spend for ibuprofen, the most used NSAID, **decreased 2.5%**, due to a decrease in the average cost per prescription.

By the numbers

-8.7%  
Trend\$102.01  
Average cost  
per prescription1.38  
Number of  
prescriptions PUPY\$141.41  
Cost  
PUPY



## PUPY COST RANK 4

# Dermatologicals

## Trends

- The trend for the class was 11.7%, driven mainly by a 15.8% increase in the average cost per prescription.
- Brand name Lidoderm® (lidocaine patch 5%) had a positive cost per prescription trend of 8.8%.
- The use of diclofenac sodium 3%, an anticancer drug indicated for actinic keratosis, had an increase in utilization of 75.7% and a decrease in cost per prescription of 4.8%. The generic for Solaraze® Gel is often confused with the generic for Voltaren™ Gel (diclofenac sodium 1%); however, their indications are quite different.

## EXHIBIT 15: TOP FIVE DERMATOLOGICALS

RANKED BY 2015 PUPY UTILIZATION

MEDICATION	PUPY UTILIZATION		COST/Rx		
	2014	2015	2014	2015	TREND
lidocaine	0.15	0.15	\$306.90	\$329.99	7.5%
Voltaren™ Gel (diclofenac sodium 1%)	0.07	0.08	\$99.32	\$105.35	6.1%
Flector® (diclofenac epolamine patch)	0.04	0.04	\$372.62	\$429.24	15.2%
Lidoderm® (lidocaine patch 5%)	0.02	0.02	\$478.89	\$520.94	8.8%
mupirocin	0.01	0.01	\$36.66	\$33.78	-7.8%

## A closer look

- Although utilization remained flat, **lidocaine** remained the **most utilized** dermatological medication.
- Other forms of topical lidocaine, like **LiDORx® gel** and **LidoPro® ointment** (which also contains capsaicin, menthol and methyl salicylate), had significant increases in utilization, reaching greater than **100% increases** between 2014 and 2015. These drugs are not on our Workers' Compensation formularies.

By the numbers

**11.7%** Trend

**\$288.42** Average cost per prescription

**0.39** Number of prescriptions PUPY

**\$112.99** Cost PUPY

## PUPY COST RANK 5

## Antidepressants

## Trends

- In addition to their primary indications for relieving depression, several antidepressants have secondary indications that include the treatment of nerve pain and/or anxiety. The PUPY cost trend for the antidepressants class was -3.0%, reflecting decreases in utilization (3.3%). The average cost per prescription remained relatively flat (0.3%).
- Amitriptyline, the second most prescribed medication in this class, had a 22.1% PUPY trend, heavily influenced by a 22.9% increase in cost per prescription.
- Several selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) drugs in this class had downward trend in utilization. They include Brintellix® (vortioxetine) and Fetzima® (levomilnacipran extended release). These drugs, along with other SSRIs and SNRIs, are part of the Express Scripts step-therapy program to encourage use of generic or therapeutic alternatives when possible.

## EXHIBIT 16: TOP FIVE ANTIDEPRESSANTS

RANKED BY 2015 PUPY UTILIZATION

MEDICATION	PUPY UTILIZATION		COST/Rx		
	2014	2015	2014	2015	TREND
duloxetine	0.22	0.22	\$222.34	\$209.86	-5.6%
amitriptyline	0.09	0.09	\$13.76	\$16.92	22.9%
trazodone	0.09	0.09	\$17.03	\$17.66	3.7%
escitalopram	0.05	0.05	\$90.09	\$86.81	-3.6%
sertraline	0.05	0.05	\$37.03	\$37.30	0.7%

## A closer look

- The FDA has approved more than a half-dozen generic versions of **Cymbalta®** (duloxetine), an SNRI indicated to treat depression, anxiety, fibromyalgia, chronic musculoskeletal pain and neuropathic pain. As a result of its full year of generic availability, **duloxetine** replaced Cymbalta as **the class leader** among antidepressants in 2015 PUPY spend. In 2015, duloxetine's cost-per-prescription trend was -5.6%, reflecting the introduction of additional generics. Cymbalta lost its place in the top five with the cost per prescription decreasing less than 2% from 2014.
- Although generics dominate the medications in this class, **Wellbutrin XL®** (bupropion extended release), the second ranked by PUPY spend, had a **77.0%** trend, reflecting a **111.0%** increase in average cost per prescription.

By the numbers

-3.0%  
Trend\$120.83  
Average cost  
per prescription0.81  
Number of  
prescriptions PUPY\$98.23  
Cost  
PUPY

# Other therapy classes

## Muscle relaxants

**M**uscle relaxants, typically used as adjunctive therapy, may reduce muscle pain and tension often associated with acute, painful musculoskeletal conditions. The PUPY cost trend for muscle relaxants was 3.9%, due to a 10.1% increase in the average cost per prescription, moderated by a 5.6% decrease in utilization. The top five medications (cyclobenzaprine, tizanidine, carisoprodol, baclofen and methocarbamol) accounted for 86.7% of all utilization in the class.

Cyclobenzaprine, the most commonly prescribed muscle relaxant in 2015, has been available generically for decades. Its average cost per prescription increased 18.0%, while its utilization decreased by 3.9%, resulting in a total trend of 13.4%. It also is the active ingredient in the brand products Amrix™ (cyclobenzaprine extended-release capsules, 15mg and 30mg), Flexeril® (cyclobenzaprine tablets, 5mg and 10mg) and Fexmid® (cyclobenzaprine tablets, 7.5mg).

Carisoprodol, generic for Soma®, had a decrease in utilization of 18.9% and a 1.6% trend for average cost per prescription. Multiple evidence-based guidelines do not recommend carisoprodol due to the tendency toward misuse because it is a Schedule IV controlled substance. Express Scripts includes carisoprodol in many alerts for drug therapy concerns, such as controlled substance misuse and dangerous drug combinations – for example, “Holy Trinity” (carisoprodol with an opioid and a benzodiazepine).

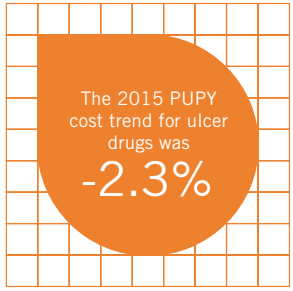
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*The cost trend for muscle relaxants was heavily influenced by the price increase of medications in this class, due to a 10.1% increase in the average cost per prescription, moderated by a 5.6% decrease in utilization.*

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## Ulcer drugs

Ulcer drugs, particularly proton pump inhibitors (PPIs), are used to treat gastroesophageal reflux disease (GERD) and to reduce risk of NSAID-associated gastric ulcer, among other indications. These medications may be prescribed along with NSAIDs to help prevent stomach ulcers for injured workers at high risk for developing them. The 2015 PUPY cost trend for the class was -2.3%, impacted by a 2.5% decrease in utilization, as well as a slight increase of 0.2% in the average cost per prescription.



Omeprazole, pantoprazole and lansoprazole account for 62.8% of ulcer drug utilization. Pantoprazole was the only one that had a positive trend at 16.6%, impacted by an 11.8% increase in cost per prescription.

Generics for Nexium® (esomeprazole magnesium) were delayed until February 2015 by quality issues of the originally approved generic manufacturer; however, the FDA approved the marketing and sale of over-the-counter (OTC) Nexium 24HR in March 2014.

## High blood cholesterol drugs

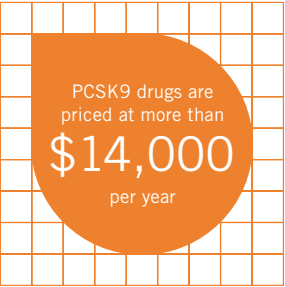
Despite the fact that most Express Scripts Workers' Compensation clients must acquire prior authorization for them, high blood cholesterol medications were ranked eighth by 2015 PUPY cost.

The 2015 PUPY cost trend for the class was 24.2%, impacted by a 16.9% increase in utilization, as well as an increase in the average cost per prescription (6.2%). Three of the top five high blood cholesterol medications ranked by 2015 PUPY spend are statins: atorvastatin, Crestor® (rosuvastatin) and simvastatin. Atorvastatin had a 23.3% increase in spend, driven largely by a 26.8% increase in utilization, which was offset slightly by a 2.8% decrease in the average cost per prescription. Crestor's trend was 40.1%, influenced by increases in both the average cost per prescription (12.6%) and utilization (24.4%). Patent protection

for Crestor expires in May 2016, which may have played a part in the increase seen in cost. Additional price increases most likely will occur before generics to Crestor come onto the market in 2016.

Zetia® (ezetimibe) had a 41.8% trend, due to a 17.3% increase in utilization and a 20.8% increase in average cost per prescription.

Workers' compensation payers should be aware of a new group of specialty injectables for the treatment of hypercholesterolemia (high blood cholesterol), with the first ones in the class approved by the FDA in the summer of 2015. These monoclonal antibodies – which target PCSK9 enzymes involved in balancing cholesterol levels – are classified as specialty medications. Known as PCSK9 inhibitors, they are priced at more than \$14,000 per year, compared to the much lower annual cost range of \$150 to \$2,400 for generic statins. Although not yet seen in the workers' compensation data as significant drivers, these medications should be watched carefully by payers to ensure that they are utilized appropriately. Given their high costs, they should be reserved for their specific indications for patients with familial hypercholesterolemia who have tried and failed statin therapy, who have maxed out the statin dose without significant reduction in LDL or who are intolerant to statins.



## Compounded medications

Products grouped under the Medi-Span® generic product identifier (GPI) of "96" are sold as bulk powders or liquids for use in preparing compounded medications. Overall trend for the chemicals used in compounded medications was -33.7%, heavily influenced by a 38.8% decrease in utilization.

The cost to payers for compounded medications averaged \$1,769.45 per prescription in 2015. Because they are not considered first-line therapy by evidence-based guidelines like ODG, compounded products are, for the most part, excluded from our Workers' Compensation formularies. As previously described, we have a specific outreach solution for physicians and injured workers to review the need for a compound over a commercially available product and to highlight safety concerns with this class of medications.

The top five most common bulk powders used in compounding – gabapentin, ketamine, hydrocodone, cyclobenzaprine and tramadol – all had significant decreases in trend, ranging from -15.3% to -77.9%. The negative trend for these medications was overwhelmingly influenced by a decrease in utilization.

A 1,256.1% increase in cost and an 11.0% increase in utilization were seen for compounded naltrexone, a commercially available opioid antagonist used to treat opioid withdrawal and addiction. Presumably, the compounded form of naltrexone is being used in lower doses off-label to treat pain, even though it is not FDA approved for pain. No large clinical trials nor other evidence-based information support this use, which nevertheless is marketed on certain websites.

Also of note is the -42.5% trend for Sanare scar care, a product marketed as a topical silicone base for scar treatment. Expensive bases such as this will often have bulk powders incorporated into them, such as fluticasone propionate and pentoxifylline, that are intended to manage scarring.

## Antipsychotics

In some cases, antipsychotic medications may be used by injured workers for the treatment of depression. Overall trend for medications in this class was -5.7%, influenced primarily by a 4.9% decrease in utilization. Three medications – quetiapine, aripiprazole and Abilify® (aripiprazole) – account for 55.3% of market share in this class. Aripiprazole is the generic medication available for Abilify, explaining the 54.2% decrease in Abilify utilization between 2014 and 2015. Latuda® (lurasidone), which had 3.1% of market share, had a 15.4% increase in trend, mostly from the 16.7% increase in cost per prescription.

## Antivirals

Medications in the antiviral class include those used to treat HIV and hepatitis C. The new generation of oral medicines to treat hepatitis C includes Harvoni and Viekira Pak. For injured workers, the antivirals trend was 85.1%, heavily influenced by a 66.7% increase in cost per prescription.



# Solutions

# Solutions for workers' compensation challenges

By practicing pharmacy smarter, Express Scripts **improves outcomes** for injured workers and **payer costs** through advanced pharmacy services.

**I**n 1986, in a small building in St. Louis, five people started Express Scripts with a vision that everyone should have access to affordable medicine. Over the past 30 years, we have worked tirelessly, building a legacy of pharmacy innovation and leadership in an industry that continuously evolves and consistently tests that vision. Because patients are at the center of everything we do, safe and effective treatment remains our top priority. Our continued success relies on our steadfast commitment to our founding principles.

As the workers' compensation marketplace becomes increasingly complex, careful management of medication therapy, drug utilization and injured-worker safety is critical. When prescribing trends emerge that pose risks to patient safety, we create solutions to mitigate any potential harmful effects. By practicing pharmacy smarter, Express Scripts improves patient outcomes and payer costs through advanced pharmacy services.

For example, as opioid prescribing and utilization continued to escalate, Express Scripts introduced proactive and retrospective looks at opioid prescribing by offering tools such as the morphine equivalent dose (MED) point-of-sale program, prescriber outreach and injured-worker narcotic education outreach. These tools provide a comprehensive look at the patient's opioid use and identify dose escalation that might be of concern. Express Scripts also has been proactively addressing compounded medications through physician and patient education and our prior-authorization capabilities. Our best-in-class prior-authorization and eligibility tool, OASIS, provides real-time connectivity at the pharmacy. Leading-edge predictive analytics and reporting allow payers to identify worrisome trends early in the injured workers' treatment course.

We are doing what is right for you and your injured workers – even when others will not. Our vocal stance on the opioid epidemic and the need for increased safety allows us to improve patient and payer outcomes. In addition, our unmatched, dedicated Workers' Compensation Compliance team is on the forefront of state and local guideline changes to ensure your pharmacy plan adheres to current standards. Express Scripts Workers' Compensation shares the same goals as patients and payers: to provide the best care for the patient, while protecting payer costs.

## Point of sale

Express Scripts point-of-sale (POS) programs provide a proactive approach to managing utilization that focuses on injured-worker safety and maximizing client savings. Examples of these programs are First Fill, Concurrent Drug Utilization Review, Formulary (Standard and Injury-Specific), Step Therapy, and other POS edits that focus on compound and narcotic utilization thresholds, including alarming levels of overutilization and morphine equivalent dose (MED). All of these programs alert the client, as well as the pharmacy, before the medication is dispensed, while managing safety and unnecessary costs. Through OASIS, a fully automated information workhorse, the client is alerted of these POS edits in real time from the pharmacy. OASIS allows the client to review valuable information and employ multiple tools to make informed, immediate decisions on prior authorizations. In the end, injured worker safety is protected while unnecessary costs are managed appropriately.

## Channel management and network solutions

The Express Scripts nationwide network of pharmacies includes our home delivery and specialty pharmacies. They provide vital access to pharmacy services that result in the best care and cost savings for Workers' Compensation payers, not only at point of sale but after the medication has been dispensed. For instance, with our Paper Bill Conversion and Physician Dispensing Management programs, payers receive the benefit of cost containment by ensuring that the medication is appropriate and meets formulary and plan design guidelines prior to payment. Express Scripts also adheres to state fee schedules and originating average wholesale price costs on repackaged drugs, when applicable, to avoid inflated costs associated with third-party billing and physician-dispensed scenarios. Additionally, home delivery is widely recognized in the workers' compensation market as the optimal channel for managing patient care and payer costs; the Express Scripts Home Delivery Education program maximizes that opportunity for our clients. Specialty pharmacies are the optimal dispensing channel for specialty drugs. The Express Scripts specialty pharmacy, Accredo, offers some of the most advanced patient services in the industry and has a solid track record of improving patient adherence and optimizing health outcomes. Given that costs will continue to increase and patients need ongoing support for these medications, clients need solutions that drive patients to the optimal channel to receive better care and eliminate wasteful expenses.

## Physician outreach and patient education

Communicating with injured workers and physicians is effective in controlling payer costs and ensuring injured-worker safety. When communicating with injured workers, we strive to demonstrate that we care about their health, understand their needs and serve as a trusted pharmacy provider. Our goal for physician outreach is to be seen as a clinical partner in the treatment of patients and to provide guidance if we notice a potential safety concern with medication prescribed. We communicate to injured workers and physicians when confronting potential overutilization, safety and cost concerns associated with compounds and narcotics, and physician-dispensing issues, and when supporting use of generics over multisource and single-source brands. When we encourage a physician's potential change in treatment, our clients experience savings associated with discontinued use or dosage changes of targeted medication.

## Consultative solutions and advanced analytics

We use data insights to uncover opportunities for action, and provide access to hundreds of customizable reports and predictive analytics, such as ScriptAlert and Early Intervention reporting, which generate actionable data for our clients. Our Pharmacist Drug Review (PDRx) provides a pharmacist review detailing drug therapy problems, alternative drug therapies and desired outcomes, which can lead to cost savings. Our self-service reporting tool, Trend Central®, and industry-leading Fraud, Waste & Abuse program further demonstrate the way we align our interests with those of our clients, to ensure that every dollar our clients spend for their injured workers makes a difference.



# Appendix





# Methodology

**P**rescription drug use was considered for clients with a stable injured-worker base, defined as having a change in user volume of less than 50% from 2014 to 2015. Nonprescription medications and prescriptions that were dispensed in hospitals, long-term care facilities and other institutional settings were not included in our analysis. Utilization, determined on a PUPY basis, was calculated by dividing the total number of 30-day adjusted prescriptions by the total number of users in a year. Market share was determined by calculating the percentage of total 30-day adjusted prescriptions represented by one medication. Prescription drug costs were calculated by adding together ingredient costs, taxes, administrative fees and dispensing fees.

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