California Workers' Compensation Institute

Spotlight Report

Cost-Driver Medications in the Top California Workers' Comp Drug Groups: Part 1, Anti-Inflammatories & Anticonvulsants

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Background

In January 2023, CWCI updated its Prescription Data Application[1] with data on medications dispensed to California injured workers between January 2007 and June 2022. The most recent full-year data showed that in 2021 there were seven therapeutic drug groups that accounted for at least 5 percent of the workers' compensation prescriptions filled in 2021: Anti-Inflammatories; Anticonvulsants; Dermatologicals; Opioids; Antidepressants; Musculoskeletal Drugs; and Ulcer Drugs. Together these seven drug groups accounted for 82.3 percent of all workers' compensation prescriptions and 69.2 percent of the total drug spend in service year 2021.[2]

CWCI research published two years ago[3] found that in service year 2020, Anti-Inflammatories represented more than a third of all drugs dispensed to injured workers in California, triple the proportion noted for Opioids, which ranked second. That study also revealed that although most of those Anti-Inflammatories were inexpensive, and utilization had been flat since the state's evidence-based prescription drug formulary took effect in 2018, Anti-Inflammatories' share of the total drug spend had soared from 14.2 percent to 23.5 percent, largely driven by increased payments for two low-volume, high-priced drugs: fenoprofen calcium and ketoprofen. Both drugs are used to treat arthritis and pain, and under the formulary, both are exempt from prospective utilization review (UR) and lack price controls. Given the disproportionate impact that these relatively low-volume Anti-Inflammatories had on the total drug spend, the authors decided to revisit the Prescription Data Application to see if other medications in the most heavily used therapeutic drug groups had an outsized impact on drug costs within their drug categories and to highlight the results in a research series.

This initial report updates the data on fenoprofen calcium and ketoprofen and notes a third low-volume, high-cost Anti-Inflammatory, etanercept (Enbrel), a biologic immunosuppressant used to treat autoimmune diseases, rheumatoid arthritis, and plaque psoriasis by interfering with a protein that causes inflammation. The report also looks at four additional drugs, lacosamide, levetiracetam, lamotrigine, and pregabalin that have become cost drivers within the Anticonvulsant drug group. The second report in the series will focus on medications found in the Dermatological, Opioid, and Antidepressant drug groups, while the final report will examine low-volume/high-cost Musculoskeletal and Ulcer Drugs.

[1] CWCI's Prescription Drug Application is an online tool available to CWCI members at www.cwci.org.
[2] Service year refers to the calendar year (January 1 through December 31) in which a prescription was dispensed.
[3] Young, B., Secia, J. and Hayes, S. California Workers' Compensation Prescription Drug Trends. *CWCI Research Update, March 2021*.

Data and Methods

CWCI's Prescription Drug Application contains detailed data on California workers' compensation prescriptions extracted from the Institute's Industry Research Information System (IRIS) database.[4] Each drug within the application is identified by its National Drug Code (NDC) and descriptive information from Medi-Span,[5] including the therapeutic drug group, active ingredient name, and its availability as a brand name or generic drug. The January 3, 2023 version of the application contains data on nearly 9.5 million prescriptions dispensed to injured workers between January 2010 and June 2022, with aggregate payments for those prescriptions totaling nearly $1.02 billion.

The service year detail in the application ranks the top drug groups based on prescription volume, and for this research series the authors limited the sample to drug groups that accounted for at least 5 percent of service year 2021 prescriptions. Including the Anti-Inflammatories and Anticonvulsant Groups that are the focus of this initial analyses, there were seven therapeutic drug groups that accounted for at least 5 percent of all California workers' compensation prescriptions in 2021 (no other drug groups represented more than 2.1 percent of the prescriptions).

For the research series, the authors used service year 2021 data from CWCI's Prescription Data Application to rank the individual drugs within the top seven drug groups based on their percentage of the dispensed medications and total payments within the group. The application includes preliminary data on prescriptions dispensed through June 2022, but the service year 2022 prescription data was not sufficiently developed for comparisons to full-year data from prior years, so the 10-year trends for the drug groups and individual drugs detailed in this research series are based on service year 2012 through service year 2021 prescription data, reported as of June 30, 2022.

In addition, because the prescription drug market is constantly evolving as new medications are introduced, older medications are retired or reformulated, patents on brand drugs expire and generic versions hit the market, and revisions are made to the Medical Treatment Utilization Schedule (MTUS) Prescription Drug Formulary, the authors focused on medications dispensed in service year 2021 (the most recent full-year data included in the Prescription Data Application) to identify those drugs that are consuming a disproportionately high share of the total dollars paid within the drug group relative to their share of the prescriptions.

The authors also used the service year detail to note changes in the average amount paid per prescription for each drug within the 10-year study period, as well as the percentage that were dispensed as brand drugs rather than as generics. Additional detail from the IRIS database identified where the medications were dispensed, the form in which they were dispensed, specific brands that were used, and additional pricing information.

[4] IRIS is CWCI's proprietary transactional database of insured and self-insured policies and their associated claims. Version 2022A, used for the latest version of the Prescription Drug Application contains detailed data on employee and employer characteristics, medical service data, benefits, and administrative costs on more than 7.6 million California workers' compensation claims.
[5] Master Drug Data Base (MDDB) Version 2.5 Documentation Manual, Wolters Kluwers Health, Medi-Span.

Objective

The goal of this research series is to identify relatively low-volume but high-cost medications within the top therapeutic drug groups currently used in California workers' compensation, (*i.e.*, those that consume a much higher share of the payments within their drug group relative to their share of the dispensed prescriptions within that group), and to determine the factors that are driving up the cost of these drugs and the extent to which those factors may be better controlled.

Findings

The top seven drug groups accounted for 82.3 percent of the prescriptions dispensed to injured workers in 2021 (Exhibit 1) and that percentage has been fairly stable since 2012, ranging from 81.1 percent to 83.6 percent. Opioids' share of the prescriptions registered the biggest drop, falling from 29.4 percent in 2012 to 9.4 percent in 2021, far more than the decline in musculoskeletal drugs, which fell from 9.7 percent to 5.9 percent of the prescriptions.

Conversely, Anti-Inflammatories had the biggest increase, climbing from 17.7 percent to 34.8 percent of the prescriptions, while Anticonvulsants jumped from 5.5 percent to 9.6 percent and Dermatologicals increased from 5.8 percent to 9.3 percent.

Notably, Antidepressants' share of the prescriptions rose from 5.9 percent in 2012 to 7.9 percent in 2021, but most of that increase (1.3 percentage points) occurred in the pandemic years of 2020 and 2021.

Exhibit 1: Top California WC Drug Groups* % of Prescriptions, 2012-2021

Therapeutic Drug Group	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	10-Yr %-age Point Change
Anti-Inflammatory	17.7%	18.2%	20.9%	24.1%	26.2%	27.4%	30.8%	33.6%	33.6%	34.8%	+17.1
Anticonvulsant	5.5%	5.8%	6.2%	6.9%	7.7%	8.5%	9.7%	10.0%	10.6%	9.6%	+4.1
Opioid	29.4%	28.7%	27.2%	23.9%	22.1%	19.6%	14.6%	11.3%	10.2%	9.4%	-20.0
Dermatological	5.8%	6.0%	5.8%	4.8%	5.0%	5.5%	6.4%	7.8%	8.5%	9.3%	+3.5
Antidepressant	5.9%	5.9%	5.3%	5.4%	5.5%	5.7%	6.4%	6.6%	7.1%	7.9%	+2.0
Musculoskeletal	9.7%	9.8%	10.1%	10.4%	10.6%	10.5%	7.0%	6.5%	6.4%	5.9%	-3.8
Ulcer	7.1%	7.3%	7.3%	7.1%	6.6%	6.4%	6.3%	6.1%	6.0%	5.4%	-1.7
Top 7 Subtotal	**81.1%**	**81.7%**	**82.8%**	**82.6%**	**83.7%**	**83.6%**	**81.2%**	**81.9%**	**82.4%**	**82.3%**	**+1.2**

* Drug group rankings based on 2021 prescription volume

The sharp decline in Opioid utilization and the increase in the use of Anti-Inflammatories and drugs that are often prescribed for off-label use as non-opioid analgesics led to a significant shift in the distribution of workers' compensation pharmaceutical payments over the 10-year study period. (Exhibit 2).

Exhibit 2: Top California WC Drug Groups* % of Total Drug Spend, 2012-2021

Therapeutic Drug Group	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	10-Yr %-age Point Change
Anti-Inflammatory	13.3%	13.1%	15.7%	17.6%	16.9%	14.6%	13.1%	15.5%	23.1%	24.5%	+11.2
Anticonvulsant	5.0%	5.4%	6.0%	7.1%	9.3%	11.4%	14.4%	14.0%	10.5%	8.1%	+3.1
Opioid	26.7%	24.8%	23.3%	20.7%	18.3%	16.0%	12.3%	9.4%	6.6%	5.8%	-20.9
Dermatological	12.8%	13.9%	13.4%	12.7%	16.1%	18.3%	16.3%	17.7%	15.2%	17.3%	+4.5
Antidepressant	5.9%	6.3%	4.8%	4.9%	4.4%	3.5%	3.4%	2.8%	3.2%	3.3%	-2.6
Musculoskeletal	5.6%	6.7%	5.8%	6.3%	6.7%	6.7%	4.1%	3.3%	4.6%	3.7%	-1.9
Ulcer	10.0%	9.7%	9.1%	8.9%	6.4%	6.8%	5.6%	5.9%	6.5%	6.5%	-3.5
Top 7 Subtotal	**79.3%**	**79.9%**	**78.1%**	**78.2%**	**78.1%**	**77.3%**	**69.2%**	**68.6%**	**69.7%**	**69.2%**	**-10.1**

* Drug group rankings based on 2021 prescription volume

While payments for opioids declined from 26.7 percent of the total workers' compensation drug spend in 2012 to just 5.8 percent in 2021, Anti-Inflammatories' share of the payments climbed from 13.3 percent to 24.5 percent, Dermatological Drugs increased from 12.8 percent to 17.3 percent, and Anticonvulsants jumped from 5.0 percent to 8.1 percent, though the Anticonvulsant's share of the payments has declined since 2019, coinciding with the approval and introduction of generic pregabalin into the market. Pregabalin was the second most heavily prescribed anticonvulsant throughout the 10-year study period, but prior to 2019, it was only available as a brand name drug (Lyrica). Drug categories that saw their share of the total drug spend decline over the decade included Ulcer Drugs (which are often prescribed for stomach issues that arise from the use of Opioids and Anti-Inflammatories) which dropped from 10.0 percent to 6.5 percent of the pharmaceutical dollars, Antidepressants, which fell from 5.9 percent to 3.3 percent of the prescription payments, and Musculoskeletal Drugs, which declined from 5.6 percent to 3.7 percent.

At the same time that the prescription and payment distributions among top drug groups were shifting, changes were also occurring within each group as new medications, formulations, and products were introduced, patents on brand drugs expired and generic versions became available, and older medications were taken off the market. After reviewing the prescription drug utilization and payment data for medications within the top seven drug groups, the authors identified several relatively low-volume, high-priced medications that had a disproportionate impact on the costs within their drug group in 2021.

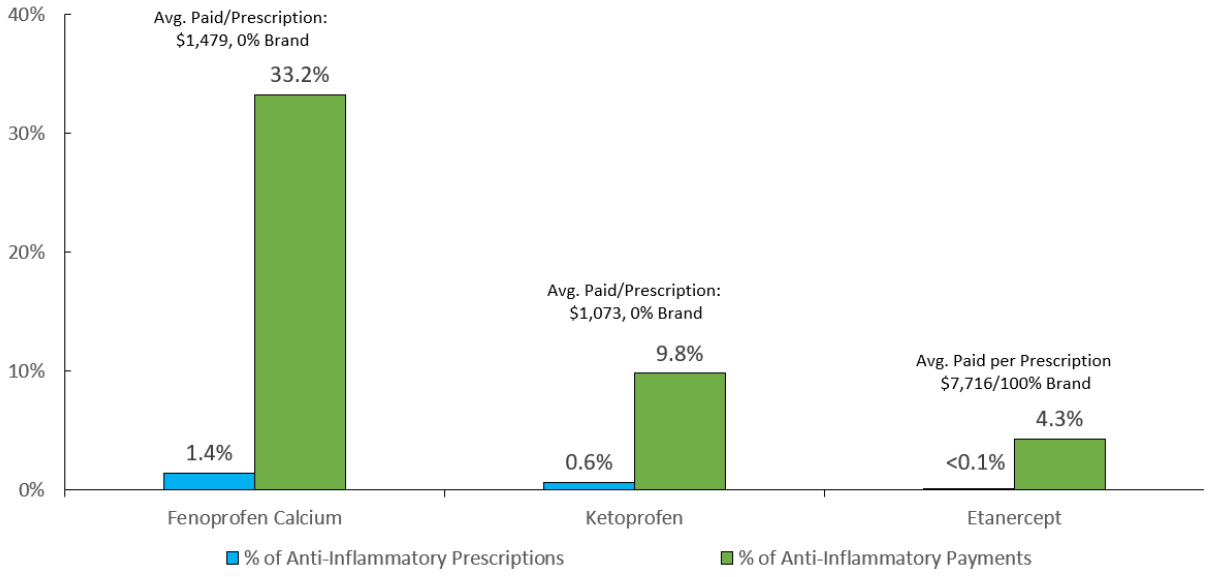
The following sections highlight the findings for what are now the two most heavily utilized drug groups, Anti-Inflammatories and Anticonvulsants, noting the most significant "cost-driver" medications that were found within each group, including their share of the prescriptions within the drug category during service year 2021, the average amount paid per prescription, the percentage of the drug spend that the medication represented within the drug group, and the percentage of the drug that was dispensed as a brand-name drug rather than as a generic.

Anti-Inflammatories

Anti-Inflammatories accounted for 34.8 percent of all California workers' compensation prescriptions dispensed in 2021, as well as 24.5 percent of the pharmaceutical payments, so they remained the number one drug group in the system both in terms of utilization and reimbursement. Ibuprofen and naproxen accounted for two-thirds of all Anti-Inflammatories dispensed to injured workers in 2021, but with average payments per prescription of $12 and $49 respectively, they were relatively inexpensive. As in 2020, it was low-volume, high-cost fenoprofen calcium and ketoprofen (*e.g.,* Oruvail) that kept Anti-Inflammatories at the top of the list in terms of total drug spend in 2021, though the latest update to the Prescription Drug Application also revealed a third Anti-Inflammatory, etanercept (Enbrel) that also consumes a disproportionately high share of the Anti-Inflammatory payments.

CWCI's March 2021 analysis noted that under the MTUS Prescription Drug Formulary that took effect in 2018, both fenoprofen calcium and ketoprofen are exempt from prospective UR, and because they are not listed in the national Medicaid database, neither has a Federal Upper Limit (FUL), which would act as a price control in California workers' compensation. Instead, they are reimbursed at 83 percent of the AWP, which is based on manufacturer pricing.[6] The impact of this can be seen in the average payment data from 2021, as the average amount paid for a fenoprofen calcium prescription was $1,479, while the average amount paid for a ketoprofen prescription was $1,073. (Exhibit 3).

Exhibit 3: **% of 2021 Anti-Inflammatory Prescriptions and Anti-Inflammatory Payments**



Thus, fenoprofen calcium, which represented 0.5 percent of all workers' compensation prescriptions in 2021, accounted for 8.1 percent of the total payments across all drug groups, by far the largest share of any single drug. Measured as a percentage of the Anti-Inflammatory prescriptions, fenoprofen calcium accounted for 1.4 percent of the prescriptions in its drug group in 2021, but 33.2 percent of the dollars.

[6] Young, B., Secia, J. and Hayes, S. California Workers' Compensation Prescription Drug Trends (p. 8).

Results were similar for ketoprofen, which comprised only 0.2 percent of all workers' compensation prescriptions in 2021 but ranked sixth among all drugs in terms of payments, with 2.4 percent of the total drug spend. Again, looking within its own drug group, ketoprofen, available as regular-release and extended-release capsules, represented just 0.6 percent of the Anti-Inflammatories dispensed in 2021, but 9.8 percent of the payments in this drug group. None of the fenoprofen calcium or ketoprofen dispensed to California injured workers in 2021 was brand, which shows that generics are not always inexpensive.

Unlike fenoprofen calcium and ketoprofen, etanercept is a biologic medication (made from living cells), and it is only available as a brand drug (Enbrel). Because they are grown from living cells, biologic medications are more difficult than conventional drugs to replicate, which makes it more difficult to develop generics, so they tend to be quite expensive.

Etanercept is listed in the MTUS Formulary as a Non-Exempt drug, so it is subject to prospective UR. This medication comes in 50 mg cartridges or syringes, including prefilled autoinjectors, and 25 mg vials or syringes, and is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis (inflammatory arthritis affecting the spine and large joints), and plaque psoriasis. It accounted for less than 0.1 percent of the workers' compensation Anti-Inflammatory drugs dispensed in 2021, but because of the high cost (the average payment was $7,716 per prescription in 2021), it represented 4.3 percent of the total Anti-Inflammatory drug spend.

The MTUS Formulary rules require that unless a prescriber provides a rationale for using the brand version of a drug, a generic should be prescribed, but because no generic version of etanercept is available, on the rare occasions it has been used in workers' compensation, brand-name Enbrel has been dispensed. In addition, like fenoprofen calcium and ketoprofen, etanercept is not listed in the national Medicaid database and does not have an FUL, so it too is reimbursed at 83 percent of the AWP, which is based on the manufacturer's pricing.

The 10-year utilization and payment growth trends for these Anti-Inflammatories, noted in Exhibit 4, show that although fenoprofen calcium has been around for most of the past decade, it was not until 2018, the year that the MTUS Formulary categorized it as exempt from prospective UR, that the average amount paid per prescription shot up to $877 and it began to have a significant impact on Anti-Inflammatory payments.

Prior to this, fenoprofen calcium only appeared in the IRIS pharmacy data in nominal amounts, representing 0.4 percent of the Anti-Inflammatories in 2014, 0.6 percent in 2015, and less than 0.1 percent in 2016, with average payments ranging from $169 to $192 per prescription during that 3-year span.

In 2017, the IRIS database had no records of fenoprofen calcium being dispensed, but in 2018 it reappeared, and since then its share of the Anti-Inflammatory prescriptions has nearly tripled from 0.5 percent to 1.4 percent in 2021, while the average paid per prescription has climbed from $877 to $1,479.

Exhibit 4: Utilization and Payment 10-Year Growth Trends, Anti-Inflammatory Cost Drivers

Drug	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Fenoprofen Calcium										
% of Anti-Inflammatory Rx	0%	0%	0.4%	0.6%	< 0.1%	0%	0.5%	0.8%	1.2%	1.4%
Avg Paid	$0	$0	$169	$171	$192	$0	$877	$1,232	$1,468	$1,479
% of Anti-Inflammatory $	0%	0%	0.7%	1.2%	0.1%	0%	11.0%	23.0%	30.3%	33.2%
Ketoprofen										
% of Anti-Inflammatory Rx	4.2%	3.0%	2.4%	1.0%	6.0%	8.7%	0.5%	0.1%	0.9%	0.6%
Avg Paid	$424	$327	$335	$458	$101	$107	$172	$859	$1,071	$1,073
% of Anti-Inflammatory $	21.1%	11.6%	8.6%	5.0%	9.3%	18.6%	2.1%	2.6%	16.2%	9.8%
Etanercept										
% of Anti-Inflammatory Rx	0.1%	0.1%	<0.1%	<0.1%	<0.1%	<0.1%	0.1%	<0.1%	<0.1%	<0.1%
Avg Paid	$1,930	$2,687	$2,976	$3,680	$4,584	$5,242	$5,719	$6,626	$6,921	$7,716
% of Anti-Inflammatory $	1.5%	1.9%	1.0%	1.2%	2.2%	4.7%	8.8%	7.4%	3.8%	4.3%

The net effect of the increase in utilization of fenoprofen calcium and the increase in the average payment over that four-year period is that this drug's share of the Anti-Inflammatory payments more than tripled from 11.0 percent in 2018 to 33.2 percent in 2021.

Trends for ketoprofen have been different, as its use fluctuated sharply over the 10-year study period. Over-the-counter versions of the drug have been discontinued in the U.S. so it is only available by prescription, and like other non-steroidal anti-inflammatories, it comes with a black box warning that was strengthened in July 2015 to note that non-aspirin NSAIDs increase the chance of a heart attack or stroke. Ketoprofen's share of the Anti-Inflammatory prescriptions fell from 4.2 percent in 2012 to 1.0 percent in 2015, during which time the average paid per prescription fell from $424 to $327, then rebounded to $458 in 2015.

Over the next two years, less expensive versions of ketoprofen became more prevalent, and the average payment fell from $458 in 2015 to $101 in 2016, then leveled off at $107 in 2017. As the average payment for ketoprofen declined from 2015 to 2017, its share of the Anti-Inflammatory prescriptions jumped from 1.0 percent to 8.7 percent and its share of the payments soared from 5.0 percent to 18.6 percent – the high point for the decade.

These increases also coincided with a sharp reduction in the use of the Anti-Inflammatory, nabumetone, which declined from 13.9 percent of the Anti-Inflammatory prescriptions in 2015 to 3.6 percent in 2017. In 2018, ketoprofen's share of the Anti-Inflammatory prescriptions plummeted to 0.5 percent, so even though the average amount paid jumped to $172, its share of the payments within its drug group fell to 2.1 percent.

In 2019, ketoprofen's share of the Anti-Inflammatories continued to decline, falling to just 0.1 percent, but the average payment increased five-fold to $859, driving its share of the payments in its drug group up from 2.1 percent to 2.6 percent. Ketoprofen's share of the Anti-Inflammatories jumped from 0.1 percent in 2019 to 0.9 percent in 2020 then fell back to 0.6 percent in 2021, though with no FUL to control the price, the average payment per prescription rose to $1,071 in 2020, driving it back up to 16.2 percent of the Anti-Inflammatory payments. The average payment for a ketoprofen prescription remained at a record level in 2021 ($1,073), but its share of the Anti-Inflammatory prescriptions declined to 0.6 percent, so its share of the payments within its drug group dropped back to 9.8 percent.

The 10-year growth trends for etanercept show that this drug has only been used in a handful of claims each year and has never represented more than 0.1 percent of the Anticonvulsants in California workers' compensation. But because it is a single-source drug and there is no FUL to control the price, the average payment per prescription increased steadily across each of the ten years studied and the average reimbursement quadrupled from $1,930 in 2012 to $7,716 in 2021. Furthermore, in nine out of the ten years, etanercept ranked first among Anti-Inflammatories in average payment per prescription. Between 2012 and 2021, etanercept's share of the Anti-Inflammatory drug spend ranged from a low of 1.0 percent in 2014 to a high of 8.8 percent in 2018 – the last year that it represented at least 0.1 percent of the prescriptions within this drug group. Even though etanercept represented less than 0.1 percent of the Anti-Inflammatory prescriptions in each of the three subsequent years, the average amounts paid per prescription for this drug continued to climb, increasing to $6,626 in 2019 (+15.9 percent); $6,921 in 2020 (+4.5 percent), and $7,716 in 2021 (+11.5 percent). As a result, despite its very marginal share of the prescriptions, etanercept consumed 4.3 percent of the 2021 Anti-Inflammatory reimbursements, making it the sixth most expensive drug within its group in terms of total payments, ranking it ahead of much more heavily utilized medications, including meloxicam, nabumetone, and diclofenac.

Altogether, the three low-volume/high payment Anti-Inflammatories identified by the Prescription Drug Data Application represented less than 2.1 percent of the Anti-Inflammatory prescriptions dispensed to California injured workers in 2021, but they represented 47.3 percent of the payments in this drug group.

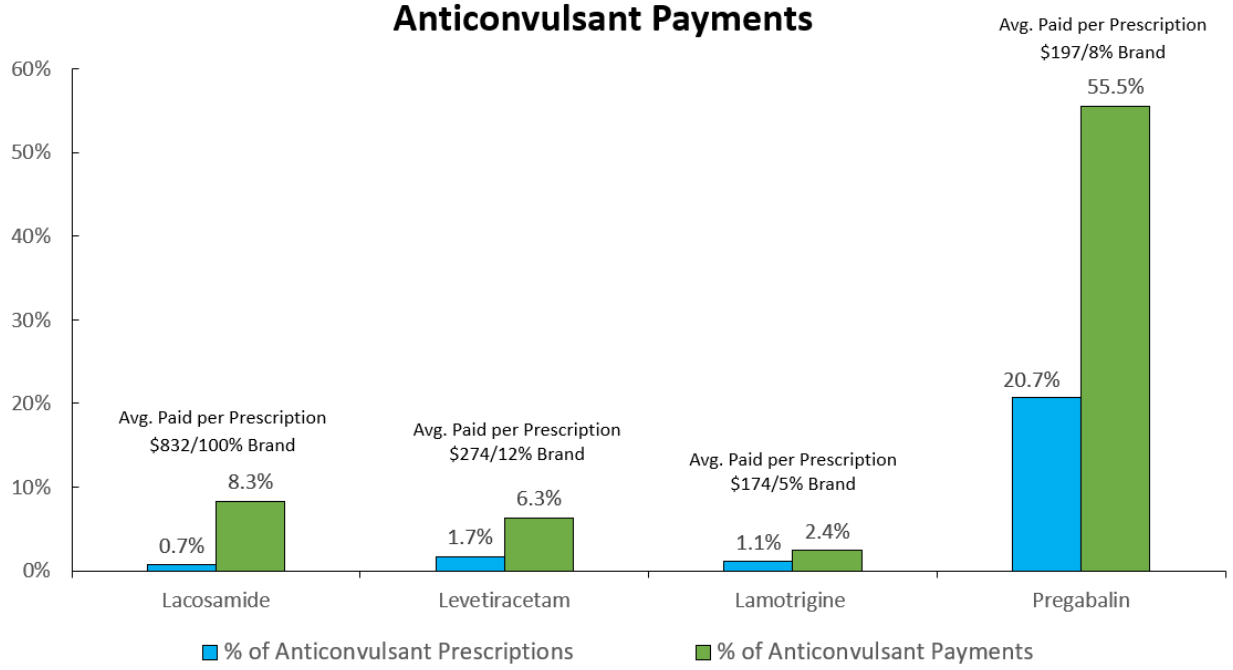
Anticonvulsants

With opioid use on the decline, Anticonvulsants have also seen their share of workers' compensation prescriptions increase, as they went from 5.5 percent of the prescriptions in 2012 to 9.6 percent in 2021, making them the second most heavily used drug group that year. Over that same decade Anticonvulsants went from 5.0 percent to 8.1 percent of the total workers' compensation drug spend.

Gabapentin (*e.g.,* Neurontin) is an Anticonvulsant used to treat seizures. It is non-narcotic and not classified as a controlled substance by the DEA and is used as an alternative to opioids to treat neuropathic pain. Over the past decade gabapentin has been the number one Anticonvulsant prescribed for injured workers in California, and in each of the six most recent years in the study (2016 through 2021) it represented about 70 percent of all Anticonvulsants dispensed. However, with an average payment of $23 per prescription in 2021, it consumed just 21.5 percent of the Anticonvulsant dollars.

On the other hand, four other Anticonvulsants, lacosamide, levetiracetam, lamotrigine, and pregabalin accounted for much smaller shares of the Anticonvulsant prescriptions, but due to their high average payment per prescription, they represented a disproportionate share of the total drug spend in this category (Exhibit 5). In 2021, these four drugs together accounted for 24.2 percent of the Anticonvulsant prescriptions, but 72.5 percent of the Anticonvulsant drug spend.

Exhibit 5: **% of 2021 Anticonvulsant Prescriptions and Anticonvulsant Payments**



Of these four drugs, pregabalin (*e.g.*, Lyrica), which is a Non-Exempt drug in the formulary, had the greatest impact as it was the second most common Anticonvulsant prescribed in 2021, but its 20.7 percent share of the Anticonvulsant prescriptions was well below its 55.5 percent share of the payments within the drug group. Like gabapentin, pregabalin is often prescribed to treat nerve pain, but it is also used to treat anxiety and has been reported to be effective in improving sleep for patients suffering from neuralgia or anxiety. Looking across all drug groups, pregabalin ranked 11th in volume of prescriptions in 2021, with 2.0 percent of the prescriptions, but with an average payment of $197 ($714 for brand versions, $152 for generics) it ranked third in terms of total drug spend, consuming 4.5 percent of the 2021 prescription payments, behind fenoprofen calcium (8.1 percent) and naproxen (4.9 percent).

Lacosamide, (*e.g.,* Vimpat), an Anticonvulsant that is Not Listed in the formulary, is also sometimes used off-label for pain management and mental health disorders; levetiracetam (*e.g.,* Keppra), is a Non-Exempt drug used to prevent seizures; and lamotrigine (*e.g.*, Lamictal) is a Non-Exempt drug used to treat seizures and is used off label as a mood stabilizer in patients with bipolar disorder. These account for much smaller shares of the workers' compensation Anticonvulsant prescriptions (0.7 percent, 1.7 percent, and 1.0 percent respectively), but high average payments make them significant cost drivers within the Anticonvulsant group. In 2021, lacosamide, with an average payment of $832, accounted for

8.3 percent of the Anticonvulsant payments, levetiracetam, with an average payment of $274, accounted for 6.3 percent, and lamotrigine, with an average payment of $174, accounted for 2.4 percent.

Exhibit 6: Utilization and Payment 10-Year Growth Trends, Anticonvulsant Cost Drivers

Drug	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Lacosamide										
% of Anticonvulsant Rx	0.1%	0.2%	0.2%	0.3%	0.3%	0.3%	0.3%	0.5%	0.5%	0.7%
Avg Paid	$430	$505	$619	$659	$728	$831	$866	$902	$951	$832
% of Anticonvulsant $	0.4%	0.7%	1.1%	1.4%	1.7%	2.1%	2.1%	3.4%	6.0%	8.3%
Levetiracetam										
% of Anticonvulsant Rx	1.7%	1.6%	1.5%	1.5%	1.5%	1.4%	1.8%	2.0%	1.9%	1.7%
Avg Paid	$162	$159	$153	$159	$182	$174	$155	$155	$188	$274
% of Anticonvulsant $	2.7%	2.2%	1.9%	1.9%	2.3%	2.0%	2.0%	2.3%	4.2%	6.3%
Lamotrigine										
% of Anticonvulsant Rx	1.4%	1.3%	1.2%	0.9%	0.9%	0.9%	1.0%	1.0%	0.9%	1.0%
Avg Paid	$71	$70	$73	$114	$129	$156	$138	$139	$156	$174
% of Anticonvulsant $	0.9%	0.9%	0.7%	0.8%	1.0%	1.1%	1.0%	1.0%	1.7%	2.4%
Pregabalin										
% of Anticonvulsant Rx	22.9%	22.5%	21.0%	19.9%	18.4%	17.5%	19.0%	20.9%	19.6%	20.7%
Avg Paid	$229	$272	$321	$378	$428	$484	$557	$494	$279	$197
% of Anticonvulsant $	51.5%	55.5%	56.5%	60.3%	65.6%	67.5%	76.1%	77.5%	64.5%	55.5%

Reviewing the utilization and payment trends over the past 10 years (Exhibit 6) shows that pregabalin's share of the Anticonvulsant prescriptions declined from 22.9 percent in 2012 to 17.5 percent in 2017. However, as noted earlier, at that point pregabalin was only available as a brand drug (Lyrica), so even though its share of the Anticonvulsant prescriptions declined during this period, with no generic alternatives available the average amount paid per prescription more than doubled from $229 to $484 and its share of the Anticonvulsant drug spend climbed from 51.5 percent to 67.5 percent.

The decline in pregabalin's share of the Anticonvulsant prescriptions reversed course and increased after the formulary and the Opioid Guidelines took effect in 2018 as the use of Anticonvulsants as an alternative to opioid painkillers increased, but the average payment per pregabalin prescription peaked at $557 that year, and by 2019 so too did its share of the Anticonvulsant drug spend (77.5 percent). In this case, the impact of generic drugs is evident because in 2019, Pfizer's patent on Lyrica expired, the FDA approved nine generic versions of the drug, and several companies immediately began distributing generics to pharmacies at a fraction of the cost of Lyrica.

The generics were expected to reduce the cost of pregabalin, but there was concern that those savings could be undermined if there was a major shift toward extended-release Lyrica (Lyrica CR), which had

been introduced in 2017 and which remained under patent. The payment data show that in 2019, Lyrica, reimbursed at an average of $582 per prescription, still represented 62 percent of the pregabalin used in California workers' compensation, but with generics (reimbursed at an average of $351) accounting for more than a third of the prescriptions, the overall cost of pregabalin began to decline, with the average payment per prescription falling to $494. In 2020 and 2021, generics increased to 92 percent of the pregabalin dispensed to injured workers, as the payment differentials between brand and generic versions widened, with the average payment for generics declining to $244 per prescription in 2020 (vs. $676 for brand versions) and continuing to decline in 2021, falling to $152 per prescription, while the average amount paid for brand pregabalin climbed to $714.

With the shift toward less expensive generics, pregabalin has continued to consume a smaller share of the total workers' compensation drug spend each year, declining from 10.9 percent in 2018 and 2019, when it ranked first among all drugs in terms of payments, to 6.8 percent in 2020, and 4.5 percent in 2021. As noted earlier, the formulary lists pregabalin as a Non-Exempt drug, so it is subject to prospective UR, which gives payers significant control over whether a brand or generic version is dispensed, so UR has become a critical tool in containing the cost of the drug.

The utilization and payment trends for lacosamide show its share of the Anticonvulsants in workers' compensation remains small but has risen steadily over the past decade, climbing from 0.1 percent in 2012 to 0.3 percent in 2018, then more than doubling to 0.7 percent by 2021. Like Lyrica, the DEA has categorized lacosamide as a Schedule V drug (limited risk of physical or psychological dependency) so although it is a controlled substance, its use is not as restricted as Schedule I to Schedule IV drugs. Because it is not listed in the formulary, lacosamide can be made available to injured workers if the treating physician can show how its use is supported by the MTUS or other acceptable treatment guidelines for the condition or injury being treated. A review of the claims in which lacosamide was dispensed revealed that most involved major head trauma injuries, with a few involving epileptic seizures, so the steady growth in lacosamide's share of the workers' compensation Anticonvulsants over the past decade does not appear to be due to off-label uses. Instead, it may simply be due to prescribers looking for alternatives to other Anticonvulsants and the broad array of lacosamide formulations that are available.

The patent for Vimpat, the brand version of lacosamide, expired in March 2022, and although less expensive generic versions have now been approved, until recently, various formulations of Vimpat (different strength tablets, an oral solution, and an injectable solution) have accounted for 100 percent of the lacosamide used in workers' compensation. Because only brand versions of this drug were available from 2012 through 2021, lacosamide has consistently been one of the costliest Anticonvulsants used to treat injured workers, with the average amount paid per prescription increasing for nine straight years, climbing from $430 in 2012 to $951 in 2020. With the steady growth in its share of the workers' compensation Anticonvulsants and the increases in the average amount paid, lacosamide's share of the total workers' compensation Anticonvulsant drug spend soared from 0.4 percent in 2012 to 6.0 percent in 2020, and with its share of the Anticonvulsant prescriptions climbing from 0.5 percent in 2020 to 0.7

percent in 2021, it jumped to a record 8.3 percent of the Anticonvulsant payments even as the average amount paid per prescription dropped from $951 to $832.

The third Anticonvulsant cost driver, the anti-seizure drug levetiracetam, has been prescribed to treat injured workers who have suffered head injuries or strokes, and it too has accounted for a relatively small share of the workers' compensation Anticonvulsant prescriptions, ranging between 1.4 and 2.0 percent of the Anticonvulsants dispensed between 2012 and 2021 (Exhibit 8). From 2012 to 2020, the average amount paid for a levetiracetam prescription fluctuated between $153 and $188, as the mix of brand versus generic versions, and the mix of the different formulations and strengths of the drug shifted within this 9-year period.

The brand version of levetiracetam is Keppra, which is also available as an extended-release tablet in different dosages. Brand-name levetiracetam declined from 11 percent of the prescriptions in 2012 to 7 percent in 2018, but in the three years following the implementation of the formulary the use of the brand versions of the drug has increased, rebounding back up to a ten-year high of 12 percent in 2021.

As with pregabalin, levetiracetam is listed as a Non-Exempt drug in the formulary, so it is subject to prospective UR, providing some control over whether a brand or generic version is used, as well as the dosage, and amount. Although only 12 percent of the levetiracetam prescriptions dispensed in 2021 were for a brand version of the drug, the recent shift toward brand-name Keppra has had a major impact on the average amount that was paid for this Anticonvulsant due to the huge price differential between the generic and brand versions. Since 2012 the average payment for generic levetiracetam has ranged between $45 and $88, while the average amount paid for brand versions of the drug have ranged from $773 to $1,880. As a result, after falling to $155 per prescription in 2018, the overall average payment for levetiracetam in the California workers' compensation system jumped 76.8 percent to $274 in 2021, and over that 4-year span this medication's share of the Anticonvulsant drug spend more than tripled from 2.0 percent to 6.3 percent.

Lamotrigine, which carries "black box warnings" used by the FDA to alert doctors about potentially dangerous side effects, is not heavily used in workers' compensation, though a review of the 2021 data found that last year it was used to treat several different conditions, including traumatic head injuries, mental health problems, and pain. Although its share of the workers' compensation Anticonvulsant prescriptions has declined over the past decade, falling from 1.4 percent of those prescriptions in 2012 to 1.0 percent in 2021, that percentage has remained within a narrow range of 0.9 to 1.1 percent in each of the past seven years. On the other hand, with the use of different versions of the drug − including the extremely high-priced extended-release brand version − the average amount paid for lamotrigine has more than doubled in the past 10 years, climbing from $71 in 2012 to $174 in 2021.

Generics, with an average payment of $62 per prescription, accounted for 95 percent of the lamotrigine dispensed in 2021 − up from 90 percent a decade ago, and up from 92 percent in 2017, the final year preceding implementation of the MTUS Drug Formulary − yet the average amount paid for all lamotrigine prescriptions in 2021 was $112 more than the average for generics, indicating that the 5 percent of the prescriptions that were brand drugs resulted in much higher reimbursements.

The brand version of lamotrigine is available in a variety of dosages and forms [Lamictal, Lamictal XR (extended release), Lamictal CD (chewable), and Lamictal ODT (dissolves on the tongue)], but a review of the 2021 payment data reveals that 200 mg Lamictal tablets accounted for nearly half the brand lamotrigine dispensed last year, and the average payment for those prescriptions was $1,132. While those prescriptions certainly helped skew the overall average reimbursement for lamotrigine upward, those were not the costliest lamotrigine prescriptions, as the subsample of 2021 Anticonvulsants included one prescription for extended-release lamotrigine (Lamicital XR), used to treat an injured worker with epilepsy, that resulted in a payment of $2,495. Even though lamotrigine represented only 1.0 percent of the Anticonvulsants dispensed to injured workers in 2021, and only 1 out of every 20 prescriptions was for a brand version of the drug, the high amounts paid for brand lamotrigine were enough to make it the fifth most costly Anticonvulsant in California workers' compensation in terms of total payments, as it consumed 2.4 percent of the Anticonvulsant drug spend.

Summary

In California workers' compensation, the total amounts paid for medications within a specific drug group reflect several factors besides the volume of prescriptions, including the fees that are allowed for the various drugs by the Pharmacy Fee Schedule, the average quantities and dosages dispensed, the mode of delivery, and the availability of generics. In addition, since 2018, both the overall utilization and total payments for each drug group have been affected by the extent to which drugs within the group are categorized by the MTUS Formulary as Exempt or Non-Exempt from prospective UR, are not listed in the Formulary (making them subject to prospective UR) or are included in the Formulary's "Special Fill" or "Perioperative" categories that restrict their use.

The results of this report highlight examples of low-volume/high-cost Anti-Inflammatory and Anticonvulsant drugs that may not draw a lot of attention, even though they have a disproportionate impact on the overall payments within their drug group. The presence of these drugs in workers' compensation is not an indictment of their ability to cure or relieve the effects of a work-related injury, though in many cases, less expensive versions of the same or similar medications are available so both payers and providers should make sure there is a sound, evidence-based rationale for prescribing them, and make that decision with full awareness of the alternatives that are available.

By definition, all of these drugs had a high average payment per prescription, though the reasons for those high payments vary, and in many instances overlap. In some cases, the drugs are single-source, brand drugs with no generic alternatives, so until the patent expires, the manufacturer has a monopoly on the medication, and in some of these situations the manufacturer has received FDA approval for a modified version of the drug (*e.g.*, an extended-release version, or a new dosage) which allows them to extend their patent and maintain control over pricing. In other cases, a medication may be a specialty drug such as a biologic, which is grown from living cells, making them more expensive to produce and more difficult to replicate, limiting the opportunities for the development of low-cost generics.

In addition, many of the low-volume/high-cost drugs are not listed in the MTUS formulary or the Medi-Cal database, and have no FUL, so reimbursements are set at 83 percent of the average wholesale price which is based on the manufacturer's pricing. Market forces come into play as well, as demand for various drugs has shifted as new formulations have been approved and come onto market, or after potential risks have come to light, resulting in the removal of a drug from the market or a mandatory black box warning, leading providers to seek alternative medications. The ten-year trends also show that average payments have often increased over time due to changes in the amount of medication dispensed per prescription, the dosage, the mode of delivery, the mix of brand vs. generic prescriptions, and the availability (or lack of availability) of over-the-counter versions of a drug.

Clearly, several drugs noted in this study experienced dramatic growth in their average reimbursement, if not in their utilization, as public awareness of the risks associated with long-term opioid use began to increase more than a decade ago and providers opted for greater use of Anti-Inflammatories and off-label use of Anticonvulsants to treat both acute and chronic pain. More recently, that trend accelerated following the adoption of the Opioid and Pain Management Guidelines and the MTUS Drug Formulary. Although the California Division of Workers' Compensation Pharmacy and Therapeutics (P&T) Committee, which recommends adjustments to the Formulary's drug lists, does not consider the cost of a medication in determining a drug's Exempt or Non-Exempt status, it continues to consider the addition of other detail, including strength and dosage, that could be used to classify a drug and help mitigate some of the factors that have led to the unfettered growth in the cost of some workers' compensation medications, including many of the low-volume/high-cost drugs spotlighted in this report.

Institute research on low-volume/high-cost medications will continue with Part II in the series, which will focus on medications found in the Dermatological, Opioid, and Antidepressant drug categories, while Part III will examine low-volume/high-cost Musculoskeletal and Ulcer Drugs. In the meantime, CWCI members who would like more detail on California workers' compensation prescription drug experience can log on to our website (www.cwci.org) and click Interactive Research Tools under the Research tab to access CWCI's Prescription Data Application as well as the MTUS Formulary Interactive Tool which has prescription data broken out by MTUS Formulary category.

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California Workers' Compensation Institute

The California Workers' Compensation Institute, incorporated in 1964, is a private, nonprofit organization of insurers and self-insured employers conducting and communicating research and analyses to improve the California workers' compensation system. Institute members include insurers that collectively write 79% of California workers' compensation direct written premium, as well as many of the largest public and private self-insured employers in the state. Additional information about CWCI research and activities is available on the Institute's website (www.cwci.org).

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