The Effects of Calcitonin Gene-Related Peptide Inhibitors on Migraine Days, Healthcare Use, and Workplace Productivity: A Markov Model Approach

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About KNG Health Consulting, LLC

KNG Health Consulting, LLC, is a health economics and policy consulting company assisting clients across all sectors of the healthcare industry. We're a small firm that thinks big. Our small size gives us the latitude to be flexible and responsive to our clients' specific and changing needs. And our big worldview, drawn from our collective experiences in the private, public, and academic sectors, drives us to create the best possible solutions to answer the health policy questions that are most important to our clients.

KNG Health provides a full range of services in partnership with our clients to assist them in navigating the changing healthcare landscape. Our work is focused in two practice areas: Evaluation and Health Economics, and Healthcare Reform and Payment Innovation. With each project, we apply our expertise in rigorous analytical techniques and qualitative research, our knowledge of health policy and payment systems, and our ability to translate our findings into actionable approaches.

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Abstract

Background: An estimated 13% of Americans are afflicted with migraine. Sufferers can experience significant healthcare and productivity costs. Many migraine sufferers find existing treatments ineffective or intolerable due to side effects. However, there have been few recent improvements in the market for preventive migraine therapies. Calcitonin gene-related peptide (CGRP) inhibitors are a new class of preventive migraine drugs, with several trials demonstrating their clinical efficacy and low rate of adverse effects.

Objective: To estimate the effect of CGRP inhibitors on patients and society for migraine sufferers not on preventive medicine because they currently lack good options, primarily due to ineffectiveness or intolerability of existing medicines.

Methods: We used a Markov model to estimate the effects of introduction of CGRP inhibitors on number of migraine days, healthcare use, and indirect costs for episodic migraine (EM) and chronic migraine (CM). The model was estimated over a 10-year period. We developed model assumptions on healthcare use, treatment effectiveness and tolerability, productivity, and population characteristics from literature review.

Results: Use of CGRP inhibitors was associated on average with fewer migraine days per year (EM: -18.68; CM: -29.20), fewer triptan uses per year (EM: -3.21; CM: -5.04), more physician visits for migraine per year (EM: 1.03; CM: 1.02), fewer emergency room visits per year (EM: -0.06; CM: -0.10), higher probability of full-time (EM: 0.03; CM: 0.02) and part-time employment (EM: 0.01; CM: 0.00), fewer lost productive hours per year (EM: -39.69; CM: -21.31), and less indirect cost over 10 years (EM: -$20,331; CM: -$11,176). Effects were generally greater for individuals with higher response to the drugs and varied by age and sex. If all migraine sufferers not on a preventive medicine used CGRP inhibitors, we estimate national indirect cost savings of $390 billion for EM and $6 billion for CM over 10 years, as well as national reductions in migraine days per year of 358 million for EM and 16 million for CM.

Conclusions: CGRP inhibitors offer potential benefits to migraine sufferers not currently on preventive treatment. These benefits include fewer migraine days, fewer uses of rescue drugs, greater likelihood of working, and less lost productive time.

I. Introduction

Migraine is a debilitating neurological condition in which painful headaches accompanied by nausea, vomiting, and sensory sensitivities occur. The International Classification of Headache Disorders, 3rd edition (ICHD-3), defines migraine as a recurrent disorder manifested by at least 5 lifetime attacks lasting 4-72 hours, with headaches encompassing at least 2 of the following 4 features: 1) unilateral predominance to pain, 2) throbbing/pulsating quality, 3) moderate/severe intensity, 4) worsening with routine activity; and also either the presence of nausea/vomiting or light and sound sensitivity.[1] Migraine is generally classified as either episodic (presence of headache fewer than 15 days per month) or chronic (presence of headache on 15 or more days per month, with headache meeting migraine criteria or being treated with acute medication at least 8 days per month, for at least 3 months)[1] with U.S. prevalence rates of 11.7%[2] and 1.0%,[3] respectively. Prevalence is much higher among women, who represent roughly 80% of sufferers.[4] For migraine sufferers who work, the amount of lost productive time, including missed work and lost productivity, is substantial. Over a 3-month period, those with episodic migraine (EM) lose an estimated 3.6 days of work while chronic migraine (CM) sufferers lose and estimated 17 days.[5] One estimate reported migraine-related healthcare costs and indirect productivity costs to be $78 billion per year.[6]

Treatments for migraine, including acute care treatment and preventive therapy, can help migraine sufferers manage their pain and reduce frequency of their attacks. However, there have been few recent improvements in the market for preventive migraine therapies. OnabotulinumtoxinA (Botox®) received approval from the U.S. Food and Drug Administration (FDA) for use in preventing CM in 2010.[7,8] Other available preventives are older medications that were originally developed to treat conditions other than migraine. Migraine sufferers often use a combination of approved and "off-label" medications on a trial and error basis in order to reduce frequency of attacks and alleviate symptoms.

Many migraine sufferers find existing treatments ineffective or intolerable due to side effects. An estimated 96% of individuals suffering from CM have a prescription for a preventive drug, while 52% of those with EM have a prescription for a preventive treatment. However, more than half of CM sufferers and more than a quarter of EM sufferers discontinue or switch drugs at least once, primarily citing lack of efficacy or tolerability/safety issues.[9]

Calcitonin gene-related peptide (CGRP) inhibitors are a new class of preventive migraine drugs that may address the need for new, effective medicines for migraine.[10] These drugs were developed primarily for reducing the burden of migraine without the problems of low adherence and tolerability associated with current preventive treatments. Several double-blinded, placebo-controlled clinical trials have established their clinical efficacy.[11] Additionally, these drugs also have the potential to diminish the number of adverse effects occurring during the treatment of migraine because of their specificity to their CGRP or CGRP-receptor targets. [12]

The purpose of this study is to estimate the value of CGRP inhibitor treatment for chronic and episodic migraine sufferers and society as a whole. As CGRP inhibitor drugs offer a new preventive therapeutic option with a novel mechanism of action, we focus on EM and CM migraine sufferers who no longer take a preventive medication, likely because of ineffectiveness or intolerability of existing treatments.

II. Methods

We developed a Markov model to assess the impact of CGRP inhibitors on clinical outcomes, healthcare utilization, and productivity for migraine sufferers not using alternative preventive treatments. Using microsimulation, we ran the model separately for EM and CM populations, performing 10,000 microsimulations under two treatment scenarios for each cohort: (1) no treatment (baseline); and (2) treatment with CGRP inhibitors. We ran all models using TreeAge Pro 2017 (TreeAge Software, Williamstown, MA). See Appendix 1 for further details on methods.

Populations. We ran the model separately for EM and CM populations, matching empirical distributions of EM and CM sufferers on age, sex, and uncontrolled migraine frequency at baseline (Table 1).

Table 1. Population Characteristics Used in Markov Model

Characteristic	Migraine Type	
	Episodic	Chronic
Sex[4]		
Female	80%	79%
Male	20%	21%
Age[4]		
<30	12%	11%
30–39	20%	16%
40–49	28%	28%
50–64	31%	34%
>65	9%	11%
Migraine Frequency[13]		
Mean days/month (sd)	4.23 (3.43)	19.13 (4.04)

Notes: sd = Standard Deviation

Treatment Scenarios. We tested two treatment scenarios for our cohort of migraine sufferers not using alternative preventive treatments:

1. Begin to use CGRP inhibitors; and
2. Baseline: continue with no preventive therapy.

We did not model the impact of CGRP inhibitors on a cohort of patients currently on existing preventive drugs, or a cohort of patients yet to try (and potentially see benefit from) existing preventive drugs. We based this decision on the following considerations. First, randomized control trials (RCTs) of existing therapies reflect outcomes for all migraine sufferers. Patients currently using these therapies are a select group, presumably seeing higher-than-average benefits from treatment. These patients are not well represented by RCTs. Second, patients who receive benefits from existing drugs may supplement with a CGRP inhibitor to see if this combination of drugs reduces the frequency and/or intensity of their

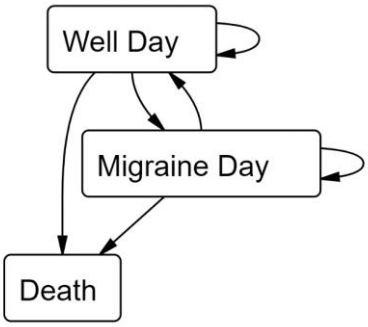
migraine. Our model, however, assumes that patients only use CGRP inhibitors. While we recognize that some patients may use multiple medications at once, to make the model tractable we did not model this scenario. Third, we expect CGRP inhibitor use mainly in patients who do not see successful treatment with existing preventive drugs, limiting the relevance of CGRP inhibitors to patients currently on or yet to try existing preventive drugs.

Model Structure*.* The Markov model structure remained similar across populations and treatment scenarios. We used a cycle length of one day and calculated results over a time horizon of ten years, with individuals aging over time. (We also looked at other time horizons, including 5-year and lifetime time horizons. Average annual impacts from CGRP inhibitor treatment did not change significantly under these alternatives and results are not shown.) The model contained three health states: (1) migraine day; (2) well day; and (3) death (Figure 1). We took the probability of transition to the death state from published actuarial tables, matching on age and sex. We took probability of transition to the migraine day state as baseline daily probability of migraine (no preventive treatment scenario) or baseline daily probability of migraine adjusted for CGRP inhibitor response (CGRP inhibitor treatment scenario), after adjusting for probability of death (See Appendix 1 for derivation of transition probabilities).

A migraine day was defined to correspond with the primary endpoint of the RCTs used for estimating CGRP inhibitor effectiveness. While these studies exhibited some variation in defining migraine day, they typically differentiated this endpoint from headache days, with migraine days being more severe and/or longer lasting. Individuals who found themselves in the migraine day state randomly chose whether to take triptans as an acute treatment, with probability of taking triptans on a given migraine day centered at 17.2%[14] but varying by individual. Triptans are a migraine-specific first-line prescription abortive treatment.[15] We capped use of triptans at 10 days out of every 30 (i.e., forced the probability of taking triptans on a given migraine day to 0 if an individual exceeded 10 triptan uses in the past 30 days), as overuse can worsen migraine.[16] Individuals in the migraine day state randomly experienced an emergency room (ER) visit due to uncontrolled migraine. Use of acute treatment reduced the probability of uncontrolled migraine.

For each individual, we randomly drew baseline probability of a migraine day, response to CGRP inhibitors, propensity to use acute treatment, probability of uncontrolled migraine, and efficacy of acute treatment in mitigating an uncontrolled attack. These values were drawn from empirical distributions obtained from published literature. We assumed no discontinuation of CGRP inhibitors due to adverse effects, as clinical trials show low rates of attrition. However, we did test the sensitivity of this assumption and report the results in the Appendix 2.

Figure 1. Markov Model Structure



Outcomes. We measured the following outcomes: migraine days, acute treatment uses, ER visits, physician visits, full-time employment, part-time employment, lost productive time (LPT), and dollar cost of disemployment and LPT. Lost productive time reflects time missed from work and time at work but less productive than during a non-migraine day. Disemployment reflects an individual not having a job because of migraine.

We tracked migraine days as the number of model stages an individual spent in the migraine day health state. We tracked acute treatment uses as the number of migraine days where an individual chose to take acute treatment. We tracked ER visits as the number of uncontrolled migraine attacks not successfully mitigated with acute treatment.

Physician visits were included based on having one visit upon initiating CGRP inhibitors and once annually thereafter for the CGRP inhibitor treatment scenario. We assumed no migraine-related physician visits for the baseline scenario. We assumed that individuals administer CGRP inhibitors without a physician office visit since the CGRP inhibitors are anticipated to predominantly be provided by self-injection, with oral versions in the pipeline.[12]

To measure the impact of CGRP inhibitors on likelihood of full- and part-time work, we attached age- and sex-specific national employment probabilities to each individual and applied a "penalty" to these probabilities for EM or CM, based on empirical employment rates among EM and CM sufferers.[4] We randomly assigned each individual a working status (full-time, part-time, not working) in the first year of the model based on these EM- and CM-adjusted probabilities. In subsequent years, we randomly assigned each individual a working status based on probabilities between the national and penalized rates, depending on the individual's rate of migraine in the prior year.

We converted empirical age- and sex-specific LPT per week estimates[17] into per migraine day figures, which we applied every time a working individual entered the migraine day state. These estimates incorporated the effect of migraine and treatment for migraine on missed work days for workers (absenteeism) and lost productivity at work (presenteeism).

We applied age- and sex-specific national wage information to estimate a dollar cost associated with disemployment and LPT. For each day of part- or full-time work, individuals accumulated wages. We calculated the cost of disemployment as wages we would expect an individual to receive if they experienced no migraine minus their accumulated wages. For each migraine day causing LPT, we tracked the lost wages associated with that LPT. We discounted these outcomes measured in dollars by 3% annually to account for the present value of future costs.

In presenting outcomes, we standardized each individual's result by their time alive in the model. In addition to average results for the entire population of EM/CM sufferers, we presented results for the top and bottom quartile of CGRP inhibitor response.

We translated average outcomes for EM and CM sufferers in our model into national figures by using empirical estimates of the number of Americans with EM or CM not on preventive treatment and multiplying average outcomes by this population size.

Empirical Parameters. Parameters were obtained from literature (Table 2). Whenever possible, we chose sources systematically reviewing primary research articles. For parameters related to CGRP inhibitors, we relied on a recently-published review of phase II and III RCTs of the new drugs.[11] We aggregated data from the RCTs cited (including results for Eptinezumab, Erenumab, Galcanezumab and Fremanezumab) in the review using a random-effects meta-analysis, implemented in Stata 14 (command -metan-). For direct and indirect costs, we searched for articles using data from the American Migraine Prevalence and Prevention study or the International Burden of Migraine Study, two prominent surveys of migraine sufferers, and utilized information from the Current Population Survey.[18,19,20,21] We took probability of death from actuarial tables,[22] adjusting based on age and sex. We tested the sensitivity of several empirical parameters and report results in the Appendix 2.

Table 2. Parameter Assumptions and Source for Markov Model

Parameter		Value (sd)	Source
Healthcare Use			
Triptan (acute medication) usage		17.2%	Friedman et al, 2009, Table 3[14]
Uncontrolled migraine/ED use		0.38% of migraine days	Friedman et al, 2009, Table 1[14]
Proportion on at least 1 preventive medication in baseline	EM	50%	Ford et al, 2017, Figure 3[9]
	CM	83%	
Treatment Effectiveness and Tolerability			
Triptan (acute treatment) effectiveness		43-76% relief	Cameron et al, 2015[23]
CGRP inhibitor effectiveness	EM	-1.664 (0.295) headache days/mo	Khan et al, 2017 (Reflects effectiveness for Eptinezumab, Erenumab, Galcanezumab, Fremanezumab)[11]
	CM	-2.248 (0.150) headache days/mo	
CGRP inhibitor attrition		0%	Khan et al, 2017[11]
Productivity			
2005 employment, migraine sufferers		Vary by age, sex, and population	Stewart et al 2010, Table 2[4]
2005/2017 employment, general population		Vary by age and sex	CPS Employment Tables 3[18] and 8[19]
2017 median weekly wages		Vary by age and sex	2017 CPS Demographic Table 3[20] (FT), 2017 CPS Table 38[21] (PT)
LPT	EM	Vary by age and sex	Serrano et al 2013 Table 3[17]
	CM	Vary by age and sex	Serrano et al 2013 Table 3[17]
Population Characteristics			
Mortality risk		Vary by age and sex	SSA 2014 Life Table[22]
National population		327,849,000	2018 Census population projection[24]
EM prevalence		11.7%	Lipton et al 2007[2]
CM prevalence		1.0%	Buse et al 2012[3]

Notes: EM = Episodic Migraine; CM = Chronic Migraine; PT = Part-time employment; FT = Full-time employment; LPT = Lost Productive Time; sd=standard deviation. See Appendix for additional details.

III. Results

We tracked average migraine days, triptan use, physician visits, ER visits, full- and part-time work, and LPT, under both treatment scenarios (no preventive treatment and CGRP inhibitors) over the full population and then separately for high- and low-responders (Table 3 and Table 5, respectively). We also reported the cost of disemployment, cost of LPT, and impact of CGRP inhibitor treatment on total productivity (disemployment plus LPT) for the same scenarios (Table 4 and Table 6). To identify high- and low-responders, we generated results for the 25% of individuals with the largest response to CGRP inhibitors (high-responders) and the 25% of individuals with the smallest response to CGRP inhibitors (low-responders). Finally, we reported national estimates of reduction in migraine days and productivity impacts from use of CGRP inhibitors by EM and CM suffers not currently on preventive treatment (Figures 2a, 2b, and 3).

Individuals receiving CGRP inhibitors experienced fewer migraine days per year (EM: -18.68; CM: -29.20) as compared to those in the baseline group not taking any preventive treatment. The average reduction in migraine days equates to removing all migraine days from 4.4 and 1.5 months of the year for EM and CM sufferers, respectively. As a result of fewer migraine days, EM and CM sufferers would take fewer triptans for uncontrolled migraine. Over the course of a year, we estimate that EM sufferers use 3.2 fewer rescue drugs (37% reduction) and that CM sufferers use 5 fewer rescue drugs (13% reduction). We estimate that CGRP inhibitor treatment would reduce average number of ER visits by 36% and 13% for EM and CM sufferers, respectively (EM: -0.06/0.18; CM: -0.10/0.82). However, use of CGRP inhibitors results in more physician visits per year (EM: 1.03; CM: 1.02) as a result of having to see a doctor to receive a prescription and for monitoring.

We estimate that use of CGRP inhibitors increases the probability of working full-time for both cohorts of migraine sufferers (EM: 0.03; CM: 0.02) (Table 3). In addition, use of CGRP inhibitors increases the probability of working part-time for EM (0.01) but does not change the probability of working part-time for CM (0.00). The use of CGRP inhibitors would significantly reduce LPT by 35% (39.69/112.78) and 9% (21.31/232.41) for EM and CM, respectively.

In Table 4, we show non-dollar average outcomes for the top and bottom quartile of individuals' responses to CGRP inhibitors. As expected, high responders to use of CGRP inhibitors experience fewer migraine days, take fewer doses of triptans, go to the ER fewer times, have higher probability of working full-time, and lose fewer productive hours than observed in the overall population. Generally, the differential effects between high- and low-responders are smaller for CM than for EM. The greatest variation appears to be in number of migraine days per year and LPT. For EM, the reduction in migraine days per year ranges from 15 days or 29% (low responders) to 22 days or 43% (high responders). With respect to LPT, we estimate a reduction of 32.6 hours or 28% (low responders) to 46.4 hours or 41% (high responders) for EM sufferers.

Among EM sufferers, use of CGRP inhibitors reduced cumulative 10-year (discounted) indirect costs by 41.3% ($20,331), with $12,458 due to higher wages because of increased likelihood of working and the rest due to reduced LPT (Table 5). Among CM sufferers, use of CGRP inhibitors reduced cumulative 10-

year indirect costs by 10.0% ($11,176), with $6,818 due to higher wages because of increased likelihood of working and $4,358 due to reduced LPT. These values translate into indirect cost benefits of roughly $2,000 and $1,000 per person per year for EM and CM, respectively. Among high-responders, the average annual indirect benefit from CGRP inhibitor use is $2,307 and $1,235 per person per year for EM and CM (Table 6). For low-responders, the corresponding values are $1,720 and $946 (Table 7). Men and individuals age 25-55, typically in the prime of their careers, experienced greater reductions in costs of disemployment and LPT than women and other age groups. The sex difference in indirect cost effects of CGRP inhibitor use is due to higher workforce participation among men than women and differences in average wages, perhaps driven by the employment of men in higher-wage occupations.

We estimate that use of CGRP inhibitors among those with EM and CM who do not currently use a preventive medication would yield a 10-year cumulative benefit of $396 billion in increased productivity. For EM sufferers, CGRP inhibitors would reduce indirect costs by $390 billion over 10 years, of which $239 billion is due to higher wages because of increased likelihood of working, $151 billion is due to reduced LPT, with $274 billion (70%) of this benefit due to improved productivity of women (Figure 2a). We estimate that using CGRP inhibitors would reduce indirect costs for CM sufferers by $6 billion over 10 years, of which $4 billion is due to higher wages because of increased likelihood of working, $2 billion is due to reduced LPT, with $5 billion (83%) accounted for by women (Figure 2b). Overall, we estimate that using CGRP inhibitors reduces total migraine days per year by 358 million for EM sufferers (women: 286 million; men: 72 million) and 16 million for CM sufferers (women: 13 million; men: 3 million) (Figure 3).

Table 3. Existing Migraine Sufferers Not on Preventive Therapy: 10-year Impact of CGRP Inhibitor Use

	Migraine Subtype	Baseline	CGRP Inhibitors	Difference	Percent Difference
Clinical Outcomes					
Migraine Days Per Year	EM	50.59	31.91	-18.68	-36.9%
	CM	232.33	203.14	-29.20	-12.6%
Acute Medication Use Per Year (Days)	EM	8.70	5.48	-3.21	-36.9%
	CM	39.95	34.91	-5.04	-12.6%
Utilization					
Physician Visits Per Year	EM	0.00	1.03	1.03	-
	CM	0.00	1.02	1.02	-
ER Visits Per Year	EM	0.18	0.11	-0.06	-36.4%
	CM	0.82	0.72	-0.10	-12.7%
Indirect costs					
Percent Working Full-Time	EM	0.46	0.48	0.03	6.0%
	CM	0.36	0.38	0.02	4.4%
Percent Working Part-Time	EM	0.10	0.11	0.01	7.7%
	CM	0.09	0.10	0.00	1.5%
Lost Productive Hours Per Year	EM	112.78	73.09	-39.69	-35.2%
	CM	232.41	211.10	-21.31	-9.2%

Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

Table 4. Existing Migraine Sufferers Not on Preventive Therapy: 10-year Impact of CGRP Inhibitor Use: High- & Low-level Responders Only

Measure	Migraine Subtype	High Responders				Low Responders			
		Baseline	CGRP Inhibitors	Difference	Percent Difference	Baseline	CGRP Inhibitors	Difference	Percent Difference
Clinical Outcomes									
Migraine Days Per Year	EM	50.93	28.90	-22.03	-43.3%	51.87	36.68	-15.19	-29.3%
	CM	232.57	200.99	-31.59	-13.6%	232.91	206.03	-26.88	-11.5%
Acute Medication Use Per Year (Days)	EM	8.76	4.98	-3.78	-43.2%	8.90	6.28	-2.62	-29.5%
	CM	39.96	34.54	-5.42	-13.6%	40.00	35.35	-4.65	-11.6%
Utilization									
Physician Visits Per Year	EM	0.00	1.02	1.02	-	0.00	1.02	1.02	-
	CM	0.00	1.01	1.01	-	0.00	1.04	1.04	-
ER Visits Per Year	EM	0.18	0.10	-0.07	-41.9%	0.18	0.13	-0.06	-30.0%
	CM	0.83	0.72	-0.11	-13.2%	0.82	0.72	-0.10	-12.1%
Indirect Costs									
Percent Working Full-Time	EM	0.45	0.48	0.03	7.3%	0.47	0.49	0.02	4.8%
	CM	0.35	0.37	0.02	5.3%	0.36	0.38	0.01	3.4%
Percent Working Part-Time	EM	0.10	0.11	0.00	2.4%	0.10	0.11	0.01	9.9%
	CM	0.10	0.10	0.00	0.4%	0.09	0.09	0.00	0.2%
Lost Productive Hours Per Year	EM	111.89	65.48	-46.41	-41.5%	116.53	83.93	-32.60	-28.0%
	CM	227.99	206.03	-21.97	-9.6%	232.38	211.06	-21.32	-9.2%

Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

Table 5. 10-year Cumulative Impact of CGRP Inhibitor on Indirect Costs Relative to Baseline (No Preventive Therapy)

Sex	Age group	Change in Cost of Disemployment	Percent Change Cost of Disemployment	Change in Cost of LPT	Percent Change Cost of LPT	Change in Total Indirect Cost	Percent Change Indirect Cost
Episodic Migraine							
Male	16-19	-9,829	-73.7%	-2,658	-32.7%	-12,487	-58.2%
	20-24	-6,450	-38.6%	-6,893	-30.7%	-13,343	-34.1%
	25-55	-19,914	-47.9%	-16,303	-36.1%	-36,217	-41.7%
	55-64	-18,617	-49.9%	-9,539	-36.1%	-28,155	-44.2%
	65-74	-6,619	-57.3%	-3,528	-30.6%	-10,146	-44.0%
	Total	-17,581	-48.8%	-12,840	-35.8%	-30,420	-42.3%
Female	16-19	-4,696	-51.7%	-3,205	-37.7%	-7,901	-44.9%
	20-24	-10,855	-48.4%	-5,816	-35.9%	-16,672	-43.2%
	25-55	-14,017	-46.6%	-8,277	-34.8%	-22,294	-41.4%
	55-64	-7,521	-38.5%	-4,741	-35.9%	-12,262	-37.4%
	65-74	-2,882	-44.2%	-1,486	-37.5%	-4,368	-41.6%
	Total	-11,194	-45.3%	-6,647	-35.1%	-17,841	-40.9%
Total		-12,458	-46.2%	-7,873	-35.3%	-20,331	-41.3%
Chronic Migraine							
Male	16-19	-1,789	-5.7%	-1,580	-11.9%	-3,369	-7.6%
	20-24	-2,956	-6.9%	-2,684	-11.7%	-5,640	-8.6%
	25-55	-12,224	-10.4%	-9,605	-9.3%	-21,829	-9.9%
	55-64	-6,986	-8.9%	-7,327	-10.1%	-14,313	-9.5%
	65-74	-3,080	-8.9%	-2,179	-9.7%	-5,259	-9.2%
	Total	-9,304	-10.0%	-7,708	-9.5%	-17,012	-9.8%
Female	16-19	-3,227	-13.9%	-552	-6.4%	-3,779	-11.9%
	20-24	-6,484	-13.3%	-1,433	-7.8%	-7,918	-11.8%
	25-55	-7,690	-10.6%	-4,273	-8.9%	-11,963	-9.9%
	55-64	-4,625	-10.7%	-3,219	-9.6%	-7,843	-10.2%
	65-74	-1,683	-12.2%	-999	-9.5%	-2,682	-11.1%
	Total	-6,147	-10.8%	-3,453	-9.0%	-9,600	-10.1%
Total		-6,818	-10.5%	-4,358	-9.2%	-11,176	-10.0%

Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

Table 6. 10-year Cumulative Impact of CGRP Inhibitor on Indirect Costs Relative to Baseline: High-level Responders Only

Sex	Age group	Change in Cost of Disemployment	Percent Change Cost of Disemployment	Change in Cost of LPT	Percent Change Cost of LPT	Change in Total Indirect Cost	Percent Change Indirect Cost
Episodic Migraine							
Male	16-19	0	-	-1,960	-21.1%	-1,960	-21.1%
	20-24	-2,431	-43.4%	-9,355	-36.2%	-11,786	-37.5%
	25-55	-25,082	-60.9%	-19,728	-42.4%	-44,811	-51.1%
	55-64	-13,141	-45.7%	-11,714	-38.2%	-24,855	-41.8%
	65-74	-6,028	-56.2%	-3,358	-39.7%	-9,386	-49.0%
	Total	-19,042	-57.9%	-15,526	-41.3%	-34,568	-49.0%
Female	16-19	-5,869	-51.7%	-3,289	-47.5%	-9,158	-50.1%
	20-24	-13,364	-56.6%	-6,814	-45.5%	-20,178	-52.3%
	25-55	-16,264	-54.5%	-9,786	-41.1%	-26,050	-48.6%
	55-64	-7,889	-41.8%	-5,161	-42.2%	-13,049	-42.0%
	65-74	-2,494	-54.2%	-1,615	-37.3%	-4,109	-45.7%
	Total	-12,602	-52.3%	-7,623	-41.5%	-20,225	-47.6%
Total		-13,882	-53.7%	-9,194	-41.4%	-23,076	-48.0%
Chronic Migraine							
Male	16-19	0	0.0%	-1,796	-13.3%	-1,796	-3.8%
	20-24	-1,178	-2.2%	-1,954	-14.7%	-3,132	-4.6%
	25-55	-14,360	-13.4%	-10,643	-10.2%	-25,003	-11.8%
	55-64	-6,326	-6.8%	-6,898	-11.7%	-13,225	-8.7%
	65-74	-4,582	-11.2%	-2,198	-9.1%	-6,780	-10.4%
	Total	-10,539	-11.5%	-8,267	-10.4%	-18,806	-11.0%
Female	16-19	-4,735	-27.8%	-422	-5.4%	-5,157	-20.8%
	20-24	-6,172	-9.2%	-1,638	-8.9%	-7,810	-9.1%
	25-55	-8,911	-11.6%	-4,091	-9.2%	-13,002	-10.7%
	55-64	-4,635	-10.6%	-3,542	-10.3%	-8,176	-10.5%
	65-74	-2,420	-18.7%	-945	-8.4%	-3,365	-13.9%
	Total	-7,047	-11.6%	-3,445	-9.3%	-10,491	-10.8%
Total		-7,827	-11.6%	-4,523	-9.8%	-12,351	-10.8%

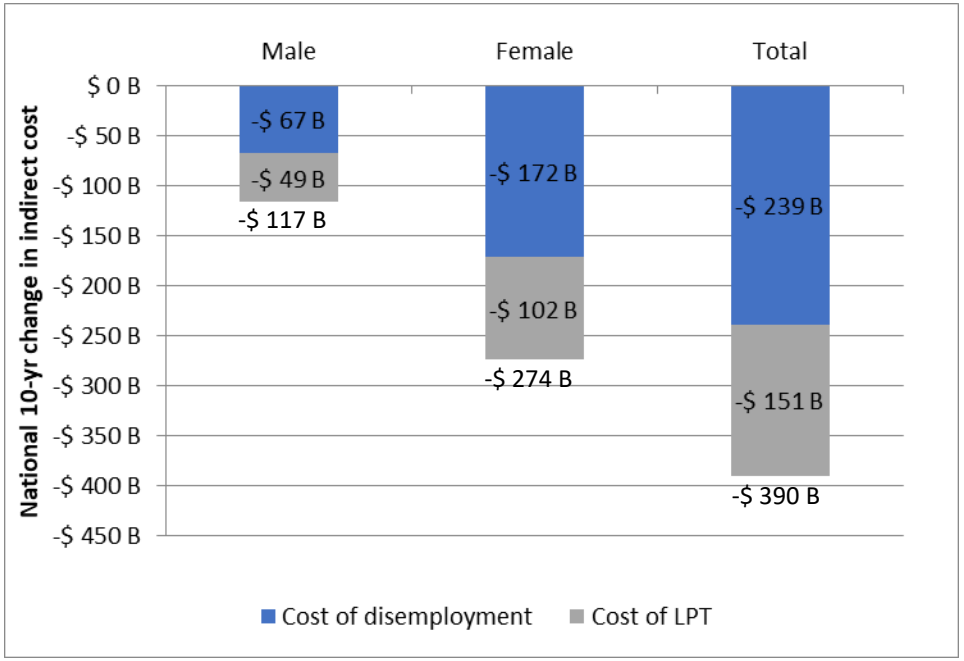
Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

Table 7. 10-year Cumulative Impact of CGRP Inhibitor on Indirect Costs Relative to Baseline: Low-level Responders Only

Sex	Age group	Change in Cost of Disemployment	Percent Change Cost of Disemployment	Change in Cost of LPT	Percent Change Cost of LPT	Change in Total Indirect Cost	Percent Change Indirect Cost
Episodic Migraine							
Male	16-19	-3,322	-30.2%	-2,904	-31.4%	-6,226	-30.7%
	20-24	-10,665	-30.4%	-5,811	-19.2%	-16,476	-25.2%
	25-55	-13,091	-35.4%	-13,580	-28.5%	-26,670	-31.5%
	55-64	-14,956	-47.4%	-7,707	-34.5%	-22,663	-42.0%
	65-74	-2,776	-21.2%	-2,537	-27.4%	-5,313	-23.8%
	Total	-12,086	-37.3%	-10,604	-29.1%	-22,691	-33.0%
Female	16-19	-4,053	-54.8%	-2,399	-27.6%	-6,452	-40.3%
	20-24	-11,779	-41.6%	-3,455	-23.3%	-15,235	-35.3%
	25-55	-12,715	-40.8%	-6,703	-27.7%	-19,428	-35.0%
	55-64	-6,931	-29.4%	-4,363	-27.9%	-11,294	-28.8%
	65-74	-3,361	-37.6%	-1,604	-34.7%	-4,966	-36.6%
	Total	-10,325	-38.7%	-5,492	-27.8%	-15,818	-34.1%
Total		-10,681	-38.4%	-6,523	-28.2%	-17,204	-33.8%
Chronic Migraine							
Male	16-19	0	0.0%	-1,003	-12.7%	-1,003	-2.5%
	20-24	0	0.0%	-3,524	-13.1%	-3,524	-5.0%
	25-55	-11,268	-9.3%	-8,397	-8.5%	-19,666	-8.9%
	55-64	-5,594	-7.1%	-8,746	-9.7%	-14,340	-8.5%
	65-74	-449	-1.6%	-2,053	-10.8%	-2,503	-5.2%
	Total	-7,747	-8.3%	-7,256	-9.0%	-15,003	-8.6%
Female	16-19	-1,557	-5.7%	-937	-9.0%	-2,494	-6.6%
	20-24	-8,673	-20.1%	-990	-5.7%	-9,663	-15.9%
	25-55	-5,054	-7.3%	-4,590	-9.3%	-9,645	-8.1%
	55-64	-4,182	-10.1%	-2,929	-9.2%	-7,111	-9.7%
	65-74	-1,370	-9.4%	-859	-9.0%	-2,229	-9.2%
	Total	-4,459	-8.2%	-3,522	-9.2%	-7,980	-8.6%
Total		-5,149	-8.2%	-4,306	-9.1%	-9,455	-8.6%

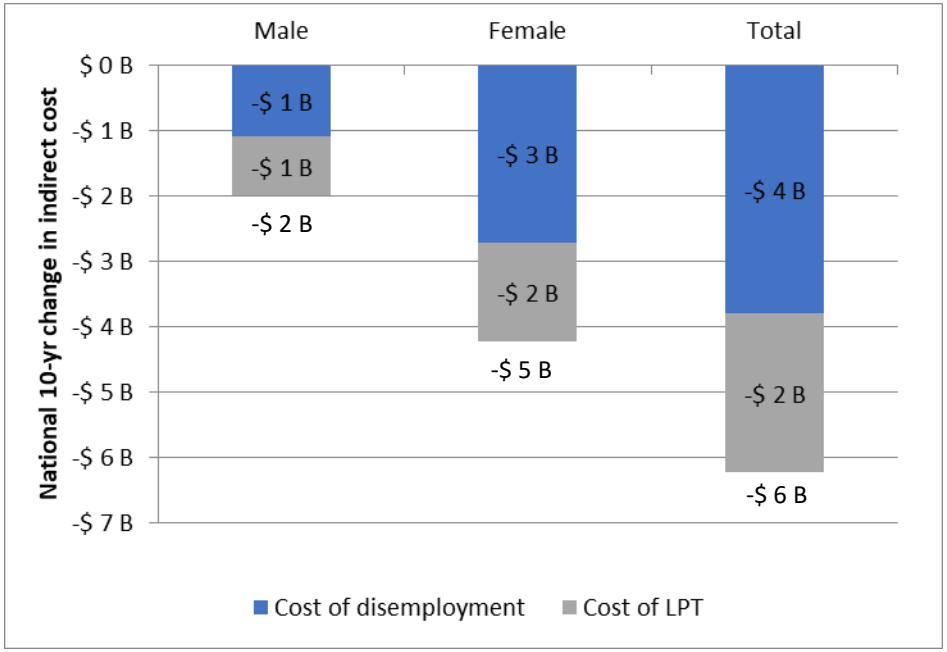
Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

Figure 2a. National 10-year Cumulative Indirect Cost Reduction from CGRP inhibitors by Sex - Episodic Migraine



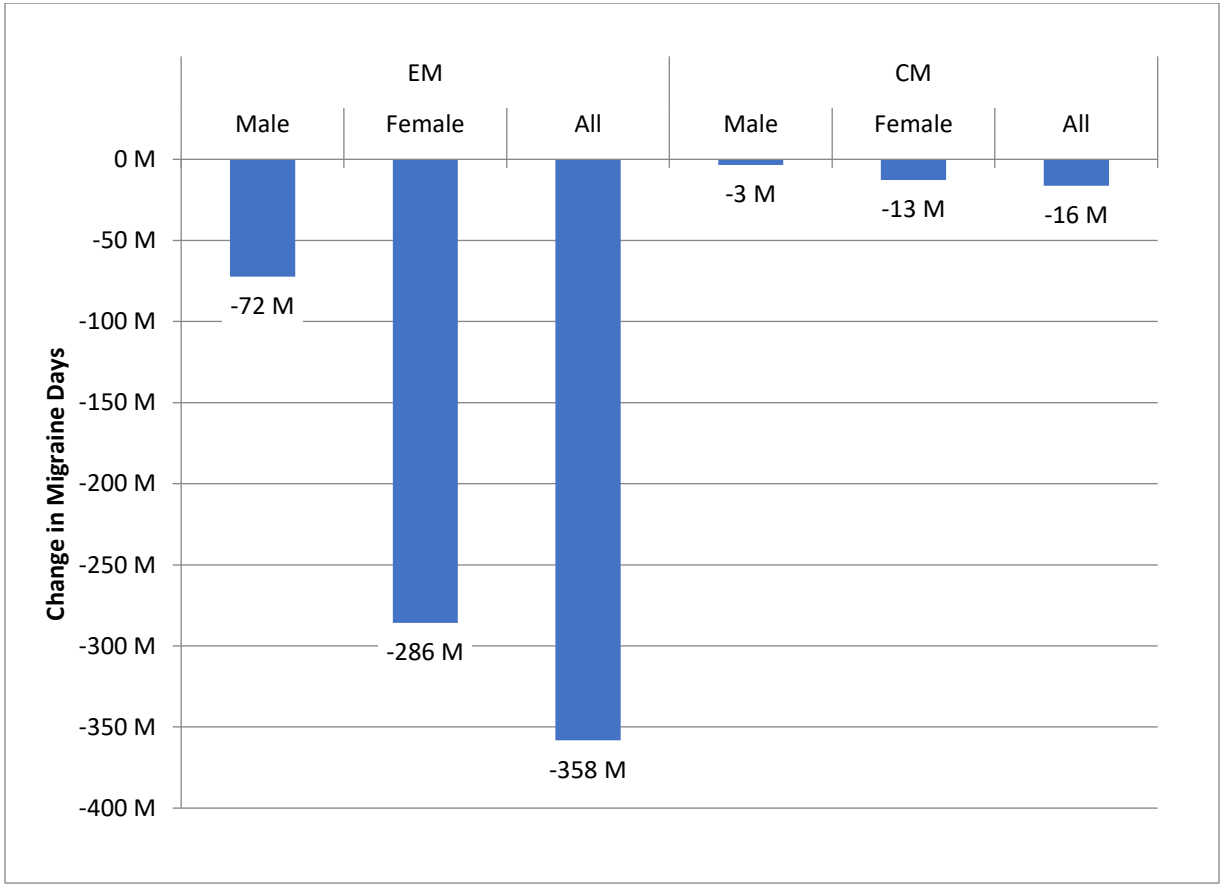
Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables.
LPT = lost productive time.

Figure 2b. National 10-year Cumulative Indirect Cost Reduction from CGRP inhibitors by Sex - Chronic Migraine



Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables. LPT = lost productive time.

Figure 3. National Change in Total Migraine Days from CGRP inhibitors per Year



Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

IV. Discussion

In this study, we estimated the value of CGRP inhibitor use for episodic and chronic migraine sufferers in terms of its potential effect on migraine days, acute drug treatments, and physician and ER visits, and its potential impact on work status and workplace productivity. We focus on EM and CM migraine suffers who do not take a preventive medication because they currently lack good options, primarily due to ineffectiveness or intolerability of existing treatments. Using published migraine prevalence rates and the percentage of migraine sufferers not on preventive treatment, we estimate this population may be as high as 19 million for EM and 557,000 for CM.

For our cohort of migraine sufferers not currently taking preventive treatment, we used a Markov model framework to examine our primary outcomes, using assumptions derived from literature and microsimulation. Overall, we find that the use of CGRP inhibitors as compared to no preventive drug therapy could reduce migraine days by between 29% and 43% (average 37%) for EM and between 12% and 14% (average 13%) for CM. The number of fewer migraine days translates into approximately 4.4 months of relief for EM sufferers and 1.5 months of relief for CM sufferers per year. We also estimate material impacts of CGRP inhibitor use on indirect costs as a result of fewer missed worked days, greater productivity at work, and more migraine sufferers in the workforce. Among EM and CM sufferers, use of CGRP inhibitors reduced cumulative 10-year (discounted) indirect costs by $20,331 and $11,176 per person, respectively. For both groups, 60% of the indirect cost benefits are attributed to higher working rates as a result of CGRP inhibitors.

With the FDA approval of CGRP inhibitors, migraine sufferers will have a new preventive therapeutic option to address this often-debilitating condition. The anticipation among migraine sufferers and the provider community is significant, as the new medicines could potentially herald a paradigm change in the way clinicians approach the disorder. CGRP inhibitors will be the first class of drugs for migraine prevention that is directly based on migraine pathophysiology and are expected to address many of the concerns with existing preventive options. A 2015 study demonstrated low adherence to the currently available oral migraine preventive medications (OMPMs), with only 26-29% of patients with chronic migraine persisting with their treatment at 6 months and only 17-20% persisting at 12 months.[25] Subsequent research has revealed that if a patient with chronic migraine discontinues his or her OMPM and switches to another drug, the likelihood that they will continue with this new medication is 10-13% at 12 months.[26] Experts have surmised that there are several reasons as to why OMPM have such poor adherence, including that these medications can take several weeks to work, require daily dosing, and may result in intolerable side effects.

The new CGRP inhibitors may address some of these issues that have resulted in non-adherence to current OMPMs. First, they are likely to be given monthly or quarterly and this less-frequent dosing schedule may result in fewer missed doses. Second, patients may see effects of CGRP inhibitors as early as 3 days after administration as compared to OMPMs, which can take several weeks before a recipient can assess their efficacy.[27] CGRP inhibitors show improved tolerability and fewer side effects over

OMPMs, with the most common side effects being injection site pain and upper respiratory tract infection.[28]

While our results suggest large benefits from CGRP inhibitor use among those not on a preventive therapy, the national impact of CGRP inhibitors on the quality of life, healthcare use, and productivity of migraine sufferers will depend on how many and who ultimately use these drugs. As payers and employers consider how to cover these new medicines, it will be critical for them to consider the lack of available alternative treatments for many patients and significant positive impacts on workforce productivity.

Our study has limitations that should be considered when interpreting the findings. First, we used effectiveness from clinical literature. However, these studies have exclusion criteria where if someone fails up to 3 prior treatments they are not included in the study. We assumed the efficacy estimates from the clinical trials would apply to a real-world, cohort of patients who are not currently taking preventive therapy. However, the clinical trial estimates may not generalize to this population. Second, we assumed that once a patient starts taking a CGRP inhibitor, they stay on the drug, although we reported on a sensitivity analysis that modifies this assumption. Third, we did not include in our productivity loss estimates the effects of migraine on productivity related to homemaking. Fourth, we did not include patients currently using other preventive treatments or newly diagnosed migraine sufferers, who may also use CGRP inhibitors and see benefits, potentially making the national impact larger than our estimates. Fifth, migraine sufferers may see their migraine frequency change over time, with some EM sufferers acquiring CM and some CM sufferers improving to EM.[3] We do not model these potential changes. Sixth, we treated all migraine sufferers not on preventive medication as potential users of CGRP inhibitors. This is likely a good assumption for those who do not use existing preventive medications because of ineffectiveness or intolerability, and those who demand faster-working medication or do not want daily doses or frequent physician visits. Others may refrain from using existing medications because of access issues or because their migraine is mild enough to control with acute medications. These sufferers may not be potential users of CGRP inhibitors. Finally, we used a 12.7% combined EM and CM prevalence rate for our national estimates, while more recent findings suggest a prevalence rate of 15.3% (roughly 1 in 6).[29] From this perspective, our national estimates may be conservative. We did not use the more recent finding because it did not break out EM and CM.

Migraine is a debilitating condition that imposes significant costs on those who suffer from the condition, their family members, and on society as a whole. In this study, we estimate significant potential benefits from the introduction of CGRP inhibitors, a new class of preventive drugs for migraine. These drugs have the potential to improve the quality of life of EM and CM sufferers as well as allow these individuals to be more productive at work.

V. Appendix 1: Methods

Population demographics. We took probability of male/female and probability of different age categories separately for EM and CM from Stewart et al 2010, Table 1. Within each age category, we assigned individuals a specific age randomly using a uniform distribution.

Baseline migraine probability. We took baseline migraine frequencies from Houle et al, 2013, a study based on AMPP data. The authors' data table lists raw and fitted population samples by headache days per month. We used their negative binomial fitted model. We took those with 1-14 headache days per month as the episodic migraine population. This population had a weighted average of 4.23 headache days per month, standard deviation 3.43. We took those with 15-30 headache days per month as the chronic migraine population. This population had a weighted average of 19.13 headache days per month, standard deviation 4.04. Individuals in the model drew an integer number of headache days per month, with probability of each integer given by the Houle et al fitted population samples. For the CGRP inhibitor treatment scenario, we modified these migraine frequencies by preventive treatment effectiveness estimates.

Transition probabilities. We took annual mortality rates from the 2014 Social Security Administration life tables, matching on age and sex. The probability of entering the death state in each stage was given by $\mathrm{P}(death) = 1 - \left(1 - MortRate_{age,sex}\right)^{\frac{1}{365.25}}$.[i] For the baseline scenario, we took probability of entering the migraine day state as $\mathrm{P}(migraine) = \left(1 - \mathrm{P}(death)\right) * ProbBaseline$).[ii] For the CGRP inhibitor treatment scenario, we took probability of entering the migraine day state as $\mathrm{P}(migraine) = \left(1 - \mathrm{P}(death)\right) * (ProbBaseline + \frac{CgrpEff}{30})$.[iii] We took probability of entering the well day state as $\mathrm{P}(well) = 1 - \mathrm{P}(death) - \mathrm{P}(migraine)$.[iv]

Triptan (acute medication) use and effectiveness. If an individual had used no more than 10 acute treatments in a 30-day cycle, we took probability of using an acute medication on a migraine day from Table 3 of Friedman et al, 2009, based on AMPP data. The authors list 2,015 Triptan or dihydroergotamine users among migraine sufferers who used the ER, and 303 users among those who did not use the ER. The study included 13,451 total migraine sufferers, yielding 17.2% probability of using acute medication. We took acute medication effectiveness from Cameron et al, 2015, which lists 43-76% migraine relief from Triptan within 2 hours as the first statistic in their discussion section. On migraine days where individuals took acute treatment, we reduced the probability of uncontrolled migraine by a factor between 0.43 and 0.76, randomly drawn from a uniform distribution.

Uncontrolled migraine/ER use. We took rate of uncontrolled migraine leading to an ER visit from Table 1 of Friedman et al, 2009. The authors present number of ER visits in the prior year for individuals with

[i] P(*death*) is probability of entering the death state, $MortRate_{age,sex}$ is annual age- and sex-specific mortality
[ii] P(*migraine*) is probability of entering the migraine day state, *ProbBaseline* is an individual's baseline daily probability of experiencing a migraine day
[iii] *CgrpEff* is an individual's response to CGRP inhibitors measured in reduced migraine days per 30
[iv] P(*well*) is probability of entering the well day state

migraine (a population distinct from chronic daily headache). The table presents the proportion of individuals with 0, 1, 2, 3, 4-6, 7-10, and >10 visits. We split the proportion for 4-6 equally between 4, 5, and 6 visits. We split the proportion for 7-10 equally between 7, 8, 9, and 10 visits. We split the proportion for >10 visits equally between 10, 11, 12, 13, 14, and 15 visits. We divided the weighted average visits per year (0.191) by average migraine days per year (50.71, from 4.23 per month) for episodic migraine to get 0.0038 ER visits per migraine day. This 0.38% probability was reduced by 43-76% on days when triptans were used.

CGRP inhibitor effectiveness and attrition. We considered clinical trials compiled by Khan et al, 2017 and focused on those trials that reported outcomes in migraine days per month and separated EM and CM populations. We took the best efficacy result over placebo for each specific drug and population, assuming that use of CGRP inhibitors will follow the treatment protocols that show the best evidence. For EM, this included Dodick et al 2014 for Epitnezumab and Galcanezumab, Goadsby et al 2017 for Erenumab, and Bigal et al 2015 for Fremanezumab. For CM, this included Tepper et al 2017 for Erenumab and Silberstein et al 2017 for Fremanezumab. We performed a random-effects meta-analysis on these efficacy figures using the -metan- command in Stata 14 to achieve a single effectiveness over placebo value and standard error for each population. For this same set of trials, we examined the rate of attrition over placebo. Performing random-effects meta-analysis, we discovered that CGRP inhibitors had a lower rate of attrition (-3%), with very low levels of attrition in both the treatment and placebo arms (0% for many, at most 5%). Accordingly, we assigned no discontinuation due to adverse effects.

Indirect costs. We calculated indirect cost data in five steps:

1. *Baseline likelihood of employment*. For each age between 16 and 99, we calculated male and female general population probabilities of full-time and part-time employment. We calculated probability of any employment (i.e., either full- or part-time) from the 2017 CPS Employment Table 3, applying the probabilities for age categories to each age in the category and using the most granular age categories reported separately for men and women. We calculated probabilities of full- and part-time work, conditional on employment, from the 2017 CPS Employment Table 8, again applying the probabilities for age categories to each age in the category and using the most granular age categories reported separately for men and women. Multiplying together yielded age- and sex-specific general population probabilities of full- and part-time employment that we applied to individuals in the model.
2. *Migraine penalty*. We took probability of full- and part-time employment for EM and CM populations from Stewart et al 2010, Table 2, based on 2005 data. We compared these empirical probabilities of migraine sufferers working to hypothetical probabilities of full- and part-time working if the migraine population displayed nationally-representative employment characteristics. To find these hypothetical probabilities, we followed a similar procedure to step 1, but using 2005 CPS data and generating a single aggregate figure for the EM population and the CM population, rather than an individual probability. To calculate the aggregate hypothetical figure, we took CPS age- and sex-specific probabilities of employment and probabilities of full- and part-time work conditional on employment. We multiplied to get age- and sex-specific probabilities of full- and part-time employment. We combined this information

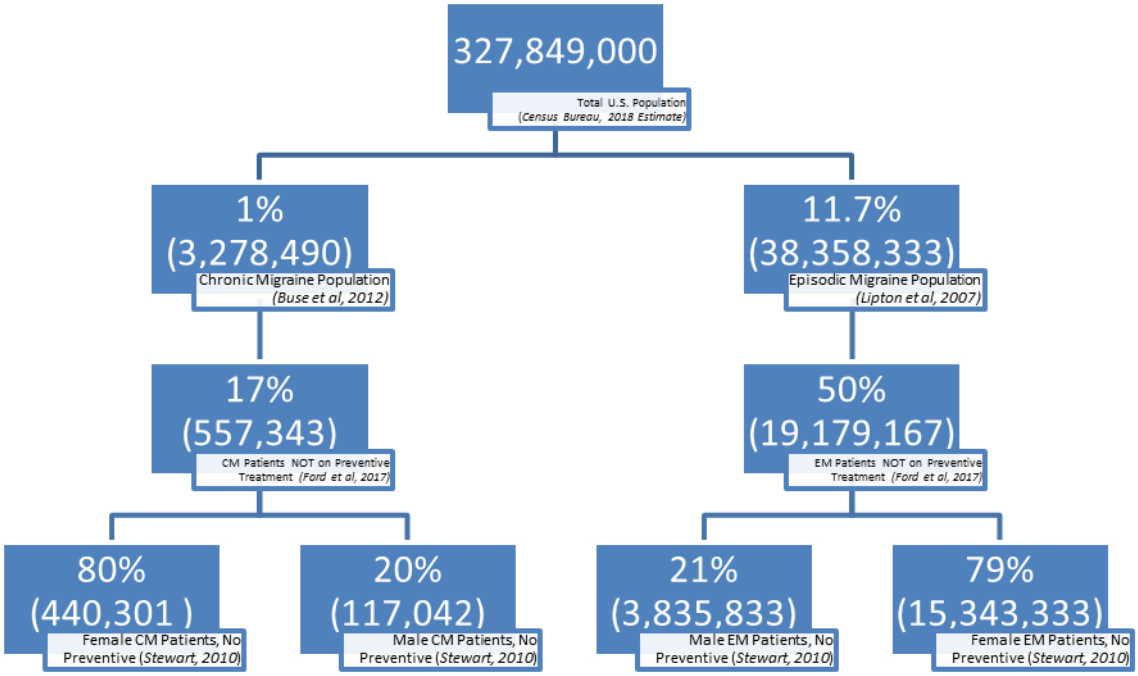
with the EM- and CM-specific distributions of sex and starting age in our model to achieve hypothetical EM and CM employment probabilities. We took the ratio of empirical rates of full- and part-time employment to the hypothetical rate as a "migraine penalty".

3. *Selection each year.* In the first year of the model, we based employment status on a penalized probability of working full- or part-time. We took the individual-specific national probabilities calculated in Step 1 and multiplied by the penalty calculated in Step 2. For each individual, we drew a random number from a uniform distribution between 0 and 1. If the random number was less than the individual's probability of working full-time, we assigned them to full-time work. If the random number was greater than the full-time probability but less than the full-time probability plus the part-time probability, we assigned them to part-time work. Otherwise, we assigned them to no work. In subsequent years, we blended the national and penalized probabilities, based on the number of migraine days incurred in the prior year. For instance, if an individual experienced a migraine frequency in the first year that was 60% lower than their baseline migraine frequency, then in the second year the employment probabilities would be weighted 60% based on the national figure and 40% based on the penalized figure. Each year, individuals randomly redrew work status based on the applicable probabilities.
4. *Lost Productive Time (LPT).* We took age- and sex-specific estimates of LPT cost per week for EM and CM from Serrano et al 2013, Table 3. We divided groups' average hourly wage (given in the same table) to get age- and sex-specific estimates of LPT per week in hours. These estimates incorporated the effects of both absenteeism and presenteeism. The estimates also combined full- and part-time workers. The paper included a sample of roughly 80% full-time workers and 20% part-time workers. We assumed that workers' likelihood of undergoing LPT was proportional to their hours worked. We also assumed that full-time employees work 40 hours per week on average and part-time employees work 20 hours per week on average. Therefore, we took weekly LPT as $\mathrm{LPT}_{fulltime,age,sex} = \frac{\mathrm{LPT}_{total,age,sex}*40}{0.8*40+0.2*20}$, $\mathrm{LPT}_{parttime,age,sex} = \frac{\mathrm{LPT}_{total,age,sex}*20}{0.8*40+0.2*20}$. We divided weekly LPT by baseline average migraine days in a week to achieve an LPT per migraine day figure, specific to EM/CM, age, and sex. Every time an individual was in the migraine day state, we incremented their LPT by the appropriate figure.
5. *Dollars*. We took average weekly full-time wages from the 2017 CPS Demographic Table 3, and average weekly part-time wages from the 2017 CPS Table 38, using the most granular age categories reported separately for men and women. We divided by seven to get daily wages. For each stage in the model an individual was alive and working, they earned wages equal to the appropriate daily wage. We divided weekly wages by 40 or 20 to get hourly figures for full- and part-time, respectively. We calculated the cost of disemployment as wages we would expect an individual to experience if they had no migraine (i.e., no penalty) minus the wages accumulated in the model. For stages in the model an individual was working and in the migraine day state, we incremented the dollar cost of their LPT by the appropriate hourly wage multiplied by LPT hours incurred on that migraine day. Wages and LPT cost were discounted by 3% annually, implemented by multiplying wages earned or LPT cost experienced on a day by $0.97^{StageNum/365.25}$.

Standardizing outcomes. We reported outcomes that accounted for differences in days alive in the model across individuals, treatment scenarios, and populations. While EM/CM and treatment scenario did not affect mortality rates, small differences in average days alive could still affect results. We divided each total outcome for an individual (e.g., total migraine days, total days worked full-time, or total LPT hours) by the individual's days alive in the model. For some outcomes (e.g., migraine days, triptan uses, and ER visits), we multiplied by 365 to attain a yearly figure, standardized for days alive. For dollar outcomes, we multiplied by 3,650 to attain a cumulative 10-year figure, standardized for days alive. For other outcomes (e.g., days working full-time), we did not re-inflate our results, attaining a proportion of days alive in which the outcome attained (i.e., a probability of that outcome occurring).

National figures. We took total a 2018 US population projection from the Census. We combined this with estimates of episodic migraine prevalence from Lipton et al 2007 and chronic migraine prevalence from Buse et al 2012 (both based on the AMPP) to get EM and CM population sizes. In these populations, our cohort of interest is those not on any preventive treatments. Ford 2017 lists rates of using no preventive treatments by EM/CM, giving a final population size of 17,539,922 for EM and 557,343 for CM. We further separated these populations into men and women, with sex ratios given in Table 1 (Figure A1). We calculated total reduction in migraine days per year and total cumulative 10-year indirect costs by taking those average outcomes, broken out by sex and adjusted for days alive, and multiplying by the sex-specific population of interest. We summed across men and women, EM and CM to get grand total figures.

Figure A1. National Migraine Populations



VI. Appendix 2: Sensitivity Analyses

In our base models, we assumed no discontinuation of CGRP inhibitors over the 10-year time horizon. Our assumption was based on a meta-analysis of CGRP inhibitor RCTs as reported in Khan et al[11]. In Table A1, we report results under an alternative assumption regarding continuation rates among CGRP inhibitor users. Specifically, we used the result of another analysis (not reported) in which we established a minimum effectiveness threshold for continuous CGRP inhibitor use. This minimum threshold value was established by running our model over existing preventive treatments and establishing the threshold at a value that produces a percent of migraine sufferers not on any preventive drugs that matches empirical estimates of this population. Applying the minimum thresholds, we found that 51% and 67% of EM and CM sufferers, respectively, would be on a CGRP inhibitor at the end of the 10-year time horizon. Relative to our base model findings, outcomes under this scenario are roughly reduced in proportion to the percentage of EM and CM sufferers that discontinue the use of a CGRP inhibitor (Table A1).

We also performed sensitivity analyses around several of our empirical parameter assumptions. In the base models, we assigned each individual using CGRP inhibitors a unique drug effectiveness drawn from a distribution given by our meta-analysis. In sensitivity analyses, we instead gave all individuals effectiveness values given by the center of the distribution, the center less the standard error, and the center plus the standard error (altered parameters in Table A2). These alternative effectiveness values altered the average reduction in migraine days per year (Figures A2a and A2b). We further examined the effects on indirect cost savings of varying migraine employment penalty, baseline wages, baseline probability of working full- and part-time, and LPT per migraine (Figures A3a and A3b). We chose lower and upper values of plus or minus 10% of base model values. Varying LPT per migraine was less impactful than varying penalty, wages, and probability of employment, likely because LPT per migraine impacts only the cost of LPT, while the other parameters affect both cost of LPT and cost of disemployment. Varying migraine penalty for EM sufferers yielded the greatest variation in indirect costs among specifications tested.

Table A1. Existing Migraine Sufferers Not on Preventive Therapy: 10-year Impact of CGRP Inhibitor Use with Discontinuation

	Migraine Subtype	Baseline	CGRP Inhibitors	Difference	Percent Difference
Clinical Outcomes					
Migraine Days Per Year	EM	50.57	41.60	-8.96	-17.7%
	CM	232.30	212.85	-19.45	-8.4%
Acute Medication Use Per Year (Days)	EM	8.69	7.16	-1.54	-17.7%
	CM	39.92	36.58	-3.34	-8.4%
CGRP Inhibitor Use					
Percent of CGRP Inhibitor (at End of 10 Year Time Horizon)	EM	0.00	0.51	0.51	-
	CM	0.00	0.67	0.67	-
Utilization					
Physician Visits Per Year	EM	0.00	0.65	0.65	-
	CM	0.00	0.76	0.76	-
ER Visits Per Year	EM	0.18	0.15	-0.03	-16.7%
	CM	0.82	0.75	-0.07	-8.5%
Indirect costs					
Percent Working Full-Time	EM	0.45	0.47	0.02	4.4%
	CM	0.35	0.36	0.01	2.9%
Percent Working Part-Time	EM	0.10	0.11	0.01	10.0%
	CM	0.09	0.09	0.00	0.0%
Lost Productive Hours Per Year	EM	109.60	90.82	-18.78	-17.1%
	CM	229.80	216.22	-13.58	-5.9%

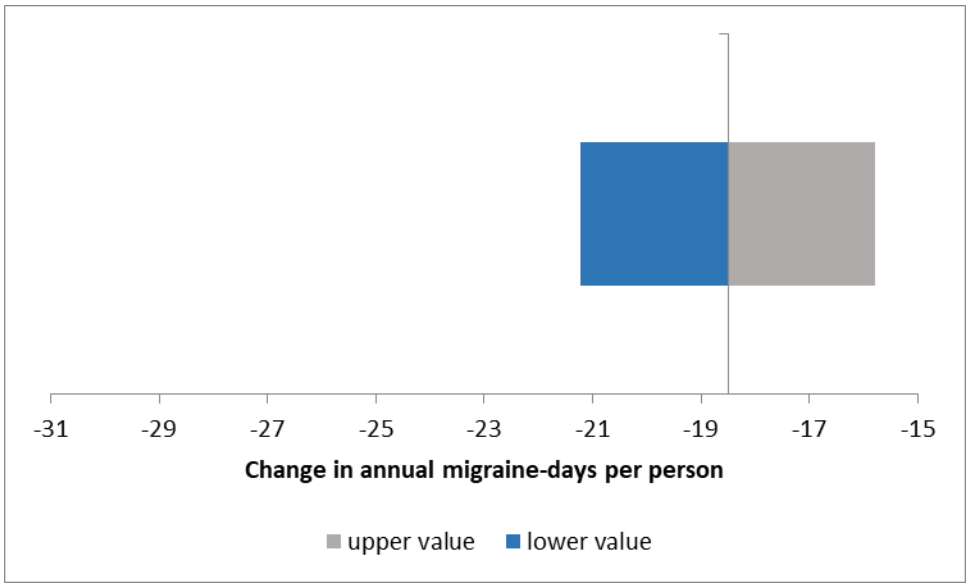
Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables

Table A2. Alternative Parameters for Tornado Diagrams

Parameter		Central Value	Lower Value	Upper Value
CGRP inhibitor effectiveness	EM	-1.664 days per month	-1.959 days per month	-1.369 days per month
	CM	-2.248 days per month	-2.398 days per month	-2.098 days per month
Migraine Employment Penalty	EM	88% of FT national rate, 85% of PT national rate	80% of FT national rate, 76% of PT national rate	97% of FT national rate, 93% of PT national rate
	CM	73% of FT national rate, 76% of PT national rate	65% of FT national rate, 69% of PT national rate	80% of FT national rate, 85% of PT national rate
Baseline Working Probability		Vary by Age and Sex	0.9 * (Central Value)	1.1 * (Central Value)
Baseline Wages		Vary by Age and Sex	0.9 * (Central Value)	1.1 * (Central Value)
LPT per Migraine Day		Vary by Age and Sex	0.9 * (Central Value)	1.1 * (Central Value)

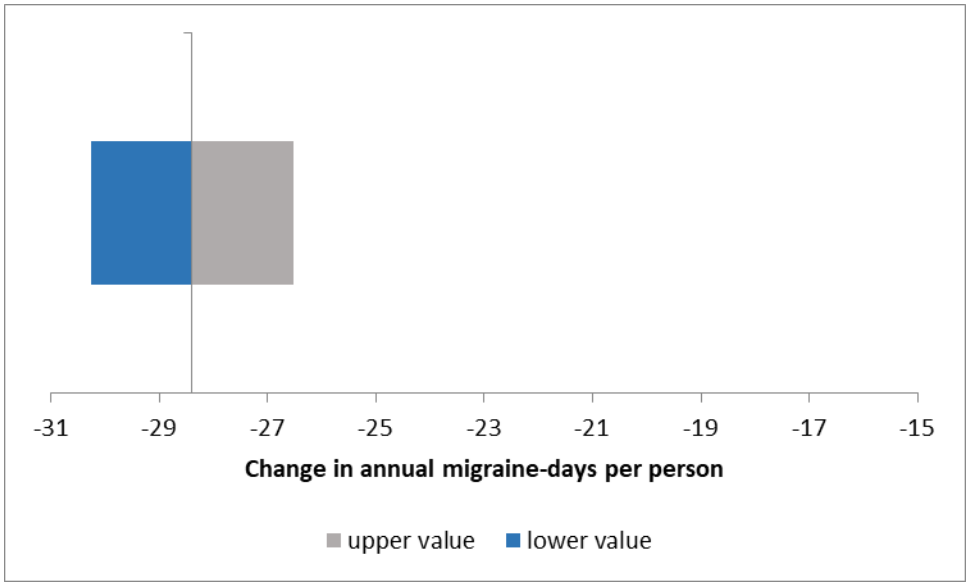
Notes: EM = Episodic Migraine; CM = Chronic Migraine; FT = Full-time; PT=Part-time; LPT = Lost Productive Time

Figure A2a. Change in Migraine Days per Year from CGRP Inhibitor Use, 1 Standard Error Around the Mean – Episodic Migraine



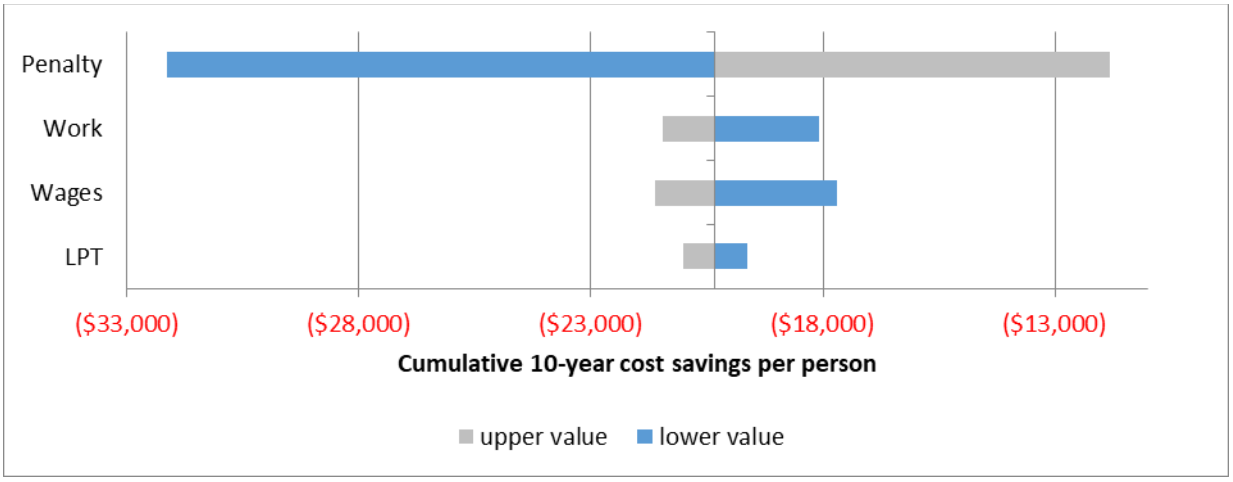
Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables.

Figure A2b. Change in Migraine Days per Year from CGRP Inhibitor Use, 1 Standard Error Around the Mean – Chronic Migraine



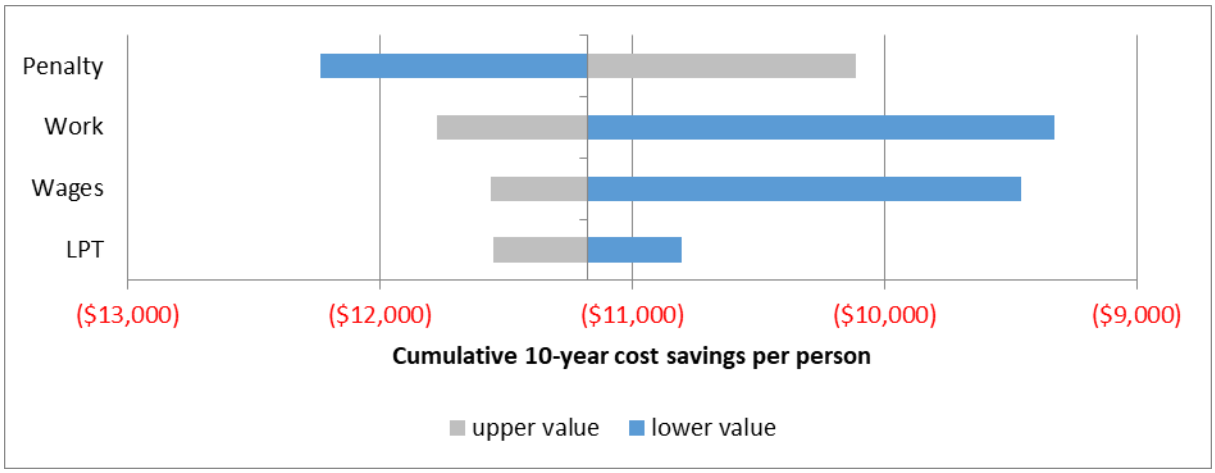
Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables.

Figure A3a. Change in Indirect Cost from CGRP Inhibitor Use, 10% Variation – Episodic Migraine



Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables.

Figure A3b. Change in Indirect Cost from CGRP Inhibitor Use, 10% Variation – Chronic Migraine



Source: KNG Analysis based on a Markov model populated using values from migraine literature and Census Bureau tables.

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