

# Subcutaneous CGRP Antagonist Injections: A Novel Approach to the Treatment of Chronic Migraines

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## Abstract

Nearly 4 million Americans suffer from chronic migraines. These patients have severe headaches that occur for 15 or more days a month, leading to a diminished quality of life. Current recommended therapy is not conducive to all patients, as one study shows 68% of these patients experience at least one medication treatment failure<sup>1</sup>. Within the last few years, the FDA has approved new medications, known as CGRP antagonists, that are proving to be efficacious in the treatment of chronic migraine.

## Introduction

A migraine is defined as a severe headache that lasts from 4-72 hours and is frequently pulsatile, unilateral and associated with certain features of neurologic dysfunction, such as photophobia, phonophobia, or vertigo. Episodes often begin following a stimulus, such as stress, the consumption of certain foods or alcohol, barometric pressure changes, hormonal fluctuations, or lack of sleep<sup>2</sup>.

## Current Treatment Options

- Headache diary and trigger avoidance
- Abortive: NSAIDs (ibuprofen, acetaminophen, Excedrin), Ergots (ergotamine tartrate), Triptans (frovatriptan, rizatriptan)
- Prophylactic: Beta blockers (metoprolol, timolol), Antiepileptics (topiramate, valproate), Antidepressants (amitriptyline, venlafaxine)<sup>3</sup>

## CGRP Antagonists

Migraines are caused by the “trigeminovascular complex”<sup>4</sup>. Intracranial vessels are innervated by fibers of the trigeminal nerve that are activated when a migraine sufferer experiences a triggering stimulus that causes vasodilation of cranial vessels. This vasodilation causes the nerve fibers within vessels to release peptides known as calcitonin gene-related peptides (CGRPs). CGRPs synapse with mast cells and muscle cells that promote inflammation within the meninges that perpetuates a migraine. In 2018, the FDA approved three CGRP antagonists for migraine prevention—erenumab, fremanezumab, and galcanezumab. These medications are monthly or quarterly subcutaneous injections that bind to the CGRP ligand or receptor to prevent migraine<sup>5</sup>.

## Summary of Findings

### Efficacy

The efficacy of erenumab, fremanezumab, and galcanezumab on chronic migraine days compared to baseline are listed in the table.

### Safety

The safety of these medications is questioned due to the lack of long-term data on their effects. Injection site reaction was the most common side effect for all medications, followed by rhinitis, constipation, diarrhea, anxiety, and depression<sup>14</sup>. Some experts advise against their use in patients with cardiovascular disease due to the medication’s antagonism of vasodilatory effects that could increase vasoconstriction<sup>14,15</sup>. However, studies did not find any significant differences in vascular events versus placebo. CGRPs are also believed to play a role in regulating placental blood flow and nutrient exchange by increasing vasodilation<sup>16</sup>. It is proposed that blocking the role of these peptides could lead to pregnancy complications, however no trials have been conducted with pregnant patients. It is not recommended to prescribe CGRP antagonists in this group.

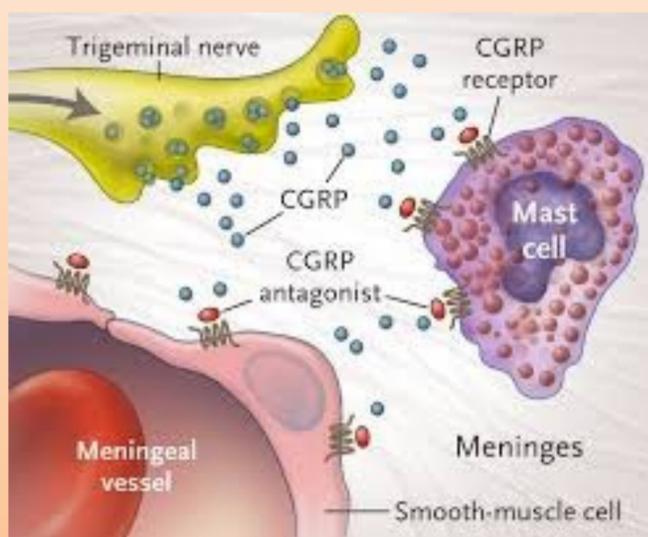
### Cost

CGRP antagonists are considered specialty medications and are only covered by 22% of insurance carriers surveyed<sup>17</sup>. Plans that cover CGRP antagonists commonly require prior authorization under the contingency that the patient failed two prior medications. GoodRx.com pricing for CGRP antagonist injections range from \$690-\$740 per unit. Injections can be given monthly or quarterly<sup>18</sup>. Alternative prophylactic medications are significantly more affordable; amitriptyline \$12.00/mo, valproate sodium \$40.00/mo, topiramate \$36.00/mo.

## Conclusion & Recommendations

- Trials show reduction in headache days vs placebo in episodic and chronic migraine groups
- CGRP antagonists diminished migraine days by between -1.8 days and -9.2 days per month
- The most common short-term side effects are injection site irritation, rhinitis, constipation, diarrhea, anxiety and depression
- Limited data on long-term side effects: caution in patients with vascular comorbidities; no studies available with pregnant subjects
- CGRP antagonists cost an average of \$600 more per month than alternative prophylactic migraine medications
- Support all therapy with headache diaries
- Suggest lifestyle modifications with trigger avoidance
- Initiate therapy with triptans for abortive coverage against breakthrough migraines; add beta-blockers or antiepileptics for prophylactic measures as needed
- If initial therapy failure occurs, CGRP antagonists are safe and effective treatment options

CGRP Antagonist Medication	Research Author	Treatment	Decrease in no. of migraine days from baseline (per month)
Erenumab	Tepper et al <sup>6</sup>	• 70 mg monthly	-6.6
		• 140 mg monthly	-6.6
	Dodick et al <sup>7</sup>	• 70 mg monthly	-2.9
		• 140 mg monthly	-3.7
	Reuter et al <sup>9</sup>	• 140 mg monthly	-1.8
Fremanezumab	Ferrari et al <sup>10</sup>	• 675 mg month 1, 225 mg month 2 & 3	-3.5
		• 675 mg quarterly	-3.1
	Dodick et al <sup>11</sup>	• 225 mg monthly • 675 mg quarterly	-8.9 -9.2
Galcanezumab	Detke et al <sup>12</sup>	• 120 mg monthly	-2.1
		• 240 mg monthly	-1.9
	Stauffer et al <sup>13</sup>	• 120 mg monthly • 240 mg monthly	-4.7 -4.6



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