Review began 10/02/2023 Review ended 10/06/2023 Published 10/10/2023

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Various Doses of Tanezumab in the Management of Chronic Low Back Pain (CLBP): A Pooled Analysis of 4,514 Patients

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Abstract

Chronic low back pain (CLBP) is a persistent and debilitating condition characterized by pain and discomfort in the lower back region that lasts more than 12 weeks. This review aims to determine the efficacy and safety of various doses of tanezumab for managing CLBP. The present meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Intervention standards. We searched multiple databases, including PubMed, Cochrane Library, Excerpta Medica Database (EMBASE), Scopus, and Web of Science, to identify randomized controlled trials comparing tanezumab to placebo or different dosage regimens for CLBP in adult patients. The primary outcome was the mean change in low back pain intensity (LBPI) score baseline to the end of treatment. Secondary outcomes included adverse events and the degree of disability or impairment. A total of six studies were included in the meta-analysis. Analysis of the data showed that tanezumab 5 mg significantly reduced LBPI compared to placebo at all time points (mean deviation (MD) ranging from -0.31 to -0.5). Similarly, tanezumab 10 mg showed a significant reduction in LBPI compared to placebo at all time points (MD ranging from -0.48 to -0.84). However, tanezumab 5 mg showed significantly less reduction of LBPI compared to 10 mg at two, four, eight, and 12 weeks (MD ranging from 0.19 to 0.32). These findings suggest that tanezumab is an effective treatment for CLBP, with 5 mg and 10 mg doses providing clinically meaningful reductions in LBPI.

Categories: Internal Medicine, Pain Management, Sports Medicine

Keywords: systematic review and meta-analysis, treating low back pain, chronic low back pain (clbp), chronic pain management, tanezumab

Introduction And Background

Pain in the lower back that lasts longer than three months is considered chronic and is referred to as chronic low back pain (CLBP) [1]. It can be a debilitating condition that can severely impact a person's quality of life [2]. Chronic low back pain is thought to affect around 20% of the world's adult population [3,4]. It is a complex condition with multifactorial causes, including physical injury, spinal deformities, nerve damage, or degenerative conditions like osteoarthritis [5]. Chronic low back pain can also be associated with a range of symptoms, including stiffness, weakness, numbness, and tingling sensations [6]. The therapy for CLBP may be difficult and often includes a mix of pharmaceutical and non-pharmacological therapies [7]. Commonly used medications for CLBP include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and muscle relaxants [8]. However, these medications can be associated with various adverse effects, including addiction, dependence, and overdose [9]. Therefore, more effective and safer therapies for CLBP are required.

Tanezumab is a monoclonal antibody that targets nerve growth factor (NGF), a protein involved in the transmission of pain sensations [10]. By inhibiting NGF, tanezumab reduces pain in a variety of illnesses, including CLBP. Tanezumab was primarily created for the treatment of osteoarthritis, but it has also been explored for CLBP, a major global source of disability [11]. The mechanism of action of tanezumab includes limiting the interaction of NGF with its receptors, thereby preventing the transmission of pain signals from peripheral neurons to the central nervous system [12,13]. This action results in a reduction of pain, inflammation, and other associated symptoms of CLBP. Tanezumab is administered through intravenous infusion, and it has been demonstrated to provide a lasting pain-relieving effect [14]. Recently, tanezumab has been administered subcutaneously to increase patient convenience, reduce healthcare costs, and allow self-administration [15].

Previous randomized controlled trials (RCTs) have evaluated tanezumab's efficacy and safety in treating CLBP. These trials have investigated different doses and routes of administration of tanezumab. For instance, one RCT examined the effectiveness of tanezumab (5 mg and 10 mg delivered every eight weeks vs.

How to cite this article

Tahir S, Sadik O, Ezenwa V, et al. (October 10, 2023) Various Doses of Tanezumab in the Management of Chronic Low Back Pain (CLBP): A Pooled Analysis of 4,514 Patients. Cureus 15(10): e46790. DOI 10.7759/cureus.46790

placebo) in individuals with CLBP [16]. This study indicated that both dosages of tanezumab were significantly more effective than placebo at reducing pain. Another RCT assessed the effectiveness of intravenous tanezumab doses of 5 mg, 10 mg, and 20 mg every eight weeks vs. placebo in individuals with CLBP. The research indicated that tanezumab was significantly related to a decrease in pain compared to placebo [17].

Despite the promising results of these studies, some concerns have been raised about the safety of tanezumab, particularly regarding its potential to increase the risk of joint damage [18]. In a recent trial of tanezumab in osteoarthritis patients, the incidence of adverse events, including joint replacement, was greater in the tanezumab group than in the placebo group [19]. However, it is important to note that the patients in the osteoarthritis study were older and had more comorbidities than the patients in the CLBP studies. Consequently, a meta-analysis of the existing information on the effectiveness and safety of multiple-dose regimens of tanezumab in the treatment of CLBP is required to offer a full and impartial evaluation of the best dosage regimen for tanezumab. This meta-analysis aims to find the most effective and safe dose regimen of tanezumab for treating CLBP by analyzing the results of previous RCTs.

Review

Methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane Handbook for Systematic Reviews of Interventions standards [20,21].

Search Strategy

A thorough investigation of electronic databases, including Excerpta Medica Database (EMBASE), PubMed, the Cochrane Library, Scopus, and Web of Science, was conducted to identify eligible studies. The search strategy used a combination of medical subject heading (MeSH) terms and keywords related to tanezumab, chronic low back pain, and randomized controlled trials. The search was limited to studies published from inception to May 2023.

Inclusion and Exclusion Criteria

Only RCTs were eligible for inclusion, and these studies had to compare at least two different dosage regimens of tanezumab or a tanezumab dosage regimen with a placebo control group. The studies also had to include adult patients 18 years of age or older with CLBP. Lastly, the studies had to be published in the English language. Non-randomized or observational studies were also excluded, as they were deemed to have lower quality and potentially biased results. Studies that included participants with other types of chronic pain or medical conditions were also excluded to ensure that the results were specific to CLBP. Finally, studies not published in English were also excluded to ensure consistency and ease of analysis.

Study Selection and Data Extraction

Two independent reviewers examined the titles and abstracts of the selected papers to determine their eligibility. Full-text papers were retrieved and assessed for potentially relevant research according to inclusion and exclusion criteria. Disagreements were addressed via dialogue and consensus. Two independent reviewers retrieved data from the included studies using a predefined data extraction form. Each study's author and publication year, study design, sample size, dose regimens for tanezumab, length of therapy, main outcomes, and conclusion were retrieved.

Risk of Bias Assessment

The risk of bias for each included study was independently evaluated by two reviewers using version 2 of the Cochrane Risk of Bias tool [22]. The tool evaluates five domains: bias caused by the randomization technique, bias caused by variations from planned interventions, bias in outcome assessment, bias caused by missing outcome data, and bias in the selection of the reported result.

Data Synthesis and Analysis

Using Review Manager Web ((RevMan Web), Version 5.4.1, The Cochrane Collaboration, 2020), the data from the included studies were analyzed. The main outcome was the mean change in pain ratings from pretreatment to post-treatment. The pain was evaluated using the low back pain intensity (LBPI) score, a selfreported assessment instrument that evaluates the severity of low back pain in a range of 0 to 10 [23]. Secondary outcomes included adverse events and the degree of disability or impairment. The degree of disability or impairment was assessed by Roland Morris Disability Questionnaire (RMDQ) scores [24].

The mean difference (MD) and 95% confidence interval (CI) were calculated for continuous outcomes. We estimated the risk ratio (RR) and 95% confidence interval for binary outcomes (CI). Using fixed-effects

models, meta-analyses were conducted. Heterogeneity was assessed using the P-value, and its extent was assessed by I2. If the data were heterogeneous, we used the random effect model and left one test. Subgroup analyses were conducted regarding doses of tanezumab or follow-up periods.

Results

Study Selection and Characteristics

Figure 1 depicts the selection process.



FIGURE 1: PRISMA flow chart depicting the process of study selection

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EMBASE: Excerpta Medica Database

A total of 213 records were identified from various databases, and 57 duplicate records were removed. After the screening, 15 reports were assessed for eligibility, and six studies were ultimately included in the systematic review [14,16-17,25-27]. Of those six studies, four were included in the meta-analysis [17,25-27]. Three reports were excluded because they were not RCTs, two were not in English, one had no available full text, and three were conference abstracts.

The average age of participants in the studies ranged from 48.4 to 54.3 years, while the percentage of female participants ranged from 40.2% to 60.9%. The majority of participants in the studies were White, with percentages ranging from 75.9% to 82.7%. The reported BMI values ranged from 23.9 kg/m² to 30.3 kg/m². The duration since a CLBP diagnosis ranged from 9.7 to 11.83 years. The reported etiology for CLBP varied among the studies, with degenerative joint disease/osteoarthritis ranging from 13.0% to 44.2%, injury/muscular strain ranging from 0% to 148 (35.5%), degenerative disc disease ranging from 16.0% to 91 (28.4%), and other causes ranging from 1.7% to 45.2%. Further details are shown in Tables *1-2*.

Study ID	NCT	Tanezumab doses	Follow- up	Primary outcomes	Conclusion
Gimbel et al., 2014 [26]	NCT00924664	10 mg and 20 mg	64 weeks	Change in brief pain inventory short form scores	The tolerability of tanezumab 10 mg was superior to tanezumab 20 mg and could be a useful treatment for chronic low back pain over an extended period.
Katz et al., 2011 [14]	NCT00584870	200 mcg/kg	16 weeks	Change in low back pain intensity	In patients with chronic lower back pain, tanezumab was more effective in reducing pain than both placebo and naproxen, both clinically and statistically.
Kivitz et al., 2013 [17]	NCT00876187	5 mg, 10 mg, and 20 mg	16 weeks	Change in Iow back pain intensity	Patients with chronic lower back pain who took tanezumab experienced significantly greater improvement in their pain levels, physical function, and overall assessment compared to those who took a placebo or naproxen.
Konno et al., 2021 [25]	NCT02725411	5 mg and 10 mg	80 weeks	Adverse events	They concluded that tanezumab was well-tolerated by most individuals and could potentially alleviate symptoms of chronic lower back pain.
Markman et, al. 2020 [16]	NCT02528253	5 mg and 10 mg	56 weeks	Change in low back pain intensity	Tanezumab at a 10 mg dosage improved pain levels and physical function compared to a placebo in patients with difficult-to-treat chronic lower back pain. However, some joint safety events were associated with tanezumab, including a few cases that required joint replacement.
Markman et al., 2022 [27]	NCT02528253	5 mg and 10 mg	80 weeks	Change in the patient's global assessment of low back pain	The evidence suggests that tanezumab could be beneficial for some patients with chronic lower back pain compared to a placebo. This is based on measurements of pain, daily function interference, patient assessment of disease status, and treatment satisfaction.

TABLE 1: Characteristics of the included studies

NR: not reported; NCT: National Clinical Trial number

			A	6	14/1-14-	BMI	Duration airea diamania at	Etiology, n (%)					BMDO
Study ID	Study arms	Sample	Mean (SD)	Female, n (%)	race, n (%)	Kg2/m ² , Mean (SD)	chronic low back pain, years, Mean (SD)	Degenerative joint disease/ osteoarthritis	Injury/muscular strain	Degenerative disc disease	others	Mean ± SD	Mean ± SD
Cimbol et al. 2014 [26]	Tanezumab 10 mg	321	53.3 (12.0)	167 (52%)	265 (82.6%)	29.5 (4.9)	11.34 (9.3)	113 (35.2)	114 (35.5)	91 (28.4)	3 (0.9)	-	-
	Tanezumab 20 mg	527	53.2 (11.0)	277 (52.6%)	436 (82.7%)	29.7 (5.2)	11.83 (10.6)	233 (44.2)	148 (28.1)	134 (25.4)	12 (2.3)	-	-
	Tanezumab 200 mcg/kg	88	49.5 (14.7)	53 (60.2%)	81 (92.0%)	28.8 (4.8)	10 (8.0)	30 (34.1)	21 (23.9)	33 (37.5)	4 (4.5)	6.5 (1.4)	12.3 (4.6)
Katz et al., 2011 [14]	Naproxen 500 mg b.i.d	88	52.1 (14.8)	42 (47.7%)	82 (93.2%)	28.6 (4.8)	13 (8.75)	21 (23.9)	20 (22.7)	37 (42.0)	10 (11.4)	6.7 (1.4)	12.4 (4.8)
	Placebo	41	52.2 (15.0)	23 (56.1%)	37 (90.2%)	28.6 (4.4)	9.7 (11.63)	9 (22.0)	10 (24.4)	16 (39.0)	6 (14.6)	6.7 (1.4)	13.7 (5.2)
	Tanezumab 5 mg	232	51.5 (11.7)	115 (49.6%)	187 (80.6%)	29.2 (4.9)	11.3 (8.93)	90 (38.8)	73 (31.5)	64 (27.6)	5 (2.2)	6.6 (1.4)	12.2 (4.9)
	Tanezumab 10 mg	295	52 (11.0)	157 (53.2%)	238 (80.7%)	29.3 (4.9)	12.3 (10.6)	98 (33.2)	109 (36.9)	82 (27.8)	6 (2.0)	6.6 (1.4)	13.0 (5.1)
Kivitz et al., 2013 [17]	Tanezumab 20 mg	295	51.2 (10.2)	165 (55.9%)	227 (76.9%)	29.3 (5.1)	11.2 (9.25)	118 (40.0)	101 (34.2)	66 (22.4)	10 (3.4)	6.7 (1.5)	13.0 (5.0)
	Naproxen 500 mg b.i.d	295	52.6 (11.5)	152 (51.5%)	224 (75.9%)	30.3 (5.0)	10.9 (11.23)	125 (42.4)	96 (32.5)	69 (23.4)	5 (1.7)	6.8 (1.4)	12.9 (4.9)
	Placebo	230	51.2 (11.2)	125 (54.3%)	190 (82.6%)	29.1 (5.2)	11.3 (9.8)	94 (40.9)	73 (31.7)	59 (25.7)	4 (1.7)	6.71 (1.4)	12.8 (4.7)
	Tanezumab 5 mg	92	53.3(9.5)	37 (40.2)	-	24.1 (3.9)	-	13 (14.1)	6 (6.5)	32 (34.8)	41 (44.6)	6.7 (1.0)	8.3 (5.0)
Konno et al., 2021 [25]	Tanezumab 10 mg	93	52.3 (9.5)	44 (47.3)		23.9 (4.2)		11 (11.8)	0	40 (43.0)	42 (45.2)	6.8 (1.1)	8.1 (4.9)
	Celecoxib 200 mg	92	54.3 (10.3)	38 (41.3)	-	23.9 (3.6)		17 (18.5)	1 (1.1)	38 (41.3)	36 (39.1)	6.7 (1.0)	7.8 (5.0)
	Tanezumab 5 mg	407	48.7 (9.5)	248 (60.9)	295 (72.5)	-	11.0 (9.7)	-	-	-	-	7.2 (1.1)	15.0 (5.2)
Markman et al., 2020 and	Tanezumab 10 mg	407	49.1 (10.3)	218 (53.6)	303 (74.4)	-	10.6 (9.7)	-	-	-	-	7.2 (1.1)	15.0 (4.9)
[16,27]	Tramadol	602	48.4 (10.3)	339 (56.3)	428 (71.1)		11.0 (9.8)	-	-	-	-	7.2 (1.2)	15.1 (5.1)
	Placebo	409	49 (10.7)	236 (57.7)	296 (72.4)	-	11.1 (10.3)	-	-	-		7.2 (1.1)	14.8 (5.1)

TABLE 2: Baseline characteristics of included studies

BMI: body mass index, LBPI: low back pain intensity, RMDQ: Roland-Morris Disability Questionnaire

Risk of Bias Assessment

All studies have a low risk of bias in domains one and two, which relate to randomization and intended interventions, as seen in Figure 2.

		2		Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Gimbel et al.,2014	+	+	X	+	+	+
	Katz et al., 2011	+	+	X	+	+	+
Л	Kivitz et al.,2013	+	+	X	+	+	+
St	Konno et al.,2021	+	+	+	+	+	+
	Markman et al., 2020	+	+	+	+	+	+
	Markman et al., 2022	+	+	+	+	+	+
		Domains: D1: Bias aris D2: Bias due D3: Bias due D4: Bias in r D5: Bias in s	sing from the to deviations to missing o neasurement selection of th	randomization from intende utcome data. of the outcom e reported res	process. d intervention ne. sult.	L	Judgement

FIGURE 2: A traffic light plot of the included studies

Sources: [14,16-17,25-27]

Also, all studies have a low risk of bias in domain four (measurement of outcome) and domain five (selection of reported results). However, three studies have a high risk of bias in domain three, which relates to missing outcome data [14,17,26].

Primary outcomes

Change in LBPI

Tanezumab 5 mg vs. placebo: Tanezumab 5 mg significantly reduced the LBPI compared to the placebo after 16 weeks [MD = -0.31 (-0.61, -0.01), P = 0.04]. The data were homogenous; I2 was 0, and the P value was 0.82, as shown in Figure 3 and Table 3.

	Tan	ezuma	ab	Pla	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 After 2 weeks									
Kivitz et al. 2013	-1.54	2.04	232	-1.31	1.96	230	29.6%	-0.23 [-0.59, 0.13]	
Markman et al. 2020	-1.54	1.72	407	-1.17	1.72	407	70.4%	-0.37 [-0.61, -0.13]	
Subtotal (95% CI)			639			637	100.0%	-0.33 [-0.53, -0.13]	◆
Heterogeneity: Chi ² = 0	1.40, df=	= 1 (P =	= 0.53);	$ ^2 = 0\%$					
Test for overall effect: 2	= 3.25	(P = 0	001)						
1.1.2 After 4 weeks									
Kivitz et al. 2013	-2	2.19	232	-1.5	2.26	230	36.3%	-0.50 [-0.91, -0.09]	
Markman et al. 2020	-2.24	2.23	407	-1.74	2.23	407	63.7%	-0.50 [-0.81, -0.19]	
Subtotal (95% CI)			639			637	100.0%	-0.50 [-0.74, -0.26]	•
Heterogeneity: Chi ² = 0	1.00, df =	= 1 (P =	= 1.00);	$I^{2} = 0\%$					
Test for overall effect: 2	= 4.01	(P < 0.	0001)						
1.1.3 After 8 weeks									
Kivitz et al. 2013	-1.87	2.19	232	-1.41	2.18	230	42.4%	-0.46 [-0.86, -0.06]	
Markman et al. 2020	-2.64	2.57	407	-2.09	2.4	407	57.6%	-0.55 [-0.89, -0.21]	
Subtotal (95% CI)			639			637	100.0%	-0.51 [-0.77, -0.25]	◆
Heterogeneity: Chi2 = 0	1.11, df=	= 1 (P =	= 0.74);	$ ^{2} = 0\%$					
Test for overall effect: 2	= 3.87	(P = 0.	0001)						
1.1.4 After 12 weeks									
Kivitz et al. 2013	-1.96	2.42	232	-1.48	2.18	230	36.5%	-0.48 [-0.90, -0.06]	
Markman et al. 2020	-2.91	2.23	407	-2.53	2.4	407	63.5%	-0.38 [-0.70, -0.06]	
Subtotal (95% CI)			639			637	100.0%	-0.42 [-0.67, -0.16]	◆
Heterogeneity: Chi2 = 0	1.14, df=	= 1 (P =	= 0.71);	$ ^2 = 0\%$					
Test for overall effect: 2	= 3.22	(P = 0.	001)						
1.1.5 After 16 weeks									
Kivitz et al. 2013	-1.6	2.5	232	-1.25	2.34	230	46.8%	-0.35 [-0.79, 0.09]	
Markman et al. 2020	-2.97	2.75	407	-2.69	3.26	407	53.2%	-0.28 [-0.69, 0.13]	
Subtotal (95% CI)			639			637	100.0%	-0.31 [-0.61, -0.01]	-
Heterogeneity: Chi ² = 0	1.05, df =	= 1 (P =	= 0.82);	$l^{2} = 0\%$					
Test for overall effect: 2	2.03	(P = 0.	.04)						
									- <u>t</u> <u>t</u> t
									-2 -1 0 1 Eavoure (Fanazumah) Eavoure (Placabe)
Test for subgroup diffe	rences:	Chi ² =	2.16, 0	if = 4 (P	= 0.71), I ² = 0	1%		ravours (ranezuniab) ravours (riacebo)

FIGURE 3: A forest plot comparing the LBPI of tanezumab 5 mg and placebo

LBPI: low back pain intensity; CI: confidence interval, SD: standard deviation, IV: inverse variance

Sources: [16-17]

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1. Tanezumab 5 mg Vs. Placebo	2			
1.1. After 2 weeks	2	1276	Mean Difference (IV, Fixed, 95% CI)	-0.33[-0.53,-0.13]
1.2. After 4 weeks	2	1276	Mean Difference (IV, Fixed, 95% CI)	-0.50[-0.74,-0.26]
1.3. After 8 weeks	2	1276	Mean Difference (IV, Fixed, 95% CI)	-0.51[-0.77,-0.25]
1.4. After 12 weeks	2	1276	Mean Difference (IV, Fixed, 95% CI)	-0.42[-0.67,-0.16]
1.5. After 16 weeks	2	1276	Mean Difference (IV, Fixed, 95% CI)	-0.31[-0.61,-0.01]
2. Tanezumab 10 mg Vs. Placebo	2			
2.1. After 2 weeks	2	1277	Mean Difference (IV, Fixed, 95% CI)	-0.48[-0.68,-0.28]
2.2. After 4 weeks	2	1277	Mean Difference (IV, Fixed, 95% CI)	-0.84[-1.09,-0.59]
2.3. After 8 weeks	2	1277	Mean Difference (IV, Fixed, 95% CI)	-0.79[-1.04,-0.53]
2.4. After 12 weeks	2	1277	Mean Difference (IV, Fixed, 95% CI)	-0.68[-0.94,-0.43]
2.5. After 16 weeks	2	1277	Mean Difference (IV, Fixed, 95% CI)	-0.60[-0.89,-0.31]
3. Tanezumab 5 mg Vs. Tanezumab 10mg	3			
3.1. After 2 weeks	3	1464	Mean Difference (IV, Fixed, 95% CI)	0.19[0.01, 0.36]
3.2. After 4 weeks	3	1464	Mean Difference (IV, Fixed, 95% CI)	0.32[0.11, 0.53]
3.3. After 8 weeks	3	1464	Mean Difference (IV, Fixed, 95% CI)	0.30[0.07, 0.54]
3.4. After 12 weeks	3	1464	Mean Difference (IV, Fixed, 95% CI)	0.27[0.03, 0.50]
3.5. After 16 weeks	2	1279	Mean Difference (IV, Fixed, 95% CI)	0.27[-0.01, 0.55]
3.6. After 24 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.00[-0.40, 0.40]
3.7. After 32 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.17[-0.58, 0.25]
3.8. After 40 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.14[-0.57, 0.30]
3.9. After 48 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.18[-0.62, 0.25]
3.10. After 56 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.13[-0.54, 0.28]

TABLE 3: Pooled analysis of the primary outcomes

Bold values under "Effect Estimate" indicate significant results.

IV: inverse variance; CI: confidence interval

Sources: [16-17,25]

Tanezumab 10 mg vs. placebo: Tanezumab 10 mg significantly reduced LBPI at 16 weeks compared to placebo [MD = -0.6 (-0.89, -0.31), P < 0.0001], as shown in Figure 4 and Table 3.

	Tan	ezuma	ab	PI	acebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.2.1 After 2 weeks									
Kivitz et al. 2013	-1.89	1.74	232	-1.31	1.96	230	35.0%	-0.58 [-0.92, -0.24]	_
Markman et al. 2020	-1.59	1.89	408	-1.17	1.72	407	65.0%	-0.42 [-0.67, -0.17]	
Subtotal (95% CI)			640			637	100.0%	-0.48 [-0.68, -0.28]	◆
Heterogeneity: Chi ² = 0	1.56, df =	= 1 (P =	= 0.45);	I ² = 0%					
Test for overall effect: 2	= 4.66	(P < 0.	00001)						
1.2.2 After 4 weeks									
Kivitz et al. 2013	-2.53	1.89	232	-1.5	2.26	230	43.1%	-1.03 [-1.410.65]	_ _
Markman et al. 2020	-2.43	2.58	408	-1.74	2.23	407	56.9%	-0.69 [-1.02, -0.36]	— —
Subtotal (95% CI)			640			637	100.0%	-0.84 [-1.09, -0.59]	•
Heterogeneity: Chi ² = 1	.75, df =	= 1 (P =	= 0.19);	² = 439	Х6				
Test for overall effect: 2	= 6.57	(P < 0.	00001)						
1.2.3 After 8 weeks									
Kivitz et al. 2013	-2.3	1.96	232	-1.41	2.18	230	45.0%	-0.89 [-1.27, -0.51]	
Markman et al. 2020	-2.79	2.58	408	-2.09	2.4	407	55.0%	-0.70 [-1.04, -0.36]	
Subtotal (95% CI)			640			637	100.0%	-0.79 [-1.04, -0.53]	◆
Heterogeneity: Chi ² = 0	1.53, df =	: 1 (P =	0.47);	$ ^2 = 0\%$					
Test for overall effect: 2	= 6.07	(P < 0.	00001)						
1.2.4 After 12 weeks									
Kivitz et al. 2013	-2.3	2.12	232	-1.48	2.18	230	43.2%	-0.82 [-1.21, -0.43]	
Markman et al. 2020	-3.11	2.58	408	-2.53	2.4	407	56.8%	-0.58 [-0.92, -0.24]	_
Subtotal (95% CI)			640			637	100.0%	-0.68 [-0.94, -0.43]	•
Heterogeneity: Chi ² = 0	.82, df =	= 1 (P =	0.37);	I ² = 0%					
Test for overall effect: 2	= 5.20	(P < 0.	00001)						
1.2.5 After 16 weeks									
Kivitz et al. 2013	-2.06	2.12	232	-1.25	2.34	230	50.8%	-0.81 [-1.22, -0.40]	_
Markman et al. 2020	-3.07	2.75	408	-2.69	3.26	407	49.2%	-0.38 [-0.79, 0.03]	
Subtotal (95% CI)			640			637	100.0%	-0.60 [-0.89, -0.31]	-
Heterogeneity: Chi ² = 2	2.11, df =	= 1 (P =	= 0.15);	I ² = 539	%				
Test for overall effect: 2	= 4.04	(P < 0.	0001)						
									-1 -0.5 0 0.5 1
Toot for oubgroup diffo	roncoe.	Chi ² =	632 (f = A P	- 0.19	0 12 - 2	6 7 96		Favours [Tanezumab] Favours [Placebo]

FIGURE 4: A forest plot comparing LBPI of tanezumab 10 mg and placebo

LBPI: low back pain intensity; CI: confidence interval, SD: standard deviation, IV: inverse variance

Sources: [16-17]

Tanezumab 5 mg vs. tanezumab 10 mg: Tanezumab 5 mg showed significantly less reduction of LBPI compared to 10 mg at 12 weeks [MD = 0.27 (0.03, 0.5), P = 0.03]. The data were homogenous (P = 0.85, I2 = 0). In contrast, there was an insignificant difference between the two groups after 40 weeks as follows: [MD = -0.14 (-0.57, 0.3), P = 0.54]. The data were homogenous (P = 0.14, I2 = 55%). In addition, there was no significant difference between the two groups after 16 weeks [MD = 0.1 (-0.37, 0.56), P = 0.68], but the data were heterogeneous (P = 0.06, I2 = 64%). This heterogeneity was resolved by excluding Konno et al. 2021 (P = 0.19, I2 = 42%), and the results remained insignificant as follows: [MD = 0.28 (-0.09, 0.65), P = 0.14]. This is evident in Figure 5 and Table 3.

Study or Subgroup	Tanez Mean	umab 5 SD	mg Total	Tanezo Mean	umab 10 SD	mg Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% Cl
1.3.1 After 2 weeks									
<ivitz 2013<="" al.="" et="" td=""><td>-1.54</td><td>2.04</td><td>232</td><td>-1.89</td><td>1.74</td><td>232</td><td>26.2%</td><td>0.35 [0.00, 0.70]</td><td></td></ivitz>	-1.54	2.04	232	-1.89	1.74	232	26.2%	0.35 [0.00, 0.70]	
Conno et al. 2021	-0.46	1.25	92	-0.76	1.3	93	23.1%	0.30 [-0.07, 0.67]	
larkman et al. 2020	-1.54	1.72	407	-1.59	1.89	408	50.7%	0.05 [-0.20, 0.30]	-
Subtotal (95% CI)			731			733	100.0%	0.19 [0.01, 0.36]	◆
leterogeneity: Chi² = 2 est for overall effect: 2	2.39, df = Z = 2.07 (2 (P = 0 P = 0.04	.30); I² :)	= 16%					
.3.2 After 4 weeks									
ivitz et al. 2013	-2	2.19	232	-2.53	1.89	232	31.3%	0.53 (0.16, 0.90)	
Conno et al. 2021	-0.82	1.5	92	-1.1	1.16	93	29.0%	0.28 [-0.11, 0.67]	
farkman et al. 2020	-2.24	2.23	407	-2.43	2.58	408	39.6%	0.19 [-0.14, 0.52]	
Subtotal (95% CI)			731			733	100.0%	0.32 [0.11, 0.53]	◆
Heterogeneity: Chi ² = 1 Test for overall effect: 2	.86, df = Z = 3.04 (2 (P = 0 P = 0.00	.40); l² : 2)	= 0%					
I.3.3 After 8 weeks									
<ivitz 2013<="" al.="" et="" td=""><td>-1.87</td><td>2.19</td><td>232</td><td>-2.3</td><td>1.96</td><td>232</td><td>38.3%</td><td>0.43 [0.05, 0.81]</td><td></td></ivitz>	-1.87	2.19	232	-2.3	1.96	232	38.3%	0.43 [0.05, 0.81]	
<onno 2021<="" al.="" et="" td=""><td>-1.23</td><td>1.82</td><td>92</td><td>-1.64</td><td>2.03</td><td>93</td><td>17.8%</td><td>0.41 [-0.15, 0.97]</td><td></td></onno>	-1.23	1.82	92	-1.64	2.03	93	17.8%	0.41 [-0.15, 0.97]	
darkman et al. 2020	-2.64	2.57	407	-2.79	2.58	408	43.9%	0.15 [-0.20, 0.50]	
Subtotal (95% CI)			731			733	100.0%	0.30 [0.07, 0.54]	-
leterogeneity: Chi ² = 1 est for overall effect; 2	.30, df = Z = 2.54 (2 (P = 0 P = 0.01	.52); I² :)	= 0%					
1.3.4 After 12 weeks			200						
<ivitz 2013<="" al.="" et="" td=""><td>-1.96</td><td>2.42</td><td>232</td><td>-2.3</td><td>2.12</td><td>232</td><td>33.5%</td><td>0.34 (-0.07, 0.75)</td><td></td></ivitz>	-1.96	2.42	232	-2.3	2.12	232	33.5%	0.34 (-0.07, 0.75)	
Konno et al. 2021	-2.19	2.21	92	-2.52	2.22	93	14.1%	0.33 [-0.31, 0.97]	
Markman et al. 2020	-2.91	2.23	407	-3.11	2.58	408	52.4%	0.20 [-0.13, 0.53]	- +
Subtotal (95% CI)			731			733	100.0%	0.27 [0.03, 0.50]	◆
Heterogeneity: Chi² = 0 Fest for overall effect: 2).31, df = Z = 2.17 (2 (P = 0 P = 0.03	.85); l² :)	= 0%					
135 After 16 weeke									
with at al. 2012	1 50	25	222	2.06	242	222	44 50	0 40 10 00 0 001	
Kivitz et al. 2013	-1.56	2.0	232	-2.00	2.12	232	44.370	0.46 [0.06, 0.90]	
Markman et al. 2021	-2.92	2.21	407	-2.42	2.75	408	55 5%	0 10 60 28 0 48	
Subtotal (95% CI)	-2.01	2.75	639	-5.07	2.15	640	100.0%	0.27 [-0.01, 0.55]	-
Heterogeneity: Chi ² = 1 Test for overall effect: 2	.73, df= Z= 1.87 (1 (P = 0 P = 0.06	.19); I² :)	= 42%					
1.3.6 After 24 weeks									
Konno et al. 2021	-2.87	2.69	92	-2.34	2.89	93	24.7%	-0.53 [-1.33, 0.27]	
Markman et al. 2020	-2.76	3.26	407	-2.93	3.44	408	75.3%	0.17 [-0.29, 0.63]	
Subtotal (95% CI)			499			501	100.0%	-0.00 [-0.40, 0.40]	-
Heterogeneity: Chi² = 2 Test for overall effect: 2	2.19, df= Z= 0.01 (1 (P = 0 P = 0.99	.14); I²∶)	= 54%					
1.3.7 After 32 weeks									
Konno et al 2021	-2.96	2,78	92	-2.32	2,89	93	26 በ%	-0.64 [-1.46 0.18]	_
Markman et al. 2020	-2.75	3,78	407	-2.75	3,26	408	74.0%	0.00 [-0.48. 0.48]	
Subtotal (95% CI)	20	0.10	499	20	0.20	501	100.0%	-0.17 [-0.58, 0.25]	
Heterogeneity: Chi ² = 1	.74, df=	1 (P = 0	.19); I ² :	= 43%					
Test for overall effect: 2	Z = 0.78 (P = 0.43)						
1.3.8 After 40 weeks									
Konno et al. 2021	-3.01	2.88	92	-2.31	3.09	93	25.8%	-0.70 [-1.56, 0.16]	
Markman et al. 2020	-2.64	3.43	407	-2.7	3.95	408	74.2%	0.06 [-0.45, 0.57]	
subtotal (95% CI)			499			501	100.0%	-0.14 [-0.57, 0.30]	
Heterogeneity: Chi² = 2 Fest for overall effect: 2	2.22, df = Z = 0.61 (1 (P = 0 P = 0.54	.14); ²∶)	= 55%					
I.3.9 After 48 weeks									
Konno et al. 2021	-3.07	2.88	92	-2.22	2.99	93	26.0%	-0.85 [-1.70, -0.00]	
Aarkman et al. 2020	-2.59	3.52	407	-2.64	3.78	408	74.0%	0.05 [-0.45, 0.55]	
Subtotal (95% CI)			499			501	100.0%	-0.18 [-0.62, 0.25]	
Heterogeneity: Chi² = 3 Fest for overall effect: 2	8.22, df = Z = 0.84 (1 (P = 0 P = 0.40	.07); l² :)	= 69%					
1 3 10 After 56 weeks									
Conno et al 2021	-20	2.82	92	-2.01	2 99	02	23.304	0.89 1.1 74 -0.041	
darkman et al. 2021	-2.9	2.00	92 407	-2.01	2.99	100	23.3%	0.03[*1.74,*0.04]	
Subtotal (95% CI)	-2.02	3.52	499	-2.02	5.20	501	100.0%	-0.13 [-0.54, 0.28]	
Heterogeneity: Chi ² = 4	1.04. df=	1 (P = 0	.04) 12:	= 75%		,			
Fest for overall effect: 2	2 = 0.63 (P = 0.53)						
									<u> </u>
									-2 -1 U 1 Favours (Tanezumab 10 mg) Favours (Tanezumab 5 mg)
act for cubarour diffe		0.62-4	117 46	- 0 /D -	0 1 2) 12.	- 20 50			

Test for subgroup differences: Chi² = 14.17, df = 9 (P = 0.12), l² = 36.5%

FIGURE 5: A forest plot comparing LBPI of tanezumab 5 mg and tanezumab 10 mg

LBPI: low back pain intensity; CI: confidence interval, SD: standard deviation, IV: inverse variance

Sources: [16-17,25]

Secondary Outcomes

Change in RMDQ

Tanezumab 5 mg vs. placebo: Tanezumab 5 mg significantly reduced RMDQ compared to placebo after 16 weeks [MD = -0.87 (-1.51, -0.24), P = 0.007], and the data were homogenous (P = 0.32, I2 = 0) as indicated in Figure 6 and Table 4.

	Tanezu	mab		Place	bo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Kivitz et al. 2013	-2.37	4.42	232	-1.75	4.4	230	62.2%	-0.62 [-1.42, 0.18]	
Markman et al. 2020	-6.25742574	6.99	407	-4.97029703	7.99	407	37.8%	-1.29 [-2.32, -0.26]	←
Total (95% CI)			639			637	100.0%	-0.87 [-1.51, -0.24]	
Heterogeneity: Chi ² = 1	.00, df = 1 (P =	0.32);	I ² = 0%						-2 -1 0 1 2
Test for overall effect: 2	2 = 2.70 (P = 0.0	107)							Favours [Tanezumab] Favours (Placebo)

FIGURE 6: A forest plot of the change in RMDQ for tanezumab 5 mg and placebo

LBPI: low back pain intensity; CI: confidence interval, SD: standard deviation, IV: inverse variance; RMDQ: Roland Morris Disability Questionnaire

Sources: [16-17]

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Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1. Tanezumab 5 mg Vs. Placebo	2	1276	Mean Difference (IV, Fixed, 95% CI)	-0.87[-1.51,-0.24]
2. Tanezumab 10 mg Vs. Placebo	2	1277	Mean Difference (IV, Fixed, 95% CI)	-1.53[-2.15,-0.92]
3. Tanezumab 5 mg Vs. Tanezumab 10mg	3			
3.1. After 2 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	0.43[-0.17, 1.03]
3.2. After 4 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	0.46[-0.14, 1.05]
3.3. After 8 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	0.55[-0.13, 1.23]
3.4. After 16 weeks	3	1464	Mean Difference (IV, Fixed, 95% CI)	0.64[0.11, 1.17]
3.5. After 24 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	0.09[-0.76, 0.94]
3.6. After 32 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.05[-0.89, 0.80]
3.7. After 40 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.33[-1.26, 0.61]
3.8. After 48 weeks	2	1000	Mean Difference (IV, Fixed, 95% CI)	-0.32[-1.23, 0.60]
3.9. After 56 weeks	2	1001	Mean Difference (IV, Fixed, 95% CI)	-0.28[-1.21, 0.66]
4. Patients with adverse events	4			
4.1. Tanezumab 5 mg Vs. Placebo	2	1278	Risk Ratio (M-H, Fixed, 95% CI)	1.07[0.96, 1.20]
4.2. Tanezumab 10 mg Vs. Placebo	2	1341	Risk Ratio (M-H, Fixed, 95% CI)	1.12[1.01, 1.24]
4.3. Tanezumab 5 mg Vs. Tanezumab 10 mg	3	1526	Risk Ratio (M-H, Fixed, 95% CI)	0.99[0.90, 1.08]
4.4. Tanezumab 10 mg Vs. Tanezumab 20 mg	2	1438	Risk Ratio (M-H, Fixed, 95% CI)	0.89[0.82, 0.96]
5. Patients with serious adverse events	4			
5.1. Tanezumab 5 mg Vs. Placebo	2	1278	Risk Ratio (M-H, Fixed, 95% CI)	1.11[0.45, 2.71]
5.2. Tanezumab 10 mg Vs. Placebo	2	1341	Risk Ratio (M-H, Fixed, 95% CI)	1.00[0.42, 2.42]
5.3. Tanezumab 5 mg Vs. Tanezumab 10 mg	3	1526	Risk Ratio (M-H, Fixed, 95% CI)	0.78[0.40, 1.53]
5.4. Tanezumab 10 mg Vs. Tanezumab 20 mg	2	1438	Risk Ratio (M-H, Fixed, 95% CI)	1.02[0.57, 1.84]
6. Patients discontinued due to adverse events	4			
6.1. Tanezumab 5 mg Vs. Placebo	2	1278	Risk Ratio (M-H, Fixed, 95% CI)	0.97[0.59, 1.59]
6.2. Tanezumab 10 mg Vs. Placebo	2	1341	Risk Ratio (M-H, Fixed, 95% CI)	1.13[0.71, 1.79]
6.3. Tanezumab 5 mg Vs. Tanezumab 10 mg	3	1526	Risk Ratio (M-H, Fixed, 95% CI)	0.82[0.52, 1.28]
6.4. Tanezumab 10 mg Vs. Tanezumab 20 mg	2	1438	Risk Ratio (M-H, Fixed, 95% CI)	0.76[0.52, 1.12]
7. Arthralgia	4			
7.1. Tanezumab 5 mg Vs. Placebo	2	1278	Risk Ratio (M-H, Fixed, 95% CI)	0.94[0.58, 1.53]

7.2. Tanezumab 10 mg Vs. Placebo	2	1341	Risk Ratio (M-H, Fixed, 95% CI)	1.57[1.02, 2.42]
7.3. Tanezumab 5 mg Vs. Tanezumab 10 mg	3	1526	Risk Ratio (M-H, Fixed, 95% CI)	0.92[0.61, 1.38]
7.4. Tanezumab 10 mg Vs. Tanezumab 20 mg	2	1438	Risk Ratio (M-H, Fixed, 95% CI)	0.86[0.65, 1.15]
8. Parathesia	3			
8.1. Tanezumab 5 mg Vs. Placebo	2	1278	Risk Ratio (M-H, Fixed, 95% CI)	1.88[0.85, 4.19]
8.2. Tanezumab 10 mg Vs. Placebo	2	1341	Risk Ratio (M-H, Fixed, 95% CI)	3.27[1.58, 6.77]
8.3. Tanezumab 5 mg Vs. Tanezumab 10 mg	2	1341	Risk Ratio (M-H, Fixed, 95% CI)	0.58[0.33, 1.03]
8.4. Tanezumab 10 mg Vs. Tanezumab 20 mg	2	1438	Risk Ratio (M-H, Fixed, 95% CI)	0.74[0.54, 1.02]

TABLE 4: A pooled analysis of secondary outcomes and adverse events

Bold values under "Effect Estimate" indicate significant results.

M-H: Mantel-Haenszal; CI: confidence interval

Sources: [16-17, 25-26]

Tanezumab 10 mg vs. placebo: While tanezumab 10 mg significantly reduced RMDQ compared to placebo after 16 weeks [MD = -1.53 (-2.15, -0.92), P < 0.00001], the data were homogenous (P = 0.66, I2 = 0), as seen in Figure 7 and Table 4.



FIGURE 7: A forest plot of the change in RMDQ for tanezumab 10 mg and placebo

LBPI: low back pain intensity; CI: confidence interval, SD: standard deviation, IV: inverse variance; RMDQ: Roland Morris Disability Questionnaire

Sources: [16-17]

Tanezumab 5 mg vs. tanezumab 10 mg: However, there was no significant difference between tanezumab 5 mg and tanezumab 10 mg in the reduction of RMDQ after 56 weeks [MD = -0.28 (-1.21, 0.66), P = 0.56]. The data were homogenous (P = 0.14, I2 = 54%). After 16 weeks, tanezumab 5 mg showed significantly less reduction of RMDQ compared to 10 mg [MD = 0.64 (0.11, 1.17), P = 0.02], and the data were homogenous (P = 0.82, I2 = 0), which is shown in Figure 8 and Table 4.

Study or Subgroup	Tanezum	ab 5 mg	Total	Tanezuma	ab 10 mg	Total	Moight	Mean Difference	Mean Difference
2 3 1 After 2 weeke	mean	30	oud	mean	30	rotdi	+veight	IV, FIXEU, 95% CI	IV, FIXEU, 55% CI
2.5.1 Alter 2 weeks	0.00	0.05	00	0.00	2.5	0.0	07.40	0.0010.70.4.40	-
Conno et al. 2021	-2.08	3.35	92	-2.28	3.5	93	37.1%	0.20[-0.79, 1.19]	
Narkman et al. 2020	-3.30363036	4.99	407	-3.86468647	ь	408	100.0%	0.56[-0.20, 1.32]	
subtotal (95% CI)			499			501	100.0%	0.45 [-0.17, 1.05]	
leterogeneity: Chiª = I est for overall effect: 2	0.32, df = 1 (P = Z = 1.39 (P = 0.1	0.57); I ² = 6)	= 0%						
22 After America		-/							
2.3.2 Alter 4 weeks	24	2.0	00	2.24	204	0.2	20.00	0.0014.40.4.00	
Kunnu et al. 2021	-2.4	3.9	92	-2.31	3.04	93	30.0%	-0.09[-1.18, 1.00]	
Markman et al. 2020 Subtetal (05% CI)	-4.5/425/43	5.66	407	-5.26/326/3	4.67	408	100.0%	0.69[-0.02, 1.41]	
Subtotal (95% CI)		0.0.0.17	499			501	100.0%	0.46 [-0.14, 1.05]	
Heterogeneity: Chir = Test for overall effect: 3	1.39, af = 1 (P = Z = 1.51 (P = 0.1	0.24); I*= 3)	= 28%						
3 3 After 9 weeke									
2.3.5 Alter & weeks	0.76	2.0	00	0.04		0.0	20.00	0.401.000.4.55	
Konno et al. 2021	-2.75	3.9	92	-3.21	3.64	93	39.0%	0.46 [-0.63, 1.55]	
Markman et al. 2020	-5.25082508	5.99	407	-5.86138614	6.67	408	61.0%	0.61 [-0.26, 1.48]	
Subtotal (95% CI)			499			501	100.0%	0.55 [-0.13, 1.23]	
Heterogeneity: Chi# = 1 Test for overall effect: 3	0.04, df = 1 (P = Z = 1.59 (P = 0.1	0.83); I ^z = 1)	= 0%						
2.3.5 After 16 weeks		28103							
Kivitz et al. 2013	.2 27	4.42	232	-319	3.96	232	48 7%	0.81/0.05/1.671	
Konno et al. 2013	-2.3/	9.92	202	-3.18	4.21	402	40.2%	0.61 [0.00, 1.07]	
Markman et al. 2021	-5.84	6.00	32	-9.39	4.21	409	21.5%	0.33 [0.60, 1.70]	
Subtotal (95% CI)	-0.20142014	0.99	40/	-0.00040000	'	408	100.0%	0.43 [-0.55, 1.39]	-
Jataragonoitr (55% CI)	0.40 44 - 2./2 -	0.031.17	- 00			155	100.0%	0.04[0.11, 1.17]	-
Test for overall effect: 2	Z = 2.36 (P = 0.0	0.82), 1-= 2)	= 0%						
2.3.6 After 24 weeks									
Konno et al. 2021	-3.59	4.74	92	-3.3	4.49	93	40.5%	-0.29 [-1.62, 1.04]	
Markman et al. 2020	-5.56435644	7.99	407	-5.91089109	8	408	59.5%	0.35 [-0.75, 1.44]	
Subtotal (95% CI)			499			501	100.0%	0.09 [-0.76, 0.94]	-
Heterogeneity: Chi ² = I Test for overall effect: 2	0.52, df = 1 (P = Z = 0.21 (P = 0.8	0.47); I² = 4)	= 0%						
2 3 7 After 32 weeks									
Konno ot al. 2024		4.46	0.2		4 77	0.2	40.6%	0.601102.002	
Morlimon et al. 2021	E 40004000	7.00	407	5 COC2COC4	4.//	400	40.3%	-0.50[-1.65, 0.65]	
Markman et al. 2020 Subtotal (95% CI)	-5.43234323	7.99	407	-5.69636964	8	408	59.5%	0.26[-0.83, 1.36]	-
Subtotal (95% CI)	0.75 - 46 - 4 /0 -	0.001.17	499			501	100.0%	-0.05 [-0.89, 0.80]	
Test for overall effect: 2	0.75, ui = 1 (P = Z = 0.11 (P = 0.9	0.39), i* = (2)	= 0%						
2 3 8 After 40 weeks									
Vonno et al 2021		5.00	00	2.05	6.06	02	41.00	1 05 1 3 50 0 401	
Medmen et al. 2021	£ 00500050	3.02	92	-2.93	0.00	93	41.370	-1.05 [-2.50, 0.40]	
Subtotal (95% CI)	-0.06060606	7.99	407	-5.20/320/3	9.67	408	100.0%	0.18[-1.04, 1.40]	
Subtotal (55% Cl)		0.000.17	433			501	100.0%	-0.55 [-1.20, 0.01]	
Test for overall effect: 2	Z = 0.69 (P = 0.4	0.20); I*= 9)	= 38%						
2.3.9 After 48 weeks									
Konno et al. 2021	-4	4.74	92	-2.95	5.05	93	42.0%	-1.05 [-2.46, 0.36]	
Markman et al. 2020	-4 92079209	8.82	407	-5 13531353	8.67	408	58.0%	0 21 60 99 1 421	
Subtotal (95% CI)		0.01	499	0.10001003	0.01	501	100.0%	-0.32 [-1.23, 0.60]	-
Heterogeneity Chiz-	1 79 df = 1 (P -	0 18) 12-	44%						
Test for overall effect.	Z = 0.68 (P = 0.5	0)	- 44 /0						
2.3.10 After 56 weeks	5								
Konno et al. 2021	-3 94	4.74	92	-2.91	4.77	93	46.6%	-1.03 [-2.40, 0.34]	
Markman et al. 2020	-4.85478548	9.33	408	-5.23432343	9.33	408	53.4%	0.38 [-0.90, 1.66]	
Subtotal (95% CI)			500			501	100.0%	-0.28 [-1.21, 0.66]	-
Heterogeneity: Chi ² = 1	2.17. df = 1 (P =	0.14): I ² =	54%						-
Test for overall effect	Z = 0.58 (P = 0.5	6)	54.0						
									-4 -2 0 2 4
	orean and a second of the								Favours (Tanezumab 10 mg) Favours (Tanezumab 5 mg)

Test for subgroup differences: Chi² = 8.33, df = 8 (P = 0.40), l² = 4.0%

FIGURE 8: A forest plot of the change in RMDQ for tanezumab 5 mg and tanezumab 10 mg

LBPI: low back pain intensity; CI: confidence interval, SD: standard deviation, IV: inverse variance; RMDQ: Roland Morris Disability Questionnaire

Sources: [16-17,25]

Adverse events

Patients with any adverse events

Concerning adverse events, there was no significant difference between tanezumab 5 mg over placebo and tanezumab 5 mg [RR = 1.07 (0.96, 1.2), P = 0.2]. The data were homogenous (P = 0.22, I2 = 35%). Compared to a placebo, tanezumab 10 mg showed a significantly higher incidence of adverse events [RR = 1.12 (1.01, 1.24), P = 0.04], and the data were homogenous (P = 0.93, I2 = 0). Moreover, tanezumab 20 mg had a substantially greater frequency of adverse events compared to tanezumab 10 mg [RR = 0.89 (0.82, 0.96), P = 0.004], and the data were homogenous (P = 0.77, I2 = 0), as shown in Figure 9 and Table 4.

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
3.1.1 Tanezumab 5 m	g Vs. Place	ebo					
Kivitz et al. 2013	141	232	120	230	39.0%	1.16 [0.99, 1.37]	
Markman et al. 2020	191	407	189	409	61.0%	1.02 [0.88, 1.18]	
Subtotal (95% CI)		639		639	100.0%	1.07 [0.96, 1.20]	-
Total events	332		309				
Heterogeneity: Chi ² = 1	1.53, df = 1	(P = 0.2)	22); I ² = 3	5%			
Test for overall effect: J	Z = 1.28 (P	= 0.20)					
3.1.2 Tanezumab 10 r	ng Vs. Plac	cebo					
Kivitz et al. 2013	171	295	120	230	41.7%	1 11 0 95 1 301	
Markman et al. 2020	211	407	189	409	58.3%	1.12 [0.97, 1.29]	
Subtotal (95% CI)		702		639	100.0%	1.12 [1.01, 1.24]	-
Total events	382		309				
Heterogeneity: Chi ² = I	0.01, df = 1	(P = 0.9)	33); I ² = 0	%			
Test for overall effect: J	Z = 2.07 (P	= 0.04)					
3.1.3 Tanezumab 5 m	g Vs. Lane	zumab	10 mg				
Kivitz et al. 2013	141	232	171	295	36.5%	1.05 [0.91, 1.21]	
Konno et al. 2021	58	92	51	93	12.3%	1.15 [0.90, 1.46]	
Markman et al. 2020 Subtotal (95% CI)	191	407 731	211	407	51.2%	0.91 [0.79, 1.04]	
Total events	200	751	122	155	100.070	0.33 [0.30, 1.00]	
Heterogeneity: Chi ² = 1	3 70 df = 2	(P = 0.1)	455 (6): F= 4	696			
Test for overall effect:	Z = 0.26 (P	= 0.79)	10),1 = 4	0.10			
reetter ereran eneet.		- 0.1 0,					
3.1.4 Tanezumab 10 r	ng Vs. Tan	ezumat	b 20 mg				32.22
Gimbel et al. 2014	198	321	370	527	59.6%	0.88 [0.79, 0.97]	
Kivitz et al. 2013	171	295	190	295	40.4%	0.90 [0.79, 1.02]	
Subtotal (95% CI)		616		822	100.0%	0.89 [0.82, 0.96]	•
Total events	369		560				
Heterogeneity: Chi ² = I	0.08, df = 1	(P = 0.7)	77); l² = 0	%			
Test for overall effect: .	Z = 2.92 (P	= 0.004	9				
							0.7 0.85 1 1.2 1.5
To al fan andersen al de			20 46 2	0-0	0000 15	70.00	Favours [experimental] Favours [control]
Test for subdroup diffe	rences: Ul	117 = 1.4	39.01 = 3	5 (M = U	.UUZ). [*=	19.230	

FIGURE 9: A forest plot of any adverse events outcomes

CI: confidence interval, M-H: Mantel-Haenszel

Sources: [16-17,25-26]

Serious Adverse Events

Regarding serious adverse events, there was no significant difference between tanezumab 5 mg and placebo [RR = 1.11 (0.45, 2.71), P = 0.82]. The data were homogenous (P = 0.49, I2 = 0). There was no significant difference between tanezumab 10 mg and placebo [RR = 1.00 (0.42, 2.42), P = 0.99], and their data were homogenous (P = 0.17, I2 = 48%). There was no significant difference in serious adverse events between tanezumab 5 mg and tanezumab 10 mg [RR = 0.78 (0.40, 1.53), P = 0.47], and the data were homogenous (P = 0.37, I2 = 0). There was also no significant difference between tanezumab 20 mg and placebo [RR = 1.02 (0.57, 1.84), P = 0.94]. The data were homogenous (P = 0.98, I2 = 0), as evident in Figure 10 and Table 4.

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
3.2.1 Tanezumab 5 m	g Vs. Place	ebo					
Kivitz et al. 2013	4	232	5	230	55.7%	0.79 [0.22, 2.92]	
Markman et al. 2020	6	407	4	409	44.3%	1.51 [0.43, 5.30]	
Subtotal (95% CI)		639		639	100.0%	1.11 [0.45, 2.71]	-
Total events	10		9				
Heterogeneity: Chi ² = I	0.48, df = 1	(P = 0.4)	9); l ² = 0	%			
Test for overall effect: 2	Z = 0.23 (P	= 0.82)					
3.2.2 Tanezumah 10 r	ng Vs. Plac	eho					
Kivitz et al. 2013	3	295	5	230	58 5%	0.47 [0.11.1.94]	
Markman et al. 2020	7	407	4	409	41.5%	1 76 [0.52 5 96]	
Subtotal (95% CI)		702		639	100.0%	1.00 [0.42, 2.42]	-
Total events	10		9			. , ,	T
Heterogeneity: Chi ² =	1.92. df = 1	(P = 0.1)	7); $ ^2 = 4$	8%			
Test for overall effect: 1	Z = 0.01 (P	= 0.99)					
2027			10				
3.2.3 Tanezumab 5 m	g vs. Tane	zumab	10 mg				
Kivitz et al. 2013	4	232	3	295	14.2%	1.70 [0.38, 7.50]	
Konno et al. 2021	4	92	y	93	48.1%	0.45 [0.14, 1.41]	
Markman et al. 2020	6	407	1	407	37.6%	0.86 [0.29, 2.53]	
Totol overte	14	751	10	195	100.076	0.78 [0.40, 1.55]	
Hotorogonoity: Chiž = 1	14 1 07 df = 2	(P = 0.2)	19 07\-18 - 0	04			
Test for overall effect	7 - 0 72 (P	(r = 0.3) = 0.47)	or),1 = 0	70			
restion overall ellect.	2 = 0.72 (F	- 0.47)					
3.2.4 Tanezumab 10 r	ng Vs. Tan	ezumal	o 20 mg				
Gimbel et al. 2014	15	321	24	527	85.8%	1.03 [0.55, 1.93]	
Kivitz et al. 2013	3	295	3	295	14.2%	1.00 [0.20, 4.91]	
Subtotal (95% CI)		616		822	100.0%	1.02 [0.57, 1.84]	•
Total events	18		27				
Heterogeneity: Chi* = 1	0.00, df = 1	(P = 0.9)	38); l* = 0	%			
rest for overall effect: .	Z = 0.07 (P	= 0.94)					
							0.01 0.1 i 10 100
Test for subaroup diffe	erences: Ch	ni² = 0.5	2 df = 3 (P = 0.9	(1) $F = 0$	%	Favours [experimental] Favours [control]

FIGURE 10: A forest plot of serious adverse events outcomes

CI: confidence interval; M-H: Mantel-Haenszel

Sources: [16-17,25-26]

Discontinuation due to Adverse Events

There was no significant difference in all the following comparisons: tanezumab 5 mg vs. placebo, tanezumab 10 mg vs. placebo, tanezumab 5 mg vs. tanezumab 10 mg, and tanezumab 10 mg vs. tanezumab 20 mg [RR = 0.97 (0.59, 1.59), P = 0.89], [RR = 1.13 (0.71, 1.79), P = 0.62], [RR = 0.82 (0.52, 1.28), P = 0.38], and [RR = 0.76 (0.52, 1.12), P = 0.16], respectively, as seen in Figure 11 and Table 4.

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
3.3.1 Tanezumab 5 m	g Vs. Place	ebo					
Kivitz et al. 2013	11	232	14	230	46.8%	0.78 [0.36, 1.68]	
Markman et al. 2020 Subtotal (95% Cl)	18	407 639	16	409 639	53.2% 100.0%	1.13 [0.58, 2.19] 0.97 [0.59, 1.59]	★
Total events	29		30				
Heterogeneity: Chi ² = 0 Test for overall effect: 2	0.52, df = 1 Z = 0.14 (P	(P = 0.4 = 0.89)	47); I² = 0	%			
3.3.2 Tanezumab 10 n	ng Vs. Pla	cebo					
Kivitz et al. 2013	19	295	14	230	49.6%	1.06 [0.54, 2.06]	
Markman et al. 2020 Subtotal (95% Cl)	19	407	16	409 639	50.4% 100.0%	1.19 [0.62, 2.29] 1.13 [0.71, 1.79]	
Total events	38		30				T
Heterogeneity: Chi ² = (0.06. df = 1	(P = 0.8)	30): I ² = 0	%			
Test for overall effect: 2	Z = 0.50 (P	= 0.62)					
3.3.3 Tanezumab 5 m	g Vs. Tane	zumab	10 mg				
Kivitz et al. 2013	11	232	19	295	41.1%	0.74 [0.36, 1.52]	_ _
Konno et al. 2021	3	92	5	93	12.2%	0.61 [0.15, 2.46]	
Markman et al. 2020	18	407	19	407	46.7%	0.95 [0.50, 1.78]	
Subtotal (95% CI)		731		795	100.0%	0.82 [0.52, 1.28]	-
Total events	32		43				
Heterogeneity: Chi ² = 0	0.47, df = 2	(P = 0.7)	79); I ² = 0	%			
Test for overall effect: 2	Z = 0.87 (P	= 0.38)					
3.3.4 Tanezumab 10 n	ng Vs. Tan	ezumal	o 20 mg				
Gimbel et al. 2014	20	321	39	527	51.3%	0.84 [0.50, 1.42]	
Kivitz et al. 2013	19	295	28	295	48.7%	0.68 [0.39, 1.19]	
Subtotal (95% CI)		616		822	100.0%	0.76 [0.52, 1.12]	•
Total events	39		67				
Heterogeneity: Chi ² = 0 Test for overall effect: 2	0.31, df = 1 Z = 1.40 (P	(P = 0.5 = 0.16)	58); I² = 0	%			
							0.01 0.1 1 10 100
Test for subgroup diffe	rences: Cl	hi² = 1.8	5, df = 3	(P = 0.6	60), I² = 09	%	Favours [experimental] Favours [control]

FIGURE 11: A forest plot of discontinuation due to adverse events

CI: confidence interval; M-H: Mantel-Haenszel

Sources: [16-17,25-26]

The data were homogenous (P = 0.47, I2 = 0), (P = 0.80, I2 = 0), (P = 0.79, I2 = 0), and (P = 0.58, I2 = 0), respectively.

Arthralgia

Regarding the incidence of arthralgia, there was no statistically significant difference between tanezumab 5 mg and placebo [RR = 1.14 (0.41, 3.22), P = 0.8]. Still, the data were heterogeneous (P = 0.10, I2 = 64%), and this heterogeneity could not be resolved. Also, tanezumab 10 mg vs. tanezumab 20 mg showed no significant difference in the incidence of arthralgia [RR = 0.86 (0.65, 1.15), P = 0.31], and the data were homogenous (P = 0.89, I2 = 0) as shown in Figure 12 and Table 4.



FIGURE 12: A forest plot of the arthralgia outcomes

CI: confidence interval; M-H: Mantel-Haenszel

Sources: [16-17,25-26]

Paresthesia

Regarding the incidence of paresthesia, there was no significant difference in the tanezumab 5 mg vs. placebo [RR = 1.88 (0.85, 4.19), P = 0.12], and the data were homogenous (P = 0.66, I2 = 0), as shown in Figure 13 and Table 4.

	Experim	nental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
3.5.1 Tanezumab 5 m	ig Vs. Plac	ebo					
Kivitz et al. 2013	11	232	5	230	55.7%	2.18 [0.77, 6.18]	
Markman et al. 2020	6	407	4	409	44.3%	1.51 [0.43, 5.30]	
Subtotal (95% CI)		639		639	100.0%	1.88 [0.85, 4.19]	-
Total events	17		9				
Heterogeneity: Chi ² =	0.20, df = 1	(P = 0.6	66); I ^z = 0	%			
Test for overall effect:	Z = 1.55 (P	'= 0.12)					
3.5.2 Tanezumab 10 i	ng Vs. Pla	cebo					
Kivitz et al. 2013	21	295	5	230	58.5%	3.27 [1.25, 8.55]	
Markman et al. 2020	13	407	4	409	41.5%	3.27 [1.07, 9.93]	_
Subtotal (95% CI)		702		639	100.0%	3.27 [1.58, 6.77]	
Total events	34		9				
Heterogeneity: Chi ² =	0.00, df = 1	(P = 1.0	00); l² = 0	%			
Test for overall effect:	Z = 3.20 (P	= 0.001)				
3.5.3 Tanezumab 5 m	ıg Vs. Tane	ezumab	10 mg				
Kivitz et al. 2013	11	232	21	295	58.7%	0.67 [0.33, 1.35]	
Markman et al. 2020	6	407	13	407	41.3%	0.46 [0.18, 1.20]	
Subtotal (95% CI)		639		702	100.0%	0.58 [0.33, 1.03]	-
Total events	17		34				
Heterogeneity: Chi ² =	0.36, df = 1	(P = 0.5	55); I² = 0	%			
Test for overall effect:	Z = 1.87 (P	' = 0.06)					
3.5.4 Tanezumab 10 ı	ng Vs. Tar	nezumal	o 20 mg				
Gimbel et al. 2014	31	321	56	527	52.7%	0.91 [0.60, 1.38]	
Kivitz et al. 2013	21	295	38	295	47.3%	0.55 [0.33, 0.92]	
Subtotal (95% CI)		616		822	100.0%	0.74 [0.54, 1.02]	◆
Total events	52		94				
Heterogeneity: Chi ² =	2.21, df = 1	(P = 0.1	4); ² = 5	5%			
Test for overall effect:	Z=1.84 (P	= 0.07)					
							0.01 0.1 1 10 100
Test for subgroup diffe	arancas: O	hi² - 10	06 df = 3	(P = 0	0003) 18	- 94 3%	Favours [control] Favours [experimental]
reactor subgroup unit	erences. C	19.	50, ui = 3	, (F = U	.0003), F	- 04.370	
FIGURE 13	: A fo	rest	plot	of p	arest	thesia outc	omes

CI: confidence interval; M-H: Mantel-Haenszel

Sources: [16-17,25-26]

Tanezumab 10 mg, compared to placebo, showed a significantly higher incidence of paresthesia [RR = 3.27 (1.58, 6.77), P = 0.001], and the data were homogenous (P = 1.00, I2 = 0).

Discussion

The purpose of this systematic review and meta-analysis was to assess the effectiveness of tanezumab in the treatment of persistent low back pain. The six RCTs included in this study were conducted in diverse patient populations with varying chronic low back pain etiologies. Despite the heterogeneity in study populations, our analysis showed consistent results in the reduction of LBPI with tanezumab treatment. Our findings show that tanezumab 5 mg and 10 mg significantly reduced LBPI compared to placebo at all time points (two, four, eight, 12, and 16 weeks) examined. The effect size was larger for the 10 mg dose, consistent with previous studies examining the efficacy of tanezumab for chronic pain conditions.

Interestingly, our analysis also revealed that tanezumab 5 mg was significantly less effective than the 10 mg dose in reducing LBPI at two, four, eight, and 12 weeks. However, there was no significant difference between the two doses at 24, 32, and 40 weeks. This suggests that a higher dose of tanezumab may be required to achieve maximum pain reduction in the earlier stages of treatment. The study also compared the efficacy of tanezumab at 5 mg and 10 mg doses against a placebo in reducing RMDQ over 16 weeks. Both doses of tanezumab significantly reduced RMDQ compared to the placebo, with the 10 mg dose having a greater effect size. There was no significant difference in the reduction of RMDQ between the two doses over two to 56 weeks, except at 16 weeks, where the 10 mg dose showed a significantly greater reduction in RMDQ compared to the 5 mg dose.

Regarding adverse events, the results showed similarities between tanezumab 5 mg and placebo, but tanezumab 10 mg and 20 mg had a higher incidence of adverse events. There was no significant difference in the incidence of serious adverse events or patient discontinuation due to adverse events among the groups. The incidence of arthralgia and paresthesia was similar among the groups, except for tanezumab 10 mg vs. placebo, which showed a higher incidence of arthralgia. A previous meta-analysis by Lian et al. (2023) showed similar results [28]. They conducted a subgroup analysis according to the dose, but almost all subgroups only included one trial. We reported significant results regarding comparing doses of tanezumab with placebo and each other. We also provided more detailed safety outcomes and follow-up periods.

Several drugs can be used to manage chronic low back pain, each with its own pros and cons. One class of drugs commonly used are NSAIDs, such as ibuprofen and naproxen. These drugs effectively reduce pain and inflammation but can cause gastrointestinal problems, such as stomach ulcers and bleeding, especially when

used for long periods [29]. Another class of drugs is opioids, such as oxycodone and hydrocodone. Opioids can provide effective short-term pain relief, often leading to dose escalation, thus carrying a high risk of addiction and overdose. They can also cause side effects such as constipation, dizziness, and nausea [9,30]. Antidepressants, such as duloxetine and amitriptyline, can also be used to treat chronic low back pain. They alter the brain's perception of pain but can cause side effects such as drowsiness, dry mouth, and blurred vision [31]. Finally, muscle relaxants such as cyclobenzaprine can relieve muscle spasms that can contribute to low back pain. However, they can cause drowsiness and dizziness and may interact with other medications [32].

This study has several strengths, as we employed a thorough search strategy across multiple databases to identify relevant studies. The primary outcome was clearly defined, and the results were reported in a standardized manner. The meta-analysis demonstrated homogeneity in most comparisons, indicating consistency of results across the included studies. We analyzed the data after up to 56 weeks and compared the different doses of tanezumab with placebo and each other. However, there are also some limitations to the study. The number of studies included in the meta-analysis is relatively small, which may limit the generalizability of the findings. Most of the included studies were conducted in developed countries with a predominantly white population, which may limit the generalizability of the findings to other populations. Three studies were deemed to have a high risk of bias in the domain of missing outcome data, which may impact the validity of the results.

Conclusions

In conclusion, tanezumab significantly reduced LBPI compared to placebo over various time intervals. Furthermore, tanezumab 10 mg exhibited superior efficacy in reducing low back pain intensity at 16 weeks compared to tanezumab 5 mg. Tanezumab reduced disability (RMDQ) scores at 16 weeks, and adverse events were comparable among groups, with tanezumab 10 mg showing a higher incidence than placebo. Tanezumab 10 mg was associated with a significantly increased risk of paraesthesia compared to placebo. Overall, the study suggests that tanezumab can effectively relieve low back pain, but careful consideration of dose-related adverse events is warranted.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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