Updates on the Evidence-Based Management of Osteoarthritis and Osteoarthritis Pain

Placebo Responses in Patients Treated for Osteoarthritis with Tanezumab

#ACR2020 ~ Abstract # 1645

Abstract Tour 1

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This activity is supported by an educational grant from Lilly.
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Disclosures:

Contracted Research: National Institutes of Health
Salary: University of Maryland, Baltimore, USA

Learning Objective

- Review clinical trial outcomes and current statuses of emerging therapies for osteoarthritis (OA) and OA pain

Placebo Group Responses in Clinical Trials of Patients With Osteoarthritis (OA): Data From the Tanezumab Development Program

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Study Context

Placebo responses in clinical trials for chronic pain are a significant challenge to evaluating the efficacy of pain therapeutics

Study Context

The anti-NGF tanezumab is currently in late-stage development for the treatment of moderate-to-severe OA-associated pain in patients with inadequate relief from or intolerance/contraindications to standard of care therapy

Study Context

The development program for tanezumab has provided data across time and administration routes that may shed light on factors that influence the placebo responses in adults with moderate-to-severe OA

Placebo Effects and Responses: Definitions

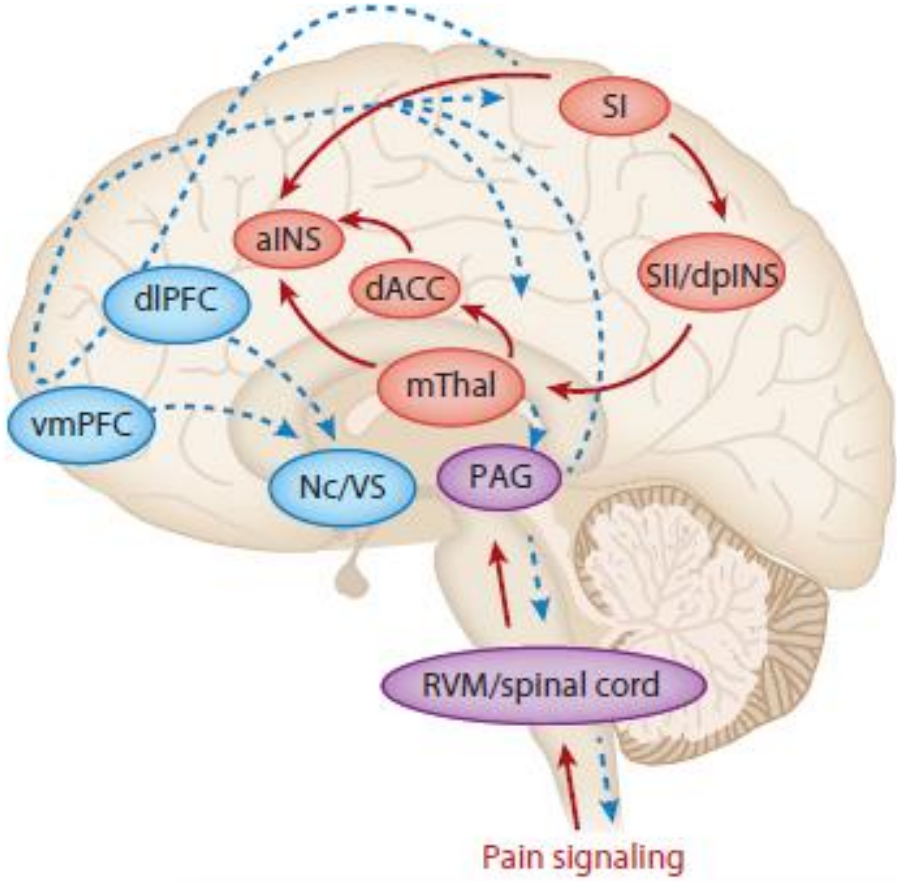
- **Placebo effects** refer to changes in neurobiological responses and clinical outcomes that result from ***positive*** patients' **expectations**, related to **prior experience** and the overall therapeutic encounter (laboratory settings)

- **Placebo responses** refer to changes in clinical outcomes that result from biases, regression to the mean, natural history, and co-interventions – **absence of a no-treatment arm and measurements of expectations** (randomized clinical trials)

Colloca. *NEJM* 2017:376;14

Placebo Effects in Pain

Expectancies



Descending pathways

Ascending pathways

activation

activation

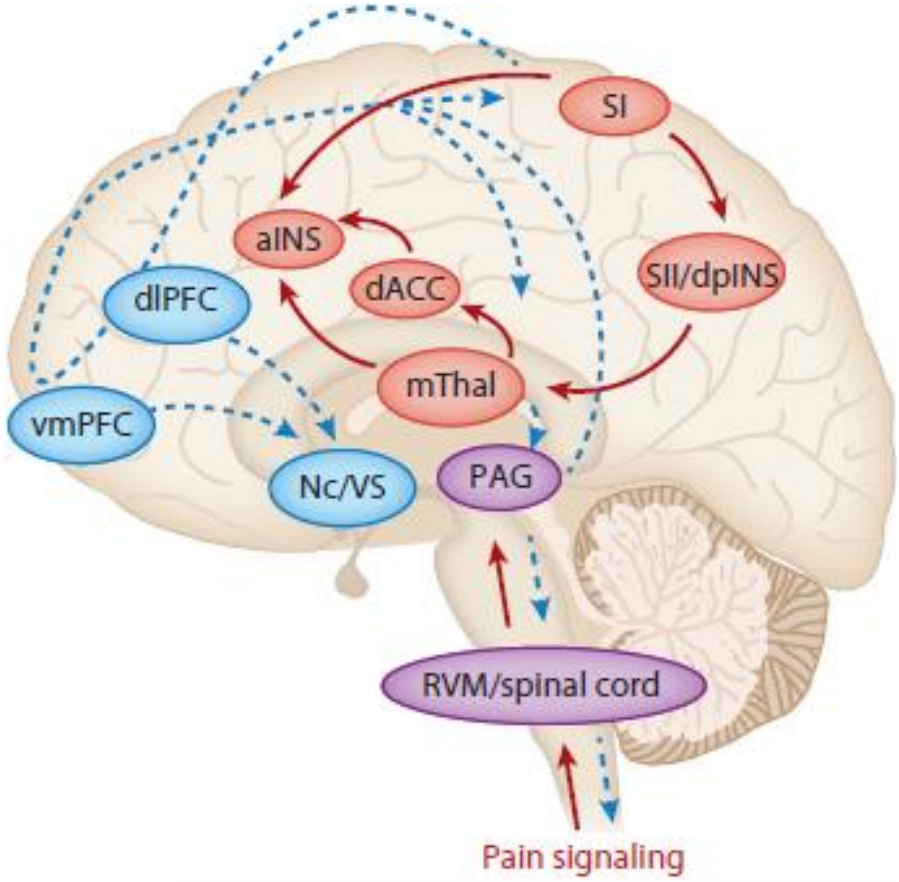
/ activation

Colloca, Annu. Rev. Pharmacol. Toxicol. 2019, 59:161-1621

Placebo Effects in Pain

- Verbal suggestions
- Therapeutic prior experiences
- Observation of benefits in others
- Contextual and treatment cues
- Interpersonal interactions

Expectancies



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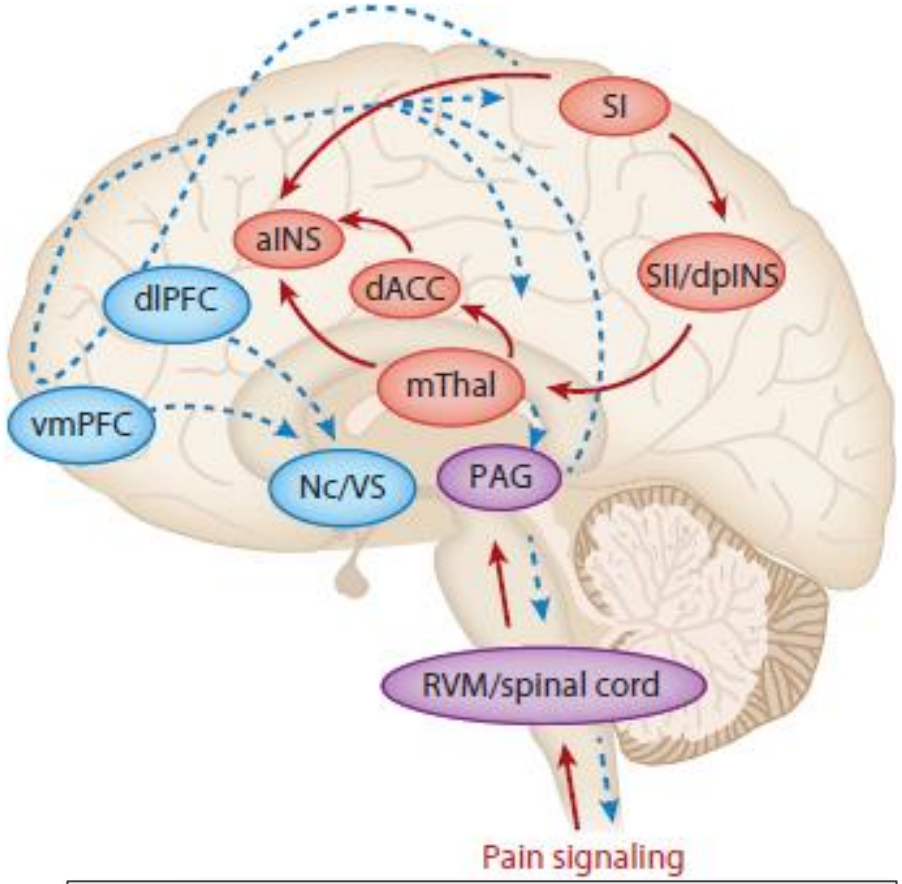


Descending pathways

Ascending pathways

activation

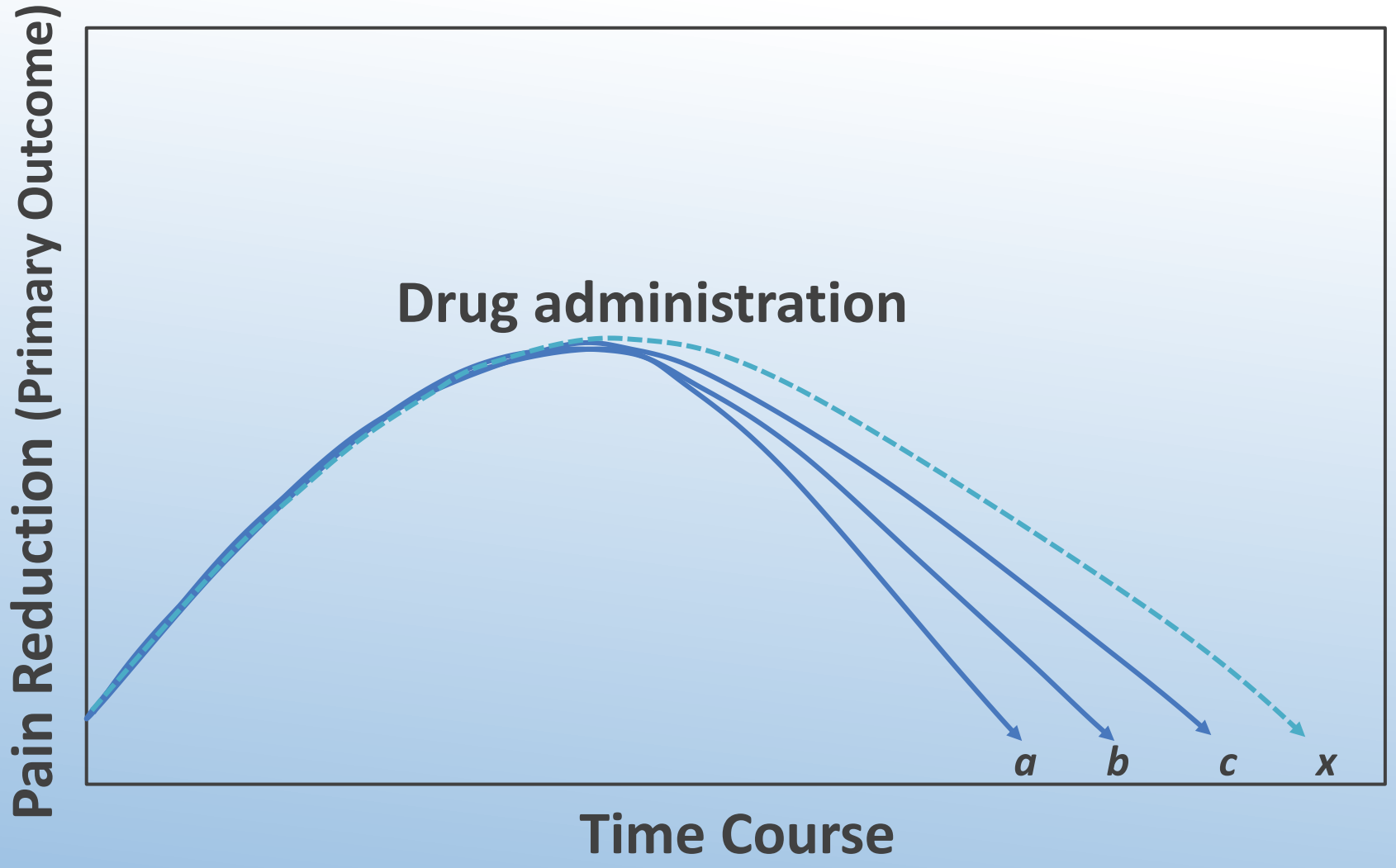
activation

/ activation

Pharmacological, integrative, psychological, and surgical interventions

Colloca, Annu. Rev. Pharmacol. Toxicol. 2019, 59:161-1621

Clinical Trials, Placebo and Drug Effects



a = active drug
b = active comparator
c = placebo
x = natural history

Colloca. *Ann Rev Pharmacol Toxicol*. 2019;59:161-1621

Development Program for Tanezumab

IV Studies (2008-2010; n=1814)

- 24-week treatment
  - 1011 (NCT007339022)
  - 1014 (NCT007444713)
- 16 week-treatment
  - 1015 (NCT008300634)
  - 1018 (NCT008633044)

SC studies (2016-2018; n=1545)

- 16-week treatment
  - 1056 (NCT026977735)
- 24-week treatment
  - 1057 (NCT027094866)

Note: Treatments were administered every 8 weeks.

IV: Intravenous route of administration
SC: Subcutaneous route of administration

Study Outcomes

Co-primary efficacy endpoints

Change from baseline in:

- WOMAC* Pain subscale.
- WOMAC Physical Function subscale
- Patient's global assessment of OA (PGA-OA)

Secondary efficacy endpoints

- Average pain scores
- WOMAC Stiffness subscale

Safety and tolerability

- Incidence of and reasons for discontinuation

*© 1996 Nicholas Bellamy. WOMAC® is a registered trademark of Nicholas Bellamy (CDN, EU, USA).
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

Patient Characteristics

Table 1. Baseline Characteristics and Disease Severity						
	IV Cohort (n=1814)			SC Cohort (n=1545)		
Characteristic	Placebo (n=744)	Tanezumab 2.5 mg (n=327)	Tanezumab 5 mg (n=743)	Placebo (n=514)	Tanezumab 2.5 mg (n=514)	Tanezumab 5 mg (n=517)
Age, mean (SD)	61.2 (10.0)	61.6 (10.1)	61.6 (10.5)	62.5 (9.8)	63.2 (9.4)	63.4 (9.9)
Female, n (%)	478 (64.2)	195 (59.6)	449 (60.4)	353 (68.7)	343 (66.7)	344 (66.5)
Index joint, n (%)						
Hip	196 (26.3)	155 (47.4)	197 (26.5)	80 (15.6)	83 (16.1)	83 (16.1)
Knee	548 (73.7)	172 (52.6)	546 (73.5)	434 (84.4)	431 (83.9)	434 (83.9)
KL grade of index joint, n (%)						
2	337 (45.3)	135 (41.7)	316 (42.6)	124 (24.1)	109 (21.2)	117 (22.7)
3	308 (41.4)	127 (39.2)	328 (44.2)	221 (43.0)	232 (45.1)	226 (43.8)
4	98 (13.2)	62 (19.1)	97 (13.1)	169 (32.9)	170 (33.1)	173 (33.5)
Disease duration, years, mean (SD)	7.3 (8.2)	6.6 (7.8)	7.0 (7.6)	8.7 (8.1)	7.9 (7.8)	8.3 (7.2)
WOMAC Pain, mean (SD)	7.2 (1.4)	7.2 (1.4)	7.3 (1.4)	6.9 (1.1)	6.9 (1.1)	6.9 (1.1)
WOMAC Physical Function, mean (SD)	6.8 (1.5)	6.8 (1.6)	6.9 (1.6)	7.0 (1.1)	7.0 (1.0)	7.0 (1.1)
PGA-OA, mean (SD)	3.4 (0.6)	3.5 (0.6)	3.4 (0.6)	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)

IV, intravenous; KL, Kellgren-Lawrence; PGA-OA, patient's global assessment of osteoarthritis; SC, subcutaneous; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Treatment Discontinuations: IV Pooled Data

Treatment Discontinuations: IV Pooled Data			
	IV Cohort (n=1814)		
Characteristic	Placebo (n=744)	Tanezumab 2.5 mg (n=327)	Tanezumab 5 mg (n=743)
All reasons	329 (44.2)	87 (26.6)	180 (24.2)
Adverse events	25 (3.4)	9 (2.8)	25 (3.4)
Death	1 (0.1)	0	0
Lost to follow-up	1 (0.1)	0	7 (0.9)
Study terminated by sponsor	2 (0.3)	0	3 (0.4)
Withdrawal by subject	45 (6.0)	10 (3.1)	32 (4.3)
Insufficient clinical response	241 (32.4)	58 (17.7)	98 (13.2)
Protocol violation	8 (1.1)	9 (2.8)	9 (1.2)
Other	6 (0.8)	1 (0.3)	6 (0.8)

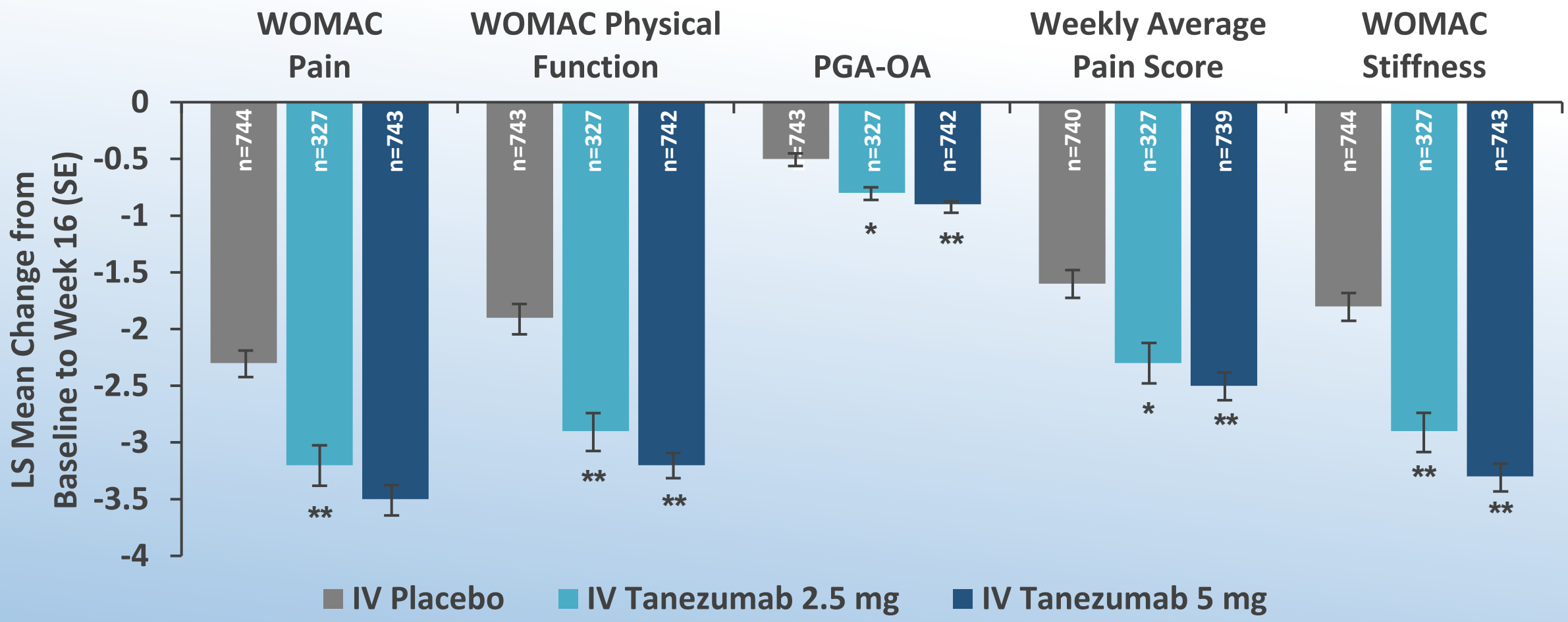
The incidence of withdrawal by reason were determined through completion of the treatment period of each study. IV, intravenous; SC, subcutaneous.

Treatment Discontinuations: SC Pooled Data

Treatment Discontinuations: SC Pooled Data			
	SC Cohort (n=1545)		
Characteristic	Placebo (n=514)	Tanezumab 2.5 mg (n=514)	Tanezumab 5 mg (n=517)
All reasons	84 (16.3)	49 (9.5)	53 (10.3)
Adverse events	12 (2.3)	8 (1.6)	7 (1.4)
Death	0	0	2 (0.4)
Lost to follow-up	3 (0.6)	3 (0.6)	3 (0.6)
Study terminated by sponsor	0	0	0
Withdrawal by subject	22 (4.3)	19 (3.7)	20 (3.9)
Insufficient clinical response	31 (6.0)	8 (1.6)	7 (1.4)
Protocol violation	4 (0.8)	4 (0.8)	1 (0.2)
Other	12 (2.3)	7 (1.4)	13 (2.5)

The incidence of withdrawal by reason were determined through completion of the treatment period of each study. IV, intravenous; SC, subcutaneous.

Change From Baseline to Week 16 in Efficacy Endpoints: IV Pooled Data



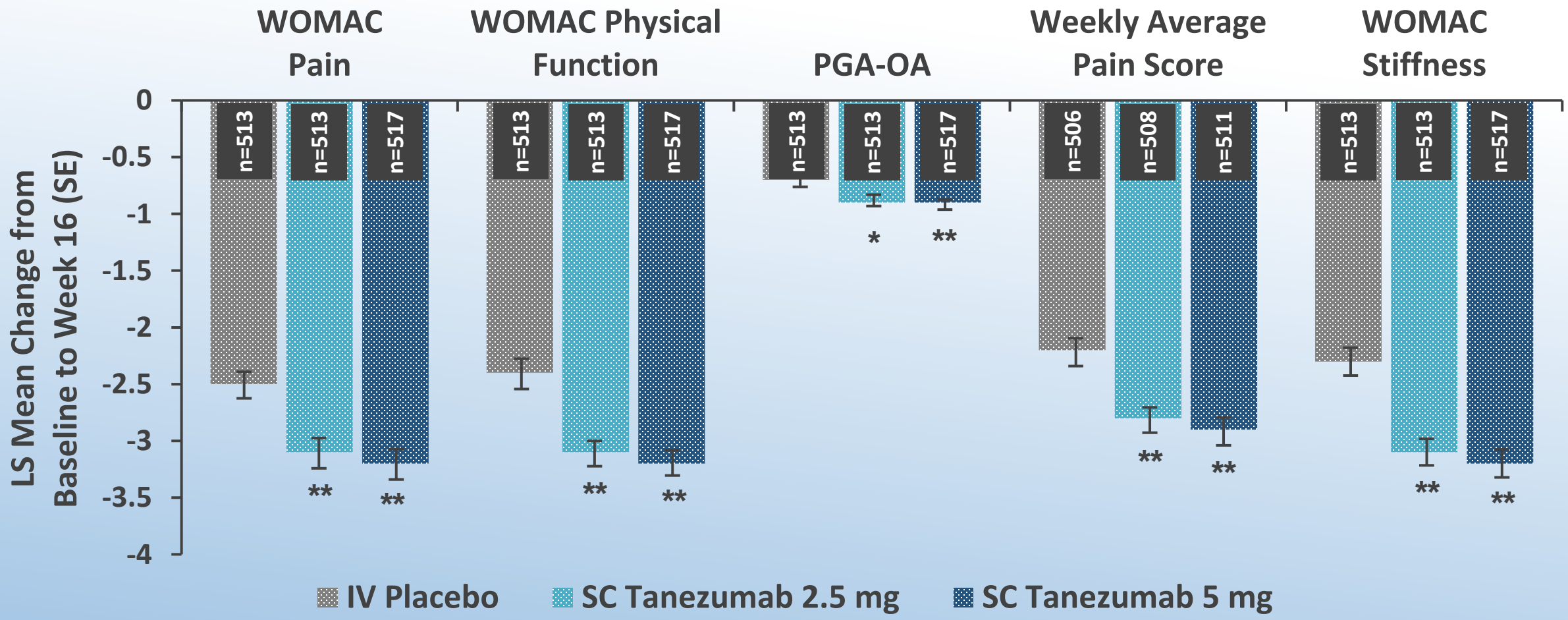
*P<0.005, **P<0.0001 vs IV placebo

WOMAC subscales and weekly average pain scores were measured on 11-point numeric rating scales. PGA-OA was measured on a 5-point numeric rating scale.

A change from baseline <0 represents an improvement in all outcomes.

IV, intravenous; LS, least squares; PGA-OA, patient's global assessment of osteoarthritis; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Change From Baseline to Week 16 in Efficacy Endpoints: SC Pooled Data



*P<0.005, **P<0.0001 vs SC placebo

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A change from baseline <0 represents an improvement in all outcomes.

LS, least squares; PGA-OA, patient's global assessment of osteoarthritis; SC, subcutaneous; SE, standard error; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Conclusions

- Tanezumab (given IV or SC) resulted in statistically significant improvements vs PBO.
- PBO yielded numerically lower response in IV vs SC studies.
- Statistical tests were not possible as no studies included both IV and SC arms.

PBO, placebo.

ACR 2020 Abstract: 1644; 1. Tuttle AH, et al. *Pain* 2015;156:2616-26.

Conclusions

- It is unclear whether results are attributable to administration route or SC studies being conducted later (2016–2018) vs IV studies (2008–2010).
- Meta-analysis indicates increasing PBO group responses over the past decades in analgesic clinical trials. The respective time period of SC vs IV studies may explain the observed results.[1]

PBO, placebo.

ACR 2020 Abstract: 1644; 1. Tuttle AH, et al. *Pain* 2015;156:2616-26.

Conclusions

- Further analyses are needed to determine if other patient and study characteristics may have contributed to the difference in the PBO group response.

PBO, placebo.

ACR 2020 Abstract: 1644; 1. Tuttle AH, et al. *Pain* 2015;156:2616-26.