Systematic Review

Anti-Nerve Growth Factor in the Treatment of Low Back Pain and Radiculopathy: A Systematic Review and a Meta-Analysis

Victor F. Leite, MD[1], Anna M. Buehler, PharmD, PhD[1], Omar El Abd, MD[2],
Ramsin M. Benyamin, MD[3,4], Daniel C. Pimentel, MD, PhD[1,5], Janini Chen, PT[1],
Wu Tu Hsing, MD, PhD[1], Danesh Mazloomdoost, MD[6], and Joao E. D. Amadera, MD PhD[1,5]

From: [1]University of São Paulo, Brazil, [2]Newton Wellesley Interventional Spine, LLC, Wellesley, MA, [3]Millennium Pain Center, Bloomington, IL, [4]University of Illinois, Urbana-Champaign, IL, [5]Spine Center, São Paulo, Brazil, [6]Pain Management Medicine, Lexington, KY

Address Correspondence:
Joao E D Amadera, MD PhD
Head and Medical Director
Spine Center
Rua Abílio Soares, 250 1º andar
São Paulo, SP Brazil
CEP: 04005-000
Email: joao@fmusp.org.br

Background: Low back pain with or without radiculopathy is an important cause of disability and economic expenditure. However, many patients are not meeting optimal pain control through existing treatments. Recent studies have linked nerve growth factor (NGF) and the pathophysiology of persistent pain. Anti-NGF could be an alternative drug treatment for low back pain.

Objective: Systematically review the efficacy and safety of anti-NGF in the treatment of low back pain.

Methods: A systematic review of the literature with no language, date or publication status restriction, using Medline, EMBASE, Cochrane Library, and the clinicaltrials.gov database. Additional literature was retrieved by conferring with experts in the field or reviewing bibliographies and annals of meetings and congresses. Search terms included "monoclonal antibodies," "nerve growth factor," "anti-ngf," "fulranumab," "tanezumab," "sciatica," "back pain," and "spine."

Study Design: Inclusion criteria were observational studies with safety as an outcome and randomized or nonrandomized controlled trials studying the efficacy and/or the safety of anti-NGF drugs on low back pain. Exclusion criteria included patients with autoimmune conditions or osteoporosis. Studies were assessed independently by 2 authors regarding inclusion/exclusion criteria, risk of bias, clinical relevance, and quality of evidence (GRADE approach).

Results: 1,168 studies were retrieved. After excluding duplicates and applying the inclusion/exclusion criteria, 4 RCTs remained (n = 2,109): 2 for tanezumab, one for REGN475, and one for fulranumab. Only the tanezumab studies showed any significant difference over placebo (n = 1,563) for both pain relief and functional improvement.

Conclusions: There is very low evidence that systemically administered anti-NGF therapy has a small positive effect compared to placebo for both pain relief (standarized mean difference [SMD] = -0.29, 95% confidence interval [CI] -0.58 to 0.00) and functional improvement (SMD = -0.21, 95%CI -0.37 to -0.05) of low back pain. There was low evidence of adverse effects (AEs) compared to placebo and low evidence of neurological AEs than placebo (relative risk = 1.93, 95%CI 1.41 to 2.64).Tanezumab, as a specific anti-NGF treatment, showed low evidence of a small to moderate effect for pain relief of low back pain (SMD = -0.44, 95%CI -0.81 to -0.07); and low evidence of a small effect for functional improvement (SMD = -0.26, 95%CI -0.40 to -0.12) with systemic administration, although not clinically significant. Tanezumab and anti-NGFs overall had, respectively, moderate and low evidence of overall AEs and serious AEs and a higher risk of developing neurological AEs when compared with placebo.

Although anti-NGF, specifically tanezumab, showed a low-to-moderate effect on pain relief and functional improvement, it cannot be recommended for low back pain treatment. Without more research on the pathophysiology of anti-NGFs and adverse effects, its use is not safe in the overall population. However, as corroborated by the US Food and Drug Administration, this meta-analysis underscores a role for greater insight into anti-NGF therapy for painful conditions that are refractory to current drugs, such as oncologic pain, chronic pancreatitis, and phantom-limb pain. Given the pathophysiology of axial pain involving inflammatory mediators and the adverse effects of systemic anti-NGF use, consideration of local therapies may warrant further exploration.

Key Words: back pain, anti-ngf, spine, sciatica, nerve growth factor, radiculopathy, treatment

Pain Physician 2014; 17:E45-E60

Low back pain (LBP), with or without radiculopathy, is an important cause of disability and economic expenditure (1-5). In fact, a recent study published by the US Burden of Disease Collaborators showed that in 2010 LBP was the disease with the largest years lived with disability, and was responsible for the third largest disability-adjusted life-years in the US (6). Evidence suggests these numbers are rising, since Freburger et al (7) showed that chronic, impairing LBP has presented an alarming increase, with prevalence in a single state in the US rising from 3.9% in 1992 to 10.2% in 2006 (7). The costs associated with LBP in the US exceeds $100 billion per year (8), with patients with severe pain incurring significantally higher costs than other patients (9,10). Expenditures also show an important growth tendency, not only due to a higher prevalence of LBP, but also by an increased cost per capita (11). Martin et al (11) showed that in an 8-year period, mean expenditure per patient with spinal pain (LBP + neck pain) had a 65% increase (11). Most cases of LBP resolve during the first 6-8 weeks (10,12-17). However, a systematic review showed that in primary care settings, the median (range) proportion of patients with a poor outcome was 11% (2% - 20%) at 3 to 6 months, and 21% (7% - 42%) at one year (17) .

Current Treatment

Possible treatments include drugs, surgery, and minimally invasive procedures (18). Guidelines usually elect painkillers and nonsteroidal anti-inflammatories (NSAIDs) as the first line of treatment (18). However, there is only limited evidence of the effectiveness and cost-effectiveness of those drugs for low back pain with or without radiculopathy (18-23). Contrary to most guidelines' recommendations (18), Ivanova et al (24) found that opioids were the most prescribed drug for patients with low back pain. Unfortunately, opioids also lack evidence of effectiveness and cost-effectiveness, and are associated with important adverse effects, tolerability, and potential misuse/abuse (25-31). Invasive methods are also possible treatments. Several systematic reviews show that minimally invasive procedures, such as epidural injections, are effective and cost-effective for discogenic lumbar radiculopathy (32-35). Despite its efficacy, data sugest that an exaggerated number of spinal invasive procedures are being performed. Manchikanti et al (36) showed that from 2000 to 2008, Medicare receipts for spinal interventional techniques increased 107.8%. An audit performed by the US Department of Health and Human Services reported that in 2007 34% of transforaminal epidural injection services did not meet Medicare requirements (37). Disc replacement surgery for degenerative disc disease did not show significant clinical improvements (38). On the other hand, surgery for radiculopathy due to a herniated disc seems to have an effect only in the short-term (39). However, there is not enough evidence to affirm that surgery is a cost-effective treatment for LBP (23). Thus, several current treatments lack effectiveness and cost-effectiveness, whereas others are highly misindicated. A high number of biologics are now being tested for diverse painful conditions (40-44). Nerve growth factor (NGF) antagonists (anti-NGF) have already been tested in phase-2 and phase-3 trials and a systematic review is needed in order to assess evidence.

NGF and Low Back Pain

NGF is a neurotrophic factor associated with pain signaling (45). NGF is released when there is tissue inflammation or nerve damage (46) and has an important role in the origin of hypersensitivity and persistent pain through several pathways. There is direct action on nociceptive neurons by causing rapid posttranslational changes in the diverse cation channels (47), and indirect action by activating mast cells, consequently releasing histamine, leukotrienes, and other inflammatory cytokines (47-49). Retrograde NGF axonal transport to the dorsal root ganglion up-regulates protein receptors that sensitize both the sensory nerve and more central second-order neurons, originating persistant pain (45). NGF is also involved in the regulation of inflammatory mediators such as bradykinin, substance P, and calcitonin gene-related peptides, as well as the activation of inflammatory cells such as neutrophils (47,50).

There is a large body of evidence linking NGF to inflammatory, visceral, and neuropathic pain (45,51-62). Animal studies on rats demonstrate the efficacy of anti-NGF therapy for inflammatory pain (54,63,64). In animal models of bone cancer pain, anti-NGF was superior to high doses of morphine (62). In addition, NGF plays a role in the evolution of persistent pain, which suggests anti-NGF could be a viable treatment for chronic pain (52,61,62). Clinical trials have been conducted showing pain reduction on osteoarthritis and interstitial cystitis (65,66).

Despite the evidence of its efficacy in clinical studies, anti-NGF has had some controversy due to adverse effects. In 2010, the US Food and Drug Administration (FDA) put a hold on anti-NGF studies due to several cases of osteonecrosis in osteoarthritis patients receiv-

ing anti-NGF therapy through studies by Janssen, Pfizer, and Regeneron/Sanofi (67). In March 2012, after reviewing the data from the sponsors, a meeting of the FDA's Arthritis Advisory Committee voted to resume the interrupted clinical studies with anti-NGF for conditions in which there are no agents with demonstrated analgesic efficacy, such as interstitial cystitis or pancreatitis (67). Given the existing potential for anti-NGF treatment and a need for novel therapies for low back pain, a systematic review of anti-NGF is needed to identify research achievements and gaps.

The objective of this systematic review is to study the efficacy and safety of anti-NGF on LBP.

METHODS

This systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (19), the Cochrane Back Review Group (CBRG) (20,21) and other guidelines (22,23). This research contains 2 parallel systematic reviews: anti-TNF-α in the treatment of LBP (68) and the present study.

The objective of the present study is to systematic review whether the use of anti-NGF is efficacious and/or safe for the treatment of low back pain.

Eligibility Criteria

Types of Studies

The following study designs were included: Randomized controlled trials (RCTs) Nonrandomized controlled trials Observational studies with safety as an outcome.

Studies were included regardless of their publication status. Observational studies were only assessed for safety outcomes.

Types of Participants

Participants were adults of at least 18 years of age with LBP (e.g., radicular and nonradicular LBP, discogenic LBP, lumbar spondylosis) of any duration.

Types of Intervention

Interventions were the use of anti-NGF (tanezumab [TNZ] or fulranumab or others) and/or anti-TNF-α (etanercept, adalimumab, golimumab, certolizumab pegol, infliximab, or others) alone or combined with other co-interventions by any route of administration.

In the present systematic review, only anti-NGF studies will be shown in the results (Fig. 1). For anti-

TNF-α studies, please review the parallel systematic review (68).

Types of Outcome Measures

Primary outcome: pain relief (using any score or scale).

Secondary outcome: functional improvement (using any score or scale) and adverse effects (number of patients with adverse effects).

Exclusion Criteria

Studies were excluded if: Participants had autoimmune conditions, such as ankylosing spondylitis, psoriatic arthritis, or rheumatoid arthritis Study included osteoporosis as an inclusion criteria Study included bone mass index as a primary outcome Studies analyzing only the osteogenic effects of anti-TNF and not pain control.

Literature Search

The search was conducted from September 2012 through October 2012 with no language or date restrictions in the following databases:

Medline (via PubMed) -- www.pubmed.com EMBASE -- www.embase.com Cochrane Library -- www.thecochranelibrary.com National Institute for Health's ClinicalTrials.gov database -- www.clinicaltrials.gov

Manual search of theses, annals of congresses and meetings (i.e. American Pain Society Annual Scientific Meeting, American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting), references and contact with experts in the field.

Search Strategy

The same keywords were used in all databases and trial registries, respecting their differences (e.g., Emtree terms and MeSH terms were mapped in Embase and Medline, respectively).

The keywords were "monoclonal antibodies," "nerve growth factor," "tumor necrosis factor," "etanercept," "infliximab," "adalimumab," "certolizumab," "golimumab," "tanezumab," "fulranumab," "anti-tnf," "anti-ngf," "sciatica," "back pain" and "spine."

Data extraction

Data for each study were extracted independently by 2 authors. Disagreements were resolved by consensus. If no consensus was achieved, a third author was consulted.

All studies had their titles and abstracts analyzed according to the inclusion and exclusion criteria. If an article seemed to be eligible, or if its eligibility was unclear, the full text was extracted. All studies that had their full text assessed are described in the Results section.

Any missing data were clarified by contacting the authors directly.

Validity assessment

Two authors performed the validity assessment in an unblinded manner. If no consensus was achieved, a third author was consulted.

Risk of bias for randomized studies was assessed using the CBRG criteria (69) (Table 1); a subjective evaluation was performed for nonrandomized studies. Randomized studies that scored ≥ 6 on the CBRG criteria were defined as having a low risk of bias. Studies were not excluded based on the risk of bias.

Clinical relevance was defined using CBRG criteria (69,70) (Table 2). No cutoff value was defined. Studies were not excluded based on their clinical relevance.

Quality of evidence

Quality of evidence for pain reduction, functional improvement, and safety was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the GRADEprofiler software(Cochrane Back Review Group, Institute for Work & Health, Toronto, Ontario, Canada), as recommended by the CBRG (68,70). In this approach, evidence for each outcome is assessed in 5 domains: limitations

Table 1. Risk of bias.

Question	Answer (1/0/0)
1.Was the method of randomization adequate?	Yes/No/Unsure
2. Was the treatment allocation concealed?	Yes/No/Unsure
3. Was the patient blinded to the intervention?	Yes/No/Unsure
4. Was the care provider blinded to intervention?	Yes/No/Unsure
5. Was the outcome assessor blinded to the intervention?	Yes/No/Unsure
6. Was the drop-out rate described and acceptable?	Yes/No/Unsure
7. Were all randomized participants analyzed in the group to which they were allocated?	Yes/No/Unsure
8. Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/Unsure
9. Were the groups similar at baseline for the most important prognostic indicators?	Yes/No/Unsure
10. Were co-interventions avoided or similar?	Yes/No/Unsure
11. Was the compliance acceptable in all groups?	Yes/No/Unsure
12. Was outcome assessment timing similar in all groups?	Yes/No/Unsure

Adapted from Furlan AD, et al; Editorial Board, Cochrane Back Review Group, 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila, Pa: 1976)* 2009; 34:1929-1941(69).

Table 2. *Clinical relevance.*

Question	Answer (1/0/0)
1. Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?	Yes/No/Unsure
2. Are the interventions and treatment settings described well enough so that you can provide the same for your patients?	Yes/No/Unsure
3. Were all clinically relevant outcomes measured and reported?	Yes/No/Unsure
4. Is the size of the effect clinically important?	Yes/No/Unsure
5. Are the likely treatment benefits worth the potential adverse effects?	Yes/No/Unsure

Adapted from Furlan AD, et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941(69,70).

of the study design, inconsistency, indirectness (inability to generalize), and imprecision (insufficient or imprecise data) of results and publication. Two authors conducted the evaluation independently in an unblinded manner. If no consensus was reached, a third author was consulted. The strength of recommendation was evaluated for the same outcomes, using the GRADE guidelines (72). Each outcome was classified in 1 of the 4 categories: strong for, weak for, weak against, strong against.

Quantitative data analysis

Pooled intervention was calculated as a weighted average of intervention effects estimated in the individual studies using a random-effects model for all outcomes. Since reported scales were different among the studies, primary outcomes (changes from baseline values in pain score for LBP), as well as functional improvement (changes from baseline values in disability score for LBP), were analyzed using a standardized mean difference (SMD) meta-analysis. For continuous outcomes, a 95% confidence interval (CI) was estimated using the inverse variance and random-effects model. Adverse effects were analyzed as a dichotomous outcome and risk ratio (RR) and its 95% CI was assessed using the Mantel-Haenszel method.

If studies had more than one anti-NGF arm (e.g., TNZ 5 mg vs. TNZ 10 mg vs. TNZ 20 mg versus placebo [PBO]), all the anti-NGF study arms were averaged in one single study arm (e.g., TNZ versus PBO), so that the final mean and standard deviation (SD) of the single anti-NGF arm was the weighted average of the multiple anti-NGF study arms. If the study did not report the SD of the groups, it was estimated from data reported in the primary study (i.e., mean values for intervention and control, and P-values that related to the differences between those means) (73). The estimation was performed so that one SD value was obtained for each anti-NGF arm (e.g., if the study had 3 TNZ arms, it would have 3 estimated SD). According to the recommendation of Higgins et al (74), the intermediate SD value was input to PBO. When exact *P*-values were not reported (e.g., *P* < 0.05), a conservative approach was used by taking the *P* value at the upper limit (e.g., for *P* < 0.05, it was estimated *P* = 0.05) (73).

The homogeneity between articles was evaluated with the Chi-square and I^2 tests and considered $I^2 > 30\%$ as evidence of heterogeneity.

The software used for the analysis was Review Manager (RevMan) version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark).

Results

Trial flow

The electronic search retrieved 1,168 studies; the manual search retrieved 9 results. After excluding duplicates and articles based on title and abstract, 54 potentially eligible studies were found (Fig.1). Of those, 11 were anti-NGF and 43 were anti-TNF-α studies, analyzed in the parallel systematic review (CITATION). There was no study with both anti-TNF-α and anti-NGF drugs. Consensus was reached between the 2 authors on all occasions.

From the 11 anti-NGF studies, seven were excluded: three were duplicates (75-77), two were reviews or commentaries (78,79) and two were terminated early -- a Pfizer's study (80) (due to the FDA-issued clinical hold on all anti-NGF studies on 2010) (81), and Sanofi-Aventis/Regeneron's study on vertebral fracture pain due to low patient recruitment and enrollment (80) .

A total of 4 studies were included on the qualitative synthesis (82-85), as shown in Table 3.

Study Characteristics

Four studies were analyzed on the qualitative synthesis (Tables 3 and 4), all of which were RCTs. All the studies were sponsored by pharmaceutical companies. Pfizer sponsored studies by Katz et al (82) and Kivitz et al (83); Johnson & Johnson sponsored the study by Sanga et al (85), and Regeneron sponsored an unpublished study (84). From the 4 studies, only the study by Katz et al (82) has been published in a peer-reviewed journal. The studies by Kivitz et al (83) and Sanga et al (85) were published only as conference abstracts, and the study by Regeneron (84) only as a protocol on the clinicaltrials.gov database. Therefore, the limited available data were supplemented by contacting the authors and accessing conference presentation files via an Internet search.

All studies had patients with chronic nonradicular LBP, except the one from Regeneron (84), whose patients had lumbar radiculopathy. Across the studies, the average patient age was 51 years old and pain scores averaged 6.7 on an 11-point pain scale. These averages were similar across the studies. Only the studies by Katz et al (82) and Kivitz et al (83) reported pain duration, which was around 11 years.

Among the 4 RCTs, only TNZ studies showed statistically significant improvement on pain control and disability. The fulranumab study was terminated in October 2010 due to lack of efficacy (85).
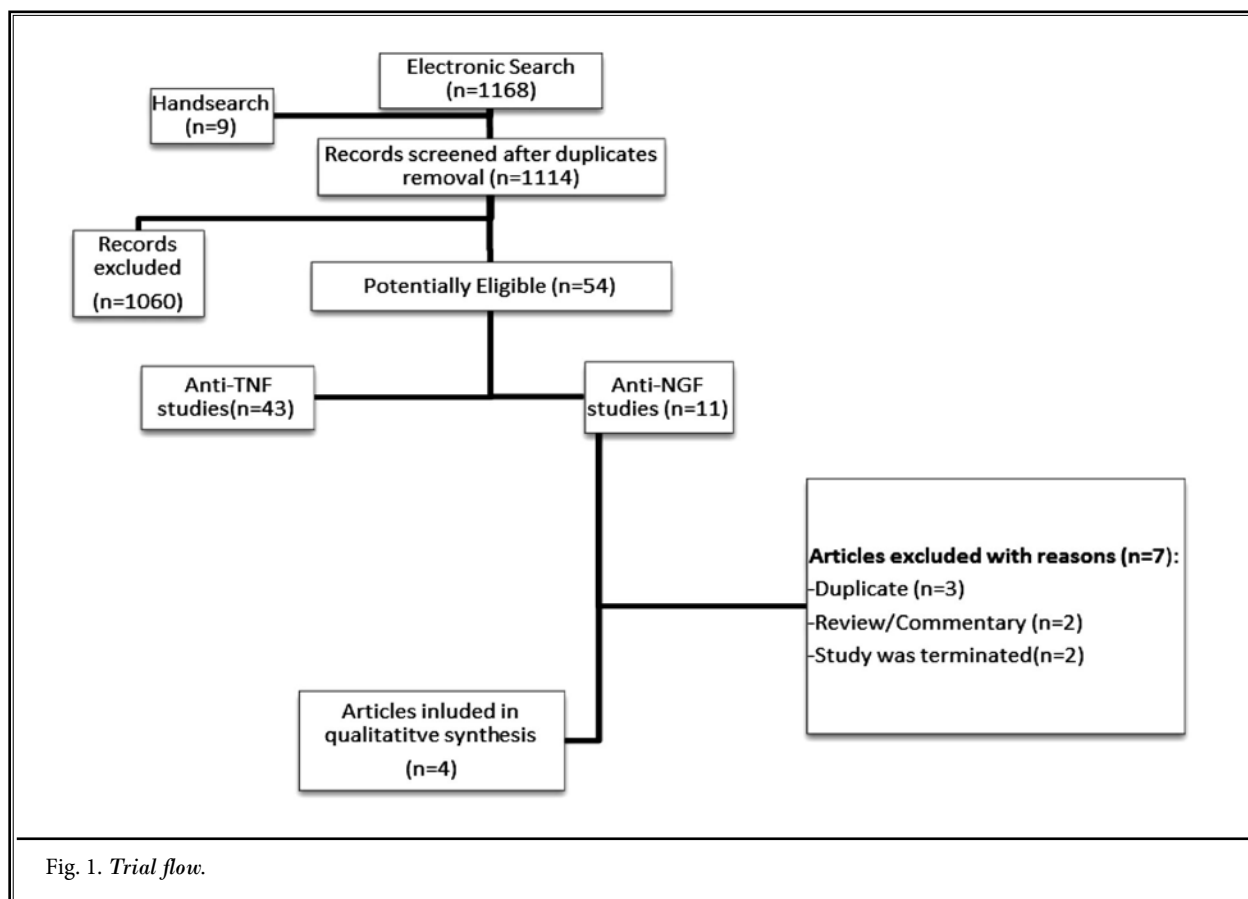
Fig. 1. *Trial flow.*

Table 3. *Study characteristics at baseline.*

Author, year	Number of patients (total = 2109)	Age (years)	Gender	Back pain (0 - 10)	Leg Pain (0 - 10)	Duration of pain (years)	Function/ Disability	Use of pain medication
Katz, 2011 (81)	Total = 216 TNZ(IV) = 88, NPX = 88, PBO = 41	51.07 (± 14.73)	M = 45.6% F = 55.4%	aLBPI = 6.6 (± 1.4)	NN.A.	10.77 (N.R.)	RMDQ = 2.6 (± 4.8)	N.R.
Kivitz, 2011 (82)	Tota l= 1347 TNZ(IV) = 822 NPX = 295, PBO = 230	51.7 (N.R)	M = 45.8% F = 54.2%	aLBPI = 6.68 (± 1.19)	NN.A.	11.4 (N.R.)	RMDQ = 2.94 (± 2.86)	N.R
Regeneron (83)	Total = 157 REGN475(SC) = 106 PBO = 51	N.R.	N.R.	N.R.	NNRS = 6.1 (± 1.35)	N.R.	N.R.	N.R.
Sanga, 2011 (84)	Total = 389 FUL(SC) = 311 PBO = 78	53.2 (± 12)	M = 54% F = 46%	APIS = 7.0 (± 1.24)	NN.A.	N.R.	ODI = 35.3 (± 13.92)	Opioid use = 45%

aLBPI= average low back pain intensity. APIs= Average Pain Intensity Score (0-10 score in last 3 days). FUL= fulranumab. IV= intravenous. N.A.=not applicable. NPX= naproxen. N.R.=not reported. ODI= Oswetry Disabilty Index. PBO=placebo. REN= REN-1654. RMDQ= Roland Morris Disability Questionnaire. SC=subcutaneous. TNZ=tanezumab

Table 4. *Study intervention and outcomes*.

Author, Year Study Type	Condition	Intervention	Number of patients (total = 2,109)	Length of follow-up	Comment
Katz, 2011 (81) RCT	cLBP	Single TNZ 200 µg/kg (IV) or NPX (PO) or PBO	Total = 216 TNZ = 88 NPX = 88 PBO = 41	12 wk	TNZ had significant pain and RMDQ improvement from 4 w-12 w and 1 w-12 w, respectively. TNZ had more neurological AEs than NPX and PBO.
Kivitz, 2011 (82) RCT	cLBP	2 injections of TNZ 5, 10 or 20 mg (IV) 8 w apart vs NPX (PO) vs PBO	Total = 1347 TNZ 5 mg = 232 TNZ 10 mg = 295 TNZ 20 mg = 295 NPX = 295 PBO=230	16 wk	TNZ 10 mg and 20 mg had signficant pain reduction and RMDQ improvement vs PBO and NPX. TNZ had more neurological AEs than NPX and PBO.
Regeneron, 2010 (83) RCT	LR	Single injection of REGN475 0.1 or 0.3mg (SC) or PBO (SC)	Total = 157 REGN475 0.1 mg = 53 REGN475 0.3 mg = 53 PBO = 51	12 wk	No significant difference on pain relief vs PBO. REGN475 had more neurological AEs.
Sanga, 2011 (84) RCT	cLBP	3 injections of FUL 1, 3, 6 + 3 **or** 10 mg (SC), 4 w apart or PBO (SC)	Total = 389 FUL 1 mg = 77 FUL 3 mg = 77 FUL 6+3 mg = 79; FUL 10 mg = 78	12 wk	No significant difference in pain relief or ODI. FUL presented more neurological AEs.

aLBPI= average low back pain intensity. AEs= adverse effects. cLBP= chronic low back pain. FUL= fulranumab. IV=intravenous. LR= Lumbar radiculopathy. NPX= naproxen. N.A.=not applicable. N.R.= not reported. ODI= Oswetry Disabilty Index. PBO=placebo. PO = by mouth. RCT= randomized controlled trial. REN= REN-1654. RMDQ= Roland Morris Disability Questionnaire. SC= subcutaneous. TNZ=tanezumab. VAS= Visual analog scale

Consensus was reached on all occasions. We relied on the authors of the studies to obtain sufficient data for scoring the articles. The study by Regeneron (83) scored < 6, defined by the CBRG as a high risk of bias, mostly because adequate information to assess it could not be obtained.

Consensus for assessing clinical relevance was achieved on all occasions. The studies by Katz et al (82) and Kivitz et al (83) failed in Category B, description of intervention, since patients had to discontinue pain medication prior to baseline assessment and were only allowed acetaminophen up to 2000 mg/d. Therefore, they could have had more pain than in a clinical setting, and thus the study may have overestimated the effect of the anti-NGF therapy. The study by Kivitz et al (83) failed in Category A, patient description, since complete patient information (e.g., use of pain medication before and during the trial) could not be assessed. Sanga et al (85) failed in Category D, clinical importance, and Category E, risk-benefit analysis, due to a lack of efficacy data from the clinical trial. Information could not be obtained for the Regeneron (84) study.

Quantitative Data Synthesis (Meta-analysis)

Pain Relief

For the pain relief analysis, the study by Regeneron (84) was excluded due to a lack of data. The studies by Kivitz et al (83) and Katz et al (82) evaluated TNZ; Sanga et al (85) evaluated fulranumab (Tables 4-6). Katz et al (82) used a single intravenous injection of 200 µg/kg of TNZ, while Kivitz et al (83) used 3 arms of TNZ (5 mg versus 10 mg versus 20 mg) in an intravenous injection repeated after 8 weeks. Sanga et al (85) studied subcutaneous fulranumab in 4 different doses (1 mg versus 3 mg versus 6 mg + 3 mg versus 10 mg) every 4 weeks for a total of 12 weeks, in a total of 3 injections. When compared to PBO, all anti-NGF therapies combined (Fig. 2) had an average reduction of 0.29 SMD (95% CI, -0.58 to 0.00). According to Cohen's rule of thumb for SMDs, 0.2 can be considered a small effect size, 0.5 a moderate effect, and 0.8 a large effect (86).Thus, our analysis showed a small effect for anti-NGF when compared to PBO for pain reduction. TNZ showed a small-to-moderate effect compared to PBO (SMD= -0.44, 95% CI [-0.81 to -0.07]).

Table 5. *Risk of bias.*

	Katz, 2011	Kivitz, 2011	Regeneron	Sanga, 2011
1. Was the method of randomization adequate?	+	+	-	+
2. Was the treatment allocation concealed?	+	+	-	+
3. Was the patient blinded to the intervention?	+	+	-	+
4. Was the care provider blinded to intervention?	+	+	-	+
5. Was the outcome assessor blinded to the intervention?	+	+	-	+
6. Was the drop-out rate described and acceptable?	-	-	+	+
7. Were all randomized participants analyzed in the group to which they were allocated?	-	+	-	+
8. Are reports of the study free of suggestion of selective outcome reporting?	+	+	-	-
9. Were the groups similar at baseline for the most important prognostic indicators?	-	+	+	+
10. Were co-interventions avoided or similar?	-	+	-	-
11. Was the compliance acceptable in all groups?	-	-	+	+
12. Was outcome assessment timing similar in all groups?	+	+	+	+
Total	7	10	4	10

Adapted from Furlan AD, et al.; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (68).

Table 6. *Clinical relevance.*

Author, year	A) Patient description	B) Description of interventions and treatment settings	C) Clinically relevant outcomes	D) Clinical importance	E) Benefits versus potential harms	Total Criteria Met
Katz, 2011 (81)	+	-	+	+	+	4/5
Kivitz, 2011 (82)	-	-	+	+	+	3/5
Regeneron (83)	-	-	-	-	-	0/5
Sanga, 2011 (84)	+	+	+	-	-	3/5

Adapted from Furlan AD, et al.; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941(68,69).
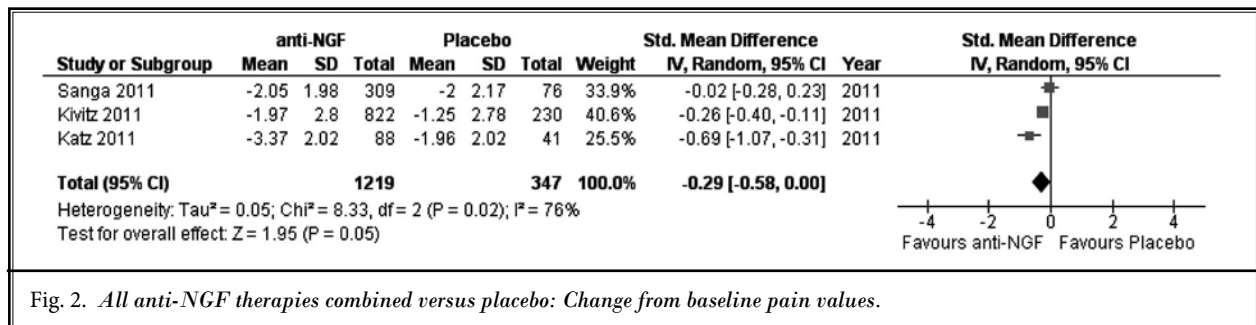

Fig. 2. *All anti-NGF therapies combined versus placebo: Change from baseline pain values.*
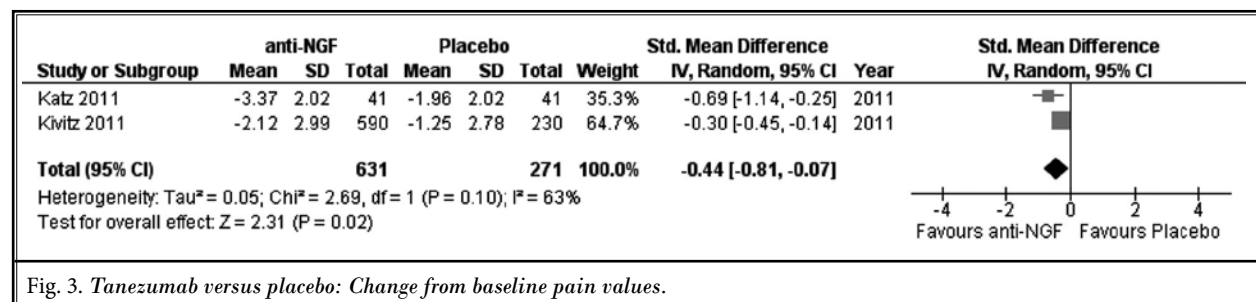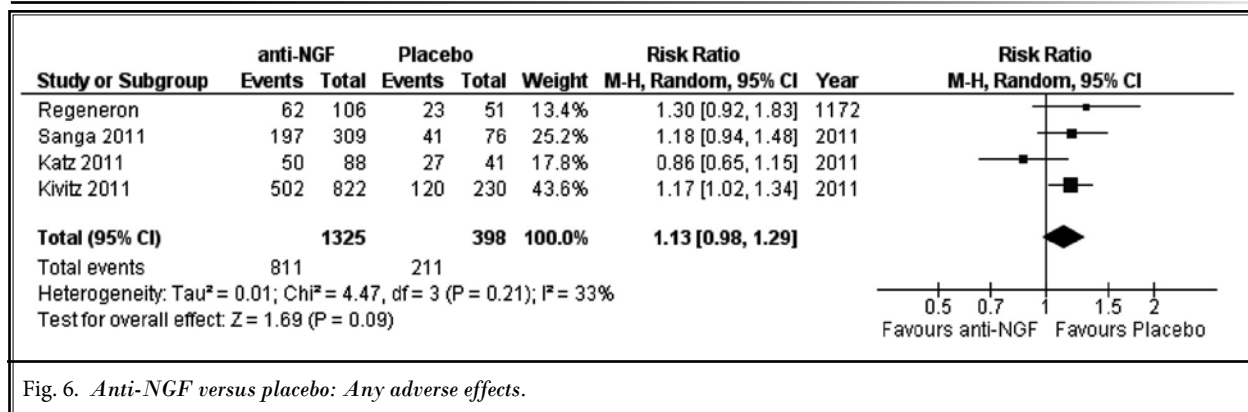

Fig. 3. *Tanezumab versus placebo: Change from baseline pain values.*

Fig. 4. *Anti-NGF versus placebo: Change from baseline disability values.*

Fig. 5. *Tanezumab versus placebo: Change from baseline disability values.*
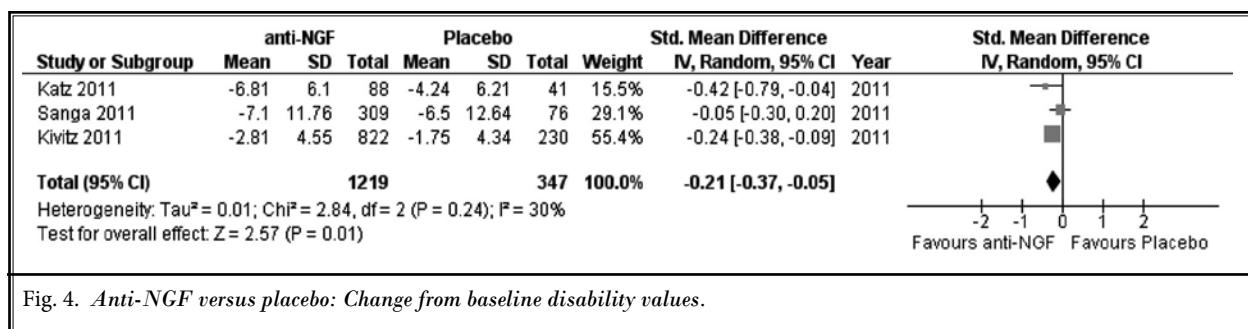

Fig. 6. *Anti-NGF versus placebo: Any adverse effects.*
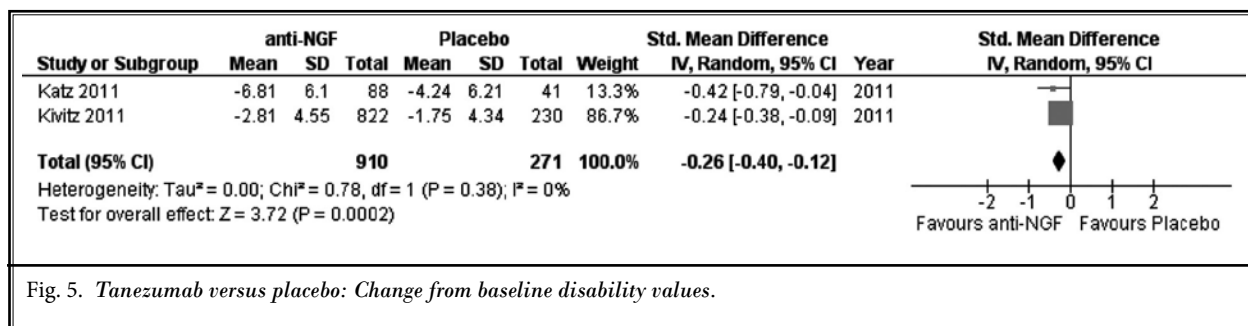
Functional improvement

Once again, the study by Regeneron (84) was not included due to the lack of data (Fig. 4). Anti-NGF showed a better functional improvement than placebo (SMD = -0.21, 95%CI [-0.37 to -0.05]). In a sub-group analysis (Fig. 5), TNZ also showed a small effect compared to PBO (SMD = -0.26, 95%CI [-0.40 to -0.12]).

Adverse effects

All studies were included in the analysis of adverse events, except for Katz et al (82) since neither the intervention group nor the control group had any adverse effects.

Patients using anti-NGF drugs (Fig. 6) had an overall higher risk of developing any adverse effects when compared to PBO, although not statistically significant (RR = 1.13, 95% CI [0.98 to 1.29]). When stratifying by neurological adverse effects (e.g., headache, hyperesthesia, abnormal peripheral sensation, dizziness), anti-NGF therapy showed a higher RR (RR = 1.93; 95% CI [1.41 to 2.64]). Nevertheless, this did not result in a higher risk of a serious adverse effect for the patients using anti-NGF therapy (RR = 0.69, 95% CI [0.32 to 1.49]).

While TNZ did not show an increased risk for overall adverse effects (RR = 0.86, 95% CI [0.65 to 1.15])
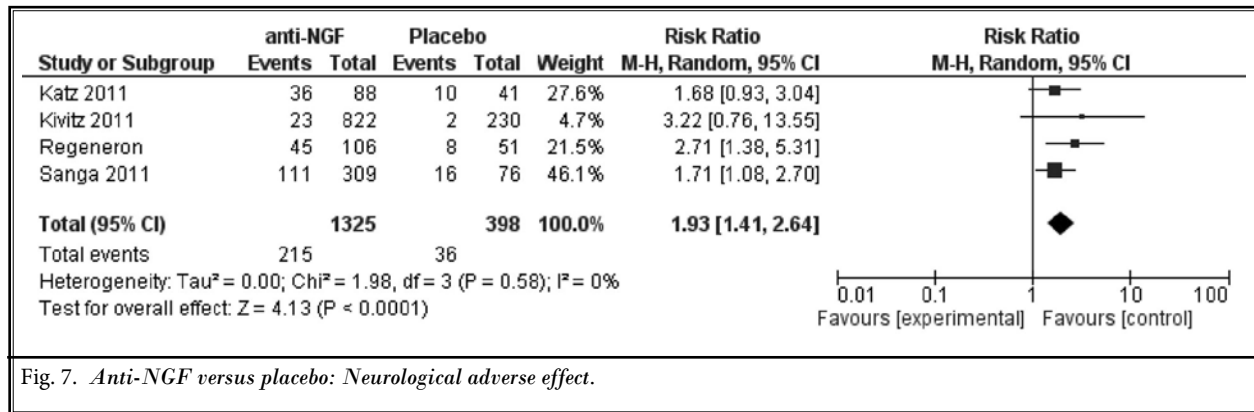
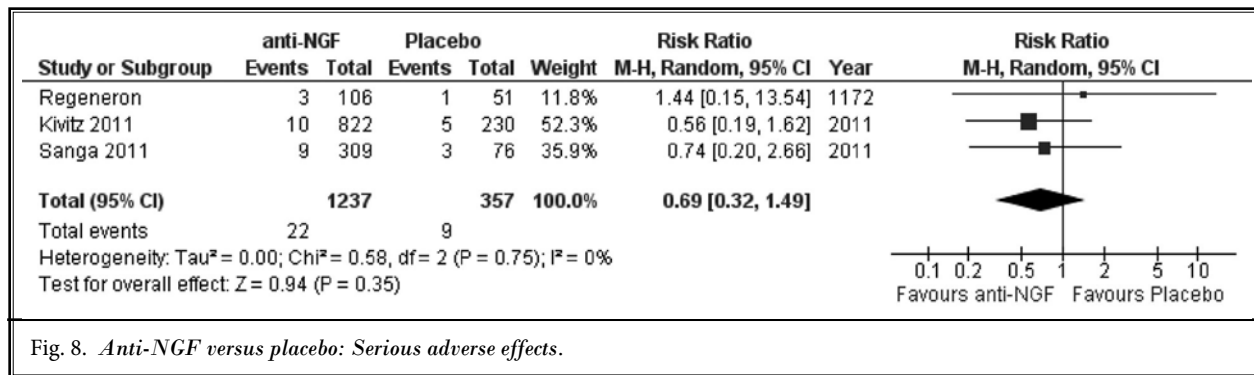Fig. 7. *Anti-NGF versus placebo: Neurological adverse effect.*

Fig. 8. *Anti-NGF versus placebo: Serious adverse effects.*

nor serious events compared to PBO, it did show an increased risk of neurological adverse effects (RR = 1.84, 95% CI [1.06 to 3.20]).

Methodological Quality Assessment

In summary (Table 7), there is very low evidence that systemic anti-NGF therapy has a small positive effect compared to PBO for both pain relief (SMD = -0.29, 95% CI [-0.58 to 0.00]) and functional improvement (SMD = -0.21, 95% CI [-0.37 to -0.05]) in LBP. There was low evidence that anti-NGF therapy had no superior incidence rate of overall adverse effects when compared to PBO. However there was low evidence that anti-NGF is associated with a higher risk of neurological adverse effects than PBO (RR = 1.93, 95% CI [1.41 to 2.64]). In a post-hoc evaluation of TNZ, there was low evidence of a small-to-moderate effect for pain relief for low back pain (SMD = -0.44, 95% CI [-0.81 to -0.07]); and low evidence of a small effect for functional improvement (SMD = -0.26, 95% CI [-0.40 to -0.12]) when compared to PBO. TNZ showed moderate evidence of a nonsuperior incidence rate for overall

adverse effects (RR 1.13, 95% CI [0.98 to 1.29]) and serious adverse effects versus PBO. However, it showed a higher risk of developing neurological adverse effects (RR = 1.84, 95% CI [1.06 to 3.20]). Despite the relatively good results found in this meta-analysis, we are strongly against using anti-NGF drugs for LBP due to data found by the FDA.

DISCUSSION

Our systematic review and meta-analysis demonstrated that TNZ has a significant small-to-moderate effect on pain relief and a small effect on functional improvement. When we consider anti-NGF as a drug class, the results were decreasd in magnitude of effect; this reduction was more significant for pain relief than for functional improvement. For both outcomes, considering anti-NGF as a drug class added heterogeneity on the pooled results, measured by the I2 statistics.

Our results could be compared with other studies investigating pharmacological interventions for the treatment of chronic nonspecific LBP. Kuijpers et al (19) demonstrated by meta-analysis that the use of NSAIDs

Table 7. *Summary of findings for Anti-NGF in patients with lown back pain using anti-NGF therapy vs. pacebo.*

Outcomes	Illustrative Comparative Risks (95% CI)	Relative Effect	No. of Participants (Studies)	Quality of the Evidence (GRADE)
Pain relief				
Least mean change in VAS/ NRS from baseline[1]. Follow-up: 6-16 weeks	The mean pain relief in the intervention groups was 0.29 standard deviations lower than placebo (-0.58 to 0.00)	Small effect[2]	1,566 (3 studies)	⊕⊗⊗⊗ very low[3,4,5,6]
Functional improvement				
ODI/RMDQ[7] Follow-up: 6-16 weeks	The mean functional improvement in the intervention groups was 0.21 standard deviations lower than placebo (-0.37,-0.05)	Small effect2	1,566 (3 studies)	⊕⊗⊗⊗ very low[4,6,8]
Adverse effects				
Number of adverse effects Follow-up: 12-16 weeks	RR 1.13 (0.98,1.29)	RR=1.13	1,714 (4 studies)	⊕⊕⊗⊗ low[6,9]

CI: Confidence interval; RR: Risk ratio;
1 Visual Analog Scale / Numerical rating scale.
2 According to Cohen's rule of thumb for standardized mean differences, 0.2 is a small effect, 0.5 a moderate effect and 0.8 a large effect.
3 Studies used different drugs. Only studies with TNZ showed a statistically significant positive effect.
4 In the studies by Katz et al (81) and Kivitz et al (82), prior to baseline assessment, patients could only use rescue medications (acetaminophen up to 2,000 mg). This could have resulted in higher baseline pain levels and a higher estimate effect of TNZ.
5 The standardized mean difference from placebo included 0, thus it is not statistically significant.
6 Among the 4 studies, only the study by Katz et al (81) was published as a journal article. We could not get adequate information for the studies by Kivitz et al (82) and Regeneron (83). In addition, all 4 studies were sponsored by pharmaceutical companies.
7 Oswetry Disability Index/ Roland-Morris Disability Questionnaire.
8 The study by Sanga et al (84) showed no statistical significance.
9 Three of the 4 studies had no statistically significant results.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

and opioids had a larger effect on pain relief then anti-NGF drugs (SMD = -12.40, 95% CI [-15.53 to -9.26] and SMD = -0.54, 95% CI [-0.72 to -0.36]), respectively. On the other hand, they found no differences in pain relief using antidepressant drugs (SMD -0.02, 95% CI, [-0.26 to 0.22]).

As the evidence provided by Kuijpers et al (19) shows, the overall quality of evidence was low. Even though the included studies had a low risk of bias, the data were poorly reported, with important baseline characteristics not reported by the trials, scatter measurements of the data were not provided, and an inappropriate statistical analysis approach was taken. In this regard, information like duration of pain and use of concomitant medication were not homogeneously reported by the trials. Further, the length of the follow-up was different across the studies, ranging from 6 weeks

by Katz et al (82) to 16 weeks by Kivitz et al (83). The treatment was also not similar in any of the included studies regarding drug dosage and the frequency of administration. All studies were supported by industry and just one of the studies was published as an original journal article. In the Kivitz et al (83) study, we had to estimate the SD for the treatment group. We also had to input the SD in the PBO group, which might have resulted in an overestimated SD and, consequently, an underestimated effect size. Moreover, the study by Katz et al (82) used a one-sided test with $\alpha = 0.1$ for the comparison of TNZ versus PBO. This could have led to an overestimation of the effect size on their study and in our meta-analysis.

Considering the safety of the interventions, our meta-analysis showed an increased risk for neurological adverse effects, with no statistical significance for

Table 8. *Summary of findings for tanezumab for low back pain in patients with low back pain. Intervention: tanezumab vs. placebo*

Outcomes	Illustrative comparative risks (95% CI)	Relative effect	No. of Participants (studies)	Quality of the evidence (GRADE)
Pain relief				
Least mean change in VAS/ NRS from baseline Follow-up: 6-16 weeks	The mean pain relief in the intervention groups was 0.44 standard deviations lower than placebo (-0.81 to 0.07)	Small-to-moderate effect[4]	1,181 (2 studies)	⊕⊕⊗⊗ low[2,3]
Functional improvement				
ODI/RMDQ Follow-up: 6-16 weeks	The mean functional improvement in the intervention groups was 0.26 standard deviations lower than placebo (-0.40, -0.12)	Small effect[4]	1,181 (2 studies)	⊕⊕⊗⊗ low[2,3]
Adverse effects				
Number of adverse effects Follow-up: median 16 weeks	RR 1.13 (0.98, 1.29)	RR 1.13	1,281 (2 studies)	⊕⊕⊕⊗ moderate[3]

CI: Confidence interval; RR: Risk ratio;
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
1 Visual Analog Scale / Numerical rating scale.
2 In the studies by Katz et al (81) and Kivitz et al (82), prior to baseline assessment, patients could only use rescue medications (acetaminophen up to 2000 g).{same as before} This could result in higher baseline pain levels and a higher estimate effect of TNZ3.There were only 2 studies and both were sponsored, which makes the studies prone to publication bias.
4 According to Cohen's conception for standardized mean differences, 0.2 is a small effect, 0.5 a moderate effect and 0.8 a large effect

serious adverse effects or for any other adverse effects. Considering the small effect of anti-NGF on the investigated outcomes, the increased risk must be taken into account when weighed against the benefits.

Furthermore, we could not ignore the information that, in 2010, the FDA put anti-NGF studies on hold due to a high incidence of rapidly progressive osteoarthritis/osteonecrosis (RPOA/ON) in patients receiving those drugs for osteoarthritis pain (87). An independent adjudication supported by the FDA confirmed an association between anti-NGF and a higher incidence of RPOA/ON (88), based apparently on only one case of RPOA/ON that occurred out of 1,325 patients receiving anti-NGF for LBP (39). This event correlates with a dose-response as well as synergistic association with the concomitant use of NSAIDs. Nevertheless, in March 2012, the FDA's Arthritis Advisory Committee stated that there was a role for the ongoing development of anti-NGF drugs for conditions where currently available pain therapies were inadequate (e.g., chronic pancreatitis, bone cancer pain), unless the patient was at a high risk for joint destruction (81,89). Furthermore, it was stated that new safety procedures should be taken in order to avoid new

cases of RPOA/ON, such as a baseline radiograph of all the joints, pelvic magnetic resonance imaging and a central pathology and radiology analysis. Finally, the committee also determined that more experimental studies were needed to better understand the effects of NGF on vascular tissue. In July 2013, the FDA lifted their partial hold on tanezumab after nonclinical data were obtained (90). To our knowledge, studies with fulranumab and REGN475 are still halted.

Experimental studies link NGF to ischemia-induced neovascularization (45,91) and to cardiac repair following myocardial infarction (92). Until data obtained by the FDA are made available, it is not safe to recommend anti-NGF therapy for low back pain.

There are some highlights in our systematic review. Our systematic review was conducted and analyzed in accordance with national and international guidelines. We consider our literature search to have been thorough; despite that, we could not assess and quantify the risk of publication bias due to the limited number of studies included.

All studies identified in the literature evaluated systemic administration of anti-NGF. Local administration, via intraarticular, facet or epidural routes, has not

been studied, for either efficacy or safety profile. Given the pathophysiology of axial pain involving inflammatory mediators and the adverse effects of systemic anti-NGF use, consideration of local therapies may warrant further exploration.

CONCLUSION

In conclusion, although this meta-analysis does not support the use of anti-NGF drugs for the treatment

of LBP, it contributes greater insights into anti-NGF therapy for other chronic painful conditions such as oncologic pain, chronic pancreatitis, and phantom-limb pain refractory to current drugs.

ACKNOWLEDGEMENTS

We would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

REFERENCES

1. Indrakanti SS, Weber MH, Takemoto SK, Hu SS, Polly D, Berven SH. Value-based care in the management of spinal disorders: A systematic review of cost-utility analysis. *Clin Orthop Relat Res* 2012; 470:1106-1123.

2. Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research*. The National Academies Press, Washington, DC, 2011.

3. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The association between chronic low back pain and sleep: A systematic review. *Clin J Pain* 2011; 27:169-181.

4. Hagen EM, Svensen E, Eriksen HR, Ihlebaek CM, Ursin H. Comorbid subjective health complaints in low back pain. *Spine (Phila Pa 1976)* 2006; 31:1491-1495.

5. Pleis JR, Ward BW, Lucas JW. Summary health statistics for U.S. adults: National Health Interview Survey, 2009. *Vital Health Stat 10* 2010; 1-207.

6. US Burden of Disease Collaborators. The state of US health, 1990-2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013; 310:591-608.

7. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.

8. Katz JN. Lumbar disc disorders and low-back pain: Socioeconomic factors and consequences. *J Bone Joint Surg Am* 2006; 88 Suppl 2:21-24.

9. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724.

10. Gore M, Sadosky A, Stacey BR, Tai KS, Leslie D. The burden of chronic low back pain: Clinical comorbidities, treatment patterns, and health care costs in usual

care settings. *Spine (Phila Pa 1976)* 2012; 37:E668-E677.

11. Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W, Sullivan SD. Expenditures and health status among adults with back and neck problems. *JAMA* 2008; 299:656-664.

12. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet* 1999; 354:581-585.

13. Coste J, Delecoeuillerie G, Cohen de Lara A, Le Parc JM, Paolaggi JB. Clinical course and prognostic factors in acute low back pain: An inception cohort study in primary care practice. *BMJ* 1994; 308:577-580.

14. Grotle M, Brox JI, Veierod MB, Glomsrod B, Lonn JH, Vollestad NK. Clinical course and prognostic factors in acute low back pain: Patients consulting primary care for the first time. *Spine (Phila Pa 1976)* 2005; 30:976-982.

15. Campbell P, Foster NE, Thomas E, Dunn KM. Prognostic indicators of low back pain in primary care: Five-year prospective study. *J Pain* 2013; 14:873-883.

16. Costa LM, Maher CG, Hancock MJ, McAuley JH, Herbert RD, Costa LO. The prognosis of acute and persistent low-back pain: A meta-analysis. *CMAJ* 2012; 184:E613-E624.

17. Chou R, Shekelle P. Will this patient develop persistent disabling low back pain? *JAMA* 2010; 303:1295-1302.

18. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J* 2010; 19:2075-2094.

19. Kuijpers T, van Middelkoop M, Rubinstein SM, Ostelo R, Verhagen A, Koes BW, van Tulder MW. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J* 2011; 20:40-50.

20. Chou R, Huffman LH. Medications for acute and chronic low back pain: A review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; 147:505-514.

21. Davies RA, Maher CG, Hancock MJ. A systematic review of paracetamol for non-specific low back pain. *Eur Spine J* 2008; 17:1423-1430.

22. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, McLachlan AJ, Koes B. Drugs for relief of pain in patients with sciatica: Systematic review and meta-analysis. *BMJ* 2012; 344:e497.

23. Dagenais S, Roffey DM, Wai EK, Haldeman S, Caro J. Can cost utility evaluations inform decision making about interventions for low back pain? *Spine J* 2009; 9:944-957.

24. Ivanova JI, Birnbaum HG, Schiller M, Kantor E, Johnstone BM, Swindle RW. Real-world practice patterns, health-care utilization, and costs in patients with low back pain: The long road to guideline-concordant care. *Spine J* 2011; 11:622-632.

25. Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I, Sehgal N, Shah R, Benyamin R, Vallejo R, Fellows B, Christo PJ. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician* 2011; 14:91-121.

26. Fischer B, Argento E. Prescription opioid related misuse, harms, diversion and interventions in Canada: A review. *Pain Physician* 2012; 15:ES191-ES203.

27. Bhamb B, Brown D, Hariharan J, Anderson J, Balousek S, Fleming MF. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin* 2006; 22:1859-1865.

28. Moore RA, McQuay HJ. Prevalence of

opioid adverse events in chronic non-malignant pain: Systematic review of randomised trials of oral opioids. *Arthritis Res Ther* 2005; 7:R1046-R1051.

29. Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, Kress HG, Langford R, Likar R, Raffa RB, Sacerdote P. Opioids and the management of chronic severe pain in the elderly: Consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract* 2008; 8:287-313.

30. Franklin GM, Stover BD, Turner JA, Fulton-Kehoe D, Wickizer TM. Early opioid prescription and subsequent disability among workers with back injuries: The Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976)* 2008; 33:199-204.

31. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain* 2009; 142:194-201.

32. Benyamin RM, Manchikanti L, Parr AT, Diwan S, Singh V, Falco FJ, Datta S, Abdi S, Hirsch JA. The effectiveness of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain. *Pain Physician* 2012; 15:E363-E404.

33. Parr AT, Manchikanti L, Hameed H, Conn A, Manchikanti KN, Benyamin RM, Diwan S, Singh V, Abdi S. Caudal epidural injections in the management of chronic low back pain: A systematic appraisal of the literature. *Pain Physician* 2012; 15:E159-E198.

34. Manchikanti L, Buenaventura RM, Manchikanti KN, Ruan X, Gupta S, Smith HS, Christo PJ, Ward SP. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician* 2012; 15:E199-E245.

35. Manchikanti L, Falco FJ, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, axial or discogenic low back pain, central spinal stenosis, and post lumbar surgery syndrome. *Pain Physician* 2013; 16:E129-E143.

36. Manchikanti L, Pampati V, Falco FJ, Hirsch JA. Growth of spinal interventional pain management techniques: Analysis of utilization trends and Medi-

care expenditures 2000 to 2008. *Spine (Phila Pa 1976)* 2013;38:157-168.

37. US Department of Health and Human Services. Office of Inspector General (OIG). Inappropriate Medicare Payments for Transforaminal Epidural Injection Services (OEI-05-09-00030). August 2010.http://oig.hhs.gov/oei/reports/oei-05-09-00030.pdf

38. Jacobs WC, van der Gaag NA, Kruyt MC, Tuschel A, de Kleuver M, Peul WC, Verbout AJ, Oner FC. Total disc replacement for chronic discogenic low back pain: A Cochrane review. *Spine (Phila Pa 1976)* 2013; 38:24-36.

39. Jacobs WC, Arts MP, van Tulder MW, Rubinstein SM, van Middelkoop M, Ostelo RW, Verhagen AP, Koes BW, Peul WC. Surgical techniques for sciatica due to herniated disc, a systematic review. *Eur Spine J* 2012; 21:2232-2251.

40. Chessell IP, Dudley A, Billinton A. Biologics: The next generation of analgesic drugs? *Drug Discov Today* 2012; 17:875-879.

41. Hunter DJ, Pike MC, Jonas BL, Kissin E, Krop J, McAlindon T. Phase 1 safety and tolerability study of BMP-7 in symptomatic knee osteoarthritis. *BMC Musculoskelet Disord* 2010; 11:232.

42. Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: Preliminary results in a group of active patients. *Sports Health* 2012; 4:162-172.

43. Orozco L, Soler R, Morera C, Alberca M, Sanchez A, Garcia-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: A pilot study. *Transplantation* 2011; 92:822-828.

44. Bae WC, Masuda K. Emerging technologies for molecular therapy for intervertebral disk degeneration. *Orthop Clin North Am* 2011; 42:585-601, ix.

45. Pezet S, McMahon SB. Neurotrophins: Mediators and modulators of pain. *Annu Rev Neurosci* 2006; 29:507-538.

46. Woolf CJ. Phenotypic modification of primary sensory neurons: The role of nerve growth factor in the production of persistent pain. *Philos Trans R Soc Lond B Biol Sci* 1996; 351:441-448.

47. Hefti FF, Rosenthal A, Walicke PA, Wyatt S, Vergara G, Shelton DL, Davies AM. Novel class of pain drugs based on antagonism of NGF. *Trends Pharmacol Sci* 2006; 27:85-91.

48. Kawamoto K, Aoki J, Tanaka A, Itakura

A, Hosono H, Arai H, Kiso Y, Matsuda H. Nerve growth factor activates mast cells through the collaborative interaction with lysophosphatidylserine expressed on the membrane surface of activated platelets. *J Immunol* 2002; 168:6412-6419.

49. Nagy I, Santha P, Jancso G, Urban L. The role of the vanilloid (capsaicin) receptor (TRPV1) in physiology and pathology. *Eur J Pharmacol* 2004; 500:351-369.

50. Schaible HG, Schmelz M, Tegeder I. Pathophysiology and treatment of pain in joint disease. *Adv Drug Deliv Rev* 2006; 58:323-342.

51. Woolf CJ, Safieh-Garabedian B, Ma QP, Crilly P, Winter J. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. *Neuroscience* 1994; 62:327-331.

52. Rukwied R, Mayer A, Kluschina O, Obreja O, Schley M, Schmelz M. NGF induces non-inflammatory localized and lasting mechanical and thermal hypersensitivity in human skin. *Pain* 2010; 148:407-413.

53. Jaggar SI, Scott HC, Rice AS. Inflammation of the rat urinary bladder is associated with a referred thermal hyperalgesia which is nerve growth factor dependent. *Br J Anaesth* 1999; 83:442-448.

54. Gwak YS, Nam TS, Paik KS, Hulsebosch CE, Leem JW. Attenuation of mechanical hyperalgesia following spinal cord injury by administration of antibodies to nerve growth factor in the rat. *Neurosci Lett* 2003; 336:117-120.

55. Halliday DA, Zettler C, Rush RA, Scicchitano R, McNeil JD. Elevated nerve growth factor levels in the synovial fluid of patients with inflammatory joint disease. *Neurochem Res* 1998; 23:919-922.

56. Ramer MS, Bisby MA. Adrenergic innervation of rat sensory ganglia following proximal or distal painful sciatic neuropathy: Distinct mechanisms revealed by anti-NGF treatment. *Eur J Neurosci* 1999; 11:837-846.

57. Obata K, Tsujino H, Yamanaka H, Yi D, Fukuoka T, Hashimoto N, Yonenobu K, Yoshikawa H, Noguchi K. Expression of neurotrophic factors in the dorsal root ganglion in a rat model of lumbar disc herniation. *Pain* 2002; 99:121-132.

58. Skoff AM, Resta C, Swamydas M, Adler JE. Nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) regulate substance P release in adult spinal sensory neurons. *Neurochem Res* 2003; 28:847-854.

59. Chen JR, Wang YJ, Tseng GF. The effects of decompression and exogenous NGF on compressed cerebral cortex. *J Neurotrauma* 2004; 21:1640-1651.

60. Watanabe K, Larsson K, Rydevik B, Kikuchi SI, Konno SI, Olmarker K. Changes in expression of sodium channels in trkA positive neurons in the dorsal root ganglion following disc puncture. An experimental study in rats. *Spine* 2010. {this entry is incomplete cannot be found on PubMed}

61. Sarchielli P, Gallai V. Nerve growth factor and chronic daily headache: A potential implication for therapy. *Expert Rev Neurother* 2004; 4:115-127.

62. Sevcik MA, Ghilardi JR, Peters CM, Lindsay TH, Halvorson KG, Jonas BM, Kubota K, Kuskowski MA, Boustany L, Shelton DL, Mantyh PW. Anti-NGF therapy profoundly reduces bone cancer pain and the accompanying increase in markers of peripheral and central sensitization. *Pain* 2005; 115:128-141.

63. Ro LS, Chen ST, Tang LM, Jacobs JM. Effect of NGF and anti-NGF on neuropathic pain in rats following chronic constriction injury of the sciatic nerve. *Pain* 1999; 79:265-274.

64. Koltzenburg M, Bennett DL, Shelton DL, McMahon SB. Neutralization of endogenous NGF prevents the sensitization of nociceptors supplying inflamed skin. *Eur J Neurosci* 1999; 11:1698-1704.

65. Evans RJ, Moldwin RM, Cossons N, Darekar A, Mills IW, Scholfield D. Proof of concept trial of tanezumab for the treatment of symptoms associated with interstitial cystitis. *J Urol* 2011; 185:1716-1721.

66. Schnitzer TJ, Lane NE, Birbara C, Smith MD, Simpson SL, Brown MT. Long-term open-label study of tanezumab for moderate to severe osteoarthritic knee pain. *Osteoarthritis Cartilage* 2011; 19:639-646.

67. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Arthritis Advisory Committee (AAC) Meeting. March, 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM307880.pdf

68. Pimentel DC, El Abd O, Benyamin RM, Buehler AM, Leite VF, Mazloomdoost D, Chen J, Hsing WT, Amadera JED. Anti-tumor necrosis factor antagonists in the treatment of low back pain and radiculopathy: A systematic review and meta-analysis. *Pain Physician* 2014; 17:E27-E44.

69. Furlan AD, Pennick V, Bombardier C, van Tulder M. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941.

70. Malmivaara A, Koes BW, Bouter LM, van Tulder MW. Applicability and clinical relevance of results in randomized controlled trials: The Cochrane review on exercise therapy for low back pain as an example. *Spine (Phila Pa 1976)* 2006; 31:1405-1409.

71. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW, Jr., Zaza S. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328:1490.

72. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *Jf Clin Epidemiol* 2013; 66:719-725.

73. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell, Chichester, England, 2009, pp 174-175.

74. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell, Chichester, England, 2009, pp 485.

75. Pfizer. A study of tanezumab in adults with chronic low back pain. http://ClinicalTrials.gov/show/NCT00876187

76. Pfizer. RN624 in adult patients with chronic low back pain. http://ClinicalTrials.gov/show/NCT00584870

77. Johnson & Johnson. A dose-ranging study of the safety and effectiveness of JNJ-42160443 as add-on treatment in patients with low back pain. http://ClinicalTrials.gov/show/NCT00973024

78. Hill R. Blocking the effects of NGF as a route to safe and effective pain relief-fact or fancy? *Pain* 2011; 152:2200-2201.

79. Ackermann PW. Katz et al., Efficacy and safety of tanezumab in the treatment of chronic low back pain [Pain 2011;152:2248-2258] and Hill, blocking the effects of NGF as a route to safe and effective pain relief - fact or fancy? [Pain 2011;152:2200-2201]. *Pain* 2012; 153:1128-1129; author reply 1129-1131.

80. Pfizer. Long-term safety study of tanezumab in chronic low back pain. http://ClinicalTrials.gov/show/NCT00924664

81. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Summary minutes of the Arthritis Advisory Committee meeting, March 12, 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM307879.pdf

82. Katz N, Borenstein DG, Birbara C, Bramson C, Nemeth MA, Smith MD, Brown MT. Efficacy and safety of tanezumab in the treatment of chronic low back pain. *Pain* 2011; 152:2248-2258.

83. Katz N, Borenstein DG, Birbara C, Bramson C, Nemeth MA, Smith MD, Brown MT. A Study of tanezumab in adults with chronic low back pain (NCT00876187). [abstract]. *Arthritis Rheum* 2011; 63:741.

84. Regeneron. A study to evaluate the safety and efficacy of subcutaneously administered REGN475(SAR164877) in patients with sciatic pain. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295206.pdf

85. Sanga P, Karcher K, Wang S, Kelly K, Oh C, Thipphawong J. Efficacy, safety, and tolerability of fulranumab in treatment of patients with moderate-to-severe, chronic low back pain. *J Pain* 2011; 12:P53.

86. Cohen J. *Statistical Power Analysis in the Behavioral Sciences.* 2nd ed.. Lawrence Erlbaum Associates, Inc., Hillsdale, NJ, 1988.

87. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Background Materials, AAC Meeting, March 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295202.pdf

88. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Background Package Addendum, AAC Meeting, March 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM295203.pdf

89. U.S. Food and Drug Administration Center for Drug Evaluation and Re-

search. Arthritis Advisory Committee (AAC) Meeting. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM307880.pdf

90. Pfizer. PFE - Q2 2013 Pfizer Earnings Conference Call - Edited transcript. 2013 www.pfizer.com/files/investors/presentations/PFE-Transcript-2013-07-30T14_00.pdf

91. Brain SD, Grant AD. Vascular actions of calcitonin gene-related peptide and adrenomedullin. *Physiol Rev* 2004; 84:903-934.

92. Caporali A, Emanueli C. Cardiovascular actions of neurotrophins. *Physiol Rev* 2009; 89:279-308.

93. Meloni M, Caporali A, Graiani G, Lagrasta C, Katare R, Van Linthout S, Spillmann F, Campesi I, Madeddu P, Quaini F, Emanueli C. Nerve growth factor promotes cardiac repair following myocardial infarction. *Circ Res* 2010; 106:1275-1284.