ORIGINAL ARTICLE

Efficacy, Safety, and Predictors of Intradiscal Methylene Blue Injection for Discogenic Low Back Pain: Results of a Multicenter Prospective Clinical Series

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■ **Abstract**

Study Design: Prospective clinical study of intradiscal methylene blue injection for the treatment of lumbar discogenic pain.
Objective: The objective of this study was to collect information about efficacy, safety, and acceptability of the intervention, gain and burden of outcome measures, and sample size assumptions for a potential following randomized controlled trial (RCT). If the pilot study demonstrates that this treatment is potentially effective and safe, and the methods and procedures used in this study are feasible, a RCT follows.

Summary of Background Data: Low back pain (LBP) is a highly common problem with a lifetime prevalence of more than 70%. A substantial part of chronic LBP is attributable to degenerative changes in the intervertebral disc. A recently published RCT assessing the treatment intradiscal injection of methylene blue for chronic discogenic LBP, showed exceptionally good results.
Methods: Patients were selected on clinical criteria, magnetic resonance imaging, and a positive provocative discogram. The primary outcome measure was mean pain reduction at 6 months.
Results: Fifteen consecutive patients with chronic lumbar discogenic pain enrolled in a multicenter prospective case series in two interventional pain treatment centers in the Netherlands. Six months after the intervention, 40% of the patients claimed at least 30% pain relief. In patients who responded, physical function improved and medication use diminished. We observed no procedural complications or adverse events. Predictors for success were Pfirrmann grading of 2 or less and higher quality of life mental component scores.
Conclusions: Our findings of 40% positive respondents, and no complications, give reason to set up a randomized, double-blind, placebo-controlled, trial. ■

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INTRODUCTION

Low back pain (LBP) has a lifetime prevalence of 70%. Although LBP often resolves spontaneously, it has a high rate of recurrence. Approximately 60% of patients who consult their general practitioner with a recent onset LBP still suffer pain after 1 year.[1] Chronic LBP often leads to a low quality of life due to pain, disability and loss of work productivity. Moreover, chronic LBP is accompanied by high health care costs for society.[2,3] Approximately 40% of chronic LBP has been reported to be of discogenic origin.[4,5]

Previous studies[6,7] suggest that discogenic LBP is caused by internal disc disruption and is closely related with vascularized granulation tissue containing nociceptive nerves, extending from the outer layer of the annulus fibrosis into the nucleus pulposus.[7,8] Sensitization of these nerve endings in the outer annulus by various inflammatory mechanisms may lead to chronic discogenic LBP. Assuming that these ingrown nerve endings play an important factor in mediating discogenic LBP, many attempts have been made to prove that reduction of inflammation and/or ablation of intradiscal nociceptors would be beneficial for patients with discogenic LBP.[9–15] Despite some promising results of these methods, the ideal interventional treatment of discogenic LBP has still to be found.

Since Methylene blue was first synthesized in 1876, it has been used in many different ways such as a tissue dye during various treatments and for diagnostic purposes.[16] Due to its neurolytic effect, methylene blue was first injected into the intervertebral disc in 2007.[17] A positive prospective study followed by a randomized controlled trial (RCT), published in 2010,[18] both showed statistical and clinically meaningful reduction in pain and disability in patients with discogenic LBP. A decrease in pain was measured by a Numeric Rating Scale (NRS) from 0 to 100. At least 20 points were seen in 89% of the patients, of which 19% reported no further pain and 28% reported dramatic improvement of symptoms. In the editorial that accompanied the publication, it was stated that 1 positive RCT should not amount to endorsement, and the author encouraged other centers to reproduce these results.[19]

The current study aimed to duplicate the original prospective case series.[17] The effects of intradiscal methylene blue injection treatment were explored in a well-selected group of 15 patients with objectified discogenic LBP for at least 6 months. It was agreed that if at least 5 of 15 patients would show a clinically relevant reduction in pain of at least 30%,[20,21] and both procedure and treatment would have no complications or serious side effects. A placebo controlled randomized clinical trial would follow this pilot study.

MATERIALS AND METHODS

This prospective clinical series is conducted in a regional interventional pain center and in a university interventional pain center in the Netherlands. Trial registration number is NTR 2547. The study was approved by the European Union Drug Regulating Authorities Clinical Trials (EudraCT) registration numbers 2010-022025-15, and the medical ethics committee (METC) of the Maastricht University Medical Centre (ref: 10-2-055). Written informed consent was obtained from all subjects included in the study.

The goal of this study was information collection about efficacy and safety of the intervention, complications and side effects, recruitment strategies, acceptability of intervention, gain, burden of outcome measures, and sample size assumptions. The study committee stated that if this pilot study indicates that this treatment is effective, a placebo controlled RCT would follow. Effectiveness was achieved if at least 30% patients responded and no major complications and side effects occurred. Patients were responder patients if the mean pain relief was clinically important;[21] ie, at least 30% pain reduction at 6 months follow-up.

Patient Selection

In the period March 2011 to September 2012, 174 consecutive patients with chronic LBP without radiculopathy were selected for eligibility. Eligibility criteria were: (1) axial LBP and impaired function of at least 6 months duration; (2) nonresponsiveness to conservative treatment for at least 6 months; (3) The suspect discs has at least 50% disc height compared to a control disc;[22] (4) Pain provocation by low pressure discography < 50 PSI (pounds per square inch above opening pressure) at the affected level(s), without pain reproduction or with discordant pain at adjacent unaffected control levels; (5) age between 18 and 65 years; and (6) mean pain intensity of 5 or higher, measured by a pain diary with NRS 3 times a day for 4 consecutive days.[23]

Exclusion criteria were: (1) severe disc degeneration at the affected level evidenced by > 50% of disc height loss on plain anteroposterior and lateral radiographs; (2) CT or MRI of the lumbar spine shows extruded or sequestrated nucleus pulposus tissue at the affected levels; (3) mean pain NRS below 5; (4) previous lumbar back surgery at the affected level(s); (5) intradiscal procedures previously performed at the affected level(s); (6) BMI > 35; (7)pregnancy; and (8)provocative discography with pressures exceeding 50PSI above opening pressure.[24,25]

Lumbar Pressure-controlled Provocative Discography

Consecutive eligible patients who for at least 6 months were treated conservatively, and who had facet blocks without pain reduction, received a provocative discography to confirm LBP of discogenic origin.

Intradiscal Methylene Blue Injection

After antibiotic prophylaxis (2 grams Cephazolin i.v.), a needle (with double needle technique) was placed in the symptomatic disc. Anteroposterior and lateral plane fluoroscopy confirms needle position. A mixture of 1 mL methylene blue 10% and 1 mL lidocaine 2% was then injected, with pressure control, into the disc. Patients were all day-care surgery submitted and after treatment and kept under bed rest observation for at least 2 hours.

Objectives

All primary and secondary outcome parameters were assessed at baseline, at 6 weeks, 3 months, and at 6 months after the intervention. Main outcome measure was the mean pain change at 6 months after the intervention. Mean pain was measured by a pain diary with NRS 3 times a day for 4 consecutive days at baseline and at the follow-up time points.[23] Furthermore, Patients Global Impression of Change (PGIC)[26] measured by a 7-point Likert Scale, and number of adverse and serious adverse events were reported.[26,27]

Secondary study parameters were disability measured by the Oswestry Disability Index,[28] and Quality of life measured by the SF-36 and EuroQol.

A tertiary objective was a retrospective comparison of Magnetic Resonance imaging (MRI)[29–32] and provocative discography[26] findings with success or failure of treatment. Magnetic resonance imaging (MRI) was performed at baseline and was repeated 1 year after treatment. Both the MRI findings (baseline and follow-up) were evaluated, blinded for success of outcome, individually by 3 authors (JK, PW, HS). Differences in MRI evaluation were discussed in a consensus meeting with all authors to derive general agreement. Because the analyses were performed on a relatively small group of patients, the Pfirrmann and Modified Dallas grading were dichotomized. Literature states that, for the Pfirrmann, grading, interobserver agreement is highest between grade II and III.[32] Therefore, Pfirrmann grade findings were dichotomized (≤ or > grade II). Furthermore, other baseline values of possible predictors were registered (ie, demographics and baseline patient characteristics).

Statistical Methods

A linear mixed model analysis for longitudinal data establishes differences in pain score changes over time. The changes in outcome between baseline and 6 months were compared between responder patients and nonresponders. Differences were tested with the Mann–Whitney test for nonparametric data. Furthermore, binary logistic regression explored possible predictors for success or failure of the procedure.

RESULTS

Participant Flow

One hundred and forty-seven patients with chronic LBP were eligible for screening and 56 reacted positive on facet blocks. After discography, 15 patients enrolled in the pilot study (Figure 1). Of the 15 patients included in the study, 12 patients completed the study protocol with follow-up data of 6 weeks, 3 months, and 6 months. The 2 two patients of the pilot were dissatisfied with the short term result and only filled in the follow-up data of 6 weeks after the intervention. In reaction to these events, patients received more information about expectations of the short time results. With this routine established, only one patient was lost to follow-up at the 6-month assessment.

Recruitment and Follow-up

Patients were recruited from March 2011 until September 2012. Patients received a pain diary and a questionnaires booklet at baseline and at standardized follow-up moments of 6 weeks, and 3 and 6 months.

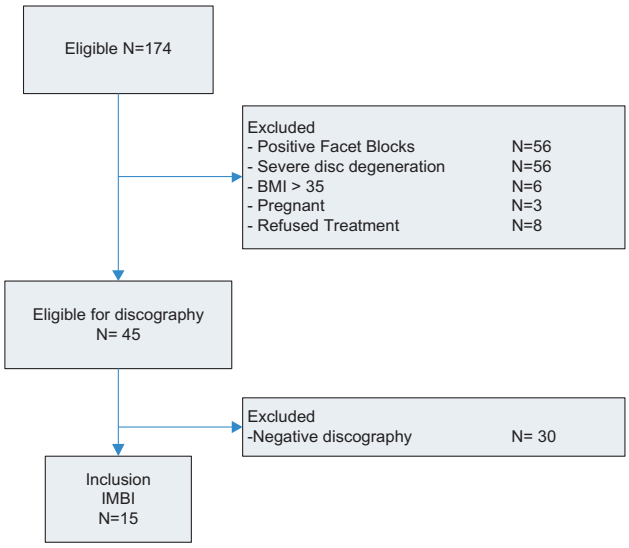

Figure 1. Flowchart of study participants.

Baseline Data

Table 1 shows baseline demographics and clinical characteristics of the study group. Ten female and 5 male patients were treated. The mean duration of LBP was 5.6 years, mean pain at baseline was NRS 6.7, and quality of life was on average rated rather low between 32 and 54. Five patients used opioids at baseline. Mean age was 40.8 (22 to 57).

Outcome

Pain and Patient Global Impression of Change. Linear mixed model analysis for pain at 6 months (Figure 2) shows that mean predicted pain reduction at 6 months is 2 points (6.4 to 0.08 × weeks). The result of responder analyses is depicted in Figure 3. Pain treatment at 6 months was successful in 40% of patients, with at least 30% pain reduction in 6 patients (more than 50% in 5 patients). Table 2 shows that the mean pain reduction at 6 months in responding patients is 7.1 (11-box NRS score 0 to10) resulting in a mean NRS pain score of 2.4. In contrast, the nonresponders mean pain score was 6.8 at 6 months. The Patient Global Impression of Change was very much improved in 5 and much improved in 1 responder patient. One nonresponding patient rated the change as minimally improved, the other 5 patients as not improved.

At 3 months follow-up, 7 patients (47%) responded with at least 30% pain reduction to the treatment (Mean NRS pain change −3.4, SD 1.6).

Table 1. Baseline Characteristics and Demographics

Variables	Value *N* (total = 15)
Sex	
Male	5
Female	10
Suspect level	
L3-L4	1
L4-L5	5
L5-S1	9

	Mean (SD)	Min–Max
Age (years)	40.8 (10.5)	22–57
Body mass index	24.4 (3.8)	15–31
Duration of LBP (years)	5.6 (5.1)	1–20
Mean pain (NRS)	6.7 (1.4)	4–9
Quality of life		
Physical component score	32.1 (7.5)	22.5–44.1
Mental components score	48.0 (11.9)	29.4–66.4
EuroQol VAS	54.2 (22.6)	15–90

Disability	%(SD)	
Oswestry	59.7 (10.9)	44–82

Analgesic use	*N* (%)
Non-NSAID	3 (20)
NSAID	3 (20)
OPIOIDS	5 (33)

NRS, Numeric Rating Score; VAS, Visual Analogue Scale; LBP, low back pain.

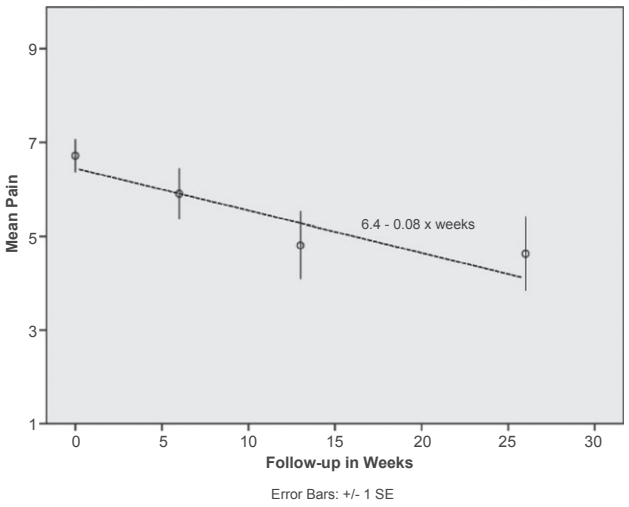

Figure 2. Mean pain over time. The points and vertical lines represent mean pain (NRS) with standard errors, at each measured time point. Linear regression line (dashed line) calculated with linear mixed model analysis.

Function and Quality of Life. Two main quality of life outcome scores were calculated from the SF-36: the Mental Components Summary (MCS) and the Physical Components Summary (PCS).[33] Decreasing values for the Oswestry, EuroQol-VAS, PCS, and MCS scores of

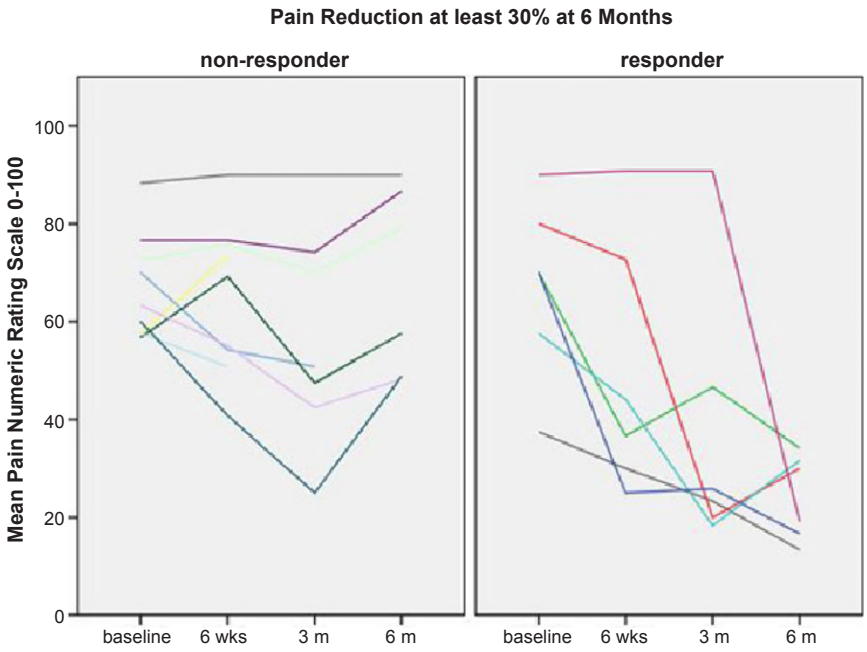

Figure 3. Result of responder analysis of pain reduction over time. Each line depicts a patient.

Table 2. Result of Responder Analyses

Outcome Variables	Responders *N* = 6 CS (Mean Score)	Nonresponders *N* = 6 Completers CS (Mean Score)	*P*-value*
Pain			
Mean pain (NRS) at 6 months	−7.1 (2.4)	−0.1 (6.8)	0.002
Quality of life			
Mean Physical Component Score	10 (44.2)	−4.0 (26.8)	0.002
Mean Mental Components Score	−1 (55.5)	3.5 (48.2)	0.818
EuroQol (VAS)	3 (65.3)	−10 (43.0)	0.126
Disability			
Oswestry (% disability)	17.3 (38)	−6.3 (67.6)	0.002

	CS (*N* Baseline)	CS (*N* Baseline)
Analgesic use (*N*)		
Non-NSAID	−2 (2)	+1 (0)
NSAID	−1 (1)	−1 (1)
OPIOIDS	0 (2)	−1 (3)
PGIC	(*N*)	(*N*)
Very much improved	5	0
Much improved	1	0
Minimally improved	0	1
Not improved	0	5

*Mann–Whitney *U*-test.
Change scores of responders vs. nonresponders.
PGIC, patients global impression of change; CS, change scores; NRS, Numeric Rating Score; VAS, Visual Analogue Scale.

the SF-36 are related to patient deterioration (increase in pain and disability, decrease in quality of life).

Responding patients improved their physical function with 17.3% on average, measured with the Oswestry Disability Index (Table 2). The PCS of the SF- 36 also showed progress (ie, 10 points improvement. The MCS and Euroqol VAS showed no improvement).

Analgesic Use. Overall, use of NSAIDs and opioids was reduced at 6 months. Of the responder patients, the 2 patients who used an opioid for their pain ceased the use of opioids during the follow-up. In the nonresponder group, 2 patients still used opioids at 6 months.

Adverse Events and Complications. No adverse events were reported. Most patients suffered a transient increase in axial LBP for 1 to 2 weeks after treatment. Some patients reported a transient (1 to 2 weeks) painful feeling of pressure in the injected spine area.

Magnetic Resonance Imaging (MRI) and Provocative Discography Findings. At baseline, the MRI of 8 (53%) patients showed a Pfirrmann grading of more than II.[32,34]

In 5 MRIs Modic signs were detected,[35] high intensity zones in 6. Twelve-month follow-up MRI findings showed no signs of rapidly progressed disc degeneration. There was no noticeable change in the presence of Modic signs, high intensity zones, or Pfirrmann grading.[16,30]

Prediction for Success or Failure

Binary logistic regression analyses assessed if success or failure is predictable by baseline variables (Table 3). The quality of life main component, MCS, appears to be a predictor for success or failure. It indicates that patients who score higher at baseline are more likely positive responding to intradiscal methylene blue injection treatment. The Pfirrmann grading was also an independent factor for failure ($P = 0.02$); 7 of the 8 patients with a Pfirrmann Grade of more than grade II were nonresponsive to treatment. Patients with a Pfirrmann grade of 2 or less were better responders ($P = 0.04$). Seven patients had a relatively well-maintained discs (Pfirrmann Grade 2 or less); 5 of these 7 responded well.

DISCUSSION

This prospective case series of 15 patients showed that intradiscal methylene blue injection treatment is successful in 40% of well-selected discogenic LBP patients. Success definition was pain relief of at least 30% at 6 months. Patients who responded well also improved in function and quality of life, and diminished their medication use. No complications or serious side effects were noted.

Since the publication of the original RCT in which methylene blue is described as a highly successful remedy for discogenic pain2 two prospective studies have been published.[36,37] First, in a study of 8 patients, no clinical effect was found. Second, in a study of 20 patients, only 20% of patients showed long-term pain reduction.[37] A possible explanation for the discrepancies in results between our study and the 2 afore mentioned prospective studies could be that our selection criteria were more stringent. For instance, in our study, the treatment logarithm dictates that patients should have had facet blocks without sufficient pain reduction before intradiscal methylene blue injection treatment is considered. Pain, mainly produced by facet arthritis is in our patient-series and therefore, excluded.

The presumed and accepted working mechanism of this treatment is denervation of the small nociceptive fibers that grow into a diseased disc's annulus fibrosis. The other working mechanism of intradiscal methylene blue could be that it alleviates inflammatory processes that may lead to fibrosis.[16,38] Methylene blue is also a direct inhibitor of nitric oxide (NO) synthesis. Nitric oxide plays an important role in the inflammatory process of disc degeneration and therefore, in discogenic pain.[16,38] A recent study that describes the positive effect of antibiotics on lumbar discogenic pain, shows that inflammatory and low-grade infectious processes could be involved in discogenic pain.[39] In that respect, Modic type 1 changes could be an indication for chronic spondylodiscitis in discogenic LBP.[29,30,39]

In our study, we duplicated the prospective study of 2007.[17] In order to select exclusively patients with discogenic pain, we performed provocative discography with pressure and velocity control using a Controlled Disc Stimulation (CDS) system. Despite our efforts, we could not duplicate the exceptionally good result of the aforementioned study and found only 40% of patients responding to this treatment. Nevertheless, the 40% of responding patients had good pain relief and improved in physical function and quality of life.

It is important to know the effect of injection(s) with methylene blue on disc tissue. Therefore, MRI's were repeated 1 year after treatment. Findings after 1 year of treatment indicate that in the patients assessed, there is no indication of rapidly degeneration of the intervertebral disc. To establish possible positive effects of methylene blue on intradiscal inflammation processes, MRI scans before and after treatment were also judged on the presence of Modic signs.[16] There was no change in the presence of Modic signs in these patients. Since only 5 patients had Modic signs at

Table 3. Results of Binary Logistic Analyses

Baseline Predictor Variable	Baseline Value of Responder	Baseline Value of Nonresponder	*P*-value
Gender			
Male (*N*)	1	4	0.28
Female (*N*)	5	5	
	Mean (SD)	Mean (SD)	
SF 36 QOL			
MCS	55.6 (3.2)	42.9 (13)	0.07
PCS	34.1 (8.8)	30.7 (6.6)	0.37
EuroQol (VAS)	54.2 (20.4)	54.2 (25.2)	0.99
Disease duration (months)	48 (34)	80 (73)	0.34
	N (%^{r})	*N* (%^{nr})	
MRI			
Modic signs	1 (17)	4 (44)	0.29
HIZ	3 (50)	3 (33)	0.52
Pfirrmann Grade > 2	1 (12.5)	7 (87.5)	0.02
Provocative discography			
Modified Dallas Scale > 2	3 (22)	3 (50)	0.27

HIZ, high intensity zone; %$^{(n)r}$ = % within (non)responder; MCS, Mental Components Summary; PCS, Physical Components Summary.

baseline, this result could be due to the small numbers assessed. Therefore, this assessment of 1-year follow-up MRI findings shall be repeated in the subsequent RCT.

The MCS appeared to be a predictive factor for success or failure, indicating that patients who score higher at baseline at this quality of life main component have a better chance of success after intradiscal methylene blue injection treatment. Although this result seems to be coherent to everyday clinical practice, we must point out that predictor analysis in such a small number of patients can only be classified as indicative. The results of the ensuing RCT will probably be more conclusive. The predictor analysis also shows that a Pfirrmann grade of 2 or less before the treatment could be a predictor for success. This matches the finding in a recent study in which patients with Pfirrmann grade ≤ 2 responded favorably on Intradiscal electro thermal therapy (IDET).[40] The presumed working mechanism of IDET therapy is similar to Intradiscal methylene blue injection insofar as the target points for treatment are the nerve endings in annular tears.

For lumbar discogenic pain patients, for whom to date there is no alternative pain remedy, intradiscal methylene blue injection could be a treatment option. It seems unlikely that the results (40% of treated patients had at least 30% pain reduction) are a product of placebo response only). Furthermore, only 15 patients were recruited and followed-up, this sample size is too small to come to firm conclusions. Therefore, a randomized double-blind placebo controlled trial will follow this study to establish whether these results are reproducible in a larger discogenic back pain population and to determine the size of a possible placebo-effect under controlled conditions. This RCT will be performed in 4 specialized interventional pain centers in the Netherlands. Based on the former published RCT, adapted by the results from this prospective study, the sample size assumption for the following RCT is 80 patients, 40 will be randomized in the treatment group and 40 patients in the control group. In this RCT, the randomized treatment group will receive an intradiscal injection with 1 mL Methylene blue, 0.5 mL Lidocaine, and 0.5 mL Iohexol contrast-dye (Iohexol-Omnipaque 300; GE Healthcare, Princeton, NJ, USA); the control group will be injected with 1 mL NaCl 0.9%, 0.5 mL Lidocaine and 0.5 mL Iohexol. Interim analysis with the data of the 6 months assessment of 50 patients is preplanned to correct for sample size assumptions.

REFERENCES

1. Itz CJ, Geurts JW, van Kleef M, Nelemans P. Clinical course of non-specific low back pain: a systematic review of prospective cohort studies set in primary care. *Eur J Pain*. 2013;17:5–15.
2. Becker A, Held H, Redaelli M, et al. Implementation of a guideline for low back pain management in primary care: a cost-effectiveness analysis. *Spine (Phila Pa 1976)*. 2012;37:701–710.
3. Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. *J Pain Palliat Care Pharmacother*. 2012;26:310–325.
4. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. *Orthop Clin North Am*. 1991;22:181–187.
5. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The relative contributions of the disc and zygapophyseal joint in chronic low back pain. *Spine*. 1994;19:801–806.
6. Bogduk N, Aprill C, Derby R. Lumbar discogenic pain: state-of-the-art review. *Pain Med*. 2013;14:813–836.
7. Garcia-Cosamalon J, del Valle ME, Calavia MG, et al. Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain? *J Anat*. 2010;217:1–15.
8. Peng B, Wu W, Hou S, Li P, Zhang C, Yang Y. The pathogenesis of discogenic low back pain. *J Bone Joint Surg Br*. 2005;87:62–67.
9. Kallewaard JW, Terheggen MA, Groen GJ, et al. Discogenic low back pain. *Pain Pract*. 2010;10:560–579.
10. Singh K, Ledet E, Carl A. Intradiscal therapy: a review of current treatment modalities. *Spine (Phila Pa 1976)*. 2005;30:S20–S26.
11. Barendse GA, van Den Berg SG, Kessels AH, Weber WE, van Kleef M. Randomized controlled trial of percutaneous intradiscal radiofrequency thermocoagulation for chronic discogenic back pain: lack of effect from a 90-second 70 C lesion. *Spine*. 2001;26:287–292.
12. Ercelen O, Bulutcu E, Oktenoglu T, et al. Radiofrequency lesioning using two different time modalities for the treatment of lumbar discogenic pain: a randomized trial. *Spine*. 2003;28:1922–1927.
13. Pauza KJ, Howell S, Dreyfuss P, Peloza JH, Dawson K, Bogduk N. A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. *Spine J*. 2004;4:27–35.
14. Kapural L, Vrooman B, Sarwar S, et al. A randomized, placebo-controlled trial of transdiscal radiofrequency, biacuplasty for treatment of discogenic lower back pain. *Pain Med*. 2013;14:362–373.
15. Rohof O. Intradiscal pulsed radiofrequency application following provocative discography for the management of degenerative disc disease and concordant pain: a pilot study. *Pain Pract*. 2012;12:342–349.
16. Wainwright M, Crossley KB. Methylene Blue–a therapeutic dye for all seasons? *J Chemother*. 2002;14:431–443.

17. Peng B, Zhang Y, Hou S, Wu W, Fu X. Intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. *Eur Spine J*. 2007;16:33–38.

18. Peng B, Pang X, Wu Y, Zhao C, Song X. A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain. *Pain*. 2010;149:124–129.

19. Bogduk N. A cure for back pain? *Pain*. 2010;149:7–8.

20. Ostelo RW, Deyo RA, Stratford P, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. *Spine (Phila Pa 1976)*. 2008;33:90–94.

21. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.

22. Carragee EJ, Hannibal M. Diagnostic evaluation of low back pain. *Orthop Clin North Am*. 2004;35:7–16.

23. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain*. 1993;55:195–203.

24. Bogduk N. Provocation discography: lumbar disc stimulation. In: Bogduk N, ed. *Practice Guidelines for Spinal Diagnostic and Treatment Procedures*. San Francisco, CA: International Spine Intervention Society; 2004:20–46.

25. O'Neill C, Kurgansky M. Subgroups of positive discs on discography. *Spine*. 2004;29:2134–2139.

26. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.

27. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale.. [see comment]. *Pain*. 2001;94:149–158.

28. Baker DJ, Pynsent PB, Fairbank JCT. The Oswestry Disability Index revisited: its reliability, repeatability and validity, and a comparison with the St Thomas Disability Index. In: Roland MO, Jenner JR, eds. *Back Pain: New Approaches to Rehabilitation and Education*. Manchester: England Manchester University Press; 1989:174–186.

29. Emch TM, Modic MT. Imaging of lumbar degenerative disk disease: history and current state. *Skeletal Radiol*. 2011;40:1175–1189.

30. Kerttula L, Luoma K, Vehmas T, Gronblad M, Kaapa E. Modic type I change may predict rapid progressive, deforming disc degeneration: a prospective 1-year follow-up study. *Eur Spine J*. 2012;21:1135–1142.

31. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166:193–199.

32. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2001;26:1873–1878.

33. Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000;25:3130–3139.

34. Pearce RH, Thompson JP, Bebault GM, Flak B. Magnetic resonance imaging reflects the chemical changes of aging degeneration in the human intervertebral disk. *J Rheumatol Suppl*. 1991;27:42–43.

35. Modic MT, Obuchowski NA, Ross JS, et al. Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome. *Radiology*. 2005;237:597–604.

36. Gupta G, Radhakrishna M, Chankowsky J, Asenjo JF. Methylene blue in the treatment of discogenic low back pain. *Pain Physician*. 2012;15:333–338.

37. Kim SH, Ahn SH, Cho YW, Lee DG. Effect of intradiscal methylene blue injection for the chronic discogenic low back pain: one year prospective follow-up study. *Ann Rehabil Med*. 2012;36:657–664.

38. Liu GZ, Ishihara H, Osada R, Kimura T, Tsuji H. Nitric oxide mediates the change of proteoglycan synthesis in the human lumbar intervertebral disc in response to hydrostatic pressure. *Spine (Phila Pa 1976)*. 2001;26:134–141.

39. Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*. 2013;22:697–707.

40. Assietti R, Morosi M, Block JE. Intradiscal electrothermal therapy for symptomatic internal disc disruption: 24-month results and predictors of clinical success. *J Neurosurg Spine*. 2010;12:320–326.