PAIN MEASUREMENT AND MANAGEMENT IN PEOPLE WITH KNEE OSTEOARTHRITIS

By

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The body of this thesis contains three original manuscripts – one is published in Critical Reviews in Physical and Rehabilitation Medicine Journal, 24(3–4), 179–195 (2012), one was accepted for publication in Osteoarthritis & Cartilage and one in preparation for submission to Osteoarthritis & Cartilage. Although multiple authors appear on each paper, Ahmed Negm was responsible for all aspects of the study, including the design, analysis, and writing of the manuscripts. The co-authors on the papers had varying involvement ranging from assistance with study design, data collection, data analysis, and manuscript review.

ABSTRACT

Pain is a multidimensional construct and its proper measurement and management is challenging. Despite the evolution of pain theories that helped to understand pain, a theoretical model to lead the pain measurement and management may be required. No gold standard for measuring pain in people with knee osteoarthritis (OA) has been identified and, as such, several pain measures are used in this population. Few studies have investigated the perspective of people with knee OA regarding preferred pain measures and/or the degree to which the pain measures represent their pain experience. In combination with this, there is a need to identify effective conservative interventions to improve knee OA pain and physical function. Low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation is an emerging potential non-pharmacologic conservative treatment of knee OA. The purpose of this thesis was to improve the understanding of pain measurement and management in people with knee OA through: 1) Developing a theoretical model that may help in pain management and measurement; 2) Exploring the knee OA individuals' views about three pain measures and 3) To determine if low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through pulsed electromagnetic field (PEMF) or pulsed electrical stimulation (PES) versus sham PEMF/PES intervention is effective in improving pain and physical function in the knee OA population.

After pain theories literature review, a theoretical model was developed to address the gap between pain theories and clinical pain measurement and management. The patient's views about three pain measures were not explored before 96 participants were

recruited and completed the Verbal Numerical Rating Scale (VNRS), Intermittent and Constant Osteoarthritis pain Questionnaire (ICOAP) and the Short Form-McGill Pain Quetionnaire-2 (SF-MPQ-2). Participants were asked how well each pain measure describes their pain on a 10 cm Visual Analogue Scale (0 = does not describe your pain at all, and 10 = describes your pain completely. The time taken to score and complete the pain measure as well as the number of errors and questions while filling the pain measures were recorded. Systematic electronic searches after determining inclusion criteria for the studies were performed. Duplicate title, abstract and full text screening, risk of bias assessment, data extraction and grading the quality of evidence were performed. Data analysis was performed using Revman 5 software.

Our sample of individuals with knee OA showed that VNRS, SF-MPQ-2 and ICOAP describe knee OA pain experience with no preference of one over the others. However, VNRS was recommended because it is easier and faster to complete. The systematic review conclusion was that PEMF/PES may be beneficial to improve physical function but not pain in people with knee OA with low and very low quality of evidence respectively. However better quality RCTs are needed to confirm the effectiveness of PEMF/PES. Overall the results of this thesis will inform and give recommendations for pain measurement and management of knee OA in individuals.

DEDICATION

This thesis is dedicated to the soul of my father who gave me all the support till he passed away on June 2013.

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LIST OF ABBREVIATIONS

BAI- Beck anxiety inventory

BDI- Beck depression inventory

BHI- Beck helplessness inventory

CaM- Calmodulin

CI- Confidence interval

CPCI- Chronic pain coping index

FGF-2- Fibroblast growth factor

HADS- Hospital anxiety depression scale

ICOAP- Measure of Intermittent and Constant Osteoarthritis Pain

IL-1- Interleukin-1

IL-1β- Interleukin-1beta

IQR- Inter quartile range

κ- Kappa

MPI- Multidimensional pain inventory

MPQ-SF- Short form of McGill pain questionnaire

NRS- Numeric rating scale

NSAIDs- Nonsteroidal anti-inflammatory drugs

OA- Osteoarthritis

OARSI- Osteoarthritis Research Society International

OMERACT- Outcome Measures in Rheumatoid Arthritis Clinical Trials

PCS- Pain catastrophizing scale

PDI- Pain disability index

PEMF- Pulsed electromagnetic field

PES- Pulsed electrical stimulation

PGROA- Physician global rating scale of knee OA severity

PRISMA- Transparent reporting of systematic review and meta-analysis

RCT- Randomized control trial

RR- Risk ratio

SD- Standard deviation

SF-MPQ-2- Short-form McGill Pain Questionnaire-2

SMD- Standardized mean difference

SPOMS-Short form of the Profile of Mood States

TGFβ- Transforming growth factor beta

TSK- Tampa scale of kinesiophobia

VAS- Visual analog scale

VEGF- Vascular endothelial growth factor

VNRS- Verbal numeric rating scale

WOMAC- Western Ontario and McMaster Universities osteoarthritis index

χ^2- Chi-squared test

CHAPTER 1: INTRODUCTION

1.1.Osteoarthritis

Osteoarthritis (OA) is a degenerative joint disease that affects all articular structures but the articular cartilage changes are the most prominent feature (1, 2). OA is the most common joint disease in adults around the world (3) where approximately one-third of all adults have radiological signs of OA (3) but an epidemiological study showed that OA of the knee, hand, or hip is clinically significant in only 8.9% of the adult population (4). Knee OA was the most common type (6% of all adults) (5).

1.1.1. Pathogenesis and biomechanics

The structural changes of OA occur due to a loss of equilibrium between the breakdown and repair of joint tissues (6). The joint tissue changes in OA include 1) loss and erosion of articular cartilage (7); 2) progressive thickening and alterations in the architecture of subchondral trabecular bone, formation of new bone at the joint margins (osteophytes) and subchondral bone cysts(8); 3) synovial hyperplasia, fibrosis, capsule thickening and sometimes lymphocytic infiltrate (9); 4) meniscal erosions or tears(10); 5) muscle weakness (11) and 6) bone marrow abnormalities (12).

Altered joint biomechanics may cause knee OA initiation and progression (13). Varus or valgus deviation of the normal mechanical axis of the lower extremity (a line drawn from the centre of the femoral head to the centre of the talus (14)) has been shown to influence the load distribution across the articular joint surface which leads to joint damage (15). Other than the mechanical axis deviation, knee dynamic load which is three times the static load has an important role in OA development and progression (16). Knee

varus or valgus movements are associated with maximum compressive stresses on the medial or lateral knee compartments respectively thereby potentially resulting in more joint derangement (17).

1.1.2. Etiology and Risk Factors

OA is usually classified as primary, or idiopathic with unknown etiology, and secondary when it follows a clearly defined pathology such as post-traumatic, congenital or metabolic events (5). Risk factors for primary knee OA include genetic factors(persons whose parents had OA, especially if the disease was polyarticular or if the onset was in middle age or earlier, are at high risk of OA due to an autosomal dominant mutation in type II procollagen) (18), age and gender (knee OA is associated with older age with 6% of adults aged greater than 30 years and 13% of persons aged 60 years and greater having symptomatic knee OA (19,20) and being female) (21), ethnicity, obesity and diet (2).

1.1.3. American College of Rheumatology Diagnostic Criteria

OA is diagnosed clinically on the basis of a history, symptoms and signs and/or radiographically thereby confirming clinical suspicion and excluding other conditions. Symptoms and signs of OA vary but are dominated by pain, joint swelling, limited range of motion and muscle power, joint instability and failure, and people may experience crepitus and night pain - particularly with knee OA. Morning stiffness due to OA, in contrast to other rheumatic disorders, lasts less than 30 minutes (22). Radiographic diagnosis of OA is typically made using a weight-bearing plain radiograph of the knee illustrating the characteristic features seen in OA as mentioned above such as

osteophytes, subchondral sclerosis, and joint space narrowing, which is a surrogate for cartilage thickness and meniscal integrity in knees (23). When radiography is used along with physical examination, the diagnosis of knee OA has a sensitivity and specificity of 91% and 86%, respectively (22).

1.2. Chronic Pain

OA is one of the most common causes of chronic pain (24) which is defined as pain for more than three to six months (25). Theoretically, chronic pain is a multidimensional construct including sensory, cognitive, and affective dimensions. In order to measure pain completely and precisely, each dimension needs to be evaluated. The chronic nature of OA pain may be better understood using a theory- based multidimensional pain assessment tool.

Pain may be assessed by direct or self-report measurement tools; however, self-report tools are more commonly used. An example of an objective pain assessment tool is recording of nociceptive evoked potentials in the somoatosensory cortex which might be indicated for direct assessment of spinothalamic tract function (26). Observational pain measurements, which assess- observed behaviors that accompany the pain experience (30), are being used to assess pain in people with cognitive impairment. Examples of commonly used observational pain measures are the facial action coding system (31) and the pain behaviour measurement (27). Pain measurement is also achieved by recording the physiologic changes accompanying the experience of pain, such as heart rate, blood pressure, and electrodermal activity (30). Numerous self-report pain measurement tools exist which span from unidimensional pain intensity measures, which may include one or

more items, to multidimensional measures having multiple items. The three most commonly used unidimensional tools to assess pain intensity are the categorical verbal rating scales, visual analogue scale and numerical rating scales (27). Multidimensional measures which consider more than pain intensity include questionnaires such as the Brief Pain Inventory (28) and the Mcgill Pain Questionnaire (29).

A recent systematic review addressing the outcome measures used in pharmacological trials to determine effectiveness of drug interventions on knee OA pain reported that the most commonly used pain measures are self-report pain measures, the visual analog scale (VAS) and numeric rating scale (NRS) which both measure pain intensity, and the pain subscale of the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) which asks five questions about pain intensity during low-level daily activities and at night in bed (32). Furthermore, a gold standard for pain assessment in individuals with knee OA has not been established thereby necessitating the use of a combination of pain outcome measures (32). In the era of evidence-based medicine and patient centered care, the patient's view of the pain measures is critical. However, few studies have investigated the views of individuals with knee OA regarding the extent to which pain measures represent their pain experience (33). More information about the pain experience of people with knee OA and their views regarding current pain measures needs is needed as this may help in determination of the appropriate methods for assessing pain in this population.

1.3. Conservative management of primary knee OA

Knee OA is a multi-factorial and complex disease with unknown etiology, therefore, current clinical management of knee OA aims to manage pain and maintain independent physical function through a combination of pharmacologic and nonpharmacologic interventions based on evidence of effectiveness in clinical trials (34). Table 1.1 shows the latest American College of Rheumatology recommendation for knee OA management. The latest guideline (2012) did not strongly recommended any pharmacological intervention (34) for knee OA due to the uncertainty and mild efficacy of most of the available pharmacologic agents such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid intra-articular injection and intra-articular viscosupplementation on pain relief (35, 36). Moreover, side effects, contraindications and interactions of the pharmacologic interventions hinder using them for individuals with knee OA. For example, NSAIDs, which continue to be among the most commonly consumed analgesics (37), carry risk of cardiovascular, renal, and gastrointestinal toxicity with their use becoming more of a concern for older adults. The use of NSAIDs is associated with increased risk of hospitalization, renal toxicity, myocardial infarction, stroke, and death (38-40). On the other hand, The American College of Rheumatology strongly recommended non-pharmacologic management such as weight loss and exercise programs. Moreover, there are adjunct interventions for pain management that are conditionally recommended such as, thermal agents, walking aids and transcutaneous electrical stimulation. However, other physical agents were not considered in the clinical practice guidelines that are proposed to reduce pain or modify knee OA pathology, such as pulsed electromagnetic field (PEMF) or pulsed electrical stimulation (PES).

Table 1.1 American College of Rheumatology non-pharmacologic and pharmacologic recommendations for knee OA management (34)

Strongly Recommended	Conditionally Recommended	Not Recommended	No Recommendation
Nonpharmacologic Interventions			
Cardiovascular (aerobic) and/or resistance Land-based exercise Aquatic exercise Lose weight (for persons who are overweight)	Self-management programs Manual therapy in combination with supervised exercise Psychosocial interventions Medially directed patellar taping Medially wedged insoles if they have lateral compartment OA Laterally wedged subtalar strapped insoles if they have medial compartment OA Thermal agents Walking aids Tai Chi programs Traditional Chinese acupuncture Transcutaneous Electrical Stimulation		Balance exercises, either alone or in combination with strengthening exercises Laterally wedged insoles Manual therapy alone Knee braces Laterally directed patellar taping
Pharmacologic Interventions			
	Oral NSAIDs Topical NSAIDs Tramadol Intraarticular corticosteroid injections	Chondroitin sulfate Glucosamine Topical capsaicin	Intraarticular hyaluronates Duloxetine Opioid analgesics

OA = osteoarthritis, NSAIDs = nonsteroidal anti-inflammatory drugs

1.3.1. Low Frequency Pulsed Subsensory Threshold Electrical Stimulation

Low frequency pulsed subsensory threshold electrical stimulation offers a physical agent for conservative treatment of knee OA (41-43) whereby bioactive electrical signals are delivered by PEMF or PES (41). PEMF and PES are categorized according to frequency into low frequency and extremely low frequency which are nonionizing and, as such, cannot break molecular bonds or inhibit cell division (44), therefore, it is safe to use as a therapeutic physical agent. There is biological rationale for using low frequency pulsed subsensory threshold electrical stimulation in the treatment of people with knee OA. PEMF and PES signals may alter the electrical environment in the target tissue, e.g., the charge or ionic concentration at the cell wall that allows a change in electrical gradients across the cell membrane. This change in the electrical gradient may transduce the mechanical stress into an electrical phenomenon capable of stimulating chondrocyte synthesis of the matrix (31). It has been suggested that signals can act as first messengers in the calmodulin, calcium binding messenger protein, (CaM)-dependent signaling pathways that organize the release of cytokines such as interleukin-1beta (IL-1β) (45) and growth factors such as basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) (46) in cellular responses to injury (47). Several animal studies examined the effect of PEMF on chondrocytes and articular cartilage as measured macroscopically, microscopically and biochemically (41,51,52). A rabbit study concluded that PEMF increases proliferation of chondrocytes compared with sham-treated controls (41). Two guinea pig studies reported that PEMF improves knee cartilage morphology and the cartilage reparative mechanism (51, 52). Therefore the electrical stimulation

provided by PEMF and PES may be able to signal and modulate tissue repair pathways (48-50) in people with knee OA.

The clinical rationale for using for using low frequency pulsed subsensory threshold electrical stimulation in the treatment of people with knee OA is less clear. Several randomized controlled trials and systematic reviews examined the effectiveness of PEMF alone or in combination with PES on knee OA pain and physical function with conflicting conclusions (53, 54). A rigorous search and synthesis of these trials is needed to clarify the findings. In addition, this line of investigation will enable exploration of the utility of a pain theory-based framework for assessing and managing knee OA pain

1.4.Thesis Objectives

Pain is the main indicator of knee OA, however, there is no gold standard for measuring knee OA pain and the views of individuals about how well current pain measures represent their knee OA pain experience is not known. Pain management is challenging due to the modest effectiveness and side effects of pharmacologic treatments in combination with the limited safe effective non-pharmacologic treatment options. Therefore, the objectives of this thesis were:

a) To develop a theoretical framework for assessing and managing knee OA pain based on current pain theories (Chapter Two)
b) To determine if people with knee OA prefer one of three self-report pain measures to represent their pain experience. The secondary purpose was to examine the burden of these measures. (Chapter Three)

c) To determine if low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF or PES versus sham intervention is effective in improving pain and physical function at treatment completion in adults with knee OA blinded to treatment (Chapter Four)

1.5. References

1. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. BMJ. 2012 Jul 30;345:e4934.

2. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. Radiol Clin North Am. 2004 v; Jan;42(1):1-9.

3. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis & Rheumatism. 1998 Aug;41(8):1343-55.

4. Andrianakos AA, Kontelis LK, Karamitsos DG, Aslanidis SI, Georgountzos AI, Kaziolas GO, et al. Prevalence of symptomatic knee, hand, and hip osteoarthritis in greece. the ESORDIG study. J Rheumatol. 2006 Dec;33(12):2507-13.

5. Michael JW, Schluter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Deutsches Arzteblatt International. 2010 Mar;107(9):152-62.

6. Eyre DR. Collagens and cartilage matrix homeostasis. Clinical Orthopaedics & Related Research. 2004 Oct(427 Suppl):S118-22.

7. Nuki G. Osteoarthritis: A problem of joint failure. Z Rheumatol. 1999 Jun;58(3):142-7.

8. Hunter DJ. Insights from imaging on the epidemiology and pathophysiology of osteoarthritis. Radiol Clin North Am. 2009 Jul;47(4):539-51.

9. Roach HI, Aigner T, Soder S, Haag J, Welkerling H. Pathobiology of osteoarthritis: Pathomechanisms and potential therapeutic targets. Curr Drug Targets. 2007 Feb;8(2):271-82.

10. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M, et al. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis & Rheumatism. 2006 Mar;54(3):795-801.

11. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am. 1999 vi; May;25(2):283-98.

12. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med. 2003 Sep 2;139(5 Pt 1):330-6.

13. Sun HB. Mechanical loading, cartilage degradation, and arthritis. Ann N Y Acad Sci. 2010 Nov;1211:37-50.

14. Cooke TD, Sled EA, Scudamore RA. Frontal plane knee alignment: A call for standardized measurement. J Rheumatol. 2007 Sep;34(9):1796-801.

15. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. Arthritis & Rheumatism. 2009 Apr 15;61(4):459-67.

16. Harrington IJ. A bioengineering analysis of force actions at the knee in normal and pathological gait. Bio-Medical Engineering. 1976 May;11(5):167-72.

17. Yang NH, Nayeb-Hashemi H, Canavan PK, Vaziri A. Effect of frontal plane tibiofemoral angle on the stress and strain at the knee cartilage during the stance phase of gait. Journal of Orthopaedic Research. 2010 Dec;28(12):1539-47.

18. Palotie A, Vaisanen P, Ott J, Ryhanen L, Elima K, Vikkula M, et al. Predisposition to familial osteoarthrosis linked to type II collagen gene. Lancet. 1989 Apr 29;1(8644):924-7.

19. Hunter DJ, Felson DT. Osteoarthritis. BMJ. 2006 Mar 18;332(7542):639-42.

20. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the united states. Arthritis & Rheumatism. 1998 May;41(5):778-99.

21. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. The epidemiology of osteoarthritis in asia. International Journal of Rheumatic Diseases. 2011;14(2):113-21.

22. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis & Rheumatism. 1986;29(8):1039-49.

23. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis & Cartilage. 2007;15(Suppl A):A1-56.

24. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health. 2011;11:770.

25. Harstall C, Ospina M. How prevalent is chronic pain. Pain Clinical Updates. 2003;11(2):1-4.

26. Garcia-Larrea L. Objective pain diagnostics: Clinical neurophysiology. Neurophysiologie Clinique. 2012 Jun;42(4):187-97.

27. Frampton CL, Hughes-Webb P. The measurement of pain. Clinical Oncology (Royal College of Radiologists). 2011 Aug;23(6):381-6.

28. Cleeland CS, Ryan KM. Pain assessment: Global use of the brief pain inventory. Ann Acad Med Singapore. 1994 Mar;23(2):129-38.

29. Melzack R. The McGill pain questionnaire: Major properties and scoring methods. Pain. 1975 Sep;1(3):277-99.

30. Katz J, Melzack,R. Measurement of Pain. Surg Clin North Am. 1999;79(2):231-52.

31. Sheu E, Versloot J, Nader R, Kerr D, Craig KD. Pain in the elderly: Validity of facial expression components of observational measures. Clin J Pain. 2011 Sep;27(7):593-601.

32. Dworkin RH, Peirce-Sandner S, Turk DC, McDermott MP, Gibofsky A, Simon LS, et al. Outcome measures in placebo-controlled trials of osteoarthritis: Responsiveness to treatment effects in the REPORT database. Osteoarthritis & Cartilage. 2011 May;19(5):483-92.

33. Turk DC. Dworkin RH. Burke LB. Gershon R. Rothman M. Scott J. Allen RR. Atkinson JH. Chandler J. Cleeland C. Cowan P. Dimitrova R. Dionne R. Farrar JT. Haythornthwaite JA. Hertz S. Jadad AR. Jensen MP. Kellstein D. Kerns RD. Manning DC. Martin S. Max MB. McDermott MP. McGrath P. Moulin DE. Nurmikko T. Quessy S. Raja S. Rappaport BA. Rauschkolb C. Robinson JP. Royal MA. Simon L. Stauffer JW. Stucki G. Tollett J. von Stein T. Wallace MS. Wernicke J. White RE. Williams AC. Witter J. Wyrwich KW. Initiative on Methods,Measurement and Pain Assessment in Clinical Trials. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain. 2006 Dec 5;125(3):208-15.

34. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American college of rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.

35. Reid MC, Shengelia R, Parker SJ. Pharmacologic management of osteoarthritis-related pain in older adults. Am J Nurs. 2012 Mar;112(3 Suppl 1):S38-43.

36. Samson DJ, Grant MD, Ratko TA, Bonnell CJ, Ziegler KM, Aronson N. Treatment of primary and secondary osteoarthritis of the knee. Evidence Report/Technology Assessment. 2007 Sep(157):1-157.

37. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. Gastroenterology. 2001 Feb;120(3):594-606.

38. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of nonsteroidal anti-inflammatory drugs: Network meta-analysis. BMJ. 2011 Jan 11;342:c7086.

39. Perez Gutthann S, Garcia Rodriguez LA, Raiford DS, Duque Oliart A, Ris Romeu J. Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. Arch Intern Med. 1996 Nov 25;156(21):2433-9.

40. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 1999 Jun 17;340(24):1888-99.

41. Thawer H. Pulsed electromagnetic fields for osteogenesis and repair. Physical therapy reviews. 1999;4(3):203-13.

42. Trock DH. Electromagnetic fields and magnets. investigational treatment for musculoskeletal disorders. Rheum Dis Clin North Am. 2000 viii; Feb;26(1):51-62.

43. Hulme J, Robinson V, DeBie R, Wells G, Judd M, Tugwell P. Electromagnetic fields for the treatment of osteoarthritis. Cochrane Database of Systematic Reviews. 2002(1):003523.

44. Cameron M. Setion two: The physical agents, electromagnetic radiation. In: Sue Bredensteiner MF, editor. Physical Agents in Rehabilitation. Second Edition ed. Saunders; 2003. p. 369-413.

45. Ren K, Torres R. Role of interleukin-1beta during pain and inflammation. Brain Res Rev. 2009 Apr;60(1):57-64.

46. Madhusoodanan KS, Murad F. NO-cGMP signaling and regenerative medicine involving stem cells. Neurochem Res. 2007 Apr-May;32(4-5):681-94.

47. Pilla A, Fitzsimmons R, Muehsam D, Wu J, Rohde C, Casper D. Electromagnetic fields as first messenger in biological signaling: Application to calmodulin-dependent signaling in tissue repair. Biochim Biophys Acta. 2011 Dec;1810(12):1236-45.

48. Nelson FR, Brighton CT, Ryaby J, Simon BJ, Nielson JH, Lorich DG, et al. Use of physical forces in bone healing. J Am Acad Orthop Surg. 2003 Sep-Oct;11(5):344-54.

49. Strauch B, Herman C, Dabb R, Ignarro LJ, Pilla AA. Evidence-based use of pulsed electromagnetic field therapy in clinical plastic surgery. Aesthet Surg J. 2009 Mar-Apr;29(2):135-43.

50. Brighton CT, Wang W, Seldes R, Zhang G, Pollack SR. Signal transduction in electrically stimulated bone cells. Journal of Bone & Joint Surgery - American Volume. 2001 Oct;83-A(10):1514-23.

51. Ciombor DM, Lester G, Aaron RK, Neame P, Caterson B. Low frequency EMF regulates chondrocyte differentiation and expression of matrix proteins. J Orthop Res. 2002 Jan;20(1):40-50.

52. Fini M, Giavaresi G, Torricelli P, Cavani F, Setti S, Cane V, et al. Pulsed electromagnetic fields reduce knee osteoarthritic lesion progression in the aged dunkin hartley guinea pig. J Orthop Res. 2005 Jul;23(4):899-908.

53. Vavken P, Arrich F, Schuhfried O, Dorotka R. Effectiveness of pulsed electromagnetic field therapy in the management of osteoarthritis of the knee: A meta-analysis of randomized controlled trials. J Rehabil Med. 2009 May;41(6):406-11.

54. McCarthy CJ, Callaghan MJ, Oldham JA. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: A systematic review. BMC Musculoskeletal Disorders. 2006;7:51.

CHAPTER 2

Integration of Pain Theories to Guide Knee Osteoarthritis Care

The following paper is published in Critical Reviews in Physical and Rehabilitation Medicine, 24(3–4), 179–195 (2012).

Integration of Pain Theories to Guide Knee Osteoarthritis Care

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Running title: Integration of Pain Theories to Guide Knee Osteoarthritis Care

2.1. Abstract: Osteoarthritis is one of the four leading causes of pain. To date, clinicians providing health care to people with knee osteoarthritis pain focus on evaluating pain intensity and its effect on physical function and provide management with foundations in theories of pain including gate control and specificity. Pain theories such as these have been driving pain management and pain research since the seventeenth century, when René Descartes proposed his reflex theory of pain. The purpose of this paper is to describe the evolution of pain theories leading up to the gate control theory and the neuromatrix theory, provide a critical review of these two theories specifically, and discuss the strengths and challenges of integrating these two theories in the guidance of knee osteoarthritis pain management. Integration of the gate control theory, which focuses on the spinal processing of pain, and the neuromatrix theory, which focuses on central processing of pain, gives a broader model for understanding and addressing the multiple dimensions of pain phenomena. The integrated gate control–neuromatrix model presented in this paper provides a theoretical basis for considering the cognitive and affective aspects in addition to the sensory aspects of osteoarthritis pain. Discussion of the multidimensional aspects of pain includes clinical implications and recommendations for evaluation and treatment approaches. Finally, future directions for research are recommended to test the proposed model and improve the management of osteoarthritis pain.

Keywords: chronic pain, theoretical model, pain measurement, pain management.

Abbreviation

BAI: Beck anxiety inventory; BDI: Beck depression inventory; BHI: Beck helplessness inventory; CPCI: chronic pain coping index; HADS: hospital anxiety depression scale; MPI: multidimensional pain inventory; MPQ-SF: short form of McGill pain questionnaire; NRS: numeric rating scale; OA: osteoarthritis; PCS: pain catastrophizing scale; PDI: pain disability index; SPOMS: short form of the Profile of Mood States; TSK: Tampa scale of kinesiophobia; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities osteoarthritis index

2.2. Introduction

Pain theories have been driving pain management and pain research since the seventeenth century, when René Descartes proposed the first documented pain theory.[1] Thereafter, theories of pain developed in combination with the accumulation of scientific facts. Theories give rise to research, which generates new facts, and these in turn, expose the inadequacies of older theories and provide the foundations for new ones. Therefore, pain theories play an important role in how we understand, assess, and treat pain.[2]

Despite the scientific facts and theories that aim to explain pain, there is no globally accepted definition of pain. One of the most widely accepted definitions describes pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[3] This pain definition reflects the multidimensional nature of the pain.

Pain has important functions to preserve human health and safety, such as the signaling of injury or disease and producing a wide array of responses to stop the signal and treat the cause(s). Abdominal pain, for instance, may be a signal of appendicitis, which requires medical attention. Memories of earlier pain prompt the recognition and avoidance of potentially hazardous situations in the future. Pain prompts people to rest or prevents them from moving an injured body part, such as a fractured limb, thereby promoting the body's healing processes. All these actions in response to pain have apparent value for survival.[4]

Despite the benefits, pain is a tremendous global problem and it has a large impact on public health. Estimates suggest that 20% of adults around the world suffer from pain and 10% are newly diagnosed with chronic pain each year.[5] Chronic pain is defined based on a duration of more than three to six months.[6] Definitions based on duration do not address the intermittent nature that, in some cases, is a feature of chronic pain.[7] Duration of pain in terms of consistency is an important consideration, since continuous pain of moderate intensity can be just as disabling as severe pain that is intermittent.[8] Thus, defining chronic pain simply in terms of duration does not reflect the multiple dimensions that comprise the chronic pain phenomenon. Depression, disrupted social relationships, and suicidal thoughts may be consequences of chronic pain.[5] Chronic pain may lead to inability to work and increased absenteeism among active workers.[5]Chronic pain affects the appetite[9] and sleep.[8] Clearly, the difference between acute and chronic pain is more than a temporal transition point at three or six months.

It has been suggested that chronic pain is not only a symptom but a disease.[4] Using factor analyses of responses to nine self-report measures, namely, the short form of the McGill pain questionnaire (MPQ-SF),[10] pain disability index (PDI),[11] Tampa scale of kinesiophobia (TSK), pain catastrophizing scale (PCS), chronic pain coping index (CPCI),[12] multidimensional pain inventory (MPI), Beck depression inventory (BDI),[13] Beck helplessness inventory (BHI),[14] and the Beck anxiety inventory (BAI),[15] Davidson et al.[16] determined the core dimensions of chronic pain. A brief description of each measure is provided in Table 2.1. Based on responses from a sample of 126 participants aged 16 to 91 years who had pain for longer than six months, the factor analysis identifies seven core dimensions: (i) pain and disability, (ii) pain description, (iii) affective distress, (iv) positive coping, (v) negative coping, (vi) support, and (vii) activity.[16] This factor analysis by Davidson et al.[16] provides empirical evidence of the multidimensionality of chronic pain and the key constructs that should be considered.

Osteoarthritis (OA) is the most common chronic joint disease and one of the most common causes of chronic pain.[5,17]Although not everyone with OA will have debilitating pain, it is the leading cause of pain among older adults around the world.[17] A recent systematic review addressing the outcome measures in pharmacological trials of knee OA[18] reported that the most commonly used pain measures are the visual analog scale (VAS) and numeric rating scale (NRS) for pain intensity, and the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) pain subscale, which asks five questions about pain intensity during low-level daily activities and at night in bed. (See Table 2.1. for a brief summary of the content.) Thus, the focus of pain assessment is

typically on the sensory experience without considering the affective and cognitive experience despite the fact that chronic pain due to OA is multidimensional in nature.

Current clinical management of knee OA aims to manage pain and maintain independent physical function through a combination of pharmacologic and non-pharmacologic interventions based on evidence of effectiveness in clinical trials.[20] However, a qualitative study including seven participants, waitlisted for knee joint replacement due to high levels of pain limiting their daily activities, reported decreased adherence and/or access to commonly used treatments for OA pain, such as exercise and anti- inflammatory medications, since the treatments were believed to lack sufficient long- term effectiveness by both participants and doctors.[21] Considering the complexity of OA chronic pain, a multidimensional approach to assessment and treatment, which aligns with current pain theories, is proposed for better OA pain management.

2.3. Objective

The overall aim of this review is to better understand and more effectively integrate current pain theories into the management of knee OA pain. The objectives of this article are to (i) summarize the evolution of pain theories, (ii) compare, contrast, and integrate the two most current pain theories, i.e., the gate control theory and neuromatrix theory, and to (iii) discuss implications of this theoretical framework for clinical assessment and treatment of knee OA pain and future research.

Table 2.1. Description of chronic pain measures (see text for corresponding references)

Scale	Description	Score interpretation§
Short form McGill pain questionnaire (SF-MPQ)	15 items: 11 sensory, 4 affective; includes present pain intensity (PPI) index and visual analog scale (VAS) for pain intensity	4-point Likert scale, 0 = none to 3 = severe; PPI, 0 = no pain to 5 = excruciating pain; VAS, 10 cm,
Pain disability index (PDI)	7 categories of life activity covering different areas of disability: family, occupation, sexual relations, social activities, recreation, self-care, and life support	11-point Likert scale, 0 = no disability to 10 = total disability, maximum score =
Tampa scale of kinesiophobia (TSK)	17 items: fear of movement, injury, and reinjury	4-point Likert scale, 1 (strongly disagree) to 4 (strongly agree),
Pain catastrophizing scale (PCS)	13 items: pain catastrophizing (degree to which thoughts or feelings are experienced during pain)	5-point Likert scale, 0 (not at all) to 4 (all the time), 0–52
Chronic pain coping index (CPCI)	65 items (coping strategies): cognitive and behavioral pain coping strategies often targeted	8-point Likert scale, 0–7 (days during previous week strategy was used), * sum of subscale means
Multidimensional pain inventory (MPI)	60 items: severity and interference of pain, responses to pain, and impact on daily activities	7-point Likert scale, 0 (not at all) to 6 (extreme), * 0–6
Beck's depression index (BDI)	21 items: depressive symptomatology, and intensity of cognitive and sensory complaints associated with depression	4-point Likert scale, 0 = none to 3 = severe, maximum score = 63
Beck's helpless index (BHI)	20 items: hopelessness; 11 negatively phrased and 9 positively phrased items	True/false, maximum score = 20
Beck's anxiety index (BAI)	21 items: anxiety severity	4-point Likert scale, 0 = none to 3 = severe, maximum score = 63
Visual analog scale (VAS)	1 item: pain intensity	Horizontal/vertical line with varying time points and descriptor anchors, 0–10 cm or 0–100 mm

Numerical rating scale (NRS)	1 item: pain intensity	11-pt numeric scale, 0–10
Western Ontario and McMaster Universities (WOMAC) pain	5 items: pain intensity during various activities and at night	5-pt Likert scale, 0 = none to 4 = extreme, maximum score = 20
Shortened version of the profile of mood states (SPOMS)	37 items, 6 affective states: tension-anxiety, depression-dejection, anger-hostility, vigour activity, fatigue-inertia, and confusion-bewilderment	5-pt Likert scale, 0 = not at all to 4 = extremely, maximum score = 148
Hospital anxiety depression scale (HADS)	14 items: anxiety and depression subscales each with 7 items	4-pt Likert scale, 0 = none to 3 = severe, maximum score = 21 for each subscale

§Higher scores indicate worse pain,*The individual items in the subscale are summed and divided by the number of items in the subscale. S = sensory, A = affective, C = cognitive.

2.4. Evolution of pain theories

Pain theories have evolved over time. We will describe the pain theories starting with the first documented pain theory and ending with the more recent gate control and neuromatrix theories. Table 2.2 summarizes the key concepts of each pain theory described.

Table 2.2. Summary of the main concepts of pain theories

Pain Concept	Theory					
	Reflex [1]	Specificity [22]	Pattern [24]	Noordenbos [25]	Gate control [45]	Neuromatrix [2]
Transmitted through a single channel from brain to skin	x	x				
Perceived by a separate sensory system		x			x	
Determined by summation in dorsal horns			x		x	
Transmitted by small-diameter fibers; inhibited by large-diameter fibers				x	x	
Neuromatrix produces the pain pattern centrally and then gets modulated by the sensory inputs from the body parts						X

2.4.1. Reflex Theory

The first reported attempt to understand pain was in 1664 when René Descartes, a philosopher and scientist, theorized that the transmission of pain is through a single channel from the skin to the brain.[20] Descartes illustrated pain using the example of stepping on a burning log and stated, "The small rapidly moving particle of fire moves the skin of the affected spot causing a thin thread to be pulled." [1] This was proposed to

open a small valve in the brain through which animal spirits are sent down to the muscles that withdraw the foot from the fire. Descartes' reflex theory guided pain management for more than 330 years.[1] People with chronic pain and no other symptoms or signs were often sent to psychiatrists because the valid pain experience was held to be proportional to tissue damage or pathology.[21]

2.4.2. Specificity Theory

Von Frey (1895), a professor of the University of Leipzig in Germany, proposed that there are specific nerve fibers that respond to different stimuli such that pain, temperature, touch, and position. These stimuli are then transmitted through different types of afferent nerve fibers. Therefore, pain fibers carry the noxious stimuli. Some impulses are relayed to the motor fibers of the reflex so that the involved muscles respond immediately, while some impulses ascend to the thalamus, where they arouse the perception of pain.[22] A single pain center in the cerebral cortex is then activated and interprets impulses in terms of intensity, location, pattern, and other characteristics of the pain stimulus.[2] The cortex generates efferent nerve impulses that result in autonomic and skeletal muscle activation

as well as other psychological responses such as mood and behavioral changes. Similar to Descartes' reflex theory, specificity theory depends on the assumption that tissue damage is proportional to the pain level, and minor tissue damage could never cause high pain intensity regardless of the roles of psychological, social, or cultural factors.[23] Specificity theory has, however, been challenged regarding its ability to explain some clinical situations such as pain persistence after nerve tract destruction.

2.4.3. Pattern Theory

Several different theories have been proposed to address the limitations of specificity theory and these have been labeled collectively as "pattern theory."[24] These pattern theories were generally indistinct and shared two common features: (i) there is not a separate system for perceiving pain and (ii) pain occurs when certain patterns of neural activity reach excessively high levels in the brain.[26] Alfred Goldscheider, Professor of Neurology at the University of Berlin, developed a pattern theory (1920) proposing that central, spatial, and temporal summation in the dorsal horns of the spinal cord is one of the critical determinants of pain. William Livingston, a neurologist from California, proposed a pattern theory (1943) that explained that summation, referred pain, and pain that persists long after healing is completed occur due to a reverberating, self-exciting loop of activity in a pool of interneurons found in the dorsal horns.[24]This theory has been challenged due to the passive role described for the brain as the passive receptor of nociceptive inputs and denial of the specificity of pathways for the perception of pain.

2.4.4. Noordenbos' Theory

Noordenbos' theory advanced the understanding of pain by proposing that input

from large-diameter fibers inhibits input from small-diameter fibers.[24] Willem Noordenbos, a Dutch neurosurgeon, theorized that the substantia gelatinosa, which contains small, densely packed cells extending the length of the dorsal horn of the spinal cord, plays a major role in the summation and other dynamic processes described by Livingston's pattern theory.[27] Similar to previous theories, Noordenbos' theory views the brain as a passive receiver of pain impulses.

2.4.5. Gate Control Theory

The gate control theory was the first theory to acknowledge the active role of the central nervous system in pain modulation.[28] In 1965, Ronald Melzack, a Canadian psychologist, and Patrick Wall, a British physiologist, sought to reconcile three pain theories (i.e., the specificity, pattern, and Noordenbos' theories) by introducing a new, more detailed theory of pain called the gate control theory.[29]

Noordenbos suggested the important role of the substantia gelatinosa without describing the interactions between substantia gelatinosa and the large and small nerve fibers. However, gate control theory (Fig. 2.1) proposes that the substantia gelatinosa acts as a gate control system.[29] The substantia gelatinosa receives the pain impulses in response to peripheral stimuli through large and small nerve fibers and modulates them before they reach the first "transmission cells." The proposed role of the substantia gelatinosa and the dorsal horn has been supported by anatomical and physiological research that describes the characteristics of dorsal horn–modulating interneurons, including many neurotransmitters and neuromodulators.[30,31] The gate control theory proposes that large non-nociceptive nerve fibers decrease the pain sensation by inhibiting

the pain impulse that is carried by smaller nociceptive nerve fibers. The gate control theory's most valuable contribution to biological and medical sciences is the suggestion that the central nervous system is an active component that could decrease or increase pain sensation and experience.[29] The active role of the brain was thought to occur through afferent patterns in the dorsal column system that activate selective brain processes affecting the modulating properties of the gate control system. However, there is no supporting research to identify the ascending and descending tracts in the dorsal horn of the spinal cord involved in central nervous system pain modulation.[30] Melzack and Wall[27] proposed that after modulation of a pain stimulus in the substantia gelatinosa, the impulse is transmitted to the first transmission cell. Consistent with pattern theory, the gate control theory proposes that the summation of pain impulses occurs in the first transmission cell. When this transmission cell output reaches the critical level of firing, many centers in the brain are stimulated, resulting in pain responses.[29] The gate control theory refutes the idea of a single pain center in the brain (as proposed by the specificity theory) and instead proposes that many brain centers are sequentially activated to develop the reactions to pain.[29]

The gate control theory had a major effect on the direction of pain research in recent decades and was mentioned in almost all major biological and medical sciences textbooks by the mid-1970s. However, it has limitations. First, details regarding this central control system and the mechanisms by which it influenced the gate were not provided. Second, the gate control theory did not explain some chronic pain syndromes such as phantom limb, when a person with an amputated limb feels pain from the portion

of the limb that has been removed.[2]

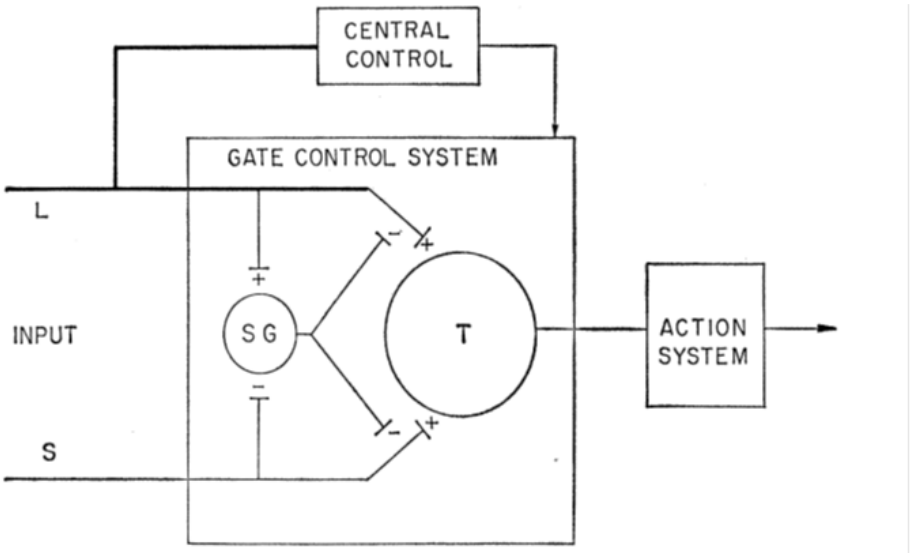

Figure2.1. A schematic diagram of the gate control theory; L–the large-diameter fibers; S– the small-diameter fibers. The fibers project to the substantia gelatinosa (SG) and first central transmission (T) cells. The inhibitory effect exerted by SG on the afferent fiber terminals is increased by activity in L fibers and decreased by activity in S fibers. The central control trigger is represented by a line running from the large fiber system to the central control mechanisms; these mechanisms, in turn, project back to the gate control system. The T cells project to the entry cells of the action system.
+ indicates excitation; – indicates inhibition[29] (reprinted with permission from The American Association for the Advancement of Science).

2.4.6. Neuromatrix Theory

In 1989, Melzack first introduced the neuromatrix theory shown in Fig. 2.2 with the aim of explaining the mechanisms by which the brain modulates pain and the role of the central nervous system in the pain experience.[32] (For a review on this theory, see Ref. 4.) Melzack and Loeser[30] discovered that severe pain was experienced in the absence of peripheral stimuli and/or neural continuity. For example, paraplegics with confirmed total discontinuity of the spinal cord experienced severe pain below the level of the spinal cord injury. Such an observation suggested a mechanism for generating a pain pattern above the level of the spinal cord damage.[33] The two unique concepts central to the neuromatrix theory include a central pattern generating mechanism and the body being perceived as a unity identified as the "self," distinct from other people and the surrounding world.[4]

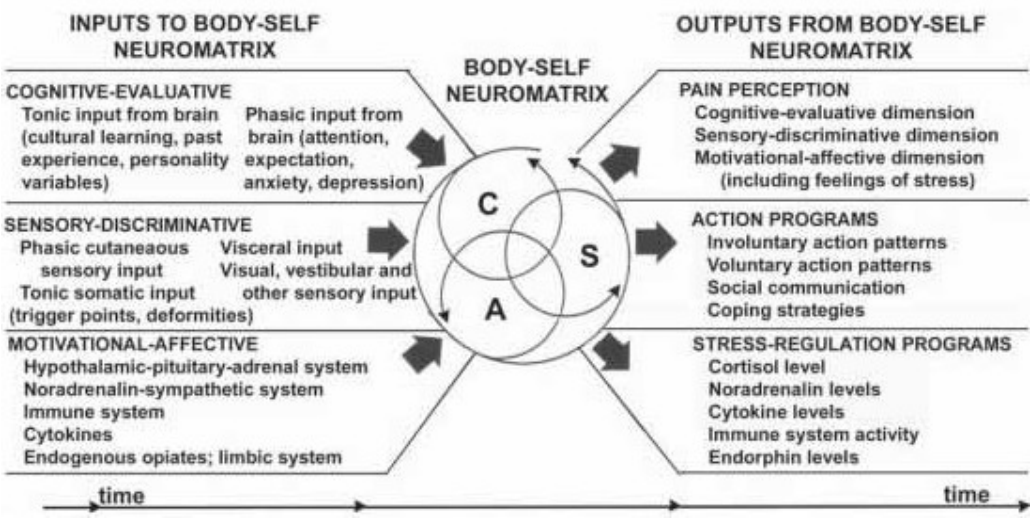

Figure 2.2. Neuromatrix theory. Factors that contribute to the patterns of activity generated by the body-self neuromatrix, which comprises sensory, affective, and cognitive neuromodules. The output patterns from the neuromatrix produce the multiple

dimensions of pain experience as well as concurrent homeostatic and behavioral responses[32] (reprinted by permission of the Journal of Dental Education).

The terms neuromatrix, neurosignature, and neuromodule are pivotal to the understanding of the neuromatrix theory; [4] therefore, these are described here. A neuromatrix is an anatomical substrate of the body-self that is composed of a large, widespread network of neurons between the thalamus and cerebral cortex as well as between the cerebral cortex and the limbic system. The spatial distribution and synaptic links of this network are initially determined genetically and are later sculpted by sensory input. The neuromatrix, which involves many brain centers including sensory, affective, evaluative, and postural, produces the neurosignature, which is a continuous message that represents the whole body.[32] The neurosignature refers to the repeated cyclical processing and synthesis of nerve impulses in the neuromatrix, which conveys a characteristic pattern. The neurosignature is modulated by the inputs from different parts of the body to produce the wide variety of pain experiences we feel.[4] To achieve this, the neurosignature bifurcates, projecting one pattern to the insula where the pattern is converted into a continually changing stream of awareness and experience of movement, and projecting a similar pattern through the neuromatrix to activate spinal cord neurons and produce muscle patterns for complex action.[2] The neuromodule is a specific type of information processing that is related to a specific major sensory event (such as injury or temperature change). The neuromodule gives a special pattern to subsignatures which, consequently, alter the neurosignature. Neuromodules occur in specialized portions of the neural network of the neuromatrix.[4]

In 1999, Melzack[23] refined the neuromatrix theory by clarifying the description of the neuromatrix output. He included a stress reaction that releases cytokines and other chemical substances aiming to mobilize and utilize glucose for necessary actions, such as the removal of debris, the repair of tissues, and (sometimes) the production of a fever to destroy bacteria and other foreign substances. At certain levels of injury severity, epinephrine and cortisol are secreted. Injury not only produces pain, but it also interrupts the brain's homeostatic regulation systems, thereby initiating complex programs to restore homeostasis.[31] If regulatory programs fail to restore homeostasis in the brain, the neuromatrix may produce neural "distress" patterns that contribute to the total neuromatrix pattern, and may also produce neural tissue destruction that gives rise to chronic pain.[23,32]

The neuromatrix theory added to the understanding of chronic pain and explained how the neuromatrix can produce the neurosignature of phantom limb pain without a nociceptive stimulus. However, the neuromatrix theory has limitations. First, the neuromatrix theory focuses on the processing of pain in the central nervous system and does not detail the mechanism(s) of pain modulation at the spinal cord level. Melzack considered the neuromatrix theory as an extension to the gate control theory, which does explain spinal modulation at the gate.[2] Second, the neuromatrix theory does not provide details about how psychological factors influence pain or how psychological variables interact and integrate within the neuromatrix.[34]

2.4.7. Gate Control–Neuromatrix Theoretical Model

The primary focus of the gate control theory is on pain modulation in the cells in the dorsal horn of the spinal cord; the primary focus of the neuromatrix theory is on central nervous system pain processing, perception, and pattern production. Therefore, combining the two foci in a single theoretical model will inform the understanding and management of pain.

The neuromatrix continuously produces the neurosignature for the whole body while it receives and interprets pain signals from the periphery. Brain centers involved in mood and cognition interact with the stimulated primary sensory cortex within association cortices sending descending neural transmissions that modulate the gate control system at the spinal cord level. The ensuing pain signals from the periphery modulate the neurosignature pattern, which replicates to follow two pathways, one traveling to the sentient neural hub (where the pattern is converted into a continually changing stream of awareness and experience of movement), and the other traveling through the neuromatrix to activate several brain and spinal cord areas that are needed for pain responses.[32]

We describe three portals to the gate control–neuromatrix model: a spinal level input, a neuromatrix level input, and a neuromatrix level output. Figure 2.3 shows the proposed interactions and connections in the integrated gate control–neuromatrix theoretical model. This model does not consider details of the interaction between the psychological factors in the modulation of the neuromatrix nor gate control system details in modulation at the spinal cord level. Notwithstanding these limitations, we propose that using the gate control–neuromatrix theoretical model as a foundation for

clinical management and research of knee OA pain will generate new knowledge and improved clinical outcomes.

2.5. Implication of The Gate Control-Neuromatrix Theoretical Model on Knee Osteoarthritis Clinical Management and Research

In this section, we illustrate the application of the proposed gate control–neuromatrix model to nonsurgical clinical management of knee OA pain and future research. The most recent clinical practice guidelines produced by the American College of Rheumatology recommend a number of nonsurgical interventions for people with knee OA including exercise, weight loss, self-management, psychosocial interventions,

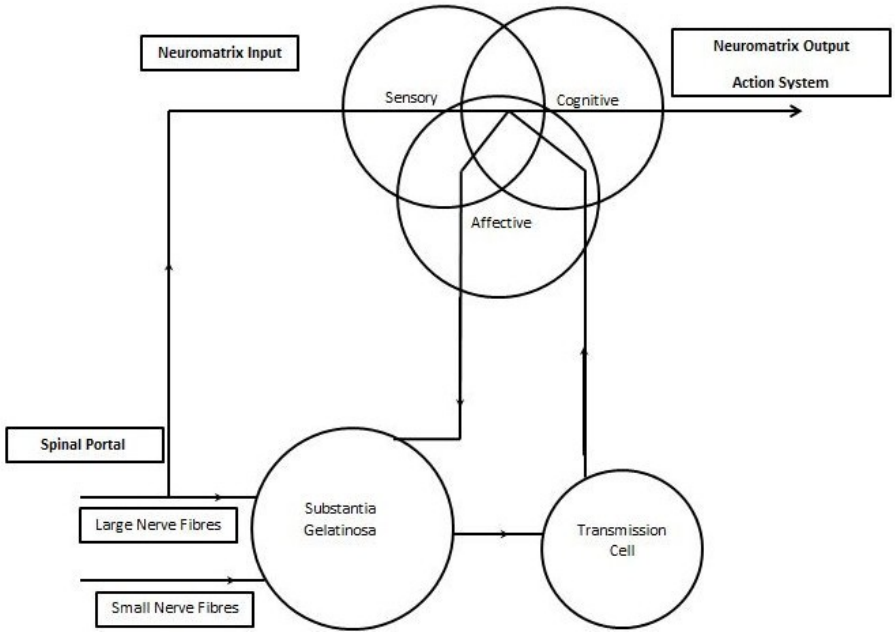

Figure 2.3. Input and output portals in the gate control–neuromatrix model

transcutaneous electrical nerve stimulation, and Tramadol.[20] We explain how the gate control– neuromatrix theoretical model can form a basis for selecting and interpreting responses to treatment.

2.5.1. Pain Measurement

Given that pain is the most consistent symptom in the knee OA population, a comprehensive pain assessment may be needed. A gold standard for pain assessment in individuals with knee OA is not established and a combination of pain outcome measures are used.[35] However, the chronic nature of OA pain may be better understood using a multidimensional pain assessment tool.[36] On the basis of the gate control–neuromatrix theoretical model, pain has sensory, cognitive, and affective dimensions, each requiring measurement in order to acquire a comprehensive and accurate evaluation of the pain experience of people with symptomatic knee OA.

In the assessment of knee OA pain, the current focus is on pain intensity and associated disability, suggesting that the assessment of one dimension will reflect the other dimensions of chronic knee OA pain adequately. However, this belief does not appear to be supported by current evidence. For example, a cohort study was conducted to examine the associations between scores of the MPQ-SF, the PCS, and the shortened version of the Profile of Mood States, SPOMS, (see Table 2.1) in patients before and after total knee arthroplasty.[36] Associations for preoperative pain, reflecting a chronic state of severe pain, revealed that younger age and higher catastrophizing were predictors of higher pain measured using the MPQ-SF ($R2 = 0.35$, $p < 0.01$) whereas affective state assessed using SPOMS was not a significant predictor ($R2 = 0.21$).[37]

In a sample of people with either hip or knee OA, the correlations between the WOMAC pain subscale and PCS, the anxiety and depression subscales of Hospital Anxiety Depression scale (HAD-anxiety and HAD-depression subscales) were r = 0.48, 0.29, and 0.35, respectively.[35] In this same sample, the MPQ-SF was strongly associated with the PCS, the HAD-anxiety, and HAD-depression subscales (r = 0.61, 0.43, and 0.41, respectively). Scores on the WOMAC pain subscale and the MPQ-SF were moderately associated (r = 0.36).[34] These results suggest that the MPQ-SF captures more of the cognitive and affective dimensions of pain as compared with the less comprehensive WOMAC pain subscale.

Appropriate pain measurement is critical to guide clinical decision making. It is crucial to assess all three dimensions of pain (sensory, affective, and cognitive) in order to fully understand the factors contributing to the pain experience and to determine the most appropriate intervention for a person given their stage along the continuum of knee OA pain and disability.

2.5.2. Pain Management

If the selection of pain interventions has a theoretical basis, then it follows that pain management for people with knee OA may be more effective. The belief that severity of OA pain indicates more damage to the knee joint tissue may motivate the use of increasingly expensive and aggressive surgical OA treatments from arthroscopy to arthroplasty. The gate control–neuromatrix theoretical model provides a different perspective regarding factors contributing to the severity of chronic knee OA pain that should be considered in order to exhaust appropriate conservative treatment. Given that

chronic knee OA pain is a multidimensional and complex problem, several approaches to pain management may be needed for optimal pain control. An example of a treatment approach that simultaneously influences the three portals that were described earlier in this paper include a self-management program and exercise that work partly through the neuromatrix input and output portals, and transcutaneous electrical nerve stimulation that works through the spinal input portal.[33] Using the gate control–neuromatrix theoretical model may facilitate pain management and decrease the waitlist for surgical OA treatment.

2.5.3. Theory-Based Arthritis Research

The gate control–neuromatrix theoretical model can provide a framework for designing and interpreting knee OA pain research. The effectiveness of treatment for knee OA pain could be evaluated in the context of the portal(s) through which it is hypothesized to operate. For example, the spinal portal based on the spinal modulation of pain signal could be the theoretical foundation for the closure of the pain control gate through pharmacological interventions that target spinal pain neurochemical transmitters or for non-pharmacological interventions (such as transcutaneous electrical nerve stimulation, mentioned above) that target the large myelinated nociceptive and other afferent inputs. The central neuromatrix input portal could be targeted by modulation of sensory, cognitive, or affective pain dimensions either independently or in combination. Examples of interventions working on the neuromatrix input portal include education in coping, relaxation, and sleep hygiene, which modulate pain perception. These components are part of many self-management programs that have been developed for

people with arthritis, including those with knee OA.[38] Self-management programs may also have an effect on the neuromatrix action output by influencing voluntary motor patterns.[38]

If experimental interventions for knee OA pain work through the affective or cognitive inputs to the neuromatrix, then preferential benefit may be observed in participants who score high on the PCS or HAD-anxiety or HAD-depression subscales. On the other hand, if there is mismatch between the recruited participant and the intervention, the results may underestimate the effectiveness of the intervention. If people with chronic knee OA have more than one dimension of the pain experience, it stands to reason that the intervention should have more than one component in order to address the different dimensions of chronic pain. Research designed in the context of the two input portals and one output portal of the gate control–neuromatrix model can enhance the theoretical bases of OA pain research. In turn, the understanding of mechanisms of action of the intervention(s) can further the development of the theoretical framework. The research and clinical implications of the gate control–neuromatrix theoretical model show how theory-based research and clinical practice may be better integrated to advance OA pain management.

2.5.4. Recommendations for Future Research

Future research has a substantial role in supporting, refining, or refuting the gate control–neuromatrix theoretical model. There is no strong evidence that pain intensity is proportional to tissue damage in knee OA.[39] However, some studies show that there are certain radiological signs that reflect structural impairment, such as subchondral bone

sclerosis, which are also associated with pain level.[40] On the basis of the gate control–neuromatrix theoretical model, tissue damage is viewed as only one of many factors that are considered when determining the severity of knee OA pain. Therefore, further research is needed to determine the relationship between the severity of knee OA pain and factors proposed to contribute to the pain experience.

Future research may provide us with new avenues for pain management. Psychological interventions are recommended in the recent guideline for knee OA and show efficacy in chronic pain management.[20] Theory-based strategies for combining pharmacologic and non-pharmacologic treatments need to be considered. For example, cognitive behavioral therapy[41] and self-management programs that have self-regulation and action planning components[42]need further study to test their effectiveness in people with knee OA.

Gene therapy is an innovative treatment approach on the horizon for people with knee OA pain. This approach aims to address the neural adaptations that occur peripherally and centrally with chronic pain. Gene therapy transfers a defined genetic material to specific target cells for the ultimate purpose of controlling or preventing pain.[42] A systematic review of studies investigating gene therapy for treating pain in animal models found that the included studies investigate the effect of controlling pain at different levels of the pain pathway by injecting genetic material that encodes pain neurotransmitters or endogenous analgesics.[43] For example, genetic material encoding an endogenous opioid, encephalin, injected at the spinal level results in the production and release of enkephalin from nerve terminals in the dorsal horn to produce an

analgesic effect. It is proposed that the neuromatrix is genetically determined; therefore, finding the genes that encode and regulate the neuromatrix will enable control of the pain pattern or block the chronic pain neurosignature.

Recent advances in cell transplant therapy appear promising. For example, primary rat sympathetic neurons harvested from the adrenal gland and transplanted into the spinal cord to mix with the cerebrospinal fluid (CSF) increases the levels of met-enkephalin and catecholamines, and decreases morphine cross-tolerance when used with morphine for neuropathic pain induced in a rat model.[44] Further studies are required to determine the effect of cell transplant therapy on chronic pain models and humans. If successful, human cell transplant therapy that considers the neuromatrix and neurosignature may lead to an effective treatment for chronic knee OA pain.

The need for collaborative research is clear, given the scope of factors that contribute to the pain experience. The common focus across disciplines will lead to a more comprehensive understanding of the pain experienced by people with knee OA and the development of treatment strategies most effective for dealing with the multiple dimensions of pain.

2.6. Conclusion

Pain is a global problem with significant public, economic, and social burden. Knee OA is the leading causes of adult pain and disability in the world.[5] Pain theories are critical for the development of pain research and management. The gate control theory focuses on the spinal modulation of pain signals in the dorsal horn cell and it was the first pain

theory to acknowledge the role of the brain in spinal modulation of pain. The neuromatrix theory concentrates on the central nervous system processing of pain signals, and proposes that the neuromatrix produces the pain pattern (neurosignature). The gate control–neuromatrix theoretical model gives a broader explanation of the pain phenomena in the context of research and clinical practice. The gate control–neuromatrix theoretical model incorporates all three dimensions of pain (affective, cognitive, and sensory) and suggests that multidimensional assessment is required in knee OA clinical management and research. Although the sensory dimension of pain is being measured in people with knee OA pain, this may not represent the affective and cognitive dimensions adequately for all people. The spinal input, the neuromatrix input, and the neuromatrix output portals could be used as a starting point to test the utility of this model in the clinical management of knee OA pain. A multicomponent design of pain management tailored to the specific needs of the person may lead to more effective knee OA pain control.

2.7. References

1. DeLeo JA. Basic science of pain. J Bone Joint Surg Am. 2006;88(Suppl 2):58–62.
2. Melzack R. Gate control theory: On the evolution of pain concepts. J Pain. 1996;5:128–38.
3. International Association for the Study of Pain. Classification of chronic pain, descriptions of chronic pain syndromes and definitions of pain terms, Subcommittee on Taxonomy. Pain. 1986;3(Suppl):S1–226.

4. Melzack R. Evolution of the neuromatrix theory of pain. The Prithvi Raj Lecture: presented at the third World Congress of World Institute of Pain, Barcelona 2004. Pain Pract. 2005;5:85–94.

5. Goldberg DS, McGee SJ. Pain as a global public health priority. BMC Public Health 2011 11:770.

6. Harstall C, Ospina M. How prevalent is chronic pain. Pain Clinical Updates 2003;11(2):1-4.

7. Smith BH, Hopton JL, Chambers WA. Chronic pain in primary care. Fam Pract. 1999;16:475–82.

8. Dewar A. Assessment and management of chronic pain in the older person living in the community. Aust J Adv Nurs. 2006;24:33–8.

9. Bosley BN, Weiner DK, Rudy TE, Granieri E. Is chronic nonmalignant pain associated with decreased appetite in older adults? Preliminary evidence. J Am Geriatr Soc. 2004;52:247–51.

10. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975;1:277–99.

11. Tait RC, Pollard CA, Margolis RB, Duckro PN, Krause SJ. The Pain Disability Index: psychometric and validity data. Arch Phys Med Rehabil. 1987;68:438–41.

12. Jensen MP, Turner JA, Romano JM, Strom SE. The chronic pain coping inventory: development and preliminary validation. Pain. 1995;60:203–16.

13. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiat. 1961;4:561–71.

14. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol. 1974;42:861–5.

15. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxi ety: psychometric properties. J Consult Clin Psychol. 1988;56:893–7.

16. Davidson MA, Tripp DA, Fabrigar LR, Davidson PR. Chronic pain assessment: a seven-factor model. Pain Res Manag. 2008;13:299–308.

17. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. The epidemiology of osteoarthritis in Asia. Int J Rheum Dis. 2011;14:113–21.

18. Dworkin RH, Peirce-Sandner S, Turk DC, McDermott MP, Gibofsky A, Simon LS, Farrar JT, Katz NP. Outcome measures in placebo-controlled trials of osteoarthritis: responsiveness to treatment effects in the REPORT database. Osteoarthritis Cartilage.

2011;19:483–92.

19. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833–40.

20. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic thera pies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:455–74.

21. McHugh GA, Silman AJ, Luker KA. Quality of care for people with osteoarthritis: a qualitative study. J Clin Nurs. 2007;16:168-76.
22. Benini A, DeLeo JA. Rene Descartes' physiology of pain. Spine 1999;24:2115–9.
23. Melzack R. From the gate to the neuromatrix. Pain. 1999;82:S121–6.
24. Keller T, Krames ES. "On the shoulders of giants": a history of the understandings of pain, leading to the understandings of neuromodulation. Neuromodulation. 2009;12:77–84.
25. Siegele DS. Pain and suffering. The gate control theory. Am J Nurs. 1974;74:498–502.
26. Nathan P. The gate-control theory of pain. Brain. 1976;99:123–58.
27. Coghill, R. Gate control theory and beyond: populations of neurons and pain. J Pain. 1996;5:40–4.
28. Wolff B. Gate control theory and the brain: Hebb revisited. J Pain. 1996;5:147–9.
29. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.
30. Sufka KJ, Price DD. Gate control theory reconsidered. Brain Mind. 2002;3:277–90.
31. Wall PD. The substantia gelatinesa. a gate control mechanism set across a sensory pathway. Trends Neurosci. 1980;3:221–4.
32. Melzack R. Pain and the neuromatrix in the brain. J Dent Educ. 2001;65:1378-82.
33. Melzack R, Loeser JD. Phantom body pain in paraplegics: evidence for a central "pattern generating mechanism" for pain. Pain. 1978;4:195–210.
34. Keefe F. From the gate control theory to the neuromatrix: revolution or evolution? J Pain. 1996;5:143–6.
35. Gandhi R, Tsvetkov D, Dhottar H, Davey JR, Mahomed NN. Quantifying the pain

experience in hip and knee osteoarthritis. Pain Res Manag. 2010;15:224–8.

36. Lund I, Lundeberg T. Aspects of pain, its assessment and evaluation from an acu puncture perspective. Acupunct Med. 2006;24:109–17.
37. Roth ML, Tripp DA, Harrison MH, Sullivan M, Carson P. Demographic and psy chosocial predictors of acute perioperative pain for total knee arthroplasty. Pain Res Manag. 2007;12:185–94.
38. Brady T. Strategies to support self-management in osteoarthritis. Am J Nurs. 2012;112(3 Suppl 1):S54–60.
39. Johnson SR, Archibald A, Davis AM, Badley E, Wright JG, Hawker GA. Is self-reported improvement in osteoarthritis pain and disability reflected in objective mea sures? J Rheumatol. 2007;34:159–64.
40. Szebenyi B, Hollander AP, Dieppe P, Quilty B, Duddy J, Clarke S, Kirwan JR. As sociations between pain, function, and radiographic features in osteoarthritis of the knee. Arthritis Rheum. 2006;54:230–5.
41. Tan EP, Tan ES, Ng BY. Efficacy of cognitive behavioural therapy for patients with chronic pain in Singapore. Ann Acad Med Singap. 2009;38:952–9.
42. May S. Self-management of chronic low back pain and osteoarthritis. Nat Rev Rheumatol. 2010;6:199–209
43. Jain KK. Gene therapy for pain. Expert Opin Biol Ther. 2008;8:1855–66.
44. Eaton MJ, Berrocal Y, Wolfe SQ, Widerstrom-Noga E. Review of the history and current status of cell-transplant approaches for the management of neuropathic pain. Pain Res Treat. 2012;2012:263972.

CHAPTER 3

The extent to which three different pain measures represent the pain experience of people with knee osteoarthritis

The following paper has been formatted for submission to Osteoarthritis & Cartilage.

The extent to which three different pain measures represent the pain experience of people with knee osteoarthritis

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3.1.Abstract

Objectives**:** To determine if people with knee osteoarthritis (OA) prefer one of three self-report pain measures addressing different pain dimensions to represent their pain experience. Secondary objectives were to examine the burden of these measures

Method**:** A cross-sectional study was conducted using a Latin square design. Eligible participants were aged 40 years or older having idiopathic knee OA pain, minimal pain in other body parts, fluent in English, and cognitively competent. All consenting participants completed a demographic form and answered questions about their OA knee using the Verbal Numeric Rating Scale (VNRS), Intermittent and Constant Osteoarthritis Pain Questionnaire (ICOAP) and Short-form McGill Pain Questionnaire-2 (SF-MPQ-2). Upon completion, participants were asked to rate how well each pain measure described their experience of pain by placing a horizontal mark on a 10 cm visual analogue scale (VAS) where 0 = "Does not describe my pain at all" and 100 = "Describes my pain completely". The Chi-square test was used to compare the number of participants who gave each pain measure the highest VAS score. Mean VAS scores for the three measures were compared using Freidman's nonparametric analysis of variance test, Associations between raw scores on the three pain measures were tested using Spearman rho correlation (r_s). Time taken to complete and score each measure and the number of errors and questions asked by participants while completing each measure were recorded.

Results**:** 96 adults (57 females) were recruited, mean (SD) age was 63.81 (9.42) and median (IQR) of VNRS score was 6 (5). Median VAS scores for VNRS, ICOAP and SF-MPQ-2 were 7.5, 7.4, and 7.8cm, respectively. No pain measure was preferred over the others($X^2_{(2, N = 87)} = 0.207$, $P = 0.9$; $X^2_{(2, N = 96)} = 1.288$, $P = 0.5$). VNRS has the least administrative burden in terms of time to complete and score ($P = 0.0001$ for both), and the least number of question ($P = 0.0001$), with no errors during completion. Scores on the three measures were similarly associated ($r_s = 0.73$ (0.62, 0.81) for VNRS and ICOAP; 0.69 (0.56, 0.78) for VNRS and SF-MPQ-2; 0.7 (0.58, 0.79) for ICOAP and SF-MPQ-2.

Conclusion**:** All three pain measures describe knee OA pain experience to a similar degree despite the fact that the ICOAP and SF-MPQ-2 took longer for participants to complete and required more explanations compared to the VNRS. VNRS is recommended for assessment of patients with knee OA pain in the clinical setting since it is quick to complete and score. Differences in the dimensions of pain assessed may explain the lack of preference among the three pain measures.

Keywords**:** Osteoarthritis, Knee, Chronic pain, Measurement, Patient Preference

3.2. Introduction

Osteoarthritis (OA) is a very common chronic disease characterized by progressive symptoms and structural changes in the joint including articular cartilage loss, osteophytes, synovial inflammation and subchondral bone changes (1, 2, 3). The knee is the most commonly affected joint and knee OA is the leading cause of pain and disability among older adults around the world (4, 5). Almost half of people diagnosed with OA experience significant pain that hinders daily activities (6). Theoretically, pain has sensory, cognitive, and affective dimensions, each requiring measurement in order to acquire a comprehensive and accurate evaluation of the pain experience of people with symptomatic knee OA (7). In the assessment of knee OA pain, the current focus is on pain intensity and associated disability, suggesting that the assessment of one dimension will reflect the other dimensions of chronic knee OA pain adequately. However, current studies dispute this assumption by showing fair correlation between unidimensional, disease-specific and multidimensional pain questionnaires (8, 9).

The Numeric Rating Scale (NRS) for pain intensity is a unidimensional measure commonly used in knee OA research and clinical practice (10). Knee OA pain typically is exacerbated by certain activities such as rising from a chair, walking, standing, or climbing stairs. Therefore, people with knee OA may be mistakenly considered pain free if the measure does not assess pain during activity. Hence, disease-specific pain measures asking about pain during daily activities may be appropriate for people with knee OA (11). The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) is a recently developed, disease specific 11-item measure (12). The ICOAP is based on

data from focus groups composed of people with hip and knee OA and it mainly addresses the intensity and consistency of pain. The questionnaire asks about constant pain (five questions) and intermittent pain (six questions) (12). Since consistency of knee OA pain is associated with an increased risk of total knee arthroplasty more so than pain intensity (13), measures addressing pain consistency such as ICOAP need to be explored. The revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2) is a multidimensional pain measure that addresses continuous, intermittent, neuropathic pain and affective dimensions (14). Since pain is a multidimensional construct (7), we need to know if using a dual-dimensional pain measure such as SF-MPQ-2) is preferable to using a single-item unidimensional (VNRS) or a multi-items disease-specific measure (ICOAP). Assessing the construct validity of VNRS, ICOAP and SF-MPQ-2 will inform us if the affective dimension to the pain is captured adequately by a single item generic measure (VNRS) and/or a multiple-items disease-specific measure (ICOAP) addressing only somatic pain characteristic in people with knee OA.

Pain in the main determinant of knee OA diagnosis, however, a gold standard for pain assessment in individuals with knee OA has yet to be established and a combination of pain outcome measures is used in research and clinical practice (15). Appropriate pain measurement is critical to guide clinical decision-making. It is crucial to determine the most appropriate intervention for a person given their stage along the continuum of knee OA pain and disability. Studies exploring the view of individuals with knee OA about pain scales are lacking. In 2010, an expert advisory group, the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials

(IMMPACT), reported that no attempt has been made to ask patients with pain about whether current outcome measures are meaningful or whether the instructions, anchors or items included in the scales are capturing their pain experience adequately (16). More information about the pain experience of people with knee OA and their views regarding the numerous pain measures currently in use is needed as this may help determined the most appropriate method(s) for assessing and treating pain in this population.

3.3. Purpose

The primary purpose of this study was to determine if people with knee OA prefer one of the three self-report pain measures to represent their pain experience. The secondary purpose was to examine the burden of these three pain measures.

Our hypothesis was that people with knee OA will identify the SF-MPQ-2 as the measure that best describes their pain experience because it addresses the intensity, frequency (intermittent versus constant) and affective components of pain. For practical reasons, the measure that takes less time to complete will have advantages in the clinical setting compared to a measure that takes longer to complete.

3.4. Methods

3.4.1. Study Design

This study was a cross-sectional design with participants completing all assessments on one occasion. The Latin square design was applied to determine the order in which the pain measures were completed to eliminate any chance of better performance in one measure than the others due to learning or fatigue factors (17). Table 3.1 shows the order of administration of the pain measures for the first three participants.

This order was repeated for all participants in the study. The study protocol was approved by our Institutional Research Ethics Board and all participants provided written informed consent prior to any data collection.

Table 3.1. The order of administration of the Verbal Numeric Rating Scale (VNRS), Short Form of the McGill Pain Questionnaire-2 (SF-MPQ-2) and the Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP) for the first three participants.

Participants	**Order of administration**		
Participant 1	VNRS	SF-MPQ-2	ICOAP
Participant 2	SF-MPQ-2	ICOAP	VNRS
Participant 3	ICOAP	VNRS	SF-MPQ-2

3.4.2. Participants

Study participants were men and women over the age of 40 years with clinical and/or radiological idiopathic knee OA according to the American College of Rheumatology modified clinical classification system (18) attending two orthopaedic surgery outpatient clinics affiliated with Hamilton Health Sciences and McMaster University. Eligible participants had knee pain and minimal pain in other joints or body parts. If the participant had bilateral knee pain, the study knee was decided to be the more symptomatic and if the same amount of pain was present in each knee, the study knee was selected by flipping a coin. Knee OA severity was determined by the treating physician's global rating of knee OA severity. Potential participants were excluded if they are unable to read, write and/or understand English; or had any cognitive deficit

resulting in inability to provide informed consent or difficulty comprehending and complying with instructions.

3.4.3. Recruitment

Recruitment occurred between January 24 and April 12; 2013. Potential participants scheduled to attend for a regular clinic visit were identified based on chart review and mailed an invitation letter. Those interested were telephoned to have questions answered, confirm eligibility, and schedule a single office visit.

3.4.4. Measures

The participants' demographics such as gender, age, ethnicity, level of education, height, weight, knee pain duration, pain medication use and the side of knee pain were collected. The participants were given three self-reported pain measures, in a predetermined order (see Table 3.1). Upon completion of each pain measure, VNRS, ICOAP, and SF-MPQ-2 (described below), the participants were asked to rate how well each pain measure describes their experience of pain by placing a horizontal mark on a 100 cm visual analogue scale (VAS) where 0 = "Does not describe my pain at all" and 100 = "Describes my pain completely" .

Pain verbal numeric rating scale

An 11-point VNRS was used. Participants were asked to verbally rate their pain level on a scale from 0 (no pain) to 10 (worst pain imaginable), considering the amount of pain in the study knee that they have experienced on average over the past 24 hours. The VNRS has a high test–retest reliability in knee OA population (ICC = 0.74) (19).

Intermittent and constant osteoarthritis pain questionnaire

The ICOAP is an 11-item disease-specific questionnaire in which each item has five response options scored on a Likert scale from 0 to 4 to describe pain over the past week (12). A separate score was produced by summing the items for each of the two subscales (constant pain over the past week (5 items) and intermittent pain over the past week (6 items)) and a total score was calculated by summing the scores on the two subscales. The ICOAP has a high internal consistency (cronbach's alpha= 0.93), test-retest reliability (ICC=0.85) and construct validity with Western Ontario and McMaster Universities (WOMAC) pain subscale (r = 0.81) in people with hip and knee OA (12).

Short-form McGill pain questionnaire-2

The SF-MPQ-2 includes four subscales (constant pain (6 items), intermittent pain (6 items), neuropathic pain (6 items) and affective descriptors (4 items)) for a total of 22 items asking about pain symptoms over the past week (14). The response to each item was scored on an 11-point numeric rating scale (0 = none; 10 = worst possible). A total score was calculated by summing the scores for each item. The SF-MPQ-2 has a high internal consistency (Cronbach's alpha = 0.96) and construct validity with the Multidimensional Pain Inventory (MPI) severity scale (r = 0.72) in people with different pain condition (53% with various types of arthritis) (20).

Burden for respondents and administration was determined for each pain measure by recording the time (in seconds) taken to complete and score each pain measure and the number of errors and questions people asked during completion of each measure.

Physician global rating scale of knee OA severity

The attending surgeon provided a global rating of knee OA severity (PGROA) for each patient on a 5-point Likert scale (0 = No OA and 4 = extremely severe) according to all the information available on the day of participant's visit including the history, physical examinations, and radiological assessment.

3.4.5. Data Analysis

SPSS 20 was used for the data analysis. Descriptive statistics were calculated to determine central tendencies and scores' distributions. The normality of statistical distribution of the study data was examined using the Shapiro-Wilk test. The Chi-square test was used to compare the number of people who gave each pain measure the highest absolute VAS score. The participants' VAS preference score for each pain measure were compared using Freidman's nonparametric analysis of variance test. Post hoc pairwise comparison using Freidman's test were used if the main effect due to pain measure were considered statistically significant ($p < 0.05$).

Based on the scores' distributions, Pearson's or Spearman's correlations were used to examine the association between scores on the three pain measures. Correlations between PGROA and the scores of all pain measures were estimated to know how well the subjective pain scores considered by the physician's global rating. Time taken to complete and score and the number of errors and questions asked for each pain measure were compared using Freidman's nonparametric analysis of variance test.

3.4.6. Sample size calculation

Peters et al (21) measured patient preference for pain measures in terms of ease of understanding and ease to complete in a sample having chronic pain due to various

musculoskeletal conditions. Five measures of pain intensity were used in this study (Horizontal and Vertical VAS, Verbal Descriptor Scale, Box-11 NRS and Box-21 NRS). and 49% of the participants selected the most preferred measure (21). Therefore, we estimated that the proportion of our participants preferring one pain measure would not be more than 49%. Given a desired 95% confidence interval with 0.10 widths for upper and lower bounds is required, 96 participants were needed for our study (22).

3.5. Results

After reviewing 454 patients' charts, 195 were deemed potentially eligible for the study and 96 participants were included in the study. Figure 3.1 shows the participants' flow chart and the reason for exclusion.

Participants' characteristics are shown in Table 3.2. and 3.3 for the total sample of 96 and by subgroups according to pain questionnaire they ranked the highest. Most of the participants were female (n = 57). Forty participants had bilateral knee pain but all of them had one knee worse than the other and the more painful knee was considered the study knee when completing the pain measures per the protocol. Most (89.6%) of the participants did not remember completing any pain measures before participating in the study; 10.4% reported completing the VNRS previously. All but 6 participants were White/Caucasians and 60 had no comorbidities with knee OA, 20 had one and 16 had two or more comorbidities. Of the included participants, 77were on pain medications, and 19 were not taking any pain medications.

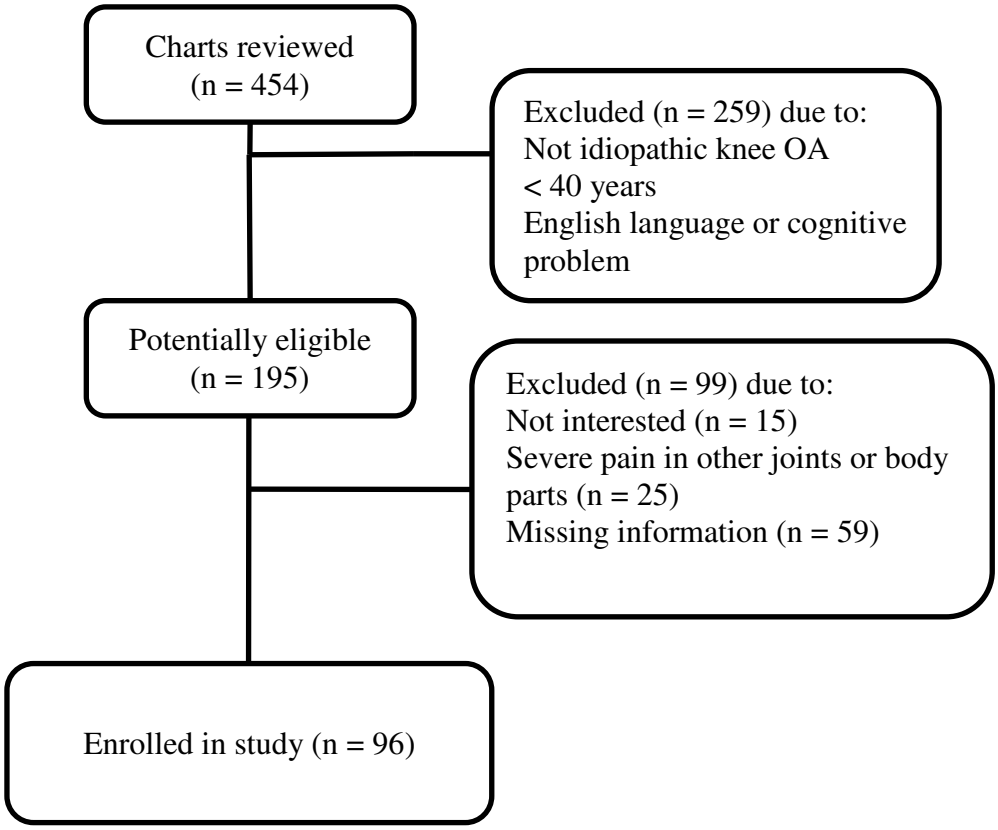

Figure 3.1. Study flow chart

3.5.1. Patients' preference

No pain measure was preferred over the others ($X^2_{(2, N = 87)} = 0.207$, $P = 0.9$; $X^2_{(2, N = 96)} = 1.288$, $P = 0.5$).

The medians and inter quartile ranges (IQRs) for the VAS scores reflecting the degree to which each pain measure represented the participant's study knee OA pain are: 7.5 (4), 7.4 (3.3) and 7.8 (3.6) cm, for VNRS, ICOAP and SF-MPQ-2 respectively. Nine participants did not rate one pain measure higher than the other two, 28 (20 females)

preferred the VNRS, 28 (14 females) preferred the ICOAP, and 31 (18 females) preferred the SF-MPQ-2.

Table 3.2. Mean/Median*(SD/IQR†) values for demographic characteristics and pain scores for the 96 participants in totoal and subgrouped based on preferred pain measure.

Characteristics	**Total sample**	**VNRS**	**ICOAP**	**SF-MPQ**
Age (yr)	63.81 (9.42)	62.93 (9.3)	66.46 (10.2)	61.81 (8.8)
Height (cm)	169.65 (12.54)	168.4 (18.3)	171 (8.3)	168.9 (9.8)
Weight (kg)	86.64 (18.51)	85.1 (18.7)	92.9 (22.4)	82.5 (12.2)
BMI ($kg/cm^{2)}$	30.2 (5.9)	30.4 (6.1)	31.7 (6.9)	29.1 (4.7)
Knee Pain Duration (yr)	8.66 (9.33)	9.5 (8)	10.1 (11.9)	7.1 (9.1)
VNRS score	6* ($5^{\dagger}$)	7.3* ($3.8^{\dagger}$)	4.75* ($4^{\dagger}$)	6* ($4^{\dagger}$)
SF-MPQ-2 score	2.4* ($3^{\dagger}$)	3.4* ($3.3^{\dagger}$)	2.1* ($2.7^{\dagger}$)	2.2* ($2.4^{\dagger}$)
ICOAP score	23* ($14.5^{\dagger}$)	26.5*($12.5^{\dagger}$)	22.5*($12.8^{\dagger}$)	21* ($16^{\dagger}$)

VNRS =Verbal Numeric Rating Scale (scores 0-10, higher = worse); ICOAP = Intermittent and Constant Osteoarthritis Pain (0-44, higher = worse; Short Form McGill Pain Questionnaire-2 = SF-MPQ-2 (scores 0-10, higher = worse)

3.5.2. Correlations among the three pain measures scores and PGROA

Table 3.4. shows the association between scores on the three pain measures and PGROA.

3.5.3. Time to complete and score the pain measures

Main effects due to pain measures were significant for time to complete (($X^2_{(2, N = 96)} = 144,8$, $P = 0.0001$), and time to score (($X^2_{(2, N = 96)} = 190$, $P = 0.0001$). Post-hoc tests showed that the VNRS was completed faster than both the SF-MPQ-2 ($P = 0.0001$)

Table 3.3. Number (%) of 96 participants according to level of education, study knee, and physical global rating of knee OA severity (PGROA) summarized for the total sample and for subgroups based on preferred pain measure.

Characteristic	Total sample	VNRS	ICOAP	SF-MPQ
Level of Education				
Secondary School	46 (47.9)	13 (46.4)	14 (50)	15 (48.4)
College	32 (33.3)	10 (35.7)	8 (28.6)	9 (29)
University	8 (8.3)	2 (7.1)	3 (10.7)	3 (9.7)
Graduate Studies	9 (9.5)	2 (7.1)	3 (10.7)	4 (12.9)
Study Knee				
Right	48 (50)	14 (50)	17 (60.7)	16 (51.6)
Left	48 (50)	14 (50)	11 (39.3)	15 (48.4)
PGROA				
Mild				
Moderate	13 (13.5)	4 (14.3)	2 (7.1)	7 (22.6)
Severe	38 (39.6)	7 (25)	15 (53.6)	12 (38.7)
Extremely Severe	40 (41.7)	16 (57.1)	9 (32.1)	10 (32.3)
	5 (5.2)	1 (3.6)	2 (7.1)	2 (6.5)

VNRS =Verbal Numeric Rating Scale; ICOAP = Intermittent and Constant Osteoarthritis Pain; Short Form McGill Pain Questionnaire-2 = SF-MPQ-2)

and ICOAP ($P = 0.0001$), but there was no difference in the time taken to complete the SF-MPQ-2 and the ICOAP ($P = 0.36$). In contrast, there were significant differences in time required to score each of the pain measures ($P = 0.0001$). The time taken to complete and the time required to score each pain measure is shown in Figure 3.3 and 3.4 respectively.

3.5.4. Number of questions and errors

The number of questions asked by the participant while completing each of the pain measures was significantly different ($X^2_{(2, N = 96)} = 27.7$, $P = 0.0001$). Post-hoc tests confirmed that the participants asked more questions while completing the SF-MPQ-2 than while completing the VNRS ($P = 0.0001$), or the ICOAP ($P = 0.002$). However, there was no significant difference between the number of question asked while completing the VNRS and the ICOAP ($P= 0.5$) as shown in Figure 3.5. There was no error when completing the VNRS or ICOAP, in contrast to SF-MPQ-2 as shown in Figure 3.5.

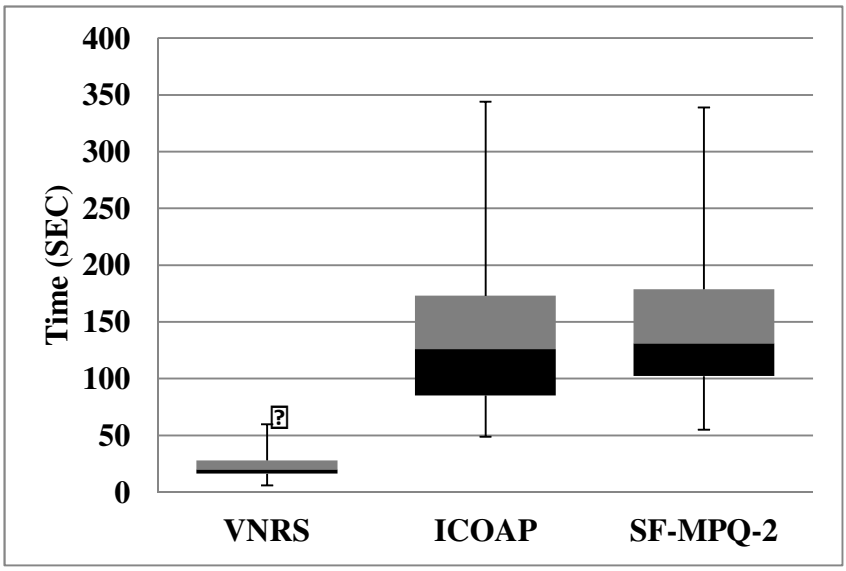

Figure 3.2. Box plots illustrating the median and interquartile range time required to complete the Verbal Numeric Rating Scale (VNRS_ the Intermittent and Constant

Osteoarthritis Pain questionnaire (ICOAP), and the Short Form McGill Pain Questionnaire-2 (SF-MPQ-2). Asterisk denotes statistical significance at $P < 0.05$

3.6.Discussion

The main finding of this study was that our sample of 96 people with knee OA reported a similar preference for a generic unidimensional single item pain measure (ie VNRS) a disease-specific unidimensional multiple item pain measure (ie ICOAP) and a multidimensional multiple item pain measure (i.e. SF-MPQ-2) . These results did not support our hypothesis that the SF-MPQ-2 would be preferred because it addresses the most dimensions of pain. These results can be interpreted in two ways. Pain intensity, which is addressed in all three pain measures, is

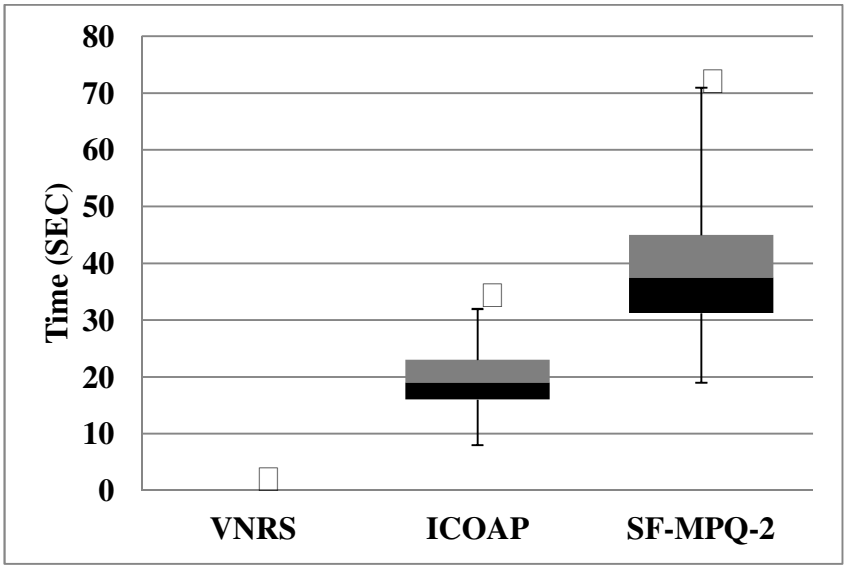

Figure 3.3. Box plots illustrating the median and interquartile range of time taken to score the Verbal Numeric Rating Scale (VNRS), Intermittent and Constant Osteoarthritis Pain (ICOAP), and the Short Form McGill Pain Questionnaire-2 (SF-MPQ-2). Asterisk denotes statistical significance at $P < 0.05$

an adequate indicator of the overall pain experience in people with knee OA pain. Alternatively, the additional participant burden associated with completing the unidimensional multiple items ICOAP and a multidimensional multiple items SF-MPQ-2 was offset by the fact that different information regarding the pain experience was conveyed and this was valued by the participants. The moderate correlations between pain measure scores support this interpretation. Pain scores for our sample were 6, 23and 2.4 for the VNRS, ICOAP, and SF-MPQ-2, respectively. These are comparable to scores on the same pain measures reported previously for people with knee OA (VNRS: 7 (23); ICOAP: 26 (24); SF-MPQ:2.7 (25)). This finding increases the generalizability of our result. Our study shows that no one pain measure was preferred over the other two. Participants completed the VNRS in the shortest time and scoring took the least amount of time. Moreover, the participants asked the least number of questions while completing the VNRS and no errors were encountered. For these reasons, we recommend using the VNRS to evaluate pain in people with knee OA in the clinical setting if time constraints preclude the use of more than one pain measure.

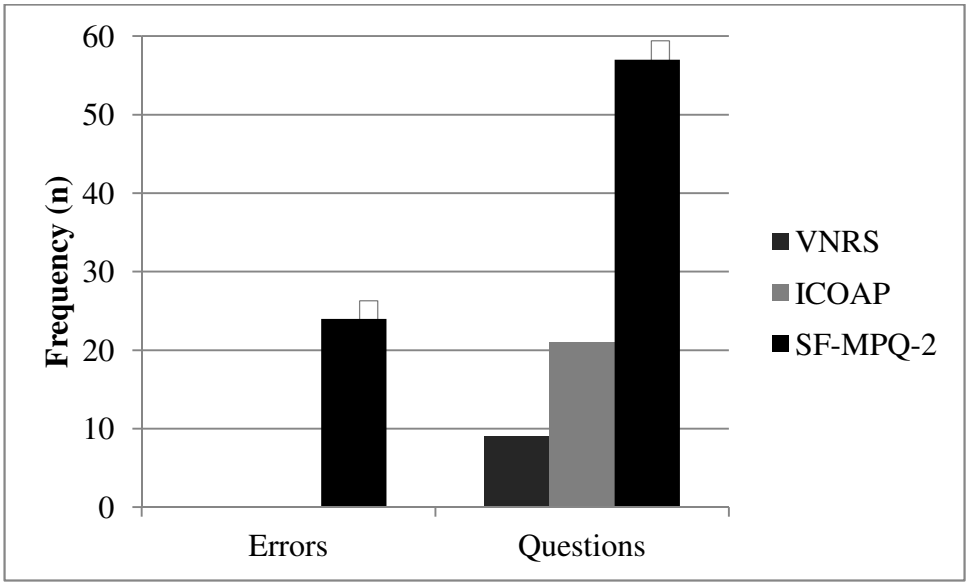

Figure 3.4. Number (n) of participant errors and questions while completing the Verbal Numeric Rating Scale (VNRS); Short Form McGill Pain Questionnaire-2 (SF-MPQ-2) and Intermittent and Constant Osteoarthritis Pain (ICOAP).

Asterisk denotes statistical significance at $P < 0.05$.

Table 3.4. Spearman Correlation Coefficients (95%CI)) for associations between scores on the Verbal Numeric Rating Scale (VNRS), Short Form McGill Pain Questionnaire-2 (SF-MPQ-2), Intermittent and Constant Osteoarthritis Pain (ICOAP), and Physician Global Rating of Osteoarthritis Severity (PGROA).

	SF-MPQ-2	**ICOAP**	**PGROA**
VNRS	0.67 (0.56, 0.78)	0.73 (0.62, 0.81)	0.189
SF-MPQ-2		0.7 (0.58, 0.79)	0.099
ICOAP			0.065

Previously, patient preference for pain measures has not been explored specifically in people with knee OA. Few studies address this topic in people with chronic pain. We estimated our sample size on the basis of a study by Peters et al (21) in which patient preference for pain measures was characterized in terms of ease of understanding and completion. Preference among five generic unidimensional single item measures of pain intensity (Horizontal VAS, Vertical VAS, Verbal Descriptor Scale, Box-11 and Box-21) was evaluated. In the group of people having chronic pain due to various musculoskeletal pain conditions, most of the participants (49%) preferred Box-21. Another study (23) determined the preferred pain measure among five generic unidimensional single item pain measures (the Verbal Descriptor Scale, the Numeric Box-11, the Faces Pain Scale, the Numeric Box-21 Scale, and the Colored Analogue Scale) to quantify post-operative pain intensity in four different age groups (young adults (20-44 yrs), middle-aged adults (45-59 yrs), elderly without cognitive impairment (≥ 60 yrs), and elderly with mild cognitive impairment (≥ 60 yrs)). The authors concluded that the Faces Pain Scale was the most preferred scale overall, although the young adults preferred the Numeric Box-11 (23). Due to the difference in methodology, sample population and the theoretical basis, our study results are not directly comparable. However, these studies did report that age and gender influence preference. Younger adults reporting post-op pain intensity and females tend to prefer the Numeric Box-11 (21, 23). Although not statistically significant, the participants in our study who preferred the ICOAP tended to be older and those who preferred the VNRS were more likely to be women (Table 3.2). More studies exploring the preference of people with

knee OA regarding the pain measure(s) that best represent their pain experience are needed.

In our study sample, scores on the VNRS, ICOAP and SF-MPQ-2 were moderately correlated. This finding indicates that the three measures are evaluating different pain dimensions. Other studies examined the correlation between measures addressing different pain dimensions and the results were comparable to our study. For example, Gandhi et al (8) found a lower correlation between scores on the WOMAC pain subscale and MPQ-SF (r = 0.36). However, other studies showed higher correlations between pain measures. Another study concluded that scores on the multiple item ICOAP and WOMAC pain subscale were highly correlated among 82 people with knee OA (r = 0.81) (12) which may indicate that scores on disease-specific pain measures are more highly correlated. Similarly, the correlation between scores on two single item pain intensity measures such as the VNRS and VAS is very high (r = 0.91) (27), which confirm that the moderate correlations in our study could be explained by the differences of pain dimensions addressed. The weak correlations between pain measure scores and PGROA (r = 0.1) agree with the previous literature. A study (28) found only a poor correlation between the objective physician-assessed knee score and the patient-reported satisfaction VAS score in people after total knee arthroplasty. Surgeons usually focus on range of motion, alignment, and stability (not pain), but patients focus on the functionality of the knee as a whole (including pain) (28). Our study confirms the low weight of pain level in determination of knee OA severity from the physician prospective.

The results of our study must be considered in the context of the limitations. We recruited people with knee OA attending clinics of orthopaedic surgeons' affiliated with a teaching hospital. The extent to which the findings can be generalized to other clinical settings is unknown. The participants in the study filled out the pain measures in an interview setting (one to one) with no limited time which does not happen in the busy clinical setting, therefore, we are not sure if the patient's pain measure preference would differ in another clinical setting. Only three pain measures were administrated in this study to decrease the burden on the participants; the inclusion of different pain measures may have yielded different results.

3.7.Conclusion

We asked people with knee OA pain, the most common cause of chronic musculoskeletal pain, to identify which of three pain measures best represented their pain experience. No preference was identified among the VNRS, the ICOAP or the SF-MPQ-2. The assessment of pain scores correlations confirmed that the three measures assessed different pain dimentions, thus a combination of pain measures may best represent the pain experience of people with knee OA. In a clinical setting interested in administering only one pain measure for to patients with knee OA, the VNRS is recommended since it is quick to complete and score.

3.8. References

1. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. BMJ. 2012 Jul 30;345:e4934.

2. Jaiprakash A, Prasadam I, Feng JQ, Liu Y, Crawford R, Xiao Y. Phenotypic characterization of osteoarthritic osteocytes from the sclerotic zones: A possible pathological role in subchondral bone sclerosis. International Journal of Biological Sciences [Electronic Resource]. 2012;8(3):406-17.

3. Troeberg L, Nagase H. Proteases involved in cartilage matrix degradation in osteoarthritis. Biochim Biophys Acta. 2012 Jan;1824(1):133-45.

4. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the united states. part II. Arthritis & Rheumatism. 2008 Jan;58(1):26-35.

5. Quintana JM, Arostegui I, Escobar A, Azkarate J, Goenaga JI, Lafuente I. Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population. Arch Intern Med. 2008;168(14):1576.

6. Centers for Disease Control and Prevention (CDC). Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation --- united states, 2007-2009. MMWR - Morbidity & Mortality Weekly Report. 2010 Oct 8;59(39):1261-5.

7. Melzack R. Evolution of the neuromatrix theory of pain. the prithvi raj lecture: Presented at the third world congress of world institute of pain, barcelona 2004. Pain Practice. 2005 Jun;5(2):85-94.

8. Gandhi R, Tsvetkov D, Dhottar H, Davey JR, Mahomed NN. Quantifying the pain experience in hip and knee osteoarthritis. Pain Research & Management. 2010 Jul-Aug;15(4):224-8.

9. Roth ML, Tripp DA, Harrison MH, Sullivan M, Carson P. Demographic and psychosocial predictors of acute perioperative pain for total knee arthroplasty. Pain Research & Management. 2007;12(3):185-94.

10. Dworkin RH, Peirce-Sandner S, Turk DC, McDermott MP, Gibofsky A, Simon LS, et al. Outcome measures in placebo-controlled trials of osteoarthritis: Responsiveness to treatment effects in the REPORT database. Osteoarthritis & Cartilage. 2011 May;19(5):483-92.

11. Tsai PF, Tak S. Disease-specific pain measures for osteoarthritis of the knee or hip. Geriatr Nurs. 2003 Mar-Apr;24(2):106-9.

12. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthritis & Cartilage. 2008 Apr;16(4):409-14.

13. Wise BL, Felson DT, Clancy M, Niu J, Neogi T, Lane NE, et al. Consistency of knee pain and risk of knee replacement: The multicenter osteoarthritis study. J Rheumatol. 2011 Jul;38(7):1390-5.

14. Dworkin RH, Turk DC, Revicki DA, Harding G, Coyne KS, Peirce-Sandner S, et al. Development and initial validation of an expanded and revised version of the short-form McGill pain questionnaire (SF-MPQ-2). Pain. 2009 Jul;144(1-2):35-42.

15. Bartlett SJ, Ling SM, Mayo N, Scott S, Bingham III CO. Identifying common trajectories of joint space narrowing over two years in knee osteoarthritis. Arthritis Care & Research. 2011.

16. Turk DC. Dworkin RH. Burke LB. Gershon R. Rothman M. Scott J. Allen RR. Atkinson JH. Chandler J. Cleeland C. Cowan P. Dimitrova R. Dionne R. Farrar JT. Haythornthwaite JA. Hertz S. Jadad AR. Jensen MP. Kellstein D. Kerns RD. Manning DC. Martin S. Max MB. McDermott MP. McGrath P. Moulin DE. Nurmikko T. Quessy S. Raja S. Rappaport BA. Rauschkolb C. Robinson JP. Royal MA. Simon L. Stauffer JW. Stucki G. Tollett J. von Stein T. Wallace MS. Wernicke J. White RE. Williams AC. Witter J. Wyrwich KW. Initiative on Methods,Measurement and Pain Assessment in Clinical Trials. Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations. Pain. 2006 Dec 5;125(3):208-15.

17. Bradley JV. Complete counterbalancing of immediate sequential effects in a latin square design. Journal of the American Statistical Association. 1958 Jun.;53(282):pp. 525-528.

18. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. classification of osteoarthritis of the knee. diagnostic and therapeutic criteria committee of the american rheumatism association. Arthritis & Rheumatism. 1986 Aug;29(8):1039-49.

19. Ruyssen-Witrand A, Fernandez-Lopez CJ, Gossec L, Anract P, Courpied JP, Dougados M. Psychometric properties of the OARSI/OMERACT osteoarthritis pain and functional impairment scales: ICOAP, KOOS-PS and HOOS-PS. Clin Exp Rheumatol. 2011 Mar-Apr;29(2):231-7.

20. Lovejoy TI, Turk DC, Morasco BJ. Evaluation of the psychometric properties of the revised short-form McGill pain questionnaire. J Pain. 2012 Dec;13(12):1250-7.

21. Peters ML, Patijn J, Lame I. Pain assessment in younger and older pain patients: Psychometric properties and patient preference of five commonly used measures of pain intensity. Pain Medicine. 2007 Oct-Nov;8(7):601-10.

22. Daniel W. Chapter 6. In: 9th EditionHoboken NJ: WILEY, editor. Biostatistics: a Foundation for Analysis in the Health Science. ; 2009.

23. Snijders GF, van den Ende CH, van den Bemt BJ, van Riel PL, van den Hoogen FH, den Broeder AA, et al. Treatment outcomes of a numeric rating scale (NRS)-guided pharmacological pain management strategy in symptomatic knee and hip osteoarthritis in daily clinical practice. Clin Exp Rheumatol. 2012 Mar-Apr;30(2):164-70.

24. Goncalves RS, Meireles AC, Gil JN, Cavalheiro LM, Rosado JO, Cabri J. Responsiveness of intermittent and constant osteoarthritis pain (ICOAP) after physical therapy for knee osteoarthritis. Osteoarthritis Cartilage. 2012 Oct;20(10):1116-9.

25. Grafton KV, Foster NE, Wright CC. Test-retest reliability of the short-form McGill pain questionnaire: Assessment of intraclass correlation coefficients and limits of agreement in patients with osteoarthritis. Clin J Pain. 2005 Jan-Feb;21(1):73-82.

26. Yinghua Zhou ,Asst. Prof. Dr. Wongchan Petpichetchian , Dr. Luppana Kitrungrote. Preference of pain assessment tools among different age groups of postoperative patients. The 2nd international conference on humanities and social sciences; April 10th, 2010; Faculty of Liberal Arts, Prince of Songkla University,Thailand. ; 2010.

27. Downie WW, Leatham PA, Rhind VM, Wright V, Branco JA, Anderson JA. Studies with pain rating scales. Ann Rheum Dis. 1978 Aug;37(4):378-81.

28. Bullens PH, van Loon CJ, de Waal Malefijt MC, Laan RF, Veth RP. Patient satisfaction after total knee arthroplasty: A comparison between subjective and objective outcome assessments. J Arthroplasty. 2001 Sep;16(6):740-7.

CHAPTER 4

Efficacy of low frequency pulsed subsensory threshold electrical stimulation versus placebo on pain and physical function in people with knee osteoarthritis: Systematic review with meta-analysis

The following paper is accepted for publication in Osteoarthritis & Cartilage on 13-JUN-2013.

Efficacy of low frequency pulsed subsensory threshold electrical stimulation versus placebo on pain and physical function in people with knee osteoarthritis: Systematic review with meta-analysis

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Running title: PEMF/PES for knee OA management

4.1. Abstract

Objective**:** To determine if low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through pulsed electromagnetic field (PEMF) or pulsed electrical stimulation (PES) versus sham PEMF/PES intervention is effective in improving pain and physical function at treatment completion in adults with knee OA blinded to treatment.

Method**:** The relevant studies were identified by searching eight electronic databases and a hand search of the past systematic reviews on the same topic until April 5, 2012.

We included RCTs of people with knee OA comparing the outcomes of interest for those receiving PEMF/PES with those receiving sham PEMF/PES. Two reviewers independently selected studies, extracted relevant data and assessed quality. Pooled analyses were conducted using inverse-variance random effects models and standardized mean difference (SMD) for the primary outcomes.

Results**:** Seven small trials (459 participants/knees) were included. PEMF/PES improves physical function (SMD = 0.22, 95% CI= 0.04, 0.41, P = 0.02, I^2 = 0%), and does not reduce pain (SMD = 0.08, 95% CI = -0.17, 0.32, P = 0.55, I^2 = 43%). The strength of the body of evidence was low for physical function and very low for pain.

Conclusion**:** Current evidence of low and very low quality suggests that low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF/PES versus sham PEMF/PES is effective in improving physical function but not pain intensity at treatment completion in adults with knee

OA blinded to treatment. Methodologically rigorous and adequately powered RCTs are needed to confirm the findings of this review.

Keywords**:** Therapeutic Electrical Stimulation, Magnetic Field Therapy, Electromagnetic Fields, Electromagnetic Phenomena, Osteoarthritis, Adults, Evidence-Based Medicine.

4.2. Introduction

Osteoarthritis (OA) is a degenerative disorder of the articular cartilage associated with hypertrophic bone changes (1). It is the most common chronic joint disease and the leading cause of pain and disability among older adults around the world (2). Knee OA has an immense public health impact due to the need for healthcare services particularly if surgical replacement of the knee joint is required (3). In 2000, 25 million people in North America had knee OA, and that number is expected to double by 2020 due to several factors including sedentary life style, increasing prevalence of obesity and population aging (4).

Effective, conservative interventions for relieving pain and improving physical function are needed for people with knee OA (5). Pulsed electromagnetic field (PEMF) and pulsed electrical stimulation (PES) are emerging non-pharmacologic conservative treatments of knee OA. Both treatments produce pulsed electric potentials below the sensory threshold either through an electromagnetic coil system (PEMF) or surface electrodes (PES) applied around the knee joint (6-8). These subsensory-threshold pulsed electric potentials stimulate intrinsic potentials (9), which alter the homeostatic balance of cartilage matrix degradation and synthesis in favour of cartilage repair (10). In cell culture and animal studies, electrical stimulation similar to that produced by PEMF/PES increases cartilage synthesis by down regulation of interleukin-1 (IL-1) and up regulation of transforming growth factor beta (TGFβ) which lead to increased aggrecan, type II collagen, and proteoglycan content in the cartilage matrix and enhanced chondrocyte proliferation

(11). In an animal model study, pulsed electrical stimulation of less than 100 Hz has shown higher efficacy than frequencies of 150 Hz or more (12). Moreover, higher frequencies have been associated with harmful changes in bone tissue (6).

Previous systematic reviews have addressed the question of efficacy of PEMF and PES for knee OA management and reached contradicting conclusions (13, 14). McCarthy et al (2006) pooled data from five RCTs (276 participants/knees) and concluded that PEMF and PES are not effective for knee OA pain or physical function (13); Vavken et al (2009) pooled data for nine RCTs (483 participants/knees) and concluded that PEMF and PES might improve physical function but not pain in the knee OA population at treatment completion (14). A systematic review conducted by We et al searched literature published to December 2011 to determine the efficacy of PEMF pooling data from 14 studies (930 participants/knees) reporting knee OA pain and physical function outcomes at four, eight, 12, and 16 weeks (15). Similar to the conclusions reported by Vavken et al (2009), We et al reported that physical function was improved at eight weeks with active PEMF (5 trials, 304 participants/knees; all interventions completed at 6 weeks) and pain was not significantly improved at any time point (maximum of 11 trials, 762 participants/knees (at 4 weeks) in which the intervention period was two, three, four, or 6 weeks). However, the inclusion of trials in which pulsed subsensory threshold electrical stimulation was applied at higher frequencies than that expected to be biologically beneficial to participants with and without knee OA who were not

blinded and/or not randomized to treatment leaves the question of efficacy unresolved.

4.3. Objective

The objective of this systematic review was to determine if low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF/PES versus sham PEMF/PES intervention is effective in improving pain and physical function at treatment completion in adults with knee OA blinded to treatment. Adverse events were the primary safety outcome. Secondary outcomes included patient global assessment, imaging-based knee joint status, health-related quality of life and physician global assessment.

4.3. Methods

The Cochrane Collaboration methodology was followed (20) in the conduct of this review and PRISMA guidelines were followed for reporting the methods and results of this systematic review and meta-analysis (21).

4.4.1. Eligibility Criteria and Search Strategy

Studies were included if: 1) participants with clinically and/or radiological confirmed knee OA; 2) PEMF/PES frequency was ≤100 Hz; 3) Comparator is sham PEMF/PES 4) primary outcome was pain and/or physical function; 5) the study design is RCT with blinded participants 5) data for knee OA participants were reported independently pre and post treatment; and 6) participants were over 30 years of age. Studies were excluded if: 1) results were reported in another trial; 2) published data were insufficient for meta-analysis and corresponding authors did not

respond to requests for further information; 3) co-interventions were applied to only one group; and 4) the trial was written in a language other than English.

The relevant studies were identified by searching five electronic databases: MEDLINE, CINAHL, EMBASE, CENTRAL and AMED. The search strategy combined medical subject headings and text terms describing knee OA with terms describing PEMF/PES. The search was limited to English language, human, adult, and randomized controlled trial. The keywords and Medical Subject Headings (MeSH) used for each of the databases and the search results are shown in Appendix A. We searched three clinical trial registries to identify ongoing trials: Clinical Trials Registry, Current Controlled Trials and the World Health Organisation International Clinical Trials Registry Platform. Hand search of the past systematic reviews on the same topic was performed. The last search was run on April 5, 2012.

4.4.2. Study Selection

The eligibility assessment of title and abstract of citations obtained from the search was performed by two independent reviewers (AN, AL) unblinded to author, journal and country. Any disagreement was resolved through consensus. After title and abstract screening for potentially eligible studies, two reviewers (AN, NM) checked the full text articles for eligibility independently and any disagreements were resolved through consensus. The agreement between the two reviewers was assessed by examining raw agreement and unweighted kappa (κ).

4.4.3. Data Extraction and Management

A data extraction form was developed for this review and pilot-tested independently on three randomly-selected studies by two reviewers (AN, NM) to ensure consistency in extraction. The extraction form was refined accordingly and data were extracted in duplicate. Six authors were contacted for further information, two authors responded and one provided numerical data that were presented graphically in the published paper (18). The extracted information included the characteristics of participants (age, gender, knee OA severity and method of diagnosis), PEMF/PES (the device, application and treatment protocol), and the type of outcome measures, baseline data, post-treatment data, and change means and standard deviations (SDs) or the information from which SD could be derived, such as standard error or confidence interval. When a trial presented outcomes at more than one time point, data for all time points were extracted; however, only data acquired immediately post-treatment were used in the meta-analysis.

4.4.4. Assessment of Risk of Bias for Included Studies

Two reviewers (AN, NM) independently assessed risk of bias for each study according to the Cochrane Handbook (chapter 8) for eight domains: sequence generation, allocation concealment, blinding of participants and care givers, blinding of outcome assessors, completeness of outcome data, completeness of outcome reporting and the potential for other threats to the validity of the study (21). Any disagreement regarding risk of bias was resolved by consensus. Risk of publication bias was examined using a funnel plot of each study's effect estimates for the primary outcomes against their standard error; no statistical test was performed.

4.4.5. Data Synthesis

The outcomes in the included studies reported continuous data (mean and SD) and used different outcome measures for each outcome with the exception of patient and physician global assessments, therefore, standardized mean differences (SMD) were used to estimate the treatment effect to facilitate comparisons across all outcomes. Change means and SDs were pooled to adjust for the baseline differences between groups in each study. Three studies (22-24) reported post-treatment means and SDs. Therefore, change means and SDs were imputed as recommended by the Cochrane Handbook (21). Relative risk and 95% confidence intervals for the reported side effects were calculated.

One study (22) did not report post-treatment SDs for the outcomes (required to calculate change SD). Furthermore, calculating the SD from the study data was not possible since other important statistics (standard error, confidence interval, or exact p-values) were not provided. Baseline SDs were used instead of post treatment SDs based on the assumption that the intervention does not change the variability between groups (21). SMDs were pooled and the inverse-variance random effects model was used considering the variability across studies (21). Review Manager Version 5 was used for data analysis (http://ims.cochrane.org/revman). Confidence intervals at the 95% level (95% CI) were calculated for pooled estimates for each outcome and the Z test was used to determine the treatment effect. Statistical significance was considered at $p < 0.05$.

4.4.6. Investigation of Heterogeneity and Subgroup Analysis

Heterogeneity among the included studies was measured using the chi-squared test (χ^2). For χ^2 values with $p < 0.1$, heterogeneity was considered to be significantly high. The I^2 was used to assess the inconsistency between the pooled studies. The I^2 of < 60% was considered to be acceptable for pooling the data across the studies (21).

The pulsed subsensory threshold electrical stimulation types, treatment duration and source of funding were hypothesized to generate heterogeneity across the studies. Therefore subgroup analyses were planned a priori for the different types of pulsed subsensory threshold electrical stimulation (PES and PEMF), treatment durations (<12 weeks and ≥12 weeks) and source of funding (non-industry and industry).

4.4.7. Grading of Evidence

Two reviewers (AN, NM) graded the strength of the body of evidence that emerged from this review using the Gradepro program (25). Five domains were assessed: risk of bias, inconsistency of the results, indirectness of the outcome, imprecision of the results and publication bias.

4.4.8. Sensitivity Analysis

To ensure the robustness of the pooled outcomes, post-hoc sensitivity analyses were conducted by repeating the meta-analyses after removing data from each of the three studies for which the change SD was imputed (22-24).

4.5. Results

Figure 4.1. shows the flow diagram for identification of eligible trials. After title and abstract screening, 11 studies were retrieved for full text review. Seven studies met the eligibility criteria. The raw agreement between the reviewers in identifying the full text studies for inclusion in this review was 100% (κ = 1).

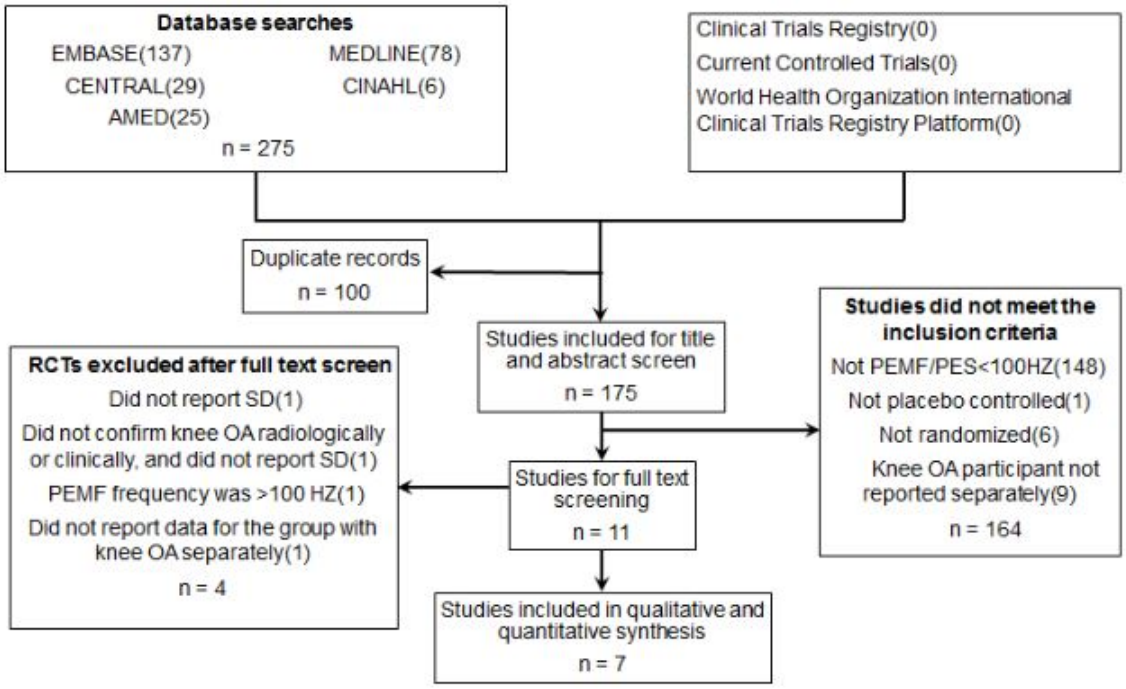

Figure 4.1. Flow diagram for identification of eligible trials evaluating the effect of PEMF/PES

4.5.1. Description of Included Studies

Seven parallel group randomized placebo controlled studies published between 1994 and 2011 were included. Two trials were conducted in USA (17, 26), two in Turkey (22, 23), and one in each of Denmark (24), Australia (18) and the UK (27). The duration of the intervention varied from two to 26 weeks and the frequency of PEMF/PES ranged from five to 100 Hz. The control groups in all the studies used sham devices. In total, the studies included 459 participants with an average age of 63.7 years and with greater proportion of females compared to males. The description and characteristics of the included studies are summarized in Table 4.1.

4.5.2. Description of Excluded Studies

After the full-text eligibility assessment, four studies were excluded (28-31) for various reasons. The RCT by Zizic et al. (1995) was excluded because the SDs or other important statistics (standard error, confidence interval, or exact p-values) were not provided (26). In the trial by Jacobson et al. (2001), radiological or clinical criteria for diagnosing knee OA was not reported and SDs for means were not provided for the intervention and placebo groups (29). Nicolakis et al. (2002) used PEMF but with frequencies exceeding 100Hz (30). Lastly, Trock et al. (1993) included five participants with hand OA, one participant with ankle OA and 21 participants with knee OA and the results for knee OA participants were not presented separately (31). We contacted these authors to get the required information to include these studies but they did not reply.

4.5.3. Risk of Bias in the Included Studies

Table 4.1. Characteristics of Participants and Interventions in the Included Studies

Study	Sample Size (N)		Age, y (Mean(SD))		Female (%)		Intervention			
	PEMF* /PES†	Control	PEMF /PES	Control	PEMF* /PES	Control	Type	Frequency (Hz)	Total Exposure (HrsxSessions/ Wk)	Duration (Wks)
Trock (26)	40	44	69.2 (11.5)	65.8 (11.7)	69	70.5	PEMF*	5-12	0.5 x 3-5	4-6
Pipitone (27)	34	35	62	64	35	20	PEMF*	3-20	0.5 x 7	6
Thamsborg (24)	42	41	60.4 (8.7)	59.6 (8.6)	47.6	60.9	PEMF*	50	2 x 5	6
Garland (17)	39	19	64.3 (10.2)	69.9 (11.4)	69.2	57.9	PES†	100	7 x 7	12
Ay.S (23)	30	25	58.9 (8.8)	57.7 (6.5)	70	76	PEMF*	50	0.5 x 5	3
Özgüçlü (22)	20	20	60.6 (7.7)	62.2 (8.2)	NR‡	NR‡	PEMF*	50	0.5 x 5	2
Fary (18)	34	36	70.7 (8.9)	68.9 (11.4)	50	44	PES†	100	7 x 7	26

* Pulsed Electromagnetic Field

† Pulsed Electrical stimulation

‡ Not Reported

Table 4.2 summarizes the risk of bias assessment for the seven included studies. The overall methodological quality assessment indicated that risk of bias was low in one study (18), unclear in another (24) and high in the other five studies (17, 22, 23, 26, 27). As a result, risk of bias across the studies is high. The raw agreement between the reviewers in evaluating the risk of bias domains was 89.5% (κ=0.81). Publication bias was not detected in the funnel plots of the primary outcomes, since they are relatively symmetrical as shown in Figure 4.2. for pain.

4.5.4. Effects of Interventions

Table 4.3 demonstrates an overall summary of the effects of PEMF and PES on all outcomes of interest.

Primary Outcomes

In the seven RCTs included for meta-analysis, pain was assessed in a total of 459 participants randomised to an active PEMF/PES group (n = 239) and a placebo PEMF/PES group (n = 220). No difference between groups was observed (SMD = 0.08, 95% CI: -0.17, 0.32, p = 0.55) as illustrated in Figure 4.3. Overall, the strength of the body of evidence for the pain outcome was judged to be very low for reasons described in Table 4.3.

Figure 4.4.illustrates the beneficial effect of PEMF/PES on physical function (SMD = 0.22, 95% CI: 0.04, 0.41, p = 0.02) in 456 of the participants with knee OA enrolled in the seven RCTs. See Table 4.3 for the summary of findings for this outcome including the rationale for judging the strength of the body of evidence as low.

Table 4.2. Methodological Quality of Included Studies

Trials	**Key Domains**								**Overall Risk of Bias**
	Random sequence generation	Allocation concealment	Blinding of participant	Blinding of care provider	Blinding of outcome assessor	Incomplete outcome data	Selective reporting	Other bias	
Trock (26)	Low*	Low*	Low*	High†	Low*	High†	Low*	Low*	High†
Pipitone (27)	Low*	Low*	Low*	Low*	Low*	Low*	High†	Low*	High†
Thamsborg (24)	Unclear	Unclear	Low*	Unclear	Low*	Low*	Low*	Low*	Unclear
Garland (17)	High†	High†	Low*	Low*	Low*	Low*	Low*	Unclear	High†
Ay.S (23)	High†	Unclear	High†	High†	Low*	Low*	Low*	Unclear	High†
Özgüçlü (22)	Low*	High†	Low*	High†	Low*	Low*	High†	Low*	High†
Fary(18)	Low*	Low*	Low*	Low*	Low*	Low*	Low*	Low*	Low*

***** Low risk of bias

† High risk of bias

‡ Unclear if high or low risk of bias

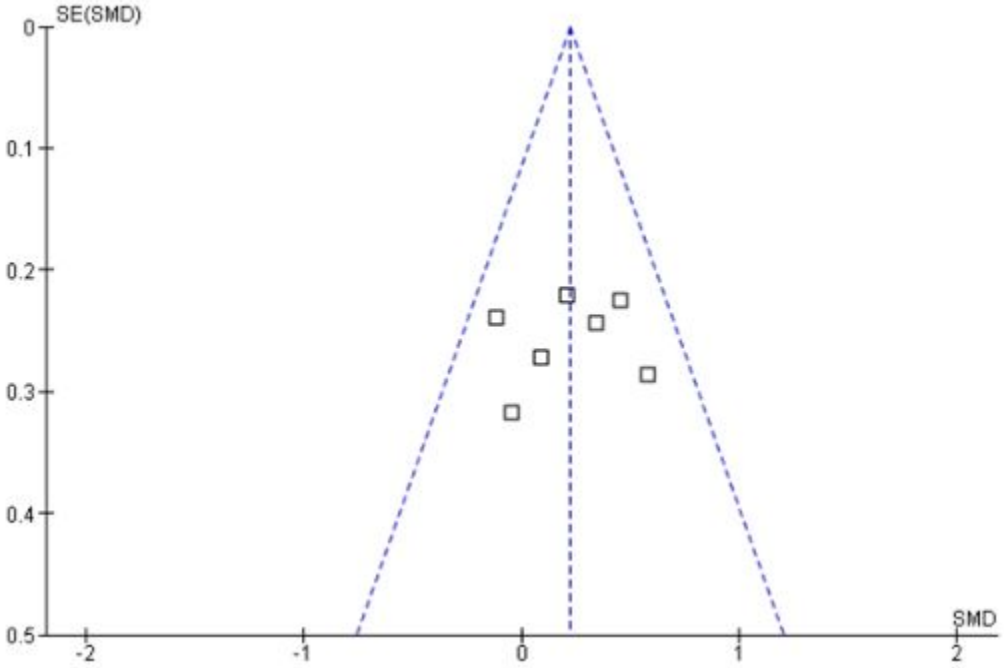

Figure 4.2. Funnel plot for the seven included studies for the pain outcome

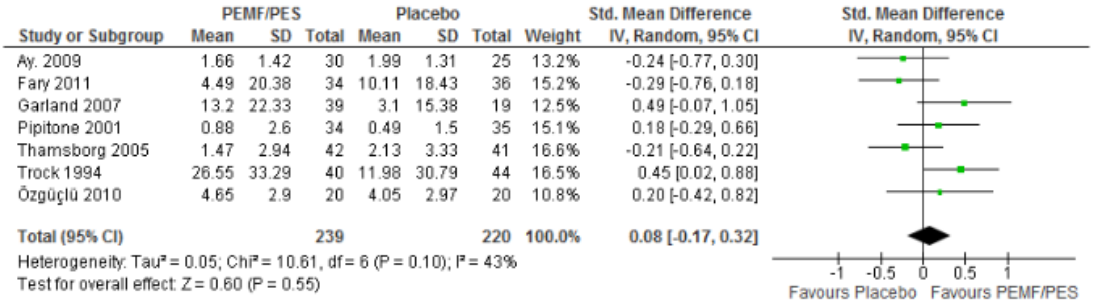

Figure 4.3. Forest plot for meta-analysis of the effect of pulsed PEMF/PES compared to sham treatment on pain

Table 4.3. Summary of Findings

Outcomes	**SMD* and RR[†] (95%CI[‡]) compared to the control group**	**Sample Size (No. of studies)**	**Quality of the evidence[§]**	**Inconsistency $I^{2\|\|}$**	**Heterogeneity χ^2 *P* Value[¶]**	**Outcome Specific Risk of Bias**
Pain reduction VAS[**] (26,23) and WOMAC[††] Pain subscale(17,18,22,24,27) Follow-up: 2-26 weeks	0.08 SD[‡‡] higher (-0.17 to 0.32)	459 (7 studies)	very low[¶¶]	43%	0.1	High risk of bias of the included studies, high results' heterogeneity, small sample size and wide CI[‡]
Physical function WOMAC[††] Physical function(17,18,22,24,27) Lequesne Index (23) ADL[§§] (26) Follow-up: 2-26 weeks	0.22 SD[‡‡] higher (0.04 to 0.41)	456 (7 studies)	Low[¶¶]	0%	0.45	High risk of bias of the included studies, small sample size and wide CI[‡]
Adverse event Skin rash(17,18) Follow-up: 12-26 weeks	RR[†] 0.96 (0.45 to 2.03)	128 (2 studies)	very low[¶¶]	0%	0.78	High risk of bias in the included studies, very small sample size and wide CI[‡]
Patient global assessment VAS[**] (17,18,26) Follow-up: 6-26 weeks	0.26 SD[‡‡] higher (-0.14, 0.66)	209 (3 studies)	very low[¶¶]	61%	0.08	High risk of bias of the included studies, results' inconsistency, small sample size and wide CI[‡]
Quality of life	Highly heterogeneous	139	very low[¶¶]	84%	0.01	High results' heterogeneity, small

SF36 (18) and EQOL[‖‖] (27) Follow-up: 6-26 weeks	result	(2 studies)				sample size and wide CI[‡]
Physician global assessment VAS[**] (26) Follow-up: 6 weeks	0.46 SD[‡‡] higher (0.02, 0.90)	81 (1 study)	very low[¶¶]	Only one study included	Only one study included	High risk of incomplete data in the included study, very small sample size and wide CI[‡]

* Standard Mean Difference

† Relative Risk

‡ Confidence interval

§ 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.

‖ Inconsistency across studies; up to 40%, might not be important; 30 to 60%, may represent moderate heterogeneity; 50 to 90%, may represent substantial heterogeneity.

¶ Chi-square *P* value; < 0.1, statistical significant heterogeneity; ≥ 0.1, non-significant heterogeneity.

** Visual analogue scale

†† Western Ontario and McMaster Universities Osteoarthritis Index

‡‡ Standard Deviation

§§ Activity of daily life questionnaire

‖‖ Euro-quality of life questionnaire

¶¶ 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.

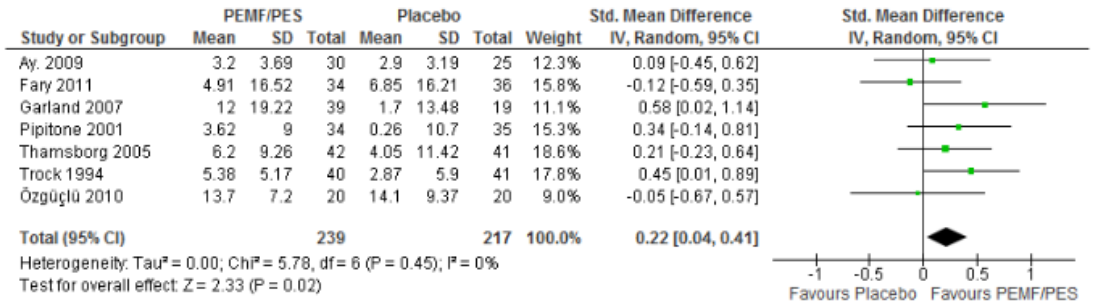

Figure 4.4 Forest plot for meta-analysis of the effect of PEMF/PES compared to sham treatment on physical function

Heterogeneity due to pulsed subsensory threshold electrical stimulation types, treatment regimens and sources of funding was hypothesised to influence treatment effect. Five studies used PEMF devices and two studies used PES devices (see Table 4.1.). Treatment duration was ≥12 weeks in two studies and <12 weeks in five studies (see Table 4.1.). Three studies were funded by industry (17,26,27), two were federally funded (18,24) and two studies did not report the source of funding (22,23). The results of subgroup analyses for pain and physical function outcomes are shown in Table 4.4.

Adverse Events

Four studies reported few, self-limited adverse events, such as temporary increase in knee pain, foot numbness and paresthesia, and sensation of warmth. The risk ratio was calculated for mild knee skin rash that was reported in two studies (RR = 0.96, 95% CI: 0.45, 2.03, p = 0.91,) and is shown in Figure 4.5. There was no difference between

Table 4.4. Summary of Standardized Mean Difference (SMD), Inconsistency (I^2), and Heterogeneity (χ^2P Value) on Subgroup Analyses for Pain and Physical Function Outcomes

Subgroup Analyses	**Pain**			**Physical Function**		
	SMD* (95% CI†)	**I^2‡**	**χ^2P Value§**	**SMD* (95% CI†)**	**I^2‡**	**χ^2P Value§**
Type						
PEMF‖ (22-24,26,27)	0.08 (-0.19, 0.35)	36%	0.18	0.24 (0.02, 0.46)	0%	0.70
PES¶ (17,18)	0.09 (-0.67, 0.85)	77%	0.04	0.21 (-0.47, 0.89)	71%	0.06
Treatment Duration						
≥ 12 Weeks (17,18)	0.09 (-0.67, 0.85)	77%	0.04	0.21 (-0.47, 0.89)	71%	0.06
< 12 Weeks (22-24,26,27)	0.08 (-0.19, 0.35)	36%	0.18	0.24 (0.02, 0.46)	0%	0.70
Funding						
Industry (17,26,27)	6.63 (-2.66, 15.91)	74%	0.02	3.65 (0.57, 6.73)	33%	0.23
Non industry (18,22-24)	-0.32 (-0.92, 0.28)	0%	0.47	0.37 (-1.20, 1.94)	0%	0.79

* Standard Mean Difference, † Confidence interval, ‡ Inconsistency across studies; up to 40%, might not be important; 30 to 60%, may represent moderate heterogeneity; 50 to 90%, may represent substantial heterogeneity, § Chi-square P value; < 0.1, statistical significant heterogeneity; ≥ 0.1, nonsignificant heterogeneity, ‖ Pulsed Electromagnetic Field, ¶ Pulsed Electrical stimulation.

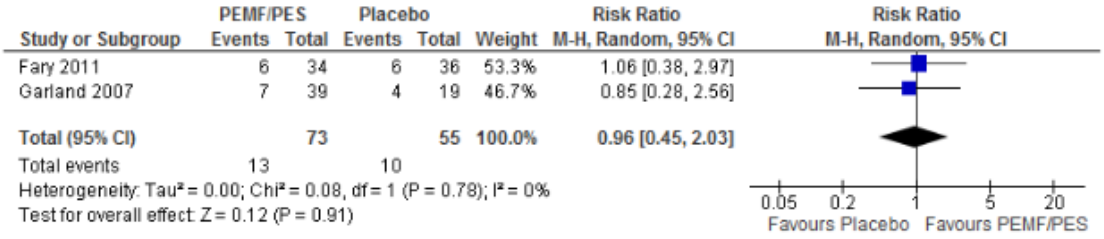

Figure 4.5. Forest plot for meta-analysis of the effect of PEMF/PES compared to sham treatment on adverse events (skin rash)

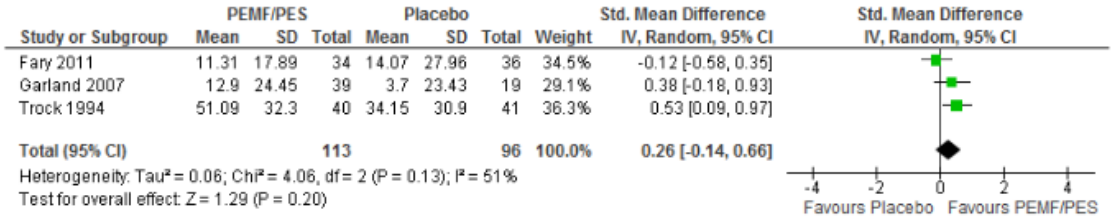

Figure 4.6. Forest plot for meta-analysis of the effect of PEMF/PES compared to sham treatment on patient global assessment

the experimental and placebo groups in terms of skin rash; however, the strengh of this body of evidence was very low as described in Table 4.3.

Secondary Outcomes

No RCT reported imaging-based knee joint status outcomes. Table 4.3 summarizes the pooled estimates of effects on health-related quality of life and physician global assessment. Figure 4.6 shows the pooled estimate for effect on patient global assessment reported in 3 trials (209 participants/knees). As summarized in Table 4.3., precision of the estimate is low (95% CI: -4.39, 18.77) and inconsistency is high.

4.5.5. Sensitivity Analyses

The pooled estimates were unchanged by the removal of each study in which change SDs was imputed (22-24).

4.5.6. Quality of Evidence

The strength of the body of evidence was assessed using the criteria recommended by the GRADE Working Group (25). The strength of the body of evidence of all outcomes was reduced by high risk of bias, small sample size (imprecision) and inconsistency of the results (high I^2 value). The strength of the body of evidence is low for physical function and very low for the other outcomes.

4.6. Discussion

The main finding of this systematic review and meta-analysis is that PEMF/PES treatment improves physical function but does not decrease pain significantly in people with knee OA. Heterogeneity was not a significant problem for pain or

physical function outcomes and subgroup analyses show that the effect estimates are similar regardless of the type of pulsed subsensory threshold electrical stimulation (PEMF and PES) and length of treatment (<12 and ≥12 weeks). The effect sizes for pain and physical function outcomes in the three studies funded by industry were larger and more inconsistent compared to the four studies that were not funded by industry. The strength of the body of evidence is low for physical function indicating that further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate. The very low strength of the body of evidence regarding the effect on pain creates great uncertainty about the estimate and future research is expected to change the estimated effect.

The proposed mechanism of action of PEMF and PES is to enhance articular cartilage regeneration (10). Because articular cartilage is poorly innervated and vascularized, it follows that this intervention may not decrease knee OA pain. Pain is perceived due to stimulation of unmyelinated and small myelinated nerve fibers in the joint and surrounding tissues such as the joint capsule, ligaments, synovium, bone and the outer edge of the menisci (32). Moreover, central sensitization (hyperexcitability of neurones in the central nervous system) has been observed in people with chronic pain due to knee OA (33). Chronic pain is a multidimensional problem (34) resulting in changes in brain areas active in sensorimotor function, affect and cognition (32). Even if future research demonstrates that PEMF/PES have a small effect on pain, this effect may be of minimal clinical significance without a corresponding intervention that addresses changes in the central nervous system.

All reported adverse events were mild and self-limited. Skin rash was the most frequently reported adverse event and rates were similar for both the active and sham PEMF/PES stimulation groups. The two studies that reported skin rash used PES devices and the longest treatment session (7 hours daily). Therefore, skin rash may be a problem for people using the PES device or may be related to the duration of contact between the electrodes and the skin. As a result, caution is warranted when applying the PES device to the knee of people prone to skin irritation. Overall, low frequency PEMF/PES appears to be safe for use in people with knee OA.

Few studies reported on our secondary outcomes of interest. Patient global assessment was reported in three studies and there was no difference between groups. Only two studies reported health related quality of life and the pooled studies were highly heterogeneous (Table 4.3.). Physician global assessment was reported in a single study that showed the effectiveness of PEMF/PES in improving this outcome. However, we have to interpret the improvement in physician global assessment with caution because the study was small and of low quality (Table 4.3.). No study reported imaging-based knee joint status outcomes. High quality studies are needed to evaluate the effectiveness of PEMF/PES on knee joint status, physician global assessment; patient global assessment and health related quality of life.

Follow up rates across the included studies ranged from 75% to 100% and studies reporting compliance rates varied from 63% to 75%. These rates for follow up and compliance suggest that PEMF/PES has acceptable tolerability in the knee OA population. Considering that three of the included studies used self-applied devices,

PEMF/PES may be a useful self-management tool for people with knee OA to improve physical function.

Our findings confirm and extend those reported in the meta-analysis conducted by Vavken et al (2009) (14) and We et al (2012) (15). Our review includes data for an additional 128 participants/knees that were not reported in the other reviews. Moreover, our study had important differences in methodology that provide greater confidence in the estimates of effect. The review by Vavken et al. (2009) included high and low frequency PEMF/PES and we excluded studies that used high frequency PEMF and did not report outcomes for participants with knee OA separate from those with hand and ankle OA. Vavken et al (2009) used the end point clinical scores and weighted mean difference to combine scores of different scales in their statistical analysis, which is inappropriate. We used the change mean to balance any differences in baseline values between the study groups and SMD to combine scores of different scales. We et al (2012) included trials administering either high or low frequency PEMF and did not perform subgroup analysis based on frequency. Sixteen sensitivity analyses were reported to determine efficacy on pain at 4 weeks (0-2 weeks prior to completion of the intervention) and 8 weeks (2 weeks following completion of the intervention). It is unclear if these analyses were planned a priori (35). Two of low frequency PEMF trials included in the review by We et al (15) were excluded from our systematic review because of our eligibility criteria (lack of participant blinding and English language limit). Despite these differences, the main results regarding efficacy of PEMF/PES on physical function, but not pain, are consistent.

The methodological rigour adopted in the review process is the main strength of this meta-synthesis. For example, a comprehensive search strategy and duplicate assessment of eligibility, extraction of data, assessment of risk of bias and judgement of the strength of the body of evidence were conducted. A data extraction form was developed and piloted for consistency between the two reviewers extracting data from the studies. In contrast to the overall risk of bias, six of the included studies had a low risk of bias due to blinding of participants and all seven included studies had low risk of bias due to blinding of outcome assessors. This is critical to the validity of the estimated effects on outcomes since lack of blinding is likely to inflate the effect size (36). These factors are strengths in our review; we hypothesize that inclusion of future larger trials will increase the confidence that PEMF/PES is effective for improving physical function and a small effect on pain may emerge.

Limitations need to be considered in interpreting the results of our review. At the level of the included trials, there is variability in treatment duration, number of sessions, treatment setting (where the treatment was provided and by whom), frequency, reported units and other parameters of PEMF/PES. Furthermore, no trials reported dose parameters at the skin surface. Therefore, we are unable to determine the therapeutic window or recommend a specific treatment protocol for administrating PEMF/PES. The small number and size of trials precluded focusing inclusion criteria further. Five of the seven included trials had a high risk of bias. Few to no studies collected data related to our secondary outcomes of interest. To examine the proposed mechanism of PEMF/PES on enhancing cartilage regeneration, future studies need to

include outcome measures that detect cartilage metabolism or change in morphology. At the review level, our literature search was limited to the English language which may have excluded relevant literature and, introduced a bias in the results. Some studies were excluded from our review due to missing methodological and statistical details; therefore, we urge future publications of RCTs to follow the CONSORT statement reporting guidelines for non-pharmacologic treatments (37).

4.7. Conclusion

Our results suggest that low frequency (≤100 Hz) pulsed subsensory threshold electrical stimulation produced either through PEMF/PES versus sham PEMF/PES is effective in improving physical function but not pain intensity at treatment completion in adults with knee OA blinded to treatment. We cannot give a conclusion about the effect of this treatment on the secondary outcomes due to the small numbers of studies that reported them. PEMF/PES is associated with few, self-limited adverse events such as skin rash. More studies are needed to confirm and extend the findings of this systematic review.

Author contributions

All authors made substantial contributions to the conceptualization, design, data collection, analysis, interpretation, drafting and revisions; and approved the final version.

Conflict of interest

None of the authors has any financial and personal relationships with other people or organizations that could potentially and inappropriately influence this work and its conclusions.

4.8. References

1. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. BMJ 2012; 30;345:e4934.

2. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. The epidemiology of osteoarthritis in asia. Int J Rheum Dis 2011;14(2):113-21.

3. Quintana JM, Arostegui I, Escobar A, Azkarate J, Goenaga JI, Lafuente I. Prevalence of knee and hip osteoarthritis and the appropriateness of joint replacement in an older population. Arch Intern Med 2008;168(14):1576.

4. Bartlett SJ, Ling SM, Mayo N, Scott S, Bingham III CO. Identifying common trajectories of joint space narrowing over two years in knee osteoarthritis. Arthritis Care Res 2011; 63(12):1722-8.

5. Mann C, Gooberman-Hill R. Health care provision for osteoarthritis: Concordance between what patients would like and what health professionals think they should have. Arthritis Care Res 2011; 63(7):963-72.

6. Thawer HA. Pulsed electromagnetic fields for osteogenesis and repair. Phys Ther Rev 1999; 4(3):203-13.

7. Trock DH. Electromagnetic fields and magnets. investigational treatment for musculoskeletal disorders. Rheum Dis Clin North Am. 2000 viii; 26(1):51-62.

8. Hulme J, Robinson V, DeBie R, Wells G, Judd M, Tugwell P. Electromagnetic fields for the treatment of osteoarthritis. Cochrane Database Syst Rev. 2002(1):003523.

9. Schmidt-Rohlfing B, Silny J, Woodruff S, Gavenis K. Effects of pulsed and sinusoid electromagnetic fields on human chondrocytes cultivated in a collagen matrix. Rheumatol Int 2008; 28(10):971-7.

10. Ciombor DM, Aaron RK, Wang S, Simon B. Modification of osteoarthritis by pulsed electromagnetic field--a morphological study. Osteoarthritis Cartilage 2003; 11(6):455-62.

11. Wang W, Wang Z, Zhang G, Clark CC, Brighton CT. Up-regulation of chondrocyte matrix genes and products by electric fields. Clin Orthop Relat Res 2004; (427 Suppl):S163-73.

12. McLeod KJ, Rubin CT. The effect of low-frequency electrical fields on osteogenesis. J Bone Joint Surg Am 1992; 74(6):920-9.

13. McCarthy CJ, Callaghan MJ, Oldham JA. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: A systematic review. BMC Musculoskeletal Disord 2006; 7:51.

14. Vavken P, Arrich F, Schuhfried O, Dorotka R. Effectiveness of pulsed electromagnetic field therapy in the management of osteoarthritis of the knee: A meta-analysis of randomized controlled trials. J Rehabil Med 2009; 41(6):406-11.

15. We SR, Koog YH, Jeong KI, Wi H. Effects of pulsed electromagnetic field on knee osteoarthritis: A systematic review. Rheumatology (Oxford) 2012; [Epub ahead of print].

16. March 1999 510(k) Clearances, U.S. Department of Health and Human Services. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/ucm092827.htm (4 December 2012, date last accessed).

17. Garland D, Holt P, Harrington JT, Caldwell J, Zizic T, Cholewczynski J. A 3-month, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a highly optimized, capacitively coupled, pulsed electrical stimulator in patients with osteoarthritis of the knee. Osteoarthritis Cartilage 2007; 15(6):630-7.

18. Fary RE, Carroll GJ, Briffa TG, Briffa NK. The effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: Results of a double-blind, randomized, placebo-controlled, repeated-measures trial. Arthritis & Rheum 2011; 63(5):1333-42.

19. Rutjes AW, Nuesch E, Sterchi R, Kalichman L, Hendriks E, Osiri M, et al. Transcutaneous electrostimulation for osteoarthritis of the knee. Cochrane Database Syst Rev 2009; (4):002823.

20. Higgins JPT, Green S, Collaboration C. Cochrane handbook for systematic reviews of interventions. Wiley Online Library; 2008.

21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol 2009; 62(10):e1-34.

22. Ozguclu E, Cetin A, Cetin M, Calp E. Additional effect of pulsed electromagnetic field therapy on knee osteoarthritis treatment: A randomized, placebo-controlled study. Clin Rheumatol 2010; 29(8):927-31.

23. Ay S, Evcik D. The effects of pulsed electromagnetic fields in the treatment of knee osteoarthritis: A randomized, placebo-controlled trial. Rheumatol Int 2009; 29(6):663-6.

24. Thamsborg G, Florescu A, Oturai P, Fallentin E, Tritsaris K, Dissing S. Treatment of knee osteoarthritis with pulsed electromagnetic fields: A randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage 2005; 13(7):575-81.

25. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 26;336(7650):924-6.

26. Trock DH, Bollet AJ, Markoll R. The effect of pulsed electromagnetic fields in the treatment of osteoarthritis of the knee and cervical spine. report of randomized, double blind, placebo controlled trials. J Rheumatol 1994; 21(10):1903-11.

27. Pipitone N, Scott DL. Magnetic pulse treatment for knee osteoarthritis: A randomised, double-blind, placebo-controlled study. Curr Med Res Opin 2001;17(3):190-6.

28. Zizic TM, Hoffman KC, Holt PA, Hungerford DS, O'Dell JR, Jacobs MA, et al. The treatment of osteoarthritis of the knee with pulsed electrical stimulation. J Rheumatol 1995; 22(9):1757-61.

29. Jacobson JI, Gorman R, Yamanashi WS, Saxena BB, Clayton L. Low-amplitude, extremely low frequency magnetic fields for the treatment of osteoarthritic knees: A double-blind clinical study. Altern Ther Health Med 2001; 7(5):54-64, 66-9.

30. Nicolakis P, Kollmitzer J, Crevenna R, Bittner C, Erdogmus CB, Nicolakis J. Pulsed magnetic field therapy for osteoarthritis of the knee--a double-blind sham-controlled trial. Wien Klin Wochenschr 2002; 30;114(15-16):678-84.

31. Trock DH, Bollet AJ, Dyer RH,Jr, Fielding LP, Miner WK, Markoll R. A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis. J Rheumatol 1993; 20(3):456-60.

32. Felson DT. The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 2005; 17(5):624-8.

33. Imamura M, Imamura ST, Kaziyama HH, Targino RA, Hsing WT, de Souza LP, et al. Impact of nervous system hyperalgesia on pain, disability, and quality of life in patients with knee osteoarthritis: A controlled analysis. Arthritis & Rheum 2008; 15;59(10):1424-31.

34. Davidson MA, Tripp DA, Fabrigar LR, Davidson PR. Chronic pain assessment: A seven-factor model. Pain Res Manag 2008; 13(4):299-308.

35. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010; 340:117.

36. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. Ann Intern Med 2002; 5;136(3):254-9

37. Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT G. Methods and processes of the CONSORT group: Example of an extension for trials assessing nonpharmacologic treatments. Ann Intern Med 2008; 19;148(4):W60-6.

CHAPTER 5

DISCUSSION/CONCLUDING REMARKS

DISCUSSION / CONCLUDING REMARKS

The findings from each of the two studies that form this thesis have addressed some of the gaps in the literature about pain measurement and management of the knee OA population based on a theoretical model. The systematic review suggests a possible beneficial effect of PEMF/PES on physical function but not pain in the knee OA population based on low and very low quality evidence respectively. The assumption that knee pain reduction will automatically lead to improvements in function is being challenged. Of 465 knee OA participants with a meaningful reduction in knee pain (41% pain reduction on VAS), 20% had a meaningful decline in walking speed at 30 months (1). Therefore, clinicians should note outcomes in both pain and function, as both may not change concomitantly. Our review results are in agreement with the findings of recently published Systematic Reviews on the same topic (2) (3). Conclusions derived from these three reviews changed previous knowledge, which stated that PEMF/PES was not effective in the management of knee OA (4), and will promote the consideration of this treatment modality for its inclusion in the treatment guidelines for the management of knee OA. In addition, the findings of these reviews stress the importance of conducting better-designed clinical trials to establish the efficacy of PEMF/PES on the pain reduction and physical function improvement. Knee OA pain management is likely to require interventions that work through different portals of the gate control-neuromatrix model. PEMF/PES is targeting a single (sensory) portal, therefore, pain was not improved either due to the lack of large, high quality trials for inclusion or because the change in pain is not the mediator for change in physical function as some hypothesize (1).

It is clear, from the studies included in the systematic review that pain is the most consistent and important outcome for the knee OA population. However, there was inconsistency in the reported pain measure, and many studies used more than one pain measure to evaluate the pre and post intervention pain level(5-8). Furthermore, studies exploring the view of individuals with knee OA about pain scales were lacking.

The result of comparing the extent to which three different pain measures represent the pain experience of people with knee osteoarthritis (Chapter 3) showed that even though, VNRS, SF-MPQ-2 and ICOAP assess different dimensions of pain; they are equally valued by people with knee OA pain. Therefore, VNRS may be recommended because it is easier and quicker to complete.

Despite the fact that there was no difference in patient's preference, this study (Chapter 3) showed the construct difference between the three pain measures (all correlation<7). These differences confirmed the multidimensionality nature of chronic pain that was suggested based on the gate control-neuromatrix model, since each pain measure evaluated different pain dimensions which, may lead to lower correlations. More studies are needed to explore the differences in pain measures and optimize the pain measurement in knee OA population.

Considering the limitations described in each of the studies that form this thesis, the gate control-neuromatrix model needs to be tested through its application on pain measurement and management, better-designed clinical trials are necessary to assess the efficacy of PEMF/PES for improving pain, physical function, patient's quality of life, patient's global rating scale, physician global rating scale and cartilage repair in patients

suffering from knee OA. In addition, other studies exploring the knee OA population's view of pain measures are required. Examining the extent to which pain measures represent pain experience in other chronic pain populations are needed to best measure pain and hence optimize pain management.

In conclusion, the findings of this thesis have made contributions to the knowledge about the integration of pain theories in clinical practice, pain measurement and the effects of PEMF/PES in the management of people with knee OA. Finally, the results of this thesis will help researchers and clinicians to choose the appropriate pain measure for knee OA population.

5.1. References

1. White DK, Felson DT, Niu J, Nevitt MC, Lewis CE, Torner JC, et al. Reasons for functional decline despite reductions in knee pain: The multicenter osteoarthritis study. Phys Ther. 2011 Dec;91(12):1849-56.

2. Ryang We S, Koog YH, Jeong KI, Wi H. Effects of pulsed electromagnetic field on knee osteoarthritis: A systematic review. Rheumatology (Oxford). 2012 Apr 13.

3. Vavken P, Arrich F, Schuhfried O, Dorotka R. Effectiveness of pulsed electromagnetic field therapy in the management of osteoarthritis of the knee: A meta-analysis of randomized controlled trials. J Rehabil Med. 2009 May;41(6):406-11.

4. McCarthy CJ, Callaghan MJ, Oldham JA. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: A systematic review. BMC Musculoskeletal Disorders. 2006;7:51.

5. Fary RE, Carroll GJ, Briffa TG, Briffa NK. The effectiveness of pulsed electrical stimulation in the management of osteoarthritis of the knee: Results of a double-blind, randomized, placebo-controlled, repeated-measures trial. Arthritis & Rheumatism. 2011 May;63(5):1333-42.

6. Ozguclu E, Cetin A, Cetin M, Calp E. Additional effect of pulsed electromagnetic field therapy on knee osteoarthritis treatment: A randomized, placebo-controlled study. Clin Rheumatol. 2010 Aug;29(8):927-31.

7. Garland D, Holt P, Harrington JT, Caldwell J, Zizic T, Cholewczynski J. A 3-month, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of a highly optimized, capacitively coupled, pulsed electrical stimulator in patients with osteoarthritis of the knee. Osteoarthritis & Cartilage. 2007 Jun;15(6):630-7.

8. Pipitone N, Scott DL. Magnetic pulse treatment for knee osteoarthritis: A randomised, double-blind, placebo-controlled study. Current Medical Research & Opinion. 2001;17(3):190-6.

Appendixes

Appendix A

Search Strategies

Database: Ovid MEDLINE(R) In-Process & Other NonIndexed Citations and Ovid MEDLINE(R) <1946 to week1 April 2012>

1 exp Electric Stimulation Therapy/ or Pulsed electrical stimulation treatment.mp. (52016)

2 electromagnetics.mp. or exp Electromagnetic Phenomena/ (308044)

3 electromagnetic$.tw. (18146)

4 exp electric stimulation therapy/ (52016)

5 electrical stimulation.tw. (34065)

6 exp Electromagnetic Phenomena/ or exp Electric Stimulation Therapy/ or exp Electromagnetic Fields/ or pulsed electromagnetic.mp. or exp Magnetic Field Therapy/ (363141)

7 osteoarthritis.mp. or exp Osteoarthritis/ or exp Osteoarthritis, Knee/ (47206)

8 Knee osteoarthritis.mp. or exp Osteoarthritis, Knee/ (8830)

9 exp Osteoarthritis/ or gonarthrosis.mp. or exp Osteoarthritis, Knee/ (38215)

10 1 or 2 or 3 or 4 or 5 or 6 (401885)

11 7 or 8 or 9 (47510)

12 10 and 11 (414)

13 limit 12 to (english language and humans and randomized controlled trial) (78)

Database: Embase <1974 to 2012 April >

1 Electric Stimulation Therapy.mp. or exp electrostimulation therapy/ (147605)

2 Electromagnetics.mp. or exp electromagnetic field/ (15534)

3 Electromagnetic Phenomena.mp. or exp electromagnetic field/ (15496)

4 Electromagnetic.mp. or exp electromagnetic field/ (28950)

5 electric stimulation therapy.mp. or exp electrostimulation therapy/ (147605)

6 Electrical stimulation.mp. or exp electrostimulation/ (89918)

7 exp pulsed electric field/ or exp electromagnetic field/ or exp electrostimulation therapy/ or pulsed

electromagnetic.mp. (162787)

8 [limit 15 to (human and english language and randomized controlled trial and english)] (0)

9 Electric Stimulation Therapy.mp. or exp electrostimulation therapy/ (147605)

10 Electromagnetics.mp. or exp electromagnetic field/ (15534)

11 Electromagnetic Phenomena.mp. or exp electromagnetic field/ (15496)

12 Electromagnetic.mp. or exp electromagnetic field/ (28950)

13 electric stimulation therapy.mp. or exp electrostimulation therapy/ (147605)

14 Electrical stimulation.mp. or exp electrostimulation/ (89918)

15 exp pulsed electric field/ or exp electromagnetic field/ or exp electrostimulation therapy/ or pulsed

electromagnetic.mp. (162787)

16 Magnetic Field Therapy.mp. or exp magnetotherapy/ (638)

17 exp electromagnetic field/ or exp electrostimulation/ or exp electrostimulation therapy/ or Pulsed electrical
stimulation treatment.mp. (223854)

18 exp knee osteoarthritis/ or Osteoarthritis.mp. or exp osteoarthritis/ (76544)

19 Knee osteoarthritis.mp. or exp knee osteoarthritis/ (13867)

20 gonarthrosis.mp. or exp knee osteoarthritis/ (13885)

21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (250541)

22 18 or 19 or 20 (76774)

23 21 and 22 (1007)

24 limit 23 to (human and english language and randomized controlled trial and english) (137)

Database: AMED (Allied and Complementary Medicine) <1985 to April 2012>

1 exp Electric Stimulation Therapy/ or Pulsed electrical stimulation treatment.mp. (0)

2 electromagnetics.mp. or exp Electromagnetic Phenomena/ (190)

3 electromagnetic$.tw. (712)

4 exp electric stimulation therapy/ (0)

5 electrical stimulation.tw. (1363)

6 exp Electromagnetic Phenomena/ or exp Electric Stimulation Therapy/ or exp Electromagnetic Fields/ or pulsed
electromagnetic.mp. or exp Magnetic Field Therapy/ (221)

7 osteoarthritis.mp. or exp Osteoarthritis/ or exp Osteoarthritis, Knee/ (2205)

8 Knee osteoarthritis.mp. or exp Osteoarthritis, Knee/ (595)

9 exp Osteoarthritis/ or gonarthrosis.mp. or exp Osteoarthritis, Knee/ (1612)

10 1 or 2 or 3 or 4 or 5 or 6 (2063)

11 7 or 8 or 9 (2227)

12 10 and 11 (26)

13 limit 12 to (english language and humans and randomized controlled trial) [Limit not valid; records wereretained] (25

Database: CINAHL (EBSCOHost Search engine) (up to April 2012)

S14 S11 and S12 Limiters - English Language; Human; Randomized Controlled Trial; Publication Type: Randomized Controlled Trial; Language: English

S13 S11 and S12 6

S12 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S10 45

S11 (MH "Osteoarthritis, Knee") OR "Knee osteoarthritis" 8521

S10 (MH "Magnet Therapy") OR "Magnetic Field Therapy" 1952

S9 (MH "Electrophoresis, Gel, Pulsed-Field") OR (MH "Electromagnetic Fields") OR (MH "Electromagnetics+") OR "pulsed electromagnetic field" 632

S8 (MH "Electrophoresis, Gel, Pulsed-Field") OR (MH "Electromagnetic Fields") OR (MH "Electromagnetics+") OR "pulsed electromagnetic field" 1674

S7 (MH "Electrophoresis, Gel, Pulsed-Field") OR (MH "Electromagnetic Fields") OR (MH "Electromagnetics+") OR "pulsed electromagnetic field" 1674

S6 (MH "Electromagnetic Fields") OR (MH "Electromagnetics+") OR (MH "Magnet Therapy") 1674

S5 (MH "Electromagnetics+") OR (MH "Electromagnetic Fields") OR "Electromagnetic Phenomena" 1812

S4 (MH "Magnet Therapy") OR (MH "Electric Stimulation+") OR (MH "Electrical Stimulation, Functional") OR (MH "Electrical Stimulation, Neuromuscular") OR "Electric Stimulation Therapy" 1226

S3 (MH "Electromagnetics+") OR "Electromagnetics" OR (MH "Electromagnetic Fields") OR (MH "Bioelectromagnetic Applications") 6925

S2 (MH "Electric Stimulation+") OR (MH "Electrical Stimulation, Functional") OR (MH "Electrical Stimulation, Neuromuscular") OR "Pulsed electrical stimulation treatment" 1246

S1 (MH "Magnet Therapy") OR (MH "Electric Stimulation+") OR (MH "Electrical Stimulation, Functional") OR (MH "Electrical Stimulation, Neuromuscular") OR "Electric Stimulation Therapy" 6383

Database: Cochrane Central Register of Controlled Trials (up to April 2012)

#1 knee osteoarthritis:ti,ab,kw in Trials 2265

#2 pulsed electromagnetic field:ti,ab,kw in Trials

#3 pulsed electrical stimulation:ti,ab,kw in Trials

#4 (#1 AND (#2 OR #3)) 29