

# BMJ Open Interventions for the prediction and management of chronic postsurgical pain after total knee replacement: systematic review of randomised controlled trials

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## ABSTRACT

**Objectives:** Total knee replacement can be a successful operation for pain relief. However, 10–34% of patients experience chronic postsurgical pain. Our aim was to synthesise evidence on the effectiveness of applying predictive models to guide preventive treatment, and for interventions in the management of chronic pain after total knee replacement.

**Setting:** We conducted a systematic review of randomised controlled trials using appropriate search strategies in the Cochrane Library, MEDLINE and EMBASE from inception to October 2014. No language restrictions were applied.

**Participants:** Adult patients receiving total knee replacement.

**Interventions:** Predictive models to guide treatment for prevention of chronic pain. Interventions for management of chronic pain.

**Primary and secondary outcome measures:** Reporting of specific outcomes was not an eligibility criterion but we sought outcomes relating to pain severity.

**Results:** No studies evaluated the effectiveness of predictive models in guiding treatment and improving outcomes after total knee replacement. One study evaluated an intervention for the management of chronic pain. The trial evaluated the use of a botulinum toxin A injection with antinociceptive and anticholinergic activity in 49 patients with chronic postsurgical pain after knee replacement. A single injection provided meaningful pain relief for about 40 days and the authors acknowledged the need for a large trial with repeated injections. No trials of multidisciplinary interventions or individualised treatments were identified.

**Conclusions:** Our systematic review highlights a lack of evidence about the effectiveness of prediction and management strategies for chronic postsurgical pain after total knee replacement. As a large number of people are affected by chronic pain after total knee replacement, development of an evidence base about care for these patients should be a research priority.

## Strengths and limitations of this study

- Reproducible systematic review methods.
- Identification of research priorities.
- Interventions for chronic pain after other surgeries may have value in total knee replacement.

## INTRODUCTION

Total knee replacement is an increasingly common procedure that aims to reduce pain and functional limitations, particularly for people with osteoarthritis of the knee. In the year to 31 March 2014, nearly 78 000 people received a primary total knee replacement in the UK,<sup>1</sup> and in 2010 approximately 719 000 procedures were performed in the USA.<sup>2</sup> It is estimated that over half of all people in the USA diagnosed with osteoarthritis will receive a total knee replacement.<sup>3</sup>

Surgery is a known risk factor for chronic pain<sup>4</sup> defined as pain ‘present for at least 3 months’.<sup>5</sup> Chronic postsurgical pain ‘develops after a surgical procedure or increases in intensity after the surgical procedure’.<sup>6</sup> Although many patients report a good outcome after their total knee replacement, at a time when recovery should have been achieved,<sup>7</sup> about 10–34% of patients report moderate to severe chronic postsurgical pain.<sup>8</sup> In the UK, this could mean 7500–25 500 potential new cases of chronic postsurgical pain every year, while in the USA this equates to between 72 000 and a quarter of a million new cases annually. As patients undergo knee replacement in order to relieve knee pain, these estimates are cause for concern.

Given the distress caused by chronic postsurgical pain,<sup>9</sup> and the predicted increases in prevalence of osteoarthritis,<sup>10</sup> and the need for knee replacement surgery,<sup>11</sup> robust

evidence is needed on effective methods for preventing the development of chronic pain, identifying patients at risk of developing chronic pain, and for the management of chronic pain. Inadequately controlled perioperative pain is a risk factor for long-term pain and, although studied widely, systematic reviews have shown that evidence on long-term benefit is limited.<sup>12–15</sup>

A large number of preoperative and early postoperative factors are associated with poor pain outcomes, including greater joint pain<sup>16–18</sup> and pain catastrophisation,<sup>19–21</sup> poor mental health,<sup>16 19 21–23</sup> and presence of musculoskeletal comorbidities.<sup>18 24</sup> As the cause of chronic pain after total knee replacement is likely to be multifactorial, with mechanical, biological and psychological features, simple interventions targeting individual issues will leave a large proportion of patients at risk of developing long-term pain with no appropriate care. The potential value of multivariable risk assessment is clear although the ability of predictive models to identify patients at risk of long-term pain has been highly variable.<sup>25 26</sup> Furthermore, as with all prognostic models guiding decision-making, evidence on their efficacy and safety in targeting interventions is required before application in clinical practice.<sup>27</sup>

Owing to the complexity of chronic pain, treatments in appropriate combinations matched to patient characteristics are advocated.<sup>28 29</sup> As with application of methods for prediction, evidence is required that pain management strategies are effective in patients with chronic postsurgical pain after total knee replacement. This may relate to specific treatments or to multifactorial assessment and management.

Our aim was to conduct a systematic review to identify randomised trials in patients with total knee replacement that have evaluated: (1) the application of predictive models in the targeting of pain management and (2) interventions for the treatment of chronic pain. Relevant outcomes related to pain severity. While our particular interest was total knee replacement, we used a broader search strategy to include any type of knee surgery as appropriate pain prediction, and management methods may have been evaluated in more diverse knee surgeries.

## METHODS

We aimed to conduct our literature reviews with transparent and unbiased methods such that they can be considered truly systematic and reproduced on the basis of sources of literature, search processes, study inclusion or exclusion, data analysis if feasible, and study quality assessment. To achieve this, we used methods described in the Cochrane Handbook of Systematic reviews.<sup>30</sup> As this review focuses on randomised controlled trials, we conducted the review with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines which aim to improve the reporting of systematic reviews.<sup>31</sup>

## Search strategy

Separate literature search strategies for predictive methods and pain management based on validated searches<sup>30 32 33</sup> were applied in MEDLINE, EMBASE and the Cochrane Library from inception up to 1 October 2014. We considered that the EMBASE coverage of conference abstracts since 2009 was an appropriate search of ‘grey literature’ in the orthopaedic context. Search strategies as applied in MEDLINE are shown in [box 1](#) with combinations of terms, such as ‘risk function, risk assessment, randomised trial, knee,’ and ‘pain, postoperative, post-surgical, randomised trial, knee.’ Search terms were in English, but no further language restrictions were applied with funds available to pay translation costs if required. If necessary author contact for additional information was planned.

## Eligibility criteria

Eligible studies satisfied PICOS criteria.

- ▶ **Patients:** adults with knee surgery
- ▶ **Intervention:** treatment guided by a predictive model or an intervention for management of chronic pain (pain reported at 3 months or more after surgery)
- ▶ **Control:** a usual care comparison group
- ▶ **Outcome:** an outcome relating to pain severity
- ▶ **Setting:** evaluation in a randomised controlled trial

## Data extraction

Articles and inclusion/exclusion decisions were catalogued in Endnote X7. All titles and abstracts were screened independently by two reviewers. Potentially relevant articles were evaluated in detail by two reviewers, independently, with decisions on relevance made after discussion. Data on study and patient characteristics, intervention and control group treatment, follow-up and outcomes and results were extracted onto a summary table.

## Outcomes

We did not exclude studies on the grounds of what outcomes were reported, as the possibility existed that authors might be able to provide unpublished outcome data. However, the outcomes of interest to this review relate to pain severity.

## Quality assessment

Study quality was assessed using criteria in the Cochrane risk of bias table,<sup>30</sup> and is summarised with other study data in [table 1](#).

## Analyses

If sufficient studies with similar outcome measures were identified, we intended to conduct an appropriate meta-analysis using Review Manager. If this was not possible, we planned a descriptive overview of studies.

**Box 1** Search strategies as applied in MEDLINE

## Prediction

- ▶ risk function.mp. or risk assessment
- ▶ risk equation\$.mp.
- ▶ risk chart.mp.
- ▶ (risk adj3 tool\$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]
- ▶ risk assessment function.mp.
- ▶ risk assessor.mp.
- ▶ risk appraisal\$.mp.
- ▶ risk calculation\$.mp.
- ▶ risk calculator\$.mp.
- ▶ risk factor\$ calculation\$.mp.
- ▶ risk engine\$.mp.
- ▶ risk equation\$.mp.
- ▶ risk table\$.mp.
- ▶ risk threshold\$.mp.
- ▶ risk scoring method?.mp.
- ▶ scoring scheme?.mp.
- ▶ risk scoring system.mp.
- ▶ risk prediction.mp.
- ▶ predictive instrument.mp.
- ▶ project\$ risk.mp.
- ▶ exp decision support techniques/  
Diagnosis, Computer-Assisted/  
Decision Support Systems, Clinical/  
algorithms/  
algorithm?.mp. or Algorithms/  
algorithym?.mp.
- ▶ decision support?.mp.
- ▶ predictive model.mp.
- ▶ treatment decision.mp.
- ▶ scoring method\$.mp.
- ▶ (prediction\$ adj3 method\$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]
- ▶ exp Risk Assessment/  
(risk? adj1 assess\$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, sh, tn, dm, mf, dv, kw]
- ▶ 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
- ▶ knee.tw.
- ▶ 34 and 35
- ▶ randomized controlled trial.pt.
- ▶ controlled clinical trial.pt.
- ▶ randomized.ab.
- ▶ placebo.ab.
- ▶ randomly.ab.
- ▶ trial.ab.
- ▶ groups.ab.
- ▶ (animals not (humans and animals)).sh.
- ▶ 37 or 38 or 39 or 40 or 41 or 42 or 43
- ▶ 45 not 44
- ▶ 36 and 46

## Treatment

- ▶ Pain, Postoperative/  
((postoperative adj6 pain\*) or (post-operative adj6 pain\*) or post-operative-pain\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

- ▶ ((post-operative adj6 analgesi\*) or (postoperative adj6 analgesi\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- ▶ ((post-surgical adj6 pain\*) or (post surgical adj6 pain\*) or (post-surgery adj6 pain\*) or (post adj surg\* adj pain\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- ▶ ((post\* adj pain\*) or pain relief after or pain following surg\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- ▶ ((posttreatment adj6 pain\*) or (pain control after adj6 surg\*) or ((post-extraction or postextraction or post-surg\*) and (pain\* or discomfort))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
- ▶ randomized controlled trial.pt.
- ▶ controlled clinical trial.pt.
- ▶ randomized.ab.
- ▶ placebo.ab.
- ▶ randomly.ab.
- ▶ trial.ab.
- ▶ 7 or 8 or 9 or 10 or 11 or 12
- ▶ 1 or 2 or 3 or 4 or 5 or 6
- ▶ 13 and 14
- ▶ knee.tw.
- ▶ 15 and 16

**RESULTS**

Main features of the review process are summarised according to PRISMA guidelines as online supplementary material. As shown in [figure 1](#), searches for evaluations of predictive models and treatments identified 1159 and 1886 articles, respectively.

**Application of predictive models**

After screening all the titles and abstracts, 16 articles were identified as potentially relevant to the review of predictive models and were evaluated in detail. Reasons for exclusion are summarised with references in the online supplementary material. No studies evaluated the effectiveness of predictive models in guiding treatment and improving long-term outcomes after knee surgery.

**Chronic pain management interventions**

In the review of treatments for chronic pain after knee surgery, a large majority of studies (66%) reported analgesia or other interventions in the perioperative period. Thirty articles were judged to be potentially relevant. Reasons for exclusion of 29 studies are summarised with references in the online supplementary material.

One intervention fulfilled all inclusion criteria, and study details are summarised in [table 1](#). Singh *et al*<sup>34</sup>

evaluated the use of a botulinum toxin A injection with antinociceptive and anticholinergic activity in a randomised controlled trial. In the original randomisation, patients with simultaneous bilateral total knee replacement were included, but the published article focused on 49 patients with a unilateral replacement (or first operation in a sequential bilateral replacement). On the basis of criteria specified in the Cochrane risk of bias table, we assessed that this study was of low risk of bias though the small size of the study is a cause for concern. Patients in the trial had received a total knee replacement at least 6 months earlier and had experienced pain in their replaced knee for more than 3 months. Reduced pain intensity was apparent for the intervention compared with placebo after 2 and 3 months, although the authors suggested that meaningful pain relief was evident up to about 40 days with no increase in adverse events. No cost-effectiveness analysis was performed. The authors concluded that the effect of repeated injections should be

assessed in a multicentre trial, but no further study was found on inspection of the Current Controlled Trials database on 5 November 2014.

## DISCUSSION

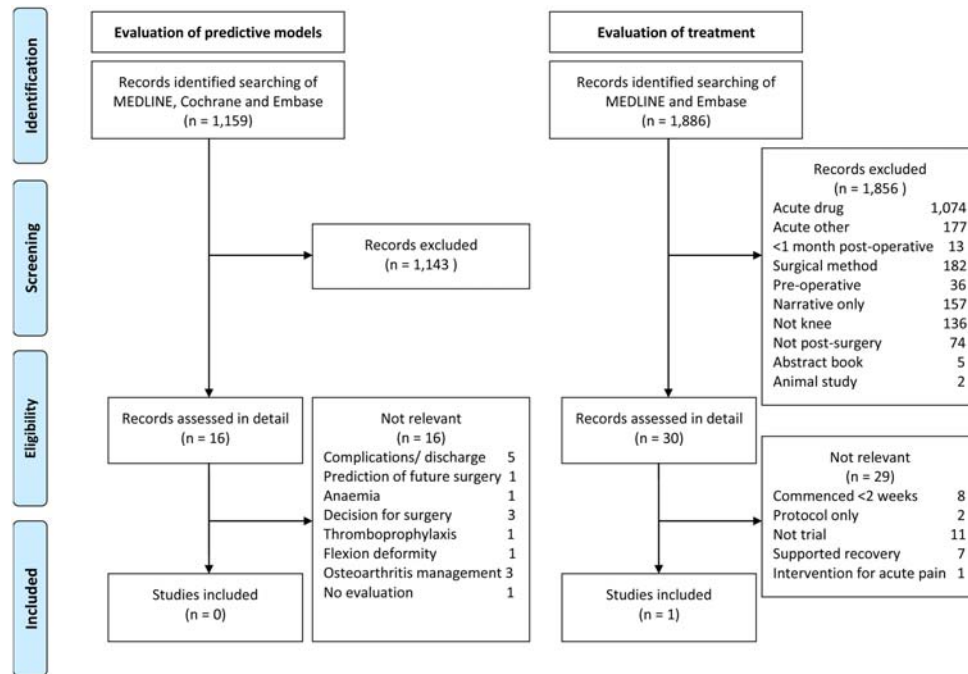
By limiting potential sources of bias, randomised controlled trials provide the best method to assess the effectiveness of healthcare interventions. Systematic reviews aim to appraise evidence from high-quality studies and can have two broad outcomes: a synthesis of knowledge to guide decision-making; or identification of deficits in the evidence base that merit further research.

The main indications for total knee replacement are pain and functional limitations caused by osteoarthritis. The widespread acknowledgement that some people will have chronic postsurgical pain after this potentially curative treatment dates largely from the introduction of patient-reported outcome measures. There is some

**Table 1** Characteristics of included study

Author	Singh <i>et al</i> <sup>24</sup>
Country	USA
Indication	Total knee replacement >6 months. Chronic pain >3 months ( $\geq 6$ points on 10-point VAS scale). Unsuccessful treatment with oral pain medication, not surgical candidate or infection identified. Mean pain duration 4.5 years
Number of patients	49 patients with 60 total knee replacements (30 intervention: 30 control)
Age	Mean: intervention 67.1 years; control 66.8 years
Sex	Female: intervention 22%; control 12%
Approach	Standardised medial or lateral
Intervention	Intra-articular injection of 100 units botulinum toxin A diluted in 5 mL sterile normal saline
Control	Intra-articular injection of 5 mL sterile normal saline
Follow-up interval	Up to 6 months
Outcome measures	Proportion of responders at 2 months ( $\geq 2$ point VAS reduction) Physicians' global assessment of change Onset and duration of pain (20 point WOMAC pain decrease) WOMAC function Timed-stands test Timed-up-and-go Active knee flexion Medical Outcomes Study Short-Form 36 (SF-36) Short-form McGill Pain Questionnaire Changes in analgesic medications Side effects and adverse outcomes
Economic evaluation	None reported
Risk of bias	Overall: low
Random sequence	Independent
Concealment	Syringes prepared independently
Blinding	Patients, surgeon, investigators, statistician all blind to group allocation
Blind outcome	Assessment blind to group allocation
Complete data	Low losses to follow-up at primary outcome intervals
Selective reporting	Appropriate range of outcomes reported
Other bias	None apparent
Losses to follow-up	2 (1:1) lost to 2 month follow-up. 7 (3:4) lost to 6 month follow-up
Power calculation	Reported to be powered for significant improvement on WOMAC scale
Results summary	Pain severity reduced in 71% of intervention patients compared with 35% in placebo group at 2 months. Benefit also at 3 months but not at 4 months. Duration of meaningful pain relief was 39.6 (SD=50.4) days in intervention group compared with 15.7 (SD=22.6) days in placebo group

VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.



**Figure 1** Systematic review flow diagram.

evidence that acute postoperative pain may impact on long-term pain,<sup>35</sup> and a considerable number of randomised treatment evaluations have targeted reduction in acute pain with perioperative multimodal anaesthesia.<sup>12–15</sup> Few studies have followed up patients long term, although the importance of this is now recognised.<sup>36</sup> While acknowledging the potential importance of such methods in preventing the development of long-term pain, an appropriate body of research should also explore the issues of prediction and management. The one trial of pain management that we identified showed promise, but further research is needed to confirm the findings. Treatment of chronic pain can be challenging, and there is a need to evaluate multidisciplinary combination treatments and the benefit of matching interventions to patient characteristics.<sup>28–29</sup>

Our study might be criticised as asking research questions that are too specific and beyond the scope of randomised evaluation. However, evaluation of predictive models in guiding healthcare is recognised in other medical disciplines. For example, risk scoring has been studied in cardiovascular disease in randomised trials both as a guide for appropriate medical treatment of risk factors<sup>37–38</sup> and lifestyle interventions.<sup>39</sup> Without evidence that application of predictive models in total knee replacement is more effective in guiding treatment and improving outcomes than existing care, they have no value in evidence-based clinical practice.

In total knee replacement, specific biological and mechanical issues, and psychological factors relating to joint replacement should be considered in the treatment of chronic pain. The identification of one randomised trial in our review reflects an understanding that approaches to pain management after total knee replacement have

features that differ from chronic pain attributable to other causes. Furthermore, a range of potential interventions with no robust evaluation were identified in our review, specifically neurostimulation,<sup>40–43</sup> radiofrequency ablation,<sup>44</sup> denervation,<sup>45–46</sup> steroid injection<sup>47</sup> and secondary resurfacing.<sup>48</sup> This can only be indicative of an awareness of the issue of treatment of pain after knee surgery as the literature searches were not designed to identify studies that did not report robust evaluations. While these relate specifically to orthopaedic surgery and to underlying musculoskeletal conditions, some strategies will be transferable from more general pain management including analgesic medication, and should be considered as potential interventions in patients with long-term pain after total knee replacement.

In summary, our systematic review highlights the lack of evidence about prediction and management of chronic postsurgical pain after total knee replacement. Given the complexity of chronic postsurgical pain and the range of possible treatment options, screening and adequate referral processes are needed, so that patients can receive appropriate interventions that have the potential to improve outcomes and reduce distress. As a large number of people are affected by chronic pain after total knee replacement, the development of an evidence base about care for these patients should be a research priority.

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**Contributors** ADB, VW and RG-H conceived and designed the study and produced the search strategy. ADB conducted the searches. ADB and VW screened abstracts and titles, assessed study inclusion and exclusion, extracted data and assessed study quality. ADB drafted the manuscript and VW and RG-H revised it critically for important intellectual content. All authors gave approval to the final manuscript.

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