**The UK NICE 2014 guidelines for osteoarthritis of the knee: lessons learned in a narrative review addressing inadvertent limitations and bias**

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**Abstract**

Several systematic reviews suggest that acupuncture is effective for knee osteoarthritis, and furthermore a safe and cost-effective treatment for this condition. A recent Clinical Practice Guideline (CPG) from the National Institute for Health and Care Excellence (NICE), in the UK recommended against the use of acupuncture on the grounds that the effect size in comparison to sham acupuncture is too small. Safety data was not considered in the review, additionally the levels of evidence for acupuncture against other recommended therapies was not compared. Consequently, we argue that this NICE guideline has limitations that lead to several potential biases in its evaluation of acupuncture, which were not addressed correctly: (i) NICE's prior scoping process limited their review (ii) NICE introduced the method of developing recommendations based on the consideration of which interventions make ’minimal important differences’ (MID) of an effect size of 0.5 or greater, rather than the statistical significance of the effect of an intervention when compared to an appropriate comparison. (iii) Evidence that sham acupuncture is not physiologically inert, and has some level of beneficial effect, hence artificially reducing the magnitude of the effect size in comparison to sham; (iv) The low adverse effects profile of acupuncture; (v) Evidence from trials comparing acupuncture to usual or standard care was not considered, nor was cost-effectiveness data. (vi) Lack of the usual CPG “head to head” comparisons between interventions. If the same criteria and methods that have been applied to acupuncture were applied to other NICE recommended therapies for knee osteoarthritis, including patient centeredness, patient education, self-management and weight loss, NSAIDs and COX-2 inhibitors, these too would no longer be recommended and opiates would become the first line of drug prescription. Given the problems with sham acupuncture, perhaps now is the time to embrace pragmatic studies and employ comparative effectiveness studies instead.

**Keywords:** NICE; clinical practice guideline; acupuncture; knee osteoarthritis; safety; recommendations

**Introduction**

Osteoarthritis (OA) of the knee is a common and costly health problem. Many Clinical Practice Guidelines (CPGs) have been published for knee OA. Table 1 lists therapies for OA of the knee as recommended in the 2010 Osteoarthritis Research Society International (OARSI) CPG1 and the 2008 UK National Institute for Health and Care Excellence, (NICE) CPG2, those in bold are listed in the NICE guidelines, those not in bold listed only in the OARSI guidelines.

The 2014 NICE guideline on osteoarthritis (CG177)3 was not a complete revision of the 2008 guidelines, it was more limited. While originally intended to be more extensive including a broader review of drugs like NSAIDs, it was decided to review those at a later date.4 Not only did the update focus on only a few of the interventions it also applied different criteria for evaluating and accepting interventions. In effect, as will be described, the process selected for evaluating acupuncture required the treatment to meet higher standards than many other included treatments. A key problem in this NICE update, is the introduction of a focus on the development of recommendations based on the consideration of which interventions make ‘minimal important differences’ (MID) to patients3 as a replacement for usual CPG comparisons of evidence.4 The MID was set as an effect size (ES), of 0.5 or greater. The analysis of the evidence for acupuncture in this review emphasized results from sham studies with a de-emphasis on evidence from pragmatic comparator studies. Despite the fact that the assessment of MID should include analysis of benefit and harm,3 this review did not include an analysis of safety data on acupuncture. This coupled with the lack of usual CPG head-to-head comparison of interventions excluded data relevant to the use of acupuncture as an intervention for knee OA in comparison with other standard recommended care options, namely that it is much safer than many other accepted interventions for knee OA pain. This shift in methodological approaches might have inadvertently biased against acupuncture. However, this has been substantiated by recent changes in the recent NICE guidelines in the UK for chronic low back pain which was highlighted in the special section on Acupuncture and Evidence published in the European Journal of Integrative Medicine. 5-8 The extent to which other guidelines have been affected in this way in other countries is unknown but should be further investigated. The aim of the current paper is to explore these UK problems and highlight their impact and relevance for other countries.

**Clinical Practice Guidelines and OA of the knee**

CPGs are developed by searching for all relevant evidence for therapies used in the treatment of a condition, then evaluating that evidence according to established criteria and procedures. CPGs not only include the clinical evidence from randomized controlled trials (RCTs) but also data related to safety and cost-effectiveness. Further, they compare the same evidence and data for different interventions. As a consequence, practical guidelines that are valid and reliable can be developed and implemented. ES are important in comparing a therapy with standard care or with a sham intervention. The advantage of ES is that they can also be used to provide comparisons between interventions for the same condition which is one of the purposes of CPGs.9 Furthermore the ES can also be judged in relation to widely accepted criteria, e.g. 0.3 or less is “small”, 0.5 is “moderate” and 0.8 is “large”. 10 If there is not yet clear evidence from clinical trials, assessment can be based on expert consensus, adverse effects and costs. We find such assessments and recommendations routinely in CPGs; e.g. patient centeredness, patient education, self-management and weight loss are judged very important for successful treatment of knee OA1, 2 despite the relative weakness of the evidence. 1, 11

**Recommendations for knee OA, effect size and adverse effects**

Commonly prescribed analgesics for knee OA such as acetaminophen have small ES (0.14 to 0.21),1, 12 whereas stronger analgesics such as NSAIDs and COX-2 inhibitors have larger ES (0.29 to 0.44)1, 12 but their adverse effects are substantial,1, 13 for example a 2000 review found around 2000 deaths in UK alone that are the result of using normal doses of NSAIDs.14 NSAIDs and COX-2 inhibitors often require targeted additional pharmaceutical treatment to counteract drug induced side effects.1, 2 Similarly questions about the topical NSAIDs persist because of their small to moderate ES with effects lasting only over the first 1-2 weeks.15 Despite the relatively weak evidence, acetaminophen, NSAIDs and topical NSAIDs are usually recommended in CPGs for knee OA.1, 11 See Table 2 comparing ES for these different therapies.

 CPGs exhibit considerable variability in their recommendations for knee OA. There is almost universal agreement that patient education, self-management and weight loss should be included in guidelines, despite the weakness and paucity of available evidence. Similarly, most guidelines include exercise regimens, usually complemented by a package of physiotherapy that may include other treatments such as TENS and ultrasound. Some guidelines also recommend use of various walking aids like taping,16, 17 insoles 2, 16-18 and braces, 2, 17, 18 etc. The evidence for exercise regimens varies from low to good,1 but many patients are resistant to exercise because of their pain hence compliance to exercise and daily activity recommendations tends to be low.19 The evidence for physiotherapy techniques like ultrasound and massage is mixed and generally not very strong.1 Opiate analgesics show stronger treatment effects, than NSAIDs, but are usually judged to be a last line of pharmaceutical treatment due to their adverse effects.1 Topical NSAIDs are generally thought to have better effects for short-term pain control but are not without side effects.1 Intra-articular injections of corticosteroids are commonly recommended and judged to show moderate to good effects.1 Since surgical interventions (which are costly) are generally considered to be the last treatment choice, for many patients with knee OA, it is thus considered important to find other pain control strategies when the usual pharmaceutical approaches do not work. As such, acupuncture has been recommended in other guidelines.20

**Acupuncture for OA of the knee**

During the last ten years, based on outcomes of several large-scale RCTs, a number of systematic reviews (SRs) and meta-analyses (MAs) have found acupuncture to be more effective than sham,21, 22 more effective than standard care21, 23 and more effective than a no acupuncture control.21 The ES is generally small (approximately 0.16 to 0.35) when acupuncture is compared to sham, but larger in the comparison to standard care.21 These estimates are similar to those for NSAIDs (0.29 to 0.44)(Table 2) for knee OA,1, 12, 24 but with significantly better adverse effect profile.13 The ES for the comparison to no acupuncture (including standard therapy) is moderate (0.57).21 A recent network meta-analysis comparing over twenty physical interventions for knee OA, including such commonly recommended interventions including acupuncture, weight loss, aerobic exercise, muscle strengthening exercise, insoles, braces, thermotherapy and TENS, found eight of the physical interventions to be more effective than standard care.23 In this network meta-analysis, only two interventions were represented by more than two high quality trials, acupuncture and muscle-strengthening exercises (11 and 8 trials respectively), and acupuncture statistically significantly outperformed muscle-strengthening exercises.23 Further, researchers have generally concluded that acupuncture is a safe 22, 25 and a cost effective therapy26 for knee OA.

**NICE guidelines and knee OA**

The following choices of the NICE committee shaped the decision to exclude acupuncture: the NICE group focused on the strength of evidence from sham controlled clinical trials, did not include safety data and did not compare the relative strength of evidence to that of other therapies. Such an approach introduces elements of selection bias. Moreover, this appears at variance with general CPG guidelines, which are meant to “include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”.9 It does not seem that such issues related to acupuncture have been adequately addressed by the NICE 2014 group.

Further, there is an additional bias implicit in how this analysis was performed. Recent publications have presented evidence showing that no sham acupuncture procedures, whether using penetrating or non-penetrating needles, are inert.27, 28 Insertion of an acupuncture needle anywhere on the body can stimulate local blood flow, increase local immune responses and induce analgesic responses. The comparative effectiveness of acupuncture depends to a considerable extent on the type of control used. Acupuncture appears less effective when penetrating needles are used as sham compared to non-penetrating needles as sham.28

However, non-penetrating sham needles, have also demonstrated greater clinical effectiveness than the test treatment when applied to the same acupoints as the test treatment.29 A recent systematic review reported that even non-penetrating sham needles have been found to be clinically active and not suitable as placebo controls.30 Consequently sham acupuncture trials will underestimate the effects of acupuncture.28 Accordingly, interpretation of SRs and MAs that have included sham trials in their analyses will need to be re-evaluated since the effect sizes in the comparison to sham will be larger but by an unknown amount. The risk of bias against acupuncture created by including such trials needs to be assessed.27 Since the NICE 2014 assessment of acupuncture focused on comparisons with sham acupuncture trials rather than with standard care, it is probable that this created bias against acupuncture.6, 7, 31

Finally, the NICE 2014 summary recommends against acupuncture, because the ES in the comparison to sham is small. In their Cochrane SR of acupuncture, Manheimer et al. also found that the “effects of acupuncture relative to sham acupuncture are too small to be perceived by participants as beneficial” according to preset criteria,22 yet they also acknowledge “few if any other commonly used treatments for osteoarthritis meet these thresholds for minimal clinically important differences,” a point not discussed in the NICE analysis.22 The adoption of the MID as a cut off point for recommending an intervention leaves considerable problems for NICE. If the same criteria were used in their selection of evidence for all interventions for knee OA then NICE must also recommend against the following therapies which are currently recommended by NICE and many other GPGs developing groups: patient centeredness, patient education, self-management and weight loss, muscle strengthening exercise, NSAIDs and COX-2 inhibitors (see Table 2). Based on the evidence, NICE would only be able to recommend opiates from the list of interventions in Table 2. Further, the 2014 NICE update3 recommended to exclude acetaminophen on the basis that newer evidence shows that it is not very effective and has more adverse effects than previously thought,32 which parallels recent exclusion of acetaminophen by other groups.11 While the inclusion of safety data for acetaminophen is appropriate, the lack of inclusion of safety data for acupuncture suggests a biased approach towards acupuncture.

**Conclusion**

By restricting the review in the manner that the NICE OA group has chosen, emphasizing sham/placebo control studies of acupuncture and adopting an MID of 0.5, NICE has inadvertently - created problems for future updates and guidelines for OA. Many commonly recommended interventions will need to stop being recommended and some interventions, such as acupuncture have been or will be improperly treated through the introduction of bias (e.g. selection bias, risk of underestimating the effects of acupuncture). We think that there are some limitations regarding NICE’s conclusion as they assess the evidence base which may inform recommendations on healthcare practice and policy rs. Firstly their pre-defined change of scoping process may inadvertently influence the outcome for acupuncture. If NICE were to apply the same criteria to OA treatments only opioids would be left and with their adverse events profile that may not be acceptable to some patients suffering from OA of the knee. Further we agree with other authors that it is time to stop performing sham acupuncture as a control treatment in acupuncture studies.33

We recommend/hope that NICE guideline developers will revisit the scoping- and the methodology decisions that were adopted in the 2014 update of the OA guideline and we suggest that it would be more realistic to perform a usual ‘head-to-head’ comparison for therapies and to reconsider the use of the MID criterion.

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**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ Contributions:**

All authors have contributed to this article. SB and TA conceived the project, performed the initial literature searches and began drafting the paper. MSL, NR, critiqued and edited the draft of the paper, contributing further arguments and literature sources. All authors then prepared, read and approved the final manuscript.

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