Title: Best-practice clinical management of flares in people with osteoarthritis: A scoping review of behavioral, lifestyle and adjunctive treatments.

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Abstract:

Introduction: Transient episodes of increased pain, stiffness or swelling are common in people with osteoarthritis (OA). Yet, evidence-based management strategies for lessening the impact of OA flares are rarely covered in clinical guidelines and have been identified as a gap by clinicians delivering OA care. We aimed to identify evidence on behavioral, lifestyle or other adjunctive flare management strategies that could be used by clinicians or consumers.

Materials and Methods: A literature search between 1990-2020 was performed in three databases using a scoping methodology. We included qualitative or quantitative studies, and reviews that examined OA flare management, or that reported OA flare outcomes at timepoints ≤2 weeks post-intervention. Outcomes included any physical or psychological OA outcome treatable with a therapeutic intervention.

Results: We included 9 studies, all of which examined the relationship between therapeutic exercise/ physical activity and OA flares. All studies reported pain outcomes at the knee. Two also included the hip. Only two studies examined specific management strategies for OA flares. Both favorably reported the benefits of undertaking an exercise program modified accordingly during an episode, but the quality of the evidence was low.

Discussion: This scoping review highlights the paucity of evidence available on non-pharmacological treatments of OA flare management that could influence clinical practice. At present, there is no robust evidence to support or reject any specific therapies for OA flare management in clinical practice. Future work is needed, particularly around outcomes beyond pain, trajectories of symptom improvement, and for joints other than the knee.

Keywords: osteoarthritis, flare, pain exacerbation, management, clinical care

Introduction

Osteoarthritis (OA) is a leading cause of pain and other symptoms in synovial joints and surrounding structures [2-6]. As with many chronic health conditions, OA symptoms fluctuate [7]. Periods of stability can be followed by temporary episodes of increased pain, stiffness, and swelling, and can be accompanied by other physical and psychological symptoms [1, 8]. These transient episodes of increased symptomatic presentation are commonly known as OA "flares", "flare-ups" or "exacerbations" [8, 9]. The incidence of OA flares has not been well-characterized. It is estimated 25-30% of people with knee OA experience substantial variability in their symptoms over time [10] and, a French survey of 10,000 people with knee, hip or hand OA reported an average of 2.4 flare episodes per person annually [11]. Despite the apparent incidence, relatively little is known about the etiology or management of OA flares.

People experiencing an OA flare commonly present to healthcare professionals such as general practitioners (GPs) or physiotherapists, seeking advice and treatment [12]. Many cannot identify specific triggers of their episode, but report considerable disruption to their daily activities, sleep, and concentration [7, 13, 14]. The sudden worsening of symptoms, particularly joint pain, can create concern that their joint health is "getting worse", apprehension about future quality-of-life, or belief that a total joint replacement is inevitable [7]. Fortunately, most OA flares are considered transient and do not represent an immediate deterioration of the joint structure [15]. There have been reports of Heberden's nodes appearing after flares in the hand joints [16], however, there are currently not enough data to evaluate long-term joint structural changes from flare episodes.

There is no cure for OA [2]. Therefore, the role of the healthcare professional is to support people to manage their symptoms [17]. With regards to a flare, this may include reassurance on prognosis, providing education and advice, assistance with maintenance of function, quality-of-life, and daily routines until the flare subsides [17]. Evidence-based management strategies for OA flares are rarely covered in clinical guidelines, probably due to lack of research in this area, and this has been flagged as an important knowledge gap by Australian clinicians [18]. Previous research on behavioral, lifestyle or other adjunctive treatment options has been restricted by lack of an agreed OA flare definition [8, 9], and accordingly, no widely accepted flare measurement tool [1]. The most common definition and outcome measure described in the literature is increased pain, which is over-simplistic given the diverse range of symptoms reported by people suffering a flare [9, 13]. Also, the highly variable nature of flares has made it difficult to predict the onset and length of each episode or differentiate treatment effects. This has resulted in

wide variation in data collection timepoints used in studies [9]. Such diversity and uncertainty in the literature has made it difficult to identify effective management options. A recent international Delphi consensus exercise undertaken with healthcare professionals and people living with OA from 17 countries has approved a more complete definition for OA in the knees and hips (see Box 1)[1], but international consensus is ongoing.

Treatment recommendations for flares that do not rely on pharmacological interventions are often extrapolated from those used for acute musculoskeletal injuries, e.g. ice or heat [19], or modified versions of the core recommended OA treatments; education, exercise, and physical activity. Recommendations for use of adjunctive therapies such as manual therapy, joint bracing/sleeves, or transcutaneous electrical nerve stimulation (TENS) are conflicting in clinical guidelines [20-22] and there is limited knowledge around their effectiveness for managing flare symptoms. Medications and other pharmacological pain relief interventions such as corticosteroid injections and non-steroidal anti-inflammatory drugs (NSAIDs) can be effective in the short-term [20, 21, 23-25]. However, they can lose effectiveness if used repeatedly, and are not suitable or wanted by all [21, 25].

Thomas and Neogi emphasize that OA management involves three main elements, namely; longer term therapy aimed at modifying the underlying disease, specific management for flares, and avoiding triggers or risk [26]. The primary aim of this scoping review was to identify any available evidence for specific short-term, reactive management strategies that lessen the impact of OA flares. Our secondary aims were to i) identify relevant concepts from studies that specifically report OA flare symptoms as outcomes, ii) consider the definitions identified and the extent to which the outcomes reported fit with the components of the current consensus (Box 1) and, iii) identify knowledge gaps for further research. Our main focus was on therapies that were commonly administered in primary healthcare and other community-based settings or could be safely self-administered by people with OA. We concentrated on behavioral, lifestyle and other physical therapies such as exercise, assistive devices, and adjunctive OA therapies. Pharmacological interventions including injectable therapies and NSAIDs were beyond our scope. We used the newly proposed flare definition as a basis for our work, but widened our scope to cover other definitions used previously and have maintained a flexible approach to time of symptom onset and flare duration [13].

Box 1: Proposed definition of an osteoarthritis flare [1]

"a transient state, different from the usual state of the condition, with a duration of a few days, characterised by onset, worsening of pain, swelling, stiffness, impact on sleep, activity, functioning, and psychological aspects that can resolve spontaneously or lead to a need to adjust therapy."

Materials and Methods:

a) Overview

We undertook a literature search to identify published studies investigating behavioral, lifestyle or other adjunctive management strategies for OA flares or reported study outcomes relevant to OA flares. We used the Joanna Briggs Institute (JBI) methodology for scoping reviews [27], and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, extension for Scoping Reviews (PRISMA-ScR) [28]. We defined our study question using the Population, Concept, and Context (PCC) elements (Appendix 1). The search strategy [27] included a preliminary test search of two databases (September 2019, MEDLINE and CINAHL), a second search of the three databases (including EMBASE) incorporated the final keywords and index terms (Appendix 2, December 2019, updated July 2020). The reference lists of included studies were searched to identify additional studies. No previous reviews on behavioral, lifestyle or other adjunctive treatment options for flares were identified prior to undertaking this study.

b) Study Selection

We selected studies in English, published January 1990-July 2020, that examined management strategies for flares, or included flare symptoms as outcomes (see Box 1) in adults with self-reported or clinician-diagnosed OA, and in any joint [1, 13]. We included any actively delivered management strategy that could be provided by a healthcare provider in a clinical setting; including primary care, outpatient or community-based services, remotely delivered, or that could be performed safely at home. These included physical interventions (physical activity or therapeutic exercise), educational programs, medical devices (e.g. electrophysical treatments), or other adjunctive treatments (e.g. heat/cold, assistive devices, manual/manipulative therapies). Included studies were required to have outcomes reported at any timepoint ≤2 weeks post-intervention. This time was selected to facilitate the identification of the rapid symptom onset and change synonymous with flare symptoms [7, 8, 13], we were concerned longer timepoints would mask these changes.

153

154 We included qualitative, quantitative, mixed methods studies and reviews that reported physical or
155 psychological outcomes related to OA that could be treated with a therapeutic intervention (e.g. pain,
156 physical function, stiffness, body mass index (BMI), sleep, quality-of-life, mood, or that provided relevant
157 patient/clinician experiences and perceptions. We excluded surgical and post-surgical interventions,
158 those solely focused on pharmacological or injectable therapies (e.g. corticosteroid injections, NSAIDs),
159 where the flare resolved without treatment, or experimental / lab-based therapies. Animal studies, and
160 other literature without original data were excluded.

161

162 ***c) Data sources and searches***

163 A comprehensive search strategy was developed iteratively by a multidisciplinary team involving an
164 academic librarian (University of Sydney), clinicians (physiotherapists, rheumatologists), and researchers.
165 The search strategy combined both MeSH terms and text words to capture OA-related terms. The final
166 database searches were undertaken in December 2019 and rerun in July 2020 to check for recently
167 published articles (Figure 1).

168

169 ***d) Study characterization, data extraction, and synthesis***

170 Retrieved studies were downloaded to Endnote, and duplicates removed. One reviewer (JB) conducted
171 title and abstract screening. The remaining full texts (n=74) were reviewed by two authors (JB/SK), and a
172 consensus reached on inclusion, with discrepancies resolved with a third reviewer (JE). Data were
173 independently extracted and synthesized by two authors (JB/SK) using the pre-determined data extraction
174 form (Appendix 3). Our data synthesis included information on strategies used to manage OA flares and
175 reported flare symptom outcomes. Descriptive results have been reported for all included studies,
176 including key classifications, settings, flare definition, flare outcome measures, and quantitative results
177 (Appendix 2, Tables 1-3).

178

179 ***e) Risk of bias (quality) assessment***

180 A risk of bias (ROB) assessment for the two randomized controlled trials (RCTs) identified was undertaken
181 using the JBI Critical Appraisal tool for RCTs [29], for reporting purposes only. Two review authors (JB &
182 SK) independently assessed ROB, arbitrated by a third person (KM). The JBI tool has 13 questions which
183 are marked as 'met', 'unmet', 'uncertain', or 'not applicable'.

184

185

Results

a) Description of included studies

The PRISMA flow diagram is presented in Figure 1. Nine studies met the inclusion criteria, and their characteristics are summarized in Table 1. Studies were delivered across a variety of healthcare settings and community locations, and all examined the role of therapeutic exercise (n=8) or physical activity (n=1). Two studies were RCTs [30, 31], three were secondary analyses from RCTs [32-34], three were observational studies [35-37], and one a cross-sectional registry-based study from the Good Life with osteoArthritis: Denmark (GLA:D) program [38]. Studies included people with knee OA, two also included people with hip OA [33, 38]. No studies reported the socio-economic status of participants, and only two reported ethnicity (Table 2). Studies were small (<50 participants), with only the registry-based study with >130 participants. Reviewers agreed on all items (2-reviewer inter-rater agreement=62%), with adjudication by a third reviewer if required. The two RCTs were assessed as having met 7/13 and 8/13 JBI tool criteria respectively. Bias was noted for blinding and randomization procedures in both studies.

b) Classification of studies

Aim 1 - Evidence on management strategies for OA flares: We identified only two studies that examined specific management strategies for OA flares (Table 1). Both examined if participation in a therapeutic exercise program could be undertaken during a flare event and if pain and/or function was impacted [30, 32]. Gondhalekar and colleagues' RCT [30] compared the effectiveness of a package of conventional activities with a retro-walking program on knee pain and disability, to conventional activities alone. Bartholdy and colleagues [32] conducted a secondary analysis from two RCTs that described the impact of participation in a modified version of a prescribed program. The modified "rescue program" described by Bartholdy included a longer cycling warm-up and excluded weight-bearing activities such as lunges and squats.

Aim 2 - Studies reporting OA flare symptoms as outcomes: The seven studies identified under our secondary aim were classified according to the duration of the exercise programs. Namely, i) flare symptoms evoked from a single session of therapeutic exercise or physical activity; and ii) flare symptoms evoked during a 6-12-week exercise program. Briefly:

i. *A single session of therapeutic exercise:* Four observational studies described the level of pain evoked after a single session of weight-bearing exercise or physical activity [35-38]. Activities included overground walking, treadmill walking, a 30s sit-to-stand exercise, and general physical activity. The flare response was primarily reported as the level of pain experienced immediately after the single session. One reported the pain level the following day.

ii. *Therapeutic exercise programs for chronic OA management:* Three studies reported flare pain outcomes that occurred during 5-12 week therapeutic exercise programs [31, 33, 34]. These studies were included as they reported a flare symptom outcome measure ≤2 weeks throughout the longer program (see Tables 1 and 3). Typically, these outcomes were reported during or immediately after each session, one study also included data from 1-2 days post-session. Exercises examined in this category included stationary cycling, neuromuscular exercises, and progressive resistance training.

c) Flare definitions, outcome measures, and minimal important change

The flare terms, outcome measures, time points, and minimal important change (MIC) reported in each study are summarized (Table 3). "Level of pain" was used in all studies to identify a flare, with the majority defining it as between 1 to 5 / 11 points on a numerical rating scale (NRS) or visual analog scale (VAS) [31-33, 35, 37, 38]. One study also used the Western Ontario and McMasters Osteoarthritis Index (WOMAC) pain subscale [31]. Two studies provided no specific definition of a flare [30, 36]. The change in pain level was also used to define the MIC in 5 studies, specifically 1-2 /11 points on an NRS scale [33-35, 37, 38].

In addition to pain, two studies reported outcomes for other flare symptoms even though they did not include these symptoms in their flare definitions for their study (Table 1). These were: knee joint effusion after exercise [34]; and the combined WOMAC score that includes pain, stiffness, and physical function [30]. Two studies reported factors analyzed as potential moderators or mediators of the flare response, including fear of movement, confidence in the joint, self-efficacy, BMI, anxiety and depression, quality-of-life, and pain catastrophizing [36, 38]. However, no studies examined changes in these factors due to a specific flare management strategy.

The time points used to measure flare symptom change were generally reported within 24 hours; specifically, during, immediately after, or before undertaking the next day's activities (Table 3). Two

studies looked at the flare response over the next 48 hours [31, 36], and two examined the response at 1-2 weeks after treatment [30, 37].

d) Summary of results from included studies:

The results presented across the included trials were varied and inconsistently reported. Briefly, the results for each aim are (Table 3):

Aim 1 – Evidence on management strategies for OA flares

Results from both studies were associated with participants being able to maintain some level of ongoing exercise or physical activity during their flare event. Bartholdy et al. [32] reported that 61% of their participants experienced decreased pain immediately after their rescue session, with a mean decrease of 2.6/11 NRS points (SD 2.3). They also reported 10% of participants had increased pain, but with a lower mean increase of 1.3/11 (SD 0.5). Gondhalekar and colleagues [30] were the only authors to report pain data at one-week post-exercise. Both their control and intervention groups undertook an exercise program. Both groups reported a mean decreased pain at the 1-week follow-up (Group A 1.83/10cm VAS, SE 0.26; Group B 1.87/10cm, SE 0.23). Neither study defined a clinically important level of change.

Aim 2: Results from studies reporting OA flares symptoms as outcomes:

A single session of therapeutic exercise: A single session of activity appeared to be safe for the majority of people with OA with minimal pain flares reported after the session. However, higher levels of physical activity or more strenuous exercise had the potential to evoke pain flares in 20-42% of participants. For example, after a 30s sit-to-stand activity, Skou and colleagues [38] reported a mean pain increase in the knee of 1.06/11 NRS points (95% CI 1.03), and 0.58/11 points (95% CI 0.54) in the hip, although they did not report longer time points. Up to 33% of their participants with knee OA and 20% with hip OA reported clinically significant pain increases of ≥2 points. Similarly, Lasaridou and colleagues [36] reported that higher levels of physical activity were significantly associated with an elevated pain response the following day (β= 0.13, SE= 0.03, P<0.001). Wallis et al. [37] were the only authors to report recovery two hours after a walking session. They found that mean pain reduced from 2.1/11 NRS points (95% CI 1.0-3.2) immediately after the session to 0.3/11 points (95% CI -0.9-1.4) two hours later. They concluded immediate exercise-induced pain was a short-term effect when walking up to 70 min, but that sessions longer than 70 min were associated with greater pain events.

Therapeutic exercise programs: The majority of studies examining therapeutic exercise programs did not report the magnitude of individual change or between-group data for individual sessions. Rather, they reported the percentage of participants who reported an increase or decrease in their pain level after each session. Mangione and colleagues [31] reported 60-70% of participants who reported >20/100 VAS score at the commencement of each session, had decreased pain immediately after completing a session of stationary cycling session, regardless of the intensity. Two studies reported that the pain evoked after each session was reduced as the program progressed. For example, Sandal et al. [33] reported a clear relationship between time and the pre-exercise pain level and demonstrated that throughout the 8-week neuromuscular training program, knee pain reduced by an average of 0.04 points (95% CI 0.03-0.05) per session. It was not clear, however, if the initial pain levels reported in these studies were related to a flare episode or a reduction in chronic OA pain. Interestingly, a 4-week program of progressive resistance training in people waiting for a total knee replacement did not evoke any increases in either pain or swelling after individual sessions throughout the program [34]. The authors concluded this type of exercise could be safely undertaken by people with severe knee pain.

Discussion

This is the first review of the literature examining the evidence on behavioral, lifestyle or other adjunctive treatment strategies to manage OA flares. Our search did not identify any large, adequately controlled clinical trials, and our results highlight the serious paucity of evidence on this topic. All identified studies examined physical activity or therapeutic exercise, but few examined other types of management. There was also an absence of studies examining flare outcomes beyond pain, and for joints other than the knee. Although the results from the two studies investigating treatments for OA flares cautiously suggested that exercise and physical activity were safe and had positive outcomes on pain for people with an OA knee flare, it was unclear if the treatments were clinically meaningful. We discuss our findings here with reference to evidence gaps and highlight potential areas for future work.

Implications for current clinical practice

The role of physical activity and therapeutic exercise in managing chronic OA is well documented [39], however, we found little evidence for, or against, its effectiveness for managing OA flares. Only two studies specifically examined exercise interventions to manage a flare episode. The single RCT compared the addition of backward walking as an adjunct to an exercise program comprising usual care (Table 1).

Both groups reduced their flare pain at 1-week. However, this was a very small trial, did not have a control or non-intervention group, and the time since onset of the flare was not reported. It was difficult to determine if their results were due to chance, natural recovery, the timepoints of pain measurements, or the intervention itself. The second study was a secondary analysis of data from two RCTs [32]. The authors reported that 61% of those who participated in the rescue sessions after developing a flare had decreased pain immediately after the session, and were able to return to the allocated exercise program within a few days. These results are promising and should be tested in robust clinical trials to determine the effectiveness of different interventions, dosage, timing, and expected trajectories of improvement. At present, however, there is no robust evidence to support specific strategies for OA flare management.

Gaps and opportunities

This scoping review highlights the potential for considerable work in this area. In addition to expanding on the initial findings around therapeutic exercise (Table 3), we did not identify any studies that examined other therapies commonly recommended by clinicians to manage an OA flare. Notable omissions were non-weight bearing activities (e.g. swimming, hydrotherapy), heat/cold therapy, joint bracing/sleeves, assistive devices, or use of electrotherapeutic devices such as TENS [19-22]. Conspicuously , there is little evidence relating to the hip or other joints, and research on the effectiveness of commonly used therapies and their application to all joints is urgently needed.

Flares can be related to a wide range of factors including sedentariness, lifestyle change, stress, discontinuation of another treatment, diet [19, 40], or poor mental health [40]. As such, there is scope to investigate new and novel therapies, beyond physical activity, that target these different triggers. Similarly, there is potential to examine combined programs targeting several factors. We did identify two observational studies that looked at several of these factors as moderators to the flare response [36, 38], however, we did not identify any studies specifically designed to test interventions addressing the underlying cause of the flare, or that addressed flare severity and/or symptom duration. Therapies such as activity pacing, stress management, or pain coping skills may be beneficial in improving chronic OA symptoms [39] and could be investigated as treatments for flares. Finally, Thomas and Neogi [26] have suggested that better methods to clinically differentiate between a flare and other OA complications (e.g. micro-fractures) are an important area for future research to ensure correct management strategies are given.

Methodological challenges of evaluating flare interventions

We recognize that there are several methodological challenges to conducting and evaluating clinical effectiveness studies for OA flare interventions. Consistent with previous reviews [9] the flare definitions in our studies (Table 1) were often vague, varied considerably in measuring onset, follow-up, and rarely included symptoms other than pain.

The identification and recruitment of prospective study participants early in their acute flare event is also problematic and appropriate methodology needs to be identified. Pharmacological trials often rely on "withdrawal flare designs' [9] which use withdrawal of pain medications to evoke a flare and does not necessarily reflect the breadth of factors associated with flare onset. We did not identify any studies utilizing this design, but if used, care should be taken to ensure the cessation of medications does not affect the results. The two studies we identified that investigated management strategies included either people referred to a clinic with pain exacerbation or identified people who developed a flare during their participation in an exercise-based RCT. The former methodology was problematic because the time of onset and time to seek treatment were unknown factors. Trials with a focus on treatments that can be initiated and easily accessed by the individual at an early phase of their flare are now needed, for example via community pharmacists, physiotherapists, or other health professionals.

Another major methodological challenge is detecting intervention effects over powerful regression to the mean and the influence of natural recovery, and thus how adequately powered trials can be designed. The time of onset and measurement time points are critical to detecting flare symptom changes, as are appropriate control observations. For example, Thomas and colleagues [25] noted that achieving substantial symptom improvement in all OA patients is unrealistic, but shifting the flare trajectory to a more favorable path may be a preferable goal and may lead to important reductions in disability and pain. However, at present little is known about typical flare duration or appropriate monitoring timepoints for outcomes other than pain. The studies identified mostly measured the outcome at a single time point, most commonly immediately after the exercise. Three looked at a single timepoint between 1-hr to 2 days after exercise, which is closer to the new proposed flare definition (Box 1). Although we limited our inclusion to outcomes reported at ≤2 weeks, a post-hoc search did not identify any additional studies within a four-week timeframe. Broad adoption of an accepted definition, combined with ongoing and recent work to better describe flare symptoms, duration, and recovery trajectories should assist in designing and testing better flare treatments in the future [13, 25, 41].

Study limitations:

There are methodological limitations to this scoping review. Firstly, although we had deliberately broad inclusion criteria, we were limited to studies in English, we lacked an accepted flare definition and there were inconsistent outcome measures used. These factors may have limited the ability of this review to capture all studies in this area. Similarly, our limitation of outcome timepoints to ≤2 weeks may have excluded relevant studies, but we felt this timeframe most appropriate for identifying rapid symptom change. We also only examined reactive management of OA flares. A related and important area is to address the prevention, and reduction of future flare frequencies. One example may be the intersection of sustained weight loss in obese people and its impact on flare occurrence. Finally, lifestyle and other core treatment options are important for many world regions, particularly low-and-middle-income countries where drug access may be limited, or high-income countries where healthcare is expensive and pharmacological OA treatment may be inequitable across socio-economic groups. As most of the studies identified here were undertaken in Europe and the USA, more work needs to be undertaken for management strategies that are successful outside those healthcare systems.

Conclusion

This review aimed to identify the currently available evidence on behavioral, lifestyle or other adjunctive therapy strategies suitable for managing OA flares. It highlights the lack of large, well-powered clinical trials on this topic, and the serious paucity of evidence on effective management strategies not involving pharmaceuticals. There is an urgent need for more consistent, high-quality randomized and cohort trials, including those investigating trajectories of symptom improvement at timeframes more relevant to flare presentation, and by joint affected. Long-term, this type of information is crucial to inform appropriate clinical practice and improve the quality-of-life for people living with OA flares.

406 **Ethics and dissemination**

407

408 Ethical approval is not required for this scoping review. Working with the knowledge users for this study,
409 we will incorporate our findings into educational and training materials for healthcare professionals
410 working with people with osteoarthritis, and their patients. Results will be published in a peer-reviewed
411 journal and presented at national and international conferences.

412

413 **Contributions**

414 JLB, KM and JPE came up with the concept. JLB, DJH, KM, GP, EP, MJT, FG and JPE designed the protocol.
415 JLB, SK and JE undertook the searches, synthesis and extraction, and along with KM interpreted the
416 findings. All authors provided input into the findings and draft article and approved the final text before
417 submission.

418

419 **Acknowledgments**

420 We thank the University of Sydney Librarian for help designing the search strategy, and Karen Schuck for
421 assistance with performing the database searches.

422

423 **Funding and role of the funding source**

424 This research did not receive any specific grant from any funding agency in the public, commercial, or not-
425 for-profit sectors. DJH is supported by a National Health and Medical Research Council (NHMRC)
426 Investigator Grant. EP received funding from a National Institute for Health Research (NIHR) In-Practice
427 Fellowship (IPF-2014-08-03), an NIHR Academic Clinical Fellowship, and an NIHR School for Primary Care
428 Research Progression Fellowship. MJT was supported by an Integrated Clinical Academic Programme
429 Clinical Lectureship from the NIHR and Health Education England (HEE) (ICA-CL-2016-02-014) and is
430 currently supported by an NIHR Development and Skills Enhancement Award (NIHR300818). The views
431 expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, HEE,
432 or the Department of Health and Social Care.

433

434 **Competing interests**

435 DJH provides consulting advice to Pfizer, Lilly, Merck Serono, and TLC bio. The other authors declare no
436 competing interests.

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