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# BMJ Open

## Defining Acute Flares in Knee Osteoarthritis: A Systematic Review

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Manuscripts

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4 **1 DEFINING ACUTE FLARES IN KNEE OSTEOARTHRITIS: A**

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7 **2 SYSTEMATIC REVIEW**

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37  
38 14 **Keywords:** knee osteoarthritis, flare, systematic review

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## 16 ABSTRACT

17 **Objective:** To identify and critically synthesise definitions of acute flares in knee  
18 osteoarthritis (OA) reported in the medical literature.

19 **Design:** Systematic review and narrative synthesis. We searched MEDLINE, EMBASE,  
20 Web of science and 6 other electronic databases (inception to July 2017) for original  
21 articles and conference abstracts reporting a definition of acute flare (or synonym) in  
22 humans with knee OA. There were no restrictions by language or study design (apart  
23 from iatrogenic induced flare-ups e.g. injection-induced). Data extraction comprised:  
24 definition, pain scale used, flare duration or withdrawal period, associated symptoms,  
25 definition rationale, terminology (e.g. exacerbation or flare), baseline OA severity,  
26 age, gender, sample size and study design.

27 **Results:** Sixty-nine articles were included (46 flare-design trials, 17 observational  
28 studies, 6 other designs; sample sizes: 15-6085). Domains used to define flares  
29 included: worsening of signs and symptoms (61 studies, 27 different measurement  
30 tools), specifically increased pain intensity; minimum pain threshold at baseline (44  
31 studies); minimum duration (7 studies, range 8-48 hours); speed of onset (2 studies,  
32 defined as 'sudden' or 'quick'); requirement for increased medication (2 studies). No  
33 definitions included activity interference.

34 **Conclusions:** The concept of OA flare appears in the medical literature but most  
35 often in the context of flare design trials. Key domains, used to define acute events in  
36 other chronic conditions, appear relevant to OA flare and could provide the basis for

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4 37 consensus on a single, agreed definition of 'naturally occurring' OA flares for  
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6 38 research and clinical application.  
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8 39 **PROSPERO registration:** CRD42014010169  
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### 18 43 **Strengths and limitations of this study**

#### 20 21 44 *Strengths*

- 23 45 • Identified key domains that are used to define acute events by undertaking a  
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25 comprehensive synthesis of definitions used in the medical literature.  
26 46  
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28 47 • Broad search strategy covering a wide range of databases including  
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30 bibliography checks and conference abstracts.  
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33 49 • Prospectively registered with Prospero  
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#### 36 50 *Limitations*

- 38 51 • Did not search grey literature  
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41 52 • Did not include potential synonyms as search terms ('attack', 'episode',  
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43 'fluctuations')  
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## 55 INTRODUCTION

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57 Recurrent acute events or episodes feature in the natural history of many chronic  
58 health conditions. The extent to which they characterise the condition varies, as do  
59 the presumed pathophysiological mechanisms, and scientific and lay terms used to  
60 describe them (e.g. an acute exacerbation of chronic obstructive pulmonary disease  
61 (COPD) or asthma, an attack of gout or a rheumatoid arthritis flare). With recognition  
62 of their importance has come concerted effort to define these phenomena.

63 Definitions for exacerbations or flares currently exist for COPD[1, 2] , asthma[3],  
64 systemic lupus erythematosus (SLE)[4], and ankylosing spondylitis (AS)[5] and there  
65 are working groups currently trying to define these for rheumatoid arthritis[6-8],  
66 gout[9], and atopic dermatitis/eczema[10]. Despite the different language used, these  
67 definitions share some common, core domains: the onset or worsening of symptoms  
68 and signs above normal day-to-day variability; speed of onset; duration of sustained  
69 worsening; and change in medication/healthcare usage.

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71 Osteoarthritis (OA) appears to comprise multiple disease trajectories[11-15] and  
72 symptom variability over time and the presence of intermittent pain is well-  
73 recognised[16]. Although OA does not typically have the same very obvious acute  
74 events as conditions like gout, flares in OA joints are encountered in practice, these

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3 75 phenomena appear in patient literature[17], have been discussed in expert  
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6 76 reviews[18], and are mentioned in 'flare design' trials in OA[19]. These studies invoke  
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9 77 acute episodes of pain or flare-ups by asking patients to withdraw their usual  
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11 78 medication.

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18 80 In 2009 Marty et al proposed scoring criteria for knee OA flares based on nocturnal  
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20 81 awakening, knee effusion, morning stiffness and limping[20] but it is unclear whether  
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23 82 this has contributed to a common understanding, shared terminology and criteria. A  
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25 83 common definition of OA flare could be important for a number of reasons; (i) to  
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28 84 facilitate communication between researchers, (ii) to allow more direct comparisons  
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30 85 between studies on frequencies, determinants and course of events, (iii) to facilitate  
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33 86 new insights into novel pathophysiological mechanisms and treatments through  
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35 87 valid and homogenous case definitions, and (iv) to help clinicians with prompt  
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38 88 diagnosis and management.

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45 90 The aim of this systematic review was to explore the extent to which a concept of OA  
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47 91 flare is reported in the medical literature and the prospects for a common, shared  
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50 92 definition of these for research and clinical application.

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For peer review only



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3 99 **METHODS**  
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8 101 This systematic review was registered with PROSPERO registration number  
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10 102 CRD42014010169. The review protocol has not been published.  
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16 104 **Literature sources and study selection**  
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22 106 We searched electronic databases from inception to July 2017; ASSIA, EMBASE, Web  
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24 107 of Science, Health Management Information Consortium (HMIC), SPORTDiscus,  
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26 108 Medline, CINAHL, PsycINFO, AMED, Ageline, Cochrane Database of Systematic  
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28 109 Reviews and Cochrane Controlled Clinical Trials (CENTRAL). The search was  
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30 110 developed using previously piloted terms for knee OA and a literature search for  
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33 111 common terms used to describe acute events. Searches used combined and/or  
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36 112 truncated key terms including: ("KNEE OSTEOARTHRITIS" OR (knee N3 pain) OR  
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39 113 (knee N3 arthrosis) OR (knee N3 joint) OR (knee N3 osteoarthritis)) AND  
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41 114 (exacerbation OR flare OR (pain AND (diary OR diaries)) OR (pain N3 variab\*) OR  
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44 115 (pain N3 pattern\$) OR (daily N3 pain)). A database search strategy is included in the  
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47 116 online supplement . Reference lists of all included full text articles retrieved for  
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49 117 detailed examination were manually searched.  
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3 119 Studies were included in the final full text peer review if they contained a description  
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6 120 or definition, with or without classification criteria based on measurement, of an  
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8 121 acute exacerbation or flare-up of knee OA in human adults (18 years or over) in the  
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10 122 general population, primary care or hospital settings. There were no restrictions on  
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12 123 study dates or design. All non-English language articles were translated to identify a  
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14 124 flare definition. Theses, dissertations, book chapters and guidelines, and animal  
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16 125 studies were excluded. Conference abstracts were included if they contained a  
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18 126 definition for an OA flare-up. Studies were excluded if the flare was induced by an  
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20 127 iatrogenic source, for example, injection-induced flares[21]. As these may have been  
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22 128 caused by a different pathophysiological process. Abstracts were included in this  
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24 129 study as the main outcome of interest was the definition of flare used and it was  
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26 130 decided that including abstracts would ensure a more comprehensive review. For  
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28 131 each abstract a search was conducted to identify a corresponding full text paper.  
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31 132 Where one was found only the full paper was included in the review.  
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### 134 **Data collection**

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136 The search and article retrieval was conducted by the first reviewer (ELP). Articles  
137 were downloaded into RefWorks© bibliography and database manager (RefWorks  
138 Copyright 2009). Duplicates were removed and all titles were screened by ELP

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4 139 against inclusion criteria. All titles were screened by the first reviewer to meet  
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6 140 inclusion criteria. The first 20 titles were checked by two reviewers (ELP and MJT) to  
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8 141 check consistency. For qualitative studies, all identified potentially eligible full text  
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10 142 articles were obtained as title and abstract searches did not always provide the full  
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12 143 information about the article content.  
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18 145 All abstracts were screened by two reviewers (ELP and MJT). Potentially eligible full  
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20 146 texts were then screened by the same two reviewers to identify articles to be  
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22 147 included in data extraction. Where there was disagreement a third reviewer (GP)  
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24 148 acted as adjudicator and following discussion agreement was reached by consensus.  
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26 149 Where articles could not be retrieved or if the flare definition used was not included  
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28 150 in the text, contact with authors was made.  
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36 152 The final included articles were screened to ensure results from the same studies  
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38 153 were not counted as separate studies as this is known to introduce bias as the  
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40 154 dataset would more strongly affect the results of the review[22]. For articles  
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42 155 containing pooled studies, the original studies were sought and included in the main  
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44 156 analysis, where available. If the original articles were not referenced or not available  
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46 157 the pooled studies were kept and a note made of this in the analysis. No full text  
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48 158 articles were required to be translated.  
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4 160 **Data extraction**  
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10 162 Information was extracted by the first reviewer (ELP), and recorded in a purpose-built

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12 163 Excel spreadsheet. For all of the information extracted every tenth article was

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14 164 independently checked by a second reviewer (MJT).  
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20 166 The following data pertaining to flares were extracted from full text articles:

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22 167 definition used for change in pain, pain scale used, duration of flare or withdrawal

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24 168 period, associated symptoms, rationale behind definition used, terminology used

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26 169 (e.g. exacerbation or flare), baseline OA severity, age range, gender, geographical

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28 170 location, number of participants and study design. Missing data was described in the

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30 171 data extraction tables.  
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37 173 **Quality assessment of included studies**  
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43 175 Our aim was to identify and contrast definitions of flare-ups used in the literature.

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45 176 We were not concerned with the methodological rigour of the studies deriving,

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47 177 evaluating or applying those definitions. However, for studies presenting definitions

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49 178 we sought supporting statements that gave the rationale for the definition.  
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4 180 **Data analysis**  
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9 182 A narrative synthesis was undertaken, guided by Popay et al's[23] four stage process  
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11 183 to develop a conceptual framework[24]. This approach was chosen as it allowed the  
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14 184 words and text in the definitions to be synthesised to summarise findings[23]. The  
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17 185 initial data extracted was grouped into drug withdrawal studies ('flare design') and  
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20 186 other studies, and frequencies of components included in definitions was tabulated,  
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22 187 these included; terminology used, onset/worsening of symptoms; signs/symptoms  
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25 188 above day-to-day variability/minimum threshold; speed of onset of symptoms;  
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27 189 duration of worsening and change in medication/healthcare usage.  
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32 191 This initial tabulation helped identify similarities and differences and allowed themes  
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34 192 to emerge. This was done with an inductive type approach, where possible i.e.  
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37 193 without an *a priori* assumption, but also deductively acknowledging that the  
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40 194 reviewers were clinicians i.e. they had some background knowledge of the topic of  
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42 195 interest. This allowed further examination of the differences of definitions used in  
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45 196 drug withdrawal and non-drug withdrawal study designs, and examination of key  
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47 197 components of definitions used.  
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49 198 **RESULTS**  
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4 200 **Study selection**  
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10 202 The literature search yielded 2194 articles of which 786 were duplicates (Figure 1).  
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12 203 After title screening 336 abstracts were reviewed, 223 were not relevant for the study  
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14 204 purpose. 113 articles were examined in full which resulted in a further 60 being  
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17 205 excluded. The main reason for exclusion was no definition of flare-up reported in text  
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19 206 (n=56). At this stage a further 16 articles were identified from the reference lists of  
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22 207 the retrieved full text articles resulting in 69 included studies for synthesis.  
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27 209 **Study characteristics**  
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33 211 Characteristics of the included studies are described in Table 1[20, 25-92]. Studies  
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35 212 ranged in size from 15-6085[20, 49] and location. Knee OA was defined by clinical  
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38 213 and/or radiological criteria.  
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215 **Table 1: Characteristics of all included studies**

<b>DRUG WITHDRAWAL DESIGN STUDIES</b>					
<b>First author, year of publication</b>	<b>Setting, geographic location</b>	<b>Participants</b>	<b>Joint</b>	<b>Severity</b>	<b>Study design</b>
Altman, 2015[25]	Multi-centre, recruitment not specified, USA	403 males & females, ≥40y	Knee and hip	KL grade 2-3	RCT, flare design
Baer, 2005[27]	17 medical centres recruiting from community and physician private practice; Canada	216 males & females, 40-85y	Knee	Radiographic evidence of OA (severity not defined)	RCT, flare design
Baraf, 2011[28]	Primary care, internal medicine, orthopaedic, rheumatology; USA	602 males & females, ≥25y	Knee	Radiographically mild to moderate (KL grade 1-3)	RCT, flare design
Battisti, 2004[29]	Clinical centres, out patients; USA	3980 males & females, ≥40y (age unavailable for Geba 2003 and Weaver 2003)	Knee	ACR functional class rating of I,II or III	RCT, pooled 4 trials, flare design
Bingham, 2007[30] Bingham 2011[76]	2x74 outpatient clinics; USA	1207 males & females, ≥40y	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design

Birbara, 2006[31]	Investigative sites; USA	808 males & females, $\geq 40y$	Knee	ARA functional class, I, II, or III	RCT, flare design
Bocanegra, 1998[32]	Clinic; USA	572 males & females, 28-88y (mean 61-62)	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design
Boswell, 2008[33]	50 centres (Europe & Australia) + 187 centres (Europe & USA)	1908 males & females, $\geq 40y$	Knee	KL scale 2 or 3 and ARA class rating of I,II or III	Pooled RCTs (2; one flare design, one non-flare), flare design
Brandt, 2006[34] (pilot studies)	Community; USA	30 males & females, mean age 62y	Knee	KL $\geq 2$	Cohort design, flare design
Case, 2003[35]	Hospital-rheumatology centre; Chicago, USA	82 males & females, 40-75y	Knee	KL $\geq 1$ , and clinical criteria (pre-enrolment ambulatory pain; moderate pain by a 5-point Likert scale or increased pain.	RCT, flare design
Day, 2000[74]	49 investigative sites in 26 countries	809 males & females, mean age range 62-65y	Knee and hip	ARA functional class I-III, symptomatic for at least 6 months	RCT, flare design
Ehrich, 1999[36]	Clinical centres; USA	219 males & females, $>40y$	Knee	ARA functional class, I, II, or III	RCT, flare design
Essex, 2012[37]	Clinical centre; African-American, USA	322 males & females, $\geq 45y$	Knee	ARA Functional capacity classification I-III	RCT, flare design
Essex 2013[77]	Hispanic population, 31 US centers	$\geq 45y$	Knee	ACR criteria, Functional capacity classification I-III	RCT, flare design
Gibofsky, 2014[38]	Not specified, USA	305 males & females, 41-90 y	Knee and hip	KL 2-3	RCT, flare design
Gineyts, 2004[39]	Subset of larger study; France	201 males & females, mean age 61-62y	Knee and hip	ARA I-III	RCT, flare design



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Goldberg, 1988[40]	Investigative sites; USA	214 males & females, 40-85y (mean 64)	Knee and hip	Radiographic evidence of knee OA-not further defined	RCT, flare design
Gottesdiener, 2002[41]	Investigative sites; USA	617 males & females, ≥40y	Knee	ARA functional class I,II,III	RCT, flare design
Hochberg, 2011[42]	Centres; USA	1234 males & females, ≥50y	Knee	ACR functional class I-III	Pooled RCTs (2), flare design
Katz, 2010[43]	Clinical sites; USA	113 males & females, 28-83y (median 57))	Knee and hip	OA of hip and knee as diagnosed using ACR criteria-no definition of severity	RCT, flare design
Kivitz, 2001[44]	Investigative sites; USA	491 males & females, 28-91y (mean 58-61)	Knee	Confirmation of OA on weight bearing radiograph- no definition of severity	RCT, flare design
Kivitz, 2004[75]	Outpatient sites; USA	1042 males & females, ≥40y	Knee	ACR rating of I, II, III.	RCT, flare design
Leung, 2002[46]	Clinic; USA	677 males & females, ≥40y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Luyten, 2007[46]	Centres; Belgium	181 males & females, ≥40y	Knee and hip	ACR Functional capacity classification I-III	RCT, flare design
Manicourt, 2005[48]	Outpatient clinic; Belgium	90 males & females, 50-81y (mean 63-67)	Knee and hip	Clinical and radiographic evidence of OA-severity not defined.	RCT, flare design
Mazzuca, 2002[49]	Not specified, USA	15 males & females, ≥45y	Knee	KL 2-3	Observational, flare design
McIlwain, 1989[50]	Investigative sites; USA	139 males & females, mean 65y	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design
Mendelsohn, 1991[51]	Investigative sites; USA	139 males & females, 21-88y (mean age 63.3y)	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design

Moskowitz, 2006[52]	Investigative sites; USA	530 males & females, $\geq 45y$	Knee	ACR Functional capacity classification I-III	RCT, flare design
Pareek, 2009[53]	Multi-centre study, India	199 males & females, 40-70y	Knee	Lequesne criteria-score of 5 and above	RCT, flare design
Pareek, 2010[54]	Hospital; India	220 males & females, 40-70y	Knee	Clinical and radiological evidence of OA- severity not defined.	RCT, flare design
Roth, 2004[89]	Physicians private practice or community; USA	326 males & females, 40-85y	Knee	Radiological evidence of OA- severity not defined.	RCT, flare design
Rother, 2007[92]	Outpatient units; Germany	397 males & females, $\geq 40y$	Knee	KL 2-3	RCT, flare design
Schnitzer, 2005[56]	Investigative sites; International (7 countries)	583 males & females, 18-75y	Knee and hip	Diagnosis based on ACR criteria- severity not defined.	RCT, flare design
Scott-Lennox, 2001[57]	Investigative sites; USA	182 males & females, mean 61y	Knee	Not defined	RCT, flare design
Silverfield, 2002[58]	Centres; USA	308 males & females, 35-75y	Knee and hip	Clinical evidence of OA- severity not defined	RCT, flare design
Simon, 2009[90]	Outpatient centres; Canada, USA	775 males & females, 40-85y	Knee	Clinical and radiological evidence of OA- severity not defined	RCT, flare design

Strand, 2011[59]	Investigative sites; Multinational-not specified including USA	875 males & females, 18-80y	Knee and hip	OA according to ACR criteria and requiring NSAID treatment to control symptoms in the month preceding screening	RCT, flare design
Weaver, 1995[91]	Investigative sites; USA	328 males & females, >50y	Knee	ACR clinical criteria-diagnostic	RCT, flare design
Wiesenhutter, 2005[60]	Medical Centres; USA	528 males & females, 40-89y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Williams, 2001[61]	Clinical sites; USA	718 males & females, mean 61-62y	Knee	ACR clinical and radiographic criteria I-III	RCT, flare design
Wittenberg, 2006[62]	Centres (not specified) ; Germany	364 males & females, 50y	Knee	Moderate to severe symptomatic OA of the knee according to ACR criteria.	RCT, flare design
Yeasted, 2014[63] (Pooled, abstract)	USA	219 (merged observational), 137 (merged trial)>40y	Not specified	ACR criteria-diagnostic	2 longitudinal observational studies, placebo arms of 2 clinical trials
Yocum, 2000[78]	USA, 62 study centres	774 males & females, ≥40y	Knee or hip	Diagnosis confirmed by XR and clinical symptoms (not further specified)	RCT, flare design
Young, 2014[64] (abstract)	Multicenter,	305 males & females, >40y	Knee or hip	KL 2-3	RCT, flare design
Zhao, 1999[65]	Centre (not specified); USA, Canada	1004 males & females, ≥18y	Knee	ACR Functional capacity classification I-III	RCT, flare design
<b>NON-DRUG WITHDRAWAL DESIGN STUDIES</b>					

Atukorala, 2016[79] (abstract)	Not specified, USA + Au + Sri Lanka	213 males & females, mean age 62y	Knee	Not specified	3-month, web based longitudinal follow up study
Atukorala, 2016[26] (abstract)		345 males & females, mean age 62y			
Bartholdy, 2016[80]	OA out-patient clinic, Denmark	131 males & females, ≥40y	Knee	Radiographic evidence of OA (severity no defined) and BMI between 20-35 kg/m <sup>2</sup>	RCT
Bassiouni 2015[81] (abstract)	Not specified, Egypt	60 participants not further specified	Knee	Not specified	Observational
Cibere, 2004[87]  Cibere, 2005[88]	Community, Canada	137 males & females, mean age 65y (43- 88) for placebo and 64y (40-83) for glucosamine group	Knee	KL ≥2 on anteroposterior radiograph	RCT
Conrozier 2012[67]	Hospital- rheumatology unit, France	44 males & females, mean age 67.6y	Knee	Radiographic evidence of knee OA-not further defined	Observational
D'Agostino 2005[68]	Hospital- European multicentre	600 males & females, ≥18y	Knee	KL grade 1-4	Observational
Erfani, 2014[45] abstract)  Erfani, 2014[82] (abstract)  Ferreira[83] 2016	Au	268 males & females, mean age 62y  345 males & females, ≥40y	Knee	ACR criteria- meet at least one, KL ≥2	Web based cross over

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Hunter 2014[84] (abstract)					
Makovey 2015[85] (Protocol)					
Jawad, 2005[69]	GPs in France	3000 (for GP study) males & females	Knee	Not defined	n/a, review of surveys. Definition relates to survey of 3000 French GPs
Marty 2009[20]	Community and hospital, France	6085+641males & females, mean age 66.4y (10.9) for flare group, 66.2y (10.2) no flare group	Knee	OA diagnosis based on ACR criteria- severity not defined	Observational
Murphy, 2015[70]	Community based, pain clinics; USA	45 males & females, 37-83y	Knee	ACR criteria- severity not defined	Qualitative
Parry, 2017[86]	Community, UK	719 males & females, ≥50y	Knee	Self-reported knee pain in previous 12 months	Observational
Ricci 2005[55]	Community, USA	329 males & females, 40-65y	Knee and hip	Clinical evidence of OA- severity not defined	Nested case control
Wise 2010[71]	Primary care, hospital, USA	303 males & females, ≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment- not further defined	Observational

Zhang 2009[72]	Primary care, hospital, USA	303 males & females, ≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment-not further defined	Observational
Zhang 2011[73] (abstract)	Not specified	52 males & females, median age 63, (50-72y)	Knee	KL>2	Case-crossover
Zobel, 2016[93]	Hospital databases, Australia	297 males & females, >40y	Knee	ACR criteria, KL ≥2, or patellofemoral OA on radiograph	Web based case-cross over

Acronyms:  
 KL- Kellgran and Lawrence  
 RCT- Randomised Controlled Trial  
 USA- United States of America  
 Au- Australia  
 ACR- Arthritis Center Research  
 ARA- American Rheumatism Association  
 GP- General Practitioner

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3 218 Twenty-one included mixed knee and hip OA groups[25, 30, 32, 38-40, 43, 46-48, 55, 56,  
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6 219 58-60, 64, 72, 74, 76, 78]. In total, 46 publications used a drug withdrawal RCT design[25,  
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8 220 27-33, 35-44, 46-54, 56-65, 74-78, 89-92], four of which were pooled studies[29, 33, 42, 63]  
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11 221 and one used a cohort drug withdrawal design[34] (Table 1). The remaining 22  
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13 222 publications included seventeen observational studies[20, 26, 45, 55, 66-68, 71-73, 79, 81-  
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15 223 86], three RCTs[80, 87, 88], one survey[69] and one qualitative interview study[70]. Nine  
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17 224 of the included studies were abstracts[26, 45, 63, 64, 73, 79, 81, 82, 84]. Two abstracts were  
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19 225 removed as the corresponding full text article was available[70, 93]. Studies using  
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21 226 pooled data or the same dataset were included if they used different definitions of  
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23 227 OA flare[29, 45, 53, 54, 63, 66, 71, 72, 75].  
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### 31 **Rationale given for flare definitions**

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37 231 Six of the included studies gave rationale for the definition used[20, 55, 57, 70, 86, 87].  
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39 232 Cibere[87] outlined face validity checks. It was specified that the flare definition had  
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41 233 been determined by study rheumatologists to be a clinically important change in the  
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43 234 WOMAC score. The definition used by Murphy et al[70] was informed by two  
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45 235 studies[29, 54] which used a drug withdrawal design and from the research team's  
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47 236 own experience. Ricci et al[55] used a combination of data-driven and clinical  
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49 237 judgement approaches to establish an agreed cut point. Parry et al based their  
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3 238 definition on OA flare design studies and flare definitions used in other chronic

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6 239 disease such as back pain and COPD.

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11 241 Marty et al[20] and Scott-Lennox et al[57] were the only studies that undertook

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13 242 empirical investigation of flare definitions.

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18 244 The study by Marty et al[20] was the only study specifically designed to validate a set

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20 245 of predetermined flare criteria, which they did using logistic regression analysis to

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22 246 assign a weight to each of the items identified. A flare up score was determined

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24 247 using a general practitioner database and this was then validated using a

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26 248 rheumatologist database. Pain was not included in the final model.

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31 250 Scott-Lennox et al[57] sought to test whether four measures for flare intensity could

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33 251 be combined to form a reliable and valid index using data from an RCT using a

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35 252 confirmatory factor analysis.

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44 255 **Flare definitions in drug withdrawal studies**

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3 257 **Terminology used**  
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6 258 The majority of publications using a drug withdrawal design used the term "flare" in  
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8 259 their description[25-31, 33, 34, 37-44, 46-50, 52, 54, 56-65, 75-78, 89-92] (n=42; Table 2).  
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261 **Table 2: Definition, terminology and measurement instruments used in all included studies**

<b>DRUG WITHDRAWAL STUDY DESIGN</b>							
<b>First author</b>	<b>Terminology used</b>	<b>Onset/worsening of symptoms/signs (symptom/sign: measurement instrument; operational definition)</b>	<b>Minimum threshold (symptom/sign: measurement instrument; operational definition)</b>	<b>Speed of onset</b>	<b>Duration</b>	<b>Change in medication/healthcare use</b>	<b>Reference / rationale</b>
Altman, 2015[25]	"Flare"	<b>Pain:</b> WOMAC Pain subscale (0-100); increase $\geq 15$ mm	<b>Pain:</b> WOMAC Pain subscale; $\geq 40$ mm	Not specified	Not specified	Not specified	None
Baer, 2005[27]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); increase $\geq 2$ points and $\geq 25\%$	<b>Pain:</b> WOMAC Pain score (0-20); $\geq 6$ and $\geq 1$ item rated 'moderate, severe, or extreme'	Interval between screening and baseline re-measurement unclear	Not specified	Not specified	None
Baraf, 2011[28]	"Flare"	<b>Pain on movement:</b> VAS (0-100mm); increase $\geq 5$ mm	Not specified	1 week washout	Not specified	Not specified	None
Battisti, 2004[29]	"Flare"	<b>Global assessment (investigator):</b> single item, 5-point LK; Worsening $\geq 1$ point	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None

<p>Bingham, 2007[30]</p> <p>Bingham 2011[76]</p>	<p>"Flare"</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100mm); increase <math>\geq 15</math>mm</p> <p>(2) <b>Global assessment of disease status (investigator):</b> single item, 5-point LK; Worsening <math>\geq 1</math> point</p>	<p>(1) <b>Pain walking on flat surface:</b> <math>\geq 40</math>mm on WOMAC VAS3.0 Q1 (0-100)</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; fair, poor, very poor (<i>acetaminophen users only</i>)</p> <p>(3) <b>Global assessment of disease status (patient):</b> VAS 0-100mm; <math>\geq 40</math>mm (<i>acetaminophen users only</i>)</p>	<p>Not specified</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>
<p>Birbara, 2006[31]</p>	<p>"Flare"</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS Q1 (0-100mm); increase <math>\geq 15</math>mm</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; Worsening <math>\geq 1</math> point</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100); <math>\geq 40</math>mm</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; Fair, poor or very poor (<i>paracetamol arm only</i>)</p>	<p>4-15 day washout</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>
<p>Bocanegra, 1998[32]</p>	<p>"Worsening of symptoms"</p>	<p>Two out of the following three:</p> <p>(1) <b>Global assessment (physician):</b> single item, 5-point LK; Increase <math>\geq 1</math> grade</p> <p>(2) <b>Global assessment (patient):</b> Patients global assessment (current symptoms and limitation of activity) 5-point LK; Increase <math>\geq 1</math> grade</p> <p>(3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); Increase <math>\geq 2</math> points</p>	<p>(1) <b>Global assessment (physician):</b> single item, 5-point LK; 'poor/very poor'</p> <p>(2) <b>Global assessment (patient):</b> Patients global assessment (current symptoms and limitation of activity) 5-point LK; 'poor/very poor'</p> <p>(3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); <math>\geq 7</math></p>	<p>3-14d washout</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>

Boswell, 2008[33]	"Flare"	(1) <b>Pain walking on flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global assessment (patient):</b> Patient Global Assessment of Arthritis Condition (PGAC) (unspecified); Worsening $\geq 1$ point	Not specified	Not specified	Not specified	Not specified	None
Brandt, 2006[34] (pilot studies)	"Flare"	Not specified	<b>Pain:</b> WOMAC LK Pain subscale (5-25); $\geq 15$ points	5 half-lives of NSAID washout	Not specified	Not specified	None
Case, 2003[35]	Not used	(1) <b>Pain walking on flat surface:</b> VAS (0-100mm); Increase $\geq 10$ mm (2) <b>Ambulatory pain;</b> 5-point LK; worsening $\geq 1$ point	Not specified	14d washout	Not specified	Not specified	None
Day, 2000[74]	Not used	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> single item, 5-point LK; worsening $\geq 1$ point (3) <b>Global assessment (patient):</b> VAS (0-100mm); increase $\geq 15$ mm ( <i>acetaminophen users only</i> )	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm; (2) <b>Global Assessment (investigator):</b> single item, 5-point LK; 'Fair, poor, or very poor'; (3) <b>Global assessment (patient):</b> VAS (0-100mm); $\geq 40$ mm	Longer than 5 plasma half-lives washout	Not specified	Not specified	None
Ehrich, 1999[36]	Not used	<b>Pain:</b> VAS (0-100mm); increase $\geq 15$ mm	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Longer than 5 plasma half-lives washout of NSAID	Not specified	Not specified	None

Essex, 2012[37]	"Flare"	(1) <b>Global Assessment (Physician):</b> 5-point LK; increase $\geq 1$ grade (2) <b>Global Assessment (patient):</b> 5-point LK; increase $\geq 1$ grade	(1) <b>Global Assessment (Physician):</b> 5-point LK; 'Fair, poor or very poor' (2) <b>Global Assessment (patient):</b> 5-point LK; 'Fair, poor or very poor' (3) <b>Pain:</b> VAS (0-100mm); 40-90mm	48 hour withdrawal	Not specified	Not specified	None
Essex 2013[77]	"Flare"	Not specified	(1) <b>Global Assessment of arthritis (Physician):</b> Minimum rating of 3 (2) <b>Global Assessment of arthritis (patient):</b> Minimum rating of 3 (3) <b>Pain:</b> VAS (0-100mm); 40-90mm	48 hour withdrawal	Not specified	Not specified	None
Gibofksy, 2014[38]	"Flare"	<b>Pain:</b> WOMAC Pain VAS; increase $\geq 15$ mm	<b>Pain:</b> WOMAC Pain VAS; $\geq 40$ mm	Not specified	Not specified	Not specified	None
Gineyts, 2004[39]	"Flare"	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point scale: worsening $\geq 1$ point	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm	5 half-lives of NSAID washout	Not specified	Not specified	None
Goldberg, 1988[40]	"Flare"	(1) <b>Pain:</b> Investigator assessed pain grade (None/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase $\geq 1$ grade in two items OR increase $\geq 2$ grade in one item	Not specified	2-14 day washout until flare	Not specified	Not specified	None
Gottesdiener, 2002[41]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (Investigator):</b> 5-point LK; Increase $\geq 1$ point	(1) <b>Pain on walking:</b> VAS (0-100mm); $\geq 40$ mm	3-15 day washout	Not specified	Not specified	None

Hochberg, 2011[42]	"Flare"	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; worsening $\geq 1$ point	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None
Katz, 2010[43]	"Flare"	Not specified	<b>Pain:</b> Pain score (0-10); $\geq 5$	Not specified-washout until flare occurred	Not specified	Not specified	None
Kivitz, 2001[44]	"Flare"	<b>Pain:</b> Patients Assessment of Pain Score (0-10) (unspecified); increase $\geq 2$ points	<b>Pain:</b> Patients Assessment of Pain Score (0-10) (unspecified); $\geq 5$	5 drug half-lives or 48 hours	Not specified	Not specified	None
Kivitz, 2004[75]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); worsening $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point LK; worsening $\geq 1$ point	Not specified	NSAID dependent half-life washout	Not specified	Not specified	None
Leung, 2002[46]	"Flare"	(1) <b>Pain on walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point LK; worsening $\geq 1$ point	(1) <b>Pain on walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm (2) <b>Global Assessment (patient):</b> (0-100mm); $\geq 40$ mm (acetaminophen users only) (3) <b>Global Assessment (investigator):</b> 5-point LK; 'Fair, poor, or very poor' (acetaminophen users only)	Determined by drug half-life washout	Not specified	Not specified	None

Luyten, 2007[47]	"Flare"	(1) <b>Global Assessment (Patient):</b> 5-point LK; Increase $\geq 1$ grade (2) <b>Global Assessment (physician):</b> 5-point LK; increase $\geq 1$ grade (3) <b>Composite definition:</b> Lequesne Osteoarthritis Severity Index (0-24); increase $\geq 2$ points	(1) <b>Global Assessment (Patient):</b> 5-point LK; 'Fair, poor or very poor' (Not on treatment – 'Poor or very poor') (2) <b>Global Assessment (physician):</b> 5-point LK; 'Fair, poor or very poor' (Not on treatment – 'Poor or very poor') (3) <b>Composite definition:</b> Lequesne Osteoarthritis Severity Index (0-24); $\geq 7$ (4) <b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	2-14 day washout	Not specified	Not specified	None
Manicourt, 2005[48]	"Flare"	<b>Pain when walking on a flat surface:</b> VAS (0-100mm) ; $\geq 10$ mm	Not specified	7-10 days washout	Not specified	Not specified	None
Mazzuca, 2002[49]	"Flare"	<b>Pain on standing:</b> WOMAC LK Pain Q5 'severe or extreme' after the washout AND decreased after resumption of usual analgesic drugs and/or NSAIDs	Not specified	Drug washout 5 half lives	Not specified	Not specified	None
McIlwain, 1989[50]	"Flare"	No measurement instrument: Increase in pain on motion, swelling, tenderness, redness and/or heat (unspecified if patient/physician/investigator reported)	Not specified	2-14 day washout	Not specified	Not specified	None
Mendelsohn, 1991[51]	"Worsening of arthritis condition"	(1) <b>Pain:</b> Pain scale (0-3) (0=none, 3=severe); worsening score (2) <b>Global (physician):</b> (0-100); worsening score	Not specified	Up to 14 days washout	Not specified	Not specified	None

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Moskowitz, 2006[52]	"Flare"	(1) <b>Global assessment (patient):</b> 5-point LK; increase $\geq 1$ grade (2) <b>Global Assessment (physician):</b> 5-point LK; $\geq 1$ grade increase (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); increase $\geq 2$ points	(1) <b>Global assessment (patient):</b> 5-point LK; '(Fair), poor, or very poor' (2) <b>Global Assessment (physician):</b> 5-point LK; '(Fair), poor or very poor' (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); Minimum $\geq 7$ (4) <b>Pain walking on a flat surface:</b> VAS (0-100mm); $\geq 40$ mm	NSAID washout of 5 half-lives or at least 2 days	Not specified	Not specified	None
17 18 19 20 21 22 23	Pareek, 2009[53]	"Flare-up"	(1) <b>Pain:</b> 11-point NRS; increase $\geq 2$ points during previous 2-5 days (2) Signs and symptoms suggestive of inflammation, morning stiffness and nocturnal pain interfering with sleep	<b>Pain:</b> Pain intensity of at least 4 on a 11-point NRS during physical activity for past 24 hours	Placebo washout for 24-48 hours	2-5 days	Not specified	None
24 25 26 27 28 29 30	Pareek, 2010[54]	"Flare"	Flare symptoms noted but not part of definition: morning stiffness, erythema, nocturnal pain, and swelling/inflammation	(1) <b>Pain with physical activity:</b> VAS 0-10; $\geq 6$ (2) <b>Composite index:</b> WOMAC Total LK; $\geq 25$ . (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); $\geq 5$	Not specified	2-5 days	Not specified	None
31 32 33 34 35 36	Roth, 2004[89]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); increase $\geq 2$ points and $\geq 25\%$	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); Score $\geq$ 'moderate' on at least 1 of the 5 items, (ii) Pain score $\geq 6$	Washout period of at least 3 days per week past month	Not specified	Not specified	None



Rother, 2007[92]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; increase $\geq 1$ grade	(1) <b>Pain on walking:</b> VAS (0-100mm); $\geq 40$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; 3-5	Not specified	Not specified	Not specified	None
Schnitzer, 2005[56]	"Flare"	No tool: increase in pain	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Not specified	24 hours	Not specified	None
Scott-Lennox, 2001[57]	"Flare"	(1) <b>Pain:</b> VAS (0-100mm); $\geq 20$ mm (2) <b>Pain (physician):</b> 4-point LK; worsening $\geq 1$ point (3) <b>Global Assessment (patient):</b> 4-point LK; worsening $\geq 1$ point (4) <b>Global Assessment (physician):</b> 4-point LK; worsening $\geq 1$ point	(1) <b>Pain:</b> VAS (0-100mm); $\geq 40$ mm at baseline (2) <b>Pain (physician):</b> 4-point LK; $\geq 2$ (3) <b>Global Assessment (patient):</b> 4-point LK; $\geq 2$ (4) <b>Global Assessment (physician):</b> 4-point LK; worsening $\geq 2$	14 day washout	Not specified	Not specified	Confirmatory Factor Analysis
Simon, 2009[90]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale; increase $\geq 2$ and $\geq 25\%$	<b>Pain:</b> WOMAC LK3.1 Pain subscale; $\geq$ 'moderate' on $\geq 1$ item	14 day washout	Not specified	Not specified	None
Silverfield, 2002[58]	"Flare"	<b>Pain:</b> No measurement tool; significant increase	Not specified	Not specified	Not specified	Pain requiring supplemental analgesic medication and/or an increase in NSAID dose	None
Strand, 2011[59]	"Flare"	<b>Global Assessment (patient):</b> 5-point LK; Increase $\geq 1$	(1) <b>Global Assessment (patient):</b> 5-point LK; 'Fair, poor or very poor' (2) <b>Pain:</b> (0-10 NRS); $\geq 4$ but $< 9$ (3) <b>Global Assessment (physician):</b> 5-point LK; 'Fair, poor or very poor'	14 day washout	Not specified	Not specified	None

Weaver, 1995[91]	"Flare"	(1) <b>Global Assessment (Physician)</b> : 5-point Likert; increase $\geq 1$ grade (2) <b>Global Assessment (patient)</b> : 5-point LK; increase $\geq 1$ grade (3) <b>Pain</b> : Worsening pain on motion and weight bearing	(1) <b>Global Assessment (Physician)</b> : 5-point Likert; $\geq 2$ (2) <b>Global Assessment (patient)</b> : 5-point LK; $\geq 2$	2-14 day washout	Not specified	Not specified	None
Wiesenhutter, 2005[60]	"Flare"	(1) <b>Pain on walking on flat surface</b> : WOMAC VAS3.0 Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (Investigator)</b> : 5-point LK; worsening $\geq 1$ unit	(1) <b>Pain on walking on flat surface</b> : WOMAC VAS3.0 Q1 (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None
Williams, 2001[61]	"Flare"	(1) <b>Global Assessment (patient)</b> : 5-point LK; Increase $\geq 1$ point (2) <b>Global Assessment (physician)</b> : 5-point LK; increase $\geq 1$ point(3) <b>Composite Index</b> : Lequesne OA Severity Index (0-24); Increase $\geq 2$ points	(1) <b>Global Assessment (patient)</b> : 5-point LK; '(Fair), poor or very poor' (2) <b>Global Assessment (physician)</b> : 5-point LK; '(Fair), poor or very poor' (3) <b>Composite Index</b> : Lequesne OA Severity Index (0-24); $\geq 7$ (4) <b>Pain</b> : VAS (0-100mm); $\geq 40$ mm	2-14 days	Not specified	Not specified	None
Wittenberg, 2006[62]	"Flare"	<b>Pain</b> : VAS (0-100mm); Increase $\geq 10$ mm	<b>Pain</b> : VAS (0-100mm); $\geq 40$ mm	2-7 day washout	Not specified	Not specified	None
Yeasted, 2014[63] (Pooled, abstract)	"Flare"	<b>Pain</b> : 0-10 NRS; Increase $\geq 2$ points over the mean pain score from the previous 3 days	<b>Pain</b> : Average daily 0-10 NRS; 4-9	Not specified	Not specified	Not specified	None
Yocum 2000[78]	"Flare"	<b>Disease activity</b> (1) <b>Global (Investigator)</b> : Reduction of $\geq 1$ grade (2) <b>Global Assessment (Patient)</b> : 100-mm VAS; Increase of $\geq 10$ mm	Not specified	$\geq 3$ days washout	Not specified	Not specified	None

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		(3) <b>Pain: Overall assessment (patient):</b> 100-mm VAS; $\geq 35$ mm					
Young, 2014[64]	"Flare"	(3) <b>Pain:</b> WOMAC pain subscale; increase $> 15$ mm	<b>Pain:</b> WOMAC Pain subscale $> 40$ mm	Not specified	Not specified	Not specified	None
Zhao, 1999[65]	"Flare"	No measurement tool: Worsening of signs and symptoms after discontinuation of NSAIDs of analgesics	Not specified	2-7 day washout	Not specified	Not specified	None
<b>NON-DRUG WITHDRAWAL STUDY DESIGN</b>							
Atukorala, 2016[79] (abstract)	"Flare"	<b>Pain:</b> (10-point NRS); increase $> 2$ points from the mildest knee OA pain intensity reported at day 0	Not specified	Not specified	Not specified	Not specified	None
Atukorala, 2016[26] (abstract)							
Bartholdy, 2016[80]	"Flare"	Not specified	<b>Pain:</b> (10-point NRS): Pain $> 5$	Not specified	Not specified	Not specified	None
Bassiouni 2015[81] (abstract)	"Flare"	Not specified	<b>Global Assessment (physician):</b> KOFUS $\geq 7$	Not specified	Not specified	Not specified	None
Cibere, 2004[87]	"Flare"	(1) Patients perception of worsening of symptoms	Not specified	Not specified	Not specified	Not specified	Definition determined by study rheumatologists to be a clinically important change in WOMAC-Ehrich2000/
Cibere, 2005[88]		(2) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100mm); increase $\geq 20$ mm (3) <b>Global Assessment (physician):</b> 5-point LK; worsening $\geq 1$ grade					

							Bellamy 1998
Conrozier 2012[67]	"Flare"	Fulfilled 4 following criteria: (1) <b>Pain:</b> No measurement tool; 'sudden aggravation of knee pain' (2) causing nocturnal awakenings, (3) clinical evidence of effusion.	Not specified	Sudden aggravatio n of knee pain, whose beginning was identifiable	Not specified	Not specified	None
D'Agostino 2005[68]	"Flare"	Not specified	<b>Pain intensity during physical activity:</b> VAS-(0-100mm); $\geq 40$ mm	Not specified	48 hours	Not specified	None
Erfani, 2014[45] abstract)  Erfani, 2014[82] (abstract)  Ferreira[83] 2016  Hunter 2014[84] (abstract)  Makovey 2015[85] (Protocol)	Exacer bation	<b>Pain:</b> VAS (0-100mm); Increase $\geq 20$ mm from mildest pain score reported at baseline	Not specified	Not specified	Not specified	Not specified	None

Jawad, 2005[69]	Exacerbation	<b>Pain symptoms:</b> Increased morning stiffness, night pain and synovial fluid effusion	Not specified	Not specified	Not specified	Not specified	None
Marty 2009[20]	"Flare"	No measurement tool: Morning stiffness >20mins, nocturnal awakening, limping, knee swelling, increased warmth, effusion	Not specified	Not specified	48 hours	Not specified	Regression analysis of cross-sectional data to validate proposed flare criteria
Murphy, 2015[70]	"Flare"	(1) Investigator definition: Inadequate pain relief for an episode of intense pain that is usually brought on by too much activity. (2) Participant definitions: Described in terms of pain quality, timing (onset and duration), antecedents and consequences. (3) <b>Pain magnitude:</b> increase in pain or 'intense' or 'severe' level of pain	<b>Pain:</b> $\geq 40$ of 100mm or $\geq 4$ of 10 on NRS	Patients described: 'Quick' or 'sudden'	Patients: 10 seconds to 15 minutes	Patients: Rest or take additional medication	For investigator definition: Battisti 2004, Pareek 2010. Plus researchers own experience.
Parry, 2017[86]	"Flare"	<b>Pain:</b> Recalled worst pain intensity in previous 6 months 0-10 NRS; $\geq 5$	<b>Pain:</b> Recalled worse pain to be $\geq 2$ points higher than recalled average pain (0-10 NRS) in previous 6 months	Not specified	Not specified	Not specified	Based on previous studies defining knee flares in OA and flares in diseases such as back

							pain and COPD.
Ricci 2005[55]	"Flare up"	<b>Pain:</b> Self-reported flare severity rating 0-10 NRS; increase $\geq 2$ point over usual pain severity	Not specified	Not specified	Not specified	Not specified	Based on statistical analysis and clinical judgement
Wise 2010[71]	"Flare"	Not specified	<b>Pain:</b> WOMAC Pain subscale (0-10); score in highest 30% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2009[72]	"Exacerbation or flare"	Not specified	(1) Pain: WOMAC pain subscale 0-10 (total score of 50 normalised to a 0-10 scale); score of $\geq 5$ , a score corresponding to highest 33% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2011[73] (abstract)	"Exacerbation"	<b>Pain:</b> WOMAC Pain score VAS (0-500); increase $\geq 100$ units	Not specified	Not specified	Not specified	Not specified	None
Zobel, 2016[93]	Exacerbation	<b>Pain:</b> 0-10 NRS; Increase $\geq 2$	(1) Disabling pain	Not specified	8 hours	Not specified	None

Acronyms:  
 COPD- Chronic Obstructive Pulmonary Disease  
 KOFUS- Knee Osteoarthritis Flare-up Score  
 NRS-Numerical Rating scale  
 VAS- Visual Analogue Score  
 WOMAC- Western Ontario and McMaster Universities Osteoarthritis Index

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3 One study used the term “flare-up”[53], two studies referred simply to “worsening of  
4 symptoms” [32, 51] and three studies used no specific label[35, 36, 74].  
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### 10 **Coverage of key components**

11 *Onset/worsening of symptoms and signs beyond normal-day-to-day variability:* Forty-  
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13 four studies included onset or worsening of signs and symptoms as part of their  
14 definition[25, 27-33, 35-42, 44, 46-54, 56-65, 74-76, 78, 89-92]. All studies included  
15 increased pain intensity in their definition. A further two[53, 54] specified further signs  
16 and symptoms. These included swelling, inflammation, erythema, morning stiffness  
17 and nocturnal pain. No studies quantified day-to-day variability.  
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31 Twenty-six measurement tools were used to define onset/worsening of symptoms  
32 and signs. The most commonly used tools were the Western Ontario & McMaster  
33 Universities Arthritis index (WOMAC) Q1 (pain on walking on flat surface) 100mm  
34 Visual Analogue Scale (VAS) (n=9)[30, 31, 33, 39, 42, 46, 60, 74, 76] and the  
35 Investigator Assessment of Disease Status (n=11)[29-31, 39, 41, 46, 60, 74-76, 78]  
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43 (Table 3).  
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**Table 3: Summary of number and type of single and multi-item measurement tools used.**

<b>Single item scales:</b>	
Pain on activity:	WOMAC Q1 3.0 VAS 'pain on walking on a flat surface' (0-100mm) [n=11] Pain on walking VAS (0-100mm) [n=5] Pain on movement VAS (0-100mm); Ambulatory pain (5-point Likert); Pain with physical activity VAS 11-point scale [n=2]
Pain (not further specified):	Pain VAS (0-100mm) [n=15] Patients Assessment of Pain Score (0-10); Pain Scale (0-3); Pain NRS (0-10) [n=11]
Standing knee pain	Item 5 WOMAC pain scale [n=1]
Global rating (physician/ investigator)	Investigator Assessment of Disease Status [n=11] Physicians Global Assessment of Arthritis [n=6] Physician Global Assessment of OA [n=2] Physician Global Assessment of Disease Status [n=2]; Investigator Assessed Pain Grade; (Physician) Overall Disease Activity (0-100); Physicians Pain Assessment (4-point LK) [n=3]
Global rating (patient)	Patients Global Assessment of Arthritis [n=7] Patient Global Assessment of OA [n=3] Patient Global Assessment of Disease Status [n=4]
<b>Multiple-item scales:</b>	
	Lequesne OA Severity Index [n=5] WOMAC LK3.1 (0-20) [n=3] WOMAC LK Pain subscale (0-25); WOMAC OA Index



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Questionnaire; WOMAC knee pain score (0-500) [n=7];  
KOFUS (0-14)

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N, number of included studies; WOMAC, Western Ontario and McMaster Universities  
Osteoarthritis Index; VAS, visual analogue scale; OA, osteoarthritis; KOFUS, Knee Osteoarthritis  
Flare-up Score.

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4 In addition, the format of global ratings appears to be variable as is use and  
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6 reporting of the WOMAC[94]. However, despite the exact format of reporting being  
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8 inconsistent, in general, studies used single items in 4 areas – pain on activity, pain  
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10 (not necessarily on activity), physician/investigator global rating and patient global  
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12 rating.  
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18 *Temporal characteristics:* None of the included drug withdrawal design studies  
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20 reported a specific time for defining the speed of onset of symptoms. However, they  
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22 did describe withdrawal or ‘washout’ periods whereby, after withdrawal of usual  
23  
24 medication, participants were given a certain time frame in which to experience ‘flare’  
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26 symptoms in order that they were entered into the study. In total 30 of the studies  
27  
28 specified a withdrawal period[28, 31, 32, 34-37, 39-41, 44, 46-53, 57, 59, 61, 62, 65, 74, 75, 77, 78,  
29  
30 89-91].For studies using a drug withdrawal design the duration of the washout period  
31  
32 differed between studies, ranging from 2-15 days.  
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38 Four studies specified a time period for minimum duration of symptoms which  
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40 ranged from 24 hours to 5 days[53, 54, 56, 58] .  
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46 *Change in medication or healthcare usage:* Only one study used increase in  
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48 medication as part of their definition; ‘pain requiring supplemental analgesic  
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50 medication and/or an increase in NSAID dose’[58].  
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4 *Additional domains:* Thirty-six studies included a minimum threshold which was  
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6 usually a minimum level of pain that was required before the participant was  
7  
8 considered to have a flare[25, 27, 29-32, 34, 36-39, 41-44, 46-48, 52-54, 56, 57, 59-64, 74, 76, 77,  
9  
10 89-92]. There was general concordance with the minimum thresholds that different  
11  
12 measurement tools used with a few exceptions. A threshold of 40mm on a 0-100mm  
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14 scale was used in eight of ten studies using the WOMAC VAS 3.0 Q1 'pain on walking  
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16 on a flat surface'[30, 31, 39, 42, 46, 60, 74, 76] and four of fourteen studies using the  
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18 Patient Global Assessment of Disease Status[30, 46, 74, 76]. In studies using various  
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20 forms of investigator/physician global assessment, the majority adopted a minimum  
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22 threshold for a flare of 'fair, poor or very poor' [30, 31, 46, 74]. The minimum threshold  
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24 on the Lequesne index (0-10) was either five[54] or seven[47, 52, 61].  
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### 33 **Flare definitions in non-withdrawal flare/ discontinuation studies**

#### 34 **Terminology used**

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44 "Flare" was the term most common used in non-withdrawal design studies[20, 26, 67,  
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46 68, 70, 71, 79-81, 86, 88](n=11) (Table 2). One study used the term "flare-up"[55], eight  
47  
48 used "exacerbation"[45, 66, 69, 73, 82-85] (five publications were from the same team)  
49  
50 and one referred to both "exacerbation" and "flare"[72]. None referred to "worsening  
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52 of symptoms" or did not use any specific label.  
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## Coverage of key components

*Onset/worsening of symptoms and signs beyond normal-day-to-day variability:*

Sixteen of twenty-two studies used onset or worsening of symptoms in their definition[26, 45, 55, 67, 69, 70, 73, 79, 82-88, 93]. Two studies did not use pain intensity as part of its definition[20, 81]. Three studies included symptoms other than pain in their definition[20, 67, 69]. These included nocturnal awakenings, effusion, morning stiffness, night pain, limping, and warmth.

The Murphy et al[70] study included an investigator definition of flare but also sought to describe patient experience of flares through face to face individual interviews.

Both investigator and patient definitions included onset/worsening of symptoms and signs however there was no differentiation from day-to-day variability.

Seven studies used a measurement tool to define onset of signs and symptoms (Table 3). These included the Pain NRS (0-10)[26, 55, 66, 79, 86], WOMAC knee pain score VAS (0-500)[73], pain walking on a flat surface (WOMAC)[87, 88], Global Assessment of Disease Status (physician) (Likert 5-point scale)[87, 88], and knee pain VAS not further specified (0-100)[45, 82-85].

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4 *Temporal characteristics:* Only one study set a definition for speed of onset,  
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6 describing this only as 'sudden' with no further specification[67]. Patients in the  
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8 Murphy et al study used the terms 'quick' and 'sudden' to describe flare onset[70].  
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10 Three studies specified a minimum duration of symptoms ranging from 8 to 48  
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12 hours[20, 66, 68]. In the Murphy et al study patients described duration of between  
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14 hours[20, 66, 68]. In the Murphy et al study patients described duration of between  
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16 10 seconds to 15 minutes[70].  
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21 *Change in medication/healthcare usage:* No studies used change in medication or  
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23 healthcare usage as part of their definition. However, in Murphy et al patients  
24  
25 reported either taking rest or using additional medication[70].  
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31 *Additional Domains:* Two studies defined distribution-based minimum thresholds for  
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33 flare as the highest 30%<sup>72</sup> or highest 33%<sup>73</sup> of WOMAC Pain Subscale scores among  
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35 participants in the Longitudinal Examination of Arthritis Pain (LEAP) cohort (total  
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37 score out of 50 was normalised to a 0-10 scale).  
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## 46 **DISCUSSION**

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52 Flares in OA are recognised in existing clinical guidance[95] and reviews[96, 97] but  
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54 typically merit little more than a passing mention. Only one recent study has sought  
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3 to define flare-ups in hip and knee OA but this only yielded 23 studies and four of  
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5 the included studies did not contain clear definitions for a flare-up[98]. Our review  
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7 was motivated by an interest in seeking greater clarity on how these phenomena  
8  
9 might be defined by undertaking a broad search strategy, noting that similar efforts  
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11 have been pursued in other chronic diseases. While we found no current single,  
12  
13 agreed definition of OA flare, our review of 69 published studies suggests a number  
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15 of common domains which may capture cardinal features. These were:  
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17 onset/worsening of symptoms and signs, attainment of a minimum symptom  
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19 threshold during flare, speed of onset/worsening, and duration of elevated  
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21 symptoms/signs. However, we found considerable variation in how these domains  
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23 have been operationalised for measurement suggesting the need for further  
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25 conceptual clarification and consensus.  
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36 Each potential cardinal feature of OA flare presents different challenges for achieving  
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38 consensus and how these are resolved depends partly on whether the goal is a  
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40 shared definition for reproducible and comparative research or for identifying these  
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42 phenomena in routine practice. Most studies included in our review required an  
43  
44 increase in pain over 'usual' or 'baseline' intensity. Although this was measured using  
45  
46 a wide range of measurement instruments several studies selected an increase of 2  
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48 or more points on a 0-10 scale providing a possible starting point for consensus. Yet  
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50 this possible 'signal' is arguably difficult to interpret without also considering the  
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3 amount of background 'noise', i.e. within-person diurnal[99] and day-to-day  
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6 variability[100], and the absolute level ('minimum threshold') of pain during a flare. In  
7  
8 the study by Marty et al an increase in pain was not independently associated with  
9  
10 flare-up after adjusting for other potential features[20]. Further research on detecting  
11  
12 flares over within-person 'normal' variability by collecting frequent repeated  
13  
14 measures of pain intensity may be valuable but this approach would not be feasible  
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16 when identifying flares presenting at the point of care in routine clinical practice.  
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18 Instead, this may have to rely on the judgement of the patient and/or clinician, the  
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20 approach used, for example, in defining exacerbations in COPD[1]. A similar  
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22 consideration surrounds the speed of onset, which was not well defined by studies in  
23  
24 our review. Drug withdrawal design studies specified washout periods between 2-15  
25  
26 days but this is unlikely to be synonymous with speed of onset. The remaining  
27  
28 studies used terms such as 'sudden' and 'quick'. In COPD, for instance, a judgement  
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30 around 'acute onset' or 'sudden onset' appears to be acceptable for clinical  
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32 recommendations but we would add that the speed of onset of OA flares ought to  
33  
34 be considered also in relation to underlying biologically plausible mechanisms.  
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36 Indeed presumed aetiology has been argued as a useful feature in defining acute  
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38 exacerbations in COPD[101]. Minimum duration ranged from 8 hours to 5 days in our  
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40 review however this was not widely reported. COPD definitions refer to a 'sustained  
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42 worsening' of symptoms[2] but does not appear to be a feature in other chronic  
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44 diseases. A minimum duration in OA may help distinguish flares from day-to-day  
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3 variability. Increase in medication was not found to be a key component in this  
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6 review despite it being a feature in other chronic diseases; AS[5], SLE[4, 102],  
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8 Inflammatory Bowel Disease[103], COPD[1]. Interference with function did not emerge  
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10 strongly from our review as a cardinal feature of OA flare. In other chronic  
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12 musculoskeletal conditions, such as back pain, interference with function was not  
13  
14 shown to be significantly associated with having a flare up[104] and this domain does  
15  
16 not feature in the definitions of exacerbations or flares in diseases such as COPD[1,  
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18 2], asthma[3], AS[5] or SLE[4].  
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26 Our review has several strengths but also some weaknesses that deserve attention.  
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28 We adopted a broad search strategy, covering a wide range of databases, and  
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30 featuring bibliography checks, contact with authors, inclusion of conference  
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32 abstracts, no language restrictions, and a minimal threshold (any description or  
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34 definition of flare) for inclusion. Five studies that were included in the Cross et al[98]  
35  
36 review were not included in this study; four did not contain a clear definition of flare-  
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38 up, including one which gave a definition of knee OA progression and the final paper  
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40 by Sands et al[105] was not in our search but the original study was[59]. We did not,  
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42 however, search the grey literature and we did not include some potential synonyms  
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44 as search terms ('attack', 'episode', 'fluctuations'). Nevertheless, we argue that our  
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46 review provides a reasonably comprehensive summary of how 'flares' in OA have  
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48 been described and defined in the medical literature. The majority of studies describe  
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3 experimental 'flare design' trials in which flares are induced by drug withdrawal prior  
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6 to enrolment and randomisation. While intentional or unintentional reduction in  
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9 usual analgesia may indeed be one trigger for flare, experimentally induced flares  
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11 should not be assumed to represent 'naturally occurring' flares. Flare design trials, for  
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13  
14 example, are unlikely to capture change in management or healthcare usage that  
15  
16 may be a common consequence of OA flares – something that is included in flare  
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18 definitions in other conditions such as AS[5], SLE[4, 102], inflammatory bowel  
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21 disease[103], and COPD[1].  
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26 A systematic review such as this cannot hope to resolve the need for a common  
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29 conception and definition of flares in OA. Definitions for exacerbations of disease  
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32 states are generally reached through a long process of consensus exercises involving  
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35 key stakeholders, experts and patients in addition to appraisal of relevant literature  
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38 from studies using multiple methods[6, 8, 106]. However, we believe that a consensus  
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41 definition that is reliable, valid, and feasible and widely acceptable both clinically and  
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44 for research purposes should now be sought.  
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## 46 **CONCLUSION**

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51 A broad range of ad-hoc definitions currently exist in the medical literature. The  
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54 majority are from drug-withdrawal or flare-induced trials rather than 'naturally'  
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3 occurring flares. The cardinal feature is pain intensity with minimum symptom  
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6 threshold being another important feature. This review has identified the need to  
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9 gain consensus on a common definition that can be used for research and clinical  
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11 application.  
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## **Contributions**

All authors were involved in conception and design of the study, analysis and interpretation of data, drafting the article, critical revision of the article for important intellectual content, final approval of the article. ELP and MJT extracted and synthesised data. ELP assembled the data.

GMP (g.m.peat@keele.ac.uk ) takes responsibility for the integrity of the work as a whole from inception to finished article.

## **Data sharing statement**

No unpublished data is available following this study

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### 31 **Competing interest statement**

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### 46 **Figure and Table Legends**

47 Figure 1: PRISMA Flowchart

48 Table 1: Characteristics of all included studies

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50 Table 2: Summary of number and type of single and multi-item measurement  
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Table 3: Definition, terminology and measurement instruments used in all included studies

Supplementary data: Database search strategy

For peer review only

## REFERENCES

- 1 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of COPD: GOLD 2016.
- 2 National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management (CG101). London: NICE 2010.
- 3 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention: GINA 2015.
- 4 Ruperto N, Hanrahan L, Alarcón G, et al. International consensus for a definition of disease flare in lupus, *Lupus* 2011;20:453-62.
- 5 Stone MA, Pomeroy E, Keat A, et al. Assessment of the impact of flares in ankylosing spondylitis disease activity using the Flare Illustration, *Rheumatology* 2008;47:1213-8.
- 6 Bingham CO, Alten R, Bartlett SJ, et al. Identifying Preliminary Domains to Detect and Measure Rheumatoid Arthritis Flares: Report of the OMERACT 10 RA Flare Workshop, *The Journal of Rheumatology* 2011;38:1751-8.

1  
2  
3  
4 7 Bykerk VP, Lie E, Bartlett SJ, et al. Establishing a Core Domain Set to Measure  
5  
6 Rheumatoid Arthritis Flares: Report of the OMERACT 11 RA Flare Workshop, *The*  
7  
8 *Journal of Rheumatology* 2014;41:799-809.  
9

10  
11  
12 8 Bartlett SJ, Hewlett S, Bingham CO, et al. Identifying core domains to assess flare in  
13  
14 rheumatoid arthritis: an OMERACT international patient and provider combined  
15  
16 Delphi consensus, *Annals of the Rheumatic Diseases* 2012;71:1855-60.  
17  
18

19  
20  
21 9 Taylor WJ, Shewchuk R, Saag KG, et al. Toward a valid definition of gout flare:  
22  
23 Results of consensus exercises using delphi methodology and cognitive mapping,  
24  
25 *Arthritis Care & Research* 2009;61:535-43.  
26  
27

28  
29  
30 10 Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for  
31  
32 Eczema (HOME) statement to assess clinical signs of atopic eczema in trials, *J Allergy*  
33  
34 *Clin Immunol* 2014;134:800-7.  
35  
36

37  
38 11 Holla JFM, van dL, Knol DL, et al. The association of body-mass index and  
39  
40 depressed mood with knee pain and activity limitations in knee osteoarthritis: results  
41  
42 from the Amsterdam osteoarthritis cohort, *BMC Musculoskeletal Disorders*  
43  
44 2013;14:296.  
45  
46

47  
48  
49 12 Collins JE, Katz JN, Dervan EE, et al. Trajectories and risk profiles of pain in persons  
50  
51 with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis  
52  
53 initiative, *Osteoarthritis and Cartilage* 2014;22:622-30.  
54  
55

1  
2  
3 13 Leffondré K, Abrahamowicz M, Regeasse A, et al. Statistical measures were  
4  
5  
6 proposed for identifying longitudinal patterns of change in quantitative health  
7  
8 indicators, *J Clin Epidemiol* 2004;57:1049-62.  
9

10  
11  
12 14 Emrani PS, Katz JN, Kessler CL, et al. Joint space narrowing and Kellgren–Lawrence  
13  
14 progression in knee osteoarthritis: an analytic literature synthesis, *Osteoarthritis and*  
15  
16 *Cartilage* 2008;16:873-82.  
17

18  
19  
20  
21 15 Bartlett SJ, Ling SM, Mayo NE, et al. Identifying common trajectories of joint space  
22  
23 narrowing over two years in knee osteoarthritis, *Arthritis Care & Research*  
24  
25 2011;63:1722-8.  
26

27  
28  
29 16 Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip  
30  
31 and knee osteoarthritis – an OARSI/OMERACT initiative, *Osteoarthritis and Cartilage*  
32  
33 2008;16:415-22.  
34  
35

36  
37  
38 17 Arthritis Research UK. Osteoarthritis: Patient Information Booklet. 2012.  
39

40  
41  
42 18 Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation,  
43  
44 *Rheumatology* 2005;44:7-16.  
45

46  
47  
48 19 Smith TO, Zou K, Abdullah N, et al. Does flare trial design affect the effect size of  
49  
50 non-steroidal anti-inflammatory drugs in symptomatic osteoarthritis? A systematic  
51  
52 review and meta-analysis, *Annals of the Rheumatic Diseases* 2016;75:1971-8.  
53  
54



1  
2  
3  
4 20 Marty M, Hilliquin P, Rozenberg S, et al. Validation of the KOFUS (Knee  
5  
6 Osteoarthritis Flare-Ups Score), *Joint Bone Spine* 2009;76:268-72.  
7

8  
9  
10 21 Rutjes AS, Jüni P, Da Costa BR, et al. Viscosupplementation for osteoarthritis of the  
11  
12 knee: A systematic review and meta-analysis, *Ann Intern Med* 2012;157:180-91.  
13

14  
15 22 Higgins J, Green S, eds. Cochrane handbook for systematic reviews of  
16  
17 interventions Version 5.1.0. Available from [www.handbook.cochrane.org](http://www.handbook.cochrane.org).: The  
18  
19 Cochrane Colloboration 2011.  
20  
21

22  
23  
24 23 Popay J, Roberts H, S, A., et al. Guidance on the conduct of narrative synthesis in  
25  
26 systematic reviews: A product of the ESRC methods programme Lancaster: ESRC  
27  
28 Method Programme, 2006.  
29  
30

31  
32  
33 24 Thomas J, Harden A, Newman M. Synthesis: Combining results systematically and  
34  
35 appropriately. In: Gough A, Oliver S, Thomas J, eds. An introduction to systematic  
36  
37 reviews. London: Sage publications limited 2013:191-2.  
38  
39

40  
41  
42 25 Altman R, Hochberg M, Gibofsky A, et al. Efficacy and safety of low-dose  
43  
44 SoluMatrix meloxicam in the treatment of osteoarthritis pain: A 12-week, phase 3  
45  
46 study, *Curr Med Res Opin* 2015;31:2331-43.  
47  
48

49  
50 26 Atukorala I, Pathmeswaran A, Makovey J, et al. Is there a relationship between the  
51  
52 intermittent and constant osteoarthritis pain score (ICOAP) and pain flares in knee  
53  
54 osteoarthritis? (abstract) [abstract]. *Osteoarthritis and Cartilage* 2016;24:S429-30.  
55  
56

1  
2  
3 27 Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a  
4 topical diclofenac solution: a randomised controlled, 6-week trial [SRCTN53366886],  
5  
6  
7  
8 *BMC Musculoskeletal Disorders* 2005;6:44.  
9

10  
11  
12 28 Baraf HSB, Gloth FM, Barthel HR, et al. Safety and Efficacy of Topical Diclofenac  
13 Sodium Gel for Knee Osteoarthritis in Elderly and Younger Patients, *Drugs Aging*  
14  
15 2011;28:27-40.  
16  
17

18  
19  
20 29 Battisti WP, Katz NP, Weaver AL, et al. Pain management in osteoarthritis: A focus  
21 on onset of efficacy—a comparison of rofecoxib, celecoxib, acetaminophen, and  
22  
23  
24  
25 nabumetone across four clinical trials, *The Journal of Pain* 2004;5:511-20.  
26  
27

28  
29 30 Bingham CO, Sebba AI, Rubin BR, et al. Efficacy and safety of etoricoxib 30 mg and  
30 celecoxib 200 mg in the treatment of osteoarthritis in two identically designed,  
31  
32  
33  
34  
35  
36  
37 randomized, placebo-controlled, non-inferiority studies, *Rheumatology* 2007;46:496-  
38  
39 507.  
40

41 31 Birbara C, Ruoff G, Sheldon E, et al. Efficacy and safety of rofecoxib 12.5 mg and  
42 celecoxib 200 mg in two similarly designed osteoarthritis studies, *Curr Med Res Opin*  
43  
44  
45 2006;22:199-210.  
46  
47

48  
49 32 Bocanegra T, Weaver A, Tindall E, et al. Diclofenac/misoprostol compared with  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60 diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized,

1  
2  
3 placebo controlled trial. Arthrotec Osteoarthritis Study Group. *Journal of*  
4  
5  
6 *Rheumatology* 1998;25:1602-11.  
7

8  
9  
10 33 Boswell DJ, Ostergaard K, Philipson RS, et al. Evaluation of GW406381 for  
11  
12 Treatment of Osteoarthritis of the Knee: Two Randomized, Controlled Studies, *The*  
13  
14 *Medscape Journal of Medicine* 2008;10:259.  
15

16  
17  
18 34 Brandt KD, Mazzuca SA, Buckwalter KA. Acetaminophen, like conventional NSAIDs,  
19  
20 may reduce synovitis in osteoarthritic knees, *Rheumatology* 2006;45:1389-94.  
21  
22

23  
24 35 Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating  
25  
26 symptomatic knee osteoarthritis: A randomized, double-blind, placebo-controlled  
27  
28 comparison trial with diclofenac sodium, *Arch Intern Med* 2003;163:169-78.  
29  
30

31  
32  
33 36 Ehrich E, Schnitzer T, McIlwain H, et al. Effect of specific COX-2 inhibition in  
34  
35 osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of  
36  
37 rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. *Journal of Rheumatology*  
38  
39 1999;26:2438-47.  
40  
41  
42

43  
44 37 Essex M, O'Connell M, Brown PB. Response to Nonsteroidal Anti-Inflammatory  
45  
46 Drugs in African Americans with Osteoarthritis of the Knee, *Journal of International*  
47  
48 *Medical Research* 2012;40:2251-66.  
49  
50

1  
2  
3 38 Gibofsky A, Hochberg MC, Jaros MJ, et al. Efficacy and safety of low-dose  
4 submicron diclofenac for the treatment of osteoarthritis pain: A 12 week, phase 3  
5 study, *Curr Med Res Opin* 2014;30:1883-93.  
6  
7  
8  
9

10  
11 39 Gineyts E, Mo JA, Ko A, et al. Effects of ibuprofen on molecular markers of  
12 cartilage and synovium turnover in patients with knee osteoarthritis, *Annals of the*  
13 *Rheumatic Diseases* 2004;63:857-61.  
14  
15  
16  
17  
18

19  
20 40 Goldberg M, McIlwain H, Poiley J, et al. Controlled-release naproxen in the  
21 treatment of osteoarthritis, *Current Therapeutic Research-Clinical and Experimental*  
22 1988;44:51-60.  
23  
24  
25  
26  
27

28  
29 41 Gottesdiener K, Schnitzer T, Fisher C, et al. Results of a randomized, dose ranging  
30 trial of etoricoxib in patients with osteoarthritis, *Rheumatology* 2002;41:1052-61.  
31  
32  
33

34  
35 42 Hochberg MC, Fort JG, Svensson O, et al. Fixed-dose combination of enteric-  
36 coated naproxen and immediate-release esomeprazole has comparable efficacy to  
37 celecoxib for knee osteoarthritis: two randomized trials, *Curr Med Res Opin*  
38 2011;27:1243-53.  
39  
40  
41  
42  
43  
44

45  
46 43 Katz N, Sun S, Johnson F, et al. ALO-01 (Morphine Sulfate and Naltrexone  
47 Hydrochloride) Extended-Release Capsules in the Treatment of Chronic Pain of  
48 Osteoarthritis of the Hip or Knee: Pharmacokinetics, Efficacy, and Safety, *The Journal*  
49 *of Pain* 2010;11:303-11.  
50  
51  
52  
53  
54  
55

1  
2  
3  
4 44 Kivitz AJ, Makarowski WS, Fiechtner JJ, et al. A Flexible Daily Dosage Regimen of  
5  
6 Oxaprozin Potassium in Patients with Acute Knee Pain Associated with Osteoarthritis,  
7  
8 *Clinical Drug Investigation* 2001;21:745-53.  
9

10  
11  
12 45 Erfani T, Zhang Y, Makovey J, et al. Intermittent analgesic use and risk of pain  
13  
14 exacerbation in knee osteoarthritis: A web based case-crossover study (abstract)  
15  
16 [abstract]. *Arthritis and Rheumatology* 2014;66.  
17  
18

19  
20  
21 46 Leung AT, Malmstrom K, Gallacher AE, et al. Efficacy and Tolerability Profile of  
22  
23 Etoricoxib in Patients with Osteoarthritis: A Randomized, Double-blind, Placebo and  
24  
25 Active-comparator Controlled 12-Week Efficacy Trial, *Curr Med Res Opin* 2002;18:49-  
26  
27 58.  
28  
29

30  
31  
32 47 Luyten FP, Geusens P, Malaise M, et al. A prospective randomised multicentre  
33  
34 study comparing continuous and intermittent treatment with celecoxib in patients  
35  
36 with osteoarthritis of the knee or hip, *Annals of the Rheumatic Diseases* 2007;66:99-  
37  
38 106.  
39  
40

41  
42  
43 48 Manicourt D, Bevilacqua M, Righini V, et al. Comparative Effect of Nimesulide and  
44  
45 Ibuprofen on the Urinary Levels of Collagen Type II C-Telopeptide Degradation  
46  
47 Products and on the Serum Levels of Hyaluronan and Matrix Metalloproteinases-3  
48  
49 and -13 in Patients with Flare-Up of Osteoarthritis, *Drugs in R & D* 2005;6:261-71.  
50  
51  
52  
53  
54  
55  
56

1  
2  
3  
4 49 Mazzuca S, Brandt K, Lane K, et al. Knee pain reduces joint space width in  
5  
6 conventional standing anteroposterior radiographs of osteoarthritic knees, *Arthritis*  
7  
8 *Rheum* 2002;46:1223-7.  
9

10  
11  
12 50 McIlwain H, Silverfield JC, Cheatum DE, et al. Intra-articular orpogtein in  
13  
14 osteoarthritis of the knee: A placebo-controlled efficacy, safety, and dosage  
15  
16 comparison, *Am J Med* 1989;87:295-300.  
17  
18

19  
20  
21 51 Mendelsohn S. Clinical efficacy and tolerability of naproxen in osteoarthritis  
22  
23 patients using twice-daily and once-daily regimens, *Clinical therapeutics* 1991;13:8-  
24  
25 15.  
26  
27

28  
29 52 Moskowitz RW, Sunshine A, Hooper M, et al. An analgesic model for assessment  
30  
31 of acute pain response in osteoarthritis of the knee, *Osteoarthritis and Cartilage*  
32  
33 2006;14:1111-8.  
34  
35

36  
37  
38 53 Pareek A, Chandurkar N, Sharma VD, et al. A randomized, multicentric,  
39  
40 comparative evaluation of aceclofenac-paracetamol combination with aceclofenac  
41  
42 alone in Indian patients with osteoarthritis flare-up, *Expert Opin Pharmacother*  
43  
44 2009;10:727-35.  
45  
46

47  
48  
49 54 Pareek A, Chandurkar N, Ambade R, et al. Efficacy and Safety of Etodolac-  
50  
51 Paracetamol Fixed Dose Combination in Patients With Knee Osteoarthritis Flare-up: A  
52  
53 Randomized, Double-blind Comparative Evaluation, *Clin J Pain* 2010;26:561-6.  
54  
55  
56

1  
2  
3 55 Ricci JA, Stewart WF, Chee E, et al. Pain Exacerbation as a Major Source of Lost  
4  
5  
6 Productive Time in US Workers With Arthritis, *Arthritis & Rheumatism: Arthritis Care*  
7  
8  
9 *& Research* 2005;53:673-81.

10  
11  
12 56 Schnitzer TJ, Fricke JR, Gitton X, et al. Lumiracoxib in the treatment of  
13  
14  
15 osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: results of  
16  
17  
18 three dose-response studies, *Curr Med Res Opin* 2005;21:151-61.

19  
20  
21 57 Scott-Lennox JA, McLaughlin-Miley C, Lennox RD, et al. Stratification of flare  
22  
23  
24 intensity identifies placebo responders in a treatment efficacy trial of patients with  
25  
26  
27 osteoarthritis, *Arthritis & Rheumatism* 2001;44:1599-607.

28  
29  
30 58 Silverfield JC, Kamin M, Wu S, et al. Tramadol/acetaminophen combination tablets  
31  
32  
33 for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized,  
34  
35  
36 double-blind, placebo-controlled, parallel-group, add-on study, *Clin Ther*  
37  
38  
39 2002;24:282-97 doi:[http://dx.doi.org/10.1016/S0149-2918\(02\)85024-X](http://dx.doi.org/10.1016/S0149-2918(02)85024-X) [published  
40  
41  
42 Online First: February 2002].

43  
44  
45 59 Strand V, Simon LS, Dougados M, et al. Treatment of osteoarthritis with  
46  
47  
48 continuous versus intermittent celecoxib, *J Rheumatol* 2011;38:2625-34.

49  
50  
51 60 Wiesenhutter CW, Boice JA, Ko A, et al. Evaluation of the Comparative Efficacy of  
52  
53  
54 Etoricoxib and Ibuprofen for Treatment of Patients With Osteoarthritis: A  
55  
56  
57 Randomized, Double-Blind, Placebo-Controlled Trial, *Mayo Clin Proc* 2005;80:470-9.

1  
2  
3 61 Williams GW, Hubbard RC, Yu SS, et al. Comparison of once-daily and twice-daily  
4 administration of celecoxib for the treatment of osteoarthritis of the knee, *Clin Ther*  
5  
6 2001;23:213-27 doi:[http://dx.doi.org/10.1016/S0149-2918\(01\)80004-7](http://dx.doi.org/10.1016/S0149-2918(01)80004-7) [published  
7  
8 Online First: February 2001].  
9  
10

11  
12  
13  
14 62 Wittenberg RH, Schell E, Krehan G, et al. First-dose analgesic effect of the cyclo-  
15 oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a  
16  
17 randomized, double-blind, placebo-controlled comparison with celecoxib  
18  
19 NCT00267215], *Arthritis Research & Therapy* 2006;8:R35.  
20  
21  
22

23  
24  
25 63 Yeasted R, McPherson J, Schnitzer T. Characterization of osteoarthritis pain  
26  
27 variability (abstract) [abstract]. *Osteoarthritis and Cartilage* 2014;22:S390-1.  
28  
29  
30

31  
32 64 Young C, Parenti D, Hochberg M. Lower-dose diclofenac capsules developed  
33  
34 using solumatrix fine particle technology result in clinically meaningful improvements  
35  
36 in pain in a phase 3 study of patients with osteoarthritis (abstract) [abstract].  
37  
38 *Osteoarthritis and Cartilage* 2014;22.  
39  
40

41  
42  
43 65 Zhao SZ, McMillen JI, Markenson JA, et al. Evaluation of the Functional Status  
44  
45 Aspects of Health-Related Quality of Life of Patients with Osteoarthritis Treated with  
46  
47 Celecoxib, *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*  
48  
49 1999;19:1269-78.  
50  
51  
52



1  
2  
3  
4 66 Zobel I, Erfani T, Bennell K, et al. Relationship of buckling and knee injury to pain  
5  
6 exacerbation in knee osteoarthritis: A web-based case-crossover stud, *Interact J Med*  
7  
8 *Res* 2014;66:S560-1.  
9

10  
11  
12 67 Conrozier T, Mathieu P, Vignon E, et al. Differences in the osteoarthritic synovial  
13  
14 fluid composition and rheology between patients with or without flare: a pilot study.  
15  
16 *Clinical and experimental rheumatology* 2012;30:729-34.  
17  
18

19  
20  
21 68 D'Agostino MA, Conaghan P, Le Bars M, et al. EULAR report on the use of  
22  
23 ultrasonography in painful knee osteoarthritis. Part 1: Prevalence of inflammation in  
24  
25 osteoarthritis, *Annals of the Rheumatic Diseases* 2005;64:1703-9.  
26  
27

28  
29  
30 69 Jawad ASM. Analgesics and osteoarthritis: are treatment guidelines reflected in  
31  
32 clinical practice? *Am J Ther* 2005;12:98-104.  
33  
34

35  
36 70 Murphy SL, Lyden AK, Kratz AL, et al. Characterizing pain flares from the  
37  
38 perspective of individuals with symptomatic knee osteoarthritis, *Arthritis Care and*  
39  
40 *Research* 2015;67:1103-11.  
41  
42

43  
44 71 Wise BL, Niu J, Zhang Y, et al. Psychological factors and their relation to  
45  
46 osteoarthritis pain, *Osteoarthritis and Cartilage* 2010;18:883-7.  
47  
48

49  
50 72 Zhang Y, Zhang B, Wise B, et al. Statistical approaches to evaluating the effect of  
51  
52 risk factors on the pain of knee osteoarthritis in longitudinal studies, *Curr Opin*  
53  
54 *Rheumatol* 2009;21:513-9.  
55  
56

1  
2  
3 73 Zhang Y, Wheaton D, N, J., et al. Recent heavy physical activities trigger knee pain  
4  
5  
6 exacerbation in persons with symptomatic knee osteoarthritis (abstract) [abstract].  
7  
8  
9 *Arthritis & Rheumatism* 2011;63(10).

10  
11  
12 74 Day R, Morrison B, Luza A, et al. A randomized trial of the efficacy and tolerability  
13  
14 of the cox-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis, *Arch*  
15  
16  
17 *Intern Med* 2000;160:1781-7.

18  
19  
20  
21 75 Kivitz AJ, Greenwald MW, Cohen SB, et al. Efficacy and Safety of Rofecoxib  
22  
23 12.5 mg Versus Nabumetone 1,000 mg in Patients with Osteoarthritis of the Knee: A  
24  
25  
26 Randomized Controlled Trial, *J Am Geriatr Soc* 2004;52:666-74.

27  
28  
29 76 Bingham CO, Smugar SS, Wang H, et al. Predictors of Response to Cyclo-  
30  
31  
32 Oxygenase-2 Inhibitors in Osteoarthritis: Pooled Results from Two Identical Trials  
33  
34  
35 Comparing Etoricoxib, Celecoxib, and Placebo, *Pain Medicine* 2011;12:352-61.

36  
37  
38 77 Essex MN, Behar R, O'Connell MA, et al. Efficacy and tolerability of celecoxib and  
39  
40  
41 naproxen vs placebo in hispanic patients with knee osteoarthritis, *Osteoarthritis and*  
42  
43  
44 *Cartilage* 2013;21.

45  
46  
47 78 Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the  
48  
49  
50 treatment of osteoarthritis: A 12-week, double-blind, multiple-dose, placebo-  
51  
52  
53 controlled trial, *Arch Intern Med* 2000;160:2947-54.

- 1  
2  
3 79 Atukorala I, Pathmeswaran A, Chang T, et al. Do Traditional Risk Factors for Knee  
4 Osteoarthritis Predict Pain Flares in Knee Osteoarthritis? *Ann Rheum Dis* 2016;75:835.  
5  
6  
7  
8  
9 80 Bartholdy C, Klokke L, Bandak E, et al. A Standardized "Rescue" Exercise Program  
10 for Symptomatic Flare-up of Knee Osteoarthritis: Description and Safety  
11 Considerations, *J Orthop Sports Phys Ther* 2016;46:942-6.  
12  
13  
14  
15  
16  
17 81 Bassiouni H. Detection of changes in the serum and synovial fluid levels of resistin  
18 during flare ups and remissions in primary knee osteoarthritis, *Arthritis and*  
19 *Rheumatology* 2015;67.  
20  
21  
22  
23  
24  
25  
26 82 Erfani T, Makovey J, Bennell K, et al. Psychosocial Factors and Pain Exacerbation in  
27 Knee Osteoarthritis: a Web Based Case-Crossover Study, *Intern Med J* 2014;44:16-.  
28  
29  
30  
31  
32  
33 83 Ferreira ML, Zhang Y, Metcalf B, et al. The influence of weather on the risk of pain  
34 exacerbation in patients with knee osteoarthritis - a case-crossover study,  
35 *Osteoarthritis and cartilage* 2016;24:2042-7.  
36  
37  
38  
39  
40  
41 84 Hunter DJ, Bennell K, Makovey J, et al. Psychosocial Factors and Pain Exacerbation  
42 in Knee Osteoarthritis: a Web Based Case-Crossover Study, *Osteoarthritis and*  
43 *Cartilage* 2014;22:S21-2.  
44  
45  
46  
47  
48  
49 85 Makovey J, Metcalf B, Zhang Y, et al. Web-Based Study of Risk Factors for Pain  
50 Exacerbation in Osteoarthritis of the Knee (SPARK-Web): Design and Rationale, *JMIR*  
51 *research protocols* 2015;4.  
52  
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3  
4 86 Parry E, Ogollah R, Peat G. Significant pain variability in persons with, or at high  
5  
6 risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of  
7  
8 cohort data, *BMC musculoskeletal disorders* 2017;18:80.  
9

10  
11  
12 87 Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled  
13  
14 glucosamine discontinuation trial in knee osteoarthritis, *Arthritis Care and Research*  
15  
16 2004;51:738-45.  
17  
18

19  
20  
21 88 Cibere J, Kopec JA, Esdaile JM, et al. Glucosamine sulfate and cartilage type II  
22  
23 collagen degradation in patients with knee osteoarthritis: randomized  
24  
25 discontinuation trial results employing biomarkers. In: Anonymous . *Journal of*  
26  
27 *rheumatology* 2005;896-902.  
28  
29

30  
31  
32 89 Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution  
33  
34 (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized,  
35  
36 double-blind, vehicle-controlled clinical trial, *Arch Intern Med* 2004;164:2017-23.  
37  
38

39  
40  
41 90 Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac  
42  
43 containing dimethyl sulfoxide (DMSO) compared with those of topical placebo,  
44  
45 DMSO vehicle and oral diclofenac for knee osteoarthritis, *Pain* 2009;143:238-45.  
46  
47

48  
49 91 Weaver A, Rubin B, Caldwell J, et al. Comparison of the efficacy and safety of  
50  
51 oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the  
52  
53 knee, *Clin Ther* 1995;17:735-45.  
54  
55

1  
2  
3  
4 92 Rother M, Lavins BJ, Kneer W, et al. Efficacy and safety of epicutaneous ketoprofen  
5  
6 in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the  
7  
8 knee: multicentre randomised controlled trial, *Annals of the Rheumatic Diseases*  
9  
10 2007;66:1178-83.  
11

12  
13  
14 93 Zobel I, Erfani T, Bennell KL, et al. Relationship of Buckling and Knee Injury to Pain  
15  
16 Exacerbation in Knee Osteoarthritis: A Web-Based Case-Crossover Study, *Interactive*  
17  
18 *journal of medical research* 2016;5:e17.  
19  
20

21  
22  
23 94 Woolacott NF, Corbett MS, Rice SJC. The use and reporting of WOMAC in the  
24  
25 assessment of the benefit of physical therapies for the pain of osteoarthritis of the  
26  
27 knee: findings from a systematic review of clinical trials, *Rheumatology* 2012;51:1440-  
28  
29 6.  
30  
31

32  
33  
34 95 National Institute for Health and Care Excellence (NICE).  
35  
36 Osteoarthritis: care and management (CG177). London: NICE 2014.  
37  
38

39  
40 96 Buttgerit F, Burmester G, Bijlsma JWJ. Non-surgical management of knee  
41  
42 osteoarthritis: where are we now and where do we need to go? *RMD Open* 2015;1.  
43  
44

45  
46 97 Porcheret M, Healey E, Dziedzic K, et al. Osteoarthritis: a modern approach to  
47  
48 diagnosis and management, *Arthritis Research UK* 2011;Series 6.  
49  
50

1  
2  
3 98 Cross M, Dubouis L, Mangin M, et al. Defining Flare in Osteoarthritis of the Hip  
4  
5 and Knee: A Systematic Literature Review- OMERACT Virtual Special Interest Group, *J*  
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101 Makris D, Bouros D. COPD exacerbation: Lost in translation, *BMC Pulmonary Medicine* 2009;9:6.

99 Bellamy N, Sothorn RB, Campbell J. Rhythmic variations in pain perception in osteoarthritis of the knee, *J Rheumatol* 1990;17:364-72.

100 Allen KD, Coffman CJ, Golightly YM, et al. Daily pain variations among patients with hand, hip, and knee osteoarthritis, *Osteoarthritis and Cartilage* 2009;17:1275-82.

101 Makris D, Bouros D. COPD exacerbation: Lost in translation, *BMC Pulmonary Medicine* 2009;9:6.

102 Fitzgerald JD, Grossman JM. Validity and reliability of retrospective assessment of disease activity and flare in observational cohorts of lupus patients, *Lupus* 1999;8:638-44.

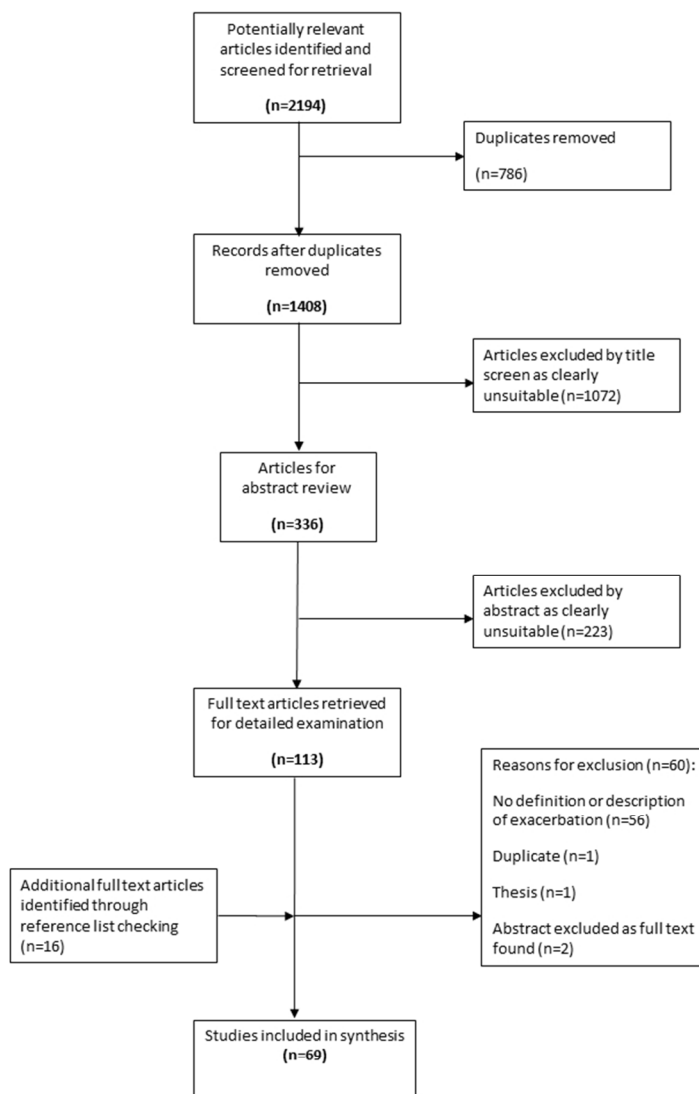
103 Lewis JD, Aberra FN, Lichtenstein GR, et al. Seasonal variation in flares of inflammatory bowel disease, *Gastroenterology*;126:665-73.

104 Suri P, Saunders KW, Von Korff M. Prevalence and Characteristics of Flare-ups of Chronic Nonspecific Back Pain in Primary Care: A Telephone Survey, *Clin J Pain* 2012;28:573-80.

1  
2  
3 105 Sands GH, Brown PB, Essex MN. The Efficacy of Continuous Versus Intermittent  
4  
5 Celecoxib Treatment in Osteoarthritis Patients with Body Mass Index  $\geq 30$  and *The*  
6  
7  
8  
9 *Open Rheumatology Journal* 2013;7:32-7.

10  
11  
12 106 Berthelot J, De Bandt M, Morel J, et al. A tool to identify recent or present  
13  
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rheumatoid arthritis flare from both patient and physician perspectives: The 'FLARE'  
instrument, *Annals of the Rheumatic Diseases* 2012;71:1110-6.

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**Online supplement: Example search strategy**

*Table 1: Key terms and MeSH headings used for EMBASE database search. The concepts were combined as follows: "KNEE JOINT" AND "ACUTE EVENTS"*

<b>Concepts</b>	<b>Search terms</b>
KNEE JOINT	"knee adj3 (pain OR painful)" or "Knee osteoarthritis" or "knee adj3 (arthrosis)" or "knee adj3 (joint OR joints OR degenerative)" or "knee adj3 (osteoarthritis)"
ACUTE EVENTS	"exacerbation" or "flare" or "daily adj3 (pain)" or "pain AND (diary OR diaries)" or "pain adj3 (variab\$)"



# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis. <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	9



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 (flowchart)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A but rationale on 18
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19-35
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	36-37
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	38
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	39
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	40

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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# BMJ Open

## Defining Acute Flares in Knee Osteoarthritis: A Systematic Review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019804.R1
Article Type:	Research
Date Submitted by the Author:	12-Feb-2018
Complete List of Authors:	Parry, Emma; Keele University, Research Institute for Primary Care and Health Sciences Thomas, M; Keele University, Research Institute for Primary Care and Health Sciences Peat, George; Keele University, Research Institute for Primary Care & Health Sciences
<b>Primary Subject Heading</b>:	Rheumatology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Flare

SCHOLARONE™  
Manuscripts

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4 **1 DEFINING ACUTE FLARES IN KNEE OSTEOARTHRITIS: A**

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7 **2 SYSTEMATIC REVIEW**

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12 4 Martin J. Thomas<sup>1</sup>, m.thomas@keele.ac.uk

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35 13 **Keywords:** knee osteoarthritis, flare, systematic review

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## 15 ABSTRACT

16 **Objective:** To identify and critically synthesise definitions of acute flares in knee  
17 osteoarthritis (OA) reported in the medical literature.

18 **Design:** Systematic review and narrative synthesis. We searched MEDLINE, EMBASE,  
19 Web of science and 6 other electronic databases (inception to July 2017) for original  
20 articles and conference abstracts reporting a definition of acute flare (or synonym) in  
21 humans with knee OA. There were no restrictions by language or study design (apart  
22 from iatrogenic induced flare-ups e.g. injection-induced). Data extraction comprised:  
23 definition, pain scale used, flare duration or withdrawal period, associated symptoms,  
24 definition rationale, terminology (e.g. exacerbation or flare), baseline OA severity,  
25 age, gender, sample size and study design.

26 **Results:** Sixty-nine articles were included (46 flare-design trials, 17 observational  
27 studies, 6 other designs; sample sizes: 15-6085). Domains used to define flares  
28 included: worsening of signs and symptoms (61 studies, 27 different measurement  
29 tools), specifically increased pain intensity; minimum pain threshold at baseline (44  
30 studies); minimum duration (7 studies, range 8-48 hours); speed of onset (2 studies,  
31 defined as 'sudden' or 'quick'); requirement for increased medication (2 studies). No  
32 definitions included activity interference.

33 **Conclusions:** The concept of OA flare appears in the medical literature but most  
34 often in the context of flare design trials (pain increases observed after stopping  
35 usual treatment). Key domains, used to define acute events in other chronic

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4 36 conditions, appear relevant to OA flare and could provide the basis for consensus on  
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6 37 a single, agreed definition of 'naturally occurring' OA flares for research and clinical  
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9 38 application.

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11 39 **PROSPERO registration:** CRD42014010169  
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### 21 43 **Strengths and limitations of this study**

#### 22 23 44 *Strengths*

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26 45 • Identified key domains that are used to define acute events by undertaking a  
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28 46 comprehensive synthesis of definitions used in the medical literature.  
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31 47 • Broad search strategy covering a wide range of databases including  
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33 48 bibliography checks and conference abstracts.  
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36 49 • Prospectively registered with Prospero  
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#### 38 50 *Limitations*

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41 51 • Did not include potential synonyms as search terms ('attack', 'episode',  
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43 52 'fluctuations')  
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46 53 • Data extraction was performed by only a single reviewer.  
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## 55 INTRODUCTION

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57 Recurrent acute events or episodes feature in the natural history of many chronic  
58 health conditions. The extent to which they characterise the condition varies, as do  
59 the presumed pathophysiological mechanisms, and scientific and lay terms used to  
60 describe them (e.g. an acute exacerbation of chronic obstructive pulmonary disease  
61 (COPD) or asthma, an attack of gout or a rheumatoid arthritis flare). With recognition  
62 of their importance has come concerted effort to define these phenomena.

63 Definitions for exacerbations or flares currently exist for COPD[1, 2] , asthma[3],  
64 systemic lupus erythematosus (SLE)[4], and ankylosing spondylitis (AS)[5] and there  
65 are working groups currently trying to define these for rheumatoid arthritis[6-8],  
66 gout[9], and atopic dermatitis/eczema[10]. Despite the different language used, these  
67 definitions share some common, core domains: the onset or worsening of symptoms  
68 and signs above normal day-to-day variability; speed of onset; duration of sustained  
69 worsening; and change in medication/healthcare usage.

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71 Osteoarthritis (OA) appears to comprise multiple disease trajectories[11-15] and  
72 symptom variability over time and the presence of intermittent pain is well-  
73 recognised[16]. Although OA does not typically have the same very obvious acute  
74 events as conditions like gout, flares in OA joints are encountered in practice, these

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3 75 phenomena appear in patient literature[17], have been discussed in expert  
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6 76 reviews[18], and are mentioned in 'flare design' trials in OA[19]. These studies invoke  
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9 77 acute episodes of pain or flare-ups by asking patients to withdraw their usual  
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11 78 medication.

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18 80 In 2009 Marty et al proposed scoring criteria for knee OA flares based on nocturnal  
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20 81 awakening, knee effusion, morning stiffness and limping[20] but it is unclear whether  
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23 82 this has contributed to a common understanding, shared terminology and criteria. A  
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25 83 common definition of OA flare could be important for a number of reasons; (i) to  
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28 84 facilitate communication between researchers, (ii) to allow more direct comparisons  
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30 85 between studies on frequencies, determinants and course of events, (iii) to facilitate  
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33 86 new insights into novel pathophysiological mechanisms and treatments through  
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35 87 valid and homogenous case definitions, and (iv) to help clinicians with prompt  
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38 88 diagnosis and management.

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45 90 The aim of this systematic review was to explore the extent to which a concept of OA  
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47 91 flare is reported in the medical literature and the prospects for a common, shared  
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50 92 definition of these for research and clinical application. A review addressing similar  
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52 93 aims but not registered on PROSPERO came to our attention when it was published  
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55 94 while we were drafting our manuscript[21]. In principle and upon comparing the

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95    respective findings of both reviews, we felt our review could justify making an  
96    original contribution.

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3 103 **METHODS**

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8 105 This systematic review was registered with PROSPERO registration number

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11 106 CRD42014010169. The review protocol has not been published.

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16 108 **Literature sources and study selection**

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22 110 We searched electronic databases from inception to July 2017; ASSIA, EMBASE, Web

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24 111 of Science, Health Management Information Consortium (HMIC), SPORTDiscus,

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26 112 Medline, CINAHL, PsycINFO, AMED, Ageline, Cochrane Database of Systematic

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28 113 Reviews and Cochrane Controlled Clinical Trials (CENTRAL). The search was

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30 114 developed using previously piloted terms for knee OA and a literature search for

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32 115 common terms used to describe acute events. Searches used combined and/or

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34 116 truncated key terms including: ("KNEE OSTEOARTHRITIS" OR (knee N3 pain) OR

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36 117 (knee N3 arthrosis) OR (knee N3 joint) OR (knee N3 osteoarthritis)) AND

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38 118 (exacerbation OR flare OR (pain AND (diary OR diaries)) OR (pain N3 variab\*) OR

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40 119 (pain N3 pattern\$) OR (daily N3 pain)). A database search strategy is included in the

41  
42 120 online supplement . Reference lists of all included full text articles retrieved for

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44 121 detailed examination were manually searched.

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3 123 Studies were included in the final full text peer review if they contained a description  
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6 124 or definition of an acute exacerbation or flare-up of knee OA in human adults (18  
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8 125 years or over) in the general population, primary care or hospital settings. Studies  
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11 126 were included even if their description was not based on clear measurement criteria  
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13 127 (e.g. stating a 'significant increase in pain' but not the amount of change on a pain  
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15  
16 128 score this would equate to). Studies that included a mixed OA population (e.g. knee  
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18 129 or hip OA) and did not separately report knee-specific findings were included. There  
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21 130 were no restrictions on study dates or design. All non-English language articles were  
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23 131 translated to identify a flare definition. Theses, dissertations, book chapters and  
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26 132 guidelines, and animal studies were excluded. Conference abstracts were included if  
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28 133 they contained a definition for an OA flare-up. Studies were excluded if the flare was  
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31 134 induced by an iatrogenic source, for example, injection-induced flares[22]. As these  
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33 135 may have been caused by a different pathophysiological process. Abstracts were  
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36 136 included in this study as the main outcome of interest was the definition of flare used  
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38 137 and it was decided that including abstracts would ensure a more comprehensive  
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41 138 review. For each abstract a search was conducted to identify a corresponding full text  
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43 139 paper. Where one was found only the full paper was included in the review.  
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50 141 The search and article retrieval was conducted by the first reviewer (ELP). Articles  
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52 142 were downloaded into RefWorks© bibliography and database manager (RefWorks  
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55 143 Copyright 2009). Duplicates were removed and all titles were screened by ELP  
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4 144 against inclusion criteria, with the first 20 titles checked by two reviewers (ELP and  
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6 145 MJT) for consistency. For qualitative studies, all identified potentially eligible full text  
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8 146 articles were obtained.  
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13 148 All abstracts and then full text articles were screened by two reviewers (ELP and MJT).  
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16 149 with disagreements resolved by consensus adjudicated by a third reviewer (GP).  
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18 150 Where articles could not be retrieved or if the flare definition used was not included  
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21 151 in the text, contact with authors was made.  
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26 153 The final included articles were checked to ensure results were not duplicated, for  
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28 154 example, where different authors were reporting on the same dataset, to reduce bias  
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31 155 [23] . For articles containing pooled studies, the original studies were sought and  
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33 156 included in the main analysis, where available.. No full text articles were required to  
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36 157 be translated.  
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### 39 40 41 159 **Data extraction**

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49 162 The following data pertaining to flares were extracted from full text articles by the  
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52 163 first reviewer: definition used for change in pain, pain scale used, duration of flare  
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55 164 (for flare design trials we extracted the duration of the withdrawal period for  
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3 165 comparison), associated symptoms, rationale behind definition used, terminology  
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6 166 used (e.g. exacerbation or flare), baseline OA severity, age range, gender,  
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8 167 geographical location, number of participants and study design. Missing data was  
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11 168 described in the data extraction tables. Extraction for every tenth article was  
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13 169 independently checked (MJT).  
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### 17 171 **Quality assessment of included studies**

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24 173 Our aim was to identify and contrast definitions of flare-ups used in the literature.

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27 174 We were not concerned with the methodological rigour of the studies deriving,

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30 175 evaluating or applying those definitions. However, for studies presenting definitions

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32 176 we sought supporting statements that gave the rationale for the definition.  
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### 36 37 178 **Data analysis**

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43 180 A narrative synthesis was undertaken, guided by Popay et al's[24] four stage process

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45 181 to develop a conceptual framework[25]. This approach was chosen as it allowed the

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48 182 words and text in the definitions to be synthesised to summarise findings[24]. The

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50 183 initial data extracted was grouped into drug withdrawal studies ('flare design') and

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53 184 other studies, and frequencies of components included in definitions was tabulated,  
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3 185 these included; terminology used, onset/worsening of symptoms; signs/symptoms  
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6 186 above day-to-day variability/minimum threshold; speed of onset of symptoms;  
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8 187 duration of worsening and change in medication/healthcare usage.  
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13 189 This initial tabulation helped identify similarities and differences and allowed themes  
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16 190 to emerge. This was done with an inductive type approach, where possible i.e.  
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18 191 without an *a priori* assumption, but also deductively acknowledging that the  
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21 192 reviewers were clinicians i.e. they had some background knowledge of the topic of  
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23 193 interest. This allowed further examination of the differences of definitions used in  
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26 194 drug withdrawal and non-drug withdrawal study designs, and examination of key  
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28 195 components of definitions used.  
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## 32 33 197 **RESULTS**

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### 37 38 39 199 **Study selection**

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45 201 The literature search yielded 2194 articles of which 786 were duplicates (Figure 1).

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48 202 After title screening 336 abstracts were reviewed, 223 were not relevant for the study  
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51 203 purpose. 113 articles were examined in full which resulted in a further 60 being  
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53 204 excluded. The main reason for exclusion was no definition of flare-up reported in text  
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4 205 (n=56). At this stage a further 16 articles were identified from the reference lists of  
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6 206 the retrieved full text articles resulting in 69 included studies for synthesis.  
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11 208 **Study characteristics**  
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17 210 Characteristics of the included studies are described in Table 1[20, 26-93]. The number  
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19 211 of participants in each study ranged from 15-6085[20, 50]. Knee OA was defined by  
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21 212 clinical and/or radiological criteria.  
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214 **Table 1: Characteristics of all included studies**

<b>DRUG WITHDRAWAL DESIGN STUDIES</b>					
<b>First author, year of publication</b>	<b>Setting, geographic location</b>	<b>Participants</b>	<b>Joint</b>	<b>Severity</b>	<b>Study design</b>
Altman, 2015[26]	Multi-centre, recruitment not specified, USA	403 males & females, ≥40y	Knee and hip	KL grade 2-3	RCT, flare design
Baer, 2005[28]	17 medical centres recruiting from community and physician private practice; Canada	216 males & females, 40-85y	Knee	Radiographic evidence of OA (severity not defined)	RCT, flare design
Baraf, 2011[29]	Primary care, internal medicine, orthopaedic, rheumatology; USA	602 males & females, ≥25y	Knee	Radiographically mild to moderate (KL grade 1-3)	RCT, flare design
Battisti, 2004[30]	Clinical centres, out patients; USA	3980 males & females, ≥40y (age unavailable for Geba 2003 and Weaver 2003)	Knee	ACR functional class rating of I,II or III	RCT, pooled 4 trials, flare design
Bingham, 2007[31] Bingham 2011[77]	2x74 outpatient clinics; USA	1207 males & females, ≥40y	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design

Birbara, 2006[32]	Investigative sites; USA	808 males & females, $\geq 40y$	Knee	ARA functional class, I, II, or III	RCT, flare design
Bocanegra, 1998[33]	Clinic; USA	572 males & females, 28-88y (mean 61-62)	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design
Boswell, 2008[34]	50 centres (Europe & Australia) + 187 centres (Europe & USA)	1908 males & females, $\geq 40y$	Knee	KL scale 2 or 3 and ARA class rating of I,II or III	Pooled RCTs (2; one flare design, one non-flare), flare design
Brandt, 2006[35] (pilot studies)	Community; USA	30 males & females, mean age 62y	Knee	KL $\geq 2$	Cohort design, flare design
Case, 2003[36]	Hospital-rheumatology centre; Chicago, USA	82 males & females, 40-75y	Knee	KL $\geq 1$ , and clinical criteria (pre-enrolment ambulatory pain; moderate pain by a 5-point Likert scale or increased pain.	RCT, flare design
Day, 2000[75]	49 investigative sites in 26 countries	809 males & females, mean age range 62-65y	Knee and hip	ARA functional class I-III, symptomatic for at least 6 months	RCT, flare design
Ehrich, 1999[37]	Clinical centres; USA	219 males & females, $>40y$	Knee	ARA functional class, I, II, or III	RCT, flare design
Essex, 2012[38]	Clinical centre; African-American, USA	322 males & females, $\geq 45y$	Knee	ARA Functional capacity classification I-III	RCT, flare design
Essex 2013[78]	Hispanic population, 31 US centers	$\geq 45y$	Knee	ACR criteria, Functional capacity classification I-III	RCT, flare design
Gibofsky, 2014[39]	Not specified, USA	305 males & females, 41-90 y	Knee and hip	KL 2-3	RCT, flare design
Gineyts, 2004[40]	Subset of larger study; France	201 males & females, mean age 61-62y	Knee and hip	ARA I-III	RCT, flare design

Goldberg, 1988[41]	Investigative sites; USA	214 males & females, 40-85y (mean 64)	Knee and hip	Radiographic evidence of knee OA-not further defined	RCT, flare design
Gottesdiener, 2002[42]	Investigative sites; USA	617 males & females, ≥40y	Knee	ARA functional class I,II,III	RCT, flare design
Hochberg, 2011[43]	Centres; USA	1234 males & females, ≥50y	Knee	ACR functional class I-III	Pooled RCTs (2), flare design
Katz, 2010[44]	Clinical sites; USA	113 males & females, 28-83y (median 57))	Knee and hip	OA of hip and knee as diagnosed using ACR criteria-no definition of severity	RCT, flare design
Kivitz, 2001[45]	Investigative sites; USA	491 males & females, 28-91y (mean 58-61)	Knee	Confirmation of OA on weight bearing radiograph- no definition of severity	RCT, flare design
Kivitz, 2004[76]	Outpatient sites; USA	1042 males & females, ≥40y	Knee	ACR rating of I, II, III.	RCT, flare design
Leung, 2002[47]	Clinic; USA	677 males & females, ≥40y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Luyten, 2007[47]	Centres; Belgium	181 males & females, ≥40y	Knee and hip	ACR Functional capacity classification I-III	RCT, flare design
Manicourt, 2005[49]	Outpatient clinic; Belgium	90 males & females, 50-81y (mean 63-67)	Knee and hip	Clinical and radiographic evidence of OA-severity not defined.	RCT, flare design
Mazzuca, 2002[50]	Not specified, USA	15 males & females, ≥45y	Knee	KL 2-3	Observational, flare design
McIlwain, 1989[51]	Investigative sites; USA	139 males & females, mean 65y	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design
Mendelsohn, 1991[52]	Investigative sites; USA	139 males & females, 21-88y (mean age 63.3y)	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design

Moskowitz, 2006[53]	Investigative sites; USA	530 males & females, $\geq 45y$	Knee	ACR Functional capacity classification I-III	RCT, flare design
Pareek, 2009[54]	Multi-centre study, India	199 males & females, 40-70y	Knee	Lequesne criteria-score of 5 and above	RCT, flare design
Pareek, 2010[55]	Hospital; India	220 males & females, 40-70y	Knee	Clinical and radiological evidence of OA- severity not defined.	RCT, flare design
Roth, 2004[90]	Physicians private practice or community; USA	326 males & females, 40-85y	Knee	Radiological evidence of OA- severity not defined.	RCT, flare design
Rother, 2007[93]	Outpatient units; Germany	397 males & females, $\geq 40y$	Knee	KL 2-3	RCT, flare design
Schnitzer, 2005[57]	Investigative sites; International (7 countries)	583 males & females, 18-75y	Knee and hip	Diagnosis based on ACR criteria- severity not defined.	RCT, flare design
Scott-Lennox, 2001[58]	Investigative sites; USA	182 males & females, mean 61y	Knee	Not defined	RCT, flare design
Silverfield, 2002[59]	Centres; USA	308 males & females, 35-75y	Knee and hip	Clinical evidence of OA- severity not defined	RCT, flare design
Simon, 2009[91]	Outpatient centres; Canada, USA	775 males & females, 40-85y	Knee	Clinical and radiological evidence of OA- severity not defined	RCT, flare design

Strand, 2011[60]	Investigative sites; Multinational-not specified including USA	875 males & females, 18-80y	Knee and hip	OA according to ACR criteria and requiring NSAID treatment to control symptoms in the month preceding screening	RCT, flare design
Weaver, 1995[92]	Investigative sites; USA	328 males & females, >50y	Knee	ACR clinical criteria-diagnostic	RCT, flare design
Wiesenhutter, 2005[61]	Medical Centres; USA	528 males & females, 40-89y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Williams, 2001[62]	Clinical sites; USA	718 males & females, mean 61-62y	Knee	ACR clinical and radiographic criteria I-III	RCT, flare design
Wittenberg, 2006[63]	Centres (not specified) ; Germany	364 males & females, 50y	Knee	Moderate to severe symptomatic OA of the knee according to ACR criteria.	RCT, flare design
Yeasted, 2014[64] (Pooled, abstract)	USA	219 (merged observational), 137 (merged trial)>40y	Not specified	ACR criteria-diagnostic	2 longitudinal observational studies, placebo arms of 2 clinical trials
Yocum, 2000[79]	USA, 62 study centres	774 males & females, ≥40y	Knee or hip	Diagnosis confirmed by XR and clinical symptoms (not further specified)	RCT, flare design
Young, 2014[65] (abstract)	Multicenter,	305 males & females, >40y	Knee or hip	KL 2-3	RCT, flare design
Zhao, 1999[66]	Centre (not specified); USA, Canada	1004 males & females, ≥18y	Knee	ACR Functional capacity classification I-III	RCT, flare design
<b>NON-DRUG WITHDRAWAL DESIGN STUDIES</b>					

Atukorala, 2016[80] (abstract)	Not specified, USA + Australia + Sri Lanka	213 males & females, mean age 62y	Knee	Not specified	3-month, web based longitudinal follow up study
Atukorala, 2016[27] (abstract)		345 males & females, mean age 62y			
Bartholdy, 2016[81]	OA out-patient clinic, Denmark	131 males & females, ≥40y	Knee	Radiographic evidence of OA (severity no defined) and BMI between 20-35 kg/m <sup>2</sup>	RCT
Bassiouni 2015[82] (abstract)	Not specified, Egypt	60 participants not further specified	Knee	Not specified	Observational
Cibere, 2004[88]  Cibere, 2005[89]	Community, Canada	137 males & females, mean age 65y (43- 88) for placebo and 64y (40-83) for glucosamine group	Knee	KL ≥2 on anteroposterior radiograph	RCT
Conrozier 2012[68]	Hospital- rheumatology unit, France	44 males & females, mean age 67.6y	Knee	Radiographic evidence of knee OA-not further defined	Observational
D'Agostino 2005[69]	Hospital- European multicentre	600 males & females, ≥18y	Knee	KL grade 1-4	Observational
Erfani, 2014[46] abstract)  Erfani, 2014[83] (abstract)  Ferreira[84] 2016	Australia	268 males & females, mean age 62y  345 males & females, ≥40y	Knee	ACR criteria- meet at least one, KL ≥2	Web based cross over

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Hunter 2014[85] (abstract)					
Makovey 2015[86] (Protocol)					
Jawad, 2005[70]	GPs in France	3000 (for GP study) males & females	Knee	Not defined	n/a, review of surveys. Definition relates to survey of 3000 French GPs
Marty 2009[20]	Community and hospital, France	6085+641males & females, mean age 66.4y (10.9) for flare group, 66.2y (10.2) no flare group	Knee	OA diagnosis based on ACR criteria- severity not defined	Observational
Murphy, 2015[71]	Community based, pain clinics; USA	45 males & females, 37-83y	Knee	ACR criteria- severity not defined	Qualitative
Parry, 2017[87]	Community, UK	719 males & females, ≥50y	Knee	Self-reported knee pain in previous 12 months	Observational
Ricci 2005[56]	Community, USA	329 males & females, 40-65y	Knee and hip	Clinical evidence of OA- severity not defined	Nested case control
Wise 2010[72]	Primary care, hospital, USA	303 males & females, ≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment- not further defined	Observational



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Zhang 2009[73]	Primary care, hospital, USA	303 males & females, ≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment-not further defined	Observational
Zhang 2011[74] (abstract)	Not specified	52 males & females, median age 63, (50-72y)	Knee	KL>2	Case-crossover
Zobel, 2016[94]	Hospital databases, Australia	297 males & females, >40y	Knee	ACR criteria, KL ≥2, or patellofemoral OA on radiograph	Web based case-cross over
<p>Acronyms:                      KL- Kellgran and Lawrence                      RCT- Randomised Controlled Trial                      USA- United States of America                      ACR- Arthritis Center Research                      ARA- American Rheumatism Association                      GP- General Practitioner</p>					

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Review only

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3 217 Twenty-one included mixed knee and hip OA groups[26, 31, 33, 39-41, 44, 47-49, 56, 57,  
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6 218 59-61, 65, 73, 75, 77, 79]. In total, 46 publications used a drug withdrawal RCT design[26,  
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8 219 28-34, 36-45, 47-55, 57-66, 75-79, 90-93], four of which were pooled studies[30, 34, 43, 64]  
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11 220 and one used a cohort drug withdrawal design[35] (Table 1). The remaining 22  
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13 221 publications included seventeen observational studies[20, 27, 46, 56, 67-69, 72-74, 80, 82-  
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15 222 87], three RCTs[81, 88, 89], one survey[70] and one qualitative interview study[71]. Nine  
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17 223 of the included studies were abstracts[27, 46, 64, 65, 74, 80, 82, 83, 85]. Two abstracts were  
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19 224 removed as the corresponding full text article was available[71, 94]. Studies using  
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21 225 pooled data or the same dataset were included if they used different definitions of  
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23 226 OA flare[30, 46, 54, 55, 64, 67, 72, 73, 76].  
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### 31 **Rationale given for flare definitions**

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37 230 Six of the included studies gave rationale for the definition used[20, 56, 58, 71, 87, 88].  
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39 231 None of the definitions were based on a consensus procedure. Marty et al[20] and  
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41 232 Scott-Lennox et al[58] were the only studies that undertook empirical investigation of  
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43 233 flare definitions. The study by Marty et al[20] was the only study specifically designed  
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45 234 to validate a diagnostic tool for knee OA flares. Potential factors associated with  
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47 235 flare-ups were identified, for example, knee swelling and the authors used a logistic  
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49 236 regression analysis to assign a weight to each of the items identified. A flare up score  
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3 237 was determined using a general practitioner database and this was then validated  
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6 238 using a rheumatologist database. Pain was not included in the final model.  
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11 240 Scott-Lennox et al[58] sought to test whether four measures for flare intensity  
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13 241 (patient's self-assessment of pain scores, physician's assessment of pain scores,  
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15 242 patient's global OA assessment and physician's global OA assessment) could be  
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17 243 combined to form a reliable and valid index using data from an RCT using a  
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19 244 confirmatory factor analysis. The authors produced three flare intensity groups (low,  
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21 245 moderate and severe) and highlighted how these could be used to examine  
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23 246 treatment effects.  
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31 248 Cibere[88] outlined face validity checks. It was specified that the flare definition had  
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33 249 been determined by study rheumatologists to be a clinically important change in the  
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35 250 WOMAC score. The definition used by Murphy et al[71] was informed by two  
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37 251 studies[30, 55] which used a drug withdrawal design and from the research team's  
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39 252 own experience. Ricci et al[56] used a combination of data-driven and clinical  
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41 253 judgement approaches to establish an agreed cut point. Parry et al based their  
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43 254 definition on OA flare design studies and flare definitions used in other chronic  
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45 255 disease such as back pain and COPD.  
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9 260 **Flare definitions in drug withdrawal studies**

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14 262 **Terminology used**

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16 263 The majority of publications using a drug withdrawal design used the term “flare” in  
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18 264 their description[26-32, 34, 35, 38-45, 47-51, 53, 55, 57-66, 76-79, 90-93] (n=42; Table 2).

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266 **Table 2: Definition, terminology and measurement instruments used in all included studies**

<b>DRUG WITHDRAWAL STUDY DESIGN</b>							
<b>First author</b>	<b>Terminology used</b>	<b>Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)</b>	<b>Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)</b>	<b>Speed of onset</b>	<b>Duration</b>	<b>Change in medication/healthcare use</b>	<b>Reference / rationale</b>
Altman, 2015[26]	"Flare"	<b>Pain:</b> WOMAC Pain subscale (0-100); increase $\geq 15$ mm	<b>Pain:</b> WOMAC Pain subscale; $\geq 40$ mm	Not specified	Not specified	Not specified	None
Baer, 2005[28]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); increase $\geq 2$ points and $\geq 25\%$	<b>Pain:</b> WOMAC Pain score (0-20); $\geq 6$ and $\geq 1$ item rated 'moderate, severe, or extreme'	Interval between screening and baseline re-measurement unclear	Not specified	Not specified	None
Baraf, 2011[29]	"Flare"	<b>Pain on movement:</b> VAS (0-100mm); increase $\geq 5$ mm	Not specified	1 week washout	Not specified	Not specified	None
Battisti, 2004[30]	"Flare"	<b>Global assessment (investigator):</b> single item, 5-point LK; Worsening $\geq 1$ point	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None

<p>Bingham, 2007[31]</p> <p>Bingham 2011[77]</p>	<p>"Flare"</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100mm); increase <math>\geq 15</math>mm</p> <p>(2) <b>Global assessment of disease status (investigator):</b> single item, 5-point LK; Worsening <math>\geq 1</math> point</p>	<p>(1) <b>Pain walking on flat surface:</b> <math>\geq 40</math>mm on WOMAC VAS3.0 Q1 (0-100)</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; fair, poor, very poor (<i>acetaminophen users only</i>)</p> <p>(3) <b>Global assessment of disease status (patient):</b> VAS 0-100mm; <math>\geq 40</math>mm (<i>acetaminophen users only</i>)</p>	<p>Not specified</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>
<p>Birbara, 2006[32]</p>	<p>"Flare"</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS Q1 (0-100mm); increase <math>\geq 15</math>mm</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; Worsening <math>\geq 1</math> point</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100); <math>\geq 40</math>mm</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; Fair, poor or very poor (<i>paracetamol arm only</i>)</p>	<p>4-15 day washout</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>
<p>Bocanegra, 1998[33]</p>	<p>"Worsening of symptoms"</p>	<p>Two out of the following three:</p> <p>(1) <b>Global assessment (physician):</b> single item, 5-point LK; Increase <math>\geq 1</math> grade</p> <p>(2) <b>Global assessment (patient):</b> Patients global assessment (current symptoms and limitation of activity) 5-point LK; Increase <math>\geq 1</math> grade</p> <p>(3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); Increase <math>\geq 2</math> points</p>	<p>(1) <b>Global assessment (physician):</b> single item, 5-point LK; 'poor/very poor'</p> <p>(2) <b>Global assessment (patient):</b> Patients global assessment (current symptoms and limitation of activity) 5-point LK; 'poor/very poor'</p> <p>(3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); <math>\geq 7</math></p>	<p>3-14d washout</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>

Boswell, 2008[34]	"Flare"	(1) <b>Pain walking on flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global assessment (patient):</b> Patient Global Assessment of Arthritis Condition (PGAC) (unspecified); Worsening $\geq 1$ point	Not specified	Not specified	Not specified	Not specified	None
Brandt, 2006[35] (pilot studies)	"Flare"	Not specified	<b>Pain:</b> WOMAC LK Pain subscale (5-25); $\geq 15$ points	5 half-lives of NSAID washout	Not specified	Not specified	None
Case, 2003[36]	Not used	(1) <b>Pain walking on flat surface:</b> VAS (0-100mm); Increase $\geq 10$ mm (2) <b>Ambulatory pain;</b> 5-point LK; worsening $\geq 1$ point	Not specified	14d washout	Not specified	Not specified	None
Day, 2000[75]	Not used	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> single item, 5-point LK; worsening $\geq 1$ point (3) <b>Global assessment (patient):</b> VAS (0-100mm); increase $\geq 15$ mm ( <i>acetaminophen users only</i> )	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm; (2) <b>Global Assessment (investigator):</b> single item, 5-point LK; 'Fair, poor, or very poor'; (3) <b>Global assessment (patient):</b> VAS (0-100mm); $\geq 40$ mm	Longer than 5 plasma half-lives washout	Not specified	Not specified	None
Ehrich, 1999[37]	Not used	<b>Pain:</b> VAS (0-100mm); increase $\geq 15$ mm	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Longer than 5 plasma half-lives washout of NSAID	Not specified	Not specified	None

Essex, 2012[38]	"Flare"	(1) <b>Global Assessment (Physician):</b> 5-point LK; increase $\geq 1$ grade (2) <b>Global Assessment (patient):</b> 5-point LK; increase $\geq 1$ grade	(1) <b>Global Assessment (Physician):</b> 5-point LK; 'Fair, poor or very poor' (2) <b>Global Assessment (patient):</b> 5-point LK; 'Fair, poor or very poor' (3) <b>Pain:</b> VAS (0-100mm); 40-90mm	48 hour withdrawal	Not specified	Not specified	None
Essex 2013[78]	"Flare"	Not specified	(1) <b>Global Assessment of arthritis (Physician):</b> Minimum rating of 3 (2) <b>Global Assessment of arthritis (patient):</b> Minimum rating of 3 (3) <b>Pain:</b> VAS (0-100mm); 40-90mm	48 hour withdrawal	Not specified	Not specified	None
Gibofksy, 2014[39]	"Flare"	<b>Pain:</b> WOMAC Pain VAS; increase $\geq 15$ mm	<b>Pain:</b> WOMAC Pain VAS; $\geq 40$ mm	Not specified	Not specified	Not specified	None
Gineyts, 2004[40]	"Flare"	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point scale: worsening $\geq 1$ point	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm	5 half-lives of NSAID washout	Not specified	Not specified	None
Goldberg, 1988[41]	"Flare"	(1) <b>Pain:</b> Investigator assessed pain grade (None/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase $\geq 1$ grade in two items OR increase $\geq 2$ grade in one item	Not specified	2-14 day washout until flare	Not specified	Not specified	None
Gottesdien er, 2002[42]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (Investigator):</b> 5-point LK; Increase $\geq 1$ point	(1) <b>Pain on walking:</b> VAS (0-100mm); $\geq 40$ mm	3-15 day washout	Not specified	Not specified	None



Hochberg, 2011[43]	"Flare"	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; worsening $\geq 1$ point	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None
Katz, 2010[44]	"Flare"	Not specified	<b>Pain:</b> Pain score (0-10); $\geq 5$	Not specified-washout until flare occurred	Not specified	Not specified	None
Kivitz, 2001[45]	"Flare"	<b>Pain:</b> Patients Assessment of Pain Score (0-10) (unspecified); increase $\geq 2$ points	<b>Pain:</b> Patients Assessment of Pain Score (0-10) (unspecified); $\geq 5$	5 drug half-lives or 48 hours	Not specified	Not specified	None
Kivitz, 2004[76]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); worsening $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point LK; worsening $\geq 1$ point	Not specified	NSAID dependent half-life washout	Not specified	Not specified	None
Leung, 2002[47]	"Flare"	(1) <b>Pain on walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point LK; worsening $\geq 1$ point	(1) <b>Pain on walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm (2) <b>Global Assessment (patient):</b> (0-100mm); $\geq 40$ mm (acetaminophen users only) (3) <b>Global Assessment (investigator):</b> 5-point LK; 'Fair, poor, or very poor' (acetaminophen users only)	Determined by drug half-life washout	Not specified	Not specified	None

Luyten, 2007[48]	"Flare"	(1) <b>Global Assessment (Patient):</b> 5-point LK; Increase $\geq 1$ grade (2) <b>Global Assessment (physician):</b> 5-point LK; increase $\geq 1$ grade (3) <b>Composite definition:</b> Lequesne Osteoarthritis Severity Index (0-24); increase $\geq 2$ points	(1) <b>Global Assessment (Patient):</b> 5-point LK; 'Fair, poor or very poor' (Not on treatment – 'Poor or very poor') (2) <b>Global Assessment (physician):</b> 5-point LK; 'Fair, poor or very poor' (Not on treatment – 'Poor or very poor') (3) <b>Composite definition:</b> Lequesne Osteoarthritis Severity Index (0-24); $\geq 7$ (4) <b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	2-14 day washout	Not specified	Not specified	None
Manicourt, 2005[49]	"Flare"	<b>Pain when walking on a flat surface:</b> VAS (0-100mm) ; $\geq 10$ mm	Not specified	7-10 days washout	Not specified	Not specified	None
Mazzuca, 2002[50]	"Flare"	<b>Pain on standing:</b> WOMAC LK Pain Q5 'severe or extreme' after the washout AND decreased after resumption of usual analgesic drugs and/or NSAIDs	Not specified	Drug washout 5 half lives	Not specified	Not specified	None
McIlwain, 1989[51]	"Flare"	No measurement instrument: Increase in pain on motion, swelling, tenderness, redness and/or heat (unspecified if patient/physician/investigator reported)	Not specified	2-14 day washout	Not specified	Not specified	None
Mendelson, 1991[52]	"Worsening of arthritis condition"	(1) <b>Pain:</b> Pain scale (0-3) (0=none, 3=severe); worsening score (2) <b>Global (physician):</b> (0-100); worsening score	Not specified	Up to 14 days washout	Not specified	Not specified	None

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Moskowitz, 2006[53]	"Flare"	(1) <b>Global assessment (patient):</b> 5-point LK; increase $\geq 1$ grade (2) <b>Global Assessment (physician):</b> 5-point LK; $\geq 1$ grade increase (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); increase $\geq 2$ points	(1) <b>Global assessment (patient):</b> 5-point LK; '(Fair), poor, or very poor' (2) <b>Global Assessment (physician):</b> 5-point LK; '(Fair), poor or very poor' (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); Minimum $\geq 7$ (4) <b>Pain walking on a flat surface:</b> VAS (0-100mm); $\geq 40$ mm	NSAID washout of 5 half-lives or at least 2 days	Not specified	Not specified	None
17 18 19 20 21 22 23	Pareek, 2009[54]	"Flare-up"	(1) <b>Pain:</b> 11-point NRS; increase $\geq 2$ points during previous 2-5 days (2) Signs and symptoms suggestive of inflammation, morning stiffness and nocturnal pain interfering with sleep	<b>Pain:</b> Pain intensity of at least 4 on a 11-point NRS during physical activity for past 24 hours	Placebo washout for 24-48 hours	2-5 days	Not specified	None
24 25 26 27 28 29 30	Pareek, 2010[55]	"Flare"	Flare symptoms noted but not part of definition: morning stiffness, erythema, nocturnal pain, and swelling/inflammation	(1) <b>Pain with physical activity:</b> VAS 0-10; $\geq 6$ (2) <b>Composite index:</b> WOMAC Total LK; $\geq 25$ . (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); $\geq 5$	Not specified	2-5 days	Not specified	None
31 32 33 34 35 36	Roth, 2004[90]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); increase $\geq 2$ points and $\geq 25\%$	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); Score $\geq$ 'moderate' on at least 1 of the 5 items, (ii) Pain score $\geq 6$	Washout period of at least 3 days per week past month	Not specified	Not specified	None

Rother, 2007[93]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; increase $\geq 1$ grade	(1) <b>Pain on walking:</b> VAS (0-100mm); $\geq 40$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; 3-5	Not specified	Not specified	Not specified	None
Schnitzer, 2005[57]	"Flare"	No tool: increase in pain	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Not specified	24 hours	Not specified	None
Scott-Lennox, 2001[58]	"Flare"	(1) <b>Pain:</b> VAS (0-100mm); $\geq 20$ mm (2) <b>Pain (physician):</b> 4-point LK; worsening $\geq 1$ point (3) <b>Global Assessment (patient):</b> 4-point LK; worsening $\geq 1$ point (4) <b>Global Assessment (physician):</b> 4-point LK; worsening $\geq 1$ point	(1) <b>Pain:</b> VAS (0-100mm); $\geq 40$ mm at baseline (2) <b>Pain (physician):</b> 4-point LK; $\geq 2$ (3) <b>Global Assessment (patient):</b> 4-point LK; $\geq 2$ (4) <b>Global Assessment (physician):</b> 4-point LK; worsening $\geq 2$	14 day washout	Not specified	Not specified	Confirmatory Factor Analysis
Simon, 2009[91]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale; increase $\geq 2$ and $\geq 25\%$	<b>Pain:</b> WOMAC LK3.1 Pain subscale; $\geq$ 'moderate' on $\geq 1$ item	14 day washout	Not specified	Not specified	None
Silverfield, 2002[59]	"Flare"	<b>Pain:</b> No measurement tool; significant increase	Not specified	Not specified	Not specified	Pain requiring supplemental analgesic medication and/or an increase in NSAID dose	None
Strand, 2011[60]	"Flare"	<b>Global Assessment (patient):</b> 5-point LK; Increase $\geq 1$	(1) <b>Global Assessment (patient):</b> 5-point LK; 'Fair, poor or very poor' (2) <b>Pain:</b> (0-10 NRS); $\geq 4$ but $< 9$ (3) <b>Global Assessment (physician):</b> 5-point LK; 'Fair, poor or very poor'	14 day washout	Not specified	Not specified	None

Weaver, 1995[92]	"Flare"	(1) <b>Global Assessment (Physician)</b> : 5-point Likert; increase $\geq 1$ grade (2) <b>Global Assessment (patient)</b> : 5-point LK; increase $\geq 1$ grade (3) <b>Pain</b> : Worsening pain on motion and weight bearing	(1) <b>Global Assessment (Physician)</b> : 5-point Likert; $\geq 2$ (2) <b>Global Assessment (patient)</b> : 5-point LK; $\geq 2$	2-14 day washout	Not specified	Not specified	None
Wiesenhutter, 2005[61]	"Flare"	(1) <b>Pain on walking on flat surface</b> : WOMAC VAS3.0 Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (Investigator)</b> : 5-point LK; worsening $\geq 1$ unit	(1) <b>Pain on walking on flat surface</b> : WOMAC VAS3.0 Q1 (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None
Williams, 2001[62]	"Flare"	(1) <b>Global Assessment (patient)</b> : 5-point LK; Increase $\geq 1$ point (2) <b>Global Assessment (physician)</b> : 5-point LK; increase $\geq 1$ point(3) <b>Composite Index</b> : Lequesne OA Severity Index (0-24); Increase $\geq 2$ points	(1) <b>Global Assessment (patient)</b> : 5-point LK; '(Fair), poor or very poor' (2) <b>Global Assessment (physician)</b> : 5-point LK; '(Fair), poor or very poor' (3) <b>Composite Index</b> : Lequesne OA Severity Index (0-24); $\geq 7$ (4) <b>Pain</b> : VAS (0-100mm); $\geq 40$ mm	2-14 days	Not specified	Not specified	None
Wittenberg, 2006[63]	"Flare"	<b>Pain</b> : VAS (0-100mm); Increase $\geq 10$ mm	<b>Pain</b> : VAS (0-100mm); $\geq 40$ mm	2-7 day washout	Not specified	Not specified	None
Yeasted, 2014[64] (Pooled, abstract)	"Flare"	<b>Pain</b> : 0-10 NRS; Increase $\geq 2$ points over the mean pain score from the previous 3 days	<b>Pain</b> : Average daily 0-10 NRS; 4-9	Not specified	Not specified	Not specified	None
Yocum 2000[79]	"Flare"	<b>Disease activity</b> (1) <b>Global (Investigator)</b> : Reduction of $\geq 1$ grade (2) <b>Global Assessment (Patient)</b> : 100-mm VAS; Increase of $\geq 10$ mm	Not specified	$\geq 3$ days washout	Not specified	Not specified	None

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		(3) <b>Pain: Overall assessment (patient):</b> 100-mm VAS; $\geq 35$ mm					
Young, 2014[65]	"Flare"	(3) <b>Pain:</b> WOMAC pain subscale; increase $> 15$ mm	<b>Pain:</b> WOMAC Pain subscale $> 40$ mm	Not specified	Not specified	Not specified	None
Zhao, 1999[66]	"Flare"	No measurement tool: Worsening of signs and symptoms after discontinuation of NSAIDs of analgesics	Not specified	2-7 day washout	Not specified	Not specified	None
<b>NON-DRUG WITHDRAWAL STUDY DESIGN</b>							
Atukorala, 2016[80] (abstract)	"Flare"	<b>Pain:</b> (10-point NRS); increase $> 2$ points from the mildest knee OA pain intensity reported at day 0	Not specified	Not specified	Not specified	Not specified	None
Atukorala, 2016[27] (abstract)							
Bartholdy, 2016[81]	"Flare"	Not specified	<b>Pain:</b> (10-point NRS): Pain $> 5$	Not specified	Not specified	Not specified	None
Bassiouni 2015[82] (abstract)	"Flare"	Not specified	<b>Global Assessment (physician):</b> KOFUS $\geq 7$	Not specified	Not specified	Not specified	None
Cibere, 2004[88]	"Flare"	(1) Patients perception of worsening of symptoms	Not specified	Not specified	Not specified	Not specified	Definition determined by study rheumatologists to be a clinically important change in WOMAC-Ehrich2000/
Cibere, 2005[89]		(2) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100mm); increase $\geq 20$ mm (3) <b>Global Assessment (physician):</b> 5-point LK; worsening $\geq 1$ grade					

							Bellamy 1998
Conrozier 2012[68]	"Flare"	Fulfilled 4 following criteria: (1) <b>Pain:</b> No measurement tool; 'sudden aggravation of knee pain' (2) causing nocturnal awakenings, (3) clinical evidence of effusion.	Not specified	Sudden aggravatio n of knee pain, whose beginning was identifiable	Not specified	Not specified	None
D'Agostino 2005[69]	"Flare"	Not specified	<b>Pain intensity during physical activity:</b> VAS-(0-100mm); $\geq 40$ mm	Not specified	48 hours	Not specified	None
Erfani, 2014[46] abstract)  Erfani, 2014[83] (abstract)  Ferreira[84] 2016  Hunter 2014[85] (abstract)  Makovey 2015[86] (Protocol)	Exacer bation	<b>Pain:</b> VAS (0-100mm); Increase $\geq 20$ mm from mildest pain score reported at baseline	Not specified	Not specified	Not specified	Not specified	None

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Jawad, 2005[70]	Exacerbation	<b>Pain symptoms:</b> Increased morning stiffness, night pain and synovial fluid effusion	Not specified	Not specified	Not specified	Not specified	None
Marty 2009[20]	"Flare"	No measurement tool: Morning stiffness >20mins, nocturnal awakening, limping, knee swelling, increased warmth, effusion	Not specified	Not specified	48 hours	Not specified	Regression analysis of cross-sectional data to validate proposed flare criteria
Murphy, 2015[71]	"Flare"	(1) Investigator definition: Inadequate pain relief for an episode of intense pain that is usually brought on by too much activity. (2) Participant definitions: Described in terms of pain quality, timing (onset and duration), antecedents and consequences. (3) <b>Pain magnitude:</b> increase in pain or 'intense' or 'severe' level of pain	<b>Pain:</b> ≥40 of 100mm or ≥4 of 10 on NRS	Patients described: 'Quick' or 'sudden'	Patients: 10 seconds to 15 minutes	Patients: Rest or take additional medication	For investigator definition: Battisti 2004, Pareek 2010. Plus researchers own experience.
Parry, 2017[87]	"Flare"	<b>Pain:</b> Recalled worst pain intensity in previous 6 months 0-10 NRS; ≥5	<b>Pain:</b> Recalled worse pain to be ≥2 points higher than recalled average pain (0-10 NRS) in previous 6 months	Not specified	Not specified	Not specified	Based on previous studies defining knee flares in OA and flares in diseases such as back



							pain and COPD.
Ricci 2005[56]	"Flare up"	<b>Pain:</b> Self-reported flare severity rating 0-10 NRS; increase $\geq 2$ point over usual pain severity	Not specified	Not specified	Not specified	Not specified	Based on statistical analysis and clinical judgement
Wise 2010[72]	"Flare"	Not specified	<b>Pain:</b> WOMAC Pain subscale (0-10); score in highest 30% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2009[73]	"Exacerbation or flare"	Not specified	(1) Pain: WOMAC pain subscale 0-10 (total score of 50 normalised to a 0-10 scale); score of $\geq 5$ , a score corresponding to highest 33% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2011[74] (abstract)	"Exacerbation"	<b>Pain:</b> WOMAC Pain score VAS (0-500); increase $\geq 100$ units	Not specified	Not specified	Not specified	Not specified	None
Zobel, 2016[94]	Exacerbation	<b>Pain:</b> 0-10 NRS; Increase $\geq 2$	(1) Disabling pain	Not specified	8 hours	Not specified	None
<p>Acronyms:  COPD- Chronic Obstructive Pulmonary Disease  KOFUS- Knee Osteoarthritis Flare-up Score  NRS-Numerical Rating scale  VAS- Visual Analogue Score  WOMAC- Western Ontario and McMaster Universities Osteoarthritis Index  LK-Likert scale</p>							

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3 One study used the term “flare-up”[54], two studies referred simply to “worsening of  
4 symptoms” [33, 52] and three studies used no specific label[36, 37, 75].  
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### 10 **Coverage of key components**

11 *Onset/worsening of symptoms and signs beyond normal-day-to-day variability:* Forty-  
12 four studies included onset or worsening of signs and symptoms as part of their  
13 definition[26, 28-34, 36-43, 45, 47-55, 57-66, 75-77, 79, 90-93]. All studies included  
14 increased pain intensity in their definition. A further two[54, 55] specified further signs  
15 and symptoms. These included swelling, inflammation, erythema, morning stiffness  
16 and nocturnal pain. No studies quantified day-to-day variability.  
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31 Twenty-six measurement tools were used to define onset/worsening of symptoms  
32 and signs. The most commonly used tools were the Western Ontario & McMaster  
33 Universities Arthritis index (WOMAC) Q1 (pain on walking on flat surface) 100mm  
34 Visual Analogue Scale (VAS) (n=9)[31, 32, 34, 40, 43, 47, 61, 75, 77] and the  
35 Investigator Assessment of Disease Status (n=11)[30-32, 40, 42, 47, 61, 75-77, 79]  
36 (Table 3). Thirty-four studies used only single item measurement tools[29-32, 34, 36-  
37 45, 47, 49, 50, 52, 54, 57, 58, 60, 61, 63-65, 75-79, 92, 93], 5 used multi-item[33, 48,  
38 53, 55, 62] and 5 used both single and multi-item tools[26, 28, 35, 91, 95].  
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**Table 3: Summary of number and type of single and multi-item measurement tools used.**

<b>Single item scales:</b>	
Pain on activity:	WOMAC Q1 3.0 VAS 'pain on walking on a flat surface' (0-100mm) [n=11] Pain on walking VAS (0-100mm) [n=5] Pain on movement VAS (0-100mm); Ambulatory pain (5-point Likert); Pain with physical activity VAS 11-point scale [n=2]
Pain (not further specified):	Pain VAS (0-100mm) [n=15] Patients Assessment of Pain Score (0-10); Pain Scale (0-3); Pain NRS (0-10) [n=11]
Standing knee pain	Item 5 WOMAC pain scale [n=1]
Global rating (physician/ investigator)	Investigator Assessment of Disease Status [n=11] Physicians Global Assessment of Arthritis [n=6] Physician Global Assessment of OA [n=2] Physician Global Assessment of Disease Status [n=2]; Investigator Assessed Pain Grade; (Physician) Overall Disease Activity (0-100); Physicians Pain Assessment (4-point LK) [n=3]
Global rating (patient)	Patients Global Assessment of Arthritis [n=7] Patient Global Assessment of OA [n=3] Patient Global Assessment of Disease Status [n=4]
<b>Multiple-item scales:</b>	
	Lequesne OA Severity Index [n=5] WOMAC LK3.1 (0-20) [n=3] WOMAC LK Pain subscale (0-25); WOMAC OA Index

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Questionnaire [n=1]; WOMAC knee pain score (0-500)  
[n=7]; KOFUS (0-14) [n=1]

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N, number of included studies; WOMAC, Western Ontario and McMaster Universities  
Osteoarthritis Index; VAS, visual analogue scale; OA, osteoarthritis; KOFUS, Knee Osteoarthritis  
Flare-up Score.

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4 In addition, the format of global ratings appears to be variable as is use and  
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6 reporting of the WOMAC[96]. However, despite the exact format of reporting being  
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8 inconsistent, in general, studies used single items in 4 areas – pain on activity, pain  
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10 (not necessarily on activity), physician/investigator global rating and patient global  
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12 rating.  
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18 *Temporal characteristics:* None of the included drug withdrawal design studies  
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20 reported a specific time for defining the speed of onset of symptoms. However, they  
21  
22 did describe withdrawal or ‘washout’ periods whereby, after withdrawal of usual  
23  
24 medication, participants were given a certain time frame in which to experience ‘flare’  
25  
26 symptoms in order that they were entered into the study. In total 30 of the studies  
27  
28 specified a withdrawal period[29, 32, 33, 35-38, 40-42, 45, 47-54, 58, 60, 62, 63, 66, 75, 76, 78, 79,  
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31 90-92].  
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36 Four studies specified a time period for minimum duration of symptoms which  
37  
38 ranged from 24 hours to 5 days[54, 55, 57, 59] .  
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43 *Change in medication or healthcare usage:* Only one study used increase in  
44  
45 medication as part of their definition; ‘pain requiring supplemental analgesic  
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47 medication and/or an increase in NSAID dose’[59].  
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4 *Additional domains:* Thirty-six studies included a minimum threshold which was  
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6 usually a minimum level of pain that was required before the participant was  
7  
8 considered to have a flare[26, 28, 30-33, 35, 37-40, 42-45, 47-49, 53-55, 57, 58, 60-65, 75, 77, 78,  
9  
10 90-93]. There was general concordance with the minimum thresholds that different  
11  
12 measurement tools used with a few exceptions. A threshold of 40mm on a 0-100mm  
13  
14 scale was used in eight of ten studies using the WOMAC VAS 3.0 Q1 'pain on walking  
15  
16 on a flat surface'[31, 32, 40, 43, 47, 61, 75, 77] and four of fourteen studies using the  
17  
18 Patient Global Assessment of Disease Status[31, 47, 75, 77]. In studies using various  
19  
20 forms of investigator/physician global assessment, the majority adopted a minimum  
21  
22 threshold for a flare of 'fair, poor or very poor' [31, 32, 47, 75]. The minimum threshold  
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24 on the Lequesne index (0-10) was either five[55] or seven[48, 53, 62].  
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### 33 **Flare definitions in non-withdrawal flare/ discontinuation studies**

#### 34 **Terminology used**

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44 "Flare" was the term most common used in non-withdrawal design studies[20, 27, 68,  
45  
46 69, 71, 72, 80-82, 87, 89](n=11) (Table 2). One study used the term "flare-up"[56], eight  
47  
48 used "exacerbation"[46, 67, 70, 74, 83-86] (five publications were from the same team)  
49  
50 and one referred to both "exacerbation" and "flare"[73]. None referred to "worsening  
51  
52 of symptoms" or did not use any specific label.  
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## Coverage of key components

### *Onset/worsening of symptoms and signs beyond normal-day-to-day variability:*

Sixteen of twenty-two studies used onset or worsening of symptoms in their definition[27, 46, 56, 68, 70, 71, 74, 80, 83-89, 94]. Two studies did not use pain intensity as part of its definition[20, 82]. Three studies included symptoms other than pain in their definition[20, 68, 70]. These included nocturnal awakenings, effusion, morning stiffness, night pain, limping, and warmth.

The Murphy et al[71] study included an investigator definition of flare but also sought to describe patient experience of flares through face to face individual interviews.

Both investigator and patient definitions included onset/worsening of symptoms and signs however there was no differentiation from day-to-day variability.

Seven studies used a measurement tool to define onset of signs and symptoms (Table 3). These included the Pain NRS (0-10)[27, 56, 67, 80, 87], WOMAC knee pain score VAS (0-500)[74], pain walking on a flat surface (WOMAC)[88, 89], Global Assessment of Disease Status (physician) (Likert 5-point scale)[88, 89], and knee pain VAS not further specified (0-100)[46, 83-86].

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4 *Temporal characteristics:* Only one study set a definition for speed of onset,  
5  
6 describing this only as 'sudden' with no further specification[68]. Patients in the  
7  
8 Murphy et al study used the terms 'quick' and 'sudden' to describe flare onset[71].  
9  
10 Three studies specified a minimum duration of symptoms ranging from 8 to 48  
11  
12 hours[20, 67, 69]. In the Murphy et al study patients described duration of between  
13  
14 10 seconds to 15 minutes[71].  
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21 *Change in medication/healthcare usage:* No studies used change in medication or  
22  
23 healthcare usage as part of their definition. However, in Murphy et al patients  
24  
25 reported either taking rest or using additional medication[71].  
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31 *Additional Domains:* Two studies defined distribution-based minimum thresholds for  
32  
33 flare as the highest 30%<sup>72</sup> or highest 33%<sup>73</sup> of WOMAC Pain Subscale scores among  
34  
35 participants in the Longitudinal Examination of Arthritis Pain (LEAP) cohort (total  
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37 score out of 50 was normalised to a 0-10 scale).  
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## 46 **DISCUSSION**

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52 Flares in OA are recognised in existing clinical guidance[97] and reviews[98, 99] but  
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54 typically merit little more than a passing mention. The recently published review that  
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3 sought to define flare-ups in hip and knee OA only yielded 23 studies and four of  
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6 the included studies did not contain clear definitions for a flare-up[21]. Furthermore,  
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9 our analysis of the definitions has resulted in the findings of common core domains  
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11 which will be useful for developing an agreed consensus definition for OA flare. From  
12  
13 a clinical perspective, a unified definition of a flare could enable clinicians to provide  
14  
15 prompt, rationalised and focussed treatment. This could also have implications for  
16  
17 delivery of self-management strategies involving patients and how episodic  
18  
19 management is advocated by clinical guidelines. Our review was motivated by an  
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21 interest in seeking greater clarity on how these phenomena might be defined by  
22  
23 undertaking a broad search strategy, noting that similar efforts have been pursued in  
24  
25 other chronic diseases. While we found no current single, agreed definition of OA  
26  
27 flare, our review of 69 published studies suggests a number of common domains  
28  
29 which may capture cardinal features. These were: onset/worsening of symptoms and  
30  
31 signs, attainment of a minimum symptom threshold during flare, speed of  
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33 onset/worsening, and duration of elevated symptoms/signs. However, we found  
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35 considerable variation in how these domains have been operationalised for  
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37 measurement suggesting the need for further conceptual clarification and consensus.  
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48 Each potential cardinal feature of OA flare presents different challenges for achieving  
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50 consensus. The goal of an agreed composite definition is to facilitate both  
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52 reproducible and comparable research, whilst enabling more consistent recognition  
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3 and identification of these phenomena in routine practice. The heterogeneity of OA  
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6 should also be considered in any definition of a flare-up Most studies included in our  
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9 review required an increase in pain over 'usual' or 'baseline' intensity. Although this  
10  
11 was measured using a wide range of measurement instruments several studies  
12  
13 selected an increase of 2 or more points on a 0-10 scale providing a possible starting  
14  
15 point for consensus. Yet this possible 'signal' is arguably difficult to interpret without  
16  
17 also considering the amount of background 'noise', i.e. within-person diurnal[100]  
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19 and day-to-day variability[101], and the absolute level ('minimum threshold') of pain  
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21 during a flare. There was general concurrence with the minimum threshold that was  
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23 adopted, for example, 40mm on a 0-100mm scale and this may indicate the potential  
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25 level of minimally important clinical difference. In the study by Marty et al an  
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27 increase in pain was not independently associated with flare-up after adjusting for  
28  
29 other potential features[20]. However, the study by Marty et al[20] and Scott-Lennox  
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31 et al[58] were the only two studies we found that had attempted to derive and/or  
32  
33 validate a prediction model for OA flares. Interestingly their approaches have not  
34  
35 been widely adopted which suggests the complexity of reaching a widely accepted  
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37 model. Further research on detecting flares over within-person 'normal' variability by  
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39 collecting frequent repeated measures of pain intensity may be valuable but this  
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41 approach would not be feasible when identifying flares presenting at the point of  
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43 care in routine clinical practice. Instead, this may have to rely on the judgement of  
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45 the patient and/or clinician, the approach used, for example, in defining  
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3 exacerbations in COPD[1]. A similar consideration surrounds the speed of onset,  
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6 which was not well defined by studies in our review. Drug withdrawal design studies  
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9 specified washout periods between 2-15 days but this is unlikely to be synonymous  
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11 with speed of onset. The remaining studies used terms such as 'sudden' and 'quick'.  
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14 In COPD, for instance, a judgement around 'acute onset' or 'sudden onset' appears to  
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16 be acceptable for clinical recommendations but we would add that the speed of  
17  
18 onset of OA flares ought to be considered also in relation to underlying biologically  
19  
20 plausible mechanisms. Indeed presumed aetiology has been argued as a useful  
21  
22 feature in defining acute exacerbations in COPD[102]. Minimum duration ranged  
23  
24 from 8 hours to 5 days in our review however this was not widely reported. COPD  
25  
26 definitions refer to a 'sustained worsening' of symptoms[2] but does not appear to  
27  
28 be a feature in other chronic diseases. A minimum duration in OA may help  
29  
30 distinguish flares from day-to-day variability. Increase in medication was not found  
31  
32 to be a key component in this review despite it being a feature in other chronic  
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34 diseases; AS[5], SLE[4, 103], Inflammatory Bowel Disease[104], COPD[1]. Interference  
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36 with function did not emerge strongly from our review as a cardinal feature of OA  
37  
38 flare. In other chronic musculoskeletal conditions, such as back pain, interference  
39  
40 with function was not shown to be significantly associated with having a flare up[105]  
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42 and this domain does not feature in the definitions of exacerbations or flares in  
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44 diseases such as COPD[1, 2], asthma[3], AS[5] or SLE[4].  
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3 Our review has several strengths but also some weaknesses that deserve attention.  
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6 We adopted a broad search strategy, covering a wide range of databases, and  
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8 featuring bibliography checks, contact with authors, inclusion of conference  
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10 abstracts, no language restrictions, and a minimal threshold (any description or  
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12 definition of flare) for inclusion. Five studies that were included in the Cross et al[21]  
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14 review were not included in this study; four did not contain a clear definition of flare-  
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16 up, including one which gave a definition of knee OA progression and the final paper  
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18 by Sands et al[106] was not in our search but the original study was[60]. We did not,  
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20 however, search the grey literature and we did not include some potential synonyms  
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22 as search terms ('attack', 'episode', 'fluctuations') although these terms appeared  
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24 often to relate to comorbidities and other phenomena (e.g. episodes of care) and  
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26 would therefore have been a less efficient search strategy than relying on snowball  
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28 references. Data extraction was performed by only a single reviewer. Nevertheless,  
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30 we argue that our review provides a reasonably comprehensive summary of how  
31  
32 'flares' in OA have been described and defined in the medical literature. In  
33  
34 comparison with Cross et al[21] our search strategy appeared comprehensive yet  
35  
36 efficient – returning 69 included articles compared with 23. The majority of studies  
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38 describe experimental 'flare design' trials in which flares are induced by drug  
39  
40 withdrawal prior to enrolment and randomisation. While intentional or unintentional  
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42 reduction in usual analgesia may indeed be one trigger for flare, experimentally  
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44 induced flares should not be assumed to represent 'naturally occurring' flares. Flare  
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3 design trials, for example, are unlikely to capture change in management or  
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5 healthcare usage that may be a common consequence of OA flares – something that  
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7 is included in flare definitions in other conditions such as AS[5], SLE[4, 103],  
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9 inflammatory bowel disease[104], and COPD[1].  
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16 A systematic review such as this cannot hope to resolve the need for a common  
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18 conception and definition of flares in OA. Definitions for exacerbations of disease  
19  
20 states are generally reached through a long process of consensus exercises involving  
21  
22 key stakeholders, experts and patients in addition to appraisal of relevant literature  
23  
24 from studies using multiple methods[6, 8, 107]. However, we believe that a consensus  
25  
26 definition that is reliable, valid, and feasible and widely acceptable both clinically and  
27  
28 for research purposes should now be sought. The cardinal features described in this  
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30 review; onset/worsening of symptoms and signs, attainment of a minimum symptom  
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32 threshold during flare, speed of onset/worsening, and duration of elevated  
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34 symptoms/signs could help start this discussion.  
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## 43 **CONCLUSION**

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48 A broad range of ad-hoc definitions currently exist in the medical literature. The  
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50 majority are from drug-withdrawal or flare-induced trials rather than 'naturally'  
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52 occurring flares. The cardinal feature is pain intensity with minimum symptom  
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3 threshold being another important feature. This review has identified the need to  
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6 gain consensus on a common definition that can be used for research and clinical  
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9 application.

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GMP (g.m.peat@keele.ac.uk ) takes responsibility for the integrity of the work as a whole from inception to finished article.

## **Data sharing statement**

No unpublished data is available following this study

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17  
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19  
20

### 21 **Competing interest statement**

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25  
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### 33 **Figure and Table Legends**

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36 Figure 1: PRISMA Flowchart  
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39 Table 1: Characteristics of all included studies  
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42 Table 2: Summary of number and type of single and multi-item measurement  
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45 Table 3: Definition, terminology and measurement instruments used in all included  
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47 studies  
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50 Supplementary data: Database search strategy  
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56



## REFERENCES

- 1 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of COPD: GOLD 2016.
- 2 National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management (CG101). London: NICE 2010.
- 3 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention: GINA 2015.
- 4 Ruperto N, Hanrahan L, Alarcón G, et al. International consensus for a definition of disease flare in lupus, *Lupus* 2011;20:453-62.
- 5 Stone MA, Pomeroy E, Keat A, et al. Assessment of the impact of flares in ankylosing spondylitis disease activity using the Flare Illustration, *Rheumatology* 2008;47:1213-8.
- 6 Bingham CO, Alten R, Bartlett SJ, et al. Identifying Preliminary Domains to Detect and Measure Rheumatoid Arthritis Flares: Report of the OMERACT 10 RA Flare Workshop, *The Journal of Rheumatology* 2011;38:1751-8.

1  
2  
3  
4 7 Bykerk VP, Lie E, Bartlett SJ, et al. Establishing a Core Domain Set to Measure  
5  
6 Rheumatoid Arthritis Flares: Report of the OMERACT 11 RA Flare Workshop, *The*  
7  
8 *Journal of Rheumatology* 2014;41:799-809.  
9

10  
11  
12 8 Bartlett SJ, Hewlett S, Bingham CO, et al. Identifying core domains to assess flare in  
13  
14 rheumatoid arthritis: an OMERACT international patient and provider combined  
15  
16 Delphi consensus, *Annals of the Rheumatic Diseases* 2012;71:1855-60.  
17  
18

19  
20  
21 9 Taylor WJ, Shewchuk R, Saag KG, et al. Toward a valid definition of gout flare:  
22  
23 Results of consensus exercises using delphi methodology and cognitive mapping,  
24  
25 *Arthritis Care & Research* 2009;61:535-43.  
26  
27

28  
29  
30 10 Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for  
31  
32 Eczema (HOME) statement to assess clinical signs of atopic eczema in trials, *J Allergy*  
33  
34 *Clin Immunol* 2014;134:800-7.  
35  
36

37  
38 11 Holla JFM, van dL, Knol DL, et al. The association of body-mass index and  
39  
40 depressed mood with knee pain and activity limitations in knee osteoarthritis: results  
41  
42 from the Amsterdam osteoarthritis cohort, *BMC Musculoskeletal Disorders*  
43  
44 2013;14:296.  
45  
46

47  
48  
49 12 Collins JE, Katz JN, Dervan EE, et al. Trajectories and risk profiles of pain in persons  
50  
51 with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis  
52  
53 initiative, *Osteoarthritis and Cartilage* 2014;22:622-30.  
54  
55

1  
2  
3 13 Leffondré K, Abrahamowicz M, Regeasse A, et al. Statistical measures were  
4  
5  
6 proposed for identifying longitudinal patterns of change in quantitative health  
7  
8 indicators, *J Clin Epidemiol* 2004;57:1049-62.  
9

10  
11  
12 14 Emrani PS, Katz JN, Kessler CL, et al. Joint space narrowing and Kellgren–Lawrence  
13  
14 progression in knee osteoarthritis: an analytic literature synthesis, *Osteoarthritis and*  
15  
16 *Cartilage* 2008;16:873-82.  
17  
18

19  
20  
21 15 Bartlett SJ, Ling SM, Mayo NE, et al. Identifying common trajectories of joint space  
22  
23 narrowing over two years in knee osteoarthritis, *Arthritis Care & Research*  
24  
25 2011;63:1722-8.  
26  
27

28  
29 16 Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip  
30  
31 and knee osteoarthritis – an OARSI/OMERACT initiative, *Osteoarthritis and Cartilage*  
32  
33 2008;16:415-22.  
34  
35

36  
37  
38 17 Arthritis Research UK. Osteoarthritis: Patient Information Booklet. 2012.  
39  
40

41  
42 18 Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation,  
43  
44 *Rheumatology* 2005;44:7-16.  
45  
46

47  
48 19 Smith TO, Zou K, Abdullah N, et al. Does flare trial design affect the effect size of  
49  
50 non-steroidal anti-inflammatory drugs in symptomatic osteoarthritis? A systematic  
51  
52 review and meta-analysis, *Annals of the Rheumatic Diseases* 2016;75:1971-8.  
53  
54  
55

1  
2  
3  
4 20 Marty M, Hilliquin P, Rozenberg S, et al. Validation of the KOFUS (Knee  
5  
6 Osteoarthritis Flare-Ups Score), *Joint Bone Spine* 2009;76:268-72.  
7

8  
9  
10 21 Cross M, Dubouis L, Mangin M, et al. Defining Flare in Osteoarthritis of the Hip  
11  
12 and Knee: A Systematic Literature Review- OMERACT Virtual Special Interest Group, *J*  
13  
14 *Rheumatol* 2017;44(12):1920-7.  
15

16  
17  
18 22 Rutjes AS, Jüni P, Da Costa BR, et al. Viscosupplementation for osteoarthritis of the  
19  
20 knee: A systematic review and meta-analysis, *Ann Intern Med* 2012;157:180-91.  
21  
22

23  
24 23 Higgins J, Green S, eds. Cochrane handbook for systematic reviews of  
25  
26 interventions Version 5.1.0. Available from [www.handbook.cochrane.org](http://www.handbook.cochrane.org).: The  
27  
28 Cochrane Colloboration 2011.  
29  
30

31  
32  
33 24 Popay J, Roberts H, S, A., et al. Guidance on the conduct of narrative synthesis in  
34  
35 systematic reviews: A product of the ESRC methods programme Lancaster: ESRC  
36  
37 Method Programme, 2006.  
38  
39

40  
41  
42 25 Thomas J, Harden A, Newman M. Synthesis: Combining results systematically and  
43  
44 appropriately. In: Gough A, Oliver S, Thomas J, eds. An introduction to systematic  
45  
46 reviews. London: Sage publications limited 2013:191-2.  
47  
48

49  
50 26 Altman R, Hochberg M, Gibofsky A, et al. Efficacy and safety of low-dose  
51  
52 SoluMatrix meloxicam in the treatment of osteoarthritis pain: A 12-week, phase 3  
53  
54 study, *Curr Med Res Opin* 2015;31:2331-43.  
55  
56

1  
2  
3  
4 27 Atukorala I, Pathmeswaran A, Makovey J, et al. Is there a relationship between the  
5  
6 intermittent and constant osteoarthritis pain score (ICOAP) and pain flares in knee  
7  
8 osteoarthritis? (abstract) [abstract]. *Osteoarthritis and Cartilage* 2016;24:S429-30.  
9

10  
11  
12 28 Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a  
13  
14 topical diclofenac solution: a randomised controlled, 6-week trial [ISRCTN53366886],  
15  
16 *BMC Musculoskeletal Disorders* 2005;6:44.  
17

18  
19  
20  
21 29 Baraf HSB, Gloth FM, Barthel HR, et al. Safety and Efficacy of Topical Diclofenac  
22  
23 Sodium Gel for Knee Osteoarthritis in Elderly and Younger Patients, *Drugs Aging*  
24  
25 2011;28:27-40.  
26

27  
28  
29 30 Battisti WP, Katz NP, Weaver AL, et al. Pain management in osteoarthritis: A focus  
30  
31 on onset of efficacy—a comparison of rofecoxib, celecoxib, acetaminophen, and  
32  
33 nabumetone across four clinical trials, *The Journal of Pain* 2004;5:511-20.  
34  
35

36  
37  
38 31 Bingham CO, Sebba AI, Rubin BR, et al. Efficacy and safety of etoricoxib 30 mg and  
39  
40 celecoxib 200 mg in the treatment of osteoarthritis in two identically designed,  
41  
42 randomized, placebo-controlled, non-inferiority studies, *Rheumatology* 2007;46:496-  
43  
44 507.  
45

46  
47  
48  
49 32 Birbara C, Ruoff G, Sheldon E, et al. Efficacy and safety of rofecoxib 12.5 mg and  
50  
51 celecoxib 200 mg in two similarly designed osteoarthritis studies, *Curr Med Res Opin*  
52  
53 2006;22:199-210.  
54  
55

1  
2  
3 33 Bocanegra T, Weaver A, Tindall E, et al. Diclofenac/misoprostol compared with  
4  
5  
6 diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized,  
7  
8  
9 placebo controlled trial. Arthrotec Osteoarthritis Study Group. *Journal of*  
10  
11 *Rheumatology* 1998;25:1602-11.

12  
13  
14 34 Boswell DJ, Ostergaard K, Philipson RS, et al. Evaluation of GW406381 for  
15  
16  
17 Treatment of Osteoarthritis of the Knee: Two Randomized, Controlled Studies, *The*  
18  
19 *Medscape Journal of Medicine* 2008;10:259.

20  
21  
22  
23 35 Brandt KD, Mazzuca SA, Buckwalter KA. Acetaminophen, like conventional NSAIDs,  
24  
25  
26 may reduce synovitis in osteoarthritic knees, *Rheumatology* 2006;45:1389-94.

27  
28  
29 36 Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating  
30  
31  
32 symptomatic knee osteoarthritis: A randomized, double-blind, placebo-controlled  
33  
34  
35 comparison trial with diclofenac sodium, *Arch Intern Med* 2003;163:169-78.

36  
37  
38 37 Ehrich E, Schnitzer T, McIlwain H, et al. Effect of specific COX-2 inhibition in  
39  
40  
41 osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of  
42  
43  
44 rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. *Journal of Rheumatology*  
45  
46  
47 1999;26:2438-47.

48  
49 38 Essex M, O'Connell M, Brown PB. Response to Nonsteroidal Anti-Inflammatory  
50  
51  
52 Drugs in African Americans with Osteoarthritis of the Knee, *Journal of International*  
53  
54  
55 *Medical Research* 2012;40:2251-66.

1  
2  
3 39 Gibofsky A, Hochberg MC, Jaros MJ, et al. Efficacy and safety of low-dose  
4 submicron diclofenac for the treatment of osteoarthritis pain: A 12 week, phase 3  
5 study, *Curr Med Res Opin* 2014;30:1883-93.  
6  
7  
8  
9

10  
11 40 Gineyts E, Mo JA, Ko A, et al. Effects of ibuprofen on molecular markers of  
12 cartilage and synovium turnover in patients with knee osteoarthritis, *Annals of the*  
13 *Rheumatic Diseases* 2004;63:857-61.  
14  
15  
16  
17  
18

19  
20 41 Goldberg M, McIlwain H, Poiley J, et al. Controlled-release naproxen in the  
21 treatment of osteoarthritis, *Current Therapeutic Research-Clinical and Experimental*  
22 1988;44:51-60.  
23  
24  
25  
26  
27

28  
29 42 Gottesdiener K, Schnitzer T, Fisher C, et al. Results of a randomized, dose ranging  
30 trial of etoricoxib in patients with osteoarthritis, *Rheumatology* 2002;41:1052-61.  
31  
32  
33

34  
35 43 Hochberg MC, Fort JG, Svensson O, et al. Fixed-dose combination of enteric-  
36 coated naproxen and immediate-release esomeprazole has comparable efficacy to  
37 celecoxib for knee osteoarthritis: two randomized trials, *Curr Med Res Opin*  
38 2011;27:1243-53.  
39  
40  
41  
42  
43  
44

45  
46 44 Katz N, Sun S, Johnson F, et al. ALO-01 (Morphine Sulfate and Naltrexone  
47 Hydrochloride) Extended-Release Capsules in the Treatment of Chronic Pain of  
48 Osteoarthritis of the Hip or Knee: Pharmacokinetics, Efficacy, and Safety, *The Journal*  
49 *of Pain* 2010;11:303-11.  
50  
51  
52  
53  
54  
55

1  
2  
3  
4 45 Kivitz AJ, Makarowski WS, Fiechtner JJ, et al. A Flexible Daily Dosage Regimen of  
5  
6 Oxaprozin Potassium in Patients with Acute Knee Pain Associated with Osteoarthritis,  
7  
8 *Clinical Drug Investigation* 2001;21:745-53.  
9

10  
11  
12 46 Erfani T, Zhang Y, Makovey J, et al. Intermittent analgesic use and risk of pain  
13  
14 exacerbation in knee osteoarthritis: A web based case-crossover study (abstract)  
15  
16 [abstract]. *Arthritis and Rheumatology* 2014;66.  
17  
18

19  
20  
21 47 Leung AT, Malmstrom K, Gallacher AE, et al. Efficacy and Tolerability Profile of  
22  
23 Etoricoxib in Patients with Osteoarthritis: A Randomized, Double-blind, Placebo and  
24  
25 Active-comparator Controlled 12-Week Efficacy Trial, *Curr Med Res Opin* 2002;18:49-  
26  
27 58.  
28  
29

30  
31  
32 48 Luyten FP, Geusens P, Malaise M, et al. A prospective randomised multicentre  
33  
34 study comparing continuous and intermittent treatment with celecoxib in patients  
35  
36 with osteoarthritis of the knee or hip, *Annals of the Rheumatic Diseases* 2007;66:99-  
37  
38 106.  
39  
40

41  
42  
43 49 Manicourt D, Bevilacqua M, Righini V, et al. Comparative Effect of Nimesulide and  
44  
45 Ibuprofen on the Urinary Levels of Collagen Type II C-Telopeptide Degradation  
46  
47 Products and on the Serum Levels of Hyaluronan and Matrix Metalloproteinases-3  
48  
49 and -13 in Patients with Flare-Up of Osteoarthritis, *Drugs in R & D* 2005;6:261-71.  
50  
51  
52  
53  
54  
55  
56



1  
2  
3  
4 50 Mazzuca S, Brandt K, Lane K, et al. Knee pain reduces joint space width in  
5  
6 conventional standing anteroposterior radiographs of osteoarthritic knees, *Arthritis*  
7  
8 *Rheum* 2002;46:1223-7.  
9

10  
11  
12 51 McIlwain H, Silverfield JC, Cheatum DE, et al. Intra-articular oryogtein in  
13  
14 osteoarthritis of the knee: A placebo-controlled efficacy, safety, and dosage  
15  
16 comparison, *Am J Med* 1989;87:295-300.  
17  
18

19  
20  
21 52 Mendelsohn S. Clinical efficacy and tolerability of naproxen in osteoarthritis  
22  
23 patients using twice-daily and once-daily regimens, *Clinical therapeutics* 1991;13:8-  
24  
25 15.  
26  
27

28  
29 53 Moskowitz RW, Sunshine A, Hooper M, et al. An analgesic model for assessment  
30  
31 of acute pain response in osteoarthritis of the knee, *Osteoarthritis and Cartilage*  
32  
33 2006;14:1111-8.  
34  
35

36  
37  
38 54 Pareek A, Chandurkar N, Sharma VD, et al. A randomized, multicentric,  
39  
40 comparative evaluation of aceclofenac-paracetamol combination with aceclofenac  
41  
42 alone in Indian patients with osteoarthritis flare-up, *Expert Opin Pharmacother*  
43  
44 2009;10:727-35.  
45  
46

47  
48  
49 55 Pareek A, Chandurkar N, Ambade R, et al. Efficacy and Safety of Etodolac-  
50  
51 Paracetamol Fixed Dose Combination in Patients With Knee Osteoarthritis Flare-up: A  
52  
53 Randomized, Double-blind Comparative Evaluation, *Clin J Pain* 2010;26:561-6.  
54  
55

1  
2  
3 56 Ricci JA, Stewart WF, Chee E, et al. Pain Exacerbation as a Major Source of Lost  
4  
5  
6 Productive Time in US Workers With Arthritis, *Arthritis & Rheumatism: Arthritis Care*  
7  
8  
9 *& Research* 2005;53:673-81.

10  
11  
12 57 Schnitzer TJ, Fricke JR, Gitton X, et al. Lumiracoxib in the treatment of  
13  
14  
15 osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: results of  
16  
17  
18 three dose-response studies, *Curr Med Res Opin* 2005;21:151-61.

19  
20  
21 58 Scott-Lennox JA, McLaughlin-Miley C, Lennox RD, et al. Stratification of flare  
22  
23  
24 intensity identifies placebo responders in a treatment efficacy trial of patients with  
25  
26  
27 osteoarthritis, *Arthritis & Rheumatism* 2001;44:1599-607.

28  
29  
30 59 Silverfield JC, Kamin M, Wu S, et al. Tramadol/acetaminophen combination tablets  
31  
32  
33 for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized,  
34  
35  
36 double-blind, placebo-controlled, parallel-group, add-on study, *Clin Ther*  
37  
38  
39 2002;24:282-97 doi:[http://dx.doi.org/10.1016/S0149-2918\(02\)85024-X](http://dx.doi.org/10.1016/S0149-2918(02)85024-X) [published  
40  
41  
42 Online First: February 2002].

43  
44  
45 60 Strand V, Simon LS, Dougados M, et al. Treatment of osteoarthritis with  
46  
47  
48 continuous versus intermittent celecoxib, *J Rheumatol* 2011;38:2625-34.

49  
50  
51 61 Wiesenhutter CW, Boice JA, Ko A, et al. Evaluation of the Comparative Efficacy of  
52  
53  
54 Etoricoxib and Ibuprofen for Treatment of Patients With Osteoarthritis: A  
55  
56  
57 Randomized, Double-Blind, Placebo-Controlled Trial, *Mayo Clin Proc* 2005;80:470-9.

1  
2  
3  
4 62 Williams GW, Hubbard RC, Yu SS, et al. Comparison of once-daily and twice-daily  
5  
6 administration of celecoxib for the treatment of osteoarthritis of the knee, *Clin Ther*  
7  
8 2001;23:213-27 doi:[http://dx.doi.org/10.1016/S0149-2918\(01\)80004-7](http://dx.doi.org/10.1016/S0149-2918(01)80004-7) [published  
9  
10 Online First: February 2001].

11  
12  
13  
14 63 Wittenberg RH, Schell E, Krehan G, et al. First-dose analgesic effect of the cyclo-  
15  
16 oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a  
17  
18 randomized, double-blind, placebo-controlled comparison with celecoxib  
19  
20 NCT00267215], *Arthritis Research & Therapy* 2006;8:R35.  
21  
22

23  
24  
25 64 Yeasted R, McPherson J, Schnitzer T. Characterization of osteoarthritis pain  
26  
27 variability (abstract) [abstract]. *Osteoarthritis and Cartilage* 2014;22:S390-1.  
28  
29

30  
31 65 Young C, Parenti D, Hochberg M. Lower-dose diclofenac capsules developed  
32  
33 using solumatrix fine particle technology result in clinically meaningful improvements  
34  
35 in pain in a phase 3 study of patients with osteoarthritis (abstract) [abstract].  
36  
37 *Osteoarthritis and Cartilage* 2014;22.  
38  
39

40  
41  
42 66 Zhao SZ, McMillen JI, Markenson JA, et al. Evaluation of the Functional Status  
43  
44 Aspects of Health-Related Quality of Life of Patients with Osteoarthritis Treated with  
45  
46 Celecoxib, *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*  
47  
48 1999;19:1269-78.  
49  
50  
51  
52  
53  
54  
55  
56

1  
2  
3  
4 67 Zobel I, Erfani T, Bennell K, et al. Relationship of buckling and knee injury to pain  
5  
6 exacerbation in knee osteoarthritis: A web-based case-crossover stud, *Interact J Med*  
7  
8 *Res* 2014;66:S560-1.  
9

10  
11  
12 68 Conrozier T, Mathieu P, Vignon E, et al. Differences in the osteoarthritic synovial  
13  
14 fluid composition and rheology between patients with or without flare: a pilot study.  
15  
16 *Clinical and experimental rheumatology* 2012;30:729-34.  
17  
18

19  
20  
21 69 D'Agostino MA, Conaghan P, Le Bars M, et al. EULAR report on the use of  
22  
23 ultrasonography in painful knee osteoarthritis. Part 1: Prevalence of inflammation in  
24  
25 osteoarthritis, *Annals of the Rheumatic Diseases* 2005;64:1703-9.  
26  
27

28  
29 70 Jawad ASM. Analgesics and osteoarthritis: are treatment guidelines reflected in  
30  
31 clinical practice? *Am J Ther* 2005;12:98-104.  
32  
33

34  
35 71 Murphy SL, Lyden AK, Kratz AL, et al. Characterizing pain flares from the  
36  
37 perspective of individuals with symptomatic knee osteoarthritis, *Arthritis Care and*  
38  
39 *Research* 2015;67:1103-11.  
40  
41

42  
43  
44 72 Wise BL, Niu J, Zhang Y, et al. Psychological factors and their relation to  
45  
46 osteoarthritis pain, *Osteoarthritis and Cartilage* 2010;18:883-7.  
47  
48

49  
50 73 Zhang Y, Zhang B, Wise B, et al. Statistical approaches to evaluating the effect of  
51  
52 risk factors on the pain of knee osteoarthritis in longitudinal studies, *Curr Opin*  
53  
54 *Rheumatol* 2009;21:513-9.  
55  
56

1  
2  
3  
4 74 Zhang Y, Wheaton D, N, J., et al. Recent heavy physical activities trigger knee pain  
5  
6 exacerbation in persons with symptomatic knee osteoarthritis (abstract) [abstract].  
7  
8 *Arthritis & Rheumatism* 2011;63(10).

9  
10  
11  
12 75 Day R, Morrison B, Luza A, et al. A randomized trial of the efficacy and tolerability  
13  
14 of the cox-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis, *Arch*  
15  
16 *Intern Med* 2000;160:1781-7.

17  
18  
19  
20  
21 76 Kivitz AJ, Greenwald MW, Cohen SB, et al. Efficacy and Safety of Rofecoxib  
22  
23 12.5 mg Versus Nabumetone 1,000 mg in Patients with Osteoarthritis of the Knee: A  
24  
25 Randomized Controlled Trial, *J Am Geriatr Soc* 2004;52:666-74.

26  
27  
28  
29 77 Bingham CO, Smugar SS, Wang H, et al. Predictors of Response to Cyclo-  
30  
31 Oxygenase-2 Inhibitors in Osteoarthritis: Pooled Results from Two Identical Trials  
32  
33 Comparing Etoricoxib, Celecoxib, and Placebo, *Pain Medicine* 2011;12:352-61.

34  
35  
36  
37 78 Essex MN, Behar R, O'Connell MA, et al. Efficacy and tolerability of celecoxib and  
38  
39 naproxen vs placebo in hispanic patients with knee osteoarthritis, *Osteoarthritis and*  
40  
41 *Cartilage* 2013;21.

42  
43  
44  
45 79 Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the  
46  
47 treatment of osteoarthritis: A 12-week, double-blind, multiple-dose, placebo-  
48  
49 controlled trial, *Arch Intern Med* 2000;160:2947-54.  
50  
51  
52  
53  
54  
55  
56

- 1  
2  
3 80 Atukorala I, Pathmeswaran A, Chang T, et al. Do Traditional Risk Factors for Knee  
4 Osteoarthritis Predict Pain Flares in Knee Osteoarthritis? *Ann Rheum Dis* 2016;75:835.  
5  
6  
7  
8  
9 81 Bartholdy C, Klokke L, Bandak E, et al. A Standardized "Rescue" Exercise Program  
10 for Symptomatic Flare-up of Knee Osteoarthritis: Description and Safety  
11  
12 Considerations, *J Orthop Sports Phys Ther* 2016;46:942-6.  
13  
14  
15  
16  
17 82 Bassiouni H. Detection of changes in the serum and synovial fluid levels of resistin  
18 during flare ups and remissions in primary knee osteoarthritis, *Arthritis and*  
19  
20  
21  
22  
23  
24  
25  
26  
27 83 Erfani T, Makovey J, Bennell K, et al. Psychosocial Factors and Pain Exacerbation in  
28 Knee Osteoarthritis: a Web Based Case-Crossover Study, *Intern Med J* 2014;44:16-.  
29  
30  
31  
32  
33 84 Ferreira ML, Zhang Y, Metcalf B, et al. The influence of weather on the risk of pain  
34 exacerbation in patients with knee osteoarthritis - a case-crossover study,  
35  
36  
37  
38  
39  
40  
41  
42 85 Hunter DJ, Bennell K, Makovey J, et al. Psychosocial Factors and Pain Exacerbation  
43 in Knee Osteoarthritis: a Web Based Case-Crossover Study, *Osteoarthritis and*  
44  
45  
46  
47  
48  
49  
50 86 Makovey J, Metcalf B, Zhang Y, et al. Web-Based Study of Risk Factors for Pain  
51 Exacerbation in Osteoarthritis of the Knee (SPARK-Web): Design and Rationale, *JMIR*  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4 87 Parry E, Ogollah R, Peat G. Significant pain variability in persons with, or at high  
5  
6 risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of  
7  
8 cohort data, *BMC musculoskeletal disorders* 2017;18:80.  
9

10  
11  
12 88 Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled  
13  
14 glucosamine discontinuation trial in knee osteoarthritis, *Arthritis Care and Research*  
15  
16 2004;51:738-45.  
17  
18

19  
20  
21 89 Cibere J, Kopec JA, Esdaile JM, et al. Glucosamine sulfate and cartilage type II  
22  
23 collagen degradation in patients with knee osteoarthritis: randomized  
24  
25 discontinuation trial results employing biomarkers. In: Anonymous . *Journal of*  
26  
27 *rheumatology* 2005;896-902.  
28  
29

30  
31  
32 90 Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution  
33  
34 (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized,  
35  
36 double-blind, vehicle-controlled clinical trial, *Arch Intern Med* 2004;164:2017-23.  
37  
38

39  
40  
41 91 Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac  
42  
43 containing dimethyl sulfoxide (DMSO) compared with those of topical placebo,  
44  
45 DMSO vehicle and oral diclofenac for knee osteoarthritis, *Pain* 2009;143:238-45.  
46  
47

48  
49 92 Weaver A, Rubin B, Caldwell J, et al. Comparison of the efficacy and safety of  
50  
51 oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the  
52  
53 knee, *Clin Ther* 1995;17:735-45.  
54  
55

1  
2  
3 93 Rother M, Lavins BJ, Kneer W, et al. Efficacy and safety of epicutaneous ketoprofen  
4  
5  
6 in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the  
7  
8 knee: multicentre randomised controlled trial, *Annals of the Rheumatic Diseases*  
9  
10 2007;66:1178-83.  
11

12  
13  
14 94 Zobel I, Erfani T, Bennell KL, et al. Relationship of Buckling and Knee Injury to Pain  
15  
16 Exacerbation in Knee Osteoarthritis: A Web-Based Case-Crossover Study, *Interactive*  
17  
18 *journal of medical research* 2016;5:e17.  
19  
20

21  
22  
23 95 Roth ML, Tripp DA, Harrison MH, et al. Demographic and psychosocial predictors  
24  
25 of acute perioperative pain for total knee arthroplasty, *Pain Research & Management*  
26  
27 2007;12:185-94.  
28  
29

30  
31  
32 96 Woolacott NF, Corbett MS, Rice SJC. The use and reporting of WOMAC in the  
33  
34 assessment of the benefit of physical therapies for the pain of osteoarthritis of the  
35  
36 knee: findings from a systematic review of clinical trials, *Rheumatology* 2012;51:1440-  
37  
38 6.  
39  
40

41  
42  
43 97 National Institute for Health and Care Excellence (NICE).  
44  
45 Osteoarthritis: care and management (CG177). London: NICE 2014.  
46  
47

48  
49 98 Buttgerit F, Burmester G, Bijlsma JWJ. Non-surgical management of knee  
50  
51 osteoarthritis: where are we now and where do we need to go? *RMD Open* 2015;1.  
52  
53  
54  
55  
56



1  
2  
3 99 Porcheret M, Healey E, Dziedzic K, et al. Osteoarthritis: a modern approach to  
4 diagnosis and management, *Arthritis Research UK* 2011;Series 6.  
5  
6

7  
8  
9 100 Bellamy N, Sothorn RB, Campbell J. Rhythmic variations in pain perception in  
10 osteoarthritis of the knee, *J Rheumatol* 1990;17:364-72.  
11  
12

13  
14  
15 101 Allen KD, Coffman CJ, Golightly YM, et al. Daily pain variations among patients  
16 with hand, hip, and knee osteoarthritis, *Osteoarthritis and Cartilage* 2009;17:1275-82.  
17  
18

19  
20  
21 102 Makris D, Bouros D. COPD exacerbation: Lost in translation, *BMC Pulmonary*  
22 *Medicine* 2009;9:6.  
23  
24

25  
26  
27 103 Fitzgerald JD, Grossman JM. Validity and reliability of retrospective assessment of  
28 disease activity and flare in observational cohorts of lupus patients, *Lupus*  
29  
30  
31  
32  
33 1999;8:638-44.  
34

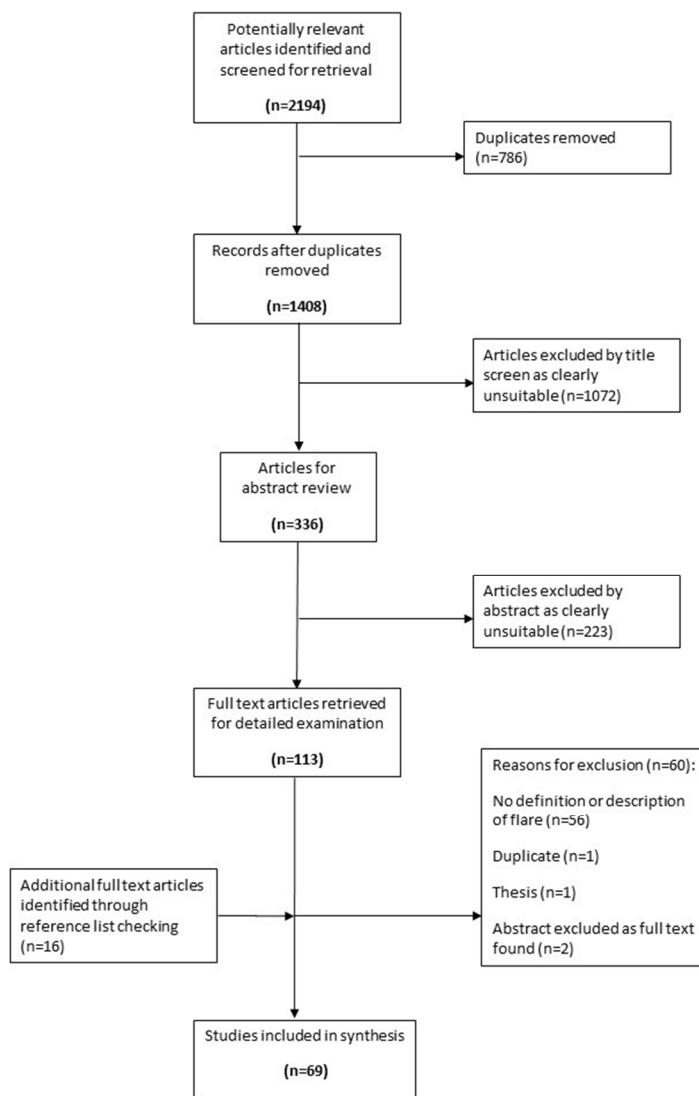
35  
36 104 Lewis JD, Aberra FN, Lichtenstein GR, et al. Seasonal variation in flares of  
37 inflammatory bowel disease, *Gastroenterology*;126:665-73.  
38  
39

40  
41  
42 105 Suri P, Saunders KW, Von Korff M. Prevalence and Characteristics of Flare-ups of  
43 Chronic Nonspecific Back Pain in Primary Care: A Telephone Survey, *Clin J Pain*  
44  
45  
46  
47 2012;28:573-80.  
48  
49

1  
2  
3 106 Sands GH, Brown PB, Essex MN. The Efficacy of Continuous Versus Intermittent  
4 Celecoxib Treatment in Osteoarthritis Patients with Body Mass Index  $\geq 30$  and *The*  
5  
6  
7  
8  
9 *Open Rheumatology Journal* 2013;7:32-7.

10  
11  
12 107 Berthelot J, De Bandt M, Morel J, et al. A tool to identify recent or present  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
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49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
rheumatoid arthritis flare from both patient and physician perspectives: The 'FLARE'  
instrument, *Annals of the Rheumatic Diseases* 2012;71:1110-6.

1  
2  
3  
4  
5  
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7  
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9  
10  
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12  
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**Online supplement: Example search strategy**

Table 1: Key terms and MeSH headings used for EMBASE database search. The concepts were combined as follows: "KNEE JOINT" AND "ACUTE EVENTS"

Concepts	Search terms
KNEE JOINT	"knee adj3 (pain OR painful)" or "Knee osteoarthritis" or "knee adj3 (arthrosis)" or "knee adj3 (joint OR joints OR degenerative)" or "knee adj3 (osteoarthritis)"
ACUTE EVENTS	"exacerbation" or "flare" or "daily adj3 (pain)" or "pain AND (diary OR diaries)" or "pain adj3 (variab\$)"



# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis. <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	9



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 (flowchart)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A but rationale on 18
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19-35
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	36-37
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	38
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	39
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	40

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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# BMJ Open

## Defining Acute Flares in Knee Osteoarthritis: A Systematic Review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019804.R2
Article Type:	Research
Date Submitted by the Author:	10-Apr-2018
Complete List of Authors:	Parry, Emma; Keele University, Research Institute for Primary Care and Health Sciences Thomas, M; Keele University, Research Institute for Primary Care and Health Sciences Peat, George; Keele University, Research Institute for Primary Care & Health Sciences
<b>Primary Subject Heading</b>:	Rheumatology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Osteoarthritis, Knee < ORTHOPAEDIC & TRAUMA SURGERY, Flare

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Manuscripts



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4 **1 DEFINING ACUTE FLARES IN KNEE OSTEOARTHRITIS: A**

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7 **2 SYSTEMATIC REVIEW**

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12 4 Martin J. Thomas<sup>1</sup>, m.thomas@keele.ac.uk

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35 13 **Keywords:** knee osteoarthritis, flare, systematic review

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## 15 ABSTRACT

16 **Objective:** To identify and critically synthesise definitions of acute flares in knee  
17 osteoarthritis (OA) reported in the medical literature.

18 **Design:** Systematic review and narrative synthesis. We searched MEDLINE, EMBASE,  
19 Web of science and 6 other electronic databases (inception to July 2017) for original  
20 articles and conference abstracts reporting a definition of acute flare (or synonym) in  
21 humans with knee OA. There were no restrictions by language or study design (apart  
22 from iatrogenic induced flare-ups e.g. injection-induced). Data extraction comprised:  
23 definition, pain scale used, flare duration or withdrawal period, associated symptoms,  
24 definition rationale, terminology (e.g. exacerbation or flare), baseline OA severity,  
25 age, gender, sample size and study design.

26 **Results:** Sixty-nine articles were included (46 flare-design trials, 17 observational  
27 studies, 6 other designs; sample sizes: 15-6085). Domains used to define flares  
28 included: worsening of signs and symptoms (61 studies, 27 different measurement  
29 tools), specifically increased pain intensity; minimum pain threshold at baseline (44  
30 studies); minimum duration (7 studies, range 8-48 hours); speed of onset (2 studies,  
31 defined as 'sudden' or 'quick'); requirement for increased medication (2 studies). No  
32 definitions included activity interference.

33 **Conclusions:** The concept of OA flare appears in the medical literature but most  
34 often in the context of flare design trials (pain increases observed after stopping  
35 usual treatment). Key domains, used to define acute events in other chronic

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4 36 conditions, appear relevant to OA flare and could provide the basis for consensus on  
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6 37 a single, agreed definition of 'naturally occurring' OA flares for research and clinical  
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9 38 application.

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11 39 **PROSPERO registration:** CRD42014010169  
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### 21 43 **Strengths and limitations of this study**

#### 22 23 44 *Strengths*

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26 45 • Identified key domains that are used to define acute events by undertaking a  
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28 46 comprehensive synthesis of definitions used in the medical literature.  
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31 47 • Broad search strategy covering a wide range of databases including  
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33 48 bibliography checks and conference abstracts.  
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36 49 • Prospectively registered with Prospero  
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#### 38 50 *Limitations*

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41 51 • Did not include potential synonyms as search terms ('attack', 'episode',  
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43 52 'fluctuations')  
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46 53 • Data extraction was performed by only a single reviewer.  
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## 55 INTRODUCTION

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57 Recurrent acute events or episodes feature in the natural history of many chronic  
58 health conditions. The extent to which they characterise the condition varies, as do  
59 the presumed pathophysiological mechanisms, and scientific and lay terms used to  
60 describe them (e.g. an acute exacerbation of chronic obstructive pulmonary disease  
61 (COPD) or asthma, an attack of gout or a rheumatoid arthritis flare). With recognition  
62 of their importance has come concerted effort to define these phenomena.

63 Definitions for exacerbations or flares currently exist for COPD[1, 2] , asthma[3],  
64 systemic lupus erythematosus (SLE)[4], and ankylosing spondylitis (AS)[5] and there  
65 are working groups currently trying to define these for rheumatoid arthritis[6-8],  
66 gout[9], and atopic dermatitis/eczema[10]. Despite the different language used,  
67 these definitions share some common, core domains: the onset or worsening of  
68 symptoms and signs above normal day-to-day variability; speed of onset; duration of  
69 sustained worsening; and change in medication/healthcare usage.

70

71 Osteoarthritis (OA) appears to comprise multiple disease trajectories[11-15] and  
72 symptom variability over time and the presence of intermittent pain is well-  
73 recognised[16]. Although OA does not typically have the same very obvious acute  
74 events as conditions like gout, flares in OA joints are encountered in practice, these

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3 75 phenomena appear in patient literature[17], have been discussed in expert  
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6 76 reviews[18], and are mentioned in 'flare design' trials in OA[19]. These studies invoke  
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9 77 acute episodes of pain or flare-ups by asking patients to withdraw their usual  
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11 78 medication.

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18 80 In 2009 Marty et al proposed scoring criteria for knee OA flares based on nocturnal  
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20 81 awakening, knee effusion, morning stiffness and limping[20] but it is unclear whether  
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23 82 this has contributed to a common understanding, shared terminology and criteria. A  
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25 83 common definition of OA flare could be important for a number of reasons; (i) to  
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28 84 facilitate communication between researchers, (ii) to allow more direct comparisons  
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30 85 between studies on frequencies, determinants and course of events, (iii) to facilitate  
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33 86 new insights into novel pathophysiological mechanisms and treatments through  
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35 87 valid and homogenous case definitions, and (iv) to help clinicians with prompt  
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38 88 diagnosis and management.

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45 90 The aim of this systematic review was to explore the extent to which a concept of OA  
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47 91 flare is reported in the medical literature and the prospects for a common, shared  
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50 92 definition of these for research and clinical application.

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3 99 **METHODS**  
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8 101 This systematic review was registered with PROSPERO registration number  
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10 102 CRD42014010169. The review protocol has not been published.  
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16 104 **Literature sources and study selection**  
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22 106 We searched electronic databases from inception to July 2017; ASSIA, EMBASE, Web  
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24 107 of Science, Health Management Information Consortium (HMIC), SPORTDiscus,  
25

26 108 Medline, CINAHL, PsycINFO, AMED, Ageline, Cochrane Database of Systematic  
27

28 109 Reviews and Cochrane Controlled Clinical Trials (CENTRAL). The search was  
29

30 110 developed using previously piloted terms for knee OA and a literature search for  
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32

33 111 common terms used to describe acute events. Searches used combined and/or  
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36 112 truncated key terms including: ("KNEE OSTEOARTHRITIS" OR (knee N3 pain) OR  
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39 113 (knee N3 arthrosis) OR (knee N3 joint) OR (knee N3 osteoarthritis)) AND  
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42 114 (exacerbation OR flare OR (pain AND (diary OR diaries)) OR (pain N3 variab\*) OR  
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45 115 (pain N3 pattern\$) OR (daily N3 pain)). A database search strategy is included in the  
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47 116 online supplement . Reference lists of all included full text articles retrieved for  
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49 117 detailed examination were manually searched.  
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4 119 Studies were included in the final full text peer review if they contained a description  
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6 120 or definition of an acute exacerbation or flare-up of knee OA in human adults (18  
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8 121 years or over) in the general population, primary care or hospital settings. Studies  
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11 122 were included even if their description was not based on clear measurement criteria  
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13 123 (e.g. stating a 'significant increase in pain' but not the amount of change on a pain  
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15 124 score this would equate to). Studies that included a mixed OA population (e.g. knee  
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17 125 or hip OA) and did not separately report knee-specific findings were included. There  
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19 126 were no restrictions on study dates or design. All non-English language articles were  
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21 127 translated to identify a flare definition. Theses, dissertations, book chapters and  
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23 128 guidelines, and animal studies were excluded. Conference abstracts were included if  
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25 129 they contained a definition for an OA flare-up. Studies were excluded if the flare was  
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27 130 induced by an iatrogenic source, for example, injection-induced flares[21]. As these  
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29 131 may have been caused by a different pathophysiological process. Abstracts were  
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31 132 included in this study as the main outcome of interest was the definition of flare used  
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33 133 and it was decided that including abstracts would ensure a more comprehensive  
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35 134 review. For each abstract a search was conducted to identify a corresponding full text  
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37 135 paper. Where one was found only the full paper was included in the review.  
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50 137 The search and article retrieval was conducted by the first reviewer (ELP). Articles  
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52 138 were downloaded into RefWorks© bibliography and database manager (RefWorks  
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54 139 Copyright 2009). Duplicates were removed and all titles were screened by ELP  
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4 140 against inclusion criteria, with the first 20 titles checked by two reviewers (ELP and  
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6 141 MJT) for consistency. For qualitative studies, all identified potentially eligible full text  
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8 142 articles were obtained.  
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13 144 All abstracts and then full text articles were screened by two reviewers (ELP and MJT).  
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16 145 with disagreements resolved by consensus adjudicated by a third reviewer (GP).  
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18 146 Where articles could not be retrieved or if the flare definition used was not included  
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21 147 in the text, contact with authors was made.  
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26 149 The final included articles were checked to ensure results were not duplicated, for  
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28 150 example, where different authors were reporting on the same dataset, to reduce  
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31 151 bias[22] . For articles containing pooled studies, the original studies were sought and  
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33 152 included in the main analysis, where available.. No full text articles were required to  
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36 153 be translated.  
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### 39 40 41 155 **Data extraction**

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49 158 The following data pertaining to flares were extracted from full text articles by the  
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52 159 first reviewer: definition used for change in pain, pain scale used, duration of flare  
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55 160 (for flare design trials we extracted the duration of the withdrawal period for  
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3 161 comparison), associated symptoms, rationale behind definition used, terminology  
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6 162 used (e.g. exacerbation or flare), baseline OA severity, age range, gender,  
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8 163 geographical location, number of participants and study design. Missing data was  
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11 164 described in the data extraction tables.  
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## 166 **Quality assessment of included studies**

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168 Our aim was to identify and contrast definitions of flare-ups used in the literature.  
169 We were not concerned with the methodological rigour of the studies deriving,  
170 evaluating or applying those definitions. However, for studies presenting definitions  
171 we sought supporting statements that gave the rationale for the definition.  
172

## 173 **Data analysis**

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175 A narrative synthesis was undertaken, guided by Popay et al's[23] four stage process  
176 to develop a conceptual framework[22]. This approach was chosen as it allowed the  
177 words and text in the definitions to be synthesised to summarise findings[23]. The  
178 initial data extracted was grouped into drug withdrawal studies ('flare design') and  
179 other studies. Frequencies of components included in definitions was tabulated,  
180 these included; terminology used, onset/worsening of symptoms; signs/symptoms

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6 182 duration of worsening and change in medication/healthcare usage.  
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11 184 This initial tabulation helped identify similarities and differences and allowed themes  
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13 185 to emerge. This was done with an inductive type approach, where possible i.e.  
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16 186 without an *a priori* assumption, but also deductively acknowledging that the  
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18 187 reviewers were clinicians i.e. they had some background knowledge of the topic of  
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21 188 interest. This allowed further examination of the differences of definitions used in  
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23 189 drug withdrawal and non-drug withdrawal study designs, and examination of key  
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26 190 components of definitions used.  
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## 30 31 192 **Patient and public involvement**

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36 194 There was no patient or public involvement in this study.  
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## 40 41 196 **RESULTS**

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### 45 46 47 198 **Study selection**

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4 200 The literature search yielded 2194 articles of which 786 were duplicates (Figure 1).  
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6 201 After title screening 336 abstracts were reviewed, 223 were not relevant for the study  
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8 202 purpose. 113 articles were examined in full which resulted in a further 60 being  
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10 203 excluded. The main reason for exclusion was no definition of flare-up reported in text  
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12 204 (n=56). At this stage a further 16 articles were identified from the reference lists of  
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14 205 the retrieved full text articles resulting in 69 included studies for synthesis.  
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### 207 **Study characteristics**

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209 Characteristics of the included studies are described in Table 1[20, 24-91]. The  
210 number of participants in each study ranged from 15-6085[20, 48]. Knee OA was  
211 defined by clinical and/or radiological criteria.  
212

213 **Table 1: Characteristics of all included studies**

<b>DRUG WITHDRAWAL DESIGN STUDIES</b>					
<b>First author, year of publication</b>	<b>Setting, geographic location</b>	<b>Participants</b>	<b>Joint</b>	<b>Severity</b>	<b>Study design</b>
Altman, 2015[24]	Multi-centre, recruitment not specified, USA	403 males & females, ≥40y	Knee and hip	KL grade 2-3	RCT, flare design
Baer, 2005[26]	17 medical centres recruiting from community and physician private practice; Canada	216 males & females, 40-85y	Knee	Radiographic evidence of OA (severity not defined)	RCT, flare design
Baraf, 2011[27]	Primary care, internal medicine, orthopaedic, rheumatology; USA	602 males & females, ≥25y	Knee	Radiographically mild to moderate (KL grade 1-3)	RCT, flare design
Battisti, 2004[28]	Clinical centres, out patients; USA	3980 males & females, ≥40y (age unavailable for Geba 2003 and Weaver 2003)	Knee	ACR functional class rating of I,II or III	RCT, pooled 4 trials, flare design
Bingham, 2007[29] Bingham 2011[75]	2x74 outpatient clinics; USA	1207 males & females, ≥40y	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design
Birbara, 2006[30]	Investigative	808 males &	Knee	ARA functional class, I, II, or III	RCT, flare design

	sites; USA	females, ≥40y			
Bocanegra, 1998[31]	Clinic; USA	572 males & females, 28-88y (mean 61-62)	Knee and hip	ARA Functional capacity classification I-III	RCT, flare design
Boswell, 2008[32]	50 centres (Europe & Australia) + 187 centres (Europe & USA)	1908 males & females, ≥40y	Knee	KL scale 2 or 3 and ARA class rating of I,II or III	Pooled RCTs (2; one flare design, one non-flare), flare design
Brandt, 2006[33] (pilot studies)	Community; USA	30 males & females, mean age 62y	Knee	KL ≥2	Cohort design, flare design
Case, 2003[34]	Hospital-rheumatology centre; Chicago, USA	82 males & females, 40-75y	Knee	KL ≥1, and clinical criteria (pre-enrolment ambulatory pain; moderate pain by a 5-point Likert scale or increased pain.	RCT, flare design
Day, 2000[73]	49 investigative sites in 26 countries	809 males & females, mean age range 62-65y	Knee and hip	ARA functional class I-III, symptomatic for at least 6 months	RCT, flare design
Ehrich, 1999[35]	Clinical centres; USA	219 males & females, >40y	Knee	ARA functional class, I, II, or III	RCT, flare design
Essex, 2012[36]	Clinical centre; African-American, USA	322 males & females, ≥45y	Knee	ARA Functional capacity classification I-III	RCT, flare design
Essex 2013[76]	Hispanic population, 31 US centers	≥45y	Knee	ACR criteria, Functional capacity classification I-III	RCT, flare design
Gibofsky, 2014[37]	Not specified, USA	305 males & females, 41-90 y	Knee and hip	KL 2-3	RCT, flare design
Gineyts, 2004[38]	Subset of larger study; France	201 males & females, mean age 61-62y	Knee and hip	ARA I-III	RCT, flare design

Goldberg, 1988[39]	Investigative sites; USA	214 males & females, 40-85y (mean 64)	Knee and hip	Radiographic evidence of knee OA-not further defined	RCT, flare design
Gottesdiener, 2002[40]	Investigative sites; USA	617 males & females, ≥40y	Knee	ARA functional class I,II,III	RCT, flare design
Hochberg, 2011[41]	Centres; USA	1234 males & females, ≥50y	Knee	ACR functional class I-III	Pooled RCTs (2), flare design
Katz, 2010[42]	Clinical sites; USA	113 males & females, 28-83y (median 57))	Knee and hip	OA of hip and knee as diagnosed using ACR criteria-no definition of severity	RCT, flare design
Kivitz, 2001[43]	Investigative sites; USA	491 males & females, 28-91y (mean 58-61)	Knee	Confirmation of OA on weight bearing radiograph- no definition of severity	RCT, flare design
Kivitz, 2004[74]	Outpatient sites; USA	1042 males & females, ≥40y	Knee	ACR rating of I, II, III.	RCT, flare design
Leung, 2002[45]	Clinic; USA	677 males & females, ≥40y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Luyten, 2007[45]	Centres; Belgium	181 males & females, ≥40y	Knee and hip	ACR Functional capacity classification I-III	RCT, flare design
Manicourt, 2005[47]	Outpatient clinic; Belgium	90 males & females, 50-81y (mean 63-67)	Knee and hip	Clinical and radiographic evidence of OA-severity not defined.	RCT, flare design
Mazzuca, 2002[48]	Not specified, USA	15 males & females, ≥45y	Knee	KL 2-3	Observational, flare design
McIlwain, 1989[49]	Investigative sites; USA	139 males & females, mean 65y	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design
Mendelsohn, 1991[50]	Investigative sites; USA	139 males & females, 21-88y (mean age 63.3y)	Knee	Radiological evidence of moderate or severe osteoarthritis- not further defined	RCT, flare design

Moskowitz, 2006[51]	Investigative sites; USA	530 males & females, $\geq 45y$	Knee	ACR Functional capacity classification I-III	RCT, flare design
Pareek, 2009[52]	Multi-centre study, India	199 males & females, 40-70y	Knee	Lequesne criteria-score of 5 and above	RCT, flare design
Pareek, 2010[53]	Hospital; India	220 males & females, 40-70y	Knee	Clinical and radiological evidence of OA- severity not defined.	RCT, flare design
Roth, 2004[88]	Physicians private practice or community; USA	326 males & females, 40-85y	Knee	Radiological evidence of OA- severity not defined.	RCT, flare design
Rother, 2007[91]	Outpatient units; Germany	397 males & females, $\geq 40y$	Knee	KL 2-3	RCT, flare design
Schnitzer, 2005[55]	Investigative sites; International (7 countries)	583 males & females, 18-75y	Knee and hip	Diagnosis based on ACR criteria- severity not defined.	RCT, flare design
Scott-Lennox, 2001[56]	Investigative sites; USA	182 males & females, mean 61y	Knee	Not defined	RCT, flare design
Silverfield, 2002[57]	Centres; USA	308 males & females, 35-75y	Knee and hip	Clinical evidence of OA- severity not defined	RCT, flare design
Simon, 2009[89]	Outpatient centres; Canada, USA	775 males & females, 40-85y	Knee	Clinical and radiological evidence of OA- severity not defined	RCT, flare design



Strand, 2011[58]	Investigative sites; Multinational-not specified including USA	875 males & females, 18-80y	Knee and hip	OA according to ACR criteria and requiring NSAID treatment to control symptoms in the month preceding screening	RCT, flare design
Weaver, 1995[90]	Investigative sites; USA	328 males & females, >50y	Knee	ACR clinical criteria-diagnostic	RCT, flare design
Wiesenhutter, 2005[59]	Medical Centres; USA	528 males & females, 40-89y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design
Williams, 2001[60]	Clinical sites; USA	718 males & females, mean 61-62y	Knee	ACR clinical and radiographic criteria I-III	RCT, flare design
Wittenberg, 2006[61]	Centres (not specified) ; Germany	364 males & females, 50y	Knee	Moderate to severe symptomatic OA of the knee according to ACR criteria.	RCT, flare design
Yeasted, 2014[62] (Pooled, abstract)	USA	219 (merged observational), 137 (merged trial)>40y	Not specified	ACR criteria-diagnostic	2 longitudinal observational studies, placebo arms of 2 clinical trials
Yocum, 2000[77]	USA, 62 study centres	774 males & females, ≥40y	Knee or hip	Diagnosis confirmed by XR and clinical symptoms (not further specified)	RCT, flare design
Young, 2014[63] (abstract)	Multicenter,	305 males & females, >40y	Knee or hip	KL 2-3	RCT, flare design
Zhao, 1999[64]	Centre (not specified); USA, Canada	1004 males & females, ≥18y	Knee	ACR Functional capacity classification I-III	RCT, flare design
<b>NON-DRUG WITHDRAWAL DESIGN STUDIES</b>					

Atukorala, 2016[78] (abstract)	Not specified, USA + Australia + Sri Lanka	213 males & females, mean age 62y	Knee	Not specified	3-month, web based longitudinal follow up study
Atukorala, 2016[25] (abstract)		345 males & females, mean age 62y			
Bartholdy, 2016[79]	OA out-patient clinic, Denmark	131 males & females, $\geq 40y$	Knee	Radiographic evidence of OA (severity no defined) and BMI between 20-35 kg/m <sup>2</sup>	RCT
Bassiouni 2015[80] (abstract)	Not specified, Egypt	60 participants not further specified	Knee	Not specified	Observational
Cibere, 2004[86]  Cibere, 2005[87]	Community, Canada	137 males & females, mean age 65y (43- 88) for placebo and 64y (40-83) for glucosamine group	Knee	KL $\geq 2$ on anteroposterior radiograph	RCT
Conrozier 2012[66]	Hospital- rheumatology unit, France	44 males & females, mean age 67.6y	Knee	Radiographic evidence of knee OA-not further defined	Observational
D'Agostino 2005[67]	Hospital- European multicentre	600 males & females, $\geq 18y$	Knee	KL grade 1-4	Observational
Erfani, 2014[44] abstract)  Erfani, 2014[81] (abstract)  Ferreira[82] 2016	Australia	268 males & females, mean age 62y  345 males & females, $\geq 40y$	Knee	ACR criteria- meet at least one, KL $\geq 2$	Web based cross over

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Hunter 2014[83] (abstract)					
Makovey 2015[84] (Protocol)					
Jawad, 2005[68]	GPs in France	3000 (for GP study) males & females	Knee	Not defined	n/a, review of surveys. Definition relates to survey of 3000 French GPs
Marty 2009[20]	Community and hospital, France	6085+641males & females, mean age 66.4y (10.9) for flare group, 66.2y (10.2) no flare group	Knee	OA diagnosis based on ACR criteria- severity not defined	Observational
Murphy, 2015[69]	Community based, pain clinics; USA	45 males & females, 37-83y	Knee	ACR criteria- severity not defined	Qualitative
Parry, 2017[85]	Community, UK	719 males & females, ≥50y	Knee	Self-reported knee pain in previous 12 months	Observational
Ricci 2005[54]	Community, USA	329 males & females, 40-65y	Knee and hip	Clinical evidence of OA- severity not defined	Nested case control
Wise 2010[70]	Primary care, hospital, USA	303 males & females, ≥50y	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment- not further defined	Observational

Zhang 2009[71]	Primary care, hospital, USA	303 males & females, $\geq 50y$	Knee and hip	Signal joint pain in a hip or knee on at least 15 out of the 30 days prior to enrolment-not further defined	Observational
Zhang 2011[72] (abstract)	Not specified	52 males & females, median age 63, (50-72y)	Knee	KL>2	Case-crossover
Zobel, 2016[92]	Hospital databases, Australia	297 males & females, >40y	Knee	ACR criteria, KL $\geq 2$ , or patellofemoral OA on radiograph	Web based case-cross over
<p>Acronyms:            KL- Kellgran and Lawrence            RCT- Randomised Controlled Trial            USA- United States of America            ACR- Arthritis Center Research            ARA- American Rheumatism Association            GP- General Practitioner</p>					

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3 216 Twenty-one included mixed knee and hip OA groups[24, 29, 31, 37-39, 42, 45-47, 54,  
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6 217 55, 57-59, 63, 71, 73, 75, 77]. In total, 46 publications used a drug withdrawal RCT  
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8 218 design[24, 26-32, 34-43, 45-53, 55-64, 73-77, 88-91], four of which were pooled  
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11 219 studies[28, 32, 41, 62] and one used a cohort drug withdrawal design[33] (Table 1). The  
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13 220 remaining 22 publications included seventeen observational studies[20, 25, 44, 54,  
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16 221 65-67, 70-72, 78, 80-85], three RCTs[79, 86, 87], one survey[68] and one qualitative  
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18 222 interview study[69]. Nine of the included studies were abstracts[25, 44, 62, 63, 72, 78,  
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21 223 80, 81, 83]. Two abstracts were removed as the corresponding full text article was  
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23 224 available[69, 92]. Studies using pooled data or the same dataset were included if they  
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26 225 used different definitions of OA flare[28, 44, 52, 53, 62, 65, 70, 71, 74].  
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### 31 **Rationale given for flare definitions**

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37 229 Six of the included studies gave rationale for the definition used[20, 54, 56, 69, 85,  
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39 230 86]. None of the definitions were based on a consensus procedure. Marty et al[20]  
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41 231 and Scott-Lennox et al[56] were the only studies that undertook empirical  
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43 232 investigation of flare definitions. The study by Marty et al[20] was the only study  
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45 233 specifically designed to validate a diagnostic tool for knee OA flares. Potential factors  
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47 234 associated with flare-ups were identified, for example, knee swelling and the authors  
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49 235 used a logistic regression analysis to assign a weight to each of the items identified.  
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51 236 A flare up score was determined using a general practitioner database and this was  
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3 237 then validated using a rheumatologist database. Pain was not included in the final  
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11 240 Scott-Lennox et al[56] sought to test whether four measures for flare intensity  
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13 241 (patient's self-assessment of pain scores, physician's assessment of pain scores,  
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15 242 patient's global OA assessment and physician's global OA assessment) could be  
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17 243 combined to form a reliable and valid index using data from an RCT using a  
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19 244 confirmatory factor analysis. The authors produced three flare intensity groups (low,  
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21 245 moderate and severe) and highlighted how these could be used to examine  
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23 246 treatment effects.  
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31 248 Cibere[86] outlined face validity checks. It was specified that the flare definition had  
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33 249 been determined by study rheumatologists to be a clinically important change in the  
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35 250 WOMAC score. The definition used by Murphy et al[69] was informed by two  
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37 251 studies[28, 53] which used a drug withdrawal design and from the research team's  
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39 252 own experience. Ricci et al[54] used a combination of data-driven and clinical  
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41 253 judgement approaches to establish an agreed cut point. Parry et al based their  
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43 254 definition on OA flare design studies and flare definitions used in other chronic  
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45 255 disease such as back pain and COPD.  
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**Flare definitions in drug withdrawal studies**

**Terminology used**

The majority of publications using a drug withdrawal design used the term “flare” in their description[24-30, 32, 33, 36-43, 45-49, 51, 53, 55-64, 74-77, 88-91] (n=42; Table 2).



267 **Table 2: Definition, terminology and measurement instruments used in all included studies**

<b>DRUG WITHDRAWAL STUDY DESIGN</b>							
<b>First author</b>	<b>Terminology used</b>	<b>Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)</b>	<b>Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)</b>	<b>Speed of onset</b>	<b>Duration</b>	<b>Change in medication/healthcare use</b>	<b>Reference / rationale</b>
Altman, 2015[24]	"Flare"	<b>Pain:</b> WOMAC Pain subscale (0-100); increase $\geq 15$ mm	<b>Pain:</b> WOMAC Pain subscale; $\geq 40$ mm	Not specified	Not specified	Not specified	None
Baer, 2005[26]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); increase $\geq 2$ points and $\geq 25\%$	<b>Pain:</b> WOMAC Pain score (0-20); $\geq 6$ and $\geq 1$ item rated 'moderate, severe, or extreme'	Interval between screening and baseline re-measurement unclear	Not specified	Not specified	None
Baraf, 2011[27]	"Flare"	<b>Pain on movement:</b> VAS (0-100mm); increase $\geq 5$ mm	Not specified	1 week washout	Not specified	Not specified	None
Battisti, 2004[28]	"Flare"	<b>Global assessment (investigator):</b> single item, 5-point LK; Worsening $\geq 1$ point	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None



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<p>Bingham, 2007[29]</p> <p>Bingham 2011[75]</p>	<p>"Flare"</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100mm); increase <math>\geq 15</math>mm</p> <p>(2) <b>Global assessment of disease status (investigator):</b> single item, 5-point LK; Worsening <math>\geq 1</math> point</p>	<p>(1) <b>Pain walking on flat surface:</b> <math>\geq 40</math>mm on WOMAC VAS3.0 Q1 (0-100)</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; fair, poor, very poor (<i>acetaminophen users only</i>)</p> <p>(3) <b>Global assessment of disease status (patient):</b> VAS 0-100mm; <math>\geq 40</math>mm (<i>acetaminophen users only</i>)</p>	<p>Not specified</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>
<p>Birbara, 2006[30]</p>	<p>"Flare"</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS Q1 (0-100mm); increase <math>\geq 15</math>mm</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; Worsening <math>\geq 1</math> point</p>	<p>(1) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100); <math>\geq 40</math>mm</p> <p>(2) <b>Global assessment (investigator):</b> single item, 5-point LK; Fair, poor or very poor (<i>paracetamol arm only</i>)</p>	<p>4-15 day washout</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>
<p>Bocanegra, 1998[31]</p>	<p>"Worsening of symptoms"</p>	<p>Two out of the following three:</p> <p>(1) <b>Global assessment (physician):</b> single item, 5-point LK; Increase <math>\geq 1</math> grade</p> <p>(2) <b>Global assessment (patient):</b> Patients global assessment (current symptoms and limitation of activity) 5-point LK; Increase <math>\geq 1</math> grade</p> <p>(3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); Increase <math>\geq 2</math> points</p>	<p>(1) <b>Global assessment (physician):</b> single item, 5-point LK; 'poor/very poor'</p> <p>(2) <b>Global assessment (patient):</b> Patients global assessment (current symptoms and limitation of activity) 5-point LK; 'poor/very poor'</p> <p>(3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); <math>\geq 7</math></p>	<p>3-14d washout</p>	<p>Not specified</p>	<p>Not specified</p>	<p>None</p>

Boswell, 2008[32]	"Flare"	(1) <b>Pain walking on flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global assessment (patient):</b> Patient Global Assessment of Arthritis Condition (PGAC) (unspecified); Worsening $\geq 1$ point	Not specified	Not specified	Not specified	Not specified	None
Brandt, 2006[33] (pilot studies)	"Flare"	Not specified	<b>Pain:</b> WOMAC LK Pain subscale (5-25); $\geq 15$ points	5 half-lives of NSAID washout	Not specified	Not specified	None
Case, 2003[34]	Not used	(1) <b>Pain walking on flat surface:</b> VAS (0-100mm); Increase $\geq 10$ mm (2) <b>Ambulatory pain;</b> 5-point LK; worsening $\geq 1$ point	Not specified	14d washout	Not specified	Not specified	None
Day, 2000[73]	Not used	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> single item, 5-point LK; worsening $\geq 1$ point (3) <b>Global assessment (patient):</b> VAS (0-100mm); increase $\geq 15$ mm ( <i>acetaminophen users only</i> )	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm; (2) <b>Global Assessment (investigator):</b> single item, 5-point LK; 'Fair, poor, or very poor'; (3) <b>Global assessment (patient):</b> VAS (0-100mm); $\geq 40$ mm	Longer than 5 plasma half-lives washout	Not specified	Not specified	None
Ehrich, 1999[35]	Not used	<b>Pain:</b> VAS (0-100mm); increase $\geq 15$ mm	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Longer than 5 plasma half-lives washout of NSAID	Not specified	Not specified	None

Essex, 2012[36]	"Flare"	(1) <b>Global Assessment (Physician):</b> 5-point LK; increase $\geq 1$ grade (2) <b>Global Assessment (patient):</b> 5-point LK; increase $\geq 1$ grade	(1) <b>Global Assessment (Physician):</b> 5-point LK; 'Fair, poor or very poor' (2) <b>Global Assessment (patient):</b> 5-point LK; 'Fair, poor or very poor' (3) <b>Pain:</b> VAS (0-100mm); 40-90mm	48 hour withdrawal	Not specified	Not specified	None
Essex 2013[76]	"Flare"	Not specified	(1) <b>Global Assessment of arthritis (Physician):</b> Minimum rating of 3 (2) <b>Global Assessment of arthritis (patient):</b> Minimum rating of 3 (3) <b>Pain:</b> VAS (0-100mm); 40-90mm	48 hour withdrawal	Not specified	Not specified	None
Gibofksy, 2014[37]	"Flare"	<b>Pain:</b> WOMAC Pain VAS; increase $\geq 15$ mm	<b>Pain:</b> WOMAC Pain VAS; $\geq 40$ mm	Not specified	Not specified	Not specified	None
Gineyts, 2004[38]	"Flare"	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point scale: worsening $\geq 1$ point	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm	5 half-lives of NSAID washout	Not specified	Not specified	None
Goldberg, 1988[39]	"Flare"	(1) <b>Pain:</b> Investigator assessed pain grade (None/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase $\geq 1$ grade in two items OR increase $\geq 2$ grade in one item	Not specified	2-14 day washout until flare	Not specified	Not specified	None
Gottesdiener, 2002[40]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (Investigator):</b> 5-point LK; Increase $\geq 1$ point	(1) <b>Pain on walking:</b> VAS (0-100mm); $\geq 40$ mm	3-15 day washout	Not specified	Not specified	None

Hochberg, 2011[41]	"Flare"	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; worsening $\geq 1$ point	(1) <b>Pain walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None
Katz, 2010[42]	"Flare"	Not specified	<b>Pain:</b> Pain score (0-10); $\geq 5$	Not specified-washout until flare occurred	Not specified	Not specified	None
Kivitz, 2001[43]	"Flare"	<b>Pain:</b> Patients Assessment of Pain Score (0-10) (unspecified); increase $\geq 2$ points	<b>Pain:</b> Patients Assessment of Pain Score (0-10) (unspecified); $\geq 5$	5 drug half-lives or 48 hours	Not specified	Not specified	None
Kivitz, 2004[74]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); worsening $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point LK; worsening $\geq 1$ point	Not specified	NSAID dependent half-life washout	Not specified	Not specified	None
Leung, 2002[45]	"Flare"	(1) <b>Pain on walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (investigator):</b> 5-point LK; worsening $\geq 1$ point	(1) <b>Pain on walking on a flat surface:</b> WOMAC VAS Q1 (0-100mm); $\geq 40$ mm (2) <b>Global Assessment (patient):</b> (0-100mm); $\geq 40$ mm (acetaminophen users only) (3) <b>Global Assessment (investigator):</b> 5-point LK; 'Fair, poor, or very poor' (acetaminophen users only)	Determined by drug half-life washout	Not specified	Not specified	None

Luyten, 2007[46]	"Flare"	(1) <b>Global Assessment (Patient):</b> 5-point LK; Increase $\geq 1$ grade (2) <b>Global Assessment (physician):</b> 5-point LK; increase $\geq 1$ grade (3) <b>Composite definition:</b> Lequesne Osteoarthritis Severity Index (0-24); increase $\geq 2$ points	(1) <b>Global Assessment (Patient):</b> 5-point LK; 'Fair, poor or very poor' (Not on treatment – 'Poor or very poor') (2) <b>Global Assessment (physician):</b> 5-point LK; 'Fair, poor or very poor' (Not on treatment – 'Poor or very poor') (3) <b>Composite definition:</b> Lequesne Osteoarthritis Severity Index (0-24); $\geq 7$ (4) <b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	2-14 day washout	Not specified	Not specified	None
Manicourt, 2005[47]	"Flare"	<b>Pain when walking on a flat surface:</b> VAS (0-100mm) ; $\geq 10$ mm	Not specified	7-10 days washout	Not specified	Not specified	None
Mazzuca, 2002[48]	"Flare"	<b>Pain on standing:</b> WOMAC LK Pain Q5 'severe or extreme' after the washout AND decreased after resumption of usual analgesic drugs and/or NSAIDs	Not specified	Drug washout 5 half lives	Not specified	Not specified	None
McIlwain, 1989[49]	"Flare"	No measurement instrument: Increase in pain on motion, swelling, tenderness, redness and/or heat (unspecified if patient/physician/investigator reported)	Not specified	2-14 day washout	Not specified	Not specified	None
Mendelson, 1991[50]	"Worsening of arthritis condition"	(1) <b>Pain:</b> Pain scale (0-3) (0=none, 3=severe); worsening score (2) <b>Global (physician):</b> (0-100); worsening score	Not specified	Up to 14 days washout	Not specified	Not specified	None

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	Moskowitz, 2006[51]	"Flare"	(1) <b>Global assessment (patient):</b> 5-point LK; increase $\geq 1$ grade (2) <b>Global Assessment (physician):</b> 5-point LK; $\geq 1$ grade increase (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); increase $\geq 2$ points	(1) <b>Global assessment (patient):</b> 5-point LK; '(Fair), poor, or very poor' (2) <b>Global Assessment (physician):</b> 5-point LK; '(Fair), poor or very poor' (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); Minimum $\geq 7$ (4) <b>Pain walking on a flat surface:</b> VAS (0-100mm); $\geq 40$ mm	NSAID washout of 5 half-lives or at least 2 days	Not specified	Not specified	None
17 18 19 20 21 22 23	Pareek, 2009[52]	"Flare-up"	(1) <b>Pain:</b> 11-point NRS; increase $\geq 2$ points during previous 2-5 days (2) Signs and symptoms suggestive of inflammation, morning stiffness and nocturnal pain interfering with sleep	<b>Pain:</b> Pain intensity of at least 4 on a 11-point NRS during physical activity for past 24 hours	Placebo washout for 24-48 hours	2-5 days	Not specified	None
24 25 26 27 28 29 30	Pareek, 2010[53]	"Flare"	Flare symptoms noted but not part of definition: morning stiffness, erythema, nocturnal pain, and swelling/inflammation	(1) <b>Pain with physical activity:</b> VAS 0-10; $\geq 6$ (2) <b>Composite index:</b> WOMAC Total LK; $\geq 25$ . (3) <b>Composite index:</b> Lequesne OA Severity Index (0-24); $\geq 5$	Not specified	2-5 days	Not specified	None
31 32 33 34 35 36	Roth, 2004[88]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); increase $\geq 2$ points and $\geq 25\%$	<b>Pain:</b> WOMAC LK3.1 Pain subscale (0-20); Score $\geq$ 'moderate' on at least 1 of the 5 items, (ii) Pain score $\geq 6$	Washout period of at least 3 days per week past month	Not specified	Not specified	None

Rother, 2007[91]	"Flare"	(1) <b>Pain on walking:</b> VAS (0-100mm); Increase $\geq 15$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; increase $\geq 1$ grade	(1) <b>Pain on walking:</b> VAS (0-100mm); $\geq 40$ mm (2) <b>Global Assessment (patient):</b> 5-point LK; 3-5	Not specified	Not specified	Not specified	None
Schnitzer, 2005[55]	"Flare"	No tool: increase in pain	<b>Pain:</b> VAS (0-100mm); $\geq 40$ mm	Not specified	24 hours	Not specified	None
Scott-Lennox, 2001[56]	"Flare"	(1) <b>Pain:</b> VAS (0-100mm); $\geq 20$ mm (2) <b>Pain (physician):</b> 4-point LK; worsening $\geq 1$ point (3) <b>Global Assessment (patient):</b> 4-point LK; worsening $\geq 1$ point (4) <b>Global Assessment (physician):</b> 4-point LK; worsening $\geq 1$ point	(1) <b>Pain:</b> VAS (0-100mm); $\geq 40$ mm at baseline (2) <b>Pain (physician):</b> 4-point LK; $\geq 2$ (3) <b>Global Assessment (patient):</b> 4-point LK; $\geq 2$ (4) <b>Global Assessment (physician):</b> 4-point LK; worsening $\geq 2$	14 day washout	Not specified	Not specified	Confirmatory Factor Analysis
Simon, 2009[89]	"Flare"	<b>Pain:</b> WOMAC LK3.1 Pain subscale; increase $\geq 2$ and $\geq 25\%$	<b>Pain:</b> WOMAC LK3.1 Pain subscale; $\geq$ 'moderate' on $\geq 1$ item	14 day washout	Not specified	Not specified	None
Silverfield, 2002[57]	"Flare"	<b>Pain:</b> No measurement tool; significant increase	Not specified	Not specified	Not specified	Pain requiring supplemental analgesic medication and/or an increase in NSAID dose	None
Strand, 2011[58]	"Flare"	<b>Global Assessment (patient):</b> 5-point LK; Increase $\geq 1$	(1) <b>Global Assessment (patient):</b> 5-point LK; 'Fair, poor or very poor' (2) <b>Pain:</b> (0-10 NRS); $\geq 4$ but $< 9$ (3) <b>Global Assessment (physician):</b> 5-point LK; 'Fair, poor or very poor'	14 day washout	Not specified	Not specified	None

Weaver, 1995[90]	"Flare"	(1) <b>Global Assessment (Physician)</b> : 5-point Likert; increase $\geq 1$ grade (2) <b>Global Assessment (patient)</b> : 5-point LK; increase $\geq 1$ grade (3) <b>Pain</b> : Worsening pain on motion and weight bearing	(1) <b>Global Assessment (Physician)</b> : 5-point Likert; $\geq 2$ (2) <b>Global Assessment (patient)</b> : 5-point LK; $\geq 2$	2-14 day washout	Not specified	Not specified	None
Wiesenhutter, 2005[59]	"Flare"	(1) <b>Pain on walking on flat surface</b> : WOMAC VAS3.0 Q1 (0-100mm); increase $\geq 15$ mm (2) <b>Global Assessment (Investigator)</b> : 5-point LK; worsening $\geq 1$ unit	(1) <b>Pain on walking on flat surface</b> : WOMAC VAS3.0 Q1 (0-100mm); $\geq 40$ mm	Not specified	Not specified	Not specified	None
Williams, 2001[60]	"Flare"	(1) <b>Global Assessment (patient)</b> : 5-point LK; Increase $\geq 1$ point (2) <b>Global Assessment (physician)</b> : 5-point LK; increase $\geq 1$ point(3) <b>Composite Index</b> : Lequesne OA Severity Index (0-24); Increase $\geq 2$ points	(1) <b>Global Assessment (patient)</b> : 5-point LK; '(Fair), poor or very poor' (2) <b>Global Assessment (physician)</b> : 5-point LK; '(Fair), poor or very poor' (3) <b>Composite Index</b> : Lequesne OA Severity Index (0-24); $\geq 7$ (4) <b>Pain</b> : VAS (0-100mm); $\geq 40$ mm	2-14 days	Not specified	Not specified	None
Wittenberg, 2006[61]	"Flare"	<b>Pain</b> : VAS (0-100mm); Increase $\geq 10$ mm	<b>Pain</b> : VAS (0-100mm); $\geq 40$ mm	2-7 day washout	Not specified	Not specified	None
Yeasted, 2014[62] (Pooled, abstract)	"Flare"	<b>Pain</b> : 0-10 NRS; Increase $\geq 2$ points over the mean pain score from the previous 3 days	<b>Pain</b> : Average daily 0-10 NRS; 4-9	Not specified	Not specified	Not specified	None
Yocum 2000[77]	"Flare"	<b>Disease activity</b> (1) <b>Global (Investigator)</b> : Reduction of $\geq 1$ grade (2) <b>Global Assessment (Patient)</b> : 100-mm VAS; Increase of $\geq 10$ mm	Not specified	$\geq 3$ days washout	Not specified	Not specified	None



		(3) <b>Pain: Overall assessment (patient):</b> 100-mm VAS; $\geq 35$ mm					
Young, 2014[63]	"Flare"	(3) <b>Pain:</b> WOMAC pain subscale; increase $> 15$ mm	<b>Pain:</b> WOMAC Pain subscale $> 40$ mm	Not specified	Not specified	Not specified	None
Zhao, 1999[64]	"Flare"	No measurement tool: Worsening of signs and symptoms after discontinuation of NSAIDs of analgesics	Not specified	2-7 day washout	Not specified	Not specified	None
<b>NON-DRUG WITHDRAWAL STUDY DESIGN</b>							
Atukorala, 2016[78] (abstract)	"Flare"	<b>Pain:</b> (10-point NRS); increase $> 2$ points from the mildest knee OA pain intensity reported at day 0	Not specified	Not specified	Not specified	Not specified	None
Atukorala, 2016[25] (abstract)							
Bartholdy, 2016[79]	"Flare"	Not specified	<b>Pain:</b> (10-point NRS): Pain $> 5$	Not specified	Not specified	Not specified	None
Bassiouni 2015[80] (abstract)	"Flare"	Not specified	<b>Global Assessment (physician):</b> KOFUS $\geq 7$	Not specified	Not specified	Not specified	None
Cibere, 2004[86]	"Flare"	(1) Patients perception of worsening of symptoms	Not specified	Not specified	Not specified	Not specified	Definition determined by study rheumatologists to be a clinically important change in WOMAC-Ehrich2000/
Cibere, 2005[87]		(2) <b>Pain walking on flat surface:</b> WOMAC VAS3.0 Q1 (0-100mm); increase $\geq 20$ mm (3) <b>Global Assessment (physician):</b> 5-point LK; worsening $\geq 1$ grade					

							Bellamy 1998
Conrozier 2012[66]	"Flare"	Fulfilled 4 following criteria: (1) <b>Pain:</b> No measurement tool; 'sudden aggravation of knee pain' (2) causing nocturnal awakenings, (3) clinical evidence of effusion.	Not specified	Sudden aggravation of knee pain, whose beginning was identifiable	Not specified	Not specified	None
D'Agostino 2005[67]	"Flare"	Not specified	<b>Pain intensity during physical activity:</b> VAS-(0-100mm); $\geq 40$ mm	Not specified	48 hours	Not specified	None
Erfani, 2014[44] (abstract) Erfani, 2014[81] (abstract) Ferreira[82] 2016 Hunter 2014[83] (abstract) Makovey 2015[84] (Protocol)	Exacerbation	<b>Pain:</b> VAS (0-100mm); Increase $\geq 20$ mm from mildest pain score reported at baseline	Not specified	Not specified	Not specified	Not specified	None

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Jawad, 2005[68]	Exacerbation	<b>Pain symptoms:</b> Increased morning stiffness, night pain and synovial fluid effusion	Not specified	Not specified	Not specified	Not specified	None
Marty 2009[20]	"Flare"	No measurement tool: Morning stiffness >20mins, nocturnal awakening, limping, knee swelling, increased warmth, effusion	Not specified	Not specified	48 hours	Not specified	Regression analysis of cross-sectional data to validate proposed flare criteria
Murphy, 2015[69]	"Flare"	(1) Investigator definition: Inadequate pain relief for an episode of intense pain that is usually brought on by too much activity. (2) Participant definitions: Described in terms of pain quality, timing (onset and duration), antecedents and consequences. (3) <b>Pain magnitude:</b> increase in pain or 'intense' or 'severe' level of pain	<b>Pain:</b> ≥40 of 100mm or ≥4 of 10 on NRS	Patients described: 'Quick' or 'sudden'	Patients: 10 seconds to 15 minutes	Patients: Rest or take additional medication	For investigator definition: Battisti 2004, Pareek 2010. Plus researchers own experience.
Parry, 2017[85]	"Flare"	<b>Pain:</b> Recalled worst pain intensity in previous 6 months 0-10 NRS; ≥5	<b>Pain:</b> Recalled worse pain to be ≥2 points higher than recalled average pain (0-10 NRS) in previous 6 months	Not specified	Not specified	Not specified	Based on previous studies defining knee flares in OA and flares in diseases such as back

							pain and COPD.
Ricci 2005[54]	"Flare up"	<b>Pain:</b> Self-reported flare severity rating 0-10 NRS; increase $\geq 2$ point over usual pain severity	Not specified	Not specified	Not specified	Not specified	Based on statistical analysis and clinical judgement
Wise 2010[70]	"Flare"	Not specified	<b>Pain:</b> WOMAC Pain subscale (0-10); score in highest 30% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2009[71]	"Exacerbation or flare"	Not specified	(1) Pain: WOMAC pain subscale 0-10 (total score of 50 normalised to a 0-10 scale); score of $\geq 5$ , a score corresponding to highest 33% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2011[72] (abstract)	"Exacerbation"	<b>Pain:</b> WOMAC Pain score VAS (0-500); increase $\geq 100$ units	Not specified	Not specified	Not specified	Not specified	None
Zobel, 2016[92]	Exacerbation	<b>Pain:</b> 0-10 NRS; Increase $\geq 2$	(1) Disabling pain	Not specified	8 hours	Not specified	None

## Acronyms:

COPD- Chronic Obstructive Pulmonary Disease

KOFUS- Knee Osteoarthritis Flare-up Score

NRS-Numerical Rating scale

VAS- Visual Analogue Score

WOMAC- Western Ontario and McMaster Universities Osteoarthritis Index

LK-Likert scale

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4 One study used the term “flare-up”[52], two studies referred simply to “worsening of  
5  
6 symptoms” [31, 50] and three studies used no specific label[34, 35, 73].  
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### 10 **Coverage of key components**

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13 *Onset/worsening of symptoms and signs beyond normal-day-to-day variability:* Forty-  
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15 four studies included onset or worsening of signs and symptoms as part of their  
16  
17 definition[24, 26-32, 34-41, 43, 45-53, 55-64, 73-75, 77, 88-91]. All studies included  
18  
19 increased pain intensity in their definition. A further two[52, 53] specified further  
20  
21 signs and symptoms. These included swelling, inflammation, erythema, morning  
22  
23 stiffness and nocturnal pain. No studies quantified day-to-day variability.  
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32 Twenty-six measurement tools were used to define onset/worsening of symptoms  
33  
34 and signs. The most commonly used tools were the Western Ontario & McMaster  
35  
36 Universities Arthritis index (WOMAC) Q1 (pain on walking on flat surface) 100mm  
37  
38 Visual Analogue Scale (VAS) (n=9)[29, 30, 32, 38, 41, 45, 59, 73, 75] and the  
39  
40 Investigator Assessment of Disease Status (n=11)[28-30, 38, 40, 45, 59, 73-75, 77]  
41  
42 (Table 3). Thirty-four studies used only single item measurement tools[27-30, 32, 34-  
43  
44 43, 45, 47, 48, 50, 52, 55, 56, 58, 59, 61-63, 73-77, 90, 91], 5 used multi-item[31, 46,  
45  
46 51, 53, 60] and 5 used both single and multi-item tools[24, 26, 33, 88, 89].  
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**Table 3: Summary of number and type of single and multi-item measurement tools used.**

<b>Single item scales:</b>	
Pain on activity:	WOMAC Q1 3.0 VAS 'pain on walking on a flat surface' (0-100mm) [n=11] Pain on walking VAS (0-100mm) [n=5] Pain on movement VAS (0-100mm); Ambulatory pain (5-point Likert); Pain with physical activity VAS 11-point scale [n=2]
Pain (not further specified):	Pain VAS (0-100mm) [n=15] Patients Assessment of Pain Score (0-10); Pain Scale (0-3); Pain NRS (0-10) [n=11]
Standing knee pain	Item 5 WOMAC pain scale [n=1]
Global rating (physician/ investigator)	Investigator Assessment of Disease Status [n=11] Physicians Global Assessment of Arthritis [n=6] Physician Global Assessment of OA [n=2] Physician Global Assessment of Disease Status [n=2]; Investigator Assessed Pain Grade; (Physician) Overall Disease Activity (0-100); Physicians Pain Assessment (4-point LK) [n=3]
Global rating (patient)	Patients Global Assessment of Arthritis [n=7] Patient Global Assessment of OA [n=3] Patient Global Assessment of Disease Status [n=4]
<b>Multiple-item scales:</b>	
	Lequesne OA Severity Index [n=5] WOMAC LK3.1 (0-20) [n=3] WOMAC LK Pain subscale (0-25); WOMAC OA Index

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Questionnaire [n=1]; WOMAC knee pain score (0-500)  
[n=7]; KOFUS (0-14) [n=1]

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N, number of included studies; WOMAC, Western Ontario and McMaster Universities  
Osteoarthritis Index; VAS, visual analogue scale; OA, osteoarthritis; KOFUS, Knee Osteoarthritis  
Flare-up Score.

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4 In addition, the format of global ratings appears to be variable as is use and  
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6 reporting of the WOMAC[93]. However, despite the exact format of reporting being  
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8 inconsistent, in general, studies used single items in 4 areas – pain on activity, pain  
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10 (not necessarily on activity), physician/investigator global rating and patient global  
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12 rating.  
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18 *Temporal characteristics:* None of the included drug withdrawal design studies  
19  
20 reported a specific time for defining the speed of onset of symptoms. However, they  
21  
22 did describe withdrawal or ‘washout’ periods whereby, after withdrawal of usual  
23  
24 medication, participants were given a certain time frame in which to experience ‘flare’  
25  
26 symptoms in order that they were entered into the study. In total 30 of the studies  
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28 specified a withdrawal period[27, 30, 31, 33-36, 38-40, 43, 45-52, 56, 58, 60, 61, 64,  
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35 73, 74, 76, 77, 88-90].

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37 Four studies specified a time period for minimum duration of symptoms which  
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39 ranged from 24 hours to 5 days[52, 53, 55, 57].  
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43 *Change in medication or healthcare usage:* Only one study used increase in  
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45 medication as part of their definition; ‘pain requiring supplemental analgesic  
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47 medication and/or an increase in NSAID dose’[57].  
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4 *Additional domains:* Thirty-six studies included a minimum threshold which was  
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6 usually a minimum level of pain that was required before the participant was  
7  
8 considered to have a flare[24, 26, 28-31, 33, 35-38, 40-43, 45-47, 51-53, 55, 56, 58-63,  
9  
10 73, 75, 76, 88-91]. There was general concordance with the minimum thresholds that  
11  
12 different measurement tools used with a few exceptions. A threshold of 40mm on a  
13  
14 0-100mm scale was used in eight of ten studies using the WOMAC VAS 3.0 Q1 'pain  
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16 on walking on a flat surface'[29, 30, 38, 41, 45, 59, 73, 75] and four of fourteen studies  
17  
18 using the Patient Global Assessment of Disease Status[29, 45, 73, 75]. In studies using  
19  
20 various forms of investigator/physician global assessment, the majority adopted a  
21  
22 minimum threshold for a flare of 'fair, poor or very poor' [29, 30, 45, 73]. The  
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24 minimum threshold on the Lequesne index (0-10) was either five[53] or seven[46, 51,  
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26 60].  
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### 36 **Flare definitions in non-withdrawal flare/ discontinuation studies**

#### 40 **Terminology used**

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46 "Flare" was the term most common used in non-withdrawal design studies[20, 25, 66,  
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48 67, 69, 70, 78-80, 85, 87](n=11) (Table 2). One study used the term "flare-up"[54],  
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50 eight used "exacerbation"[44, 65, 68, 72, 81-84] (five publications were from the same  
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3 team) and one referred to both "exacerbation" and "flare"[71]. None referred to  
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5  
6 "worsening of symptoms" or did not use any specific label.  
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### 10 11 **Coverage of key components**

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13 *Onset/worsening of symptoms and signs beyond normal-day-to-day variability:*

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16 Sixteen of twenty-two studies used onset or worsening of symptoms in their  
17  
18 definition[25, 44, 54, 66, 68, 69, 72, 78, 81-87, 92]. Two studies did not use pain  
19  
20 intensity as part of its definition[20, 80]. Three studies included symptoms other than  
21  
22 pain in their definition[20, 66, 68]. These included nocturnal awakenings, effusion,  
23  
24 morning stiffness, night pain, limping, and warmth.  
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31 The Murphy et al[69] study included an investigator definition of flare but also  
32  
33 sought to describe patient experience of flares through face to face individual  
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35 interviews. Both investigator and patient definitions included onset/worsening of  
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37 symptoms and signs however there was no differentiation from day-to-day  
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39 variability.  
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46 Seven studies used a measurement tool to define onset of signs and symptoms  
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48 (Table 3). These included the Pain NRS (0-10)[25, 54, 65, 78, 85], WOMAC knee pain  
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50 score VAS (0-500)[72], pain walking on a flat surface (WOMAC)[86, 87], Global  
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3 Assessment of Disease Status (physician) (Likert 5-point scale)[86, 87], and knee pain  
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5  
6 VAS not further specified (0-100)[44, 81-84].  
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11 *Temporal characteristics:* Only one study set a definition for speed of onset,  
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13 describing this only as 'sudden' with no further specification[66]. Patients in the  
14  
15 Murphy et al study used the terms 'quick' and 'sudden' to describe flare onset[69].  
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17 Three studies specified a minimum duration of symptoms ranging from 8 to 48  
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19 hours[20, 65, 67]. In the Murphy et al study patients described duration of between  
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21 10 seconds to 15 minutes[69].  
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29 *Change in medication/healthcare usage:* No studies used change in medication or  
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31 healthcare usage as part of their definition. However, in Murphy et al patients  
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33 reported either taking rest or using additional medication[69].  
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39 *Additional Domains:* Two studies defined distribution-based minimum thresholds for  
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41 flare as the highest 30%<sup>72</sup> or highest 33%<sup>73</sup> of WOMAC Pain Subscale scores among  
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43 participants in the Longitudinal Examination of Arthritis Pain (LEAP) cohort (total  
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45 score out of 50 was normalised to a 0-10 scale).  
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## 53 **DISCUSSION**

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7 Flares in OA are recognised in existing clinical guidance[94] and reviews[95, 96] but  
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9 typically merit little more than a passing mention. Our analysis of the definitions has  
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11 resulted in the findings of common core domains which will be useful for developing  
12  
13 an agreed consensus definition for OA flare. From a clinical perspective, a unified  
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15 definition of a flare could enable clinicians to provide prompt, rationalised and  
16  
17 focussed treatment. This could also have implications for delivery of self-  
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19 management strategies involving patients and how episodic management is  
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21 advocated by clinical guidelines. Our review was motivated by an interest in seeking  
22  
23 greater clarity on how these phenomena might be defined by undertaking a broad  
24  
25 search strategy, noting that similar efforts have been pursued in other chronic  
26  
27 diseases. While we found no current single, agreed definition of OA flare, our review  
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29 of 69 published studies suggests a number of common domains which may capture  
30  
31 cardinal features. These were: onset/worsening of symptoms and signs, attainment of  
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33 a minimum symptom threshold during flare, speed of onset/worsening, and duration  
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35 of elevated symptoms/signs. However, we found considerable variation in how these  
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37 domains have been operationalised for measurement suggesting the need for  
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39 further conceptual clarification and consensus.  
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52 Each potential cardinal feature of OA flare presents different challenges for achieving  
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54 consensus. The goal of an agreed composite definition is to facilitate both  
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4 reproducible and comparable research, whilst enabling more consistent recognition  
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6 and identification of these phenomena in routine practice. The heterogeneity of OA  
7  
8 should also be considered in any definition of a flare-up. Most studies included in  
9  
10 our review required an increase in pain over 'usual' or 'baseline' intensity. Although  
11  
12 this was measured using a wide range of measurement instruments several studies  
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14 selected an increase of 2 or more points on a 0-10 scale providing a possible starting  
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16 point for consensus. Yet this possible 'signal' is arguably difficult to interpret without  
17  
18 also considering the amount of background 'noise', i.e. within-person diurnal[97] and  
19  
20 day-to-day variability[98], and the absolute level ('minimum threshold') of pain  
21  
22 during a flare. There was general concurrence with the minimum threshold that was  
23  
24 adopted, for example, 40mm on a 0-100mm scale and this may indicate the potential  
25  
26 level of minimally important clinical difference. In the study by Marty et al an  
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28 increase in pain was not independently associated with flare-up after adjusting for  
29  
30 other potential features[20]. However, the study by Marty et al[20] and Scott-Lennox  
31  
32 et al[56] were the only two studies we found that had attempted to derive and/or  
33  
34 validate a prediction model for OA flares. Interestingly their approaches have not  
35  
36 been widely adopted which suggests the complexity of reaching a widely accepted  
37  
38 model. Further research on detecting flares over within-person 'normal' variability by  
39  
40 collecting frequent repeated measures of pain intensity may be valuable but this  
41  
42 approach would not be feasible when identifying flares presenting at the point of  
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44 care in routine clinical practice. Instead, this may have to rely on the judgement of  
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3 the patient and/or clinician, the approach used, for example, in defining  
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6 exacerbations in COPD[1]. A similar consideration surrounds the speed of onset,  
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8  
9 which was not well defined by studies in our review. Drug withdrawal design studies  
10  
11 specified washout periods between 2-15 days but this is unlikely to be synonymous  
12  
13 with speed of onset. The remaining studies used terms such as 'sudden' and 'quick'.  
14  
15  
16 In COPD, for instance, a judgement around 'acute onset' or 'sudden onset' appears to  
17  
18 be acceptable for clinical recommendations but we would add that the speed of  
19  
20 onset of OA flares ought to be considered also in relation to underlying biologically  
21  
22 plausible mechanisms. Indeed presumed aetiology has been argued as a useful  
23  
24 feature in defining acute exacerbations in COPD[99]. Minimum duration ranged from  
25  
26 8 hours to 5 days in our review however this was not widely reported. COPD  
27  
28 definitions refer to a 'sustained worsening' of symptoms[2] but does not appear to  
29  
30 be a feature in other chronic diseases. A minimum duration in OA may help  
31  
32 distinguish flares from day-to-day variability. Increase in medication was not found  
33  
34 to be a key component in this review despite it being a feature in other chronic  
35  
36 diseases; AS[5], SLE[4, 100], Inflammatory Bowel Disease[101], COPD[1]. Interference  
37  
38 with function did not emerge strongly from our review as a cardinal feature of OA  
39  
40 flare. In other chronic musculoskeletal conditions, such as back pain, interference  
41  
42 with function was not shown to be significantly associated with having a flare up[102]  
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44 and this domain does not feature in the definitions of exacerbations or flares in  
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46 diseases such as COPD[1, 2], asthma[3], AS[5] or SLE[4].  
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6 Our review has several strengths but also some weaknesses that deserve attention.  
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8 We adopted a broad search strategy, covering a wide range of databases, and  
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10 featuring bibliography checks, contact with authors, inclusion of conference  
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12 abstracts, no language restrictions, and a minimal threshold (any description or  
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14 definition of flare) for inclusion. Five studies that were included in a similar review by  
15  
16 Cross et al[103] were not included in this study; four did not contain a clear definition  
17  
18 of flare-up, including one which gave a definition of knee OA progression and the  
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20 final paper by Sands et al[104] was not in our search but the original study was[58].  
21  
22 We did not, however, search the grey literature and we did not include some  
23  
24 potential synonyms as search terms ('attack', 'episode', 'fluctuations') although these  
25  
26 terms appeared often to relate to comorbidities and other phenomena (e.g. episodes  
27  
28 of care) and would therefore have been a less efficient search strategy than relying  
29  
30 on snowball references. Data extraction was performed by only a single reviewer.  
31  
32 Nevertheless, we argue that our review provides a reasonably comprehensive  
33  
34 summary of how 'flares' in OA have been described and defined in the medical  
35  
36 literature. In comparison with Cross et al[103] our search strategy appeared  
37  
38 comprehensive yet efficient – returning 69 included articles compared with 23. We  
39  
40 feel that our review expands on the findings of the Cross et al review and adds  
41  
42 strength to this important area. The majority of studies describe experimental 'flare  
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44 design' trials in which flares are induced by drug withdrawal prior to enrolment and  
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3 randomisation. While intentional or unintentional reduction in usual analgesia may  
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5 indeed be one trigger for flare, experimentally induced flares should not be assumed  
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7 to represent 'naturally occurring' flares. Flare design trials, for example, are unlikely to  
8  
9 capture change in management or healthcare usage that may be a common  
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11 consequence of OA flares – something that is included in flare definitions in other  
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13 conditions such as AS[5], SLE[4, 100], inflammatory bowel disease[101], and COPD[1].  
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21 A systematic review such as this cannot hope to resolve the need for a common  
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23 conception and definition of flares in OA. Definitions for exacerbations of disease  
24  
25 states are generally reached through a long process of consensus exercises involving  
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27 key stakeholders, experts and patients in addition to appraisal of relevant literature  
28  
29 from studies using multiple methods[6, 8, 105]. However, we believe that a consensus  
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31 definition that is reliable, valid, and feasible and widely acceptable both clinically and  
32  
33 for research purposes should now be sought. The cardinal features described in this  
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35 review; onset/worsening of symptoms and signs, attainment of a minimum symptom  
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37 threshold during flare, speed of onset/worsening, and duration of elevated  
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39 symptoms/signs could help start this discussion. Furthermore, observational studies  
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41 with repeated measures could give an important insight into the nature of these  
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43 phenomena.  
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## 53 **CONCLUSION**

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6 A broad range of ad-hoc definitions currently exist in the medical literature. The  
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8 majority are from drug-withdrawal or flare-induced trials rather than 'naturally'  
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10 occurring flares. The cardinal feature is pain intensity with minimum symptom  
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12 threshold being another important feature. This review has identified the need to  
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14 gain consensus on a common definition that can be used for research and clinical  
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16 application.  
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All authors were involved in conception and design of the study, analysis and interpretation of data, drafting the article, critical revision of the article for important intellectual content, final approval of the article. ELP and MJT extracted and synthesised data. ELP assembled the data.

GMP (g.m.peat@keele.ac.uk ) takes responsibility for the integrity of the work as a whole from inception to finished article.

## Data sharing statement

No unpublished data is available following this study

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### 26 **Competing interest statement**

27  
28  
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30  
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32  
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### 38 **Figure and Table Legends**

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41 Figure 1: PRISMA Flowchart  
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44 Table 1: Characteristics of all included studies  
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46 Table 2: Summary of number and type of single and multi-item measurement  
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48 Table 3: Definition, terminology and measurement instruments used in all included  
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50 studies  
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53 Supplementary data: Database search strategy  
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58  
59  
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For peer review only

## REFERENCES

- 1 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of COPD: GOLD 2016.
- 2 National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management (CG101). London: NICE 2010.
- 3 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention: GINA 2015.
- 4 Ruperto N, Hanrahan L, Alarcón G, et al. International consensus for a definition of disease flare in lupus, *Lupus* 2011;20:453-62.
- 5 Stone MA, Pomeroy E, Keat A, et al. Assessment of the impact of flares in ankylosing spondylitis disease activity using the Flare Illustration, *Rheumatology* 2008;47:1213-8.
- 6 Bingham CO, Alten R, Bartlett SJ, et al. Identifying Preliminary Domains to Detect and Measure Rheumatoid Arthritis Flares: Report of the OMERACT 10 RA Flare Workshop, *The Journal of Rheumatology* 2011;38:1751-8.

1  
2  
3  
4 7 Bykerk VP, Lie E, Bartlett SJ, et al. Establishing a Core Domain Set to Measure  
5  
6 Rheumatoid Arthritis Flares: Report of the OMERACT 11 RA Flare Workshop, *The*  
7  
8 *Journal of Rheumatology* 2014;41:799-809.  
9

10  
11  
12 8 Bartlett SJ, Hewlett S, Bingham CO, et al. Identifying core domains to assess flare in  
13  
14 rheumatoid arthritis: an OMERACT international patient and provider combined  
15  
16 Delphi consensus, *Annals of the Rheumatic Diseases* 2012;71:1855-60.  
17  
18

19  
20  
21 9 Taylor WJ, Shewchuk R, Saag KG, et al. Toward a valid definition of gout flare:  
22  
23 Results of consensus exercises using delphi methodology and cognitive mapping,  
24  
25 *Arthritis Care & Research* 2009;61:535-43.  
26  
27

28  
29  
30 10 Schmitt J, Spuls PI, Thomas KS, et al. The Harmonising Outcome Measures for  
31  
32 Eczema (HOME) statement to assess clinical signs of atopic eczema in trials, *J Allergy*  
33  
34 *Clin Immunol* 2014;134:800-7.  
35  
36

37  
38 11 Holla JFM, van dL, Knol DL, et al. The association of body-mass index and  
39  
40 depressed mood with knee pain and activity limitations in knee osteoarthritis: results  
41  
42 from the Amsterdam osteoarthritis cohort, *BMC Musculoskeletal Disorders*  
43  
44 2013;14:296.  
45  
46

47  
48  
49 12 Collins JE, Katz JN, Dervan EE, et al. Trajectories and risk profiles of pain in persons  
50  
51 with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis  
52  
53 initiative, *Osteoarthritis and Cartilage* 2014;22:622-30.  
54  
55

1  
2  
3 13 Leffondré K, Abrahamowicz M, Regeasse A, et al. Statistical measures were  
4  
5  
6 proposed for identifying longitudinal patterns of change in quantitative health  
7  
8 indicators, *J Clin Epidemiol* 2004;57:1049-62.  
9

10  
11  
12 14 Emrani PS, Katz JN, Kessler CL, et al. Joint space narrowing and Kellgren–Lawrence  
13  
14 progression in knee osteoarthritis: an analytic literature synthesis, *Osteoarthritis and*  
15  
16 *Cartilage* 2008;16:873-82.  
17

18  
19  
20  
21 15 Bartlett SJ, Ling SM, Mayo NE, et al. Identifying common trajectories of joint space  
22  
23 narrowing over two years in knee osteoarthritis, *Arthritis Care & Research*  
24  
25 2011;63:1722-8.  
26

27  
28  
29 16 Hawker GA, Stewart L, French MR, et al. Understanding the pain experience in hip  
30  
31 and knee osteoarthritis – an OARSI/OMERACT initiative, *Osteoarthritis and Cartilage*  
32  
33 2008;16:415-22.  
34  
35

36  
37  
38 17 Arthritis Research UK. Osteoarthritis: Patient Information Booklet. 2012.  
39

40  
41  
42 18 Bonnet CS, Walsh DA. Osteoarthritis, angiogenesis and inflammation,  
43  
44 *Rheumatology* 2005;44:7-16.  
45

46  
47  
48 19 Smith TO, Zou K, Abdullah N, et al. Does flare trial design affect the effect size of  
49  
50 non-steroidal anti-inflammatory drugs in symptomatic osteoarthritis? A systematic  
51  
52 review and meta-analysis, *Annals of the Rheumatic Diseases* 2016;75:1971-8.  
53  
54

1  
2  
3  
4 20 Marty M, Hilliquin P, Rozenberg S, et al. Validation of the KOFUS (Knee  
5  
6 Osteoarthritis Flare-Ups Score), *Joint Bone Spine* 2009;76:268-72.  
7

8  
9  
10 21 Rutjes AS, Jüni P, Da Costa BR, et al. Viscosupplementation for osteoarthritis of the  
11  
12 knee: A systematic review and meta-analysis, *Ann Intern Med* 2012;157:180-91.  
13

14  
15 22 Thomas J, Harden A, Newman M. Synthesis: Combining results systematically and  
16  
17 appropriately. In: Gough A, Oliver S, Thomas J, eds. An introduction to systematic  
18  
19 reviews. London: Sage publications limited 2013:191-2.  
20  
21

22  
23 23 Popay J, Roberts H, S, A., et al. Guidance on the conduct of narrative synthesis in  
24  
25 systematic reviews: A product of the ESRC methods programme Lancaster: ESRC  
26  
27 Method Programme, 2006.  
28  
29

30  
31  
32 24 Altman R, Hochberg M, Gibofsky A, et al. Efficacy and safety of low-dose  
33  
34 SoluMatrix meloxicam in the treatment of osteoarthritis pain: A 12-week, phase 3  
35  
36 study, *Curr Med Res Opin* 2015;31:2331-43.  
37  
38

39  
40  
41 25 Atukorala I, Pathmeswaran A, Makovey J, et al. Is there a relationship between the  
42  
43 intermittent and constant osteoarthritis pain score (ICOAP) and pain flares in knee  
44  
45 osteoarthritis? (abstract) [abstract]. *Osteoarthritis and Cartilage* 2016;24:S429-30.  
46  
47

48  
49  
50 26 Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a  
51  
52 topical diclofenac solution: a randomised controlled, 6-week trial [SRCTN53366886],  
53  
54 *BMC Musculoskeletal Disorders* 2005;6:44.  
55  
56



1  
2  
3  
4 27 Baraf HSB, Gloth FM, Barthel HR, et al. Safety and Efficacy of Topical Diclofenac  
5  
6 Sodium Gel for Knee Osteoarthritis in Elderly and Younger Patients, *Drugs Aging*  
7  
8 2011;28:27-40.  
9

10  
11  
12 28 Battisti WP, Katz NP, Weaver AL, et al. Pain management in osteoarthritis: A focus  
13  
14 on onset of efficacy—a comparison of rofecoxib, celecoxib, acetaminophen, and  
15  
16 nabumetone across four clinical trials, *The Journal of Pain* 2004;5:511-20.  
17  
18

19  
20  
21 29 Bingham CO, Sebba AI, Rubin BR, et al. Efficacy and safety of etoricoxib 30 mg and  
22  
23 celecoxib 200 mg in the treatment of osteoarthritis in two identically designed,  
24  
25 randomized, placebo-controlled, non-inferiority studies, *Rheumatology* 2007;46:496-  
26  
27 507.  
28  
29

30  
31  
32 30 Birbara C, Ruoff G, Sheldon E, et al. Efficacy and safety of rofecoxib 12.5 mg and  
33  
34 celecoxib 200 mg in two similarly designed osteoarthritis studies, *Curr Med Res Opin*  
35  
36 2006;22:199-210.  
37  
38

39  
40  
41 31 Bocanegra T, Weaver A, Tindall E, et al. Diclofenac/misoprostol compared with  
42  
43 diclofenac in the treatment of osteoarthritis of the knee or hip: a randomized,  
44  
45 placebo controlled trial. Arthrotec Osteoarthritis Study Group. *Journal of*  
46  
47 *Rheumatology* 1998;25:1602-11.  
48  
49

1  
2  
3 32 Boswell DJ, Ostergaard K, Philipson RS, et al. Evaluation of GW406381 for  
4  
5  
6 Treatment of Osteoarthritis of the Knee: Two Randomized, Controlled Studies, *The*  
7  
8 *Medscape Journal of Medicine* 2008;10:259.  
9

10  
11  
12 33 Brandt KD, Mazzuca SA, Buckwalter KA. Acetaminophen, like conventional NSAIDs,  
13  
14 may reduce synovitis in osteoarthritic knees, *Rheumatology* 2006;45:1389-94.  
15  
16

17  
18 34 Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating  
19  
20 symptomatic knee osteoarthritis: A randomized, double-blind, placebo-controlled  
21  
22 comparison trial with diclofenac sodium, *Arch Intern Med* 2003;163:169-78.  
23  
24

25  
26  
27 35 Ehrich E, Schnitzer T, McIlwain H, et al. Effect of specific COX-2 inhibition in  
28  
29 osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of  
30  
31 rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. *Journal of Rheumatology*  
32  
33 1999;26:2438-47.  
34  
35

36  
37  
38 36 Essex M, O'Connell M, Brown PB. Response to Nonsteroidal Anti-Inflammatory  
39  
40 Drugs in African Americans with Osteoarthritis of the Knee, *Journal of International*  
41  
42 *Medical Research* 2012;40:2251-66.  
43  
44

45  
46  
47 37 Gibofsky A, Hochberg MC, Jaros MJ, et al. Efficacy and safety of low-dose  
48  
49 submicron diclofenac for the treatment of osteoarthritis pain: A 12 week, phase 3  
50  
51 study, *Curr Med Res Opin* 2014;30:1883-93.  
52  
53

1  
2  
3 38 Gineyts E, Mo JA, Ko A, et al. Effects of ibuprofen on molecular markers of  
4  
5  
6 cartilage and synovium turnover in patients with knee osteoarthritis, *Annals of the*  
7  
8 *Rheumatic Diseases* 2004;63:857-61.  
9

10  
11  
12 39 Goldberg M, McIlwain H, Poiley J, et al. Controlled-release naproxen in the  
13  
14 treatment of osteoarthritis, *Current Therapeutic Research-Clinical and Experimental*  
15  
16 1988;44:51-60.  
17

18  
19  
20  
21 40 Gottesdiener K, Schnitzer T, Fisher C, et al. Results of a randomized, dose ranging  
22  
23 trial of etoricoxib in patients with osteoarthritis, *Rheumatology* 2002;41:1052-61.  
24

25  
26  
27 41 Hochberg MC, Fort JG, Svensson O, et al. Fixed-dose combination of enteric-  
28  
29 coated naproxen and immediate-release esomeprazole has comparable efficacy to  
30  
31 celecoxib for knee osteoarthritis: two randomized trials, *Curr Med Res Opin*  
32  
33 2011;27:1243-53.  
34

35  
36  
37  
38 42 Katz N, Sun S, Johnson F, et al. ALO-01 (Morphine Sulfate and Naltrexone  
39  
40 Hydrochloride) Extended-Release Capsules in the Treatment of Chronic Pain of  
41  
42 Osteoarthritis of the Hip or Knee: Pharmacokinetics, Efficacy, and Safety, *The Journal*  
43  
44 *of Pain* 2010;11:303-11.  
45

46  
47  
48  
49 43 Kivitz AJ, Makarowski WS, Fiechtner JJ, et al. A Flexible Daily Dosage Regimen of  
50  
51 Oxaprozin Potassium in Patients with Acute Knee Pain Associated with Osteoarthritis,  
52  
53 *Clinical Drug Investigation* 2001;21:745-53.  
54

1  
2  
3 44 Erfani T, Zhang Y, Makovey J, et al. Intermittent analgesic use and risk of pain  
4  
5 exacerbation in knee osteoarthritis: A web based case-crossover study (abstract)  
6  
7 [abstract]. *Arthritis and Rheumatology* 2014;66.  
8  
9

10  
11 45 Leung AT, Malmstrom K, Gallacher AE, et al. Efficacy and Tolerability Profile of  
12  
13 Etoricoxib in Patients with Osteoarthritis: A Randomized, Double-blind, Placebo and  
14  
15 Active-comparator Controlled 12-Week Efficacy Trial, *Curr Med Res Opin* 2002;18:49-  
16  
17 58.  
18  
19  
20  
21

22  
23 46 Luyten FP, Geusens P, Malaise M, et al. A prospective randomised multicentre  
24  
25 study comparing continuous and intermittent treatment with celecoxib in patients  
26  
27 with osteoarthritis of the knee or hip, *Annals of the Rheumatic Diseases* 2007;66:99-  
28  
29 106.  
30  
31  
32

33  
34 47 Manicourt D, Bevilacqua M, Righini V, et al. Comparative Effect of Nimesulide and  
35  
36 Ibuprofen on the Urinary Levels of Collagen Type II C-Telopeptide Degradation  
37  
38 Products and on the Serum Levels of Hyaluronan and Matrix Metalloproteinases-3  
39  
40 and -13 in Patients with Flare-Up of Osteoarthritis, *Drugs in R & D* 2005;6:261-71.  
41  
42  
43

44  
45 48 Mazzuca S, Brandt K, Lane K, et al. Knee pain reduces joint space width in  
46  
47 conventional standing anteroposterior radiographs of osteoarthritic knees, *Arthritis*  
48  
49 *Rheum* 2002;46:1223-7.  
50  
51  
52

1  
2  
3  
4 49 McIlwain H, Silverfield JC, Cheatum DE, et al. Intra-articular orgotein in  
5  
6 osteoarthritis of the knee: A placebo-controlled efficacy, safety, and dosage  
7  
8 comparison, *Am J Med* 1989;87:295-300.  
9

10  
11  
12 50 Mendelsohn S. Clinical efficacy and tolerability of naproxen in osteoarthritis  
13  
14 patients using twice-daily and once-daily regimens, *Clinical therapeutics* 1991;13:8-  
15  
16 15.  
17

18  
19  
20  
21 51 Moskowitz RW, Sunshine A, Hooper M, et al. An analgesic model for assessment  
22  
23 of acute pain response in osteoarthritis of the knee, *Osteoarthritis and Cartilage*  
24  
25 2006;14:1111-8.  
26

27  
28  
29 52 Pareek A, Chandurkar N, Sharma VD, et al. A randomized, multicentric,  
30  
31 comparative evaluation of aceclofenac-paracetamol combination with aceclofenac  
32  
33 alone in Indian patients with osteoarthritis flare-up, *Expert Opin Pharmacother*  
34  
35 2009;10:727-35.  
36  
37

38  
39  
40 53 Pareek A, Chandurkar N, Ambade R, et al. Efficacy and Safety of Etodolac-  
41  
42 Paracetamol Fixed Dose Combination in Patients With Knee Osteoarthritis Flare-up: A  
43  
44 Randomized, Double-blind Comparative Evaluation, *Clin J Pain* 2010;26:561-6.  
45  
46

47  
48  
49 54 Ricci JA, Stewart WF, Chee E, et al. Pain Exacerbation as a Major Source of Lost  
50  
51 Productive Time in US Workers With Arthritis, *Arthritis & Rheumatism: Arthritis Care*  
52  
53 *& Research* 2005;53:673-81.  
54  
55

1  
2  
3  
4 55 Schnitzer TJ, Fricke JR, Gitton X, et al. Lumiracoxib in the treatment of  
5  
6 osteoarthritis, rheumatoid arthritis and acute postoperative dental pain: results of  
7  
8 three dose-response studies, *Curr Med Res Opin* 2005;21:151-61.  
9

10  
11  
12 56 Scott-Lennox JA, McLaughlin-Miley C, Lennox RD, et al. Stratification of flare  
13  
14 intensity identifies placebo responders in a treatment efficacy trial of patients with  
15  
16 osteoarthritis, *Arthritis & Rheumatism* 2001;44:1599-607.  
17  
18

19  
20  
21 57 Silverfield JC, Kamin M, Wu S, et al. Tramadol/acetaminophen combination tablets  
22  
23 for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized,  
24  
25 double-blind, placebo-controlled, parallel-group, add-on study, *Clin Ther*  
26  
27 2002;24:282-97 doi:[http://dx.doi.org/10.1016/S0149-2918\(02\)85024-X](http://dx.doi.org/10.1016/S0149-2918(02)85024-X) [published  
28  
29 Online First: February 2002].  
30  
31  
32

33  
34 58 Strand V, Simon LS, Dougados M, et al. Treatment of osteoarthritis with  
35  
36 continuous versus intermittent celecoxib, *J Rheumatol* 2011;38:2625-34.  
37  
38

39  
40 59 Wiesenhutter CW, Boice JA, Ko A, et al. Evaluation of the Comparative Efficacy of  
41  
42 Etoricoxib and Ibuprofen for Treatment of Patients With Osteoarthritis: A  
43  
44 Randomized, Double-Blind, Placebo-Controlled Trial, *Mayo Clin Proc* 2005;80:470-9.  
45  
46  
47

48  
49 60 Williams GW, Hubbard RC, Yu SS, et al. Comparison of once-daily and twice-daily  
50  
51 administration of celecoxib for the treatment of osteoarthritis of the knee, *Clin Ther*  
52  
53  
54  
55  
56

1  
2  
3 2001;23:213-27 doi:[http://dx.doi.org/10.1016/S0149-2918\(01\)80004-7](http://dx.doi.org/10.1016/S0149-2918(01)80004-7) [published

4  
5  
6 Online First: February 2001].

7  
8  
9 61 Wittenberg RH, Schell E, Krehan G, et al. First-dose analgesic effect of the cyclo-  
10 oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a  
11  
12 randomized, double-blind, placebo-controlled comparison with celecoxib  
13  
14  
15  
16  
17 NCT00267215], *Arthritis Research & Therapy* 2006;8:R35.

18  
19  
20 62 Yeasted R, McPherson J, Schnitzer T. Characterization of osteoarthritis pain  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
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54  
55  
56  
57  
58  
59  
60  
variability (abstract) [abstract]. *Osteoarthritis and Cartilage* 2014;22:S390-1.

63 Young C, Parenti D, Hochberg M. Lower-dose diclofenac capsules developed  
using solumatrix fine particle technology result in clinically meaningful improvements  
in pain in a phase 3 study of patients with osteoarthritis (abstract) [abstract].  
*Osteoarthritis and Cartilage* 2014;22.

64 Zhao SZ, McMillen JI, Markenson JA, et al. Evaluation of the Functional Status  
Aspects of Health-Related Quality of Life of Patients with Osteoarthritis Treated with  
Celecoxib, *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*  
1999;19:1269-78.

65 Zobel I, Erfani T, Bennell K, et al. Relationship of buckling and knee injury to pain  
exacerbation in knee osteoarthritis: A web-based case-crossover stud, *Interact J Med  
Res* 2014;66:S560-1.

1  
2  
3  
4 66 Conrozier T, Mathieu P, Vignon E, et al. Differences in the osteoarthritic synovial  
5  
6 fluid composition and rheology between patients with or without flare: a pilot study.  
7  
8 *Clinical and experimental rheumatology* 2012;30:729-34.  
9

10  
11  
12 67 D'Agostino MA, Conaghan P, Le Bars M, et al. EULAR report on the use of  
13  
14 ultrasonography in painful knee osteoarthritis. Part 1: Prevalence of inflammation in  
15  
16 osteoarthritis, *Annals of the Rheumatic Diseases* 2005;64:1703-9.  
17  
18

19  
20  
21 68 Jawad ASM. Analgesics and osteoarthritis: are treatment guidelines reflected in  
22  
23 clinical practice? *Am J Ther* 2005;12:98-104.  
24  
25

26  
27 69 Murphy SL, Lyden AK, Kratz AL, et al. Characterizing pain flares from the  
28  
29 perspective of individuals with symptomatic knee osteoarthritis, *Arthritis Care and*  
30  
31 *Research* 2015;67:1103-11.  
32  
33

34  
35 70 Wise BL, Niu J, Zhang Y, et al. Psychological factors and their relation to  
36  
37 osteoarthritis pain, *Osteoarthritis and Cartilage* 2010;18:883-7.  
38  
39

40  
41 71 Zhang Y, Zhang B, Wise B, et al. Statistical approaches to evaluating the effect of  
42  
43 risk factors on the pain of knee osteoarthritis in longitudinal studies, *Curr Opin*  
44  
45 *Rheumatol* 2009;21:513-9.  
46  
47  
48

49  
50 72 Zhang Y, Wheaton D, N, J., et al. Recent heavy physical activities trigger knee pain  
51  
52 exacerbation in persons with symptomatic knee osteoarthritis (abstract) [abstract].  
53  
54 *Arthritis & Rheumatism* 2011;63(10).  
55  
56



1  
2  
3  
4 73 Day R, Morrison B, Luza A, et al. A randomized trial of the efficacy and tolerability  
5  
6 of the cox-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis, *Arch*  
7  
8 *Intern Med* 2000;160:1781-7.  
9

10  
11  
12 74 Kivitz AJ, Greenwald MW, Cohen SB, et al. Efficacy and Safety of Rofecoxib  
13  
14 12.5 mg Versus Nabumetone 1,000 mg in Patients with Osteoarthritis of the Knee: A  
15  
16 Randomized Controlled Trial, *J Am Geriatr Soc* 2004;52:666-74.  
17  
18

19  
20  
21 75 Bingham CO, Smugar SS, Wang H, et al. Predictors of Response to Cyclo-  
22  
23 Oxygenase-2 Inhibitors in Osteoarthritis: Pooled Results from Two Identical Trials  
24  
25 Comparing Etoricoxib, Celecoxib, and Placebo, *Pain Medicine* 2011;12:352-61.  
26  
27

28  
29 76 Essex MN, Behar R, O'Connell MA, et al. Efficacy and tolerability of celecoxib and  
30  
31 naproxen vs placebo in hispanic patients with knee osteoarthritis, *Osteoarthritis and*  
32  
33 *Cartilage* 2013;21.  
34  
35

36  
37  
38 77 Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the  
39  
40 treatment of osteoarthritis: A 12-week, double-blind, multiple-dose, placebo-  
41  
42 controlled trial, *Arch Intern Med* 2000;160:2947-54.  
43  
44

45  
46 78 Atukorala I, Pathmeswaran A, Chang T, et al. Do Traditional Risk Factors for Knee  
47  
48 Osteoarthritis Predict Pain Flares in Knee Osteoarthritis? *Ann Rheum Dis* 2016;75:835.  
49  
50

1  
2  
3  
4 79 Bartholdy C, Klokke L, Bandak E, et al. A Standardized "Rescue" Exercise Program  
5  
6 for Symptomatic Flare-up of Knee Osteoarthritis: Description and Safety  
7  
8 Considerations, *J Orthop Sports Phys Ther* 2016;46:942-6.  
9

10  
11  
12 80 Bassiouni H. Detection of changes in the serum and synovial fluid levels of resistin  
13  
14 during flare ups and remissions in primary knee osteoarthritis, *Arthritis and*  
15  
16 *Rheumatology* 2015;67.  
17  
18

19  
20  
21 81 Erfani T, Makovey J, Bennell K, et al. Psychosocial Factors and Pain Exacerbation in  
22  
23 Knee Osteoarthritis: a Web Based Case-Crossover Study, *Intern Med J* 2014;44:16-.  
24  
25

26  
27 82 Ferreira ML, Zhang Y, Metcalf B, et al. The influence of weather on the risk of pain  
28  
29 exacerbation in patients with knee osteoarthritis - a case-crossover study,  
30  
31 *Osteoarthritis and cartilage* 2016;24:2042-7.  
32  
33

34  
35 83 Hunter DJ, Bennell K, Makovey J, et al. Psychosocial Factors and Pain Exacerbation  
36  
37 in Knee Osteoarthritis: a Web Based Case-Crossover Study, *Osteoarthritis and*  
38  
39 *Cartilage* 2014;22:S21-2.  
40  
41

42  
43  
44 84 Makovey J, Metcalf B, Zhang Y, et al. Web-Based Study of Risk Factors for Pain  
45  
46 Exacerbation in Osteoarthritis of the Knee (SPARK-Web): Design and Rationale, *JMIR*  
47  
48 *research protocols* 2015;4.  
49  
50

1  
2  
3  
4 85 Parry E, Ogollah R, Peat G. Significant pain variability in persons with, or at high  
5  
6 risk of, knee osteoarthritis: preliminary investigation based on secondary analysis of  
7  
8 cohort data, *BMC musculoskeletal disorders* 2017;18:80.  
9

10  
11  
12 86 Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled  
13  
14 glucosamine discontinuation trial in knee osteoarthritis, *Arthritis Care and Research*  
15  
16 2004;51:738-45.  
17

18  
19  
20  
21 87 Cibere J, Kopec JA, Esdaile JM, et al. Glucosamine sulfate and cartilage type II  
22  
23 collagen degradation in patients with knee osteoarthritis: randomized  
24  
25 discontinuation trial results employing biomarkers. In: Anonymous . *Journal of*  
26  
27 *rheumatology* 2005;896-902.  
28

29  
30  
31 88 Roth SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution  
32  
33 (pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized,  
34  
35 double-blind, vehicle-controlled clinical trial, *Arch Intern Med* 2004;164:2017-23.  
36  
37

38  
39  
40 89 Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac  
41  
42 containing dimethyl sulfoxide (DMSO) compared with those of topical placebo,  
43  
44 DMSO vehicle and oral diclofenac for knee osteoarthritis, *Pain* 2009;143:238-45.  
45  
46

47  
48  
49 90 Weaver A, Rubin B, Caldwell J, et al. Comparison of the efficacy and safety of  
50  
51 oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the  
52  
53 knee, *Clin Ther* 1995;17:735-45.  
54  
55

1  
2  
3  
4 91 Rother M, Lavins BJ, Kneer W, et al. Efficacy and safety of epicutaneous ketoprofen  
5  
6 in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the  
7  
8 knee: multicentre randomised controlled trial, *Annals of the Rheumatic Diseases*  
9  
10 2007;66:1178-83.  
11

12  
13  
14 92 Zobel I, Erfani T, Bennell KL, et al. Relationship of Buckling and Knee Injury to Pain  
15  
16 Exacerbation in Knee Osteoarthritis: A Web-Based Case-Crossover Study, *Interactive*  
17  
18 *journal of medical research* 2016;5:e17.  
19  
20

21  
22  
23 93 Woolacott NF, Corbett MS, Rice SJC. The use and reporting of WOMAC in the  
24  
25 assessment of the benefit of physical therapies for the pain of osteoarthritis of the  
26  
27 knee: findings from a systematic review of clinical trials, *Rheumatology* 2012;51:1440-  
28  
29 6.  
30  
31

32  
33  
34 94 National Institute for Health and Care Excellence (NICE).  
35  
36 Osteoarthritis: care and management (CG177). London: NICE 2014.  
37  
38

39  
40 95 Buttgerit F, Burmester G, Bijlsma JWJ. Non-surgical management of knee  
41  
42 osteoarthritis: where are we now and where do we need to go? *RMD Open* 2015;1.  
43  
44

45  
46 96 Porcheret M, Healey E, Dziedzic K, et al. Osteoarthritis: a modern approach to  
47  
48 diagnosis and management, *Arthritis Research UK* 2011;Series 6.  
49  
50

51  
52 97 Bellamy N, Sothorn RB, Campbell J. Rhythmic variations in pain perception in  
53  
54 osteoarthritis of the knee, *J Rheumatol* 1990;17:364-72.  
55  
56

1  
2  
3 98 Allen KD, Coffman CJ, Golightly YM, et al. Daily pain variations among patients  
4 with hand, hip, and knee osteoarthritis, *Osteoarthritis and Cartilage* 2009;17:1275-82.  
5  
6  
7

8  
9 99 Makris D, Bouros D. COPD exacerbation: Lost in translation, *BMC Pulmonary*  
10 *Medicine* 2009;9:6.  
11  
12  
13

14  
15 100 Fitzgerald JD, Grossman JM. Validity and reliability of retrospective assessment of  
16 disease activity and flare in observational cohorts of lupus patients, *Lupus*  
17 1999;8:638-44.  
18  
19  
20  
21  
22

23  
24 101 Lewis JD, Aberra FN, Lichtenstein GR, et al. Seasonal variation in flares of  
25 inflammatory bowel disease, *Gastroenterology*;126:665-73.  
26  
27  
28

29  
30 102 Suri P, Saunders KW, Von Korff M. Prevalence and Characteristics of Flare-ups of  
31 Chronic Nonspecific Back Pain in Primary Care: A Telephone Survey, *Clin J Pain*  
32 2012;28:573-80.  
33  
34  
35  
36  
37

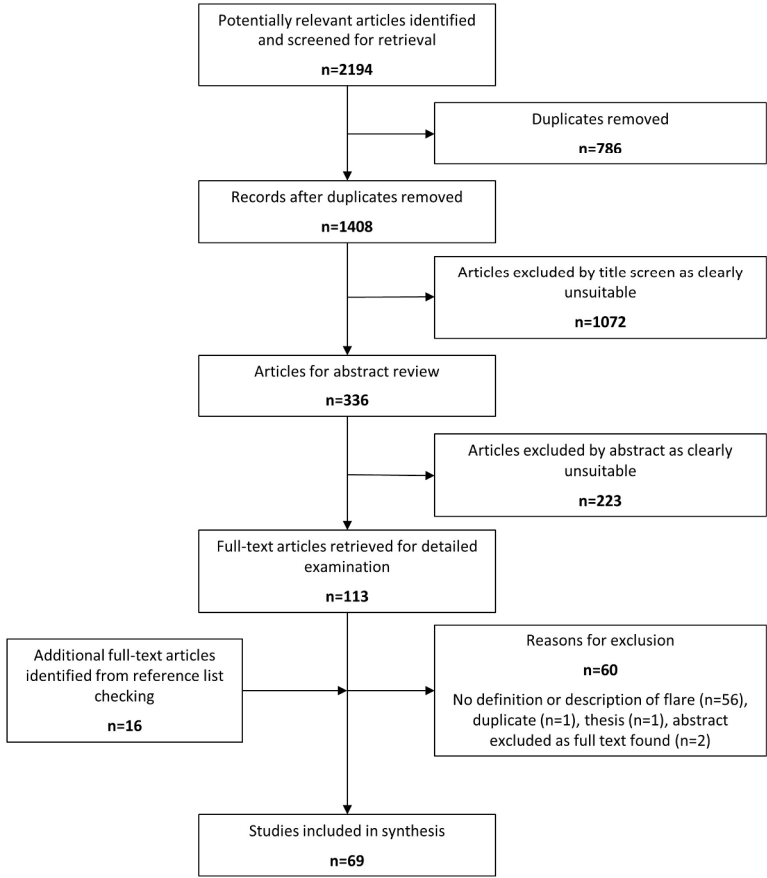
38  
39 103 Cross M, Dubouis L, Mangin M, et al. Defining Flare in Osteoarthritis of the Hip  
40 and Knee: A Systematic Literature Review- OMERACT Virtual Special Interest Group, *J*  
41 *Rheumatol* 2017;44(12):1920-7.  
42  
43  
44  
45

46  
47 104 Sands GH, Brown PB, Essex MN. The Efficacy of Continuous Versus Intermittent  
48 Celecoxib Treatment in Osteoarthritis Patients with Body Mass Index  $\geq 30$  and *The*  
49 *Open Rheumatology Journal* 2013;7:32-7.  
50  
51  
52  
53  
54

1  
2  
3 105 Berthelot J, De Bandt M, Morel J, et al. A tool to identify recent or present  
4  
5  
6 rheumatoid arthritis flare from both patient and physician perspectives: The 'FLARE'  
7  
8  
9 instrument, *Annals of the Rheumatic Diseases* 2012;71:1110-6.  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
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PRISMA Flowchart

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### Online supplement: Example search strategy

Table 1: Key terms and MeSH headings used for EMBASE database search. The concepts were combined as follows: "KNEE JOINT" AND "ACUTE EVENTS"

Concepts	Search terms
KNEE JOINT	"knee adj3 (pain OR painful)" or "Knee osteoarthritis" or "knee adj3 (arthrosis)" or "knee adj3 (joint OR joints OR degenerative)" or "knee adj3 (osteoarthritis)"
ACUTE EVENTS	"exacerbation" or "flare" or "daily adj3 (pain)" or "pain AND (diary OR diaries)" or "pain adj3 (variab\$)"





# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplement
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis. <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	9



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 (flowchart)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A but rationale on 18
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19-35
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	36-37
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	38
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	39
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	40

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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# PRISMA 2009 Checklist

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