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Defining acute flares in knee osteoarthritis: a systematic review

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ABSTRACT

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

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

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

Conclusions The concept of OA flare appears in the medical literature but most often in the context of flare design trials (pain increases observed after stopping usual treatment). Key domains, used to define acute events in other chronic conditions, appear relevant to OA flare and could provide the basis for consensus on a single, agreed definition of 'naturally occurring' OA flares for research and clinical application.

PROSPERO registration number CRD42014010169.

Strengths and limitations of this study

- ► Identified key domains that are used to define acute events by undertaking a comprehensive synthesis of definitions used in the medical literature.
- ► Broad search strategy covering a wide range of databases including bibliography checks and conference abstracts.
- ► Prospectively registered with an international register of systematic reviews (PROSPERO).
- ► Did not include potential synonyms as search terms ('attack', 'episode', 'fluctuations').
- ► Data extraction was performed by only a single reviewer.

INTRODUCTION

Recurrent acute events or episodes feature in the natural history of many chronic health conditions. The extent to which they characterise the condition varies, as do the presumed pathophysiological mechanisms, and scientific and lay terms used to describe them (eg, an acute exacerbation of chronic obstructive pulmonary disease (COPD) or asthma, an attack of gout or a rheumatoid arthritis flare). With recognition of their importance has come concerted effort to define these phenomena. Definitions for exacerbations or flares currently exist for COPD,[1 2] asthma,[3] systemic lupus erythematosus (SLE)[4] and ankylosing spondylitis (AS)[5] and there are working groups currently trying to define these for rheumatoid arthritis,[6–8] gout[9] and atopic dermatitis/eczema.[10] Despite the different language used, these definitions share some common, core domains: the onset or worsening of symptoms and signs above normal day-to-day variability; speed of onset; duration of sustained worsening and change in medication/healthcare usage.

Osteoarthritis (OA) appears to comprise multiple disease trajectories[11–15] and symptom variability over time and the presence of intermittent pain is well-recognised.[16] Although OA does not typically have the same very obvious acute events as conditions like gout, flares in OA joints are encountered in practice, these phenomena appear in patient literature,[17] have been discussed in expert reviews[18] and are mentioned in 'flare design' trials in OA.[19] These studies induce acute episodes of pain or flare-ups by asking patients to withdraw their usual medication.

In 2009, Marty *et al* proposed scoring criteria for knee OA flares based on nocturnal awakening, knee effusion, morning stiffness and limping,[20] but it is unclear whether this has contributed to a common understanding, shared terminology and criteria. A common definition of OA flare could be important for a number of reasons: (i) to facilitate communication between researchers, (ii) to allow

more direct comparisons between studies on frequencies, determinants and course of events, (iii) to facilitate new insights into novel pathophysiological mechanisms and treatments through valid and homogenous case definitions and (iv) to help clinicians with prompt diagnosis and management.

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

METHODS

This systematic review was registered with PROSPERO registration number CRD42014010169. The review protocol has not been published.

Literature sources and study selection

We searched electronic databases from inception to July 2017; ASSIA, EMBASE, Web of Science, Health Management Information Consortium (HMIC), SPORTDiscus, Medline, CINAHL, PsycINFO, AMED, Ageline, Cochrane Database of Systematic Reviews and Cochrane Controlled Clinical Trials (CENTRAL). The search was developed using previously piloted terms for knee OA and a literature search for common terms used to describe acute events. Searches used combined and/or truncated key terms including: ('KNEE OSTEOARTHRITIS' OR (knee N3 pain) OR (knee N3 arthrosis) OR (knee N3 joint) OR (knee N3 osteoarthritis)) AND (exacerbation OR flare OR (pain AND (diary OR diaries)) OR (pain N3 variab*) OR (pain N3 *) OR (pain N3 *) OR (pain N3 *) OR (pain N3 pattern$) OR (daily N3 pain)). A database search strategy is included in the online supplementary table 1. Reference lists of all included full-text articles retrieved for detailed examination were manually searched.

Studies were included in the final full-text peer-review if they contained a description or definition of an acute exacerbation or flare-up of knee OA in human adults (aged 18 years or over) in the general population, primary care or hospital settings. Studies were included even if their description was not based on clear measurement criteria (eg, stating a 'significant increase in pain' but not the amount of change on a pain score this would equate to). Studies that included a mixed OA population (eg, knee or hip OA) and did not separately report knee-specific findings were included. There were no restrictions on study dates or design. All non-English language articles were translated to identify a flare definition. Theses, dissertations, book chapters and guidelines and animal studies were excluded. Conference abstracts were included if they contained a definition for an OA flare-up. Studies were excluded if the flare was induced by an iatrogenic source, for example, injection-induced flares,[21] as these may have been caused by a different pathophysiological process. Abstracts were included in this study as the main outcome of interest was the definition of flare used and it was decided that including abstracts would ensure a more comprehensive review. For each abstract, a search was conducted to identify a corresponding full-text paper. Where one was found only the full paper was included in the review.

The search and article retrieval was conducted by the first reviewer (ELP). Articles were downloaded into RefWorks bibliography and database manager (RefWorks Copyright 2009). Duplicates were removed and all titles were screened by ELP against inclusion criteria, with the first 20 titles checked by two reviewers (ELP and MJT) for consistency. For qualitative studies, all identified potentially eligible full-text articles were obtained.

All abstracts and then full-text articles were screened by two reviewers (ELP and MJT), with disagreements resolved by consensus adjudicated by a third reviewer (GP). Where articles could not be retrieved or if the flare definition used was not included in the text, contact with authors was made.

The final included articles were checked to ensure results were not duplicated, for example, where different authors were reporting on the same dataset, to reduce bias.[22] For articles containing pooled studies, the original studies were sought and included in the main analysis, where available. No full-text articles were required to be translated.

Data extraction

The following data pertaining to flares were extracted from full-text articles by the first reviewer: definition used for change in pain, pain scale used, duration of flare (for flare design trials we extracted the duration of the withdrawal period for comparison), associated symptoms, rationale behind definition used, terminology used (eg, exacerbation or flare), baseline OA severity, age range, gender, geographical location, number of participants and study design. Missing data were described in the data extraction tables.

Quality assessment of included studies

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

Data analysis

A narrative synthesis was undertaken guided by the four-stage process of Popay *et al*.[22 23] This approach was chosen as it allowed the words and text in the definitions to be synthesised to summarise findings.[23] The initial data extracted were grouped into drug withdrawal studies ('flare design') and other studies. Frequencies of components included in definitions was tabulated, these included; terminology used, onset/worsening of symptoms; signs/symptoms above day-to-day variability/minimum threshold; speed of onset of symptoms; duration of worsening and change in medication/healthcare usage.

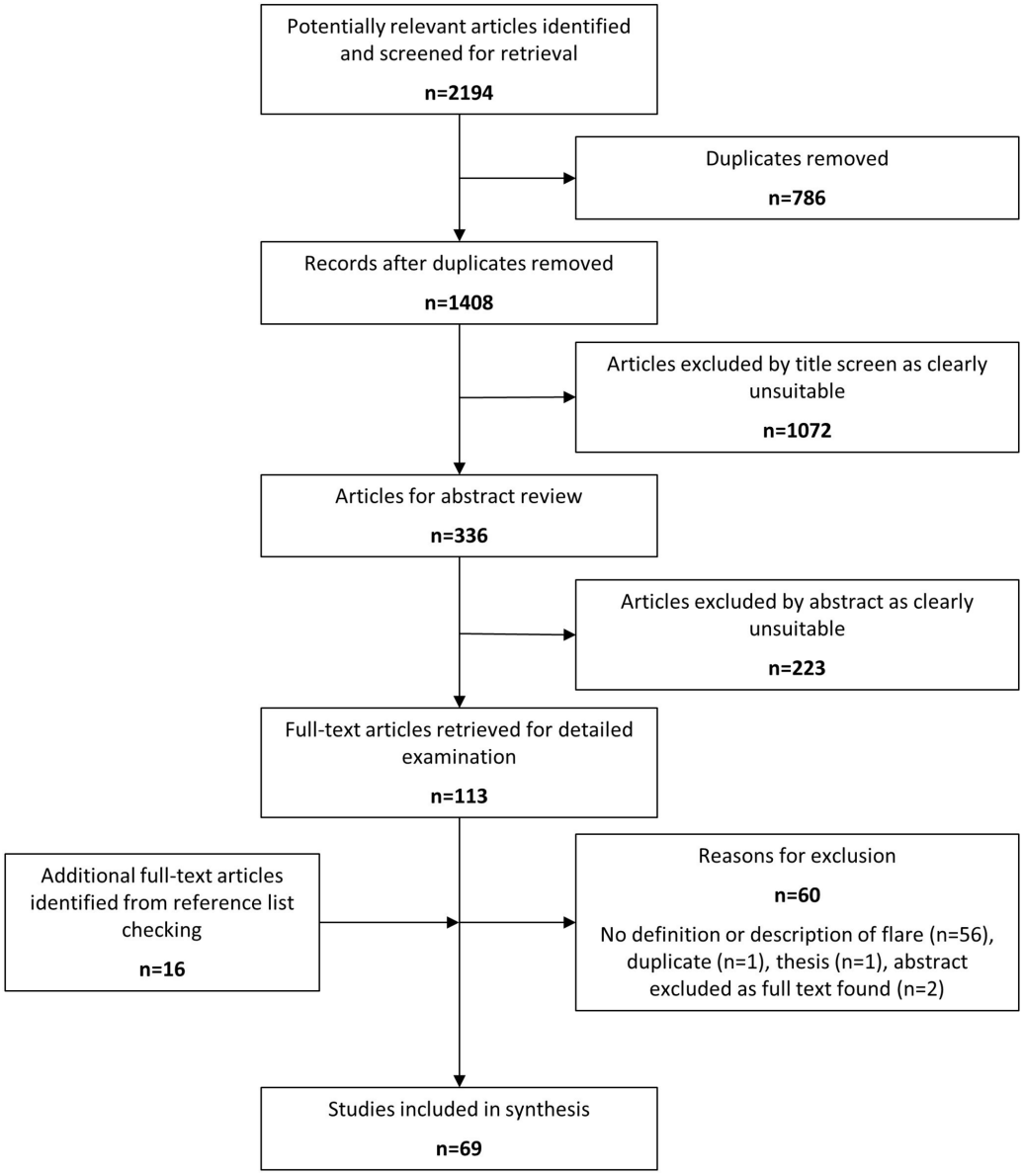

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

This initial tabulation helped identify similarities and differences and allowed themes to emerge. This was done with an inductive-type approach, where possible, that is, without an a priori assumption, and deductively acknowledging that the reviewers were clinicians, that is, they had some background knowledge of the topic of interest. This allowed further examination of the differences of definitions used in drug withdrawal and non-drug withdrawal study designs, and examination of key components of definitions used.

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Study selection

The literature search yielded 2194 articles, of which 786 were duplicates (figure 1). After title screening, 336 abstracts were reviewed, 223 were not relevant for the study purpose. One hundred thirteen articles were examined in full, which resulted in a further 60 being excluded. The main reason for exclusion was no definition of flare-up reported in text (n=56). At this stage, a further 16 articles were identified from the reference lists of the retrieved full-text articles resulting in 69 included studies for synthesis.

Study characteristics

Characteristics of the included studies are described in table 1.[20 24–91] The number of participants in each study ranged from 15 to 6085.[20 48] Knee OA was defined by clinical and/or radiological criteria.

Twenty-one included mixed knee and hip OA groups.[24 29 31 37–39 42 45–47 54 55 57–59 63 71 73 75 77] In total, 46 publications used a drug withdrawal RCT design,[24 26–32 34–43 45–53 55–64 73–77 88–91] 4 of which

Table 1 Characteristics of all included studies

First author, year of publication	Setting, geographic location	Participants	Joint	Severity	Study design
Drug withdrawal design studies					
Altman, 2015[24]	Multicentre, recruitment not specified, USA	403 males and females, ≥40 years	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 and females, 40–85 years	Knee	Radiographic evidence of OA (severity not defined)	RCT, flare design
Baraf, 2011[27]	Primary care, internal medicine, orthopaedic, rheumatology; USA	602 males and females, ≥25 years	Knee	Radiographically mild to moderate (KL grade 1–3)	RCT, flare design
Battisti, 2004[28]	Clinical centres, outpatients; USA	3980 males and females, ≥40 years (age unavailable for Geba 2003 and Weaver 2003)	Knee	ACR functional class rating of I, II or III	RCT, pooled four trials, flare design
Bingham, 2007[29] Bingham, 2011[75]	2×74 outpatient clinics; USA	1207 males and females, ≥40 years	Knee and hip	ARA functional capacity classification I–III	RCT, flare design
Birbara, 2006[30]	Investigative sites; USA	808 males and females, ≥40 years	Knee	ARA functional class, I, II or III	RCT, flare design
Bocanegra, 1998[31]	Clinic; USA	572 males and females, 28–88 years (mean 61–62)	Knee and hip	ARA functional capacity classification I–III	RCT, flare design
Boswell, 2008[32]	50 centres (Europe and Australia)+187 centres (Europe and USA)	1908 males and females, ≥40 years	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 and females, mean age 62 years	Knee	KL≥2	Cohort design, flare design
Case, 2003[34]	Hospital-rheumatology centre; Chicago, USA	82 males and females, 40–75 years	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 and females, mean age range 62–65 years	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 and females, >40 years	Knee	ARA functional class, I, II or III	RCT, flare design
Essex, 2012[36]	Clinical centre; African-American, USA	322 males and females, ≥45 years	Knee	ARA functional capacity classification I–III	RCT, flare design
Essex 2013[76]	Hispanic population, 31 US centres	≥45 years	Knee	ACR criteria, functional capacity classification I–III	RCT, flare design
Gibofsky, 2014[37]	Not specified, USA	305 males and females, 41–90 years	Knee and hip	KL 2–3	RCT, flare design
Gineyts, 2004[38]	Subset of larger study; France	201 males and females, mean age 61–62 years	Knee and hip	ARA I–III	RCT, flare design
Goldberg, 1988[39]	Investigative sites; USA	214 males and females, 40–85 years (mean 64)	Knee and hip	Radiographic evidence of knee OA, not further defined	RCT, flare design
Gottesdiener, 2002[40]	Investigative sites; USA	617 males and females, ≥40 years	Knee	ARA functional class I–III	RCT, flare design
Hochberg, 2011[41]	Centres; USA	1234 males and females, ≥50 years	Knee	ACR functional class I–III	Pooled RCTs (2), flare design
Katz, 2010[42]	Clinical sites; USA	113 males and females, 28–83 years (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 and females, 28–91 years (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 and females, ≥40 years	Knee	ACR rating of I–III	RCT, flare design
Leung, 2002[45]	Clinic; USA	677 males and females, ≥40 y	Knee and hip	ARA functional class, I, II, or III	RCT, flare design

Continued

Table 1 Continued

First author, year of publication	Setting, geographic location	Participants	Joint	Severity	Study design
Luyten, 2007[45]	Centres; Belgium	181 males and females, ≥40 years	Knee and hip	ACR functional capacity classification I–III	RCT, flare design
Manicourt, 2005[47]	Outpatient clinic; Belgium	90 males and females, 50–81 years (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 and females, ≥45 years	Knee	KL 2–3	Observational, flare design
McIlwain, 1989[49]	Investigative sites; USA	139 males and females, mean 65 years	Knee	Radiological evidence of moderate or severe osteoarthritis, not further defined	RCT, flare design
Mendelsohn, 1991[50]	Investigative sites; USA	139 males and females, 21–88 years (mean age 63.3 years)	Knee	Radiological evidence of moderate or severe osteoarthritis, not further defined	RCT, flare design
Moskowitz, 2006[51]	Investigative sites; USA	530 males and females, ≥45 years	Knee	ACR functional capacity classification I–III	RCT, flare design
Pareek, 2009[52]	Multicentre study, India	199 males and females, 40–70 years	Knee	Lequesne criteria, score of 5 and above	RCT, flare design
Pareek, 2010[53]	Hospital; India	220 males and females, 40–70 years	Knee	Clinical and radiological evidence of OA severity not defined	RCT, flare design
Roth, 2004[88]	Physicians private practice or community; USA	326 males and females, 40–85 years	Knee	Radiological evidence of OA, severity not defined	RCT, flare design
Rother, 2007[91]	Outpatient units; Germany	397 males and females, ≥ 40 years	Knee	KL 2–3	RCT, flare design
Schnitzer, 2005[55]	Investigative sites; International (seven countries)	583 males and females, 18–75 years	Knee and hip	Diagnosis based on ACR criteria, severity not defined	RCT, flare design
Scott-Lennox, 2001[56]	Investigative sites; USA	182 males and females, mean age 61 years	Knee	Not defined	RCT, flare design
Silverfield, 2002[57]	Centres; USA	308 males and females, 35–75 years	Knee and hip	Clinical evidence of OA, severity not defined	RCT, flare design
Simon, 2009[89]	Outpatient centres; Canada, USA	775 males and females, 40–85 years	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 and females, 18–80 years	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 and females, >50 years	Knee	ACR clinical criteria, diagnostic	RCT, flare design
Wiesenhutter, 2005[59]	Medical centres; USA	528 males and females, 40–89 years	Knee and hip	ARA functional class I, II or III	RCT, flare design
Williams, 2001[60]	Clinical sites; USA	718 males and females, mean age 61–62 years	Knee	ACR clinical and radiographic criteria I–III	RCT, flare design
Wittenberg, 2006[61]	Centres (not specified); Germany	364 males and females, 50 years	Knee	Moderate-to-severe symptomatic OA of the knee according to ACR criteria	RCT, flare design
Yeasted, 2014[62] (poled, abstract)	USA	219 (merged observational), 137 (merged trial) >40 years	Not specified	ACR criteria, diagnostic	Two longitudinal observational studies, placebo arms of two clinical trials
Yocum, 2000[77]	USA, 62 study centres	774 males and females, ≥40 years	Knee or hip	Diagnosis confirmed by XR and clinical symptoms (not further specified)	RCT, flare design
Young, 2014[63] (abstract)	Multicentre	305 males and females, >40 years	Knee or hip	KL 2–3	RCT, flare design
Zhao, 1999[64]	Centre (not specified); USA, Canada	1004 males and females, ≥18 years	Knee	ACR functional capacity classification I–III	RCT, flare design

Continued

Table 1 Continued

First author, year of publication	Setting, geographic location	Participants	Joint	Severity	Study design
Non-drug withdrawal design studies					
Atukorala, 2016[78] (abstract) Atukorala, 2016[25] (abstract)	Not specified, USA+Australia+Sri Lanka	213 males and females, mean age 62 years 345 males and females, mean age 62 years	Knee	Not specified	3-month, web-based longitudinal follow-up study
Bartholdy, 2016[79]	OA outpatient clinic, Denmark	131 males and females, ≥40 years	Knee	Radiographic evidence of OA (severity no defined) and BMI between 20 and 35 kg/m^2	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 and females, mean age 65 years (43–88) for placebo and 64 years (40–83) for glucosamine group	Knee	KL≥2 on anteroposterior radiograph	RCT
Conrozier 2012[66]	Hospital-rheumatology unit, France	44 males and females, mean age 67.6 years	Knee	Radiographic evidence of knee OA, not further defined	Observational
D'Agostino 2005[67]	Hospital-European multicentre	600 males and females, ≥18 years	Knee	KL grade 1–4	Observational
Erfani, 2014[44] (abstract) Erfani, 2014[81] (abstract) Ferreira, 2016[82] Hunter, 2014[83] (abstract) Makovey, 2015[84] (protocol)	Australia	268 males and females, mean age 62 years 345 males and females, ≥40 years	Knee	ACR criteria, meet at least one, KL≥2	Web-based crossover
Jawad, 2005[68]	GPs in France	3000 (for GP study) males and 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+641 males and females, mean age 66.4 years (10.9) for flare group, 66.2 years (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 and females, 37–83 years	Knee	ACR criteria, severity not defined	Qualitative
Parry, 2017[85]	Community, UK	719 males and females, ≥50 years	Knee	Self-reported knee pain in previous 12 months	Observational
Ricci 2005[54]	Community, USA	329 males and females, 40–65 years	Knee and hip	Clinical evidence of OA, severity not defined	Nested case-control
Wise 2010[70]	Primary care, hospital, USA	303 males and females, ≥50 years	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 and females, ≥50 years	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 and females, median age 63 years (50–72 years)	Knee	KL>2	Case-crossover
Zobel 2016[92]	Hospital databases, Australia	297 males and females, >40 years	Knee	ACR criteria, KL≥2 or patellofemoral OA on radiograph	Web-based case-crossover

ACR, Arthritis Center Research; ARA, American Rheumatism Association; GP, general practitioner; KL, Kellgran and Lawrence; RCT, randomised controlled trial.

were pooled studies[28 32 41 62] and 1 used a cohort drug withdrawal design[33] (table 1). The remaining 22 publications included 17 observational studies,[20 25 44 54 65–67 70–72 78 80–85] 3 RCTs,[79 86 87] 1 survey[68] and 1 qualitative interview study.[69] Nine of the included studies were abstracts.[25 44 62 63 72 78 80 81 83] Two abstracts were removed as the corresponding full-text article was available.[69 92] Studies using pooled data or the same dataset were included if they used different definitions of OA flare.[28 44 52 53 62 65 70 71 74]

Rationale given for flare definitions

Six of the included studies gave rationale for the definition used.[20 54 56 69 85 86] None of the definitions was based on a consensus procedure. The studies by Marty *et al*[20] and Scott-Lennox *et al*[56] were the only ones that undertook empirical investigation of flare definitions. The study by Marty *et al*[20] was the only study specifically designed to validate a diagnostic tool for knee OA flares. Potential factors associated with flare-ups were identified, for example, knee swelling and the authors used a logistic regression analysis to assign a weight to each of the items identified. A flare-up score was determined using a general practitioner database and this was then validated using a rheumatologist database. Pain was not included in the final model.

Scott-Lennox *et al*[56] sought to test whether four measures for flare intensity (patient's self-assessment of pain scores, physician's assessment of pain scores, patient's global OA assessment and physician's global OA assessment) could be combined to form a reliable and valid index using data from an RCT using a confirmatory factor analysis. The authors produced three flare intensity groups (low, moderate and severe) and highlighted how these could be used to examine treatment effects.

Cibere *et al*[86] outlined face validity checks. It was specified that the flare definition had been determined by study rheumatologists to be a clinically important change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. The definition used by Murphy *et al*[69] was informed by two studies,[28 53] which used a drug withdrawal design and from the research team's own experience. Ricci *et al*[54] used a combination of data-driven and clinical judgement approaches to establish an agreed cut point. Parry *et al* based their definition on OA flare design studies and flare definitions used in other chronic disease such as back pain and COPD.

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).

One study used the term 'flare-up',[52] two studies referred simply to 'worsening of symptoms'[31 50] and three studies used no specific label.[34 35 73]

Coverage of key components

Onset/worsening of symptoms and signs beyond normal-day-to-day variability: forty-four studies included onset or worsening of signs and symptoms as part of their definition.[24 26–32 34–41 43 45–53 55–64 73–75 77 88–91] All studies included increased pain intensity in their definition. A further two[52 53] specified further signs and symptoms. These included swelling, inflammation, erythema, morning stiffness and nocturnal pain. No studies quantified day-to-day variability.

Twenty-six measurement tools were used to define onset/worsening of symptoms and signs. The most commonly used tools were the Western Ontario and McMaster Universities Arthritis index (WOMAC) Q1 (pain on walking on flat surface) 100 mm Visual Analogue Scale (VAS) (n=9)[29 30 32 38 41 45 59 73 75] and the Investigator Assessment of Disease Status (n=11)[28–30 38 40 45 59 73–75 77] (table 3). Thirty-four studies used only single-item measurement tools,[27–30 32 34–43 45 47 48 50 52 55 56 58 59 61–63 73–77 90 91] five used multiitem[31 46 51 53 60] and five used both single-item and multiitem tools.[24 26 33 88 89]

In addition, the format of global ratings appears to be variable as is use and reporting of the WOMAC.[93] However, despite the exact format of reporting being inconsistent, in general, studies used single items in four areas—pain on activity, pain (not necessarily on activity), physician/investigator global rating and patient global rating.

Temporal characteristics: none of the included drug withdrawal design studies reported a specific time for defining the speed of onset of symptoms. However, they did describe withdrawal or 'washout' periods, whereby after withdrawal of usual medication, participants were given a certain time frame in which to experience 'flare' symptoms in order that they were entered into the study. In total 30 of the studies specified a withdrawal period.[27 30 31 33–36 38–40 43 45–52 56 58 60 61 64 73 74 76 77 88–90]

Four studies specified a time period for minimum duration of symptoms, which ranged from 24 hours to 5 days.[52 53 55 57]

Change in medication or healthcare usage: only one study used increase in medication as part of their definition; 'pain requiring supplemental analgesic medication and/or an increase in non-steroidal anti-inflammatory drug dose'.[57]

Additional domains: thirty-six studies included a minimum threshold, which was usually a minimum level of pain that was required before the participant was considered to have a flare.[24 26 28–31 33 35–38 40–43 45–47 51–53 55 56 58–63 73 75 76 88–91] There was general concordance with the minimum thresholds that different measurement tools used with a few exceptions. A threshold of 40 mm on a 0–100 mm scale was used in 8 of 10 studies using the WOMAC VAS 3.0 Q1 'pain on walking on a flat surface'[29 30 38 41 45 59 73 75] and 4 of 14 studies using the Patient Global Assessment of Disease Status.[29 45 73 75] In studies using various forms of Investigator/Physician Global Assessment, the majority adopted a minimum threshold for a flare of 'fair, poor

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

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Drug withdrawal study design							
Altman[24]	'Flare'	*Pain*: WOMAC Pain subscale (0–100); increase≥15 mm	*Pain:* WOMAC Pain subscale; ≥40 mm	Not specified	Not specified	Not specified	None
Baer 2005[26]	'Flare'	*Pain:* WOMAC LK3.1 Pain subscale (0–20); increase≥2 points and ≥25%	*Pain:* WOMAC Pain score (0–20); ≥6 and ≥1 item rated 'moderate, severe or extreme'	Interval between screening and baseline remeasurement unclear	Not specified	Not specified	None
Baraf 2011[27]	'Flare'	*Pain on movement:* VAS (0–100 mm); increase≥5 mm	Not specified	1 week washout	Not specified	Not specified	None
Battisti 2004[28]	'Flare'	*Global assessment (investigator):* single item, 5-point LK; worsening≥1 point	*Pain:* VAS (0–100 mm); ≥40 mm	Not specified	Not specified	Not specified	None
Bingham 2007[29] Bingham 2011[75]	'Flare'	1. *Pain walking on flat surface:* WOMAC VAS 3.0 Q1 (0–100 mm); increase≥15 mm 2. *Global assessment of disease status (investigator):* single item, 5-point LK; worsening≥1 point	1. *Pain walking on flat surface:* ≥40 mm on WOMAC VAS 3.0 Q1 (0–100) 2. *Global assessment (investigator)*: single item, 5-point LK; fair, poor, very poor (*acetaminophen users only*) 3. *Global assessment of disease status (patient):* VAS 0–100 mm; ≥40 mm (*acetaminophen users only*)	Not specified	Not specified	Not specified	None
Birbara 2006[30]	'Flare'	1. *Pain walking on flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global assessment (investigator):* single item, 5-point LK; worsening≥1 point	1. *Pain walking on flat surface:* WOMAC VAS 3.0 Q1 (0–100); ≥40 mm 2. *Global assessment (investigator):* single item, 5-point LK; fair, poor or very poor (*paracetamol arm only*)	4–15 days washout	Not specified	Not specified	None
Bocanegra 1998[31]	'Worsening of symptoms'	Two out of the following three: 1. *Global assessment (physician):* single item, 5-point LK; increase≥1 grade 2. *Global assessment (patient):* patients global assessment (current symptoms and limitation of activity) 5-point LK; increase≥1 grade 3. *Composite index:* Lequesne OA Severity Index (0–24); increase≥2 points	1. *Global assessment (physician):* single item, 5-point LK; 'poor/very poor' 2. *Global assessment (patient):* patients global assessment (current symptoms and limitation of activity) 5-point LK; 'poor/very poor' 3. *Composite index:* Lequesne OA Severity Index (0–24); ≥7	3–14 days washout	Not specified	Not specified	None
Boswell 2008[32]	'Flare'	1. *Pain walking on flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global assessment (patient):* Patient Global Assessment of Arthritis Condition (PGAC) (unspecified); worsening≥1 point	Not specified	Not specified	Not specified	Not specified	None
Brandt 2006[33] (pilot studies)	'Flare'	Not specified	*Pain:* WOMAC LK Pain subscale (5–25); ≥15 points	Five half-lives of NSAID washout	Not specified	Not specified	None
Case 2003[34]	Not used	1. *Pain walking on flat surface:* VAS (0–100 mm); increase≥10 mm 2. *Ambulatory pain*; 5-point LK; worsening≥1 point	Not specified	14 days washout	Not specified	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Day 2000[73]	Not used	1. *Pain walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator):* single item, 5-point LK; worsening≥1 point 3. *Global assessment (patient):* VAS (0–100 mm); increase≥15 mm (*acetaminophen users only*)	1. *Pain walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); ≥40 mm 2. *Global Assessment (investigator):* single item, 5-point LK; 'fair, poor or very poor' 3. *Global Assessment (patient):* VAS (0–100 mm); ≥40 mm	Longer than five plasma half-lives washout	Not specified	Not specified	None
Ehrich 1999[35]	Not used	*Pain:* VAS (0–100 mm); increase≥15 mm	*Pain:* VAS (0–100 mm); ≥40 mm	Longer than five plasma half-lives washout of NSAID	Not specified	Not specified	None
Essex 2012[36]	'Flare'	1. *Global Assessment (physician):* 5-point LK; increase≥1 grade 2. *Global Assessment (patient):* 5-point LK; increase≥1 grade	1. *Global Assessment (physician):* 5-point LK; 'fair, poor or very poor' 2. *Global Assessment (patient):* 5-point LK; 'fair, poor or very poor' 3. *Pain:* VAS (0–100 mm); 40–90 mm	48 hours withdrawal	Not specified	Not specified	None
Essex 2013[76]	'Flare'	Not specified	1. *Global Assessment of arthritis (physician):* Minimum rating of 3 2. *Global Assessment of arthritis (patient):* Minimum rating of 3 3. *Pain:* VAS (0–100 mm); 40–90 mm	48 hours withdrawal	Not specified	Not specified	None
Gibofksy 2014[37]	'Flare'	*Pain:* WOMAC Pain VAS; increase≥15 mm	*Pain:* WOMAC Pain VAS; ≥40 mm	Not specified	Not specified	Not specified	None
Gineyts 2004[38]	'Flare'	1. *Pain walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator):* 5-point scale: worsening≥1 point	1. *Pain walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); ≥40 mm	five half-lives of NSAID washout	Not specified	Not specified	None
Goldberg 1988[39]	'Flare'	1. *Pain:* Investigator assessed pain grade (none/mild/mod/severe): (i) at rest, (ii) on passive motion, (iii) on palpation, (iv) weight bearing; increase≥1 grade in two items OR increase≥2 grade in one item	Not specified	2–14 days washout until flare	Not specified	Not specified	None
Gottesdiener 2002[40]	'Flare'	1. *Pain on walking*: VAS (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator):* 5-point LK; increase≥1 point	1. *Pain on walking*: VAS (0–100 mm); ≥40 mm	3–15 days washout	Not specified	Not specified	None
Hochberg 2011[41]	'Flare'	1. *Pain walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (patient):* 5-point LK; worsening≥1 point	1. *Pain walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); ≥40 mm	Not specified	Not specified	Not specified	None
Katz 2010[42]	'Flare'	Not specified	*Pain:* pain score (0–10); ≥5	Not specified-washout until flare occurred	Not specified	Not specified	None
Kivitz 2001[43]	'Flare'	*Pain:* Patients Assessment of Pain Score (0–10) (unspecified); increase≥2 points	*Pain:* Patients Assessment of Pain Score (0–10) (unspecified); ≥5	Five drug half-lives or 48 hours	Not specified	Not specified	None
Kivitz 2004[74]	'Flare'	1. *Pain on walking:* VAS (0–100 mm); worsening≥15 mm 2. *Global Assessment (investigator):* 5-point LK; worsening≥1 point	Not specified	NSAID-dependent half-life washout	Not specified	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Leung 2002[45]	'Flare'	1. *Pain on walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator):* 5-point LK; worsening≥1 point	1. *Pain on walking on a flat surface:* WOMAC VAS Q1 (0–100 mm); ≥40 mm 2. *Global Assessment (patient):* (0–100 mm); ≥40 mm (*acetaminophen users only*) 3. *Global Assessment (investigator):* 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. *Global Assessment (patient):* 5-point LK; increase≥1 grade 2. *Global Assessment (physician):* 5-point LK; increase≥1 grade 3. *Composite definition:* Lequesne Osteoarthritis Severity Index (0–24); increase≥2 points	1. *Global Assessment (patient):* 5-point LK; 'fair, poor or very poor' (*not on treatment—'poor or very poor'*) 2. *Global Assessment (physician):* 5-point LK; 'fair, poor or very poor' 3. *(Not on treatment— 'poor or very poor')* 4. *Composite definition:* Lequesne Osteoarthritis Severity Index (0–24); ≥7 5. *Pain:* VAS (0–100 mm); ≥40 mm	2–14 days washout	Not specified	Not specified	None
Manicourt 2005[47]	'Flare'	*Pain when walking on a flat surface:* VAS (0–100 mm); ≥10 mm	Not specified	7–10 days washout	Not specified	Not specified	None
Mazzuca 2002[48]	'Flare'	*Pain on standing*: 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 five 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 days washout	Not specified	Not specified	None
Mendelsohn 1991[50]	'Worsening of arthritis condition'	1. *Pain:* Pain scale (0–3) (0=none, 3=severe); worsening score 2. *Global (physician):* (0–100); worsening score	Not specified	Up to 14 days washout	Not specified	Not specified	None
Moskowitz 2006[51]	'Flare'	1. *Global assessment (patient):* 5-point LK; increase≥1 grade 2. *Global Assessment (physician)*: 5-point LK; ≥1 grade increase 3. *Composite index:* Lequesne OA Severity Index (0–24); increase≥2 points	1. *Global assessment (patient):* 5-point LK; '(fair), poor or very poor' 2. *Global Assessment (physician):* 5-point LK; '(fair), poor or very poor' 3. *Composite index*: Lequesne OA Severity Index (0–24); minimum≥7 4. *Pain walking on a flat surface:* VAS (0–100 mm); ≥40 mm	NSAID washout of five half-lives or at least 2 days	Not specified	Not specified	None
Pareek 2009[52]	'Flare-up'	1. *Pain:* 11-point NRS; increase≥2 points during previous 2–5 days 2. Signs and symptoms suggestive of inflammation, morning stiffness and nocturnal pain interfering with sleep	*Pain:* 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

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Pareek 2010[53]	'Flare'	Flare symptoms noted but not part of definition: morning stiffness, erythema, nocturnal pain and swelling/inflammation	1. *Pain with physical activity*: VAS 0–10; ≥6 2. *Composite index:* WOMAC total LK; ≥25. 3. *Composite index*: Lequesne OA Severity Index (0–24); ≥5	Not specified	2–5 days	Not specified	None
Roth 2004[88]	'Flare'	*Pain:* WOMAC LK3.1 Pain subscale (0–20); increase≥2 points and ≥25%	*Pain:* WOMAC LK3.1 Pain subscale (0–20); score ≥ 'moderate' on at least 1 of the five items, pain score≥6	Washout period of at least 3 days/week past month	Not specified	Not specified	None
Rother 2007[91]	'Flare'	1. *Pain on walking:* VAS (0–100 mm); increase≥15 mm 2. *Global Assessment (patient):* 5-point LK; increase≥1 grade	1. *Pain on walking:* VAS (0–100 mm); ≥40 mm 2. *Global Assessment (patient):* 5-point LK; 3–5	Not specified	Not specified	Not specified	None
Schnitzer 2005[55]	'Flare'	No tool: increase in pain	*Pain:* VAS (0–100 mm); ≥40 mm	Not specified	24 hours	Not specified	None
Scott-Lennox 2001[56]	'Flare'	1. *Pain:* VAS (0–100 mm); ≥20 mm 2. *Pain (physician):* 4-point LK; worsening≥1 point 3. *Global Assessment (patient):* 4-point LK; worsening≥1 point 4. *Global Assessment (physician)*: 4-point LK; worsening≥1 point	1. *Pain:* VAS (0–100 mm); ≥40 mm at baseline) 2. *Pain (physician):* 4-point LK; ≥2 3. *Global Assessment (patient):* 4-point LK; ≥2 4. *Global Assessment (physician)*: 4-point LK; worsening≥2	14 days washout	Not specified	Not specified	Confirmatory Factor Analysis
Simon 2009[89]	'Flare'	*Pain:* WOMAC LK3.1 Pain subscale; increase≥2 and ≥25%	*Pain:* WOMAC LK3.1 Pain subscale; ≥ 'moderate' on ≥1 item	14 days washout	Not specified	Not specified	None
Silverfield 2002[57]	'Flare'	*Pain:* 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'	*Global Assessment (patient):* 5-point LK; increase≥1	1. *Global Assessment (patient):* 5-point LK; 'fair, poor or very poor' 2. *Pain*: (0–10 NRS); ≥4 but <9 3. *Global Assessment (physician)*: 5-point LK; 'fair, poor or very poor'	14 days washout	Not specified	Not specified	None
Weaver 1995[90]	'Flare'	1. *Global Assessment (physician)*: 5-point Likert; increase≥1 grade 2. *Global Assessment (patient)*: 5-point LK; increase≥1 grade 3. *Pain:* worsening pain on motion and weight bearing	1. *Global Assessment (physician):* 5-point Likert; ≥2 2. *Global Assessment (patient)*: 5-point LK; ≥2	2–14 days washout	Not specified	Not specified	None
Wiesenhutter 2005[59]	'Flare'	1. *Pain on walking on flat surface:* WOMAC VAS 3.0 Q1 (0–100 mm); increase≥15 mm 2. *Global Assessment (investigator):* 5-point LK; worsening≥1 unit	1. *Pain on walking on flat surface:* WOMAC VAS 3.0 Q1 (0–100 mm); ≥40 mm	Not specified	Not specified	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Williams 2001[60]	'Flare'	1. *Global Assessment (patient):* 5-point LK; increase≥1 point 2. *Global Assessment (physician)*: 5-point LK; increase≥1 point 3. *Composite Index*: Lequesne OA Severity Index (0–24); increase≥2 points	1. *Global Assessment (patient):* 5-point LK; '(fair), poor or very poor' 2. *Global Assessment (physician)*: 5-point LK; '(fair), poor or very poor' 3. *Composite Index*: Lequesne OA Severity Index (0–24); ≥7 4. *Pain:* VAS (0–100 mm); ≥40 mm	2–14 days	Not specified	Not specified	None
Wittenberg 2006[61]	'Flare'	*Pain:* VAS (0–100 mm); increase≥10 mm	*Pain:* VAS (0–100 mm); ≥40 mm	2–7 days washout	Not specified	Not specified	None
Yeasted 2014[62] (pooled, abstract)	'Flare'	*Pain:* 0–10 NRS; increase≥2 points over the mean pain score from the previous 3 days	*Pain:* average daily 0–10 NRS; 4–9	Not specified	Not specified	Not specified	None
Yocum 2000[77]	'Flare'	Disease activity 1. *Global (Investigator)*: reduction of ≥1 grade 2. *Global Assessment (patient)*: 100 mm VAS; increase of ≥10 mm 3. *Pain: overall assessment (patient):* 100 mm VAS; ≥35 mm	Not specified	≥3 days washout	Not specified	Not specified	None
Young 2014[63]	'Flare'	(3) *Pain:* WOMAC pain subscale; increase>15 mm	*Pain:* 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 days washout	Not specified	Not specified	None
Non-drug withdrawal study design							
Atukorala 2016[78] (abstract) Atukorala 2016[25] (abstract)	'Flare'	*Pain:* (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
Bartholdy 2016[79]	'Flare'	Not specified	*Pain:* (10-point NRS): Pain>5	Not specified	Not specified	Not specified	None
Bassiouni 2015[80] (abstract)	'Flare'	Not specified	*Global Assessment (physician):* KOFUS≥7	Not specified	Not specified	Not specified	None
Cibere 2004[86] Cibere 2005[87]	'Flare'	1. Patients perception of worsening of symptoms 2. *Pain walking on flat surface:* WOMAC VAS 3.0 Q1 (0–100 mm); increase≥20 mm 3. *Global Assessment (physician):* 5-point LK; worsening≥1 grade	Not specified	Not specified	Not specified	Not specified	Definition determined by study rheumatologists to be a clinically important change in WOMAC-Ehrich 2000/Bellamy 1998
Conrozier 2012[66]	'Flare'	Fulfilled four following criteria: 1. *Pain:* 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	*Pain intensity during physical activity:* VAS (0–100 mm); ≥40 mm	Not specified	48 hours	Not specified	None

Continued

Table 2 Continued

First author	Terminology used	Amount of change in symptoms/signs (symptom/sign: measurement instrument; operational definition)	Minimum absolute level of symptoms/signs (symptom/sign: measurement instrument; operational definition)	Speed of onset	Duration	Change in medication/healthcare use	Reference/rationale
Erfani 2014[44] abstract) Erfani 2014[81] (abstract) Ferreira 2016[82] Hunter 2014[83] (abstract) Makovey 2015[84] (protocol)	Exacerbation	*Pain:* VAS (0–100 mm); increase≥20 mm from mildest pain score reported at baseline	Not specified	Not specified	Not specified	Not specified	None
Jawad 2005[68]	Exacerbation	*Pain symptoms:* 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>20 min, 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. *Pain magnitude:* increase in pain or 'intense' or 'severe' level of pain	*Pain:* ≥40 of 100 mm or ≥4 of 10 on NRS	Patients described: 'Quick' or 'sudden'	Patients: 10 s to 15 min	Patients: rest or take additional medication	For investigator definition: Battisti 2004, Pareek 2010[28 53] Plus researchers own experience
Parry 2017[85]	'Flare'	*Pain:* recalled worst pain intensity in previous 6 months 0–10 NRS; ≥5	*Pain:* 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'	*Pain:* self-reported flare severity rating 0–10 NRS; increase≥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	*Pain:* 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 ≥5, a score corresponding to highest 33% of all WOMAC scores	Not specified	Not specified	Not specified	None
Zhang 2011[72] (abstract)	'Exacerbation'	*Pain:* WOMAC Pain score VAS (0–500); increase≥100 units	Not specified	Not specified	Not specified	Not specified	None
Zobel 2016[92]	Exacerbation	*Pain:* 0–10 NRS; increase≥2	Disabling pain	Not specified	8 hours	Not specified	None

COPD, chronic obstructive pulmonary disease; KOFUS, Knee Osteoarthritis Flare-up Score; LK, Likert scale; NSAID, non-steroidal anti-inflammatory drug; NRS, Numerical Rating scale; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3 Summary of number and type of single-item and multiitem measurement tools used

Single-item scales:	
Pain on activity:	WOMAC Q1 3.0 VAS 'pain on walking on a flat surface' (0–100 mm) (n=11) Pain on walking VAS (0–100 mm) (n=5) Pain on movement VAS (0–100 mm); ambulatory pain (5-point Likert); pain with physical activity VAS 11-point scale (n=2)
Pain (not further specified):	Pain VAS (0–100 mm) (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)
Multiple-item scales:	
	Lequesne OA Severity Index (n=5) WOMAC LK3.1 (0–20) (n=3) WOMAC LK Pain subscale (0–25); WOMAC OA Index Questionnaire (n=1); WOMAC knee pain score (0–500) [n=7]; KOFUS (0–14) (n=1)

KOFUS, Knee Osteoarthritis Flare-up Score; LK, Likert scale; N, number of included studies; OA, osteoarthritis; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

or very poor'.[29 30 45 73] The minimum threshold on the Lequesne index (0–10) was either 5[53] or 7.[46 51 60]

Flare definitions in non-withdrawal flare/discontinuation studies

Terminology used

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

Coverage of key components

Onset/worsening of symptoms and signs beyond normal day-to-day variability: 16 of 22 studies used onset or worsening of symptoms in their definition.[25 44 54 66 68 69 72 78 81–87 92] Two studies did not use pain intensity as part of its definition.[20 80] Three studies included symptoms other than pain in their definition.[20 66 68] These included nocturnal awakenings, effusion, morning stiffness, night pain, limping and warmth.

The study by Murphy *et al*[69] included an investigator definition of flare and 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),[25 54 65 78 85] WOMAC knee pain score VAS (0–500),[72] pain walking on a flat surface (WOMAC),[86 87] Global Assessment of Disease Status (physician) (5-point Likert scale)[86 87] and knee pain VAS not further specified (0–100).[44 81–84]

Temporal characteristics: only one study set a definition for speed of onset, describing this only as 'sudden' with no further specification.[66] Patients in the study by Murphy *et al* used the terms 'quick' and 'sudden' to describe flare onset.[69] Three studies specified a minimum duration of symptoms ranging from 8 to 48 hours.[20 65 67] In the study by Murphy *et al*, patients described duration between 10 s and 15 min.[69]

Change in medication/healthcare usage: no studies used change is medication or healthcare usage as part of their definition. However, in the study by Murphy *et al*, patients reported either taking rest or using additional medication.[69]

Additional domains: two studies defined distribution-based minimum thresholds for flare as the highest 30%[72] or highest 33%[73] of WOMAC Pain subscale scores among participants in the Longitudinal Examination of Arthritis Pain cohort (total score out of 50 was normalised to a 0–10 scale).

DISCUSSION

Flares in OA are recognised in existing clinical guidance[94] and reviews,[95 96] but typically merit little more than a passing mention. Our analysis of the definitions has resulted in the findings of common core domains, which will be useful for developing an agreed consensus

definition for OA flare. From a clinical perspective, a unified definition of a flare could enable clinicians to provide prompt, rationalised and focused treatment. This could also have implications for delivery of self-management strategies involving patients and how episodic management is advocated by clinical guidelines. Our review was motivated by an interest in seeking greater clarity on how these phenomena might be defined by undertaking a broad search strategy, noting that similar efforts have been pursued in other chronic diseases. While we found no current single, agreed definition of OA flare, our review of 69 published studies suggests a number of common domains, which may capture cardinal features. These were: onset/worsening of symptoms and signs, attainment of a minimum symptom threshold during flare, speed of onset/worsening and duration of elevated symptoms/signs. However, we found considerable variation in how these domains have been operationalised for measurement suggesting the need for further conceptual clarification and consensus.

Each potential cardinal feature of OA flare presents different challenges for achieving consensus. The goal of an agreed composite definition is to facilitate both reproducible and comparable research, while enabling more consistent recognition and identification of these phenomena in routine practice. The heterogeneity of OA should also be considered in any definition of a flare-up. Most studies included in our review required an increase in pain over 'usual' or 'baseline' intensity. Although this was measured using a wide range of measurement instruments, several studies selected an increase of 2 or more points on a 0–10 scale providing a possible starting point for consensus. Yet this possible 'signal' is arguably difficult to interpret without also considering the amount of background 'noise', that is, within-person diurnal[97] and day-to-day variability,[98] and the absolute level ('minimum threshold') of pain during a flare. There was general concurrence with the minimum threshold that was adopted, for example, 40 mm on a 0–100 mm scale and this may indicate the potential level of minimally important clinical difference. In the study by Marty *et al*, an increase in pain was not independently associated with flare-up after adjusting for other potential features.[20] However, the studies by Marty *et al*[20] and Scott-Lennox *et al*[56] were the only ones that had attempted to derive and/or validate a prediction model for OA flares. Interestingly, their approaches have not been widely adopted which suggests the complexity of reaching a widely accepted model. Further research on detecting flares over within-person 'normal' variability by collecting frequent repeated measures of pain intensity may be valuable but this approach would not be feasible when identifying flares presenting at the point of care in routine clinical practice. Instead, this may have to rely on the judgement of the patient and/or clinician, the approach used, for example, in defining exacerbations in COPD.[1] A similar consideration surrounds the speed of onset, which was not well defined by studies in our review. Drug withdrawal design studies specified washout periods between 2 and 15 days, but this is unlikely to be synonymous with speed of onset. The remaining studies used terms such as 'sudden' and 'quick'. In COPD, for instance, a judgement around 'acute onset' or 'sudden onset' appears to be acceptable for clinical recommendations, but we would add that the speed of onset of OA flares ought to be considered also in relation to underlying biologically plausible mechanisms. Indeed, presumed aetiology has been argued as a useful feature in defining acute exacerbations in COPD.[99] Minimum duration ranged from 8 hours to 5 days in our review; however, this was not widely reported. COPD definitions refer to a 'sustained worsening' of symptoms,[2] but does not appear to be a feature in other chronic diseases. A minimum duration in OA may help distinguish flares from day-to-day variability. Increase in medication was not found to be a key component in this review despite it being a feature in other chronic diseases such as AS,[5] SLE,[4 100] inflammatory bowel disease and[101] COPD.[1] Interference with function did not emerge strongly from our review as a cardinal feature of OA flare. In other chronic musculoskeletal conditions, such as back pain, interference with function was not shown to be significantly associated with having a flare-up[102] and this domain does not feature in the definitions of exacerbations or flares in diseases such as COPD,[1 2] asthma,[3] AS[5] or SLE.[4]

Our review has several strengths and some weaknesses that deserve attention. We adopted a broad search strategy, covering a wide range of databases, and featuring bibliography checks, contact with authors, inclusion of conference abstracts, no language restrictions and a minimal threshold (any description or definition of flare) for inclusion. Five studies that were included in a similar review by Cross *et al*[103] were not included in this study; four did not contain a clear definition of flare-up, including one which gave a definition of knee OA progression and the final paper by Sands *et al*[104] was not in our search but the original study was.[58] We did not, however, search the grey literature and we did not include some potential synonyms as search terms ('attack', 'episode', 'fluctuations'), although these terms appeared often to relate to comorbidities and other phenomena (eg, episodes of care) and would therefore have been a less efficient search strategy than relying on snowball references. Data extraction was performed by only a single reviewer. Nevertheless, we argue that our review provides a reasonably comprehensive summary of how 'flares' in OA have been described and defined in the medical literature. In comparison with the study by Cross *et al*,[103] our search strategy appeared comprehensive yet efficient—returning 69 included articles compared with 23. We feel that our review expands on the findings of the review by Cross *et al* and adds strength to this important area. The majority of studies describe experimental 'flare design' trials in which flares are induced by drug withdrawal prior to enrolment and randomisation. While intentional or unintentional reduction in usual analgesia may indeed be one trigger for flare, experimentally induced flares

should not be assumed to represent 'naturally occurring' flares. Flare design trials, for example, are unlikely to capture change in management or healthcare usage that may be a common consequence of OA flares—something that is included in flare definitions in other conditions such as AS,[5] SLE,[4 100] inflammatory bowel disease[101] and COPD.[1]

A systematic review such as this cannot hope to resolve the need for a common conception and definition of flares in OA. Definitions for exacerbations of disease states are generally reached through a long process of consensus exercises involving key stakeholders, experts and patients in addition to appraisal of relevant literature from studies using multiple methods.[6 8 105] However, we believe that a consensus definition that is reliable, valid and feasible and widely acceptable both clinically and for research purposes should now be sought. The cardinal features described in this review; onset/worsening of symptoms and signs, attainment of a minimum symptom threshold during flare, speed of onset/worsening and duration of elevated symptoms/signs could help start this discussion. Furthermore, observational studies with repeated measures could give an important insight into the nature of these phenomena.

CONCLUSION

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

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