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.

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, 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 gout9 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 trajectories11–15 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 reviews18 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

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.
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 osteoarthrits) 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, 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.

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. This approach was chosen as it allowed the words and text in the definitions to be synthesised to summarise findings. 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.
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, 225 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. The number of participants in each study ranged from 15 to 6085. Knee OA was defined by clinical and/or radiological criteria.

Twenty-one included mixed knee and hip OA groups. In total, 46 publications used a drug withdrawal RCT design, of which
| First author, year of publication | Setting, geographic location | Participants | Joint | Severity | Study design |
|---------------------------------|----------------------------|--------------|-------|----------|--------------|
| **Drug withdrawal design studies** |                           |              |       |          |              |
| Altman, 2015                     | Multicentre, recruitment not specified, USA | 403 males and females, ≥40 years | Knee and hip | KL grade 2–3 | RCT, flare design |
| Baer, 2005                      | 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                     | 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                   | 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, 2005; Bingham, 2011    | 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                   | Investigative sites; USA | 808 males and females, ≥40 years | Knee | ARA functional class, I, II or III | RCT, flare design |
| Bocanegra, 1998                 | 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                   | 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; (pilot studies)  | Community; USA | 30 males and females, mean age 62 years | Knee | KL=2 | Cohort design, flare design |
| Case, 2003                      | 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                      | 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                    | Clinical centres; USA | 219 males and females, ≥40 years | Knee | ARA functional class, I, II or III | RCT, flare design |
| Essex, 2012                    | Clinical centre; African-American, USA | 322 males and females, ≥45 years | Knee | ARA functional capacity classification I–III | RCT, flare design |
| Essex 2013                     | Hispanic population, 31 US centres | ≥45 years | Knee | ACR criteria, functional capacity classification I–III | RCT, flare design |
| Gibofsky, 2014                  | Not specified, USA | 305 males and females, 41–90 years | Knee and hip | KL 2–3 | RCT, flare design |
| Gineyts, 2004                   | 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                  | 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              | Investigative sites; USA | 617 males and females, ≥40 years | Knee | ARA functional class I–III | RCT, flare design |
| Hochberg, 2011                  | Centres; USA | 1234 males and females, ≥50 years | Knee | AOR functional class I–III | Pooled RCTs (2), flare design |
| Katz, 2010                      | 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                    | 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                    | Outpatient sites; USA | 1042 males and females, ≥40 years | Knee | ACR rating of I–III | RCT, flare design |
| Leung, 2002                     | Clinic; USA | 677 males and females, ≥40 y | Knee and hip | ARA functional class, I, II, or III | RCT, flare design |

Continued
| First author, year of publication | Setting, geographic location | Participants | Joint | Severity | Study design |
|----------------------------------|----------------------------|-------------|-------|----------|--------------|
| **Luyten, 2007**<sup>45</sup>  | Centres; Belgium           | 181 males and females, ≥40 years | Knee and hip | ACR functional capacity classification I–III | RCT, flare design |
| **Manicourt, 2005**<sup>47</sup> | 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**<sup>48</sup> | Not specified, USA         | 15 males and females, ≥45 years | Knee | KL 2–3 | Observational, flare design |
| **McIlwain, 1989**<sup>49</sup> | 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**<sup>50</sup> | 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 |
| **Moskovitz, 2005**<sup>51</sup> | Investigative sites; USA  | 530 males and females, ≥45 years | Knee | ACR functional capacity classification I–III | RCT, flare design |
| **Paepke, 2009**<sup>52</sup>  | Multicentre study, India  | 199 males and females, 40–70 years | Knee | Lequesne criteria, score of 5 and above | RCT, flare design |
| **Paepke, 2010**<sup>53</sup>  | Hospital; India           | 220 males and females, 40–70 years | Knee | Clinical and radiological evidence of OA severity not defined | RCT, flare design |
| **Roth, 2004**<sup>54</sup>    | 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**<sup>55</sup>  | Outpatient units; Germany | 397 males and females, ≥40 years | Knee | KL 2–3 | RCT, flare design |
| **Schnitzer, 2005**<sup>56</sup> | 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**<sup>57</sup> | Investigative sites; USA  | 182 males and females, mean age 61 years | Knee | Not defined | RCT, flare design |
| **Silverfield, 2002**<sup>58</sup> | Centres; USA              | 308 males and females, 35–75 years | Knee and hip | Clinical evidence of OA, severity not defined | RCT, flare design |
| **Simon, 2009**<sup>59</sup>   | 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**<sup>60</sup>  | 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**<sup>61</sup>  | Investigative sites; USA  | 328 males and females, >50 years | Knee | ACR clinical criteria, diagnostic | RCT, flare design |
| **Wiesenbutter, 2005**<sup>62</sup> | 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**<sup>63</sup> | 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**<sup>64</sup> | 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 |
| **Yeeasted, 2014**<sup>65</sup> | (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**<sup>66</sup>   | 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**<sup>67</sup>   | Multicentre               | 305 males and females, ≥40 years | Knee or hip | KL 2–3 | RCT, flare design |
| **Zhao, 1999**<sup>68</sup>    | Centre (not specified); USA, Canada | 1004 males and females, ≥18 years | Knee | ACR functional capacity classification I–III | RCT, flare design |

**Table 1 Continued**
| First author, year of publication | Setting, geographic location | Participants | Joint | Severity | Study design |
|----------------------------------|----------------------------|--------------|-------|----------|--------------|
| **Non-drug withdrawal design studies** | | | | | |
| Atukorala, 201678 (abstract) | Not specified, USA+Australia+Sri Lanka | 213 males and females, mean age 62 years | Knee | Not specified | 3-month, web-based longitudinal follow-up study |
| Atukorala, 201625 (abstract) | OA outpatient clinic, Denmark | 131 males and females, ≥40 years | Knee | Radiographic evidence of OA (severity not defined) and BMI between 20 and 35 kg/m² | RCT |
| Bassiounei 201530 (abstract) | Not specified, Egypt | 60 participants not further specified | Knee | Not specified | Observational |
| Cibere, 200486 Cibere, 200577 | 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 |
| Conozier 201288 | 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 200567 | Hospital-European multicentre | 600 males and females, ≥18 years | Knee | KL grade 1–4 | Observational |
| Erfani, 201445 (abstract) Erfani, 201445 (abstract) Ferreira, 201645 | Australia | 268 males and females, mean age 62 years | Knee | ACR criteria, meet at least one, KL≥2 | Web-based crossover |
| Hunter, 201483 (abstract) Makovey, 201584 (protocol) | | 345 males and females, ≥40 years | Knee | ACR criteria, meet at least one, KL≥2 | Web-based crossover |
| Jawad, 200568 | GPs in France | 3000 (for GP study) males and females | Knee | Not specified | n/a, review of surveys. Definition relates to survey of 3000 French GPs |
| Marty 200949 | 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, 201526 | Community based, pain clinics; USA | 45 males and females, 37–83 years | Knee | ACR criteria, severity not defined | Qualitative |
| Panry, 201475 | Community, UK | 719 males and females, ≥50 years | Knee | Self-reported knee pain in previous 12 months | Observational |
| Ricci 200574 | Community, USA | 329 males and females, 40–65 years | Knee and hip | Clinical evidence of OA, severity not defined | Nested case-control |
| Wise 201076 | 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 200971 | 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 201177 (abstract) | Not specified | 52 males and females, median age 63 years (50–72 years) | Knee | KL≥2 | Case-crossover |
| Zobel 201652 | 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, Kellgren and Lawrence; RCT, randomised controlled trial.
were pooled studies and 1 used a cohort drug withdrawal design (table 1). The remaining 22 publications included 17 observational studies, 3 RCTs, and 1 qualitative interview study. Nine of the included studies were abstracts. Two abstracts were removed as the corresponding full-text article was available. Studies using pooled data or the same dataset were included if they used different definitions of OA flare.

Rationale given for flare definitions

Six of the included studies gave rationale for the definition used. None of the definitions was based on a consensus procedure. The studies by Marty et al and Scott-Lennox et al were the only ones that undertook empirical investigation of flare definitions. The study by Marty et al 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 dermatologist database. Pain was not included in the final model.

Scott-Lennox et al 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.

Gibere et al 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 was informed by two studies, which used a drug withdrawal design and from the research team’s own experience. Ricci et al 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 and 1 survey. Nine of the included studies were abstracts. Two abstracts were removed as the corresponding full-text article was available. Studies using pooled data or the same dataset were included if they used different definitions of OA flare.

| Coverage of key components |
|-----------------------------|
| **Onset/worsening of symptoms and signs beyond normal-dy-to-day variability:** forty-four studies included onset or worsening of signs and symptoms as part of their definition. All studies included increased pain intensity in their definition. A further two 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) and the Investigator Assessment of Disease Status (n=11). Thirty-four studies used only single-item measurement tools, five used multitem and five used both single-item and multitem tools. |

In addition, the format of global ratings appears to be variable as is use and reporting of the WOMAC. 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.

Four studies specified a time period for minimum duration of symptoms, which ranged from 24 hours to 5 days.

**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’.

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. 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’ and 4 of 14 studies using the Patient Global Assessment of Disease Status.
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 2004 | ‘Flare’ | Pain: WOMAC Pain subscale (0–100); increase≥15mm | Pain: WOMAC Pain subscale; ≥40mm | Not specified | Not specified | Not specified | None |
| Baer 2005 | ‘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 | ‘Flare’ | Pain on movement: VAS (0–100mm); increase≥5mm | Not specified | 1 week washout | Not specified | Not specified | None |
| Battisti 2004 | ‘Flare’ | Global assessment (investigator): single item, 5-point LK; worsening≥1 point | Pain: VAS (0–100mm); ≥40mm | Not specified | Not specified | Not specified | None |
| Bingham 2007, Bingham 2011 | ‘Flare’ | 1. Pain walking on flat surface: WOMAC VAS 3.0 Q1 (0–100); increase≥15mm 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): WOMAC VAS 0–1000; ≥40 mm (acetaminophen users only) | Not specified | Not specified | Not specified | None |
| Birbara 2006 | ‘Flare’ | 1. Pain walking on flat surface: WOMAC VAS Q1 (0–100); increase≥15mm 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); ≥40mm 2. Global assessment (investigator): single item, 5-point LK; fair, poor, very poor (paracetamol arm only) 3. Composite index: Lequesne OA Severity Index (0–24); ≥7 | 4–15 days washout | Not specified | Not specified | None |
| Bocanegra 1998 | ‘Worsening of symptoms’ | Two out of the following three: 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; 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 | ‘Flare’ | 1. Pain walking on flat surface: WOMAC VAS Q1 (0–100); increase≥15mm 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 2003 (pilot studies) | ‘Flare’ | Not specified | Pain: WOMAC LK Pain subscale (6–25); ≥15 points | Five half-lives of NSAID washout | Not specified | Not specified | None |
| Case 2003 | Not used | 1. Pain walking on flat surface: VAS (0–100mm); increase≥10mm 2. Ambulatory pain; single item, 5-point LK; worsening≥1 point | Not specified | 14 days washout | Not specified | Not specified | None |

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[7] | 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 |
| Ehrlich 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[36] | ‘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 |
| Gubofsky 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’ | 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 |
| Gottlieber 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[44] | ‘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 |
| 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<sup>45</sup> | ‘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<sup>46</sup> | ‘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’  
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<sup>47</sup> | ‘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<sup>48</sup> | ‘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<sup>49</sup> | ‘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<sup>50</sup> | ‘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<sup>51</sup> | ‘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 |
| Paireek 2009<sup>52</sup> | ‘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 |

Table 2 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 201053 | '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 200448  | 'Flare'          | Pain: WOMAC LK3.1 Pain subscale (0–20); increase≥2 points and ≥25%  1. Pain on walking: VAS (0–100 mm); increase≥15 mm  2. Global Assessment (patient): 5-point LK; increase≥1 grade | 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 | Not specified |
| Rother 200791 | '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 | Not specified | Not specified | Not specified | None |
| Schnitzer 200555 | 'Flare'          | No tool: increase in pain  1. Pain: VAS (0–100 mm); ≥40 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 |
| Scott-Lennox 200156 | 'Flare'        | Pain: no measurement tool; significant increase  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  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 | None |
| Simon 200999 | 'Flare'          | Pain: WOMAC LK3.1 Pain subscale; increase≥2 and ≥25%  1. Pain: WOMAC LK3.1 Pain subscale; ≥40 mm  2. Pain: WOMAC LK3.1 Pain subscale; ≥'moderate' on ≥1 item | Pain: WOMAC LK3.1 Pain subscale; ≥40 mm  2. Pain: WOMAC LK3.1 Pain subscale; ≥'moderate' on ≥1 item | 14 days washout | Not specified | Not specified | None |
| Silverfield 200257 | 'Flare'        | 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 201158 | '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’ | 1. Global Assessment (patient): 5-point LK; ≥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 | None |
| Weaver 199592 | '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 200599 | '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
| 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     | '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   | '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      | '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        | '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        | 'Flare'          | (3) Pain: WOMAC pain subscale; increase≥15 mm                                                                             | Pain: WOMAC Pain subscale≥40 mm                                                                   | Not specified   | Not specified | Not specified | None                                |
| Zhao 1999         | '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    | '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    | 'Flare'          | Not specified                                                                                                             | Pain: (10-point NRS); Pain≥5                                                                     | Not specified   | Not specified | Not specified | None                                |
| Bassiouuni 2015   | 'Flare'          | Not specified                                                                                                             | Global Assessment (physician): KOFUS≥7                                                           | Not specified   | Not specified | Not specified | None                                |
| Cihee 2004        | '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 | None                                |
| Cihee 2005        | '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                                |
| Conzozier 2012    | '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   | 'Flare'          | Pain intensity during physical activity: VAS (0–100 mm); ≥40 mm                                                             | Not specified                                                                                     | 48 hours        | Not specified | Not specified | None                                |

Table 2 Continued
| First author (year) | 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 (abstract) | Exacerbation | Pain: VAS (0–100 mm); increase ≥20 mm from mildest pain score reported at baseline | Not specified | Not specified | Not specified | None |
| Erfani 2014 (abstract) | | | | | | |
| Ferreira 2016 (abstract) | | | | | | |
| Hunter 2014 (abstract) | | | | | | |
| Makovey 2015 (abstract) | Exacerbation | Pain: symptoms increased morning stiffness, night pain and synovial fluid effusion | Not specified | Not specified | Not specified | None |
| Jawad 2005* | Exacerbation | | | | | |
| Marty 2009* | ‘Flare’ | No measurement tool: morning stiffness ≥20 min, nocturnal awakening, limping, knee swelling, increased warmth, effusion | Not specified | 48 hours | Not specified | Regression analysis of cross-sectional data to validate proposed flare criteria |
| Murphy 2015* | ‘Flare’ | 1. Investigator definition: inadequate pain relief for an episode of intense pain that is usually brought on by too much activity | Patients described: ‘Quick’ or ‘sudden’ | Patients: 10 s to 15 min | Patients: rest or take additional medication | For investigator definition: Battisti 2004, Pareek 2010* Plus researchers own experience |
| Parry 2017* | ‘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 | Based on previous studies defining knee flares in OA and flares in diseases such as back pain and COPD |
| Ricci 2005* | ‘Flare-up’ | Pain: self-reported flare severity rating 0–10 NRS; increase ≥2 point over usual pain severity | Not specified | Not specified | Not specified | Based on statistical analysis and clinical judgement |
| Wise 2010* | ‘Flare’ | | | | | |
| Zhang 2009* | ‘Exacerbation or flare’ | | | | | |
| Zhang 2011 (abstract) | ‘Exacerbation’ | Pain: WOMAC Pain score VAS (0–600); increase ≥100 units | Not specified | Not specified | Not specified | None |
| Zobel 2016* | Exacerbation | Pain: 0–10 NRS; increase ≥2 | Disabling pain | Not specified | 8 hours | None |

Note: 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.
or very poor’. The minimum threshold on the Lequesne index (0–10) was either 553 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 studies20 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 al69 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), 96 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 10s and 15min.69

Change in medication/healthcare usage: no studies used change in 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 guidance94 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.

| 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 Disease Status (n=2); Investigator Assessed Pain Grade; (Physician) Overall Disease Activity (0–100); Physicians Pain Assessment (4-point Likert) (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.
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 diurnan and day-to-day variability, and the absolute level (‘minimum threshold’) of pain during a flare. There was general concurrence with the minimum threshold that was adopted, for example, 40mm on a 0–100mm 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. However, the studies by Marty et al and Scott-Lennox et al 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 with-in-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. 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. 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 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, inflammatory bowel disease and COPD. 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 and this domain does not feature in the definitions of exacerbations or flares in diseases such as COPD, asthma, AS or SLE.

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 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 was not in our search but the original study was. We did not, however, search the grey literature and we did not include some potential synonyms as search terms (‘attack’, ‘epis ode’, ‘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, 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, SLE, inflammatory bowel disease and COPD.

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. 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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