Methods for studying naturally occurring human pain and their analogues

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Running Head: Methods for investigating pain

Keywords: Methods; everyday pain; experiment

COI: The authors have no conflicts of interest in this work.

Number of pages: 48

Number of tables: 1

Abstract

Methods for investigating human pain have been developed over the last 100 years. Typically researchers focus on people with clinical pain, or on healthy participants undergoing laboratory controlled pain-induction techniques focussed mostly on exogenously generated skin nociception. Less commonly investigated are acute pain experiences that emerge naturally. Six common painful complaints were identified: headache, muscular pain, visceral pain, menstrual pain, dental pain, and pain associated with Upper Respiratory Tract Infection. Methods used to recruit participants with the natural occurrence of each pain complaint were identified, and features of their use reviewed. Also reviewed were experimental analogues designed to mimic these pains, with the exception of menstrual pain. Headache and menstrual pain appear to be most effectively researched in their naturally occurring form, whereas muscle and dental pain may be more easily induced. URTI and abdominal pain provide further challenges for researchers. Summary guidance is offered, and directions for methods development outlined.

1. Introduction

Human pain research relies on the artificial production of pain in experimental or clinical environments. Popular and well validated techniques include exposure to exogenous thermal, mechanical, chemical, and electrocutaneous stimulation (e.g., [26; 32; 49; 119]). The relative merits and challenges of each approach have been considered extensively elsewhere (e.g., [92]). Controlled nociceptive stimulation techniques used in the laboratory often produce very brief and spatially distinct stimuli. Most techniques are delivered exogenously and are focussed on skin nociceptor activation. Naturally occurring pain is often endogenous, of longer duration, can be diffuse, and typically involves multiple pain systems. Additionally, the experimenter introduction of pain is normally done to ethical standards that mitigate the threat of the pain, fundamentally altering the emotional and motivational significance of pain, arguably a key feature of pain that emerges naturally [21]. There are many benefits of standard laboratory techniques, not least their well validated performance and stable replication across settings and populations. The cost of such control, however, is the potential lack of relevance to naturally occurring pain, [91; 93]. The methodological challenge is to recruit people with the pain of interest or to develop techniques that combine the benefits of laboratory control with the relevance of pain that emerges naturally.

The primary aim of this investigation was to review the range of possible methods used for conducting research into common naturally occurring pains. We first included sampling methods in which people with pain of interest are recruited into studies. Second, because it is not always possible to recruit people with pain we

investigated analogue methods of pain production. Analogues are defined as techniques developed explicitly to mimic pain, in which the resulting pain is judged to be the same as or close to that which might naturally occur. We excluded from our investigation the laboratory methods of pain induction that are not common naturally occuring human pain experiences (e.g., electrical pain induction, cold pressor, thermal plate induction, etc). Here we are interested to capture and critically appraise innovations in methods that can be used in the study of pain that emerges, occurs, or is delivered in everyday environments.

2. Methods

A narrative approach was adopted, using bibliographic abstracting services (PubMed, PsychInfo) to identify papers that might contain details about recruitment protocols, as well as methods of natural pain induction. Our approach was deliberately narrative rather than systematic because we were interested in reporting with equal emphasis both common and unusual methods. We were not concerned with the primary results of the studies reported, only in the operation of their methods. As our goal was to focus on common painful conditions we selected headache, muscular pain, visceral (abdominal) pain, menstrual pain, and dental pain. We also included pain associated with upper respiratory tract infections, e.g., ‘sore throat’ [121; 122].

All methods reported were categorized into one of these six pain conditions. Reference sections from identified publications were searched for unidentified further publications. Citation searches using Web of Knowledge were also undertaken to attempt to identify further use of methods. For the recruitment methods part of the review, we categorised approaches based on how the sample was identified and

participants recruited. These typically fell into one of four approaches: (1) identifying those with the relevant pain e.g., from locations where people seek analgesia, (2) identifying those about to experience the pain e.g., those scheduled to undertake painful non-clinical procedures, (3) identifying people at risk of pain e.g., recruiting those who report frequent complaints such as headache, or (4) by recruiting a normal sample of people and following them moment to moment, recording pain episodes as they arise [115].These approaches were appraised in terms of ease and effectiveness within each condition. For the pain induction analogue part of the review, methods were considered where there was any systematic attempt to experimentally control or induce one of the six naturally occurring pain conditions. These can involve inducing the exact pain under investigation, as in pains that arise from exertion, or those studies that were designed to be close to the naturally occurring experience.

For each of the main types of pain, we start by providing a brief description of the condition. Next we consider the recruitment methods by which each pain condition has been examined. Where relevant we then consider analogue versions of each pain type. All methods are appraised for their performance as a method of pain investigation, with particular regard to experimental controllability, relevance to naturally occurring pain, and novelty.

3. Results

3.1. Headache

Description and incidence of headache: Headache is a common painful complaint [109; 111; 116]. Based on a UK community based sample an estimate of 38.7% of the population (99% CI 26.2-41.3%) could be considered to have had

headache symptoms within the previous two weeks [75]. The International Headache Society recognizes at least 14 separate forms of headache, including migraine, cluster headache, headache attributed to substance withdrawal and headache attributed to infection [40]. The most prevalent form is 'tension type headache' [86] with a lifetime prevalence of 66% with incidence rates for migraine in the region of 12-23% [42; 86; 108].

Recruiting people with headache: Most headache studies either recruit people who self-identify as frequent headache sufferers (e.g., [39]), or those deemed at risk of frequent headaches (e.g., [44; 66; 99]). Criteria for inclusion vary, but often involve the use of standardized assessment tools. As a typical example, Kuhajda et al. [66] recruited participants from the community who met the criteria for frequent tension type headaches as defined by the Headache Classification Subcommittee of the International Headache Society [40]. Their recruitment strategy involved university participant pools, medical referrals and community advertisement.

Some studies recruit people when they experience headache. Such approaches have traditionally been difficult to administer and participant withdrawal or loss from protocol is high. However, recent technological developments in mobile computing [56], and increased use of Ecological Momentary Analysis (EMA) have meant that it is possible to administer core tests remotely, at the point at which pain begins. EMA is a diary based method in which target events are recorded either when they occur or at a particular time [101]. For example, Kikuchi et al. [57] asked chronic headache sufferers to complete watch-triggered electronic diaries four times a day for seven days, with additional entries being made for headache events. Of the 44 participants

recruited, four did not complete the entries well enough to be included in the analysis, suggesting that the intensive nature of the method, even in short duration, can lead to attrition.

Rarely used as a method is the recruitment of people who present with headache seeking analgesia. For example, common headache treatments are available ‘over-the-counter’ in many countries and ‘point of sale/collection’ may be an alternative method of ensuring a broader population. The problem (or perhaps advantage) with these approaches is that one recruits from a specific population who have a greater than average number of headaches, and who identify as sufferers.

Analogue versions of headache: Muscle tensing techniques have been used to induce tension type headaches [14; 50; 80]. Christensen et al. [14], for example, asked participants to perform static isometric contractions of the trapezius muscle by raising the shoulders with 10% of maximum force for 30 minutes. Within 24 hours this technique had induced a tension type headache in 60% of tension type headache sufferers and 20% of controls. Similarly, Neufeld, Holroyd and Lipchick [80] instructed participants to perform tooth clenching for three 10 minute periods. Within 20 hours this technique had induced a tension type headache in 50% of tension type headache sufferers and 30% of controls, with the peak time for headache in controls being at 2 hours post induction. Whilst these studies appear to indicate that induction of headache pain is possible, the percentage of participants who experienced headache as a result of these protocols was small (20-30%). In addition the time between induction and maximal headache sensation was at least 2 hours and as much as 24 hours. Pragmatically this makes these techniques difficult to use because their

unpredictable timing and effectiveness are prohibitive. It also seems as if headache induction is less easily achieved using these approaches in non-headache sufferers.

There are other methods that could be used to induce headache. For example, physical exertion, including exercise is known to induce headaches [40]. However, we are not aware of this approach being used as a specific pain induction procedure. Another example of headache induction can be seen in studies that report headache as an adverse effect of certain drugs [96]. Interestingly, some pharmacologically induced headaches seem to be clinically indistinguishable from spontaneous migraine [45]. This approach has been utilized mostly within studies that pharmacologically induce migraines within migraine sufferers. For example, Kruuse, et al. [65] administered Sildenafil to patients with a history of migraine. Sildenafil resulted in a migraine similar to the participants' usual migraine in 10 of the 12 participants, whereas only 2 of the 12 participants experienced a migraine after the placebo. Others have examined withdrawal headache following chronic caffeine usage, which is of interest given this drug has analgesic properties [94]. This suggests that a drug induction procedure may be more successful than muscular techniques for experimentally inducing headache, although this is untested.

Summary and appraisal of methods: Headache is common, and there are internationally accepted criteria to measure the quality and the intensity of headache. However, the time of onset and duration of headaches are difficult to predict. It is possible to recruit people with headaches, as well as identify those at risk of frequent headache. An alternative, but rarely used method, is to recruit people who seek out

over-the-counter analgesics for headaches. Although those who purchase may not necessarily be those who require treatment and may not be in pain at the time, this may be worth further investigation, especially in light of recent technological developments that allow for remote measurement. In terms of developing experimental analogues of headache, techniques of pain induction have been developed but with variable success. Therefore, for headache, optimal methods for most studies are likely to be a mixed strategy of recruiting people either when they are in pain, by site or by EMA, or focussing on those who frequently report pain.

3.2. Muscle pain

Description and incidence of muscle pain: The human body has nearly 700 separate skeletal muscles, which are highly innervated [117]. Muscle pain relates to locomotor disturbance (e.g., trips and falls), exertion (e.g., exercise, lifting, etc), inflammation (e.g., post exercise muscle inflammation), or inactivity (e.g., immobilisation). The sensory manifestation of muscular pain is reported to be a cramp–like, diffuse, aching sensation [77]. Acute musculoskeletal pain is very common with annual incident rates of 48% in men and 60% in women [48] and an approximate annual incidence for muscle cramps of 36% [47]. In its chronic form, musculoskeletal pain complaints such as back pain, neck pain, and shoulder pain, are also very common [16; 28] [64].

Recruiting people with muscle pain: Given the prevalence of chronic musculoskeletal pain conditions a common method of sampling is to recruit those identified as patients (e.g., [126]). However, recruiting patients with acute muscle pain is more challenging. There are clinical examples where people are recruited when

currently in pain, as well as being recruited at point of analgesia. For example, Warburton et al. [124] recruited participants who presented to primary care for leg cramps into a study examining the effects of quinine in treating their condition. Other examples include Ylinen et al. [126] who recruited people with neck pain at first attendance in an occupational health site, and Kasch, Stengaard-Pedersen, Arendt-Nielsen and Jensen [53] who recruited those with various musculoskeletal injuries at the Emergency Room.

Somewhat surprisingly we found few studies that employed a systematic pre-injury recruitment strategy. The identification of 'at risk' groups does not seem to be a common approach for identifying those prone to acute muscle pain. This is surprising given that within the sports and exercise literature there is considerable interest in the causes and consequences of muscle impairment. Indeed a number of risk factors have been identified for musculoskeletal pain including poor trunk muscle strength, depression, pre-existing musculoskeletal pain and increased spine mobility [68]. Rarely used, and worthy of further exploration, is the recruitment of populations at risk of sports-related muscle pain. For example, an estimated 36,000 people ran the 2012 26.2 mile London marathon, with similar numbers running the New York marathon. One study estimated that 419,000 people finished marathons in the US in 1998, and predicted that figures will increase to almost 700,000 people by 2010 [13]. Given a dropout rate in training reported to be 30–50%, with the most common reason being injury [15; 27], recruiting from mass involvement amateur sports events such as running races can be an useful technique. We know of only one study to use such a

strategy; they tested the efficacy of Acetaminophen on muscle soreness post marathon running and successfully recruited over 600 participants [84].

Analogue versions of muscle pain: There are examples of analogues of muscle pain [33]. Endogenous techniques involve the induction of pain by natural stimuli, and include ischemic stimulation and exercise-induced pain. The ischemic stimulation method involves the temporary disruption of blood flow to the muscle, via the application of a tourniquet and asking participants to perform a series of muscle contractions [72]. This leads to a painful sensation through the entire occluded limb (e.g., skin, muscle, periosteum). The advantages of this technique are that it provides an immediate pain sensation of the same quality as that experienced naturally. The difficulty however is that it requires participants to make sub-maximal muscle contractions which may be difficult to accurately reproduce and may be unreliable between participants.

An alternative is exercise-induced muscle pain. This is achieved through concentric muscle work, usually resulting in short lived pain due to reduced blood flow during exercise [33]. Exercise has been used to induce Delayed Onset Muscle Soreness (DOMS) (e.g., [3; 6; 81]), with a peak being reached at about 24 hours post exercise [3]. For example, Bakhtiary, Safavi-Farokhi and Aminian-Far [4] instructed participants to walk downhill on a 10^0 declined treadmill for 30 minutes at a constant speed of 4km/h. This not only resulted in muscle soreness, lower pressure pain thresholds and a decrease in maximum isometric contraction force, but was sensitive to moderation from a pre-trial vibrotactile stimulation. A similar design was used by Blacker et al. [6] who asked participants to walk for 2 hours carrying a 25kg backpack

at 6.5 km/h. This resulted in a significant decrease in maximum force contraction, however data for pain levels were not reported. These studies suggest that there are a number of potential exercise methods for inducing DOMS experimentally. While exercise induced pain may seem a good model of muscle pain there are some issues to consider. For example, Graven-Neilsen and Arendt-Neilsen [33] note that there is often no pain at rest and so either an external pressure stimulus or further exercise is needed to restart the pain sensation. Additionally the method of exercise induced pain relies on participants exerting maximal force as a standardisation measure, making inter-participant comparison difficult.

An alternative to these endogenous methods are those that induce pain through the application of an external stimuli, such as intramuscular electrical stimulation. The advantages are that they offer reliability, reproducibility and tissue site specificity, although there are problems with muscular spasm [69; 70]. Some of these problems can be overcome, and deeper pain sensations achieved using electrocutaneous stimuli. By placement of an electrode over the posterior tibial nerve and stimulating at a maximum tolerable level significant muscle cramp can been induced [110]. Mechanical stimulation methods using pressure can also be applied in a reproducible fashion to a specific site [26; 49]. However, this also has limitations, in that stimulation of both the muscle and skin occurs. Attempts to counter these unwanted effects include the use of local anaesthetic to reduce skin sensitivity [35; 62].

Exogenous techniques that allow for deeper pain sensations include chemical pain induction by intramuscular injection of algogenic substances [36]. The most frequent substance is hypertonic saline, as the pain is comparable to acute clinical

muscle pain [54; 113]. These models are useful because they result in a referred pain sensation which allows for models of clinical conditions such as fibromyalgia, ‘whiplash’, and osteoarthritis to be examined. Additionally through consistent infusion a repeatable sensation can be achieved. It is also possible to induce muscle cramps by injection of glutamate into myofascial trigger points which is not present with isotonic saline [30]. The disadvantages associated with this technique include a lack of control over the timing of the pain, with hypertonic saline resulting in a few minutes of pain. Induced muscular heat pain has also been suggested as a method for pain induction by either injection of heated isotonic saline [34] or focused ultrasound [17; 125]. The advantages of these approaches are that they can be used to induce a pain within the joints which offers a model of frequently experienced joint pain not offered by a number of other endogenous techniques

Summary and appraisal of methods: Despite the high incidence of acute muscle pain, this is not an area that seems to have been well used. Although muscle pains are common, there is a large variety of presentation. It may be possible to recruit from populations that are at risk of muscle pain and/or injury e.g., endurance sport competitors. New assessment and measurement technologies may open avenues for investigating muscle pain in more detail. Despite the difficulties associated with recruiting into muscle pain studies, there are many experimental analogue techniques that have been used. Numerous techniques are in common use, which include a range of highly controllable and reliable approaches.

3.3. Visceral pain

Description and incidence of visceral pain: Visceral pain is a common reoccurring problem, and includes conditions such as irritable bowel syndrome, dyspepsia, recurrent abdominal pain, angina pectoris, appendicitis, etc [7; 85]. Visceral pain has a similar quality to muscle pain as it is reported to be ‘deep’ ‘grinding’ and ‘aching’, often with associated vascular and gastric problems. In adults, incidence rates are high, with almost 50% of people reporting some abdominal symptoms lasting at least a day within a year [114].

Recruiting people with visceral pain: At risk and self-identified sufferers are the most common form of participant recruitment, and the same benefits and risks apply as with other populations. For example, in the chronic case Posserud et al. [83] recruited self-identifying referrals of individuals with gastrointestinal (GI) complaints. By contrast Cain et al. [12] report a study in which people with recurring stomach pain were recruited using only a community advertisement approach.

Recruitment of people with clinically less complicated stomach pain is more difficult. We found no studies which recruited participants in acute pain as a result of stomach cramps or dyspepsia or any other clear acute visceral pain condition in the absence of a long term clinical history. We are unclear whether this approach is simply untried, or has been attempted and not reported due to practical difficulties. If these methods are possible then there is currently little or no guidance on how this can be done.

Analogue versions of visceral pain: A number of methods have been developed to induce and control visceral pain. Techniques can be split into those that induce pain through upper or lower abdominal regions. Lower abdominal pain has most commonly

been induced by stretching of the colon through the inflation of a balloon in the rectal passage [8]. For example, Ritchie [90] examined the effects of the inflation of a balloon in the lower GI tract. When the balloon was inflated to 100-150ml of air 56% of the healthy participants reported a painful sensation.

Upper abdominal pain can also be experimentally induced. For example, Kingham and Dawson [58] describe a study in which a latex balloon was swallowed and inflated, producing a pain sensation similar to that reported in naturally occurring GI pain. Bradette, Pare, Douville and Morin [10] also examined upper GI stimulation, by inserting a balloon at the gastric side of the lower oesophageal sphincter, which was found to successfully induce pain in both patients and healthy participants. These techniques seem to be particularly useful for those interested in studying sensations of fullness, pressure and general pain. Other GI pain sensations, such as those commonly associated with acid reflux, have been developed. For example, Hammer and Vogelsang [38] suggested using capsaicin to improve gastric models of induced pain. They infused capsaicin into either the mid duodenum or jejuna, where discomfort was reported after 8.9 minutes and 15.8 minutes, respectively. The infusion of capsaicin resulted in a qualitatively different pain sensation, with greater stinging, warmth and cramps being reported. These upper and lower GI distension studies succeed in inducing an internal dull sensation which may provide a good model for visceral pain. The challenges of this approach however are that they are invasive and require expertise and specialist equipment. In addition participant recruitment can be adversely affected by the embarrassing nature of some techniques.

A final method that has been used within pediatric abdominal pain studies is the water load test, which has been developed from clinical studies of gastric myoelectrical activity [60; 61]. For example, Walker et al. [123] asked children aged 8-16 to drink water through a straw from a bottle which could not be seen by participants (to ensure there were no visual cues to the amount of water consumed) until 'completely full'. Increased pain was found in both healthy children and those with abdominal pain conditions. This method appears to induce pain which has a quality similar to recurrent abdominal pain. This pain/discomfort however is not very intense and lasts only a short time, making this an unappealing method for pain induction. An adult version of water loading has been reported, in an analogue of bladder pain [71]. Participants were asked to drink 250ml of water every 15 minutes until they were unable to resist the urge to urinate. After each 15 minute period participants were asked to rate their desire to void, pain and discomfort. This technique was successful in inducing a pain sensation in participants, however the average time to reach this peak pain was on average two hours and 20 minutes.

Summary and appraisal of methods: For some visceral pains there are relatively good standard descriptions and typologies that allow for control over heterogeneity of samples via selection. It seems that there are good experimental methods for inducing pain sensations similar to those experienced by people with naturally occurring painful abdominal conditions. Although stimulation of the GI tract may be common, this technique is highly invasive and does not allow participants to perform many additional tasks during induction. Water loading tasks are emerging as potentially useful methods.

3.4. Menstrual pain

Description and incidence of menstrual pain: Menstrual-related pain is common, and characterised by abdominal pain (e.g., bloating, cramping), as well as headache, lower-back pain, and breast tenderness. Some women also report emotional changes across the menstrual cycle, including depression. Incident rates of menstrual-related pain are wide ranging, and depend on how symptoms are defined. Studies suggest that up to 80% of women report menstrual-related pain [19; 103], although figures can depend on how symptoms are defined.

Recruiting women with menstrual pain: Investigations into menstrual-related pain have tended to recruit from either a general adult female population or to focus on those who suffer from more extreme recurrent cyclical pain. Recruiting from the general population has all the advantages of a large participant pool. Given the provision of over-the-counter medications, some branded for menstrual pain, it could be possible to recruit women in pain at the point of sale/collection, in much the same way as described above for headache. We are unaware of studies using this method.

An additional feature of menstrual related pain is its relatively predictable course. This has been particularly useful in that studies have been able to exploit the regularity of pain by examining participants at different phases of the menstrual cycle, and from this making predictions about the potential role that sex hormones may have in mediating pain. Although menstrual pain is common and predictable, there are a number of methodological issues that need to be carefully considered [89; 100]. For example, cycle lengths vary between women, with average durations ranging from 22 to 32 days [100]. Therefore, it is important to be able to accurately predict phase when

testing, especially if trying to combine data from various participants. Estimates of cycle of phase are notoriously inaccurate, and often are based on a combination of self-estimates and counting of days since last menstruation. Recently, advances in mobile communication, and the development of applications to specifically record and predict phase may have some utility in ensuring accurate estimate of phase [87]. Alternative strategies have been to take blood or urine samples to detect changes in sex hormone production around ovulation and menstruation. Home-ovulation detection devices provide an easy non-invasive alternative to blood plasma sampling.

An additional issue to consider is the use of oral contraceptives, which not only produce a stable hormonal profile, but can help control dysmenorrhea. Interestingly there are some studies that actually exploit this by including women taking oral contraceptive as controls. Although men have occasionally been included as a control comparison group [63], on the whole males tend to be excluded from such studies. Therefore, this model is not without its limitations; however, generally it can be considered to be a common, reliable and predictable model of naturally occurring pain.

Analogue versions of menstrual pain: Given the nature of menstruation-related pain, there are no experimental analogues to consider here. However, it should be noted that menstrual cycle related changes in pain sensitivity have been examined in combination with other pain induction methods [43; 89; 100]. For example, menstrual related changes in experimental pain sensitivity have been examined using the main types of induced pain i.e., thermal heat, cold pressor, pressure, and electrical pain [2; 24; 31; 120]. There are also recent suggestions that menstrual cycle may influence the efficacy of some analgesics [88]. For example, Ribeiro-Dasilva et al. [88] examined the

efficacy of morphine and pentazocine to relieve experimentally induced pain at different phases of the menstrual cycle.

Summary and appraisal of methods: The methods used to investigate menstrual-related pain are variable. Greater standardization is required, with a particular focus on the selection of samples homogenous in terms of health status and phase of cycle [18; 25]. However, where menstrual pain is the main focus of investigation, its prevalence, regularity, and the ability to measure associated hormonal features make self-selection or recruitment of those at risk of pain a good solution.

3.5. Dental pain

Description and incidence of dental pain: Oral-facial pains, including dental pain, are common [102]. The most prevalent form of oral-facial pain originates from the teeth and surrounding structures [98]. Dental pain can result from changes in temperature or exposure to sweet substances, inflammation, insult to the surround areas of the teeth or procedural intervention. This pain is often poorly localised and patients often struggle to identify within 2-3 teeth of the damaged region [98]. The incident rates of these types of pain are also high, with some estimates suggesting that fifteen per cent of adults experience oral-facial pain (toothache, oral sores, jaw pain, face pain, or burning mouth) within any given 6 month period [73], and more recent estimates suggesting that 17.7% of individuals may experience dental pain within a 6 month period [5]. For the purposes of the current review, we chose to focus on common dental pains associated with normal conditions of ageing such as third molar eruption, leading to removal, and elective procedures used cosmetically or for hygiene.

Recruiting people with dental pain: One approach to investigating dental pain is to prospectively identify those at risk of developing painful episodes. However, we found no examples of population or at risk studies. This is perhaps unsurprising given that dental pain is relatively slow to materialise, and so predict. An alternative method of risk identification has been to recruit from groups likely to have some form of dental intervention that will result in pain. Indeed, given the frequency of dental procedures that are painful (e.g., third molar extraction, periodontal interventions) the recruitment of participants prior to procedure is common (e.g. [74]), and third molar extraction is considered by some the industry standard for the evaluation of analgesic medication [1]. For example, Malmstrom et al. [74] included adults who were scheduled to have a minimum of two third molars removed with at least one partially embedded in the mandibular bone. There is also evidence of the use of non-surgical periodontal therapy as a model of dental pain. For example, Sullivan and Neish [112] recruited 80 students into a study in exchange for which they received free dental hygiene treatment. This resulted in moderate pain ratings from participants especially those who scored high on pain catastrophizing measures. Ettlin et al. [23] also recruited participants with mild to moderate periodontitis attending a dental clinic in Switzerland. This resulted in a mild to moderate pain level in participants. One disadvantage to this approach is that it took almost a year to recruit 64 participants. The advantages of this approach are that it is possible to 'standardize' the intervention, as well as predict when the painful episodes are likely to occur.

Although at-risk sampling is relatively rare, there are many more studies recruiting participants with current episodes of dental pain. Segura-Egea et al. [97]

recruited 176 participants who had undergone root canal treatment. Current dental pain has also been investigated by targeting individuals as they attempt to self-manage their pain [22]. For example, Edwards et al. [22] used a 'point of sale' type approach and recruited participants through a local dental practice with pain caused by acute pulpitis. Standard tools exist to measure the extent of procedural damage and repair [127].

Analogue versions of dental pain: Pain induction techniques for human dental/facial pain have been considered. For example, Bowley and Gale [9] examined five competing methods for inducing jaw pain, all of which are similar to muscle pain induction techniques as they involve the manipulation of jaw and facial musculature into particular positions, and then the hold and/or repetition of these positions. All five methods resulted in an induced pain sensation. The predicted time to develop pain was within a minute for two of the exercises and 2-3 hours for the remaining. Again, as with headache, these timings may be unsatisfactory as the onset of this pain is often delayed, and with the exception of one exercise these may result in jaw pain in a small proportion of participants. Additionally, the pain induced by these techniques is more musculoskeletal in nature rather than dental pain.

In addition to muscular techniques, external stimuli have been applied to teeth to induce pain. For example, McGrath et al. [76] applied electrical stimuli to the participant's tooth pulp. These stimuli varied in frequency from 5-500 Hz, the minimum frequency required to induce a pain response was 100 Hz. Brown et al. [11] showed that 11 participants in their study were able to clearly distinguish between a pain and non-pain electrical stimulation applied to one or two teeth. The application of pain

using an electrical pain stimulus provides a repeatable and reliable pain sensation. However, applying electrical stimuli to the tooth pulp requires participants to keep their mouths open in an unnatural position which may result in additional pain outside of the pain of interest.

Summary and appraisal of methods: Dental pain is a frequently used human pain model, with third molar extraction procedural pain the most common method. In addition to third molar extraction we also found a number of other procedural techniques for recruiting dental pain patients. Although these were successful in resulting in a reliable pain sensation they required either a large cost or amount of time to recruit participants using these techniques. We could find no examples of population or at risk studies. Techniques for pain induction have been developed, in particular as they relate to motor function of the jaw. These however are difficult to achieve and not very effective.

3.6. Pain associated with Upper Respiratory Tract Infection

Description and incidence of upper respiratory tract infection (URTI): Common URTIs create symptoms such as sore throat, 'runny nose', sneezing, nasal congestion, fever and muscle aches [20]. They can be caused by a wide range of viruses including Rhinoviruses, Coronaviruses and Influenza Viruses, with over 100 different Rhinovirus stereotypes having been identified alone. It is estimated that the average annual incidence per person is two episodes [41].

Recruiting people with URTI: There are few attempts to recruit people 'at risk' of developing pain associated with upper respiratory tract infection (e.g., infants, those with compromised immune systems). Instead, there are more examples of recruitment

of those with current upper respiratory tract infection. From a general population sample, one can recruit people with cold symptoms, including pain in the throat, and in the case of influenza, muscular pain also. Reliable methods of describing the severity of infection through virology, and symptoms via self-report, exist. There are also epidemiological methods for increasing the reliability of measuring influenza incidences [82]. To examine the effects of various common analgesics on sore throat Schachtel et al. [95] used a 'point of sale' approach by recruiting participants who were seeking primary care assistance for sore throat. Participants had to have onset within 4 days, score greater than 66mm of 100mm on a Visual Analogue Scale measuring sore throat pain intensity, and objective evidence of tonsillopharyngitis.

Although chest and muscle pain often accompany upper respiratory tract infections, this is a group that has not traditionally been sampled in acute pain studies. There are, however, examples where this approach has been used, and which may prove to be useful in the future. For example, Smith and colleagues (e.g., [104-106]) have conducted a number of experimental studies of the effects of the common cold on cognitive performance using largely epidemiological recruitment methods. These are interesting approaches, especially as it has been argued that pain has interruptive effects on human cognitive performance [78; 79], and so the common cold/influenza could be used to specifically investigate the effects of pain. Although the above studies suggest that researching the common cold and sore throat in a naturally occurring presentation of these conditions is possible there are a number of additional considerations. These conditions are particularly seasonal in occurrence [59], making recruitment seasonal also.

Analogue versions of URTI: Induction of the common cold is possible, and protocols have been developed [107]. Smith et al. [107] described a 10 day procedure in which participants were initially quarantined to ensure no cold was present. Upon arrival they were then given nasal drops which contained a virus (Influenza, Rhinovirus or Corona virus). Following an incubation period of 48-72 hours participants who are infected begin to show symptoms. These are objectively measured by assessment of sublingual temperature, and quantity of nasal secretion. Such an approach could be applied to pain by inducing URTI and recording pain experience and the effects of this pain on other behaviour, by examining how this operates and controlling for viral effects it would be possible to examine the effects of pain.

Summary and appraisal of methods: Colds and associated symptoms of sore throat are common, although seasonal. Population based approaches have been used to good effect, although we found no studies of 'at-risk' samples. Recruiting from those seeking treatment has also been used, although in this case these are largely self-management products at point of sale, rather than physician office recruitment. For greater control, protocols do exist for inducing cold, but these methods require greater laboratory infrastructure and participant commitment over a longer period of time and are therefore likely to be unappealing for general use in pain studies.

4. Discussion

Methods have been developed to examine naturally occurring pain. We identified innovative approaches used in the common six domains of headache, muscular pain, visceral pain, menstrual pain, dental pain and pain from URTI. Overall, studies have focused on people currently in pain, at risk of pain, or scheduled to

experience pain. Analogue methods of pain induction also exist for most of these common pain conditions. Each of these types of pain possesses their own set of benefits and challenges, which we have summarized in Table 1.

ENTER TABLE 1 HERE

Based on our appraisal methods a number of recommendations emerge. First, both headache and menstrual pain appear to be most effectively researched in their naturally occurring form. These pains are both highly prevalent, and have standardised methods for recruitment and screening in a non-clinical context. By comparison muscle and dental pain may be most easily investigated using either an induced analogue or procedural method. There is a range of induction analogues for muscular pains (e.g. DOMS, electrical, pressure) which offer standardised pain protocols for creating pain that highly resembles naturally occurring pain. For dental pain, third molar extraction is the industry standard for testing analgesics [1] and common methods have been described. Upper respiratory tract pain and visceral pain however present challenges to researchers. The naturally occurring forms of each of these conditions are either difficult to recruit because of lower incidences and a need for clinical input in diagnosis, or are seasonal. Additionally, experimental analogues are being developed but at present are novel, are in need of replication, or are highly invasive and so resource intensive.

Recruiting from sites where people are likely to be in pain may be the optimal strategy for assessing naturally occurring pain in the context in which it occurs.

Practically, this means recruiting people from where they present when in pain, which are typically sites of analgesic purchase or delivery such as pharmacies, hospital emergency rooms, etc. Some studies have successfully managed this recruitment (e.g., [52; 53; 55; 83; 126]), and appear to achieve populations homogenous on pain complaint, and heterogeneous on other demographic and biographical characteristics. However, we did not find any examples of recruitment strategies focussed on recruiting people in pain outside of clinical environments. We believe that these strategies are possible, as in the example of those seeking analgesia following exercise, or following cosmetic procedures (e.g., piercing, tattooing, depilation). Recruiting people whilst in pain provides both technical and ethical challenges, as it is not clear the extent to which people are able to consent to participation, especially if the study protocol requires temporarily withholding analgesia.

What was found to be less common was recruiting participants ‘at risk’ of developing acute pain. Although we found evidence of studies recruiting participants who suffer with recurrent headaches and recruitment for menstrual pain studies can be seen to fit an ‘at risk’ strategy there was no evidence of this in other pain complaints. This is surprising given that risk factors are known for muscle pain [15; 27] and the identification of those ‘at risk’ of pain complaints would appear to be an efficient method for recruiting participants for pain related study.

A procedural pain approach is also popular, although largely due to the dominance of dental pain models in analgesic efficacy studies. This is attractive because the pain is naturally occurring, and many features of the procedures can be controlled experimentally. However, it should be noted that dental pain, despite being

common, is not uncomplicated. For example, dentistry is associated with a high level of anxiety and fear (e.g. [29; 37; 67]) and often requires rescue analgesia (e.g., [46]). Other interesting procedural pain models have been attempted such as post-dural headache pain [118], and it is possible to consider a number of other procedures which might provide additional pain models (e.g., mammography & needle pain). Other non-clinical painful procedures associated with goals other than health are rarely investigated (e.g., depilation, tattooing, piercing) and we found no standardized methods reported. These may be interesting to pursue, in particular because of the different psychological context of these procedures.

The alternative approach to recruitment of those in pain or likely to experience pain, is to experimentally induce the pain of interest. Standard methods have been developed in headache, some visceral pains, and some muscle pains. Perhaps the most developed are muscle pain protocols [33]. These methods are attractive as one has more control over experimental parameters that affect pain exposure (e.g., time of onset), and can often measure the physical parameters of the method of pain insult (e.g., pressure applied), and the pathophysiology of the pain is often better mapped. However, their performance is relatively sensitive to operator characteristics and appropriate training is required [51]. The investment in infrastructure, training, and participant commitment should also not be underestimated. Overall we judge that in most cases there are too few incidences of different laboratories and teams undertaking these methods to make reliable judgements as to their general value. It appears that recent uses of some methods are very promising. Work by Walker and colleagues [123], for example, and by Lewis et al. [71] in re-introducing the water-load

test is instructive. The method clearly adds valuable and unique insights, and is complementary to clinical studies. However their success will have required significant scientific and organizational leadership. Cross laboratory, perhaps international, collaboration will be necessary to produce standards and common protocols for these methods. Additionally, whereas the psychophysical parameters of other pain induction methods are well specified, these foundational investigations are still to be performed for the methods reviewed here.

This analysis was limited to a methodological and largely procedural discussion of methods, of use principally in behavioural or observational studies. Not included here was any consideration of the pathophysiology of the pain under investigation. In part this is due to the number and variety of techniques reviewed, but also due to the lack of clarity in many cases as to the exact physiological mechanism involved. Some pains are likely to be principally neuropathic, others inflammatory, and others still a mixture (eg., third molar extraction). For each method, it would be instructive to research in detail the involvement of physiological mechanisms. This is particularly important given the presumed heterogeneity and combinatorial complexity of mechanism involvement in many of the methods reviewed. At present, for research in which it is important to know exactly the physiological mechanism underlying the pain experienced, many of these techniques will be inadmissible without further investigation.

A number of implications for studying acute pain in humans can be drawn from this review. First, for most of the pains investigated methods do exist and have been used. Standard laboratory pain induction techniques do not always need to be the first

recourse. Second, although methods of recruitment are in common use, some variants of these methods deserve more investigation. In particular, rarely used are methods of working with people who undergo non-clinical common painful procedures, and those who are in predictable non-clinical pain from planned over-exertion. Third, although there are some examples of real-time data capture using ecological momentary assessment, these remain rare. As mobile communication and sensor technology develops the possibilities of these approaches have not yet been fully appreciated, and deserve serious attention. Finally, although some methods of inducing pain have achieved popularity and are in common use, other methods are only used infrequently and by a small number of groups. The field could benefit significantly by the increased use of methods by different research teams, and attempts at establishing evidence based consensus on protocols for pain induction.

Studying pain as it naturally occurs, and in the contexts in which it naturally occurs, is an important goal for researchers interested in pain and analgesia. Various methods are currently in use, although often by a small number of people and groups. There is significant scope for innovation and development, from the invention of new technologies of pain delivery and data capture, to the improvement of standards and guidelines, and the piloting of never before investigated populations of people planning to be in pain.

Disclosures

The authors have no conflicts of interest to declare in relation to this article. This research is part supported by an unrestricted grant for research from Reckitt Benckiser Healthcare (UK) Limited.

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Table 1: Methods employed to recruit people with naturally occurring pain, or the use of analogues designed to mimic such pain

		Headache	*Muscle*	*Visceral*	*Menstrual*	*Dental*	*URTI*
Natural	Incidence	Tension type headache 66% lifetime [86] Migraine 12-23% [44; 66; 99]	Annual incident; men 48%, women 60% [48] muscle cramps 36% [47]	50% at least one day within a year [114]	80% regular menstrual pain [19; 103]	17.7% within 6 months [5] 28.24% have oral lesions at any time [102]	Average person between 1 and 3 periods of cold per year[41]
	Current pain	Recruitment in pain has been conducted [39] as have EMA techniques [57]	Recruitment of participants when they report for pain treatment [124]	Participants have been recruited at the point they seek treatment [83]	Recruitment of those in pain is viable for menstrual pain	Third molar extraction [74] Root canal treatment [97] and periodontitis [23]	Recruitment of people when in pain [104-106] or seeking treatment is common [95]
	At risk	Frequent recruitment of those at risk of pain[44; 66; 99]	No studies were found recruiting those 'at risk' however risk factors are know [15; 27]	No evidence for at risk recruitment	Women who suffer from menstrual pain usually suffer frequently making at risk recruitment attractive.	No evidence of at risk sampling	No evidence of at risk sampling
	Evaluation	Common and standard techniques for recruiting headache. Excellent model.	Not well utilised. Heterogeneous conditions, hard to control.	Some evidence for effective techniques for recruitment from conditions such as IBS, sample sizes may be small.	Its prevalence, regularity, and predictability make self-selection or recruitment of those at risk of pain a good solution	Third molar extraction is effective and industry standard. Identification of those in pain is also possible.	Identification of those in pain is preferable; however this is a seasonal pain.

Induced analogue	Analogue	Muscle tensing [14; 50; 80] Drug induced [65]	Yes, a range in common usage; inc: DOMS, pressure, topical	Distension [90], water load [123]	N/A	Possible, but uncommon tooth pulp [76] and muscular techniques [9] have been used	Induction is possible by infecting participants.
	Evaluation	Muscular techniques are time consuming and not effective . Some drug induced methods tried	A range of effective techniques exist.	Invasive or not very effective.	N/A	Difficult to achieve and not very effective	Induction requires a large amount of time and complex laboratory infrastructure