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Predictors of treatment outcome in contextual cognitive and behavioural therapies for chronic pain: a systematic review

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Running title: Predictors in contextual CBT for chronic pain

Abstract

There is increasing evidence that Contextual forms of Cognitive Behavioural Therapy (CBT) are effective in the management of chronic pain, yet little is understood about the factors that moderate or predict outcomes in these treatments. This systematic review aimed to identify pre-treatment participant characteristics associated with positive treatment responses in Contextual CBT for chronic pain. Medline, EMBASE, PsychINFO and CENTRAL were searched to identify eligible studies. Studies were included if the participants were adults with chronic pain, designs were longitudinal, treatments focused on psychological flexibility or mindfulness, and reported results allowed for examination of moderators or predictors of standard treatment outcomes. Out of 991 records initially identified, 20 were eligible for inclusion in the review. Some evidence suggested that baseline emotional functioning predicts treatment response, but the direction of this association varied between studies. Substantive findings were inconsistent and inconclusive, however, methodological limitations were consistent. These included treatment heterogeneity, and a lack of theoretical*, a priori* guidance in examining potential predictors. Future research should adopt a theoretically based approach to examining moderators in relation to specific treatment methods and therapeutic processes. Considering moderation without first considering mediation is probably a limited strategy. PROSPERO registration number: CRD42016038795.

Perspective:

In this systematic review we examined evidence for potential predictors or moderators of outcomes in Contextual Cognitive Behavioural Therapy for chronic pain. Substantive findings were inconclusive but important methodological limitations and a lack of theoretical guidance were found. Future research should explicitly plan relevant methods and follow clear theoretical models.

Key words:

Chronic pain; acceptance and commitment therapy; mindfulness; psychological flexibility; predictor

Introduction

There is an established and growing body of evidence that psychological interventions, in particular Cognitive Behavioural Therapy (CBT), can be effective in the management of chronic pain [11, 14, 21, 28, 40, 51, 62]. At the same time there is increasing interest in the use of contextual forms of CBT such as Acceptance and Commitment Therapy (ACT) and mindfulness-based approaches to target chronic pain [37]. Rather than a predominant focus on control and change in the *content* of feelings, thoughts, and beliefs as in conventional CBT, the main focus of these approaches is on changing the *influence* of these experiences on a person's behaviour to improve overall quality of life [43]. ACT in particular is based on the psychological flexibility model, a model of a person's ability to act in line with meaningful goals and values whilst maintaining awareness and acceptance of thoughts and feelings [18-20]. Importantly, ACT emphasises a functional, contextual, and pragmatic approach to psychological experiences, and success is defined as progress toward one's goals. There is a growing, though certainly not definitive, evidence base suggesting that ACT and mindfulness-based interventions are effective in the treatment of chronic pain, including both individual trial data [3, 5, 24, 31-33, 35, 46, 57, 59-61] and systematic reviews [16, 22, 41, 53, 54].

Despite the growing body of research indicating that contextual CBT may be effective for persistent pain, little is understood about the factors that predict or moderate treatment outcome. *Predictors* are factors that are correlated with outcomes regardless of whatever treatment is under study, whilst *moderators* are associated with the strength of the relationship of a particular treatment with outcome [15, 27]. Turk, [48] among others, highlighted a need to better understand the characteristics of patients who respond or fail to respond to psychological treatment in order to develop more effective individualised treatment approaches. This call is echoed in recent meta-analyses where we are urged to find "which components of CBT work for which type of patient on which outcome/s and to try to understand why" (p 2, [62]). Attempts to identify subgroups of patients that respond best to treatment have generally been exploratory and ad hoc, with little grounding in psychological theory. Further, most previous reviews have focused on psychological pain management interventions as a whole, rather than specifically focusing on one or several theoretically

related treatment approaches. A systematic review of 16 RCTs of self-management approaches [38] concluded that self-efficacy and depression may be important predictors of outcome, but highlighted a lack of evidence on treatment moderators. In a review of moderators of psychosocial pain management interventions, Day and colleagues [8] again highlighted inconsistencies in the literature. It is possible that the inconsistencies in identifying moderators of outcome may be attributed to the wide variability in the treatment approaches and active treatment mechanisms represented in the included studies. The number of existing studies of contextual forms of CBT for chronic pain has now reached a level that a specific focus on moderators in these treatments may be possible. As far as we are aware this has never been done.

The purpose of the current study was to systematically review the evidence for moderators or predictors of outcome in studies of contextual CBT for chronic pain. This review aims to summarise the findings of published studies of any longitudinal design that aimed to identify participant characteristics associated with responses to ACT or mindfulness-based treatments for adults with chronic pain. These results will be divided according to available standard clinical outcomes in these studies. Study quality will also be examined.

Methods

The review protocol was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/; registration number: CRD42016038795). This review followed the statement on preferred reporting items of systematic reviews and meta-analyses (PRISMA; [39] see figure 1).

Literature search

A systematic literature search was conducted to identify eligible studies in relevant electronic databases (Medline, EMBASE, PsycINFO and CENTRAL). The search was conducted on 20th April 2016 and the time period of the search was set as January 1974 to April 2016 across all databases. Additional studies were identified from the references of studies included in the current review. The search was conducted by one reviewer (HG) and included free text terms alongside electronic database indexing terms, where possible. The search terms were selected to identify studies of any longitudinal design focused on ACT or mindfulness-

based interventions for chronic pain syndromes (for further details of search strategy, see Supplementary Information).

Screening and Selection

Articles identified from the initial search strategy were screened by two independent reviewers (HG, RG) based on title and abstract according to the inclusion criteria agreed in the protocol for this systematic review. Any disagreements were resolved through discussion with a third reviewer (AK). Potentially eligible articles were then assessed for inclusion based on the full text of the article by two independent reviewers (HG, AK). Again, any disagreements were resolved through discussion with a third reviewer (LM). Studies were included in the current review if they employed longitudinal design and included an attempt to identify predictors or moderators of outcome from an ACT or mindfulness-based intervention for chronic pain. Only published studies of adults aged 18 years or over with chronic pain (defined as pain persisting for at least 3 months), reported in English, were included. Based on previous similar systematic reviews [38, 53] included conditions were non-specific musculoskeletal pain, chronic widespread pain, fibromyalgia, arthritis and osteoarthritis, neuropathic pain, whiplash associated disorders, complex regional pain syndrome, and chronic headache. Included treatments were delivered by any method, face-to-face, group, telephone- or internet-based, either in an individual or group format. The ACT or mindfulness methods could be conducted in any setting by therapists from any combination of disciplines, either as a stand-alone treatment or in conjunction with other treatment modalities. Finally, to be included in the review, studies must have used outcome measures from at least one of the following domains: pain intensity; pain interference; physical functioning; emotional functioning; social functioning; ability to work; sleep; or healthcare use.

Data extraction

Data was extracted by two independent reviewers (HG, RG), recorded on a standardized scoring sheet and cross-checked before inclusion in the review. Data extracted from the studies included in the final review included year of publication, study design, sample size, intervention setting, content, format, facilitators and

duration/intensity, outcome assessment tools and timing, and potential moderators or predictors (associations with relevant outcomes).

Quality assessment

The methodological quality of each study included in this review was assessed by two reviewers (HG, AK) independently to determine risk of bias. When discrepancies arose in quality assessment ratings between the two reviewers, these were discussed with a statistician (DS) acting as third reviewer, until a consensus was reached. Quality assessment was conducted using an adapted version of the Hayden criteria [17], a tool specifically designed to assess quality of studies of prognosis and prognostic factors. Hayden and colleagues [17] highlighted that there is limited consensus on methods by which to assess the quality of prognosis studies and developed a framework focusing on six areas of potential bias in study design: 1) study participation, 2) study attrition, 3) prognostic factor measurement, 4) measurement of confounding variables, 5) outcome measurement and 6) analysis. Risk of bias for each item was rated as low, moderate or high based on scoring guidelines. Consistent with the protocol described in Hayden et al. [17], studies were classified as low quality when one or more areas of bias were rated as high risk, and high quality when risk of bias ratings for all six areas were low or moderate. There was an initial agreement rate of 77% between the two reviewers with regard to the rating of methodological quality of studies and the majority (89%) of the identified discrepancies were resolved in discussion between the two reviewers. The few cases where this was not possible were focused mainly on the suitability of statistical analysis to look at prognosis/ predictors of outcome. The discrepancies were resolved in consultation with the statistician.

Analyses

Results of studies were examined to identify baseline variables associated with relevant treatment outcomes. Outcomes were categorized under separate headings **after** data extraction, based on the particular outcome measures employed in the included studies. The aim was to combine associated outcome measures for ease of interpretation and to avoid redundant categories due to limited studies.

Because of the large variability in study design, predictors, outcomes and treatment protocols between the studies included in this systematic review, a meta-analysis was not performed.

Results

Included studies

The initial electronic search strategy produced 958 articles and another 33 from hand searching of reference lists of identified studies and closely related studies. After duplicates were removed 484 article titles and abstracts were screened and 144 full length articles were obtained and reviewed for eligibility. After full-article screening, 90 articles were identified as potentially eligible treatment outcome studies of contextual CBT for chronic pain. At this stage, studies were not screened for predictor or moderator analyses but were included if they met all other inclusion criteria. Out of these 90 treatment outcome papers, 20 articles were considered eligible for final inclusion in the review because they included an analysis of predictors or moderators of outcome (see Figure 1 for flow chart). In only 7 of these 20 papers was the study designed to investigate predictors or moderators as opposed to these analyses being exploratory or post-hoc. Several studies used the same dataset but considered different predictors or different follow-up time periods. These duplications were noted and each of these 20 papers were included in the final review.

INSERT FIG 1 ABOUT HERE

Outcome measures

Following data extraction, outcome measures were categorized under eight main headings: pain, health-related quality of life, social functioning, psychosocial disability, physical functioning, emotional functioning, overall pain-related interference and 'other'. For the purposes of this review, single items from the Brief Pain Inventory (BPI) interference subscale were categorized separately under the most relevant heading, with the

items ‘interference in enjoyment in life’ and ‘interference in general activity’ classified under the category ‘health-related quality of life’. When *total* interference score was used (from either the Brief Pain Inventory or Multidimensional Pain Inventory interference subscales), this was classified under the heading ’overall pain-related interference’. Due to small numbers of articles reporting on some outcomes (global treatment response, sleep, fatigue, work, medical visits, patient impression of change)**,** these outcomes were incorporated under the heading ‘other’. For the purposes of this review, the term ‘global treatment response’ refers to cases where a combination of measures from different outcome domains were used to generate composite scores or to classify treatment ‘responders’ vs ‘non-responders’.

Characteristics of included studies

Characteristics of the 20 included studies are presented in Supplementary Table 1. The majority were cohort studies or RCTs, eight of each, with the remainder of the studies comprising three controlled clinical trials and one cohort analytic design. Sample size ranged from 58 to 590 participants, with the majority of samples comprising adults with mean age between 39 and 62 years (two studies did not specify mean age). Two studies included women only. In most of the remaining studies the majority of participants were women, with the exception of two studies [12, 58] where the ratio of men to women was approximately 1:1. Eleven studies used a mindfulness-based intervention, and nine used an acceptance-based approach. Seven studies used an intensive, typically residential, rehabilitation approach whilst eleven were outpatient programs consisting of weekly, fortnightly or bi-weekly sessions. Two studies focused on internet-based interventions, one nine weeks and one up to six weeks in duration. For chronic pain conditions, thirteen studies included mixed chronic pain samples, whilst one specified chronic musculoskeletal pain, two included fibromyalgia (FM) samples, two included Rheumatoid Arthritis samples, one “provoked vestibulodynia”, and one chronic tension-type headache.

Quality of included studies

Out of the twenty studies included in the current review, nine scored as ‘low quality’ and eleven scored as ‘high quality’ as rated using the Hayden criteria [17]. None of the twenty studies scored as low risk across all six

areas of bias (see Table 1). It is important to note that the majority of studies, thirteen of the twenty, were not designed primarily to look at moderators or predictors; as such, quality ratings of the statistical analysis of studies in accordance with the quality assessment tool (specifically developed for studies evaluating prognostic factors) were reduced as consequence. Therefore, a rating of low quality in this review does not necessarily indicate that the study was not methodologically sound overall, but just that the methods employed were considered not robust for evaluating prognostic factors. See Table 1 for a full summary of risk of bias ratings and overall study quality for the twenty studies included in this review.

INSERT TABLE 1 ABOUT HERE

Predictors of outcome

Pain

There were eight studies that investigated predictors of pain outcomes, two of which identified significant predictors (see Table 2 and Supplementary Table 2). One high quality study used a mindfulness-based intervention with a female sample (n=85) seeking treatment for Provoked Vestibulodynia [2]. The second low quality study used an ACT intervention with a mixed gender and mixed chronic pain condition sample (n=287) [34]. Findings suggest that higher pre-treatment allodynia severity [2], being highly disabled [34] and having a higher number of comorbid chronic pain conditions [2] may predict worse pain outcomes. None of these three possible predictors were investigated as predictors of pain outcomes in any other studies.

Six other studies found no significant associations with pain outcomes from baseline anxiety scores [4], history of depression [6] or history of recurrent depression [7, 64], as well as longer pain duration, years of education, older age and gender [55, 56]. Four of these six studies were rated as high quality [7, 55, 56, 64]

Health-related quality of life

Three studies investigated predictors of outcomes in health-related quality of life (HRQL), all of which identified significant predictors (see Table 2 and Supplementary Table 2). All three included mindfulness-based interventions. One study included a female only sample with chronic musculoskeletal pain [1] whilst two included mixed-gender samples of mixed chronic pain conditions [13, 42]. Across these three studies, four potential predictors of HRQL were identified. One high quality study (n=115) reported that longer pain duration predicted less interference in enjoyment of life [13]. However, the same study also found a non-significant association between duration of pain and interference in general activity. One low quality study (n=133) found that having arthritis as the diagnosed pain condition (compared to back/neck pain, headache/migraine, fibromyalgia or comorbid pains) [42] predicted better outcomes for HRQL and one high quality study (n=269) found that having a lower baseline HRQL [1] predicted better outcomes for HRQL. Having chronic headache or migraine as the diagnosed pain condition predicted worse outcomes for HRQL [42]. None of these four possible predictors were investigated in relation to HRQL outcomes in any other studies.

In contrast, one high quality study using a mindfulness-based intervention [13] did not find evidence for an association between gender, age, years of education, income level or baseline opioid misuse with outcomes for interference in enjoyment of life or general activity.

Social functioning/interpersonal relations

Three studies investigated predictors of social functioning outcomes [6, 7, 13], two of which identified possible predictors (see Table 2 and Supplementary Table 2). Both included mindfulness-based interventions, with one focused on a fibromyalgia sample (n=79) [6] and the other on a mixed chronic pain condition sample (n=115) [13]. Between these two studies, two potential predictors of social functioning outcomes were identified. One high quality study [13] found an association between longer pain duration at baseline and less interference in relationships post-treatment. Pain duration was not investigated in relation to social functioning outcomes in any other study. One low quality study [6] found that depression history moderated group effects on loneliness and family stress, such that those with a positive history of depression showed

greater improvements in family stress and loneliness that were specific to the mindfulness-based intervention compared to a control intervention. However, the same study also found no significant associations between history of depression and social activity engagement or family enjoyment [6]. A further high quality study of a mindfulness-based intervention (n=144) found no significant association between history of recurrent depression and improvements in interpersonal stress [7]. No significant associations were found between gender, age, years of education, income level, and baseline opioid misuse with social functioning outcomes on the basis of one study [13].

Psychosocial disability

Five studies investigated predictors of psychosocial disability outcomes, two of which identified possible predictors (see Table 2 and Supplementary Table 2). Both included mixed chronic pain condition samples and an ACT intervention [34, 55]. Between these two studies, two possible predictors were identified. One low quality study (n=287) identified that those who were more highly disabled appeared to make greater improvements in psychosocial disability outcomes [34]. Disability was not investigated as a predictor in any other study. One high quality study (n=171) identified that greater years of education was associated with larger improvements in psychosocial disability [55]. In contrast, two other low quality studies and one high quality study, all using ACT interventions found that years of education was not significantly associated with psychosocial disability outcomes [32, 56, 57]. On the basis of two low quality and two high quality studies of ACT interventions, no associations were found between gender, older age and pain duration with psychosocial disability outcomes [32, 55-57].

Emotional functioning

There were twelve studies that investigated predictors of emotional functioning outcomes, six of which identified potential predictors (see Table 2 and Supplementary Table 2). Four studies included mixed chronic pain samples [25, 34, 42, 55], one study included a fibromyalgia sample [6] and one study focused on participants with rheumatoid arthritis [64]. Four were studies of mindfulness-based interventions [6, 25, 42, 64] and two were of ACT interventions [34, 55]. Across these six studies, five potential predictors were identified for various aspects

of emotional functioning. One low quality study (n=90) reported better outcomes for psychological distress were predicted by being female [25]. However, three high quality studies [13, 55, 56] and two low quality studies [32, 57] found no association between gender and emotional functioning outcomes. Being in pain for longer [55] led to better outcomes for depressive symptoms at post-treatment on the basis of one high quality study (n=171). However, two other high quality studies [13, 56] and two low quality studies [32, 57] found no association between pain duration and emotional functioning outcomes. On the basis of one low quality study (n=79), having a positive history of depression was associated with an increase in positive affect [6] but not with a reduction in negative affect. One high quality study (n=144) identified that history of recurrent depression was associated with better outcomes for both positive and negative affects but not for depressive symptoms [64]. History of recurrent depression was investigated as a predictor of emotional functioning outcomes in one other high quality study, which found no significant association [7]. One low quality study (n=133) identified that having fibromyalgia compared to other conditions predicted smaller improvements in psychological distress [42]. Another low quality study (n=287) identified that being highly disabled led to better outcomes for emotional functioning [34]. Neither of these predictors were investigated in relation to emotional functioning outcomes in any other studies.

Three high quality and two low quality studies (four ACT, one mindfulness) found no significant associations between age or years of education with emotional functioning outcomes [13, 32, 55-57]. No significant associations were found between income level [13], pre-treatment pain intensity [12], history of recurrent depression [7], Pictorial Representation of Illness and Self Measure (PRISM) score and helplessness at baseline [12], and baseline opioid misuse [13] in mindfulness-based interventions with emotional functioning outcomes.

Physical functioning/ physical disability/ functional measures

There were nine studies that investigated predictors of outcomes in physical functioning or physical disability and four identified possible predictors (see Table 2 and Supplementary Table 2). All studies used mixed chronic pain samples; three included ACT [34, 52, 55] and one a mindfulness-based intervention [12]. Four potential predictors were identified for various aspects of physical functioning and physical disability. Gender was

found to be a significant predictor of physical activity outcomes on the basis of one low quality study (n=87), with women showing greater increases in physical activity than men [52]. However, three high quality studies and two low quality studies found no association between gender and physical functioning outcomes [13, 32, 55-57]. One high quality study (n=119) suggested that lower pre-treatment pain intensity significantly predicted greater improvements in physical functioning [12]. However, one low quality study suggested no association between pre-treatment pain intensity and physical functioning outcomes [52]. Higher numbers of years of education was found to predict greater improvements in physical functioning at post-treatment based on one high quality study (n=171) [55]. However, two high quality studies [13, 56], and two low quality studies [32, 58] found no association between years of education and physical functioning outcomes. One low quality study suggested that being highly disabled led to smaller improvements in physical disability and functional performance measures (n=287) [34]. Disability was not investigated as a possible predictor in any other study.

There were also many findings of non-significant associations with physical outcomes. Five studies (four ACT, one Mindfulness-based; three high quality, two low quality) reported non-significant findings for older age and pain duration [13, 32, 55-57]. Physical outcomes were also not found to be significantly associated with income level and baseline opioid misuse [13], history of recurrent depression [7], baseline PRISM and helplessness scores [12] in mindfulness-based interventions. Additionally, one low quality study of ACT [52] found that baseline pain intensity and interference, presence of major depressive disorder, baseline depression and pain-anxiety scores, or baseline physical and mental health as measured by the SF-12, did not predict outcomes for physical functioning.

Overall pain-related interference

Two studies investigated predictors of overall pain-related interference or impact on daily living for an ACT intervention in a mixed chronic pain sample [47, 58] (see Table 2 and Supplementary Table 2). One high quality study (n=114) found that the interaction between age and treatment was a significant predictor of treatment response for overall interference, with older adults responding better specifically to ACT [58]. Age was not investigated as a predictor of overall interference outcomes in any other study. One high quality

study (n=238) found that higher psychological wellbeing at baseline led to better outcomes specifically for ACT [47]. Having lower depression and anxiety and higher emotional wellbeing at baseline were also significant predictors of better outcome for pain-related interference, although these were not specific to the ACT intervention [47]. In contrast, one high quality study [58] found no significant association between baseline depression and outcomes for overall interference. On the basis of one high quality study, higher baseline pain intensity was associated with better outcomes specifically for ACT [47]. Baseline pain intensity was not investigated in relation to pain-related interference outcomes in any other studies.

Other outcomes (global treatment response, sleep, fatigue, work, medical visits, patient impression of change)

Two studies investigated predictors of global treatment response (i.e. where a combination of measures from different outcome domains were used to generate composite scores or to classify treatment 'responders' vs 'non-responders')[25, 26] (see Table 2 and Supplementary Table 2). One low quality study of a mindfulness-based intervention in a fibromyalgia sample found that being employed might predict better outcomes in terms of global treatment response (n=77) [26]. Being employed was not investigated in relation to global treatment response in any other studies. The same study [26] found no significant associations with gender, age, education and pain duration, whilst another low quality study (n=90) [25] also found no significant associations between gender or diagnostic category (low back, headache, or neck and shoulder pain) with global treatment response in a mindfulness-based intervention.

Two high quality studies investigated predictors of improvements in sleep or fatigue, both of which identified possible predictors [7, 13] (see Table 2 and Supplementary Table 2). One study of a mindfulness-based intervention with participants with rheumatoid arthritis (n=144) [7] identified that a history of recurrent depression moderated improvements in fatigue, such that those with a history of recurrent depression showed greater improvements in a mindfulness-based therapy compared to a CBT or education-based intervention. The other focused on a mindfulness-based intervention in a mixed chronic pain condition sample (n=115) and suggested that longer pain duration was associated with greater improvements in

interference with sleep [13]. Neither history of depression nor pain duration were investigated in relation to outcomes for sleep or fatigue in any other studies. Gender, age, years of education, income level, or baseline opioid misuse, were not found to be associated with sleep interference outcomes on the basis of one high quality study [13].

Finally, six studies (four high quality, two low quality; five ACT, one mindfulness) reported on outcomes for work, medical visits or patient impression of change. Gender, age and pain duration [13, 32, 43, 55-57], years of education [13, 32, 55-57], income level and baseline opioid misuse [13] were investigate as potential predictors for one or more of these outcomes, but no significant associations were found.

INSERT TABLE 2 ABOUT HERE

Discussion

To our knowledge this is the first attempt to systematically review predictors or moderators of treatment outcome in response to contextual CBT for chronic pain. The findings demonstrate a relative absence of high-quality evidence in this area of research. Out of ninety studies that investigated treatment outcomes for contextual CBT for chronic pain, only twenty investigated predictors or moderators and only seven were specifically designed to investigate predictors or moderators rather than these analyses being post-hoc or exploratory. For the majority of predictors the evidence was inconclusive due to the small number of studies investigating each predictor or inconsistent findings between several studies.

On the basis of this review, there was some evidence that higher psychological distress or history of depression might lead to greater improvements in mindfulness-based interventions for chronic pain [6, 7, 64]. These findings appear consistent with the general literature suggesting that Mindfulness-Based Cognitive Therapy (MBCT) may be more effective for those with a history of several depressive episodes [29, 30, 44, 63]. In

contrast, one high quality RCT [47] found that *lower* psychological distress led to greater improvements in pain-related interference, whilst another found no association between baseline depression diagnosis and outcomes for pain-related interference [58]. One explanation for these apparently opposing findings could be that the latter studies [47, 58] included online ACT interventions in contrast to the face-to-face mindfulness-based approach adopted in the other studies [6, 7, 64], but the number of studies included in this review is too small to draw conclusions. A further consideration is that smaller improvements for those with lower psychological distress at baseline may not reflect less susceptibility to treatment but may merely be due to ceiling effects. That is, those with greater psychological distress at baseline may have more room for improvement. Future research should aim to identify which aspects of emotional functioning predict better treatment response in contextual CBT, and whether these predictors differ depending on the specific treatment approach, the specific methods or delivery mode used, and the outcomes used to define treatment response.

The findings of the current review with regard to demographic predictors of outcome were largely inconsistent, but most typically nonsignificant [13, 25, 26, 32, 43, 52, 55-58]. These findings appear consistent with the previous literature, where attempts to identify any significant relationships between demographic variables and treatment outcome have been largely unsuccessful [36]. In terms of baseline symptoms, the findings of this review were again mixed. Multiple studies investigated pre-treatment pain intensity as a potential predictor with conflicting findings [2, 12, 47, 52] and there were inconsistent findings on the role of longer pain duration across different outcome domains [13, 55, 26, 32, 43, 55-57]. Previous findings on the impact of pain intensity [45, 49, 50] and pain duration [9] on outcome have also been inconsistent and the possible role of ceiling effects should again be considered when interpreting findings related to baseline symptomology. There was limited evidence on the role of chronic pain diagnosis on outcomes [2, 42, 25], although one high quality study found that having a higher number of comorbid chronic pain conditions may predict worse outcomes for pain in a mindfulness-based intervention [2]. A recent systematic review of ACT and mindfulness-based interventions suggested no differences in treatment response between different types of chronic pain [53].

Importantly, no differential patterns were identified between ACT and mindfulness-based methods across any of these potential predictors.

Although the treatments examined here are members of the class of contextual forms of CBT, the designs of treatment reflect significant variability including methods, dose, delivery format and so forth. In many cases, intervention packages also included several components that were modified from, or in addition to, ACT or mindfulness-based approaches (e.g. education around nutrition/ sexual function/ communication/ sleep hygiene etc.). Interventions most likely also include differences in the therapeutic mechanisms or processes they were able to engage. We regard this as important. In fact, it may be precisely these differences in treatment protocols and therapeutic mechanisms that help to clarify differences in individual responsiveness and explain the inconsistent and sometimes contradictory findings between studies. Without thoroughly considering mediators in prediction models we run the risk of masking potential predictor effects. We argue that it may be only when we determine the mechanisms activated in differing treatments that clear predictors and moderators will emerge.

Given that ACT draws on the psychological flexibility model as its theoretical base, it is striking that none of the studies applied this model to investigating predictors or moderators of outcome. It has been proposed that a focus on theoretically-based mechanisms may be key in guiding more effective treatment development and improving outcomes [37]. Of course, an intrinsic part of effective mechanism requires a fit between mechanism and the problems experienced by those seeking treatment. In this sense, if we are to better understand which treatments work best for whom, then we also need to take a theoretically-driven approach to identifying moderators of outcome. We propose that the psychological flexibility model could provide a framework to guide the selection of potential moderators. As a starting point it may be that high or low levels on facets of psychological flexibility may interact with the facets best addressed in a particular treatment and the intensity at which they are addressed. For instance, (a) a person with pain and distress but very good daily engagement may not do well in ACT at all, (b) a person with very low openness may not do well in a treatment unless it helps them to successfully reverse patterns of avoidance, or (c) a person with

profound cognitive fusion, distress, and over identification with beliefs about pain and harm may only do well in a version of ACT that helps them to successfully adopt a separate perspective or sense of self-as-context. Investigating facets of psychological flexibility as possible moderators of outcome may be valuable in developing more targeted and effective interventions for chronic pain.

There were several limitations of this systematic review. Firstly, the majority of the included studies, thirteen of twenty, were not designed to investigate predictors or moderators of outcome. This meant that for some studies, although methodologically sound as treatment outcome studies, the precise methodology adopted for the predictor analyses were unclear and susceptible to bias including selective reporting of positive results (e.g. see Ioannidis [23]). Further research in this area should explicitly plan relevant methods and consider the problems of multicollinearity and potential mediators when investigating predictors. There is also a risk of publication bias as only published articles were included in the review. Second, this review combined studies of ACT and mindfulness-based interventions due to the small number of relevant studies. Whilst both falling under the bracket of contextual CBT approaches, the treatment protocols and mechanisms are, to a degree, unique to each type of therapy. One way to address this variability is to consistently examine moderators in relation to specific therapeutic processes, as we suggested. As the body of evidence increases, these interventions should be investigated separately to identify their unique treatment effects and moderators. Finally, the inconsistencies in the methods used to evaluate outcomes prevented meaningfully combining data across trials, and arguably may contribute to the lack of coherence in the pattern of findings. As has been frequently recommended in the chronic pain literature, the selection of appropriate outcomes in a standardized way is of primary importance if we are to effectively compare the efficacy of interventions across trials [10, 16, 43].

Conclusions

This review aimed to investigate predictors and moderators of treatment outcome in contextual CBT for chronic pain. The findings highlight a relative lack of evidence in this area of research, and even more so a lack of consistency where evidence does exist, with no strong evidence to suggest any one predictor or

pattern of predictors of outcome. Overall, we conclude that whilst many people with chronic pain are likely to benefit from contextual CBT for chronic pain, another proportion will not, and we are not yet able to precisely predict how much benefit is likely for whom.

Some of the most persuasive results identified that higher levels of emotional distress at baseline may predict better outcomes, yet even here results were not fully consistent. It seems likely that the impact of baseline emotional functioning may vary across different treatment approaches and outcome domains. We highlight that it may actually be differences in mediators or therapeutic mechanisms that clarify these apparently inconsistent results in both this and other domains of predictors. We argue that if we are to better understand which treatments work best for whom, then we need to take a theoretically-driven approach to examining both moderators and mediators of outcome. We propose that investigating facets of psychological flexibility as possible moderators of outcome may be valuable in developing more targeted and effective interventions for chronic pain.

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Fig. 1 PRISMA 2009 flow diagram: study search and process

Table 1. Risk of bias and overall study quality

Table 2. Summary of main findings

Supplementary Table 1. Study characteristics

Lead author, Year	Study design (sample size)	Sample characteristics	Intervention and treatment characteristics: modality, duration, format, setting, therapists.	Control/ comparison group	Timing of outcome assessment	Outcomes Predictors (univariate or multivariate associations with outcomes)
Bjornsdottir, 2015 [1]	**COHORT STUDY** Participated in study: 269 **Treatment arms:** Traditional pain management programme: 122 Neuroscience patient education and MBCT: 90 Wait list controls: 57 Completed: 269	Females with chronic pain.	Setting: Inpatient, rehabilitation centre in Iceland Content: Treatment arm (NEM): motor control in conjunction with neuroscience patient education and MBCT. Form: group multidisciplinary rehabilitation programme. Facilitators: Inter-professional team - psychologist, physical therapists, psychiatric nurse, sport therapist, rehabilitation physician, medical massage therapist, nutritionist. Intensity: 4 week programme, 101 hours of activity.	Traditional pain management program (TMP). Waiting list controls	Post-treatment	**HRQL (Icelandic Quality of Life questionnaire).** Low HRQL at baseline (+). *(Mean change TMP = 13.4 and NEM = 12.9 if HRQL < 35 vs. mean change TMP = 6.6 and NEM = 7.8 if HQRL > 35).*
Brotto, 2015 [2]	**CONTROLLED TRIAL** Participated in study: 91 Immediate treatment arm: 62 Wait-list/ delayed treatment: 23 Completed/ analysed: 85	Females with diagnosis of PV, seeking treatment. Immediate treatment arm: mean age 39 years, SD 13.8. Delayed treatment arm: mean age 40.4 years, SD 11.4.	Setting: Outpatient Content: Integrated Mindfulness for Provoked Vestibulodynia (IMPROVED) Treatment – integrated mindfulness-based intervention comprising mindfulness meditation skills, CBT, pain management education and information on sexual function. Form: group intervention. Facilitators: 3 individuals, unknown professions or training. Intensity: 4 sessions, once every 2 weeks.	Wait-list/ delayed treatment. 3 months delay before start of treatment.	4-6 weeks post-treatment, and 6 month follow-up.	**Allodynia (assessed using cotton swab exam) immediately post-treatment:** Higher severity of pretreatment allodynia (-). (p<0.001) Number of chronic pain conditions: ns. **Allodynia (assessed using cotton swab exam) at 6 month follow up:** Higher severity of pretreatment allodynia (-). (p<0.001) Number of comorbid chronic pain conditions (-). (p=0.023).
Cathcart, 2014 [4]	**RCT** Allocated to treatment group: 29 Allocated to wait list control: 29 Completed: 42 (treatment	Chronic tension-type headache. Treatment condition: 43% male Mean age 45.78 years (SD = 13.10)	Setting: Outpatients. University of South Australia Form: group Facilitator: psychologist with formal training in mindfulness therapy and extensive clinical experience in delivery. Content: Brief mindfulness-based therapy (MBT), based on MBCT and MBSR. Focus on headache pain management and related psycho-social sequelae, and stress management. Included body	Wait list control	Post-treatment	**Mindfulness (FFMQ)** **Headache activity (recorded over 2 week period; mean headache intensity, frequency and duration calculated):** Baseline anxiety (DASS-21): ns

	group = 23; wait list control = 19)		scan meditation, formal sitting meditation and 3 minute breathing space. Intensity: Twice-weekly sessions over 3 weeks. Daily 30-min mindfulness meditation practice.			
Davis, 2013 [6]	**RCT** Participated in study: 79 Participated in treatment arm MSER: 39 Participated in treatment arm HT: 40 Completed: 79	Adults (over 18 years) with diagnosis of FM. 98% Female 61% unemployed Mean age = 46.12 years, range = 22-81	Setting: internet-based Form: Individual Facilitators: Access to modules overseen by research assistant. Content: Mindful socioemotional regulation intervention (MSER) based on a mindfulness-based group intervention for emotional regulation. Training focused on mindfulness meditation to increase awareness and acceptance of emotions and use of mindful awareness skills to enhance social experience. Intensity: 12 modules, self-paced, up to 6 weeks duration.	Healthy tips: served as control condition. Online course providing information on daily habits of healthy living.	Up to 40 daily diary reports	**Pain (NRS 0-100):** Depression history = ns **Positive affect (Positive and Negative Affect schedule):** Positive history of depression (+). *Depression history moderated group effects (Depression history×Time×Group slope estimate= −.2029, SE slope estimate = 0.073, t=−2.78, p<.006).* **Negative affect rated 1-5 (Positive and Negative Affect schedule)** Depression history = ns **Social activity engagement (modified item from SF-36 social functioning subscale):** Depression history = ns **Loneliness (1-5 scale):** Positive history of depression (+). *Depression history moderated group effects (Depression history×Time×Group slope estimate=−0.2069, SE slope estimate = 0.096, t=−2.16, p<.04)* **Family stress (1-4 scale):** Positive history of depression (+). *Depression history moderated group effects (Depression history×Time×Group slope estimate = 0.199, SE slope estimate = 0.084, t=−2.36, p<.02)* **Family enjoyment (1-4 scale):** Depression history = ns

Davis, 2015 [7] (based on diary data obtained from Zautra, 2008)	**RCT** Participated in the study: 144 Participated in treatment arm CBT-P: 52 Participated in treatment arm M: 48 Participated in treatment arm E: 44 Completed: 143 (1 drop out from M)	Physician-confirmed diagnosis of rheumatoid arthritis. 68.5% Female mean age 54.28 years (*SD* = 13.80, range 21 to 81).	Setting: primary care Form: Manualized group intervention. Facilitators: doctoral-level clinical health psychologist and an advanced doctoral student in clinical psychology. Prior training in CBT and mindfulness methods for treatment of chronic pain. Content: Mindful awareness and acceptance therapy (M). Focused on developing skills to reduce negative impact of pain and stress and increase positive affect engagement. Intensity: 8 modules, delivered in weekly 2 hour group meetings over 8 weeks.	Comparison groups: CBT for pain (CBT-P); Arthritis education condition (E)	Post-treatment. Up to 30 daily diary reports completed immediately following intervention.	**Pain (NRS 0-100):** History of recurrent depression = ns **Fatigue (NRS 0-100):** History of recurrent depression (+). *History of recurrent depression moderated pre- to post-treatment changes in pain reactivity for fatigue (RD x Group x Time x Δ Pain F = 6.56, p < .0002).* **Morning disability (Rated 1-5):** History of recurrent depression = ns **Interpersonal stress (4 domains: spouse, friends, family, work) (rated 1-4):** History of recurrent depression = ns **Serene affect (rated three adjectives describing serene affect on 1-5 scale):** History of recurrent depression = ns **Anxious affect (rated four adjectives describing anxious affect on 1-5 scale):** History of recurrent depression = ns
Gardner-Nix, 2014 [12]	**CONTROLLED TRIAL** Participated in study: 183 Participated in treatment arm MBCPM: 60 Participated in waiting list control: 59 Completed: 119 (59 dropped out)	Chronic non-cancer pain patients, mixed chronic pain conditions. 90 females. Mean age 52 (range 32 to 79).	Setting: tertiary level hospital pain clinics. Form: group, 12-22 participants in each group, mixture of on-site and off-site participants communicating via telemedicine link from local hospital sites. Facilitator: Physician trained in MBSR Content: Mindfulness-Based Chronic Pain Management Program (MBCPM), adapted from MBSR. More detailed exposure to relationship between pain and the mind-body connection, and training in enhanced self-care (e.g. nutrition, exercise and sleep hygiene). Supplied with CD of meditations relevant to chronic pain sufferers. Intensity: 12 weekly sessions	Control group: waiting list for > 14 weeks prior to start of treatment.	Week 10	**HRQL, Physical Component Score (SF-36):** Lower baseline pain intensity (+). *β = −1.42, t (48) = −2.97, p<0.01.* Baseline burden of suffering and intrusiveness and controllability of illness (PRISM): ns Baseline helplessness (helplessness score of PCS): ns. **HRQL, Mental Component Score (SF-36):** Baseline Usual Pain Intensity (PI NRS): ns Baseline burden of suffering and intrusiveness and controllability of illness (PRISM): ns Baseline helplessness (helplessness score of PCS): ns.

Garland, 2014 [13]	**RCT** Participated in study: 115 Participated in treatment arm MORE: 57 Participated in treatment arm SG: 58 Completed: 67	Chronic non-cancer related pain patients (mixed conditions). All had been prescribed and taken opiods daily/nearly daily for > past 90 days. 68% female Mean age 48 (SD 14) years. Pain average duration 11.2 (SD 10.1) years.	Setting: Primary care Form: manualised group intervention, 8-12 per group. Facilitator: Masters-level clinical social worker, 10 years experience in mindfulness practise. Content: MORE intervention. Involved mindfulness training for increasing metacognitive awareness and acceptance of distress; reappraisal training to regulate negative emotions and enhance sense of meaning; training in savouring techniques to reverse anhedonia and strengthen motivation to engage in valued activities. Participants asked to engage in daily 15 minute mindfulness practice sessions at home guided by a CD. Intensity: 8 weekly 2 hour group sessions	Active control condition: Support group (SG) intervention. Client centred, discussion on chronic pain and opioid use, no change based interventions.	Post-treatment and three-month follow up.	**<u>Functional interference from pain (seven items from pain interference subscale of BPI)</u>** **General activity:** Baseline opioid misuse, gender, age, years of education, income level, pain duration: all ns **Mood:** Baseline opioid misuse, gender, age, years of education, income level, pain duration: all ns **Walking ability:** Baseline opioid misuse, gender, age, years of education, income level, pain duration: all ns **Normal work:** Baseline opioid misuse, gender, age, years of education, income level, pain duration: all ns **Relations with others:** Greater years in pain (+). *β = -0.08, SE = 0.03, P = 0.004* Baseline opioid misuse, gender, age, years of education, income level: all ns **Sleep:** Greater years in pain (+). *β = -0.08, SE = 0.03, P = 0.004* Baseline opioid misuse, gender, age, years of education, income level: all ns **Enjoyment of life:** Greater years in pain (+). *β = -0.10, SE = 0.03, P < 0.001* Baseline opioid misuse, gender, age, years of education, Income level: all ns
Kabat-Zinn, 1985 [25]	**CONTROLLED TRIAL** Participated in study: 90 Participated in treatment-as-usual control group: 21 Completed: 90	Chronic pain (mixed conditions). Females (66.7%) Mean age: 44 years Mean chronicity: 8.1 years. Main diagnosis: LBP (31),	Setting: Outpatients. Hospital clinic, Department of Medicine at the University of Massachusetts Medical Center. Form: group Facilitator: each instructor had practiced mindfulness regularly for many years. Content: Meditation training within a Stress Reduction and Relaxation training programme (SR&RP). Based on the practical application of meditation for coping with stress and pain. A	Control: Treatment as usual (in pain clinic). Monitored over 10 weeks.	Post-treatment Follow-up: 2.5, 4.5, 7, 12 and 15 months after programme completion.	**Average degree of change (Summary Outcome Questionnaire):** Diagnostic category (low back pain; headache; neck and shoulder pain): ns Gender: ns. **Psychological symptoms (GSI from SCL-90-R):** Diagnostic category (low back pain; headache; neck and shoulder pain): Patients with neck and shoulder pain had

		Headache (24), Neck/shoulder (15), other (20)	variety of mindfulness meditations taught and practiced in classes. Intensity: 10 weeks, 2 hour classes once per week. Meditation for 45 minutes minimum per day, 6 days per week for homework.			higher mean pre and post scores than low back-pain patients. *Statistical significance not reported.* Gender (female) (+). *Statistical significance not reported.* **Total Mood Disturbance (POMS):** Diagnostic category (low back pain; headache; neck and shoulder pain: Patients with neck and shoulder pain had higher mean pre and post scores than low back-pain patients. *Statistical significance not reported.* Gender (female) (+). *Statistical significance not reported.*
Kaplan, 1993 [26]	**COHORT STUDY** Participated in study: 77 Completed: 59	FM patients Responders: 87% female 15.7 years in education 6.2 years symptom duration Non responders: 93% female 14.1 years in education 6.8 years symptom duration	Setting: outpatient Form: group format, standardized treatment programme (7-12 individuals per group) Facilitator: ? 2 therapists Content: MBSR programme, modified to include focus on sleep, pain and fatigue. Sessions included meditation, focus on physical, psychological, cognitive and affective reactions to stressors. Emphasis on role of kindness to oneself and its effect on FM. Intensity: once weekly, two hour sessions running for 10 consecutive weeks.	None	Post-treatment	**Global treatment response. Responders (25% improvement in at least 50% of 10 outcome measures) vs nonresponders:** Gender: ns Years of education: ns Age: ns Symptom duration: ns Being currently employed (+). *A greater number of responders (17; 57%) were currently employed than nonresponders (8; 28%).*
McCracken, 2011 [32]	**COHORT STUDY** Participated in study: 225 Completed (and attended follow-up): 168	Adults with chronic pain (mixed conditions) 66.7% female Mean age 46.2 years, SD 10.1. Mean of 13.6 years of education (SD 3.6)	Setting: tertiary care rehabilitation unit. Residential – patients lived independently in apartments close to site. Form: Primarily group sessions, interdisciplinary pain management programme. Facilitator: interdisciplinary team consisting of clinicians from clinical psychology, physical therapy, occupational therapy, nursing, and medicine. Content: ACT treatment programme. Focused on enhancing acceptance of pain and other psychological experiences, contact with the present moment, self-as-observer, cognitive defusion, values, and committed action. Intensity: 3 - 4 weeks depending on severity and complexity. Treatment delivered 5 days per week, 6 1/2 hours per day (including 2 1/4 hours physical conditioning, 1 hour psychological methods, 30	None	Post-treatment and 3 month follow up.	**Depression measure (BCMDI):** Age, gender, education, duration of pain: all ns **Pain-related anxiety measure (PASS-20):** Age, gender, education, duration of pain: all ns **Physical disability (SIP):** Age, gender, education, duration of pain: all ns **Psychosocial disability (SIP):** Age, gender, education, duration of pain: all ns **Medical visits in last 6 months:** Age, gender, education, duration of pain: all ns **Pain intensity (average over past week; NRS 0-10):** Age, gender, education, duration of pain: all ns

			mins mindfulness training, 1 hour activity management, remainder of time other skills training/ health education.)			
McCracken, 2007 [34]	**COHORT ANALYTIC** Participated in study: 287 Participated in highly disabled group: 53 Completed: 53 3 month follow up: 29 (highly disabled group only) Participated in clinical comparison (standard, less disabled group): 234 Completed: ?	Chronic pain (mixed conditions). Highly disabled group: 64.2% female Mean age 47.6 years (SD= 11.6) Pain duration 140 months (SD = 103) Standard group: Mean age 46 years (SD = 11.7) Mean chronicity of pain 138.8 months (SD = 132.2)	Setting: Hospital-based. Highly-disabled group were accommodated onsite with nursing care provided. Form: group Facilitators: ? Content: Interdisciplinary pain management programme based on contextual CBT. Main treatment elements were daily general physical exercise, education, skills training for activity management, psychology sessions. Treatment processes incorporated principles of exposure, acceptance, cognitive defusion, mindfulness and values-based methods. Intensity: 80hrs of treatment over 3 weeks.	Clinical comparison: Standard, less disabled group.	Post-treatment and 3 month follow up.	**Psychosocial disability (SIP):** Being highly disabled (+). *Highly disabled group achieved higher effect size: .94 versus .77 for standard group. No p values reported.* **Physical disability (SIP):** Being highly disabled (-). *Standard group achieved higher affect size. No p values reported.* **Depression (BDI):** Being highly disabled (+). *Highly disabled group achieved higher effect size: 1.22 vs .84 for standard group. No p values reported.* **Pain-related anxiety measure (PASS):** Effect size similar between groups. **Functional measure (sit-to-stand task performance):** Being highly disabled (-). *Standard group achieved higher effect size. No p values reported.* **Usual pain intensity (NRS 0-10):** Being highly disabled (-). *Standard group achieved higher affect size. No p values reported.* **Pain-related distress (NRS 0-10):** Effect size similar between groups.
Rosenzweig, 2010 [42]	**COHORT STUDY** Participated in study: 133 Completed: 99	Adults with chronic pain (mixed conditions) Mean age 49.8 years, range 23 – 78 years 84% (n=111) female	Setting: outpatients, academic medical centre (University Hospital, USA) Form: Group Facilitator: professionally trained MBSR instructors Content: Standard MBSR course. Focused on mindfulness meditation techniques. Intensity: 8 week course, weekly 2.5 hour classes. Participants instructed to practice 20-25 minutes per day, 6 days per week, + 1 full day (7 hrs) practice.	None	Post-treatment	**Health-related quality of life (SF-36)** Having arthritis (+). *Those with arthritis showed greatest change (mean d=.67).* Having chronic headache/migraine (-). *Those who reported chronic headache/migraine showed the smallest magnitude change (mean d=.41).* **Psychological distress (SCL-90-R)** Having fibromyalgia (-). *Those with fibromyalgia showed small to medium reduction in distress (mean d=.39),*

		Mean pain duration = 12.1 (SD 10.2) years.				*compared to medium to large reductions in other chronic pain subgroups (mean d's between .53 and .86).*
Scott, 2015 [43]	**COHORT STUDY** Participated in study: 575 Completed:476	Adults with chronic pain (mixed conditions). 318 female Mean age 46.20 years (SD = 11.20 years). Mean pain duration of 150.30 (SD = 127.31) months. Mean years of education 13.27 (SD = 4.07).	Setting: residential, specialty pain treatment centre, London. Content: ACT within an interdisciplinary treatment context. Included experiential exercises, metaphor, mindfulness practice, cognitive defusion techniques, and other values and goals-focused methods. Form: Group Facilitators: MDT of psychologists, occupational therapists, physical therapists, nurses and physicians. Intensity: 4 full days of treatment per week for 4 weeks.	None	Post-treatment	**Patient Global and Specific Impressions of Change (PGIC and PIC):** Age: ns Duration of pain: ns Gender: ns
Trompetter, 2016 [47]	**RCT** Participated in study: 238 Participated in ACT: 82 Participated in EW: 79 Participated in wait list: 77 Completed: 167 (ACT = 53; EW = 50; wait list = 64)	Chronic pain (mixed conditions). 76% female Mean age 52.80 years (SD = 12.37) 63% suffered from pain for over 5 years	Setting/ form: internet-based self-help program. Facilitators: trained clinical psychology students. Content: ACT. Modules consisted of text, metaphors and exercises based on principles of ACT. Two additional modules focused on psychoeducation and communicating about pain complaints within social context. Intensity: 9 week program, advised to spend 30 mins per day or 3h per week on program.	Controls: Expressive Writing, Wait List.	3 month follow-up.	**Pain-interference (MPI pain interference subscale):** <u>Potential moderators of outcome:</u> Age: ns Gender: ns Educational level: ns Employment status: ns Pain duration: ns Higher baseline pain intensity (0-10 NRS) (+). *ACT vs EW: b = -2.018, p = 0.003. ACT more effective than EW for those with higher baseline pain intensity.* ACT vs WL: ns Pain Disability (PDI): ns Depression (HADS): ns Anxiety (HADS): ns Emotional wellbeing (MHC-SF): ns Higher psychological wellbeing (MHC-SF) (+): *ACT vs. EW: b = −0.424, p = 0.035; ACT vs. WL: b = −0.419, p = 0.022. ACT was more effective than EW and WL for those with higher psychological wellbeing at baseline.* Social wellbeing (MHC-SF): ns

						Potential predictors of outcome: Age: ns Gender: ns Educational level: ns Employment status: ns Pain duration: ns Pain intensity (0-10 NRS): ns Pain Disability (PDI): ns Lower depressive symptoms (HADS) (+): *ACT vs EW: b = 0.632, p = 0.003* *ACT vs WL: b = 0.628, p = 0.001* Lower anxiety (HADS) (+): *ACT vs EW: b = 0.806, p < 0.001* *ACT vs WL: b = 0.529, p = 0.013* Higher emotional wellbeing (MHC-SF) (+): *ACT vs EW: b = −0.554, p = 0.007* *ACT vs WL: b = −0.627, p = 0.001* Higher psychological wellbeing (MHC-SF) (+): *ACT vs EW: b = -0.384, p < 0.001* *ACT vs WL: b = -0.377, p < 0.001* Social wellbeing (MHC-SF): ns
VanBuskirk, 2014 [52]	**RCT** Participated in study: 87 Participated in treatment arm ACT: 46 Participated in treatment arm CBT: 41 Completed/ analysed: 87	Chronic non-malignant pain, duration > 6 months. 55.2% female. Mean age 56.25 (SD = 11.93).	Setting: Primary care Content: ACT intervention focused on changing expectations from elimination of pain to living with pain; mindfulness strategies; focus on values and goals. Form: group Facilitators: 2 therapists (one with doctorate and one doctoral student) + one additional licensed psychologist who led one ACT group. Intensity: Eight 90-min weekly sessions	8 week group CBT intervention	Post-treatment and 6 month follow up.	**Physical activity level (accelerometer data)** Gender (female) (+). *(b = 6804.08, p = .02, sr2 = .629).* BPI severity: ns BPI interference: ns Mental health (SF-12): ns Physical health (SF-12): ns Pain-anxiety (PASS-20): ns Depressive symptoms (BDI): ns Presence of major depressive disorder: ns
Vowles, 2008 [55]	**COHORT STUDY** Participated in study: 187 Participated in 3 week course of treatment: 145 (77.5%) Participated in 4 week course of	Chronic pain (mixed conditions). 64.2% Female Mean age 47.3 years (*SD* 11.4) Mean years of education 12.5 (*SD* 3.0).	Setting: tertiary care pain rehabilitation unit, Southwest England. Form: group format Facilitator: a team of psychologists, physical therapists, occupational therapists, nurses, and physicians. Content: ACT and mindfulness-based methods adapted to an interdisciplinary rehabilitation treatment setting. Included mindfulness training,	None	Post-treatment and 3 month follow up.	**Pain intensity (NRS 0-10) (pre-to post-treatment and post-treatment to follow up)** Gender, age, education and pain duration: ns **Depression (BCMDI) (post-treatment)** Longer pain duration (+). *Pain duration accounted for significant variance: $\Delta r^2 = .05$, $p < .05$, β (final) = -.23, $p < .01$* Gender, age, education: ns

	treatment: 42 (22.5%) Completed: 171 Provided data at 3 month follow up: 114 (66.7% of treatment completers)	Median pain duration 96.0 months (range: 8.0 to 516.0 months).	values clarification, exposure-based techniques, and cognitive defusion exercises. Intensity: 3 or 4 weeks in duration. 5 days of treatment per week for 6.5 hours per day. Each day had 2.25 hr of physical conditioning sessions and 1.5 hr of psychological session content, including mindfulness training. Remaining time focused on activity skills management and health/medical education.			**Depression (post-treatment to follow-up)** Gender, age, education and pain duration: ns **Pain-related anxiety (PASS-20) (pre- to post-treatment and post-treatment to follow up)** Gender, age, education and pain duration: ns **Physical disability (SIP) (pre- to post-treatment)** Greater years of education (+). *Education accounted for significant variance from pre-to post treatment: $\Delta r^2 = .04$, $p < .05$, β (final) = -.21, $p < .01$* Gender, age and pain duration: ns **Physical disability (post-treatment to follow-up)** Gender, age, education and pain duration: ns **Psychosocial disability (SIP) (pre- to post-treatment)** Greater years of education (+). *Education accounted for significant variance and regression co-efficient was significant. $\Delta r^2 = .04$, $p < .05$, β (final) = -.22, $p < .01$* Gender, age, pain duration: ns **Psychosocial disability (post-treatment to follow-up)** Gender, age, education and pain duration: ns **Physical measures (two-min walk and sit-to-stand; pre-to post treatment and post-treatment to follow-up)** Gender, age, education and pain duration: ns **Medical visits (pre-to post treatment and post-treatment to follow-up)** Gender, age, education and pain duration: ns
Vowles, 2010 [56]	**COHORT STUDY** Participated in study: 187 Completed/ analysed: 114	Chronic pain (mixed conditions). 64.2% female Mean age 46.1 years (SD = 10.0) Median pain duration 96.0 months (range: 8.0–360.0).	Setting: specialist chronic pain setting. Form: group format with individual meetings once weekly. Residential pain management programme (patients housed adjacent to hospital during treatment). Facilitator: interdisciplinary team of psychologists, physical therapists, occupational therapists, nurses, and physicians. Content: ACT for use in chronic pain settings within an interdisciplinary team. Focus on psychological flexibility.	None	Post-treatment and 3 month follow up.	**Pain intensity (average over past week, 0 to 10 NRS):** Age, education, gender and pain duration = ns **Depressive symptoms (BCMDI):** Age, education, gender and pain duration = ns **Pain-related anxiety measure (PASS):** Age, education, gender and pain duration = ns **Physical and psychosocial disability (SIP):** Age, education, gender and pain duration = ns

			Intensity: 3 or 4 weeks in duration (depending on level of disability). 5 per week, 6.5 hours per day. Each treatment day included approximately 2.25 h of physical conditioning, 1 h of psychological methods, 30 min of mindfulness training, and 1 h of activity management. Remainder of the time focused on skills training and health/medical education.			**Pain-related medical visits (patient estimates over past 6 months):** Age, education, gender and pain duration = ns **Physical functioning measures (two-min walk and sit-to-stand):** Age, education, gender and pain duration = ns
Vowles, 2011 [57] (follow-up data from Vowles, 2008)	**COHORT STUDY** Participated in study: 171 Completed 3 year follow-up: 108	Chronic pain (mixed conditions). Female (62%) Average age 47.1 years (SD =10.7), 13.2 years of formal education (SD = 2.8). Median pain duration 96 months (range: 13-360).	Setting: specialist chronic pain setting. Form: group format with individual meetings once weekly. Residential pain management programme (patients housed adjacent to hospital during treatment). Facilitator: interdisciplinary team of psychologists, physical therapists, occupational therapists, nurses, and physicians. Content: ACT for use in chronic pain settings within an interdisciplinary team. Focus on psychological flexibility. Intensity: 3 or 4 weeks in duration (depending on level of disability). 5 days per week, 6.5 hours per day (approx 2.25 hrs of physical conditioning, 1 hr of psychological methods, 30 min of mindfulness training. Remaining time focused on skills training or medical/health education.)	None	3 year follow-up.	**Pain-related medical visits (patient estimates over past 6 months):** Age, gender, education and pain duration = ns **Depressive symptoms (BCMDI)** Age, gender, education and pain duration = ns **Pain-related anxiety measure (PASS):** Age, gender, education and pain duration = ns **Physical and psychosocial disability (SIP):** Age, gender, education and pain duration = ns
Wetherell, 2016 [58]	**RCT** Participated in CBT treatment arm: ? Participated in ACT treatment arm: ? Completed: 114	Adults with non-malignant chronic pain conditions. Female (50.9%). Mean age 55 (SD=12.5; range = 18-89) years. Average pain duration 15 years (SD=13.5).	Setting: ? Form: group Facilitator: ? Content: ACT Intensity: Once weekly 90- minute sessions over 8 weeks.	Comparison group: CBT, same format as ACT	Post-treatment and at 6-month follow up.	**Treatment response (defined as at least 30% decrease on BPI interference subscale), post-treatment:** Baseline depression diagnosis: ns Older age (+). *Age x treatment interaction was significant predictor of treatment response (OR 1.07, z = 3.84, p < .049). Older adults responded better to ACT and younger adults responded better to CBT.* **Treatment response (defined as at least 30% decrease on BPI interference subscale), follow-up:** Baseline depression diagnosis: ns Older age (+). *Age x treatment interaction was significant predictor of treatment response (OR 1.08, z = 4.66, p < .031. Older adults responded better to ACT and younger adults responded better to CBT.*

Zautra, 2008 [64]	**RCT** Allocated to treatment/control arm: 144 Participated in P treatment arm: 51 Participated in M treatment arm: 47 Participated in E (control) arm: 44 Completed/ analysed (pre-post): 137 (P = 50; M = 44; E = 43) Completed/ analysed (follow-up): 131 (P = 47 M = 44; E = 40)	Rheumatoid Arthritis. 68.1% female. Mean age: women (50.62 years); men (62.11 years) RA duration: women (11.59 years); men (15.43 years)	Setting: hospital outpatients Form: Group, 5 to 8 participants. Facilitator: Doctoral-level psychologists, advanced doctoral student and predoctoral students. Content: Mindfulness-based emotion regulation therapeutic program, drawing on MBSR. Skills to reduce negative impact of stressful life events and illness burden and enhance positive social engagements despite pain and stress. 10 minute meditations in sessions and for home practice. Intensity: 8 week intervention, 2-hr weekly sessions.	Comparison: CBT for pain Control: Education group.	Daily diaries over 30 days post-intervention.	**Pain (NRS 0-100):** History of recurrent depression (RD): ns. **Positive affect (Positive and Negative Affect Schedule):** History of recurrent depression (+) *Time X Group X RD interaction, F(2, 121) = 8.63, p < .001. Those with history of recurrent depression in the mindfulness condition showed greater increase in positive affect than participants in other groups. D = 0.78* **Negative affect (Positive and Negative Affect Schedule):** History of recurrent depression (+) *Time x Group x RD interaction, F(2, 121) = 6.51, p < .01. Those with history of RD in the mindfulness condition reported greater decreases in negative affect than participants in other treatment groups. D = -0.89* **Depressive symptoms (six items rated yes or no):** Time X Group X RD interaction = ns.

Supplementary Table 2. Summary of all findings by quality and treatment type

Predictor	Significant findings		Non-significant findings	
	Treatment	*Outcome/s*	*Treatment*	*Outcome/s*
Demographics				
Gender (female)			<u>High quality</u>	
			ACT	pain; psychosocial disability; emotional functioning; physical functioning; medical visits [55]
			ACT	pain; psychosocial disability; emotional functioning physical functioning; medical visits [56]
			ACT	patient impression of change [43]
			M	HRQL; social functioning; emotional functioning; physical functioning; sleep; work [13]
	<u>Low quality</u>		<u>Low quality</u>	
	M	+ emotional functioning [25]	M	Global treatment response [25]
	ACT	+ physical functioning [52]	ACT	psychosocial disability; emotional functioning; physical functioning; medical visits [57]
			M	Global treatment response [26]
			ACT	psychosocial disability; emotional functioning; physical functioning; medical visits [32]
Older age	<u>High quality</u>		<u>High quality</u>	
	ACT	+ overall interference [58]	ACT	Pain; psychosocial disability; emotional functioning; physical functioning; medical visits [55]
			M	HRQL; social functioning; emotional functioning; physical functioning; sleep; work [13]
			ACT	Patient impression of change [43]
			ACT	pain; psychosocial disability; emotional functioning; physical functioning; medical visits [56]
			<u>Low quality</u>	
			ACT	psychosocial disability; emotional functioning; physical functioning; medical visits [32]
			ACT	psychosocial disability; emotional functioning; physical functioning; medical visits [57]
			M	global treatment response [26]

Higher years of education	High quality ACT	+ psychosocial disability (post-treatment) + physical functioning (post-treatment) [55]	High quality ACT M ACT Low quality ACT ACT M	pain; psychosocial disability (follow-up); emotional functioning; physical functioning (follow-up); medical visits [55] HRQL; social functioning; emotional functioning; physical functioning; sleep; work [13] pain; psychosocial disability; emotional functioning; physical functioning; medical visits [56] psychosocial disability; emotional functioning; physical functioning; medical visits [32] psychosocial disability; emotional functioning; physical functioning; medical visits [57] Global treatment response [26]
Being employed	Low Quality M	+ global treatment response [26]		
Income level			High quality M	HRQL; social functioning; emotional functioning; physical functioning; sleep; work [13]
Symptoms				
Higher pre-treatment pain intensity/ allodynia severity	High quality M M ACT	- pain [2] - physical functioning [12] + overall interference [47]	High quality M Low quality ACT	emotional functioning [12] Physical functioning [52]
Lower pain interference			Low quality ACT	Physical functioning [52]
Longer pain duration	High quality M ACT	+ HRQL (interference in enjoyment of life) + social functioning + sleep [13] + emotional functioning (depression; post-treatment) [55]	High quality ACT M ACT ACT	pain; psychosocial disability; emotional functioning (depression, follow-up; anxiety, post-treatment & follow-up); physical functioning; medical visits [55] HRQL (interference in general activity); emotional functioning; physical functioning; work [13] pain; psychosocial disability; emotional functioning; physical functioning; medical visits [56] patient impression of change [43]

		Low quality ACT psychosocial disability; emotional functioning; physical functioning; medical visits [57] ACT psychosocial disability; emotional functioning; physical functioning; medical visits [32] M global treatment response [26]
More highly disabled	Low quality ACT - pain + psychosocial disability + emotional functioning - physical functioning [34]	
Chronic pain condition		
Arthritis	Low quality M + HRQL [42]	
Chronic headache/ migraine	Low quality M - HRQL [42]	
Fibromyalgia	Low quality M - emotional functioning [42]	
Diagnostic category (low back/ headache/ neck and shoulder pain)		Low quality M Global treatment response [25]
Higher number of comorbid pain conditions	High quality M - Pain [2]	
Emotional factors		
Positive history of depression/ presence of depressive disorder	Low quality M + social functioning (family stress; loneliness) + emotional functioning (positive affect) [6]	High quality ACT Overall interference [58] Low quality ACT Physical functioning [52] M pain, social functioning (social activity engagement; family enjoyment); emotional functioning (negative affect) [6]

History of recurrent depression	<u>High quality</u> M M	+ emotional functioning: positive and negative affect [64] + fatigue [7]	<u>High quality</u> M M	pain; emotional functioning; physical functioning; social functioning [7] pain; emotional functioning: depression [64]
Higher baseline psychological wellbeing (MHC-SF)	<u>High quality</u> ACT	+ overall interference [47]		
Higher baseline emotional wellbeing (MHC-SF)	<u>High quality</u> ACT	+ overall interference [47]		
Lower baseline depression (HADS)	<u>High quality</u> ACT	+ overall interference [47]	<u>Low quality</u> ACT	Physical functioning [52]
Lower baseline anxiety (HADS)	<u>High quality</u> ACT	+ overall interference [47]	<u>Low quality</u> M ACT	Pain [4] Physical functioning [52]
Baseline opioid misuse			<u>High quality</u> M	Interference in enjoyment of life; interference in general activity; social functioning; emotional functioning; physical functioning; sleep; work [13]
Baseline PRISM score			<u>High quality</u> M	Emotional functioning; physical functioning [12]
Baseline helplessness			<u>High quality</u> M	Emotional functioning; physical functioning [12]
Baseline physical health (SF-12)			<u>Low quality</u> ACT	**helen gilpin** Physical functioning [52]
Baseline mental health (SF-12)			<u>Low quality</u> ACT	Physical functioning [52]
Other				
Lower baseline HRQL	<u>High quality</u> M	+ HRQL [1]		

+ = associated with better outcome. - = associated with poorer outcome for the specified outcome domain, regardless of direction of scale. ACT = ACT intervention; M = Mindfulness-based intervention.

Supplementary information: Search strategy (EMBASE)

1. mindfulness.mp. or exp mindfulness/ or vipassana.mp. or meditation.mp. or exp meditation/ or "mindfulness-based stress reduction".mp. or "MBSR".mp. or "mindfulness-based cognitive therap*".mp. or "MBCT".mp. or "acceptance-based".mp. or "acceptance based".mp. or "acceptance and commitment".mp. or exp "acceptance and commitment therapy"/
2. chronic pain/ or "complex regional pain syndrome"/ or musculoskeletal pain/ or backache/ or low back pain/ or neck pain/ or fibromyalgia/ or referred pain/ or neuropathic pain/ or Osteoarthritis/
3. ("chronic pain" or "generalised pain" or "generalized pain" or "complex regional pain syndrome*" or "CRPS" or "back pain" or "low back pain" or "musculoskeletal pain" or "neck pain" or fibromyalgia or "neuropathic pain" or "shoulder pain" or "knee pain" or "hip pain" or "osteoarthritis" or "complaints arm neck shoulder" or "CANS" or "whiplash associated disorder" or "WAD" or "repetitive strain injury").tw.
4. or/2-3
5. 1 and 4
6. limit 5 to (human and english language and (adult <18 to 64 years> or aged <65+ years>))