






# BMJ Open Use of behavioural activation to manage pain: a systematic scoping review

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## ABSTRACT

**Background** Behavioural activation (BA) is an effective treatment for depression; however, it is unclear if it can be used to manage pain.

**Objectives** To conduct a scoping review of primary research that reported using BA to support people living with chronic pain to understand how BA had been used in relation to pain. In addition, we wanted to understand whether there were any reported changes in that pain, and how and who delivered BA.

**Eligibility criteria** Primary research published in English.

**Sources of evidence** We searched seven databases MEDLINE, Ovid Embase, Ovid Emcare, PsycINFO, CINAHL, Scopus and Web of Science, for primary research. No initial date limit was used with the date the searches were conducted used as the end date limit (1 July 2021).

**Charting methods** A customised data extraction table was developed, piloted and used.

**Results** 551 papers were screened for inclusion, with 15 papers included in our review. Studies were conducted in North America and in Canada. These included three case studies, nine uncontrolled trials and three randomised controlled trials. Only two studies reported pain as the primary outcome. BA was applied across a range of pain related conditions. The dose of BA ranged from 3 to 16 sessions. Duration of treatment was 3 weeks to 12 months. Most studies reported reductions in pain following exposure to BA.

**Conclusion** BA has the potential to reduce pain. Caution needs to be exercised in the interpretation of these findings as a high risk of bias was observed in most studies. High-quality research is required to test if BA is an effective intervention for chronic pain.

## INTRODUCTION

One in three people will experience chronic pain in their lifetime.<sup>1</sup> Living with pain can prevent participation in enjoyable and everyday activities, and reduce overall well-being.<sup>1</sup> In 2018, chronic pain was estimated to cost \$A80b, affecting 3.24 million people.<sup>2</sup> In some Western countries, chronic pain surpasses heart disease, cancer and diabetes in terms of total costs.<sup>2</sup> International guidelines for chronic pain management consider education, physical activity and psychological therapies as first line intervention.<sup>3</sup> Systematic reviews suggest that

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We provide a comprehensive summary of the published literature on the application of behavioural activation (BA) to manage pain.
- ⇒ We aimed for optimal transparency by publishing our a priori protocol and rigour by adhering to Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines.
- ⇒ We excluded research involving children, conducted in hospital settings, and where BA was not the primary focus.

cognitive-behavioural therapy (CBT) and acceptance and commitment therapy (ACT), are effective for the treatment of chronic pain<sup>4 5</sup> and depression.<sup>6 7</sup> Currently, these are the only psychological treatments recommended in the National Institute for Health and Care Excellence<sup>3</sup> guidelines for chronic pain. However, CBT and ACT are complex psychological treatments, requiring extensive and expensive training.<sup>8</sup> This represents a barrier for communities where accessing specialist workers is challenging which, in part, compels us to identify alternative treatments for pain.

Behavioural activation (BA) is an alternative to CBT and ACT, as a treatment for depression. It is based on the idea that when people plan and set aside time for pleasurable activities, their mood is enhanced. Recent trials indicate that BA may be as effective as CBT for the treatment of depression. In an equivalence trial,<sup>9</sup> CBT was compared with BA with 440 trial participants, (adults with moderate to severe depression). BA was delivered by junior mental health workers (no formal psychological qualifications or training) who received 5 days of training, whereas CBT was delivered by qualified psychotherapists (post-graduate CBT qualification). BA was shown to be equally effective in reducing depressive symptoms. If BA can deliver similar outcomes for depression as CBT, could it also be an alternative treatment for chronic pain? If so,

it may increase access to interventions for people living with pain.

There are several reasons why BA might be beneficial in chronic pain management. People with chronic pain often perceive activity as being unsafe or inducing increased pain, although activity may gradually decrease pain.<sup>10</sup> There is significant evidence that exercise interventions are an effective treatment for pain<sup>11 12</sup>; authors and peak bodies recommend primary care physicians prescribe exercise, noting its effectiveness at reducing pain without the side effects of opioid medications.<sup>11 13</sup> In this sense, we consider exercise to be activity rather than a strenuous endeavour. For people living with chronic pain, it is important to consider activity that is both within the means of the person and that which may challenge someone to extend a little further. There is a complex, yet poorly understood, relationship between chronic pain and depression. Their coexistence can exacerbate each other, and people with chronic pain are more likely to develop depression and people living with depression may be more likely to develop chronic pain.<sup>14 15</sup> The existence of one in the presence of the other also leads to poorer prognosis and outcomes.<sup>14 15</sup> In this sense, it is possible that if BA can reduce depression for someone with chronic pain, it may reduce the chronic pain itself. Additionally, it may improve well-being and the potential to cope with chronic pain. Developing a sense of mastery (a core component of BA) and the reward that comes from undertaking activities and achieving goals may be pivotal in this. Despite the inference and theoretical argument that BA may be an effective intervention for people with chronic pain,<sup>16</sup> the extent to which this has been tested is not clear.

This scoping review considers primary research into BA for chronic pain in people with or without a comorbid psychological condition. We were interested in understanding how BA has been used in relation to pain management, potential changes in pain, and how and by whom BA was delivered.

## METHODS AND ANALYSIS

A scoping review is appropriate when the intent is to scan the body of literature and explore the research conducted.<sup>17</sup> Consistent with this approach, evidence relating to BA and chronic pain, study types, measures, and samples, were mapped.

### Design

The methodological approach proposed by Arksey and O'Malley<sup>18</sup> and Peters *et al*<sup>19</sup> was used. The protocol was published in the *BMJ Open*.<sup>20</sup>

### Review questions

The following questions were used to frame the review:

1. What studies have been published on the use of BA to support patients living with chronic pain?

2. How has BA been applied to support patients with chronic pain?
3. How has BA been integrated with other models of care/treatments for people living with chronic pain?
4. What was the reported effect of BA on pain and pain outcomes?

The fourth question was added to those originally identified in the protocol. It was believed the effect of BA on pain outcomes was an important aspect when considering whether it is a worthwhile treatment.

## Selection criteria

### Population

The population of interest was people over 18 years with chronic pain, such as back or musculoskeletal pain, arthritis and cancer.

### Concept

We were interested in how BA has been used to support people living with chronic pain, with a focus on activity scheduling. BA aims to increase activity, which introduces routine, feelings of reward and mastery of daily activities. We excluded studies where BA was not the primary focus of the intervention.

### Context

Our focus was on the application of BA for the longer-term management of pain in community settings. Patients needed to be living in their own or residential homes. As hospitals are primarily focused on acute care, we excluded studies where BA was delivered in inpatient settings.

## Types of studies

We included primary research including observational studies, experimental studies, case studies and clinical audits. Opinion papers and systematic/scoping reviews were excluded on the basis they were not primary research, this reflects a refinement of our protocol.

## Search strategy

The following three steps were followed:

Step 1: As recommended by Arksey and O'Malley,<sup>18</sup> we searched one relevant online database (MEDLINE) to inform the search strategy, which is detailed in the protocol.<sup>20</sup>

Step 2: Keywords, Medical Subject Headings (MeSH), and index terms, were identified across the included databases.

Step 3: A search strategy was developed for each database (see online supplemental file 1). Studies were restricted to English. A preliminary search of MEDLINE, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science was conducted with no start date applied, and an end limit of 22 July 2020 (date searches conducted). This was completed to gain an understanding of the studies that may be yielded and ensure an empty review would not ensue. All databases (MEDLINE, Cochrane Central Register of Controlled Trials, Scopus, Web of Science,

PsycINFO, Ovid EMCARE, Ovid EMBASE and CINAHL) were then searched with no start date and an end date of 1 July 2021 (date searches conducted).

### Study selection

Citations were imported to Endnote (Clarivate Analytics, Boston, Massachusetts, USA), duplicates removed, then uploaded to Covidence ([www.covidence.org](http://www.covidence.org)). Title and abstracts were screened by SW/MJ/TE/KT and full-text screening was conducted by MJ and SW, with disagreements resolved by RG. Reasons for exclusion were noted. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews Checklist.<sup>21</sup>

### Data extraction, charting and presentation

The data extraction form was tested with three studies from the initial search to ensure relevant results (interventions, populations, study methods and outcomes of significance to the review) were extracted. It informed the final data extraction form design. Included studies were entered into the data extraction tool which provided a transparent summary of studies, addressing specific subquestions and thereby the overarching review question.

### Patient and public involvement

A person with a lived experience of chronic pain (TC) was involved in developing/preparing the protocol<sup>20</sup> and manuscript.

## RESULTS

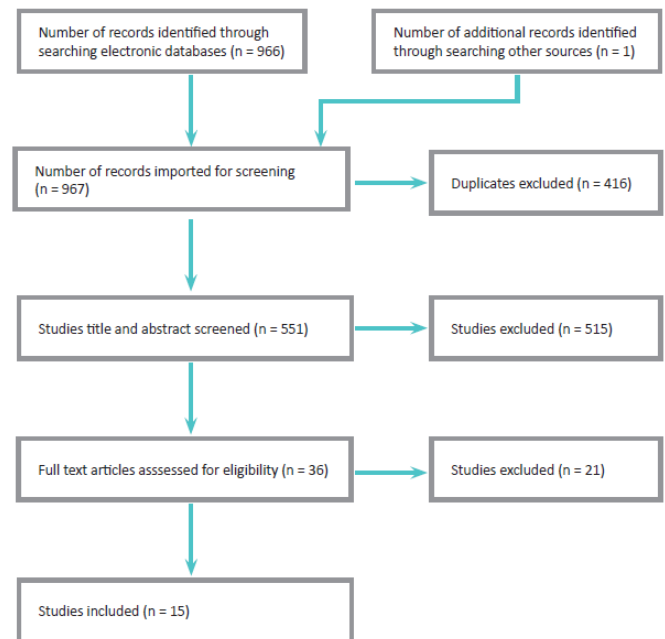
Of the 967 identified papers, 551 were screened by title and abstract, and 36 by full text. Reasons for exclusion at full text included: wrong intervention (12), wrong study design (2), duplication (1), not in English (1), wrong outcomes (3) or conference paper (2). Fifteen publications were included in the review (see figure 1).

### Characteristics of included studies

Thirteen studies were conducted in the USA, and two<sup>22 23</sup> in Canada. Three studies<sup>24–26</sup> were randomised controlled trials (RCTs), nine<sup>22 23 27–33</sup> uncontrolled trials and three<sup>34–36</sup> case studies (table 1).

### Study settings

Studies were conducted across a range of settings including outpatient services at university hospitals/medical centres,<sup>24 26 30–32</sup> veteran medical centre,<sup>29</sup> psychology clinic,<sup>34</sup> primary care practices,<sup>25</sup> and four studies occurred in rehabilitation services.<sup>22 23 27 36</sup> One study<sup>28</sup> delivered BA via non-government organisations; while another<sup>33</sup> reported BA delivered in a community-based ageing centre and a community-based mental health site. In the final study,<sup>35</sup> it was evident that delivery



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

occurred in the community, however, we were unable to determine the setting.

### Pain as primary outcome and secondary outcome

In two studies,<sup>34 35</sup> pain was the primary outcome; in the remaining studies, it was a secondary outcome. Pain and post-traumatic stress disorder (PTSD) were reported as the primary outcomes in two studies,<sup>23 29</sup> while depression and PTSD were the primary outcomes in two studies.<sup>26 36</sup> In five studies,<sup>24 27 28 30 31</sup> the primary outcome was depression. Three studies<sup>25 32 33</sup> considered feasibility as the primary outcome. In the remaining study,<sup>22</sup> the primary outcome was return to work.

### Pain-related conditions

BA was applied to a variety of pain related conditions, including lower back pain,<sup>34</sup> physical injuries,<sup>26 36</sup> work-related musculoskeletal disorders or work-related disability,<sup>22 23 27</sup> cancer,<sup>24 30 31</sup> HIV<sup>25 35</sup> and chronic pain.<sup>29 32 33</sup> One study<sup>28</sup> included people with a range of chronic health conditions.

### Comorbid psychological conditions

In seven studies, patients had comorbid psychological conditions including depression,<sup>24 25 27 28 30 31 35</sup> and PTSD.<sup>23 26 29 34 36</sup> In one study,<sup>33</sup> enrolled participants were experiencing a variety of mental health disorders. Two studies<sup>22 32</sup> did not focus on patients with comorbid psychological conditions.

### Assessments of pain

The studies used different pain assessment approaches, including the Pain Interference Short Form Scale (PROMIS)<sup>37 32</sup> the bodily pain component of the Medical Outcomes Study Short Form (SF36-BP)<sup>38 24 28 30 31</sup> and the

**Table 1** Characteristics of included studies

Study	Study design/ methodology	Aim/research question/s	Population	n =	Pain and pain measures	Setting	Intervention	Outcome/ findings
Brooks <i>et al</i> 2021 USA <sup>33</sup>	Mixed-methods - pre- and post-intervention and semi-structured interview	To examine acceptability, feasibility, and preliminary effectiveness of BA-PR	50 years+comorbid chronic pain and mental health conditions Age: 55–62 years (M=57.1, SD 2.12)	8	Comorbid chronic pain. NRS 0–10; Chronic Pain Coping Inventory	Community-based ageing centre and Community-based mental health site.	BA-PR 6 weeks, 2 hours, group-based, weekly, older peer and clinician co-facilitated pain rehab intervention	Non-significant reductions in pain intensity. Improvements in active and passive pain coping strategies.
Hooker <i>et al</i> 2020 USA <sup>32</sup>	Single-arm, mixed methods—preintervention and postintervention and interview at follow-up	To evaluate feasibility and acceptability of BA in urban family medicine clinic.	18+living with chronic pain Age: 24–72 years (M=47.8, SD11.6)	30	Chronic pain. PROMIS	Primary care clinic (urban family medicine clinic).	10 min or less values-based BA. Two parts: (a) values-card sort (b) values-based BA (goal setting).	Statistically significant reduction in mean pain interference (p=0.001) baseline (26.3 SD 4.1) to follow-up (24.8 SD 5.0)
Hopko <i>et al</i> 2005 USA <sup>30</sup>	Uncontrolled preliminary clinical trial—pre, post, 3 months follow-up.	To assess effectiveness of BATD among depressed cancer patients in primary care.	18+, cancer, diagnosis MDD moderate severity Age: 28–66 years (M=46.4, SD 14.1)	6	Chronic pain. SF-36BP	Primary care.	BATD: 9×1 hour including psychoeducation, treatment rationale, activity and goal selection, and BA.	Significant improvement SF-36BP means pre- (40.0 SD 16.0) to post-treatment (52.3 SD 29.4) moderate effect size (d 0.5). 3 months follow-up (68.3 SD 28.6) treatment gains maintained (nonsignificant)
Hopko <i>et al</i> 2011 USA <sup>24</sup>	RCT	To conduct a randomised trial using BATD, comparing it to PST for depressed breast cancer patients.	18+years women diagnosed with breast cancer and moderate-severe MDD Age: range not reported (M=55.4, SD 11.9)	80 42 BATD 38 active control (PST). Post-treatment follow-up (n=65), 12 month (n=41).	Bodily pain. SF-36 BP	University medical care setting.	BATD and PST. BATD 8 sessions x 1 hour.	SF-36 BP - BATD showed significantly more post-treatment improvement than PST. BATD showed continued post-treatment improvement on 7/14 outcomes, compared with PST (2/14).
Hopko <i>et al</i> 2009 USA <sup>31</sup>	Pre-post study Measures pretreatment and post-treatment, 3 months follow-up.	To examine frequency and significance of sudden gains experienced by depressed cancer patients undergoing brief BA	18+years, cancer patients with moderate to severe MDD. Age: range not reported (M=52.8, SD 11.1)	n=37 pre-treatment phase, n=26 completed BA protocol. n=13 sudden gains; n=13 no sudden gains	Chronic pain. SF-36 measured bodily pain.	University medical centre.	9-sessions. - Contemporary BA (CB intervention with BA core component) and 'pure' BA.	Individuals with sudden gain had less severe depression, less somatic anxiety, greater physical functioning, less bodily pain.

Continued

**Table 1** Continued

Study	Study design/ methodology	Aim/research question/s	Population	n =	Pain and pain measures	Setting	Intervention	Outcome/ findings
Kim <i>et al</i> 2017 USA <sup>34</sup>	Case study	To detail the assessment and use of BA to treat a patient with low back and bilateral foot pain.	Veteran 30-year-old, single, African American female, 3-year history low back pain, 10 years bilateral foot pain	1	Low back pain and bilateral foot pain. NRS average pain (10-point scale-10 reflecting greater pain) PCS PDI	Home	nine sessions. BA proposed to Veteran as intervention to help re-establish purpose-driven activities.	NRS avg pain level pre-7, range 5-8 previous week; post-treatment 8, range 7 to 8. Four-week follow-up avg pain 7, range 5 to 7 previous week. PCS pre-treatment=7. PDI pre-treatment=42/70; post-treatment=32/70.
Moitra <i>et al</i> 2019 USA <sup>35</sup>	Case study	To reduce pain-related interference in physical and psychosocial functioning	PLWH Age not reported	1	Comorbid chronic pain depression. No reported outcome measures	Community – therapist office and telephone-based.	7-sessions, 4 core strategies to improve domains of health and well-being.	No outcomes reported
Pimentel <i>et al</i> 2020 Canada <sup>23</sup>	Uncontrolled pre, mid and post measures	To examine sequential relation between symptom catastrophising and PTSD severity	Work-disabled adults with PTSD referred to an occupational rehabilitation service. Age: range not reported (M=47.0, SD 9.7)	73 (n=39 women, n=34 men)	Chronic pain. MPQ-SF	Occupational rehabilitation service.	PGAP—10-week standardised risk targeted BA to facilitate return to work.	Significant reductions in scores on MPQ-SF, t(72) = 4.9, p<0.001, d=0.59.
Plagge <i>et al</i> 2013 USA <sup>29</sup>	Uncontrolled trial, premeasures and postmeasures	To explore preliminary clinical effectiveness and feasibility of BA to treat comorbid chronic pain and PTSD	Iraqi veterans self-reported pain (3+months), significant PTSD symptoms. Age: range not reported (full sample M=33.0 SD 9.2; completers M=38.8 SD 10.5)	n=58 (full sample) 30 (completers)	Chronic pain. Chronic Pain Grade (Pain severity and Pain interference), PCS	Veterans Affairs Medical Centre.	Adapted BA for Treatment of PTSD manual. 8x75-90 mins individual sessions	Pain severity: pre- 6.8 (1.4); mid- 6.1 (2.0); post-5.8 (2.2). Pain interference: pre- 6.9 (2.1); mid- 5.1 (2.4); post-4.9 (2.5); Pain catastrophising pre- 32.9 (13.0); post-intervention 23.9 (10.5).
Quijano <i>et al</i> 2007 USA <sup>28</sup>	Uncontrolled study, pre and post measures.	To evaluate BA for depression delivered to high-risk, diverse older adults by case managers.	All new and existing clients 60+years in community, receive services at community-based service. Age: range not reported (all clients M=75.9 SD 9.5; eligible M=72.5 SD 9.4)	n=49 measured on QoL (pain); 42 people participated in BA—unknown if they were the same people	Chronic pain. SF-36 (used to measure pain)	Two non-profit community-based agencies and one county social service agency.	Contemporary BA identifying behavioural goals important to individual patients.	Pain reduced to no-mild pain 16.3% (baseline) 44.9% (6 months). % participants reporting change in pain significant (p=0.003).
Sullivan <i>et al</i> 2020 Canada <sup>27</sup>	Uncontrolled study, pre, mid and post measures—crossed-lagged panel de-sign	To examine the role of perceived injustice as a determinant of symptom severity in individuals with MDD.	Work-disabled adults with MDD at occupational rehabilitation service. Age range not reported (males M=45.8 SD 9.8 females M=45.2 SD 9.8)	253	Chronic pain. NRS (10-point scale-10 reflecting greater pain)	Occupational rehabilitation service.	PGAP—10 week standardised risk targeted BA to facilitate return to work.	Significant reductions in pain pretreatment 4.5(SD 2.5) mid-treatment 4.1 (SD 2.4) post-treatment 3.5 (SD 2.3) (p<0.001 Cohen's d 0.42)

Continued

Table 1 Continued

Study	Study design/ methodology	Aim/research question/s	Population	n =	Pain and pain measures	Setting	Intervention	Outcome/ findings
Turner and Jakupcak 2010 USA <sup>36</sup>	Single case study	To describe BA for PTSD and depressive symptoms in veteran with physical injuries	22 years male soldier PTSD—multiple severe fractures, pain left leg	1	Weight bearing pain. NRS (10-point scale—10 reflecting greater pain)	Veterans Administration inpatient rehab unit (initial admission) and two primary care practices.	Weekly treatment over 4 months; based on BA protocol by Jacobson <i>et al</i>	Recovered from physical injuries and surgeries, weight bearing pain reduced from 8 to 0, improved ambulation.
Uebelacker <i>et al</i> 2016 USA <sup>25</sup>	RCT. Assessments at baseline, 1 2 3 months (endpoint), 4 months (1 month follow-up).	To assess feasibility and acceptability of BA for pain and depressive symptoms in PLWH.	18+PLWH; 6 months chronic pain; pain interference BPI-I $\geq 5$ ; pain severity $\geq 4$ on 0 to 10 NRS. Age: range not reported (HIV-PASS M=52.0 SD 7.2 HE M=49.7 SD 9.4)	23	Chronic pain. Average pain in past week - NRS (10-point scale - 10 reflecting greater pain).	Two primary care practices	HIV-PASS -modified manualised BA for primary care.	Effect size for avg pain in HE direction. BPI medium effect favouring HIV-PASS. Means decreased at 1 2 3 4 months for BPI and avg pain.
Wagner <i>et al</i> 2007 USA <sup>26</sup>	Small, randomised effectiveness trial	To examine the impact of BA on PTSD (and range of factors that contribute to avoidance including pain)	Adults recently injured with PTSD 1-month post-injury, recruited from surgical ward. Age: range not reported (BA M=28.0 SD 15.4 TAU M=39.0 SD 16.2)	Total n=8 TAU n=4, BA n=4	Chronic pain (some injury related). SF-12 (PCS-12)	Community - Harborview Medical Centre Seattle	BA over 6 sessions 60–90 min each.	PCS-12 pre-treatment BA 34.2 (5.0) TAU 30.6 (8.7); post-treatment BA 35.7 (8.3) TAU 25.4 (8.1). BA reported higher physical function.
Yamada <i>et al</i> 2020 Canada <sup>22</sup>	Uncontrolled study, pre and post measures	To examine role of fatigue as determinant of work-disability in individuals with WRMDs	Individual with WRMDs Age: range not reported (Male M=46.3 SD 8.5 Female M=45.7 SD 9.3)	117 (n=64 women, n=53 men)	Chronic pain. NRS pain measure (10-point scale - 10 reflecting greater pain). PDI	Occupational rehabilitation service	PGAP—10-week standardised risk targeted BA to facilitate return to work.	PDI reduced pre (34.9, SD 8.7) to post assessment (27.5, SD 11.7) p value<0.001. NRS reduced pre (6.4, SD 1.8) to post assessment (5.2, SD 2.6) p value<0.001

BA-PR, behavioural activation for pain rehabilitation; BATD, behavioural activation treatment for depression; BPI-I, Brief Pain Inventory-Interference scale; CB, cognitive behavioural; MDD, major depressive disorder; MPQ-SF, McGill Pain Questionnaire-Short-Form; NRS, Numerical Rating Scale; PCS, Physical Component Score; PDI, Pain Disability Index; PLWH, person/s living with HIV/AIDS; PROMIS, Pain Interference-Short Form scale; PST, problem solving therapy; PTSD, post-traumatic stress disorder; RCT, randomised controlled trial; SF, Short Form; SF-36 BP, Medical Outcomes Study Short Form, Bodily Pain component; TAU, treatment as usual; WRMD, work-related musculoskeletal disorders.

**Table 2** Overview of how BA was delivered

Study	No of sessions	Duration of sessions	Frequency of sessions	Duration of treatment
Brooks <i>et al</i> <sup>33</sup>	6	2 hours	Weekly	6 weeks
Hooker <i>et al</i> <sup>32</sup>	3 (including initial visit and follow-up)	10 min	Once	3–5 weeks
Hopko <i>et al</i> 2005 <sup>30</sup>	9	1 hour	Weekly	9 weeks
Hopko <i>et al</i> 2009 <sup>31</sup>	9	1 hour	Weekly	9 weeks
Hopko <i>et al</i> 2011 <sup>24</sup>	8	1 hour	Weekly	8 weeks
Kim <i>et al</i> <sup>34</sup>	10	Not reported	Not reported	Not reported
Moitra <i>et al</i> <sup>35</sup>	7	Not reported	Not reported	Not reported
Pimentel <i>et al</i> <sup>23</sup>	10	Not reported	Weekly	10 weeks
Plagge <i>et al</i> <sup>29</sup>	8	75–90 min	Not reported	Mean no of days between initial in-person contact and intervention completion 110 days, median of 106, range 24–224
Quijano <i>et al</i> <sup>28</sup>	10	Not reported	Not reported	6 months
Sullivan <i>et al</i> <sup>27</sup>	10	Not reported	Weekly	10 weeks
Turner and Jakupcak <sup>36</sup>	16	Not reported	Weekly	4 months (tapering up to 12 months)
Uebelacker <i>et al</i> <sup>25</sup>	7	30–50 min	2 weeks on average	3 months
Wagner <i>et al</i> <sup>26</sup>	4–6	60–90 min	Weekly (not always consecutive)	9.8 weeks avg
Yamada <i>et al</i> <sup>22</sup>	10	Not reported	Weekly	10 weeks

BA, behavioural activation.

Physical Component Summary of the SF-12 Health Survey (PCS-12).<sup>39 26</sup> Five studies<sup>22 25 27 33 36</sup> asked the patient to rate their pain on a 10-point Numerical Rating Scale (NRS) anchored with 0 (no pain) and 10 (the most pain one could experience). The application of the NRS was varied in these studies measuring current pain,<sup>22 27</sup> pain on weight bearing<sup>36</sup>; and average pain intensity during the past week.<sup>25 33</sup> Two studies<sup>29 34</sup> assessed pain-specific thoughts and beliefs via the Pain Catastrophising Scale (PCS)<sup>40</sup>. One case study<sup>35</sup> was concerned with pain-related interference but did not employ a measure. Sullivan *et al*<sup>27</sup> and Pimentel *et al*<sup>23</sup> assessed pain catastrophising using the Symptom Catastrophising Scale (SCS)<sup>41</sup>; the latter<sup>23</sup> also measured pain severity using the McGill Pain Questionnaire–Short-Form (MPQ-SF).<sup>42</sup> In addition to an NRS for pain during the past week, Uebelacker *et al*<sup>25</sup> considered pain interference using the Brief Pain Inventory-interference scale.<sup>43</sup> Other pain-related measures included the Chronic Pain Grade (CPG)<sup>44</sup> Chronic Pain Coping Inventory<sup>45 33</sup> Chronic Pain Acceptance Questionnaire<sup>46 25</sup> and the Pain Disability Index.<sup>47 22 34</sup>

### BA programmes

All studies reported employing fundamental principles of BA; scheduling activity informed by patient values and gradually increasing patient activity through scheduling. In some instances, the purpose of the activity scheduling was to either break avoidance patterns or help the person return to their ‘normal’ activities. Two studies<sup>26 29</sup> focused on activity scheduling aimed to break avoidance patterns. In both studies, patients experienced PTSD after a traumatic event. In other studies,<sup>27 36 48–50</sup> activity scheduling was aimed at supporting people to reintroduce

themselves to their previous role, such as returning to the workplace. Several studies reported using a particular BA programme. BA for the treatment of depression (BATD)<sup>51</sup> was used in three studies.<sup>24 30 31</sup> However, in one of these studies, this was not explicitly stated,<sup>31</sup> instead referring to BA or enhanced BA referencing previous studies using BATD.

Risk-targeted BA interventions were employed in three<sup>22 23 27</sup> studies. Yamada *et al*<sup>22</sup> referred to Progressive Goal Attainment Programme (PGAP) and, while not explicitly stated, Pimentel *et al*<sup>23</sup> and Sullivan *et al*<sup>27</sup> mentioned a similar programme, with wording consistent to other papers referring to PGAP.<sup>52</sup> Sullivan *et al*<sup>52</sup> explain that PGAP is a risk targeted BA intervention as it ‘specifically targets disability-relevant psychosocial risk factors’ (p.291). Sullivan *et al*<sup>27</sup> included additional techniques related to perceptions of injustice. PGAP is a manual-based intervention, with a workbook the basis for intervention techniques. An educational video is used in the first session to orient the client to PGAP and provide an overview of relevant conditions, such as depression<sup>27</sup> or PTSD.<sup>23</sup> The initial sessions seek to establish a strong working relationship between clinician and patient, subsequent sessions focus on structured activity scheduling and reviewing progress towards these goals, with the ultimate goal to decrease barriers to rehabilitation, encourage engagement in daily activities and return-to-work.<sup>52</sup>

Brooks *et al*<sup>33</sup> used BA for Pain Rehabilitation (BA-PR), noting it is ‘the first pain rehabilitation intervention for middle-aged and older adults with varying types of mental health conditions’.<sup>(p.563)</sup> Wagner *et al*<sup>26</sup> used a modified

**Table 3** Overview of effect of BA on pain

Study	Pain measure	Baseline mean (SD)	Mid mean (SD)	Post mean (SD)	Follow-up mean (SD)	P value	D	T
Brooks <i>et al</i> <sup>33</sup>	0–10 NRS	7.00 (1.60)	n/a	6.67 (1.02)	n/a	0.594	n/a	0.558
Hooker <i>et al</i> <sup>32</sup>	PROMIS	26.3 (4.1)	n/a	24.8 (5.0)	n/a	0.001	– 0.72	
Hopko <i>et al</i> 2005 <sup>30</sup>	SF36 (Bodily Pain)	40.0 (16.0)	n/a	52.3 (29.4)	68.3 (28.6) (3 month)	<0.05	0.5	
Hopko <i>et al</i> 2009 <sup>31</sup>	SF36 (Bodily Pain)	44.5 (21.4) (sudden gains) 29.1 (15.4) (no sudden gains)	n/a	n/a	n/a	n/a	n/a	n/a
Hopko <i>et al</i> 2011 <sup>24</sup>	SF36	46.4 (26.6)	n/a	55.5 (22.7)	65.0 (15.3) (12 month)	<0.05	0.33	
Kim <i>et al</i> <sup>34</sup>	0–10 NRS	7 (range 5–8)	n/a	8 (range 7–8)	n/a	n/a	n/a	
	PCS	32, 80th percentile	n/a	7, 17th percentile	n/a	n/a	n/a	
	PDI-recreation	42/70	n/a	32/70	n/a	n/a	n/a	
Moitra <i>et al</i> <sup>35</sup>	Pain-related interference	Descriptive	n/a	Descriptive	n/a	n/a	n/a	
Pimentel <i>et al</i> <sup>23</sup>	MPQ-SF	13.7 (8.0)	11.5 (7.9)	9.0 (7.9)	n/a	<0.001	0.59	
Plagge <i>et al</i> <sup>29</sup>	Pain severity (NRS)	6.8 (1.4)	6.1 (2.0)	5.8 (2.2)	n/a	0.050	0.47	
	Pain interference (NRS)	6.9 (2.1)	5.1 (2.4)	4.9 (2.5)	n/a	<0.001	0.88	
	PCS	32.9 (13.0)	n/a	23.9 (10.5)	n/a	<0.001	0.79	
Quijano <i>et al</i> <sup>28</sup>	SF36	16.3% (no pain or mild pain at 6 months)	n/a	44.9% (no pain or mild pain at 6 months)	n/a	0.003	n/r	
Sullivan <i>et al</i> <sup>27</sup>	11-point NRS	4.6 (2.5)	4.1 (2.4)	3.5 (2.3)	n/a	<0.001	0.42	
Turner and Jakupcak <sup>36</sup>	Weight bearing pain (NRS)	8	n/a	5 (2 month)	0 (12 month)	n/a	n/a	
Uebelacker <i>et al</i> <sup>25</sup>	NRS (pain in the past week)	6.9 (1.6)	n/a	5.8 (1.3) (4 month)	n/a	0.332	0.67 (–0.30; 1.64) compared with health education control	
Wagner <i>et al</i> <sup>26</sup>	BPH-I	7.3 (1.6)	n/a	5.5 (1.9)	n/a	0.566	–0.39 (–1.36; 0.58)	
	SF-12 - PCS-12	34.2 (5.0)	n/a	35.7 (8.3)	n/a	0.05	n/a	1.89
Yamada <i>et al</i> <sup>22</sup>	11-point NRS	6.4 (1.8)	n/a	5.2 (2.6)	n/a	<0.001	0.59	
	PDI	34.9 (8.7)	n/a	27.5 (11.7)	n/a	<0.001	0.75	

BA, behavioural activation; BATD, Behavioural Activation Treatment for Depression; BPH-I, Brief Pain Inventory interference scale; MDD, major depressive disorder; MPQ-SF, McGill Pain Questionnaire-Short-Form; n/a, not applicable; NRS, Numerical Rating Scale; PCS, Pain Catastrophising Scale; PCS, Physical Component Score; PDI, Pain Disability Index; PROMIS, Pain Interference-Short Form scale; SF, Short Form.



**Table 4** Critical appraisal tool for included studies

Type of study	Critical appraisal tool	Study
RCTs	Risk of Bias 2	Hopko <i>et al</i> 2011, <sup>24</sup> Uebelacker <i>et al</i> 2016 <sup>25</sup> and Wagner <i>et al</i> 2007 <sup>25</sup>
Pre-post studies	National Institutes of Health quality assessment tool for before-and-after (pre-post) study with no control group	Brooks <i>et al</i> , <sup>33</sup> Hooker <i>et al</i> , <sup>32</sup> Hopko <i>et al</i> 2005, <sup>30</sup> Hopko <i>et al</i> 2009, <sup>31</sup> Pimentel <i>et al</i> , <sup>23</sup> Plagge <i>et al</i> , <sup>29</sup> Quijano <i>et al</i> , <sup>28</sup> Sullivan <i>et al</i> , <sup>27</sup> Yamada <i>et al</i> <sup>22</sup>
Case studies	Checklist for case reports	Kim <i>et al</i> , <sup>34</sup> Moitra <i>et al</i> , <sup>35</sup> Turner and Jakupcak <sup>36</sup>

RCTs, randomised controlled trials.

BA manual<sup>53</sup> to allow for delivery in a reduced number of sessions. Turner and Jakupcak<sup>36</sup> adopted a modified BA intervention<sup>54</sup> tailored to suit patients with PTSD and symptoms reflecting patterns of avoidance. Plagge *et al*<sup>29</sup> described being part of a larger programme which used BA for the treatment of PTSD.<sup>55 56</sup> The BA approach was not reported in four studies.<sup>28 32 34 35</sup> We do note, however, one study<sup>35</sup> referred to a larger study and it is assumed the intervention used was the same, HIV-Pain and Sadness Study (HIV-PASS).<sup>25</sup>

### Frequency and duration of sessions

Table 2 provides an overview of how BA was delivered in terms of the number, duration, frequency of sessions and treatment duration.

There was variation in session elements across studies. For example, Hooker *et al*<sup>32</sup> used a novel one-off BA session with a follow-up 2–3 weeks later. BA was condensed into 10 min, with the follow-up lasting 10–20 min, and incorporated into routine pain management care. In one case study,<sup>36</sup> 16 sessions were delivered over 4 months, with an additional session after 12 months.

### Delivery of BA

There was variation in who delivered BA. In three studies by Hopko *et al*,<sup>24 30 31</sup> the principal investigator trained graduate students to deliver BA. In four studies,<sup>25 29 32 35</sup> a psychologist delivered BA, whereas Kim *et al*<sup>34</sup> described the person as a ‘therapist’. Two studies<sup>26 36</sup> did not report who delivered BA. In the study by Brooks *et al*<sup>33</sup> a PhD trained psychotherapist cofacilitated delivery with older peers to people over the age of 50.

In the remaining studies, non-mental health professionals were trained to deliver BA. Quijano *et al*<sup>28</sup> reported case managers delivered BA and provided a brief description of the training: 15 case managers and three supervisors were prepared by specialist mental health workers

in social work and psychology. Training included group sessions, assignment of a coach and semiannual follow-up training sessions to address issues. During the intervention, the coach met the case manager twice monthly. Two studies<sup>22 27</sup> used occupational therapists (OTs) to deliver BA. Sullivan *et al*<sup>27</sup> trained 24 OTs, who had experience with mental health clients. Training was a 2-day intensive workshop with ongoing access to videos for support. The OTs received weekly supervision, which the authors state ensured ‘fidelity to the protocol’ (p. 291). Similarly, Yamada *et al*<sup>22</sup> trained OTs ‘to competency’ and weekly supervision ensured ‘fidelity to the standardised treatment protocol’ (p. 137). We assume that three other studies<sup>22 23 27</sup> were drawing on a similar clinician sample, as the description of training OTs was identical.

### Delivery modalities

BA was delivered face to face in three studies,<sup>27 32 34</sup> one study delivered BA by telephone,<sup>35</sup> and four studies<sup>25 26 28 29</sup> used a combination of face to face and telephone. Seven studies<sup>22–24 30 31 33 36</sup> did not report how BA was delivered, but face to face was implied. Wagner *et al*<sup>26</sup> noted a flexible approach was used to determine where BA was delivered, due to physical limitations of patients.

### Effect on pain

Eight uncontrolled trials reported improvements in pain for BA participants (see table 3); while the remaining study<sup>31</sup> did not comment on improvement in pain, they noted less bodily pain at baseline was associated with improvements. Sullivan *et al*<sup>27</sup> using an NRS with 253 work-disabled individuals with Major Depressive Disorder, reported a modest decrease in mean current pain scores from pretreatment (4.6 SD 2.5) to mid-treatment (4.1 SD 2.4) to post-treatment (3.5 SD 2.3) (p<0.001 pretreatment to post-treatment). Yamada *et al*<sup>22</sup> using an NRS with 117 people with work-related musculoskeletal disorders,

**Table 5** Randomised controlled trials—Risk of Bias Assessment 2

Study	Randomisation process	Deviations from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported result	Overall
Hopko <i>et al</i> <sup>24</sup>	High	Some concerns	High	Some concerns	Some concerns	High
Uebelacker <i>et al</i> <sup>25</sup>	High	Major concerns	High	Major concerns	High	High
Wagner <i>et al</i> <sup>26</sup>	High	High	Low	Some concerns	Some concerns	High

**Table 6** Critical appraisal—National Institutes of Health quality assessment tool for before-and-after (pre–post) study with no control group

Study	Study question	Selection criteria	Representative	Eligible participants enrolled	Sample size confidence	Intervention clearly described	Outcome measures	Assessors blinded	Loss after baseline	Statistical methods	Repeated measures	Individual level	Overall
Brooks <i>et al</i> <sup>33</sup>	Yes	Yes	No	CD	No	Yes	Yes	NR	Yes	Yes	No	n/a	Fair
Hooker <i>et al</i> <sup>32</sup>	Yes	Yes	CD	CD	NR	Yes	Yes	No	Yes	Yes	No	Yes	Fair
Hopko <i>et al</i> 2005 <sup>30</sup>	Yes	Yes	CD	Yes	NR	Yes	Yes	No	No	Yes	Yes	Yes	Fair
Hopko <i>et al</i> 2009 <sup>31</sup>	Yes	Yes	CD	CD	NR	Yes	Yes	No	No	Yes	Yes	Yes	Fair
Pimentel <i>et al</i> <sup>23</sup>	Yes	Yes	CD	CD	NR	Yes	Yes	No	Yes	Yes	No	Yes	Fair
Plagge <i>et al</i> <sup>29</sup>	Yes	Yes	CD	Yes	NR	Yes	Yes	No	Yes	Yes	No	Yes	Fair
Quijano <i>et al</i> <sup>28</sup>	Yes	Yes	CD	Yes	NR	Yes	Yes	No	No	Yes	No	Yes	Fair
Sullivan <i>et al</i> 2020 <sup>27</sup>	Yes	Yes	CD	Yes	NR	Yes	Yes	No	Yes	Yes	No	Yes	Fair
Yamada <i>et al</i> <sup>22</sup>	No	Yes	CD	Yes	R	Yes	Yes	No	Yes	Yes	No	Yes	Fair

CD, cannot determine; n/a, not applicable; NR, no reported.

reported a decrease in average current pain from pretreatment (6.4 SD 1.8) to post-treatment (5.2 SD 2.6). They reported decreases on PDI means from pretreatment (34.9 SD 8.7) to post-treatment (27.5 SD 11.7). Brooks *et al*<sup>33</sup> reported a nonsignificant reduction (t-test 0.558, p=0.594) in average pain intensity during the past week (NRS)—pretreatment (7.00 SD 1.60) to post-treatment (6.67 SD 1.02).

Two studies<sup>28 30</sup> used the SF-36-BP to assess pain. Quijano *et al*,<sup>28</sup> reported a significant increase (p=0.003) in the percentage of participants reporting no or mild pain from preintervention (16.3%) to 6 months later (44.9%). Hopko *et al*<sup>30</sup> reported bodily pain symptoms, at 3-month follow-up, had improved to a clinically significant margin, suggesting the positive effects of BATD may continue after therapy termination. Although it was noted that pre–post treatment improvement was nonsignificant; SF36-BP mean scores improved from pretreatment (40.0 SD 16.0) to post-treatment (52.3 SD 29.4) to 3 months follow-up (68.3 SD 28.6).

Pimentel *et al*<sup>23</sup> using MPQ-SF, reported significant reductions in pain severity from pretreatment (mean 54.8 SD 15.5) to post-treatment (mean 40.8 SD 14.0), (t(72)=4.9, p<0.001, d=0.59) for 73 work-disabled individuals. Hooker *et al*<sup>32</sup> used PROMIS and reported a small (not clinically significant) decrease in mean pain interference scores from baseline (26.3 SD 4.1) to post-treatment (24.8 SD 5.0). Plagge *et al*<sup>29</sup> used three pain-related assessments: pain severity, pain interference and pain catastrophising. For pain severity, there was a decrease pretreatment (mean 6.8 SD 1.4), mid-treatment (mean 6.1 SD 2.0) to post-treatment (mean 5.8 SD 2.2). For 20% of participants who completed the study, there was a clinically significant reduction in pain severity. For pain interference, scores decreased from pretreatment (mean 6.9 SD 2.1), mid-treatment (mean 5.1 SD 2.4), to post-treatment (mean 4.9 SD 2.5). For 40% of participants, there was clinically significant reductions in pain interference. PCS scores decreased from pretreatment (mean 32.9 SD 13.0) to post-treatment (mean 23.9 SD 10.5).

The three RCTs<sup>24 26</sup> reported varied results. In the study by Hopko *et al*<sup>24</sup> patients with breast cancer received either BATD or problem-solving therapy. Using the SF-36-BP, patients in the BATD group showed more improvement (pretreatment mean 46.4 SD 26.6, post-treatment mean 55.5 SD 22.7) than the PST group (pretreatment 51.4 SD 26.7, post-treatment 62.6 SD 22.1). They noted the BATD group had significantly more post-treatment improvement than the PST group. Wagner *et al*<sup>26</sup> employed BA with patients experiencing PTSD and physical injuries. Assessing pain with the PCS-12, the BA group showed modest improvement from pretreatment (34.2 SD 5.0) to post-treatment (35.7 SD 8.3) while the treatment as usual (TAU—‘as accessed by trauma patients from this type of trauma care facility’ p.344) group declined pretreatment (30.6 SD 8.7) to post-treatment (25.4 SD 8.1). Notably, this was a small sample with four participants in each group. Uebelacker *et al*<sup>25</sup> compared two groups who

**Table 7** Critical appraisal—checklist for case reports

Study	Demographics	History	Clinical condition	Assessment	Interventions	Post-intervention	Adverse events	Takeaway	Overall
Kim <i>et al</i> 2017 <sup>34</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Moitra <i>et al</i> 2019 <sup>35</sup>	No	No	No	No	Yes	No	No	No	Poor
Turner and Jakupcak <sup>36</sup>	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

received either BA (HIV-PASS) or health education (HE). For both groups, average pain on an NRS decreased, relative to baseline, in the post-treatment months. However, the effect size for change in average pain score favoured the HE group.

Three case studies reported mixed results. Kim *et al*<sup>34</sup> noted no change in the patient's pain but reported increase in activity. Moitra *et al*<sup>35</sup> made no claim whether there was an effect on pain. Turner and Jakupcak<sup>36</sup> reported the patient recovered from physical injuries and surgeries, and weightbearing pain reduced from 8 (baseline) to 0 (end of intervention) on the NRS.

### Critical appraisal of studies

Table 4 summarises the tools used to critically appraise the included studies.

The three RCTs<sup>24–26</sup> were rated as high risk of bias (table 5). The RCTs did not describe the allocation process, such as steps they took to conceal allocation of participants to BA. In addition, none of the papers reported steps taken to prevent awareness that participants were being allocated to BA. We could not confirm if the trials followed their protocols as we could not locate their protocols. All<sup>22 27–32</sup> uncontrolled studies were rated as fair (table 6). Two case studies<sup>34 36</sup> were rated good and one<sup>35</sup> poor (table 7).

## DISCUSSION

The purpose of this scoping review was to investigate if and how BA had been used in relation to people with chronic pain. We were interested in reported changes in pain, and how and by whom BA was delivered. We used a broad search strategy, with a theoretical rationale for the potential benefit of BA in reducing pain.

### Effect of BA on pain

The low number of studies and mixed methodological quality makes it difficult to make clear conclusions about the effectiveness of BA to manage pain. However, there is some positive evidence to warrant further exploration. In general, participants were in less pain or less impacted by their pain after BA than they were beforehand. Where a comparison intervention existed, the effect of BA on pain was mostly superior to that observed in the comparison group. That studies involved people with chronic pain, not recurrent or acute pain, reduced the likelihood (but importantly does not exclude it completely) that the passing of time, or regression to the mean, explains the effects. None of the studies reported adverse events or

identified potential risks, which may suggest that BA is safe for people with chronic pain. However, it may be due to authors failing to collect or report harms. We found no mediation analyses to explore whether reductions in pain were mediated by reductions in comorbid conditions (such as depression, PTSD) or vice versa.

### Could BA be an accessible psychological treatment for chronic pain?

Several different approaches to BA have been trialled with people with pain. The number of sessions varied from 2 to 16; duration of sessions varied from 10 min to 90 min; and length of intervention period varied from 3 weeks to 12 months. There was insufficient data to postulate optimal number, duration or frequency of sessions.

Different healthcare workers used BA to manage pain with their clients. Some were specialist mental health workers, such as psychologists or therapists; others were non-specialist healthcare workers. Hooker *et al*<sup>32</sup> embedded psychologists in primary care to provide a 10 min BA session and as part of a physician appointment. Patients reported 'a significant decrease in pain interference'.<sup>(p.8)</sup> In the approach employed by Plagge *et al*<sup>29</sup> psychologists delivered BA and acted as case managers. Pain severity and pain interference decreased from pre-intervention to postintervention. As noted by Plagge *et al*<sup>29</sup> using psychologists to work as case managers is expensive and a pragmatic limitation. This could be also be said of the study by Hooker *et al*.<sup>32</sup> Alternatively, Quijano *et al*<sup>28</sup> trained case managers to deliver BA to older adults. That more participants reported no pain or mild pain at 6 months than at baseline is encouraging. Studies by Sullivan *et al*<sup>27</sup> and Yamada *et al*<sup>22</sup> trained OTs, some with previous experience in mental health,<sup>27</sup> to deliver BA. This may be a viable approach in areas where access to psychologists is limited but allied health professionals less so. There seems to be no obvious barrier to training non-psychologists. Perhaps allied health professionals, nurses including mental health nurses, or case managers are well positioned to effectively deliver BA for pain. One issue that may require further consideration is whether previous mental health experience is important to prepare workers to deliver BA. It was difficult to determine the quality of training provided or assess the competency of the workforce who delivered BA. Quality research is required to address concerns of training and competency and determine whether BA can safely and effectively be delivered by non-specialist workers



## Recommendations

The risk and effectiveness data are encouraging. However, larger, more robust trials are required. We did identify one study protocol<sup>57</sup> for an RCT that may contribute to a growing body of knowledge. Comparing three treatment groups (TAU, TAU with ACT, TAU with BA), with pain as a primary outcome measure, patients with chronic low back pain and moderate to severe depression will participate in the study with measures taken pretreatment, post-treatment and 1 year later. This will hopefully improve our understanding of the effectiveness of BA in relation to pain.

Further research should consider the range of settings and professions that are able to deliver BA to people living with chronic pain. From an implementation perspective, it would be important to consider the appropriateness and understand the experience of the workers and patients if delivery occurs in novel settings with non-mental health professionals. For example, are OTs well positioned to deliver BA in a community health setting, do they consider this within their scoping of practice and are they competent/confident to do so, and is this considered appropriate by patients. If this approach is taken, feasibility should consider the number of non-mental health professionals who commence and complete training in BA and the number of patients who are willing, in comparison to the number of patients asked, to participate.

## LIMITATIONS

As this scoping review was restricted to peer-reviewed studies, publication bias is a potential limitation. Furthermore, research involving children was excluded, in part, as the therapeutic intervention may vary due to the cognitive and emotional stages of children participants. It would be pertinent to undertake another review that explores the use of BA with children experiencing pain.

## CONCLUSION

BA has the potential to reduce pain. There is a need for further research to better understand any mechanism of action which may explain an association between BA and pain relief. The studies have potentially affirmed a complex relationship between pain and depression. It is possible the therapeutic effect of BA on pain is mediated through depression. It may also be that the therapeutic effect is achieved by directly working on pain, drawing on the evidence that supports exercise as a treatment for pain. Caution needs to be exercised in the interpretation of these findings as a high risk of bias was observed in most studies. There is a need for well-designed studies to test the association between BA and pain.

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manuscript and accepted to be accountable for all aspects of the work. All authors conceptualised the project, drafted the manuscript, contributed to the development of the research questions, study design and reviewed and edited the manuscript for important intellectual content. All authors approved the final manuscript. SW is the authors acting as guarantor.

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