Title

Operationalisation of a biopsychosocial approach for the non-pharmacological management of patients with chronic musculoskeletal pain in low- and middle-income countries: A systematic review

Abstract

Background

Chronic musculoskeletal pain is a major health concern. The biopsychosocial approach is an evidence-based approach recommended for managing chronic musculoskeletal pain. However, the evidence for this approach is largely reported from high-income countries; therefore, it is important to ascertain how biopsychosocial approaches are operationalised in low-and middle-income countries to inform practice.

Aim

To examine the evidence for the operationalization of biopsychosocial interventions in managing patients with chronic musculoskeletal pain in low-and middle-income countries.

Methods

The search included studies published in English from 2008 to September 2019 in: Cochrane library, OVID, CINAHL, Scopus, PUBMED, Web of Science, and SportDiscus. Randomised and non-randomised trials utilizing a biopsychosocial intervention were considered. The review team developed a search strategy; two independent reviewers screened and assessed results for quality.

Results

Sixteen studies were included (n = 996) with mainly low back pain populations (n = 11 studies). Others were osteoarthritis (n = 1) and other musculoskeletal pain (n = 4). The majority (n = 12) of studies attained fair to poor quality, three had good quality, one scored excellent quality. Interventions applied biopsychosocial principles such as cognitive functional therapy, and graded activity, delivered by healthcare professionals such as physiotherapists and doctors. However, most results provided insufficient information regarding healthcare professionals' capacity to deliver interventions, lack of information regarding intervention delivery and training of healthcare professionals.

Conclusions

The results highlight the potential for delivering biopsychosocial interventions in low-and middle-income countries; however, future research should consider robust methodological approaches with clear details to achieve high-quality trials.

Keywords: Chronic musculoskeletal pain, biopsychosocial, non-pharmacological, low-and middle-income countries

Introduction

Musculoskeletal disorders are a leading cause of health problems, and also contribute substantially to healthcare costs globally (White & Harth, 1999; Murray et al., 2012). It affects populations from both low- and middle-income, and high-income countries (Hoy et al., 2014; Wáng, Wáng & Káplár, 2016; Morris, Daniels, Ganguli, & Louw, 2018). The global prevalence of musculoskeletal disorders is estimated between 20 – 33% (WHO, 2019); this is consistent with that of low- and middle-income countries (25%) (Jackson, et al., 2016).

Low back pain (LBP) is a leading musculoskeletal disorder resulting in substantial years lived with disability (YLD) (Hoy, Brooks, Blyth, & Buchbinder, 2010; Hoy et al., 2014)**.** Estimates from the global burden of disease (GBD), ranks LBP as the number one cause of YLD out of 354 injuries and diseases (James et al., 2018). Neck pain and other musculoskeletal pain rank fourth and sixth, with a global point prevalence of 5% and 8% respectively (Hoy et al., 2014). The global point prevalence of LBP is estimated at 9.4%; with prevalence rates increasing with increasing age (Vos et al., 2012; Hoy et al., 2014).

The point prevalence of LBP in low- and middle-income countries notably from Africa is estimated at 39% (Morris et al., 2018); this is higher than high-income countries such as Sweden (23.3%), Denmark (12 – 13.7%) and Canada (28.7%) (Hoy et al., 2010). The high prevalence of LBP observed in Africa may be attributed to the fact that LBP is considered a much lower priority than other health concerns such as HIV/AIDS. In addition, systems are less established, and budgets are limited; furthermore, half of the studies under review included industry-related jobs (involving labour intensive manual activity), which may have contributed to the observed high prevalence of LBP (Morris et al., 2018).

Musculoskeletal disorders therefore constitute a global burden; however, this remains less prioritised in most low- and middle-income countries especially in Africa (Morris et al., 2018).

The world bank defines low and middle income, and high-income countries based on gross national income of </= USD$12,055 (The World Bank, 2019). There is also a significant gap in evidence regarding high-quality studies for the management of musculoskeletal disorders from low- and middle-income countries (Kamper et al., 2015; van Erp, Huijnen, Jakobs, Kleijnen, & Smeets, 2019).

Previous reviews (Mason, Moore, Edwards, Derry, & McQuay, 2004; Roelofs, Deyo, Koes, Scholten, & van Tulder, 2008; Scascighini, Toma, Dober-Spielmann, & Sprott, 2008; Koes & van Tulder, 2011) reported low to moderate quality evidence for various approaches for the management of musculoskeletal disorders. The low to moderate quality evidence were assessed based on the estimation of effect sizes among treatment arms in the included studies, and methodological issues including consistency of results, ability to generalise findings, sufficiency of data, study design, and biases in study reporting (Atkins et al., 2004)

These approaches range from pharmacological (Mason, Moore, Edwards, Derry, & McQuay, 2004; Roelofs, Deyo, Koes, Scholten, & van Tulder, 2008), to non-pharmacological (Scascighini, Toma, Dober-Spielmann, & Sprott, 2008; Koes & van Tulder, 2011). However, the optimal management intervention(s) for musculoskeletal disorders have not been established. It is recognised that interventions need to be individualised to the patient and that various factors inform decisions regarding choice of interventions.

Current management approaches for musculoskeletal disorders have been proposed based on theory of the biopsychosocial (BPS) model (Deyo et al., 2015; NICE, 2016). The BPS model, originally postulated by Engel, 1977, considers biological, psychological, and social factors in the diagnosis and management of patients with chronic musculoskeletal disorders (Nielson & Weir, 2001; Kamper et al., 2015). This approach is recommended by international guidelines

including the National Institute of Care Excellence, (NICE, 2016) and National Institute of Health Taskforce on Research Standards for chronic low back pain (CLBP) (Deyo et al., 2015).

The BPS model of healthcare is a framework that considers the interactions between biological, social, and psychological factors to determine the manifestation, cause, management, and outcomes of a patient's condition (Engel, 1977). A key consideration in the management of musculoskeletal disorders are the range of factors that have been shown to predict patients' outcomes (Moseley & Arntz, 2007; Milesl et al., 2011; Lobanov, Zeidan, McHaffie, Kraft, & Coghill, 2014); there is strong evidence to suggest that social and psychological factors predict patient outcomes regardless of the choice of intervention (Milesl et al., 2011).

Furthermore, substantial evidence suggests that positive changes in social (lifestyle, occupation, misconceptions, belief system, lack of social support), psychological (fear and avoidance of movement, anxiety, depression) and biological (physical activity) factors, are mediators in the attainment of favourable outcomes for patients (Milesl et al., 2011; Lee et al., 2015; Pinheiro et al., 2015). This necessitates interventions that address these factors during management.

A number of high quality reviews have appraised BPS interventions for the management of chronic musculoskeletal disorders (Jordan, Holden, Mason. & Foster, 2010; Kamper et al., 2015; van Erp et al., 2019). However, these reviews (38 from high-income, 3 from low- and middle-income for Kamper et al., 2015; and 7 high-income, 0 low- and middle-income for van Erp et al., 2019) demonstrate a large gap in the evidence base in low- and middle-income countries. Therefore, it is difficult to conclude how BPS interventions can be effectively operationalised in low- and middle-income countries. Operationalisation in healthcare research is defined as, translation of a conceptualised theory into practical and measurable constructs (Jespersen, Michelsen, Holstein, Tjørnhøj-Thomsen & Due, 2018).

No previous review has appraised the operationalisation of BPS interventions in low- and middle- income countries. This evidence can inform the implementation of similar interventions in low- and middle-income countries; therefore, the rationale for this review is to appraise BPS interventions from low- and middle-income countries and ascertain how they are operationalised in the management of patients with chronic musculoskeletal pain.

Aim

To conduct a systematic search, critically appraise, and synthesize the evidence base for BPS approaches for the management of patients with chronic musculoskeletal pain in low- and middle-income countries.

Specific objectives

1. Identification of interventions based on a BPS approach for the management of patients with chronic musculoskeletal pain in low- and middle-income countries.
2. Critical appraisal and quality assessment of included studies.
3. Detailed description of the range of BPS interventions in included studies.
4. Discussion and conclusion on how BPS interventions are operationalised in low- and middle-income countries.

Methods

Types of studies

Studies considered for this review include all RCTs and non-RCTs from low- and middle-income countries that are published in English, and with a BPS intervention. We defined BPS interventions as interventions that include a physical component (for example, exercise), a psychological and/or social component (for example, awareness of cognitive influence on pain,

self-management); this was informed from literature and previous reviews (Waddell, 2004; Kamper et al., 2015; van Erp et al., 2019). Low- and middle-income countries were identified based on data from the World Bank (The World Bank, 2019). Cohort, quasi-experimental, and RCTs were considered for this review (Simic, Hinman, Wrigley, Bennell, & Hunt, 2011). Case reports and case series were excluded based on the fact that they are low on the hierarchy of evidence (Gopalakrishnan & Ganeshkuma, 2013).

Types of participants

Populations considered in this review included all adults (18 years and older) with musculoskeletal pain or disability persisting for three months or more; these related to populations who were diagnosed with chronic; mechanical or simple musculoskeletal pain, non-specific musculoskeletal pain, axial joint pain, low back, neck, or peripheral joint pain (shoulder, knee, hip) (Jordan et al., 2010; Smith et al., 2017). Populations were excluded from this review if they had pain of non-musculoskeletal origin such as cancer, gastrointestinal pain, migraine, fibromyalgia, rheumatoid arthritis, and chest pain (Jordan et al., 2010; Smith et al., 2017).

Interventions

BPS interventions included all forms of non-pharmacological interventions that combined biomedical, psychological, and/or social considerations (Waddell, 2004; Kamper et al., 2015; van Erp et al., 2019). Interventions that were delivered in a clinical setting were considered for this review; clinical settings included out-patient, in-patient, primary care, or secondary care settings (Jordan et al., 2010). Also considered were interventions that were delivered either on an individual or group basis. Interventions relating to surgery for the management of musculoskeletal pain were excluded from this review (Jordan et al., 2010).

Outcome measures

Although the rationale for this review was to synthesize the evidence on the delivery of non-pharmacological BPS interventions from low- and middle-income countries, an appraisal of the outcome measures considered in these studies were also considered. The rationale was to inform the conduct of similar studies in other low- and middle-income countries. Outcome measures included validated measures that considered factors such as pain, disability, function, depression, anxiety, self-efficacy, or quality of life (Kamper et al., 2015; van Erp et al., 2019). Where pilot or feasibility studies were involved, outcomes such as recruitment and retention rate were considered (Craig et al., 2008).

Identification of studies

The review team developed a search strategy; this was also augmented with advice from an information scientist. Studies were identified based on mapped terms to subject (MeSH) headings, keywords, and search terms. Because there was a possibility of studies not reporting their intervention as a BPS approach in the title or abstract, all searches were broadened to 'all text' in databases to ensure a comprehensive search.

The search included all studies published in English spanning 2008 to September 2019 in the following databases: Cochrane library, OVID database (AMED, EMBASE, MEDLINE), CINAHL, Scopus, PUBMED, Web of science, and SportDiscus. The rationale for identifying studies spanning 2008 to 2019 was to identify current evidence. Database search was followed by hand searching of reference lists. Grey literature and ongoing studies were also searched from: www.clinicaltrials.com, www.opengrey.eu, www.controlled-trials.com and www.guidelines.gov.

Study selection process

Two independent reviewers (PKA and JA) undertook the search followed by screening of titles and abstracts of identified studies. PKA and JA addressed any disparities through consensus; where consensus was not reached, a third reviewer (PH) was available to address disparities. Percentage level for inter-rater reliability was 87.5%, while Cohen's kappa statistic was K = 0.63 signifying a moderate level of agreement (McHugh, 2012). Four studies required further information regarding their intervention protocol and the roles of healthcare professionals (HCPs) involved in the conduct of the studies (Castro, Daltro, Kraychete, & Lopes., 2012; Saedi, Hatami, Asgari, Ahadi, & Poursharifi, 2016; Ibrahim, Akindele & Ganiyu, 2018; Nazari, Ebrahimi, Naseh, & Sahebi, 2018). Two authors responded; both independent reviewers (PKA and JA) came to a consensus to include the responses (Castro et al., 2012; Ibrahim et al., 2018). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis group (PRISMA) checklist was utilized in the reporting of studies (Moher, Liberati, Tetzlaff, & Altman, 2009).

Data extraction

Data was extracted and tabulated independently by one reviewer (PKA); another reviewer (JA) independently checked the extracted data. Data extraction was based on indicators of operationalisation (Jespersen et al., 2018) such as; type of study, information on participants, details and setting of intervention, HCPs involved, outcomes measures utilized, and country of origin. A data extraction form was customised based on guidance from the Cochrane Handbook of Systematic Reviews (Higgins & Green, 2011).

Quality rating

Quality rating and risk of bias assessment of included studies was conducted by two independent reviewers (PKA and JA) and agreed by consensus. The modified Downs and

Black quality rating scale was used to appraise each study (Downs & Black, 1998; O'Connor et al., 2015). This scale has been successfully utilized in quality rating reviews involving both RCTs and non-RCTs (Simic et al., 2011; Richmond et al., 2013; Morton, Barton, Rice, & Morrissey, 2014). The scale is made up of 27 items relating to four domains; internal validity, external validity, statistical power, and quality of reporting (Downs & Black, 1998). The scale has a high internal consistency (0.89 - Kuder-Richardson 20) (Downs & Black, 1998; O'Connor et al., 2015). Items in each domain were assigned either Yes = 1, No = 0, or unable to determine = 0. The overall grade for studies were rated as: Excellent = 24 – 28; Good = 20 – 23; Fair = 15 – 19; Poor = <14 (O'Connor et al., 2015).

Results

Identification of studies and selection

The database search identified 19724 unique results, with two additional results from hand searching of reference lists of identified studies (Onac, Moldovan, Onac, Igna, & Pop, 2012; Aliyu, Wasiu & Bello, 2018). The results are presented in a PRISMA flow diagram (Figure 1). After removal of duplicates, 16676 records were screened by title and abstract. This resulted in a removal of 16490 based on title or abstract. 186 full-text articles were screened for eligibility; 170 were subsequently excluded.

This resulted in 16 articles being included in the final review (Onac et al., 2012; Castro et al., 2012; Khan, Akhter, Soomro, & Ali, 2014; Nochit, Kaewthummanukul, Srisuphan, & Senaratana, 2014; Igna et al., 2014; Magalhães et al., 2015; Bello, Quartey & Lartey, 2015; Babai, Sepavand, Nokani, Aghamohammadi, & Sheybani, 2016; Saedi et al., 2016; Elshiwi et al., 2016; Ghadyani, Tavafian, Kazemnejad, & Wagner, 2017; Aliyu, Wasiu & Bello, 2018; Nazari et al., 2018; Ogunlana, Odole, Adejumo, Olagbegi, & Williams, 2018; Ibrahim, Akindele & Ganiyu, 2018; Lopes, Vannucchi, Demarzo, Cunha, & Nunes, 2019). All included

articles were published in English. One study published a follow-up publication based on mid-term outcome assessment (Magalhães et al., 2015, 2018).

Description of studies

The main findings and characteristics of the 16 included studies are summarised in Table 1. Nine studies were RCTs (Castro et al., 2012; Onac et al., 2012; Igna et al., 2014; Khan et al., 2014; Bello, Quartey & Lartey, 2015; Magalhaes et al., 2015; Elshiwi et al., 2016; Aliyu et al., 2018; Ibrahim et al., 2018); of the seven remaining, five were quasi-experimental studies (Nochit et al., 2014; Babai et al., 2016; Saedi et al., 2016; Nazari et al., 2018; Ogunlana et al., 2018), and two cohort studies (Ghadyani et al., 2017; Lopes et al., 2019).

Two out of the nine RCTs were feasibility RCTs investigating the feasibility of implementing a BPS approach for the management of patients with CLBP in African settings (Ghana, Nigeria) (Bello et al., 2015; Ibrahim et al., 2018). The country distribution of all 16 studies included in this review are as follows:

Iran – 4 (Babai et al., 2016; Saedi et al., 2016; Ghadyani et al., 2017; Nazari et al., 2018)

Nigeria – 3 (Aliyu et al., 2018; Ibrahim et al., 2018; Ogunlana et al., 2018)

Brazil – 3 (Castro et al., 2012; Magalhaes et al., 2015; Lopes et al., 2019)

Romania – 2 (Onac et al., 2012; Igna et al., 2014)

Ghana – 1 (Bello et al., 2015)

Pakistan – 1 (Khan et al., 2014)

Egypt – 1 (Elshiwi et al., 2016)

Thailand – 1 (Nochit et al., 2014)

Most included studies (n = 15) were conducted in hospital-based settings; 2 (Onac et al., 2012; Igna et al., 2014) out of the 16 were conducted in an in-patient setting, with 13 conducted in an out-patient setting. However, one study lacked information on the setting (Nochit et al., 2014). Overall, there were 996 patients; fourteen studies had participants of a similar age range (18 – 80 years). One study (Nazari et al., 2018) was conducted in older adults (60 – 90 years). One study (Nochit et al., 2014) did not indicate the age range of participants.

Eleven studies included patients with LBP (Onac et al., 2012; Igna et al., 2014; Khan et al., 2014; Nochit et al., 2014; Bello et al., 2015; Magalhaes et al., 2015; Elshiwi et al., 2016; Ghadyani et al., 2017; Aliyu, Wasiu and Bello, 2018; Ogunlana et al., 2018; Ibrahim et al., 2018) with three (Castro et al., 2012; Babai et al., 2016; Nazari et al., 2018) including general musculoskeletal pain populations such as osteoarthritis and non-specific musculoskeletal pain.

Two studies however did not state the nature of the musculoskeletal pain although they indicated the criteria utilized in concluding that conditions were of musculoskeletal nature as the Nordic Musculoskeletal Questionnaire (NMQ) (Lopes et al., 2019) and specialist assessment (Saedi et al., 2016). The NMQ however is not a tool used in diagnosing musculoskeletal disorders but rather a questionnaire for comparing musculoskeletal disorders in epidemiological studies (Crawford, 2007). Another study which included chronic musculoskeletal pain patients did not indicate the criteria for diagnosis (Castro et al., 2012).

BPS interventions

BPS interventions included exercises plus patient education (n = 1) (Ibrahim et al., 2018), exercise-based behavioural graded activity (n = 4) (Nochit et al., 2014; Bello et al., 2015; Magalhaes et al., 2015; Ogunlana et al., 2018), physical activity-based cognitive behavioural therapy (n = 9) (Castro et al., 2012; Onac et al., 2012; Igna et al., 2014; Khan et al., 2014; Babai et al., 2016; Elshiwi et al., 2016; Saedi et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018),

and physical activity-based mindfulness, acceptance, and commitment therapy (n = 2) (Nazari et al., 2018; Lopes et al., 2019).

Only one study (Ibrahim et al., 2018), utilized a validated format for reporting trials such the Consolidated Standards for Reporting Trials (CONSORT) (Moher et al., 2010). However, the majority (n = 8) (Castro et al., 2012; Onac et al., 2012; Igna et al., 2014; Magalhaes et al., 2015; Elshiwi et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018; Ogunlana et al., 2018) of the studies utilized a flow chart to report the processes of their study. The remaining seven (Khan et al., 2014; Nochit et al., 2014; Bello et al., 2015; Babai et al., 2016; Saedi et al., 2016; Nazari et al., 2018; Lopes et al., 2019) did not report the processes in any standardized format.

Methodological quality and risk of bias assessment

Table 2 summarises the assessment of methodological quality in the included studies. Overall, no study blinded participants to treatment allocation. Only one study attained an excellent rating (24) (Ibrahim et al., 2018). The majority (n = 12) (Onac et al., 2012; Castro et al., 2012; Nochit et al., 2014; Igna et al., 2014; Khan et al., 2014; Bello et al., 2015; Babai et al., 2016; Saedi et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018; Nazari et al., 2018; Lopes et al., 2019) rated fair to poor on methodological quality with the majority of the poor scores resulting from failure to identify and report confounders. General reporting of studies was also poorly done; attributable to the lack of utilization of validated reporting guidelines or inherent methodological deficits regarding internal and external validity.

Description of BPS interventions

There was inherent heterogeneity among included studies regarding the content, design, and delivery of the BPS interventions; despite this, studies were explored based on two broad areas based on indicators of operationalisation such as:

- Design and content of the BPS interventions
- Delivery, dosage and frequency of BPS interventions

Design and content of BPS intervention

The majority (n = 9) of the studies included core components of physical activity/exercise, and education (Onac et al., 2012; Khan et al., 2014; Nochit et al., 2014; Bello, Quartey and Lartey, 2015; Magalhaes et al., 2015; Babai et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018; Ibrahim et al., 2018). Physical activity/exercise interventions ranged from motor control exercises (Nochit et al., 2014; Aliyu et al., 2018; Ibrahim et al., 2018; Ogunlana et al., 2018), balance and flexibility exercises (Magalhaes et al., 2015; Ibrahim et al., 2018), general (aerobic) exercises (Khan et al., 2014; Babai et al., 2016; Ghadyani et al., 2017), and functional exercises (Bello et al., 2015).

Education interventions highlighted maladaptive beliefs, self-management, lifestyle modification, postural hygiene, staying active, returning to activities of daily living, coping and pacing strategies (Onac et al., 2012; Khan et al., 2014; Nochit et al., 2014). The exercise and patient education intervention was designed based on altered spinal control and stability in LBP, and self-management through cognitive behavioural strategies respectively (Ibrahim et al., 2018). Exercise-based behavioural graded activity interventions were designed based on operant conditioning and self-management (Bello et al., 2015), activity-based cognitive behavioural principles (Ogunlana et al., 2018), cognitive behavioural therapy (Magalhaes et al., 2015), and positive motivation theory (Nochit et al., 2014).

Physical activity-based cognitive behavioural therapy interventions were designed based on problem-solving and operant behavioural graded activity (Khan et al., 2014), cognitive behavioural therapy principles (Elshiwi et al., 2016; Aliyu et al., 2018), and principles of expectancy of therapeutic change and exposure to avoidance behaviours (Onac et al., 2012;

Igna et al., 2014). Two studies however lacked information on the intervention protocol (Saedi et al., 2016; Nazari et al., 2018).

Delivery, dosage and frequency of BPS intervention

The majority (9) of studies (Igna et al., 2014; Khan et al., 2014; Bello et al., 2015; Magalhaes et al., 2015; Babai et al., 2016; Elshiwi et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018; Ibrahim et al., 2018; Ogunlana et al., 2018), involved physiotherapist-led interventions; where physiotherapists were the sole HCP involved in the BPS intervention. Other HCPs involved in the delivery of the BPS intervention included orthopaedic surgeons (Nochit et al., 2014), rehabilitation physicians (Onac et al., 2012; Nochit et al., 2014), nurses (Nochit et al., 2014), clinical masseurs (Onac et al., 2012), and health education specialists (Ghadyani et al., 2017). Regarding treatment sessions, duration of each session ranged from 45 minutes (Bello et al., 2015; Babai et al., 2016; Nazari et al., 2018), one hour (Igna et al., 2014; Lopes et al., 2019) to 2 hours (Castro et al., 2012; Ghadyani et al., 2017).

Furthermore, the number of treatment sessions ranged from two (Magalhães et al., 2015; Aliyu et al., 2018; Ibrahim et al., 2018) to three sessions per week (Onac et al., 2012; Igna et al., 2014; Khan et al., 2014; Elshiwi et al., 2016; Ogunlana et al., 2018) for a period ranging from six weeks (Magalhães et al., 2015; Elshiwi et al., 2016; Aliyu et al., 2018; Ibrahim et al., 2018) to twelve weeks (Khan et al., 2014; Bello et al., 2015). Only one study (Aliyu et al., 2018) included a booster session; this booster session was utilized to evaluate the intervention programme from the participating patients perspective.

There was a general lack of information regarding the level of experience and training of HCPs in included studies. One study (Bello et al., 2015), indicated that physiotherapists were involved in a four-day workshop to design the intervention. Another study indicated that HCPs were trained on delivering the exercise component; however, the principal investigator (PI)

undertook the patient education component (Ibrahim et al., 2018). Five studies (Onac et al., 2012; Igna et al., 2014 ; Magalhães et al., 2015; Ibrahim et al., 2018 ; Ogunlana et al., 2018), reported that HCPs had formal training on the delivery of the intervention; however, the details of the training was not reported.

Description of outcome measures

Thirteen included studies reported outcomes on the intensity of pain (visual analogue scale, numeric rating scale, pain self-effectiveness questionnaire, and brief pain inventory) (Castro et al., 2012; Onac et al., 2012; Igna et al., 2014; Khan et al., 2014; Bello et al., 2015; Magalhaes et al., 2015; Babai et al., 2016; Elshiwi et al., 2016; Saedi et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018; Ibrahim et al., 2018; Ogunlana et al., 2018). Disability/function was also an outcome for nine studies (Oswestry disability index and Rolland Morris disability questionnaire) (Onac et al., 2012; Khan et al., 2014; Magalhaes et al., 2015; Elshiwi et al., 2016; Ghadyani et al., 2017; Aliyu et al., 2018; Ibrahim et al., 2018; Nazari et al., 2018; Ogunlana et al., 2018).

Psychosocial outcomes included pain catastrophising (Ogunlana et al., 2018; Lopes et al., 2019), fear avoidance beliefs (Aliyu et al., 2018), anxiety and depression (Castro et al., 2012; Igna et al., 2014; Lopes et al., 2019), quality of life (Castro et al., 2012; Bello et al., 2015; Magalhaes et al., 2015; Lopes et al., 2019), self-efficacy (Ogunlana et al., 2018) and kinesiophobia (Magalhaes et al., 2015; Ogunlana et al., 2018). Two studies (Bello et al., 2015; Ibrahim et al., 2018) conducted a pilot/feasibility trial; however, only one (Ibrahim et al., 2018) study investigated feasibility outcomes such as retention/dropout rate, treatment compliance, and perceived helpfulness. Only one study (Ibrahim et al., 2018) reported on adverse events; however, no adverse events were recorded.

Discussion

Summary of findings

Overall, the evidence (n = 16 studies) shows BPS interventions and how they are operationalised in low- and middle-income countries; however, the majority (n = 12) of studies had insufficient and/or no information at the individual level (for example, insufficient information on the level of training and/or capabilities of the HPCs to deliver the BPS interventions), organisational level (for example, insufficient and/or inconsistent information on the delivery of the BPS intervention) and were of low methodological quality. Despite this, most included studies (n = 11) included studies referenced evidence-based BPS approaches such as cognitive behavioural therapy, graded activity, and cognitive functional therapy to inform the delivery of the BPS intervention. This is the first review that has looked at the operationalisation of BPS approaches in low- and middle-income countries to the best of our knowledge.

Implications for research and clinical practice

Although the methodological quality of most included studies was generally low, the potential for implementing a BPS intervention for the management of chronic musculoskeletal pain in low- and middle-income countries appears feasible. Generally, most included studies provided little or no indication of the level of expertise or training given to HCPs to deliver the BPS interventions. Even within the high-quality study (Ibrahim et al., 2018), physiotherapists were only trained to deliver the exercise arm of the intervention while the PI conducted all the patient education sessions. This is a potential flaw as the feasibility of physiotherapists to deliver the education component was not tested.

The low methodological quality of most studies necessitates the establishment of high-quality clinical trials to assess the feasibility of implementing BPS interventions in such contexts.

Nonetheless, researchers can be guided by some of the methodologically good (Magalhães et al., 2015; Elshiwi et al., 2016; Ogunlana et al., 2018) and excellent (Ibrahim et al., 2018) studies to inform the development and implementation of similar interventions in low- and middle-income countries. The Medical Research Council recommends a systematic review of available evidence in similar contexts to inform the development and implementation of similar approaches (Craig et al., 2008).

The general insufficiency of information and low methodological quality of studies from low- and middle-income countries is consistent with a previous review on low- and middle-income countries by Alemayehu, Mitchell, & Nikles, 2018, which investigated the challenges of conducting clinical trials in low- and middle-income countries; Alemayehu et al., 2018, identified challenges such as individual, financial, organisational, competing demands, and lack of research environment. This has implications for implementation into practice; thus, it is essential for trials from low- and middle-income countries to recognise and address these challenges in the conduct of clinical trials.

Strengths and weaknesses of this review

The strength of this review is the robust search, synthesis, and appraisal of BPS interventions in low- and middle-income countries. A limitation of this review is the inclusion of studies in the English language only; this may have resulted in potential studies being missed. Furthermore, a potential limitation relates to the fact that BPS interventions may be described in different ways; the search strategy was therefore expanded to ‘all text’, there is still a possibility of missed articles.

A limitation in included studies is the generally low methodological quality; low quality ratings were found in all categories of methodological quality ratings (reporting, external validity, internal validity – bias, internal validity - confounding). Thus, there is a need for high quality

studies in low- and middle-income countries to ascertain the potential for implementation of BPS interventions in routine clinical practice.

Conclusions

The results of this review indicate various BPS approaches aimed at the management of patients with chronic musculoskeletal pain, and how they are operationalised in low- and middle-income countries. It also highlights methodological insufficiencies in the operationalisation of BPS interventions in low- and middle-income countries. Finally, it highlights the need to conduct high quality clinical trials with the potential of implementation in routine clinical practice in low- and middle-income countries.

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Table 1: Description of included studies							
#	**Reference**	**Population**	**BPS Intervention and theory**	**Design of BPS intervention**	**Setting, Delivery and training of HCPs**	**Outcomes**	**Country**
1	Ibrahim et al., 2018 Feasibility randomised clinical trial	CLBP patients; recruited from a village in Nigeria and facilitated by a traditional ruler. N = 10 (PE), 10 (MCE), 10 (PE + MCE) Persistent pain for at least 3 months Age: 49.9±8.82 years Duration of pain: 5.40±4.76 years	Patient Education (PE) Plus Motor control exercises (MCE) Comparators: MCE alone, PE alone. MCE was based on the theory that spinal control and stability is altered in LBP. PE was based on cognitive-behavioural strategies emphasising self-management.	PE: Meaning of LBP, Common facts, Self-management, Postural hygiene, Increasing activity level, modification, Warning signs of LBP MCE: Abdominal drawer in manoeuvre in varied positions Stretching exercises	Hospital-based Out-patient physiotherapy setting HCP involved - physiotherapists – Number not stated Principal investigator (physiotherapist) delivered the PE to patients Physiotherapists were trained on MCE MCE: 2*weekly for 6 weeks PE: Once a week for 6 weeks	**Feasibility outcomes** – Recruitment rate, treatment compliance, retention/dropout rate, clinical outcome of pain (NRS), functional disability (ODI), adverse effects, perceived helpfulness	Nigeria
2	Bello et al., 2015 Randomized feasibility RCT –	NSCLBP patients; selected from referred patients by orthopaedic specialists from 3 selected hospitals N = 33 (experimental-BGE), 29 (control - CET) Age 18 – 65 years	Behavioural Graded Activity – BGE Control: Conventional exercise therapy BGE was based on operant conditioning and self-management principles.	Aerobic training phase Warm up exercise Cool down exercise. Strengthening of lower limbs Generalization phase Prevention and self-management of relapses through back care education.	Hospital-based Out-patient physiotherapy unit HCP involved - physiotherapists Physiotherapist delivered intervention – number not stated 45 minutes per session Total of 12 weeks	**Feasibility outcomes** – none **Other outcomes** – Pain – NRS, Quality of life – RAND 36- item	Ghana

		Mean age = 45±12.2 – CET, 43.1±13.2 BGE Duration of pain: LBP persistent for at least 3 months Mean duration not stated			Physiotherapists took part in a 4-day interactive session to design the BGA	Health Survey, Cost effectiveness – self-designed healthcare cost questionnaire	
3	Ogunlana et al., 2018 Quasi-experimental study –	NSCLBP patients; selected from referred patients by orthopaedic surgeons or family physicians of a federal hospital. N = 35 (experimental), 35 (control) Duration of Chronic LBP: 20(57.1%) weeks	Progressive goal attainment programme (PGAP) + Back education, soft tissue mobilisation, transcutaneous electrical nerve stimulation, exercises, drug treatment Control: Conventional treatment. PGAP was based on an activity-based cognitive behavioural intervention by; Sullivan, 2010	PGAP Use of disclosure and validation techniques, Plus: Soft tissue mobilisation, TENS therapy, isometric trunk muscle strengthening exercises, flexibility and coordination exercises and ergonomics counselling, McKenzie exercises, The Back-School book	Hospital-based Physiotherapy out-patient unit HCP involved - physiotherapists PGAP: 10 sessions of an activity-based CBT intervention Standard physiotherapy: Thrice a week for 10 weeks	Pain intensity - VAS, Pain catastrophising - PCS, Kinesiophobia - TSK, Perceived disability RODQ, Self-efficacy - SER	Nigeria
4	Nochit et al., 2014 Quasi experimental – group pre-test	LBP; recruited from rice farmers in one province in central Thialand. N = 40 (experimental), 40 (control)	Working Behaviour Modification Program (WBMP) (education program + stabilization back modification program) – Based on protection	Giving education, enhancing perceived self-efficacy, Live modelling presentation, Follow up through home visits.	Local health centre – setting not clearly described Multidisciplinary team comprising, two rehabilitation physicians,	LBP prevention Behaviours - LBP-PBQ, Back muscle endurance - Prone Double	Thailand

	post-test design. –	Male = 40 Female = 40 Duration not stated Age range and mean age not stated	motivation theory and self-efficacy Control: Regular LBP behaviour education WBMP designed based on Protection Motivation Theory		one orthopaedic surgeon, and two nurses 9-week intervention period	Straight-leg Raise Test	
5	Elshiwi et al., 2016 RCT	Low back pain due to postural scoliosis; recruited from outpatient physiotherapy clinic. N = 15 (experimental), 15 (control) Duration of pain not stated All female participants Age range = 18 – 25 years Age = (26.5±6.6 – experimental, 25.4±4.8 – control)	Cognitive functional therapy (CFT) Plus Therapeutic exercises Control: Therapeutic exercises CFT + exercises were developed based on the BPS theory – exercise (physical outcomes), CFT (psychosocial outcomes)	CFT + Therapeutic exercise Body awareness and pain intensity. Progressive pressure technique, MFS exercise. Cognitive concentration of posture of spine, cognitive concentration, Progressive pressure technique, Myofascial stretching exercise (MFS)	Out-patient physiotherapy clinic – tertiary hospital HCP involved - physiotherapists Physiotherapists number not stated Three sessions a week for six weeks	Severity of pain - VAS, Functional disability - ODI, Cobb's angle - loaded x-ray, Lumbar range of motion - Modified Schober test MMST	Egypt
6	Khan et al., 2014 RCT	NSCLBP; patients were recruited from an out-patient physiotherapy clinic. N = 27 (experimental), 27 (control)	Cognitive Behavioural Therapy (CBT) plus general Exercises Control: General exercises CBT plus exercise was based on problem	CBT Operant behavioural graded activity and problem-solving training. Graded activity gradual increase or pacing of activities, modification of	Physiotherapy unit – outpatient tertiary rehabilitation centre HCP involved - Physiotherapist, number not stated 3 sessions a week for 12 weeks	Pain – VAS, disability - RMDQ	Pakistan

		Duration of LBP: LBP for at least three months Age range= 29 – 50 Age: 39.61±5.3 years	solving training and operant behavioural graded activity	dysfunctional beliefs and general exercises, Home exercises			
7	Magalhaes et al., 2015, 2018 RCT – to investigate the effectiveness of a graded activity intervention on selected outcomes	NSCLBP patients; recruited from referral list of orthopaedists from specialist rehabilitation center N = 33 (experimental), 33 (control) Age range = 18 – 65 Age: 47.2(10.5) – experimental, 46.6(9.5) – control Duration of low back pain – 24 (12 – 108) months	Graded activity – Cognitive behavioural therapy + exercises Control: Physiotherapy exercise Graded activity developed based on cognitive behavioural therapy and adopted from protocols of Smeets et al., 2006 and Macedo et al., 2012	Graded Activity Individual sessions of progressive and sub-maximal exercises. Aerobic training on a treadmill and lower limb and trunk strengthening exercises. Educational booklet (based on the Back Book)	Hospital-based – Out-patient rehabilitation centre, HCP involved – Physiotherapist, number not sated (Physiotherapists received 10 hours of training), Intervention – twice a week for six weeks. Total of 12 hours	Pain - NRS, Disability - RMDQ, Quality of pain - McGill Pain Questionnaire, Quality of life - HRQoL, Global perceived effect - global perceived effect scale, Return to work - post-treatment assessment, Kinesiophobia - TSK, Daily physical activity -	Brazil

						Baecke Questionnaire of Habitual Physical Activity, Physical capacity - Sit-to-stand and 15.2 m walking test	
8	Aliyu et al., 2018 RCT – to determine the effects of implementing CBT and LSE on selected outcomes	NSCLBP patients, recruited from a teaching hospital in Kano, Nigeria. N = 23 (experimental), 23 (control) Age range: 18 – 55 years Age: 44.26 ± 13.11 - experimental, 40.28+11.80 – control Duration of pain: 6.21 ± 1.40	Cognitive behavioural therapy (CBT) + Lumbar Stabilization exercises (LSE) Control: Lumbar stabilization exercises Administration of CBT was based on manual by Murphy et al., 2014. LSE was administered based on the protocol by McGill, 2003.	CBT – Based on Murphy et al., 2014: Exercise and Pacing, Relaxation Training, Pleasant Activities, Cognitive Coping, Sleep. Strategies for improving sleep despite pain, Discharge Planning. Plan for flare ups and review of CBT skills, Booster Session. LSE – Based on McGill, 2003: Exercises	Hospital-based out-patient physiotherapy unit in a teaching hospital, HCP involved - Physiotherapists CBT + LSE – twice a week for 6 weeks. (12 sessions), Physiotherapist delivering CBT had formal training – mode and content of training not stated One physiotherapist delivered the LSE. Group/ individual intervention not stated	Pain – VAS, Disability – ODI, Fear avoidance beliefs: FABQ	Nigeria
9	Igna et al., 2014 RCT	CLBP patients; recruited from	Mindfulness-based Cognitive behavioural	CBT Expectancy component: Cognitive restructuring,	Hospital-based in-patient setting	Pain intensity: VAS, MPQ	Romania

		primary care recovery hospital. N = 43 (experimental), 25 (control) Age range: 24 – 74 years Mean age: 47 years, CLBP – persistent pain for at least 3 months	therapy (CBT) + Physiotherapy Control: Physiotherapy plus medication CBT + physiotherapy was based on expectancy of therapeutic change, targeted irrational beliefs, and exposure to avoidance behaviours (developed based on protocol by Onac et al., 2012)	Physical activity, Behavioural activation. Physiotherapy (based on Onac et al., 2012) - Iontophoresis, Ultra sonophoresis, TENS, Kinesiotherapy programme.	HCP involved - Physiotherapist led CBT + physiotherapy intervention, Physiotherapists received formal training on CBT Number of physiotherapists not stated, CBT – 6 sessions, 60 minutes each, 3 sessions a week Physiotherapy – 10 sessions, 5 sessions a week	Emotional distress: Anxiety - STAI-T, depression – BDI, mood - POMS-SV Wellbeing: FACT-Cella Mechanisms of change: GABSs, PASS-20, PCS, ATQ, MAAS, CPAQ	
10	Onac et al., 2012 RCT	CLBP patients; invited to participate in a free treatment at a rehabilitation hospital. N = 35 (experimental), 60 (control) Age range: 23 – 78, Mean age: 47 CLBP – persistent pain for at least 3 months	Cognitive behavioural therapy (CBT) + Physiotherapy Control: medication plus physiotherapy CBT + physiotherapy was based on expectancy of therapeutic change, targeted irrational beliefs, and exposure to avoidance behaviours	CBT Virtual Reality – Disputing beliefs, progressive muscle relaxation, Teaching the patient to become one's own therapist. Physiotherapy: - Iontophoresis, Ultra sonophoresis, TENS Kinesiotherapy, Patient education – based on 'back school'	In-patient clinical rehabilitation hospital CBT – 6 sessions, 60 minutes each, 3 sessions a week Physiokinetotherapy – 10 sessions, 5 sessions a week Multidisciplinary team – Physician, physiotherapist, masseur, kinetotherapist	Pain intensity – VAS Mood - POMS-SV Disability - RMDQ	Romania

11	Ghadyani et al., 2017 Prospective Cohort study – to investigate the effectiveness of a Multidisciplinary group-based intervention	CLBP patients; recruited from nurses with CLBP at a hospital in Iran. N = 66 (intervention), 70 (control) Age: 18 – 48 Duration of LBP – more than 90 days	Multidisciplinary Group-Based Intervention – Physiotherapy educational program + health educational program based on social cognition theory Control: Physiotherapy educational program	Physiotherapy education: Specific exercises for LBP and complying with the proper ergonomic posture of the vertebra during daily activities. Health educational program based on the predictive constructs of SCT, such as emotional coping, environmental perception, self-efficacy	Hospital-based Out-patient physiotherapy clinic Multidisciplinary team – physiotherapist, health education specialist Physiotherapy - 120-minute session Health education – 120-minute session Physiotherapists and health education specialist delivered intervention (number not stated)	Pain intensity – VAS, Disability - RMDQ	Iran
12	Babai et al., 2016 Quasi experimental pretest-posttest design	Chronic musculoskeletal pain patients; recruited from referred patients for physiotherapy at physiotherapy and pain clinics in Iran. N = 14 (CBT), 14 (ABM), 14 (control) Mean age: 41.36 (SD=18.3), Duration of pain: at least three months	Cognitive behavioural therapy (CBT) Control: Classic Dot-probe sessions	CBT Education and household assignment: Cognitive restructuring, exercise, ABC model, stress management; maintain exercise activity, problem solving, dealing with setbacks, and relapse prevention.	Hospital-based Out-patient physiotherapy clinic HCP involved - Physiotherapists 11 sessions-each 45 minutes with CBT program Number of therapists and level of training not stated	Pain intensity: BPI, Changes in biased attention to emotional stimuli – Dot-probe tasks	Iran

13	Castro et al., 2012 RCT - to investigate the effectiveness of CBT for managing chronic pain	Chronic musculoskeletal pain patients; recruited from a pain clinic in Brazil. N = 48 (experimental), 45 (control) Mean age: 45.9 (8.1) – CBT, 48.7(14.3) – control, years Duration of pain: pain persisting for more than 3 months	Cognitive behavioural therapy – CBT Control: Standard treatment (not described)	*Psychoeducation, Dysfunctional thinking record training and relaxation training, Problem-Solving Training (PST).	Hospital-based Out-patient pain clinic Number of therapists and level of training not stated 2-hour session, once a week for 10 weeks, 11 sessions, 120 minutes in total	Pain – VAS, Anxiety and depressive symptoms - HADS, Quality of life - SF-36	Brazil
14	Saedi et al., 2016 quasi-experimental pre-test and post-test design – to investigate the effectiveness of CBT for managing chronic pain	Chronic musculoskeletal pain patients; recruited from patients with musculoskeletal pain visiting a therapeutic center. N = 15 (experimental), 15 (control) Age range: 20 – 50 years, Duration of pain: not stated	Cognitive behavioural therapy – CBT Control: not described	Intervention not described	Hospital-based - Therapeutic Sanitary centre Number of therapists and level of training not stated 8 sessions in total, 90 minutes each, for five weeks	Alexithymia – Toronto, questionnaire, Pain – pain self-effectiveness questionnaire	Iran
15	Lopes et al., 2019	Chronic musculoskeletal pain patients; recruited	Mindfulness-based intervention (MBI) No control group	MBI focused – Pain management, breathing techniques,	Brazilian University Hospital clinic setting	Musculoskeletal	Brazil

	Clinical, uncontrolled, prospective, open, repeated measures trial – to investigate the effectiveness of MBI on chronic musculoskeletal pain	from a Brazilian University hospital. N = 64 All female Age: 18 or more, Mean age: 47.01 (9.50), Duration of pain: persistent pain for more than 6 months		Body scanning, Mindfulness walking, Conscious movements with light body postures, sitting, lying down, and compassion meditation, Audio guided home medication program (20 minutes)	Number of therapists and level of training not stated 7 participants per session 8 sessions in total, 60 minutes each for 8 weeks	symptoms: NMQ Pain-catastrophizing: PCS Anxiety symptoms: STAI Depression: BDI Dispositional mindfulness: MAAS Self-compassion: SELFCS Quality of life: WHOQOL-BREF	
16	Nazari et al., 2018 Quasi-experimental pretest-posttest research	Chronic musculoskeletal pain patients; recruited from physical and therapeutic centers in Iran. N = 15 experimental, 15 control All Female patients, Age range: 60 – 90 years,	Acceptance and community-based therapy (ACT) Control: no intervention	Intervention not described	Hospital-based Physical and therapeutic clinic Number of treating therapists and level of training not stated 8 sessions, 45 minutes per session	Pain - pain severity from 0 to 10, Disability - RMDQ	Iran

		Duration of pain: persistent pain lasting at least 6 months					

NRS: Numeric Pain Rating Scale, ODI: Oswestry Disability Index, VAS: Visual Analogue Scale, PCS: Pain Catastrophising Scale, TSK: Tampa Scale for Kinesiophobia, RODQ: Revised Oswestry Disability Questionnaire, SER: Self-Efficacy for Rehabilitation Outcome Scale, LBP-PBQ: Low Back Pain Prevention Behaviours Questionnaire, RMDQ: Rolland Morris Disability Questionnaire, HRQoL: Health Related Quality of Life, FABQ: Fear Avoidance Beliefs Questionnaire, MPQ: McGill Pain Questionnaire, STAI-T: State-trait Anxiety Inventory, ABM: Attentional Bias Modification, BDI: Beck Depression Inventory, POMS-SV: Profile of Mood States Short Version, FACT-Cella: Functional Assessment of Cancer Therapy Scale, GABSs: General Attitudes and Beliefs Scale, PASS-20: Pain Anxiety Systems Scale, ATQ: Autonomic Thoughts Questionnaire, MAAS: Mindful Attention Awareness Scale, CPAQ: Chronic Pain Acceptance Questionnaire, POMS-SV: Profile of Mood States Short Version, VNP: Verbal Numerical Pain Scale, PSFS: Pain Specific Functional Scale, GPE: Global Perceived Index, BPI: Brief Pain Inventory, HADS: Hospital Anxiety and Depression Scale, SF-36: Quality of Life Scale, NMQ: Nordic Musculoskeletal Questionnaire, STAI: Spielberger Strate-trait Anxiety Inventory, MAAS: Mindful Attention Awareness Scale, SELFCS: Self-Compassion Scale, WHOQOL-BREF: Quality of Life Scale of the World Health Organisation, NSCLBP – Non-specific Chronic Low Back Pain

***Information obtained from author which was not captured in publication**

Table 2: Assessment of methodological quality (modified Downs and Black Quality assessment tool)

	Reporting										External validity			Internal validity (bias)							Internal validity (confounding)						Power	
Reference	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Overall**
Ibrahim et al., 2018	1	1	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	24
Bello et al., 2015	1	1	1	1	0	1	1	0	0	1	1	1	1	0	1	1	0	0	0	1	1	1	0	0	1	1	0	17
Ogunlana et al., 2018	1	1	1	1	0	1	1	0	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	23
Wisut Nochit et al., 2014	1	1	0	1	0	1	1	0	0	1	1	1	1	0	0	1	0	0	1	1	1	1	0	0	0	0	0	14
Elshiwi et al., 2016	1	1	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	0	20
Khan et al., 2014	1	1	1	0	0	1	1	0	0	1	1	0	1	0	1	0	1	0	0	1	1	1	0	0	0	0	1	14
Magalhaes et al., 2015	1	1	1	1	0	1	1	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	21
Aliyu et al., 2018	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	1	1	1	0	0	0	1	19
Igna et al., 2014	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	0	0	1	1	1	0	0	0	0	0	16
Onac et al., 2012	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	1	0	0	0	0	18
Ghadyani et al., 2017	1	1	1	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0	18
Babai et al., 2016	1	1	1	1	0	1	0	0	0	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	0	0	15
Castro et al., 2012	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	1	1	1	1	1	1	1	0	0	0	0	0	16
Saedi et al., 2016	1	1	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	6

Demarzo and Nunes, 2018	1	1	1	0	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	7
Nazari et al., 2018	1	1	1	0	0	1	1	0	1	1	1	1	1	0	0	1	0	1	0	0	1	1	0	0	0	0	0	14

Key: 1= Yes, 0= No. For question 5; 2 = Yes, 0 = No, 1 = Partially. For 11 – 27; 0 also means unable to determine, For 27; 2 = Yes two outcomes or more, 1 = Yes one outcome, 0 = no outcome

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given
4. Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.
6. Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).
7. Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data, the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.
8. Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).
9. Have the characteristics of patients lost to follow-up been described? This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a

list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes, the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.
14. Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dredging", was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.
18. Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.
19. Was compliance with the intervention/s reliable? Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.
20. Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case control studies where there is no information concerning the source of patients included in the study.

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.
23. Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.
26. Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%.

Excellent= 24–28; Good= 20 – 23; Fair = 15–19; Poor = <14

(Downs and Black, 1998; O'Connor et al., 2015)