A Systematic Review of the Use of Interoceptive Exposure Interventions in Chronic Pain

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Abstract

Interoceptive exposure (IE), which refers to a behavioural intervention designed to reduce anxiety sensitivity and distress associated with somatic sensations, has been suggested to be a potentially effective technique in treating chronic pain. This systematic review aims to review the literature on the use of IE interventions for chronic pain, to identify with which populations these interventions can be most effective, and to suggest directions for future research. A comprehensive search of databases, including Scopus, PsycINFO via OVID, Web of Science, and the Cochrane Library, was undertaken to locate and identify relevant studies. A quality assessment of the identified studies was undertaken using a modified Downs and Black checklist for quality assessment. Fourteen studies were identified as relevant and utilised in the analysis, including seven randomised controlled trials. Data central to the study objective were extracted, examined and synthesised, and studies were analysed and categorised into three outcome categories: pain and function outcomes; emotion-related outcomes; and cognitive process outcomes. Findings provided encouraging evidence for the use of IE interventions in reducing pain, increasing function, improving emotional status and cognitive processes. Findings also suggest that IE is an effective intervention that is comparable to other psychosocial strategies for pain management, such as relaxation and distraction. Specifically, IE showed the most potential for people exhibiting high levels of fear before treatment, people with abdominal pain, and people with chronic pain and comorbid posttraumatic stress disorder (PTSD). The findings of this review also highlight the need for more high-quality research on IE as a chronic pain treatment, particularly with regard to the use of active controls and more unified outcome measures. Strengthening future research in this area may pave the way for stronger clinical recommendations.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), not material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Date: 15th February 2021

Signature:

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Chapter 1 Introduction

1.1 What is chronic pain and why does it matter?

1.1.1 Definition of pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020, p. 1977). There are additional notes clarifying pain as a person's lived experience, that may not be associated with tissue injury. It also emphasises the difference between pain and nociception, noting that pain cannot be solely described as activity in sensory neurons. In 2020, the revised notes by IASP state that pain is influenced by biological, psychological, and social factors, and can be learned through life experiences. Additionally, by acknowledging that people can feel and express pain in other ways, even if they cannot verbally describe pain, pain is likely to be understood among the vulnerable populations such as neonates and people with intellectual disabilities (Sharma, 2020).

Loeser (1980) suggested that pain can be understood as a complex phenomenon consisting of four broad elements: nociception, perception of pain, suffering, and pain behaviours. Nociception is the physiological processes resulting from the stimuli of any actual tissue damage or potential tissue damage, such as inflammation, injury, and mechanical irritant (Doleys, 2014). Nociceptive pain is typically acute and localised. It functions as a protective mechanism that shields the body from actual or potential harm (Loeser & Melzack, 1999). However, the terms nociception and pain should not be used synonymously, as one may experience pain without the occurrence of nociception. Perception of pain is multi-dimensional including a sensory aspect in terms of intensity, location, and types of stimulation, an affective aspect such as the associative fear and

tension, as well as an evaluative aspect in terms of the total subjective experience of pain (Melzack, 1987). Finally, a specific pattern of pain behaviours may occur as a result of pain and suffering. For example, avoidance and escape are typical behaviours related to pain. These behaviours can be observed, quantified, and measured as inferences of the extent of pain (Loeser & Melzack, 1999).

1.1.2 Acute vs. chronic pain

Acute pain is a sudden and short physiological response elicited by an adverse chemical, thermal, or mechanical stimulation. It is usually caused by an injury, surgery, trauma, or illness, and stops long before the healing of the causes (Loeser & Melzack, 1999). Acute pain is adaptive as it signals potential harm and motivates responses to avoid harm. By definition, acute pain lasts no longer than six months, or the expected time of healing.

Chronic pain is described in the latest version of International Classification of Diseases (ICD-11) as pain that persists past the normal healing time following an injury (Treede et al., 2015). There is a wide range of conditions of chronic pain based on the site of injury (e.g., back, head, viscera) and type of injury (e.g., neuropathic, arthritic, cancer) (Apkarian, Baliki, & Geha, 2009). Unlike acute pain, chronic pain is not adaptive, and is often associated with physical disability, emotional distress, and dysfunctions in social and occupational lives.

1.1.3 Prevalence of chronic pain

Chronic pain is a growing public health concern that leads to considerable individual, social, and economic impacts all over the world (Siddall & Cousins, 2004). A global survey conducted by Vos et al. (2015) showed that low back pain has been recognised as the leading reason of permanent disability in 86 countries, and the second or third-leading reason in 67 countries. Among the top 10 causes of permanent disability in

2013, there were four causes related to chronic pain, including low back pain, neck pain, migraine, and other musculoskeletal disorders. The prevalence of unspecified chronic pain in low and middle-income countries was about 34%, with higher prevalence among older adults, female, and people living in poverty (Jackson et al., 2016).

According to the latest survey conducted by the New Zealand Ministry of Health (MoH, 2019), chronic pain affects an estimated 19.4% of adults, and 13.1% of children in New Zealand. In 2018/19, about 763,000 adults in New Zealand suffered from pain almost every day. The prevalence of chronic pain increases by age group, ranging from 8.5% in the age group of 15 – 24 years to 33.5% in ages 75 years and above. Older people, Maori, and people living in deprived areas were more likely to suffer chronic pain (Moore & Davies, 2018). A survey conducted by Swain and Johnson (2014) gathered information from 142 people in the New Zealand community who suffer from chronic pain. Consistent with international data, the most common pain site is low back pain (59%), followed by pelvis or stomach pain (49%) and joints pain (39%). Over half of the respondents endorsed more than one cause of their pain, with the top three reasons as injury (21%), arthritis (20%), and indeterminate reasons (23%).

1.1.4 Impact of chronic pain—individual, societal, and economic

Chronic pain impairs patients' physical and mental functioning, affects their quality of working and daily lives, and social wellbeing (Apkarian et al., 2009). Swain and Johnson (2014) found that people with chronic pain often experience a high level of disability, with the majority having difficulty walking or moving (76%), sleeping (75%), and keeping concentration (64%). In addition to the physical difficulties, 19% of people with chronic pain also suffered from clinically relevant depression and 33% reported having an anxiety disorder. More than half of the patients reported having difficulty maintaining relationships with family and friends, and around a quarter of

people reported that they had lost their job or chances of promotion because of chronic pain (Swain & Johnson, 2014).

Chronic pain not only burdens individuals, but also society in many ways. First, individuals with chronic pain utilise healthcare more, which directly causes medical costs to the health system, community and individuals. Second, loss of productivity is associated with chronic pain, which leads to indirect costs to the society. Further, patients with chronic pain often live with a lower quality of life. Therefore, extra economic costs are needed for changes in the quality of life and care resulting from the disease. Moore and Davies (2018) reported that chronic pain cost New Zealand an estimated NZ$14 billion in 2016, and it is projected to increase to NZ$24 billion by 2048 due to direct medical care, productivity losses, health system costs, and welfare costs.

1.2 The biopsychosocial model of pain

1.2.1 The biopsychosocial model and its relevance for treatment of chronic pain

Scientific investigations have brought a greater understanding of the neurological and biological processes leading to the development and maintenance of pain. In addition, efforts have been made in an attempt to relieve pain and suffering. However, the traditional biomedical model, which views the specific biochemical defect as the ultimate criterion defining a disease, failed to explain the presence of pain without identifiable objective pathology, pathology in the absence of experience of pain, and diversity in responses to identical treatments (Andrasik, Flor, & Turk, 2005). Engel (1977) introduced a new model, referred to as a biopsychosocial model, fulfilling an understanding of the relationships between psychosocial and physiological factors associated with a disease. The biopsychosocial model concerns the personal experience of illness and the subjective sense of suffering (Hyams & Hyman, 1998). From this

perspective, the different responses of patients to symptoms and treatments result from a complex interaction of predispositional characteristics, biological changes, psychological status, and social and cultural contexts. For example, predispositional factors such as experiences of early life, may initiate, maintain, and modulate illness; psychological factors may affect the perception of physiological signs; and social and cultural factors influence the way patients experience and respond to their illness.

The biopsychosocial model of chronic pain includes predisposing factors from early life experiences, precipitating stimuli, precipitating responses, and maintaining processes (Turk & Flor, 1999). First, genetic variables, trauma from early life, and social learning experiences may contribute to a reduced threshold for nociception. Studies suggest that both genetic factors and parental attitudes are important to the development of the clinical expression of irritable bowel syndrome (IBS) (Tanaka, Kanazawa, Fukudo, & Drossman, 2011). Second, persistent aversive events such as pain-related stressors, negative emotional states, or other life stresses may act as an unconditioned or conditioned stimulus that activates somatic symptoms and motivates avoidance responses. Numerous studies have found the strong association between mental illness and chronic pain: The development of an enduring pain condition would likely increase the risk for the subsequent diagnosis of a mood disorder. In contrast, psychological disorders such as depression, anxiety, and distress often predict the transition from acute to chronic pain (Baker, Gibson, Georgiou‐Karistianis, & Giummarra, 2018; Csupak, Sommer, Jacobsohn, & El-Gabalawy, 2018; Müller et al., 2017). In addition, evidence suggests that negative psychological states and processes are correlated to a decrease in the benefit from pain-reducing treatments (Wasan et al., 2015). Third, a precipitating response is a maladaptive behavioural, cognitive, or physiological process that fails to help an individual adjust to the impacts of the aversive event. Finally, operant and respondent learning processes cause implicit and explicit memories of pain that play an

important role in maintaining pain experience and disability (Birbaumer, Flor, Lutzenberger, & Elbert, 1995). In this model, treatments should focus on changes in the patient's thoughts, feelings, and cognitions related to chronic pain, thus influencing their behaviours and physiology.

1.2.2 Biological mechanisms

Regarding biological mechanisms, pain can be categorised as nociceptive pain, neuropathic pain, and nociplastic pain. Nociceptive pain relates to neural activation arising from actual or potential damage to non-neural tissue. It refers to the processes of neural activations that carry noxious information from the peripheral nervous system (PNS) to the central nervous system (CNS) (Doleys, 2014). Nociceptors recognise the location and types of stimulation, thereby protecting the body from actual or potential harm. Neuropathic pain is the type of pain caused by a lesion or disease of the somatosensory system including peripheral nerves, spinal cord, and certain CNS regions (Jensen et al., 2011). The onset of neuropathic pain is more likely to be chronic, with the sensation of burning, shooting, stabbing, and electric shock. It may spread to the neighbouring cutaneous distribution of the damaged nerve, or develop bilateral pain sites (Colloca et al., 2017). Finally, nociplastic pain is a new descriptor proposed by the IASP in 2017, describing the type of pain that arises from altered nociception despite no clear evidence of actual or potential tissue damage, or evidence for disease or lesion of the somatosensory system (Kosek et al., 2016). While nociceptive pain is generally acute and localised, neuropathic and nociplastic pain are more likely to be chronic and diffuse.

1.2.3 Psychosocial mechanisms

In addition to biological factors, two psychosocial models associated with chronic pain are conditioning and fear avoidance.

Conditioning

Classical conditioning. In learning theories, an unconditioned stimulus (UCS) is a biological potent event that naturally elicits an unconditioned response (UR). A conditioned stimulus (CS) is a neutral event with relatively less biological meaning (Vlaeyen, 2015). When a CS is repeatedly presented with the UCS, a conditioned response (CR) occurs which is often similar to the UR. Classical conditioning refers to the learning procedure in which after the CS becomes associated with the UCS, a CR can be elicited when the CS is presented alone (Schneider, Palomba, & Flor, 2004). This learning procedure enables the prediction of potentially harmful stimuli, hence eliciting protective responses to avoid the harm (Rescorla, 1988).

With respect to pain, both the nociceptive sensation and the negative affective component of acute pain are USs. The affective component associated with pain ranges from immediate unpleasantness such as distress, annoyance, and fear, to long-lasting negative emotions such as depression, frustration, anger, and anxiety (Price, 2000). Typical pain-related UR includes psychophysiological arousal such as muscle tension, increased heart rate and skin conductance, followed by defensive responses such as escape, avoidance, and other safety-seeking behaviours (Bolles & Fanselow, 1980). When a relatively neutral stimulus, either exteroceptive (e.g., visual, auditory), proprioceptive (e.g., specific movements and position), or interoceptive, repeatedly co-occurs with nociceptive sensation, it can be considered as a CS. The CS signals an expectancy of pain, thus eliciting CRs such as escape and avoidance behaviours (Vlaeyen, 2015).

Interoceptive conditioning (IC), as defined by Razran (1961), is one type of classical conditioning in which the conditioning is directly related to the internal bodily sensations. In an interoceptive fear conditioning model proposed by De Peuter, Van Diest, Vansteenwegen, Van den Bergh, and Vlaeyen (2009), various interoceptive

sensations that often co-occur with pain may be interpreted as predictors of pain. These sensations (e.g., heartbeats, muscle fatigue, stiff joints, and gastrointestinal sensations) may become CSs, leading to pain-related fear responses. Furthermore, De Peuter et al. (2009) proposed that mild pain may act as a CS for more severe and longer-lasting pain. Evidence suggested that conditioning elicited by interoceptive stimuli is more powerful, occurs more rapidly, and appears to be more resistant to extinction compared to conditioning with exteroceptive stimuli (Domjan, 2005).

Operant conditioning. Operant conditioning is a learning procedure in which an association is built between behaviours and the positive or negative consequences for the behaviours (Bouton, 2007). A behaviour is likely to increase in frequency if it is followed by a positive or negative reinforcement. If a positive or negative punishment is followed, the behaviour is likely to decrease in frequency (Fordyce, Fowler, Lehmann, & Delateur, 1968). In the operant perspective, once an acute pain occurs, individuals may develop avoidance behaviours and a fear of pain-related activity. These pain behaviours are negatively reinforced, maintained by non-occurrence of pain, thus an operant conditioning process may follow the original classical conditioning. While chronic pain may develop under the classical conditioning process, operant conditioning functions to maintain the chronicity, whereby avoidance behaviours will occur without the presence of nociceptive stimuli (Flor, 2012).

Fear-avoidance model

The fear-avoidance model is one of the most widely known and influential mechanism-oriented models that describe the pathway by which particular processes can influence pain-related outcomes (Edwards, Dworkin, Sullivan, Turk, & Wasan, 2016). This model proposes that pain-related disability is resultant from the interaction of a series of fear-related cognitive, affective, and behavioural processes (Vlaeyen, Kole-Snijders, Boeren, & Van Eek, 1995). For most people, pain resulting from an injury is perceived and

appraised to be unpleasant, but can be responded to adaptively. However, some patients may develop a catastrophic expectation of pain, thereby generating fear of pain and pain-related anxiety. The development of catastrophic thinking is often affected by predispositional characteristics and psychological status. Individuals suffering from chronic pain tend to respond to pain with fear and anxiety. The fear of pain and pain-related anxiety, in turn, may promote and maintain avoidance behaviours, dysfunction, emotional distress, and additional pain (Asmundson, Noel, Petter, & Parkerson, 2012). According to the fear-avoidance model, catastrophic thinking about pain and pain-related consequences lead to fear of pain and anxiety. Escape and avoidance of daily activities motivated by fear lead to functional disability. In addition, avoidance behaviours may persist as the unhelpful expectancies and beliefs about pain are unable to be corrected. Prolonged avoidance behaviours and reduction of activity impair the body system, which may worsen the pain. Finally, inactivity is often accompanied by negative emotions such as depression, which also leads to a lower threshold of pain (Romano & Turner, 1985).

1.2.4 Psychosocial factors influencing pain-related outcomes

A number of psychosocial variables have been suggested as predicting factors that are strongly associated with the development and maintenance of chronic pain. Meanwhile, some variables are influential factors for treatment outcomes. For example, research and clinical settings in chronic pain management often assess patients' affective disorders including depression, anxiety, and emotional distress, as one aspect of treatment outcomes. Diatchenko et al. (2013) and Howe et al. (2015) both found that not only chronic musculoskeletal pain can lead to elevated negative emotions, but patients with premorbid psychological dysfunction are more likely to transit from acute pain to chronic. Rudy, Kerns, and Turk (1988) also reported a mutually reinforcing relationship between chronic pain and depression. More than that, these psychological symptoms

also contribute to worse pain-related consequences such as physical dysfunction, work disability, more costs in health care, mortality, and suicide (Hassett, Aquino, & Ilgen, 2014).

Early life trauma such as childhood physical, sexual, and psychological abuse, as well as combat exposure and post-traumatic stress disorder (PTSD) in adulthood have been suggested as strong influencing factors that may facilitate subsequent chronic pain development. A meta-analysis reported that people who are exposed to early life trauma are twice or three times more likely to develop chronic widespread pain, and childhood abuse is associated with a nearly twofold increase in risk for the adult development of painful somatic syndrome (Afari et al., 2014). Posttraumatic stress disorder (PTSD) is a psychological illness resulting from exposure to a traumatic event, with the presence of dysfunctional cognitive and behavioural responses such as emotional hyperarousal, avoidance behaviours, and re-experiencing of the traumatic event. A number of studies have identified PTSD as a risk factor for the transition from acute to chronic pain, and for the development of pain and disability in abuse victims (Jenewein, Moergeli, et al., 2009; Kongsted et al., 2008; Wuest et al., 2010). Lang et al. (2006) suggested that PTSD symptoms mediated the relationship between childhood abuse and the presence and severity of chronic pain. Additionally, Jenewein, Wittmann, Moergeli, Creutzig, and Schnyder (2009) found that PTSD and pain were mutually maintaining conditions in the first six months following an injury related accident, and PTSD was a maintaining factor for pain in the chronic phase. Therefore, Andersen, Lahav, Ellegaard, and Manniche (2017) proposed that interventions targeting both PTSD and pain would be promising in pain management.

Pain catastrophising can be defined as an exaggerated negative orientation towards actual or anticipated pain experiences. It comprises negative cognitions and emotions

such as a feeling of helplessness, being pessimistic, rumination about pain-related symptoms, and a tendency to magnify pain reports (Edwards, Cahalan, Mensing, Smith, & Haythornthwaite, 2011). There has been much evidence that has suggested that evaluated levels of pain catastrophising are a risk factor for developing chronic pain as well as for worsening long-term outcomes. For example, studies in patients with low back pain and joint pain found that higher levels of pain catastrophising are associated with higher pain severity, increased physical disability, higher health care costs, and increased psychological dysfunction (Campbell et al., 2010; Edwards et al., 2013). Hill, Lewis, Sim, Hay, and Dziedzic (2007) indicated that pain-relieving interventions were less likely to be effective for patients with musculoskeletal pain who reported higher levels of pain catastrophising before treatment. Furthermore, some studies argued that CBT and similar psychosocial interventions are effective in chronic pain management because they can produce substantial reductions in catastrophising and negative affects rather than clinical pain (Litt, Shafer, Ibanez, Kreutzer, & Tawfik-Yonkers, 2009; Thorn & Burns, 2011).

Another vulnerability factor that may lead to maladaptive pain cognitions is anxiety sensitivity (AS). AS is defined as the fear of arousal-related bodily sensations arising from beliefs that these sensations have harmful consequences (Reiss, 1991). High levels of AS have been found in several psychological disorders, especially in panic disorder (Taylor, 1995). People with elevated levels of AS have a tendency to interpret unpleasant somatic sensations as a sign of danger. Several studies that have examined the role of AS on the development and maintenance of chronic pain have found positive associations between AS, fear of pain, and pain escape or avoidance behaviours. For example, Asmundson and Taylor (1996) found that patients with chronic back pain who had higher levels of AS reported greater pain-related fear and showed greater avoidance behaviours. Similarly, Norton and Asmundson (2004) provided evidence that AS plays

a predictive role in the fear of pain, and escape and avoidance behaviour in patients with recurrent headaches. Moreover, evidence suggests that people with higher AS show an attentional bias for sensory pain words (Asmundson, Carleton, & Ekong, 2005), a greater interpretative bias for negative material, and more negative pain experiences (Keogh & Cochrane, 2002).

Self-efficacy is an individual's belief in his or her ability to perform a certain behaviour to achieve a desired outcome, and is a major determinant of whether an individual is able to cope with difficult challenges (Stewart & Yuen, 2011). For patients with chronic pain, higher levels of pain-related self-efficacy are positively related to the ability to tolerate pain, control pain symptoms and to function with the presence of pain (Turk, Fillingim, Ohrbach, & Patel, 2016). Studies have demonstrated that high self-efficacy before treatment and larger improvement of self-efficacy during treatment are correlated to greater improvements in pain, physical function, and psychological status, as well as better long-term outcomes among people with chronic pain (Costa, Maher, McAuley, Hancock, & Smeets, 2011; Stewart & Yuen, 2011). A prospective treatment study reported self-efficacy as one of the most potent mediators of improvements in pain and disability among patients with chronic orofacial pain who received CBT interventions (Turner, Holtzman, & Mancl, 2007). High self-efficacy is considered as a protective factor for chronic pain experience. One reason proposed by Gatchel, Peng, Peters, Fuchs, and Turk (2007) is that people with high self-efficacy often have higher expectancies for performance success, and are more likely to persevere in activities, enabling them to be motivated to follow treatment instructions and to engage in health promoting behaviours.

For people with chronic pain, the perception of pain severity and intensity is assumed to be correlated to the degree of attention to pain. Eccleston and Crombez (1999)

explained the relationship between pain and attention, indicating that the experience of pain interrupts ongoing attention and behaviour, and shifts attention to the pain. The interruption is moderated by a range of pain-related factors such as intensity, novelty, predictability, the threat value of pain, emotional arousal, and awareness of somatic information. McCracken (1997) assessed the degree of pain attention for people with chronic low back pain through a range of pain responses, such as awareness, vigilance, preoccupation, and observation of pain. This study found that people with greater attention to pain also reported higher scores in pain intensity, depression, anxiety, and physical disability, as well as more pain-related healthcare. Tabira et al. (2020) also reported that people with chronic pain often show hypervigilance, an excessive attention to pain which can cause evaluated levels of disability, catastrophising, as well as increased avoidance behaviours.

1.3 Treatments for chronic pain

Chronic pain, persisting disability and treatment-related outcomes are affected by the interaction of somatic pathology as well as psychological and social factors. Pain, as a complex health problem, often requires a comprehensive treatment approach that focuses on medical and physiological aspects, physical functioning, and emotional impairment (Hechler et al., 2015). Over the last few decades, multidisciplinary interventions on the basis of cognitive-behavioural principle have rapidly developed and have become a well-accepted approach for chronic pain management (Gatchel & Okifuji, 2006). Multidisciplinary interventions involve a comprehensive treatment approach that combine therapies such as physiotherapy, pain management by medication, patient education, and engagement with one or more types of psychological interventions (Scascighini, Toma, Dober-Spielmann, & Sprott, 2008). For example, cognitive-behavioural therapy is one of the most commonly used psychological interventions for reducing pain and disability by modifying cognitive processes toward

pain, and pain control behaviours. Operant-behavioural treatment, aimed at supporting healthy behaviours by positive reinforcement and minimising pain behaviours by reduced or absent positive reinforcement, has also been utilised in multidisciplinary approaches to pain management. The strategies that are often used include graded activity, time-contingent intake of medication, and training in assertive pain-incompatible behaviours (Thieme & Turk, 2012). Additionally, education about the relationship between pain and muscular tension is often involved in treatments, with attempts to reduce pain through relaxation techniques. Finally, the graduated activity exposure, or pacing, is also commonly used teaching patients to regulate their activity, and to gradually increase their activity level after establishing a regime of paced activity, thereby controlling the development or exacerbations of pain (Harding & Watson, 2000).

1.3.1 Cognitive behavioural therapy

As cognitive factors play an important role in the development of chronic pain and the treatment outcomes, cognitive behavioural therapy (CBT) has been developed as an effective method for pain management. The cognitive behavioural approach suggests that individuals' interpretation, evaluation and beliefs about their pain condition and disability will influence the degree of pain-related physical and emotional dysfunction (Sullivan, Feuerstein, Gatchel, Linton, & Pransky, 2005). In the context of chronic pain treatment, a patient referred for CBT may receive varying selections or combinations of intervention strategies, including self-instructions for instance motivational self-talk, relaxation or biofeedback, development of coping strategies such as distraction and imagery, increasing assertiveness, minimising negative or self-defeating thoughts, changing maladaptive beliefs about pain, and goal setting (Linton & Andersson, 2000). Morley, Eccleston, and Williams (1999) concluded from their systematic review and meta-analysis that the primary aim of CBT is to replace patients' maladaptive

cognitions and behaviours with more adaptive ones, and found this treatment as effective for a variety of chronic pain conditions. In a later study, Linton and Nordin (2006) demonstrated that early CBT intervention for back pain led to significant reduction in pain, an increase in activity and quality of life, better general health, as well as greater economic benefits compared to the controls. This study also demonstrated the long-term positive effects of CBT as the improvements largely maintained at a five-year follow-up.

A number of studies and reviews have demonstrated the effectiveness of CBT for a wide range of chronic pain conditions (e.g., Carpenter, Stoner, Mundt, & Stoelb, 2012; Jungquist et al., 2010; Pigeon et al., 2012), and researchers have become interested in the mediators, moderators, and predictors of the treatment effects of CBT. For example, Turner et al. (2007) investigated the changes in specific cognitions throughout CBT intervention, and found that an increase in self-efficacy plays the most important role in chronic pain patients' improvements across outcomes. In addition, CBT led to an increase in the perceived ability to control pain, a decrease in the negative beliefs about pain, and catastrophising, which were interrelated, and all substantially mediated treatment effects. In addition, Turner et al. (2007) identified several patient baseline characteristics including depression, multiple pain sites, rumination, catastrophic thinking, and emotional distress as predictors of treatment outcomes, and suggested more intensive CBT to patients with these characteristics.

1.3.2 Acceptance and mindfulness-based interventions

In recent years there has been growing interest in acceptance-based interventions in chronic pain treatment such as mindfulness-based stress reduction (MBSR) programmes and acceptance and commitment therapy (ACT). These interventions are considered as alternative therapies for CBT, which focus on acceptance of pain rather than controlling

or fighting pain (Veehof, Oskam, Schreurs, & Bohlmeijer, 2011). Mindfulness is described as a state of consciousness which involves consciously attending to one's moment-to-moment experience with acceptance, openness, and a non-judgemental attitude (Brown & Ryan, 2003). An MBSR programme may include various types of meditation practices, body scanning, yoga, and exercising mindfulness in everyday life (Veehof et al., 2011). The practice of body scanning involves gradually diverting attention throughout the body from feet to head, focusing on sensations or feeling in any part of the body with an attitude of acceptance whilst using periodic breathing awareness and relaxation suggestions. Sitting meditation not only involves mindful attention on breathing, the rise and fall of the abdomen and other perceptions, but also a state of non-judgmental awareness of cognitions and of the stream of thoughts and distractions that are constantly flowing through the mind. Hatha yoga exercise includes practices of breathing, simple stretching exercises, and postures designed to strengthen and relax the musculoskeletal system (Chiesa & Serretti, 2011). Mindfulness has also been integrated with specific exercises or psychological techniques such as cognitive therapy (Segal, Williams, & Teasdale, 2018). Chiesa and Serretti (2011) observed the effects of MBSR in reducing pain-related symptoms and depression for chronic pain patients. Further, patients receiving MBSR showed an increase of pain acceptance, tolerance, and significant alleviation of their emotional distress and improvement of quality of life. The study also suggested that higher levels of mindfulness was associated with a decrease in pain perception and an overall improved functioning (Chiesa & Serretti, 2011).

ACT is another commonly used therapy in chronic pain treatment which primarily addresses ineffective control strategies and experiential avoidance. Instead of attempting to change irrational thoughts, patients who receive ACT are taught to approach and be open to experiences of negative emotions, sensations, and thoughts associated with pain

(Dahl, Wilson, & Nilsson, 2004). ACT also focuses on the client's values and attempts to increase the ability to commit to these values in daily life, to facilitate behavioural change, and to improve functioning (Hughes, Clark, Colclough, Dale, & McMillan, 2017). The primary aim of ACT is to help clients produce greater psychological flexibility, which is defined as the ability of being open, aware and in contact with the present moment, and effectively engage in values-based actions (Bond, Hayes, & Barnes-Holmes, 2006). Psychological flexibility describes six processes that enable an individual to function optimally: to actively accept unwanted emotions, feelings, and experiences, without attempting to change them; to be in contact with the present moment rather than ruminating on the past or the future, or on negative thoughts; to separate from identification with difficult thoughts and feelings; to view self as context rather than as a conceptualisation; to identify values; and to commit actions in order to fulfil these values (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). There have been many studies that have evaluated the efficacy of ACT for chronic pain management, which have overall yielded positive outcomes. For example, Vowles and McCracken (2008) reported that patients with chronic pain who received ACT showed significant increases in pain acceptance and values-based actions, as well as amelioration of anxiety, depression, and disability. Later, McCracken and Gutiérrez-Martínez (2011) found that during the treatment period, patients reported significant increases in pain acceptance, general psychological acceptance, mindfulness, and values-based actions. Additionally, they also reported significant decreases in depression, anxiety, and disability at a three-month follow-up, which were independent of changes in pain. Specifically, Wicksell, Olsson, and Hayes (2010) indicated that the effects of ACT in improving functioning and life satisfaction in people with chronic pain are mediated by psychological flexibility, rather than pain, emotional distress, fear, and self-efficacy.

1.3.3 General exposure therapies

Graded exposure is a commonly used intervention in the management of chronic pain. At the first stage of graded exposure, patients are required to rate fear activities according to the intensity of fear, and construct an exposure fear hierarchy. The patient is first exposed to the least feared activity, and the therapist helps the patient to evaluate the consequences of the exposure. During the exposure, the therapist guides the patient to challenge irrational thoughts, negative beliefs about pain, and catastrophic interpretations of the consequences of the activity, thereby minimising the activity-related anxiety (Macedo, Smeets, Maher, Latimer, & McAuley, 2010). Once the negative associations disappear, the patient is then exposed to activities associated with higher levels of fear until the patient is able to perform the most feared activities. Studies consistently suggest that graded exposure is an effective strategy for modifying fear-avoidance beliefs, reducing catastrophising, and improving pain and disability in chronic pain patients (Boersma et al., 2004). George, Wittmer, Fillingim, and Robinson (2010) evaluated the outcomes from graded exposure for patients participating in a multidisciplinary rehabilitation program for chronic low back pain, and found significant clinical outcomes for pain intensity and disability, which were associated with reductions in depression and pain catastrophising. Similarly, Vlaeyen, de Jong, Geilen, Heuts, and van Breukelen (2001) reported that during the graded exposure in vivo, patients with chronic low back pain showed significant alleviation of pain-related fear, pain catastrophising, and pain disability.

1.4 Interoceptive exposure

Goldstein and Chambless (1978) found from their clinical observation that patients with panic disorder and agoraphobia often interpret the changes of bodily sensations as a prediction of an upcoming panic attack. They employed the concept “interoceptive conditioning” to explain this phenomenon, and suggested that desensitisation may

produce some alleviation of anxiety. A decade later, interoceptive exposure (IE) as a psychological intervention was first introduced by Barlow (1988) in treating panic disorder. IE describes a method that induces patients suffering from panic disorder to be exposed to the bodily sensations that they typically experience before or during a panic attack.

1.4.1 History of interoceptive exposure

Research employing IE as a part of the treatment for symptoms of panic disorder began to emerge in the mid-20th century (Boettcher, Brake, & Barlow, 2016). For example, inhalations of carbon dioxide oxygen (CO_2/O_2) mixtures were considered to be a promising technique in the treatment of anxiety that might be interpreted as a form of IE. Although the initial aim of CO_2 inhalations was to promote relaxation and lead to reciprocal inhibition of anxiety, an alternative rationale suggested by Barlow (2004) indicated that inhalations may reduce anxiety by repeatedly exposing patients to their feared anxiety-related somatic sensations within a safe context. Wolpe (1958) administered repeated CO_2 inhalations to patients with anxiety in the procedures of systematic desensitisation, and reported a powerful relief of anxiety. In another case study conducted by Latimer (1977), the patient suffering from panic attacks reported both immediate and prolonged improvements following repeated CO_2 inhalations.

Similarly, lactate infusion is another technique that was used to induce bodily symptoms associated with panic and anxiety. Bonn, Harrison, and Rees (1971) administered sodium lactate infusions to 33 patients suffering from anxiety, in order to induce intense somatic discomforts such as respiratory distress, cardiovascular activation, and panic. They found the repeated administration resulted in a significant decrease in anxiety, and the effect was largely maintained at 6 weeks follow-up. Specifically, the authors demonstrated that the patients' "fear of fear" was substantially reduced after lactate

infusions. Later, however, Haslam (1974) found that patients suffering from anxiety were more likely to react with panic attacks to lactate infusion, but were more likely to benefit from repeated CO2 inhalations.

Some studies employed physical activities in the treatment of anxiety and panic, which might be considered as a type of IE exercise. Orwin (1973) introduced a technique in the treatment of agoraphobia by requesting patients to run or walk rapidly toward anxiety-provoking situations, where the running was performed in order to bring on marked breathlessness. Eleven patients were successfully treated by this method. An explanation suggested by Stewart and Watt (2008) was that running repeatedly exposed the patients to the same sensations associated with panic, resulting in the reduction of fear of these sensations. Physical exercise has been found not only effective in reducing symptoms of anxiety and panic (Broocks et al., 1998), but also in reducing anxiety sensitivity (Broman-Fulks, Berman, Rabian, & Webster, 2004; Smits et al., 2008).

The idea was formally suggested for the first time by Goldstein and Chambless (1978) that repeated exposure to interoceptive cues might be effective in reducing the fear of sensations associated with panic disorder. Following that, a series of experiments were conducted by Griez and Van den Hout (1982, 1983, 1986), in which they treated patients with anxiety and agoraphobia by using repeated inhalations of CO_2/O_2 mixtures to induce anxiety-related bodily symptoms. They suggested that bodily sensations associated with anxiety should be considered as conditional stimuli that lead to panic attacks. Their studies demonstrated the therapeutic effects of repeated and prolonged exposure to somatic sensations in reducing unexpected panic attacks. Furthermore, one rationale for IE in the context of panic attacks treatment was provided from their studies: panic attacks are conditional responses resulting from fear and anxiety-related

bodily symptoms, therefore patients are most likely to benefit from repeated and prolonged exposure to these symptoms.

In addition, a variety of techniques beyond biochemical substances were proposed and verified by Barlow and Czerny (1988), which were considered to be more applicable and feasible in inducing somatic symptoms. For example, hyperventilation and spinning were found to be effective in inducing dizziness. Patients also commonly experienced shortness of breath while breathing through a straw, or during and after physical exercises. Additionally, Antony, Ledley, Liss, and Swinson (2006) found that feelings of choking and breathlessness were easy to be induced by using a tongue depressor. Generally, these techniques were effective in provoking anxiety-related symptoms, and approximately 90% of the patients tended to respond with self-reported anxiety (Schmidt & Trakowski, 2004). The introduction of these techniques in research saw IE implemented outside of research context, resulting in a fast spread to clinical practice. In 1988, the term interoceptive exposure was first introduced by Barlow, and today it is considered to be one of the most essential methods in the treatment of anxiety and panic disorders.

1.4.2 IE's mechanisms

Several mechanisms have been proposed to explain the effectiveness of IE in reducing fear of aversive bodily symptoms. For example, learning theory proposes that fears of aversive sensations are acquired and maintained via conditioning, and IE reduces these feared sensations via extinction and habituation (Barrera, Grubbs, Kunik, & Teng, 2014). Extinction refers to the gradual weakening of a conditioned response that results in the behaviour decreasing or disappearing (Miltenberger, 2011). Extinction happens in classical conditioning when a conditioned stimulus is repeatedly presented with the absence of the unconditioned stimulus, and happens in operant conditioning when a

response is no longer reinforced following a discriminative stimulus. Therefore, an individual who is repeatedly exposed to a feared stimulus without experiencing the feared consequences may learn that the respective stimulus does not necessarily signal an impending anxiety attack. Mystkowski, Craske, and Echiverri (2002) suggested that exposure to feared bodily symptoms should be repeated in various situations and under various internal conditions in order to broaden the basis for the new learning.

From another perspective, cognitive theories propose that IE may be effective through resultant cognitive restructuring and changes in self-efficacy (Gerlach & Neudeck, 2012). Cognitive models suggest that repeated exposure to aversive bodily symptoms provides individuals an opportunity to change irrational beliefs, and to learn that there are no negative consequences to experiencing arousal-related sensations (Stewart & Watt, 2008). IE thus not only restructures the catastrophic consequences of the experience of anxiety-related sensations, but also allows for the development of positive cognitions regarding the consequences of these somatic experiences. Further, CBT-based IE implies that exposure to aversive bodily symptoms and the symptom-related anxiety may increase an individual's self-efficacy, enabling him or her to cope with these symptoms and emotions more effectively. As self-efficacy increases, an individual may become more confident in being able to cope with aversive bodily symptoms, thus symptom-related anxiety should be reduced when encountering these sensations in the future (Gerlach & Neudeck, 2012).

Finally, from an acceptance-based perspective, higher levels of acceptance and tolerance to arousal-related sensations without the need to avoid or change them are strong protective factors for anxiety pathology (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). People with both high anxiety sensitivity and low acceptance of emotional distress are more likely to experience anxiety and worry. Therefore, people

high in anxiety sensitivity may benefit from new learning to emotionally accept anxiety-related sensations, emotional states, and associated negative thoughts (Kashdan, Zvolensky, & McLeish, 2008). Repeated exposure to anxiety-related sensations via IE allows an individual with high anxiety sensitivity to attend to the current situation rather than engaging in distraction or avoidance. This provides the opportunity to learn to accept the fear of aversive sensations, and thereby facility cognitive changes (Stewart & Watt, 2008). Unlike the cognitive restructuring model, which primarily targets the changes of negative beliefs and catastrophic thoughts, acceptance-based perspectives focus on changes in cognitions regarding the unacceptability of the emotions and sensations.

1.4.3 Utilisation of IE in anxiety and PTSD

IE was initially designed to reduce anxiety sensitivity and distress associated with somatic sensations, and has been found to be effective for social anxiety and specific phobias (Boettcher et al., 2016). Social anxiety disorder is often associated with high levels of AS, and the experience of fearful physical sensations such as a flushed face or trembling hands (Deacon & Abramowitz, 2006). Individuals with social anxiety disorder are more likely to pay excessive attention to these physical sensations, and to develop maladaptive cognitions (e.g., catastrophic thoughts) and avoidance behaviours. Collimore and Asmundson (2014) conducted a study testing the effect of IE techniques on anxiety responses in people with social anxiety disorder. They suggested spinning, while standing and breathing through a straw, and hyperventilation as the most effective methods to elicit anxiety, and most frequently provoke symptoms including increased heart rate, shortness of breath and dizziness. In addition, compared to non-clinical controls, people with social anxiety reported more intense responses to the provocation techniques (Collimore & Asmundson, 2014).

Studies have also found that IE has the potential to be beneficial in the treatment of specific phobias. For example, Kahana and Feeny (2005) evaluated the effectiveness of a variety of cognitive behavioural techniques in the treatment of a child with the phobia of vomiting. IE techniques were used to provoke gastrointestinal and audio-vestibular symptoms, thereby triggering the fear of vomiting. Results suggested that IE can be effective in reducing symptoms and behavioural impairments related to illness phobias. Later, Hunter and Antony (2009) presented a case in which a CBT intervention combined with interoceptive exposure was used in the treatment of phobia of vomiting. This case study reported significant reductions in physical symptoms, psychological distress, anxiety sensitivity, and improvements in functions after treatment and at three years follow-up, all of which implicated the potential benefits of interoceptive exposure for people with emetophobia.

In addition, IE is often used as a powerful adjunct to trauma-related interventions in the treatment of PTSD. Individuals with PTSD often report a high level of AS, which may enhance the core PTSD symptoms such as hyperarousal and hypervigilance to trauma cues. Wald and Taylor (2008) conducted a series of studies investigating the effect of IE followed by trauma-related interventions in early PTSD treatment. They found that employing IE before trauma-related interventions could be effective in reducing AS and improving outcomes. IE provides an opportunity for exposure to both the emotions and accompanying physical sensations being experienced during the initial traumatisation, thereby enhancing the effects of the following trauma-related interventions. Positive effects of IE for PTSD have been supported in a various of subpopulations such as PTSD in refugees (Otto & Hinton, 2006), combat-related PTSD (Wald & Taylor, 2010), and PTSD with comorbid chronic pain from motor vehicle accidents (Wald, Taylor, Chiri, & Sica, 2010).

1.4.4 Utilisation of IE in chronic pain management

Within the context of chronic pain management, research regarding the application of IE focuses on strategies that are not often used in the treatment of anxiety and panic disorders. Instead of directly inducing pain through symptom provocation methods, patients with chronic pain are expected to focus their attention on already existing pain symptoms (Gerlach & Neudeck, 2012). “Mindfulness” or “somatic experiencing” were commonly used strategies, by gradually guiding the client to sustain attention to difficult bodily sensations. Through the interventions, patients with chronic pain learn that pain associated sensations are safe and tolerable through repeated exposure to feared internal sensations without escape or avoidance, thus reducing pain anxiety (Andersen et al., 2017). Meanwhile, acceptance of pain is expected to increase and avoidance behaviours can be reduced. Some studies, however, use the pain provocation technique (PPT), in which participants are instructed to provoke increases in pain intensity by focusing on pain-related thoughts, memories, emotions, and bodily sensations (Flack et al., 2018). Once a previously defined level of pain is reached, the clients were asked to reduce the experience of pain through pain coping strategies. The repeated exposure is supposed to reduce fear of pain and avoidance behaviours. In addition, a type of interoceptive exposure may also involve provocation techniques that expose the client to the physical symptoms provoked by formerly avoided activities, thereby reducing such avoidance behaviours (Gerlach & Neudeck, 2012).

Evidence pointing toward the effectiveness of IE in chronic pain management has begun to emerge over the last decade. For example, a preliminary experimental study conducted by Flink, Nicholas, Boersma, and Linton (2009) utilised a combination of IE and a relaxation breathing-based technique for back pain and found moderately high improvements in pain acceptance and corresponding decreases in pain-related distress. Cayoun, Simmons, & Shires (2020) examined the effect of IE on chronic pain and

found significant reductions in pain anxiety, pain duration, and pain intensity immediately after each treatment session, and the effect was maintained at two-month follow-up. Furthermore, a study conducted by Hechler et al. (2010) investigated the effectiveness of an IE intervention for adolescents suffering from chronic pain. This study demonstrated a significant decrease in pain intensity and emotional distress.

There is some evidence to suggest that IE inhibits pain by reducing fear of pain and pain-related sensitivity. For example, Watt, Stewart, Lefaivre, and Uman (2006) found that a brief CBT intervention with aerobic exercise was significantly effective in reducing AS and pain-related anxiety for people high in anxiety sensitivity before treatment. Moreover, the study provided evidence of AS changes as a mediator of the effect of CBT in reducing fear of pain. In a recent study, Flack et al. (2018) compared the outcomes of IE and relaxation therapy (RT) as an adjunctive treatment in the context of intensive interdisciplinary pain treatment for patients with paediatric chronic pain. They concluded that although both interventions lead to significant reductions in fear of pain and pain characteristics, patients with a high fear of pain before treatment strongly benefitted from IE rather than RT. Similarly, Craske et al. (2011) used CBT incorporating pain provocation procedures that directly targeted fear and avoidance of visceral sensations for patients with IBS, and revealed the outstanding effects of this intervention in reducing pain and sensitivity to internal sensations. Following this study, Wolitzky-Taylor, Craske, Labus, Mayer, and Naliboff (2012) suggested reduction in visceral sensitivity as a mediator of improvements in IBS symptoms and quality of life outcomes.

1.5 Study aims

This study aims to review the current evidence for interoceptive exposure (IE) as an effective treatment for chronic pain. It also aims to identify in which populations these

interventions show the most potential. The literature in other healthcare populations suggests that IE interventions are effective in treating a variety of mental illnesses, especially panic disorder, PTSD, social anxiety, and phobias. Various studies exist in relation to the application of IE interventions for chronic pain treatment. However, to date, no systematic review of this topic has been published. This means that practitioners and researchers have only limited resources in order to gain an overview. Moreover, little is known about how IE interventions may work and for which populations. A systematic review of current evidence is therefore needed in order to establish whether the outcomes of IE as a treatment option are robust and merit further investigation. Consequently, findings and insights drawn from a thorough systematic review may help provide recommendations for future research and clinical practice.

Chapter 2 Methods

The aim of this study was to explore the effectiveness of interoceptive exposure (IE) interventions for the treatment of chronic pain. In this chapter, concepts of the systematic research review will be discussed, and the process of the review will be described.

A systematic review is a form of research which uses explicit, accountable, rigorous research methods in reviewing an existing research question (Boland, Cherry, & Dickson, 2017). The methods involve an extensive search process to identify all relevant papers that address a particular topic, critical evaluation and assessment of quality studies to select the most robust and objective evidence, as well as a systematic synthesis of the characteristics of the search results and findings of the research question (Siddaway, Wood, & Hedges, 2019). This process enables subjectivity and bias to be minimised. The nature of systematic reviews makes them more likely to draw robust and broad findings on a particular question and give a valid answer (Mulrow & Cook, 1998). Therefore, systematic reviews are an important element of research and clinical practice.

This study followed the five steps of a systematic review process as described by Khan, Kunz, Kleijnen, and Antes (2003), which includes framing questions, identifying relevant work, assessing the quality of studies, summarising the evidence, and interpreting the findings. This chapter will respond to the first three steps. The summarisation and synthesis of the evidence will be presented in the results chapter and the interpretation and recommendations will be presented in the discussion.

2.1 The research questions

The first step of a systematic review is to define a clear, unambiguous, and structured question. Khan et al. (2003) illustrated four elements of a structured question: the populations under study, the interventions or exposures, the outcomes, and the study designs. The research question of this study was identified as "Are interoceptive exposure interventions effective in treating chronic pain?" From this question, a secondary question followed: "For which populations are IE interventions effective?" Therefore, this study looked at the existing research that has explored the application of IE interventions in chronic pain treatment, in order to answer the above questions, and to propose any implications for future research and clinical practice. Pain-related outcomes are the main outcomes of interest for this study.

2.2 Search strategy

A comprehensive process was undertaken to locate and identify studies. The search process was conducted through Auckland University of Technology (AUT) library's electronic databases. Databases included: Scopus, PsycINFO via OVID, Web of Science, and the Cochrane Library. These databases cover a wide variety of peer-reviewed journals in a wide range of subject areas, thus providing access to a comprehensive range of up-to-date scientific research.

An initial simplified search term ("interoceptive exposure" AND "chronic pain") was derived from the formulated question, and a preliminary search was conducted through Scopus. The search field was limited to title, abstract, and keywords, and date of publication was limited up to July 2020. An initial short review of the limited literature that was yielded from this preliminary search provided foundational understanding of the background of the research question and allowed for identification of alternative search terms to be applied in the full search. The use of a variety of search terms and

phrases was employed to ensure maximisation of the search process in identifying as much of the relevant literature as possible.

Table 1 lists the terms used in the full search process. All the alternative search terms of "chronic pain" were linked with Boolean operators "OR" as "search 1" (S1), and all the alternative terms of "interoceptive exposure" were linked with "OR" as "search 2" (S2). The final step of the search process was to combine S1 and S2 with "AND". As with the preliminary search, the search field was limited to title, abstract, and keywords, and the date of publication was limited up to July 2020. The same search process was performed to each of the above databases, ensuring that as many relevant studies were identified as possible. In addition, the reference lists from the selected articles were reviewed for potentially relevant studies that were not identified by the database search.

Table 1 Key terms and search words

Order of terms searched	Search terms
Search 1	("Chronic pain" OR "pain chronicity" OR "persistent pain" OR "persisting pain" OR "ongoing pain" OR "longstanding pain" OR "recurrent pain" OR "recurring pain" OR "long-term pain")
Search 2	("Interoceptive exposure" OR "interoceptive training" OR "interoceptive technique" OR "Interoceptive approach" OR "desensitis*" OR "somatic experiencing" OR "cognitive exposure" OR "pain provocation" OR "sensation exposure" OR "habituat*" OR "extinction")

2.3 Study selection and eligibility criteria

After discarding duplicates, the titles, abstracts, and keywords of all identified studies were screened for relevance and to ascertain whether they met the inclusion criteria (see below). Full-text copies of the articles were obtained when inclusion criteria were met,

or when relevance could not be determined by the titles, abstracts, and keywords. These were reviewed to determine whether they met the inclusion and exclusion criteria.

Studies were included according to the following criteria: (1) an IE intervention was applied as a treatment or a part of treatment for adults or children with a chronic, persistent, or recurrent pain condition; (2) pain-related outcomes were reported as primary or secondary findings; (3) the study was a randomised controlled trial, cohort study, or case study, where quantitative data were reported; and (4) the study was published in English language.

Studies were excluded under these criteria: (1) the content focused on non-psychological treatment such as medical management, physiotherapy, and pharmacological treatment; (2) treatment focused on exposure in vivo, graded exposure, and other exposure therapy without the element of the interoceptive experience of pain; (3) full texts were not available; and (4) studies that employed animal models in their design.

2.4 Quality assessment

The quality assessment of included studies is essential in assessing the strength of bias and making recommendations for future research (Khan et al., 2003). This study used a modified quality index developed by Downs and Black (1998) to assess the quality of the selected articles (see Appendix A). Whereas numerous appraisal tools have been developed to provide guidelines for assessing study quality, most have concentrated exclusively on randomised trials. This quality index was chosen for the study as it can be used to assess not only randomised controlled trials but also non-randomised studies such as cohort studies and case-control studies.

The Downs and Black checklist for quality assessment is a 27-item checklist that provides a numerical value for study quality, with the total score ranging from 0 to 32. It comprises five subscales (reporting, external validity, bias, confounding, and power), which along with providing an overall score for study quality, also provides a profile of scores for the above five aspects. The ten items in the reporting subscale assess whether a paper provided sufficient information, enabling a reviewer to assess the findings of the study with minimum bias. The three items in the external validity subscale assess whether the findings of a paper can be generalised to the population from which participants were derived. There are seven items to address any biases in the measurement and outcomes of a paper. The confounding subscale consists of six items, which address bias in the recruitment of study participants. Finally, one item in the power subscale assesses whether a study has sufficient power to detect a clinically important effect (Downs & Black, 1998).

Answers to the original checklist were scored either 0 or 1, except for item 5, which was scored from 0 to 2, and item 27 which was scored from 0 to 5. Item 27 was modified in this study. A study would be scored 2 points if it mentioned having conducted a power analysis to determine the sample size needed to detect a significant difference in effect size, and sufficient power was emphasised. If a power analysis was conducted, but not sufficient enough to detect a clinically important effect, the study would be scored 1 point. 0 points would be given if the study did not mention having conducted a power analysis. Therefore, the total of the maximum score of this checklist was 29 points. Hooper, Jutai, Strong, and Russell-Minda (2008) have used this modified checklist in their published systematic review and recommended score ranges corresponding to quality levels of studies as follows: 14 points or less as poor, 15–19 points as fair, 20–25 points as good, and 26–29 points as excellent.

The Downs and Black checklist for quality assessment was reported by the authors to have sufficient reliability and validity (Downs & Black, 1998). Internal consistency was assessed using the Kuder-Richardson formula 20 (KR-20), and a high level of internal consistency (KR-20: 0.89) was reported for both randomised and non-randomised studies. Adequate internal consistency for all the subscales was also reported, with only one exception for the external validity subscale (KR-20: 0.54). Additionally, the Downs and Black checklist for quality assessment has been found to be reliable, with a test-retest correlation of $r = .88$, and good inter-rater reliability ($r = .75$) was also reported. Finally, the scores of the quality index have been found to be highly correlated with the Standards of Reporting Trials Group checklist ($r = .90$), indicating a high level of concurrent validity (Downs & Black, 1998).

2.5 Data extraction and synthesis

Data from each study were extracted and tabled on an Excel spreadsheet, enabling ease of analysis and comparison between studies. Data that were extracted regarding the study details included authors, year of publication, sample size, design of studies, participant characteristics, intensity and duration of interventions, follow-up measures, outcome measures, findings, and discussion points. For each of the outcome measures, the proportion of statistically significant outcomes, confidence intervals, and effect size were extracted where available.

After extraction, findings from the data were examined and synthesised to provide a narrative review of the current evidence base. Narrative review also guided the exploration of the secondary question: “For which populations are IE interventions effective?” Narrative synthesis is described as a method of presenting and making sense of data using summary text, with reference to the data in tables (Boland, Cherry, &

Dickson, 2017). An explanatory summary was reported with overall findings and highlighted similarities and differences between studies.

Chapter 3 Results

3.1 Description of the included studies

Figure 1 illustrates the process undertaken to select the studies included for quality appraisal and data extraction. The initial search across databases identified 935 articles. This total was reduced to 642 following the discard of duplicates. There were 505 articles identified via Scopus, and an additional 22 via PsycINFO, 33 via Cochrane, 82 via Web of Science. Following the screening of the titles and abstracts across databases, 597 articles were excluded. This resulted in identifying 45 articles with probable or possible relevance to the topic, or with relevance that could not be determined by titles and abstracts alone. There were two articles for which full texts were not available, and another four articles which were published in non-English language. Therefore, 39 articles were read in full text. After reading full texts, a further 10 articles were excluded due to irrelevant content. Eighteen articles were excluded because they were not quantitative studies, or quantitative results were not reported. Three additional articles were identified through screening of reference lists. Fourteen articles were included for final quality appraisal and data extraction.

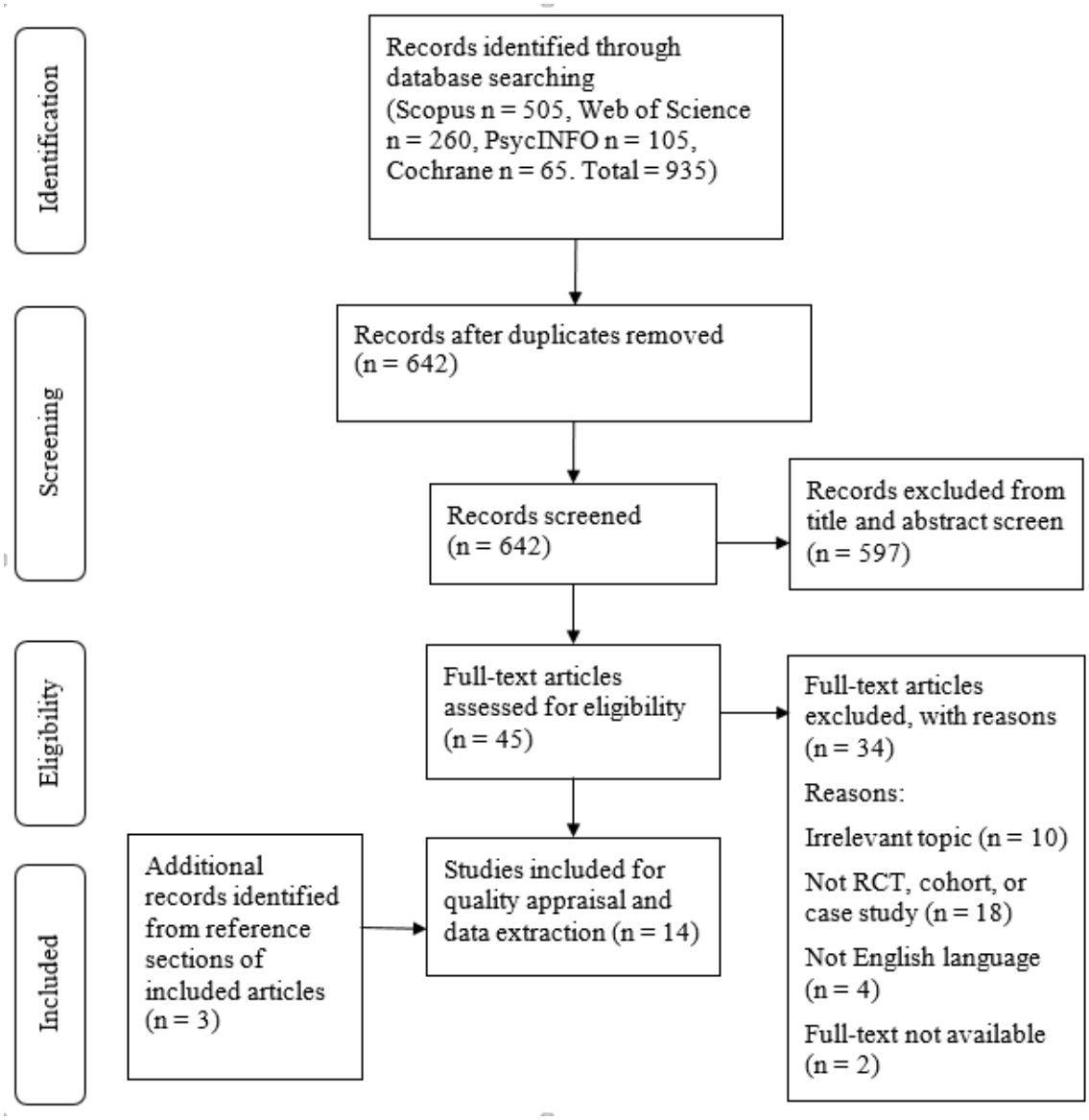

Figure 1. Flowchart showing the process of selecting studies to include in the review

3.2 Characteristics of included studies

The general characteristics of each included study are provided in Table 2. All the studies were conducted between 2008 and 2020. Nine of the studies were conducted in Europe (Andersen et al., 2017; Dobe, Hechler, & Zernikow, 2009; Flack et al., 2018; Flink et al., 2009; Hechler et al., 2010; Linton, 2010; Simshäuser, Lüking, Kaube, Schultz, & Schmidt, 2020; Wicksell, Ahlqvist, Bring, Melin, & Olsson, 2008; Wicksell, Melin, Lekander, & Olsson, 2009), three in North America (Craske et al., 2011;

Wald et al., 2010; Zucker et al., 2017), and two in Australia (Cayoun et al., 2020; Nicholas et al., 2014).

3.2.1 Study Design

Of the 14 studies, there were seven randomised controlled trials (RCT) (Andersen et al., 2017; Craske et al., 2011; Flack et al., 2018; Nicholas et al., 2014; Simshäuser et al., 2020; Wicksell et al., 2008; Wicksell et al., 2009), two case studies (Dobe et al., 2009; Linton, 2010), two cohort studies (Cayoun et al., 2020; Zucker et al., 2017), one case-control study (Hechler et al., 2010), one cross-sectional study (Wald et al., 2010), and one cross-over study (Flink et al., 2009).

3.2.2 Sample Size

Overall, the sample sizes of the studies were relatively small. Four RCT studies recruited 91, 104, 110, and 140 participants, respectively (Andersen et al., 2017; Craske et al., 2011; Flack et al., 2018; Nicholas et al., 2014). The samples sizes of other studies ranged from 1 to 62 (M = 20.6, SD = 19.7). The proportion of female participants was higher than males in the majority of the studies, with only one exception where Dobe et al. (2009) recruited one male participant in their case study. One study recruited young children as participants, with ages ranging from 5 to 9 years (M = 7.1, SD = 1.1) (Zucker et al., 2017). There were four other studies with adolescent participants ranging from 11 to 18 years (Dobe et al., 2009; Flack et al., 2018; Hechler et al., 2010; Wicksell et al., 2009). For the studies with adult participants, the mean age of participants ranged from 39.5 to 55.1 years. Of the 14 studies, there were nine studies that recruited participants solely from primary care clinics, pain centres, or from physician referrals (Andersen et al., 2017; Cayoun et al., 2020; Dobe et al., 2009; Flack et al., 2018; Hechler et al., 2010; Linton, 2010; Nicholas et al., 2014; Wicksell et al., 2009; Zucker et al., 2017). Three studies recruited participants from local media advertising and clinics (Craske et al., 2011; Simshäuser et al., 2020; Wald et al., 2010). One study

recruited participants from a local newspaper (Flink et al., 2009). One study recruited participants from Swedish Association of Survivors of Traffic Accidents and Polio (Wicksell et al., 2008). Ten studies indicated explicitly the eligible criteria, including diagnosis of chronic pain, or pain lasting longer than 3 months (Cayoun et al., 2020; Craske et al., 2011; Dobe et al., 2009; Flink et al., 2009; Hechler et al., 2010; Nicholas et al., 2014; Simshäuser et al., 2020; Wald et al., 2010; Wicksell et al., 2008; Wicksell et al., 2009). Types of pain and pain locations of the participants are presented in Table 2.

3.2.3 Characteristics of the Intervention

In all of the 14 studies, IE interventions were delivered as an adjunctive component of multi-modal treatment. Two studies delivered CBT-based interventions, where IE was combined with education, self-monitoring of sensations, strategies of identifying and responding to unhelpful cognitions, engaging in activities, and attentional control skills (Craske et al., 2011; Nicholas et al., 2014). Four studies delivered ACT-based IE interventions by emphasising acceptance and defusion as alternatives to avoidance in coping with negative pain reactions (Flink et al., 2009; Wicksell et al., 2008; Wicksell et al., 2009; Zucker et al., 2017). Seven studies delivered IE or pain provocation technique by mindfully experiencing pain sensations, followed by relaxation strategies (Andersen et al., 2017; Cayoun et al., 2020; Dobe et al., 2009; Flack et al., 2018; Hechler et al., 2010; Simshäuser et al., 2020; Wald et al., 2010). Finally, Linton (2010) delivered an intervention based on dialectical behaviour therapy that included goal setting, validation, behavioural experiments and interoceptive exposure. Furthermore, two studies indicated that the IE interventions were delivered in addition to treatment as usual (TAU) (Andersen et al., 2017; Wicksell et al., 2008). One study implemented IE as an adjunctive treatment in the context of intensive interdisciplinary pain treatment (IIPT) for paediatric chronic pain patients (Flack et al., 2018). In the study by Hechler et

al. (2010), mindfulness-based PPT was delivered in addition to standard multimodal inpatient treatment.

3.2.4 Comparisons

In RCT studies, treatment groups were compared to TAU (Andersen et al., 2017; Simshäuser et al., 2020; Wicksell et al., 2008), multidisciplinary treatment and amitriptyline (MDT) (Wicksell et al., 2009), relaxation therapy (Flack et al., 2018), distraction to pain (Nicholas et al., 2014), CBT-based stress management and attention control (Craske et al., 2011). In Craske et al. (2011), both stress CBT-based management and IE consisted of education, self-monitoring, attentional control skills training, cognitive therapy, and in vivo exposure to external stressful situations that were not directly related to the experience of IBS sensations. A unique component in the IE group involved repeated exposure to visceral sensations to reduce fear of the sensations. The attention control condition only included education and self-monitoring of IBS symptoms. In the case-control study, adolescents utilising PPT within multimodal inpatient treatment were compared with adolescents in standard multimodal inpatient treatment matched for age, gender, and diagnosis (Hechler et al., 2010). In the cross-over study conducted by Flink et al. (2009), comparison was made between two groups, in which one group used IE for three weeks, then crossed over to the relaxion or distraction breathing-based technique, and the other group did the reverse. Finally, in the cross-sectional study, all the participants received the same treatment that consisted of four sessions of IE followed by eight sessions of trauma-related exposure therapy (Wald et al., 2010).

Table 2. Characteristics of included studies

Authors	Design of study	N (% finished)	Pain type and site	Age (years)	Country	Gender	Intervention model	Control group	Duration (Total hours)	Group & individual	Who delivered	Outcomes (measures)	Follow-up (months)	D & B score
Andersen et al. (2017)	RCT	91, dropouts 6	LBP and comorbid PTSD	18-65, *M*=50.6	Denmark	54.2% F	Mindfulness based SE + TAU	TAU	TAU 4-12 sessions, SE 6-12 hrs		SE therapist, pain nurse	Pain intensity Disability PTSD Fear of injury Catastrophizing	12 mths	26
Wicksell et al. (2008)	RCT	20	WAD (mainly neck pain, headache) Continuous/ recurrent	20+, *M*=48.2-55.1	Sweden	16 F	Value-based exposure and acceptance strategies + TAU	TAU	10 sessions	ind	psychologists physician	Pain intensity Disability Pain interference Quality of life Depression Anxiety PTSD Fear of injury Psychological inflexibility	4 mths 7 mths	25
Nicholas et al. (2014)	RCT	140	LBP and legs, shoulder/arms/ neck, lower limbs, others	*M*=42.1-43.2	Australia	51-55% F	CBT + IE	CBT + distraction	115h, 3 wks	group	psychologist	Pain intensity Medication use Disability Depression Fear of injury Self-efficacy Catastrophizing Acceptance Treatment adherence Treatment credibility	1 mth, 6 mths, 12 mths	27

Authors	Design of study	N (% finished)	Pain type and site	Age (years)	Country	Gender	Intervention model	Control group	Duration (Total hours)	Group & individual	Who delivered	Outcomes (measures)	Follow-up (months)	D & B score
Craske et al. (2011)	RCT	110	IBS	*M*=39.5	U.S.	74.3% F	CBT based IE	CBT based stress management Attention control	10 sessions			Pain intensity Pain interference Anxiety Attention to pain Treatment adherence Treatment credibility	3 mths	26
Flack et al. (2018)	RCT	104	Headache, abdominal pain, MSK	11-17 years	Germany	76 F	IIPT + mindfulness-based PPT	IIPT + Relaxation therapy	5 sessions	group	psychologist	Pain intensity School absence Disability Anxiety Anxiety sensitivity Fear of injury Catastrophizing Treatment credibility	3 mths	27
Wicksell et al. (2009)	RCT	32	Headache, back/neck pain, widespread MSK, CRPS	10.8-18.1, *M*=14.8	Sweden	25 F, 7 M	Exposure + ACT	MDT	10 sessions individually 2 sessions with parents		psychologists	Pain intensity Disability Pain interference Quality of life Depression Fear of injury Pain impairment beliefs Pain-related discomfort Catastrophizing	3 mths 6 mths	26

Authors	Design of study	N (% finished)	Pain type and site	Age (years)	Country	Gender	Intervention model	Control group	Duration (Total hours)	Group & individual	Who delivered	Outcomes (measures)	Follow-up (months)	D & B score
Simshäuser et al. (2020)	RCT	62	Migraine	18-65, *M*=44	Germany	92% F	MBSR	TAU	8 sessions	group	Psycho-therapists	Pain intensity Medication use Disability Quality of life Depression Anxiety Distress Self-efficacy Pain perception Acceptance Treatment adherence Treatment credibility	12 mths	23
Hechler et al. (2010)	Case-control study	40 study grp, 40 cntrl	Headache, recurrent abdominal pain, back pain, others	*M*=14	Germany	21 F, 19 M	PPT (mindfulness)+ standard multimodal treatment	Standard multimodal inpatient treatment	3 mths	ind, grp, family		Pain intensity School absence Disability Depression Anxiety	3 mths	22
Zucker et al. (2017)	Cohort study	24	Functional abdominal pain	5-9 yrs, *M*=7.1	U.S.	66% F	Acceptance-based IE		10 sessions	grp		Pain intensity Pain interference Distress Affective symptoms Treatment response		17

Authors	Design of study	N (% finished)	Pain type and site	Age (years)	Country	Gender	Intervention model	Control group	Duration (Total hours)	Group & individual	Who delivered	Outcomes (measures)	Follow-up (months)	D & B score
Cayoun et al. (2020)	Cohort study	15	Chronic back pain, Fibromyalgia	26-73, *M*=47.3	Australia	8 F, 7 M	Mindfulness integrated CBT which consisted of IE task		30s MIET during 2 wks	ind	psychologist	Pain intensity Anxiety Distress Affective symptoms Pain perception Treatment credibility	2 mths	18
Flink et al. (2009)	cross-over	6	Chronic back pain, neck, arms, and shoulders	39-63 yrs		4 F, 2 M	Acceptance based IE (attention) + Relaxation/ distraction		3 wks R/D + 3 wks IE, or reversed	ind	psychologists	Pain intensity Disability Fear of injury Catastrophizing Acceptance	3 mths	17
Linton (2010)	Case study	1	Back and neck pain	52 yrs	Sweden	F	Dialectical behaviour therapy-based IE		16 sessions	ind		Pain intensity Disability Sleep quality Fear of injury Catastrophizing Acceptance	3 mths	14
Dobe et al. (2009)	Case study	1	Chronic headache	15 yrs	Germany	M	PPT			ind		Pain intensity School absence Disability Depression Anxiety	3 mths 6 mths 12 mths	14

Authors	Design of study	N (% finished)	Pain type and site	Age (years)	Country	Gender	Intervention model	Control group	Duration (Total hours)	Group & individual	Who delivered	Outcomes (measures)	Follow-up (months)	D & B score
Wald et al. (2010)	Cross-sectional study	5	Chronic MSK several regions, recurrent headaches	33-60, *M*=42.4	Canada	F	IE exercises + traumatic-related exposure		4 sessions IE + 8 sessions TRE	ind	doctoral students in clinical psychology	Pain intensity Pain interference Depression Anxiety Anxiety sensitivity PTSD Fear of injury	3 mths	14

Abbreviations: LBP, low back pain; MSK, musculoskeletal pain; WAD, whiplash-associated disorders; IBS, irritable bowel syndrome; CRPS, complex regional pain syndrome; SE, somatic experiencing; MBSR, mindfulness-based stress reduction; TAU, treatment as usual; IIPT, intensive interdisciplinary pain treatment; PPT, pain provocation technique; MDT, multidisciplinary treatment and amitriptyline;

3.3 Quality of included studies

Table 2 provides the total scores of the Downs and Black checklist for each included study. Studies varied in quality with scores ranging from 14 to 27 out of 29 points. Five studies were categorised as excellent quality (Andersen et al., 2017; Craske et al., 2011; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009), three studies as good quality (Hechler et al., 2010; Simshäuser et al., 2020; Wicksell et al., 2008), three studies as fair quality (Cayoun et al., 2020; Flink et al., 2009; Zucker et al., 2017), and three studies as poor quality (Dobe et al., 2009; Linton, 2010; Wald et al., 2010).

Overall, RCT studies achieved higher scores than other study designs, with scores ranging from 23 to 27, followed by the case-control study (Hechler et al., 2010), which scored 22 points. The case studies (Dobe et al., 2009; Linton, 2010) and the cross-sectional study (Wald et al., 2010) presented the lowest quality with each scoring only 14 points out of 29. All the studies presented a high quality of description of objectives, measures, inclusion criteria, treatments, statistical results and main findings. Accurate outcome measures, appropriate statistical tests, and adequate analyses to adjust different lengths of follow-up were used by all the studies. In all the RCT studies, participants were randomly assigned to one of the groups, and they were not able to know which intervention they would receive before the treatment had started. Efforts were made in all the RCT studies to blind the study statistician who conducted the analysis to treatment allocation. Only one study did not report the characteristics of patients lost to follow-up.

About half of the studies failed to provide details regarding the confounding variables in each group and the adverse events that may have affected the intervention outcomes. Nine studies demonstrated an attempt to recruit participants' representative of the general clinical population, but only half of the studies indicated that treatments were

conducted in pain treatment service or other clinical settings, which resulted in limited generalisability. Only the RCT studies demonstrated attempts in minimising selection bias well. Nine studies did not report any power analysis, and one study conducted a power calculation but had insufficient power to detect a clinically important effect (Hechler et al., 2010).

3.4 Pain and function outcomes

Table 3 presents pain-related outcomes including pain intensity, disability, pain interference, quality of life, medication use, and school absence.

Fourteen studies evaluated the effects of IE interventions on pain intensity, and all observed decreased pain following treatment. The quality scores of these studies ranged from 14 to 17, including five excellent quality (Andersen et al., 2017; Craske et al., 2011; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009), three good quality (Hechler et al., 2010; Simshäuser et al., 2020; Wicksell et al., 2008), three fair quality (Cayoun et al., 2020; Flink et al., 2009; Zucker et al., 2017), and three poor quality studies (Dobe et al., 2009; Linton, 2010; Wald et al., 2010). Ten studies conducted statistical analysis (Andersen et al., 2017; Cayoun et al., 2020; Craske et al., 2011; Flack et al., 2018; Hechler et al., 2010; Nicholas et al., 2014; Simshäuser et al., 2020; Wicksell et al., 2008; Wicksell et al., 2009; Zucker et al., 2017). Two studies found a significant decrease of pain from post-treatment assessments (Flack et al., 2018; Zucker et al., 2017), and six studies found a significant decrease of pain from 1 – 12 months follow-up assessments (Andersen et al., 2017; Craske et al., 2011; Flack et al., 2018; Hechler et al., 2010; Nicholas et al., 2014; Wicksell et al., 2009). In the other two studies, decrease of pain did not reach significance from post-treatment assessment (Simshäuser et al., 2020; Wicksell et al., 2008). Where reported, the effect sizes ranged from small to large (range $\eta^2 p$ = .03 – .56, range d = 0.37 – 1.71). In the four studies

where statistical analysis was not conducted, the pre-post design revealed a decreasing trend of pain intensity. The effects of IE interventions on reducing pain intensity were compared to the effects of TAU (Andersen et al., 2017; Simshäuser et al., 2020; Wicksell et al., 2008), distraction (Nicholas et al., 2014), relaxation therapy (Flack et al., 2018), MDT (Wicksell et al., 2009), stress management and attention control strategy (Craske et al., 2011), and standard multi-model inpatient treatment (Hechler et al., 2010), respectively. Four studies reported significant decreases in pain intensity for both study groups and control groups (Craske et al., 2011; Flack et al., 2018; Hechler et al., 2010; Nicholas et al., 2014). Only one study found a significant difference between IE group and stress management group in terms of decrease in pain intensity with a small effect size (d = 0.44), where those in the IE group reported a greater reduction in pain intensity (Craske et al., 2011).

Ten studies evaluated the effects of IE interventions on disability, including four excellent quality studies (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009), three good quality studies (Hechler et al., 2010; Simshäuser et al., 2020; Wicksell et al., 2008), one fair quality study (Flink et al., 2009), and two poor quality studies (Dobe et al., 2009; Linton, 2010). One study reported significant decreases in the level of disability at both post treatment and three-month follow-up assessments (Flack et al., 2018). Four studies only reported significant decreases effects at 3 – 12 months follow-up assessments (Andersen et al., 2017; Hechler et al., 2010; Nicholas et al., 2014; Wicksell et al., 2009). Where reported, the effect sizes ranged from medium to large (range η^2p = .19 – .41, range d = 0.64 – 0.66). Seven studies compared the effect of IE interventions in improving disability to the effect of TAU (Andersen et al., 2017; Simshäuser et al., 2020; Wicksell et al., 2008), distraction (Nicholas et al., 2014), relaxation therapy (Flack et al., 2018), MDT (Wicksell et al., 2009), stress management and attention control strategy (Craske et al., 2011), and

standard multi-model inpatient treatment (Hechler et al., 2010) respectively. However, only one study reported a significant difference between the IE group and the TAU control group in favour of the IE group in terms of changes of disability at post-treatment assessment, with a large effect size (η^2p = .44) (Wicksell et al., 2008). In four studies, significant improvements in disability were found from both study groups and control groups (Flack et al., 2018; Hechler et al., 2010; Nicholas et al., 2014; Wicksell et al., 2009), and one study only reported significant decrease of disability in the TAU group (Simshäuser et al., 2020). Although significance improvement was not reached in six of the studies, all the ten studies revealed a decreasing trend of pain-related disability following treatment. For example, in one case study, the patient reported an increase in number of participated activities and employment after treatment (Linton, 2010).

Five studies compared pain-related interferences pre- and post-treatment, including two excellent quality studies (Craske et al., 2011; Wicksell et al., 2009), one good quality study (Wicksell et al., 2008), one fair quality study (Zucker et al., 2017), and one poor quality study (Wald et al., 2010). One reported significant improvement post-treatment (Zucker et al., 2017), and two of them reported significant improvement effects at the three to seven months follow-up assessments (Craske et al., 2011; Wicksell et al., 2008). The effect sizes range from medium to large (range η^2p = .28 – .36, range d = 0.63 – 0.78). The effects of IE interventions on pain interference were compared to TAU, MDT, stress management, and attention control strategy, respectively, but none of them found significant differences from controls (range η^2p = .16 – .31, range d = 0.46) (Craske et al., 2011; Wicksell et al., 2008; Wicksell et al., 2009), Specifically, two studies observed significant improvements for both study groups and control groups (i.e., IE, stress management, and attention control, and TAU) (Craske et al., 2011;

Wicksell et al., 2008), and in one study none of the IE group and the MDT group reported significant improvement in interference (Wicksell et al., 2009).

Quality of life was assessed by five studies in the aspects of sleep quality, life satisfaction, and the extent of food avoidance resulting from bowel problems. There were two excellent studies (Craske et al., 2011; Wicksell et al., 2009), two good quality studies (Simshäuser et al., 2020; Wicksell et al., 2008), and one poor quality study (Linton, 2010). Linton (2010) indicated that the patient reported significant improvement in sleep quality post-treatment that was maintained at the three-month follow-up. Craske et al. (2011) study reported improvement in the IBS-related food avoidance after IE treatment, and the improvement reached significance at the three-month follow-up assessment, with a large effect size (d = 0.91). Simshäuser et al. (2020) and Wicksell et al. (2008) both reported significant improvements in life satisfaction post-treatment, and the improvement reported in Wicksell et al. (2008) study was maintained at the seven-month follow-up assessment, with a large effect size (η^2p = .53). In addition, Wicksell et al. (2008) also found that life satisfaction in the IE group improved significantly more than the TAU control group, with a large effect size (η^2p = .40). The other study did not find significant improvement for both IE group and MDT group in terms of quality of life (Wicksell et al., 2009).

One excellent quality study and one good quality study assessed the amount of medication used by patients pre- and post-treatment (Nicholas et al., 2014; Simshäuser et al., 2020). They both found significant decreases in the IE treatment groups, with effect sizes ranging from medium to large (range d = 0.60 – 1.01), but did not find significant differences between the IE groups and the control groups. Nicholas et al. (2014) reported that the decreases of medication used by patients in both the IE group and the distraction group reached significance. On the other hand, in the Simshäuser et

al. (2020) study, significant decrease of medication consumption was only reported in the IE group, but not in the TAU group.

Among the studies applying IE interventions in children and adolescent participants, one excellent quality study (Flack et al., 2018), one good quality study (Hechler et al., 2010), and one poor quality study (Dobe et al., 2009) reported changes in school absence before and after treatments. Flack et al. (2018) found a significant reduction in the pain-related school absence after treatment in both IE group and the relaxation group, with a large effect size (η^2p = .24), but did not find significant difference between groups. Similarly, Hechler et al. (2010) also reported that school absence decreased significantly after treatment in both groups, but did not find a difference between the treatment group and control group. Dobe et al. (2009) reported that the client was absent from school more than ten days in the four weeks before treatment, but was able to attend school regularly post-treatment.

Table 3. Pain and function outcome measures

Outcomes	Studies	Improvement post-intervention (ES)	Compared to control (ES)	Maintained at follow-up (ES)	Quality
Pain intensity	Andersen et al. (2017)	-	Non-significant, η^2p = .00	Significant, η^2p = .22, Medium	14 – 27
	Wicksell et al. (2008)	-	Non-significant, η^2p = .01, small	Non-significant, η^2p = .03, small	
	Nicholas et al. (2014)	-	Non-significant	Significant, d = −0.50, small	
	Craske et al. (2011)	Significant, d = 1.32, large	Significant, d = 0.44 (SM) small	Significant, d = 1.71, large	
	Flack et al. (2018)	Significant, η^2p = .13, medium	Non-significant	Significant, η^2p = .56, large	
	Wicksell et al. (2009)	-	Non-significant, η^2p = .13, medium	Significant, η^2p = .35, large	
	Simshäuser et al. (2020)	Non-significant, d = 0.37, small	Non-significant, η^2p = .00	-	
	Hechler et al. (2010)	-	Non-significant	Significant	
	Zucker et al. (2017)	Significant, d = 0.65 – 0.85 medium–large	-	-	
	Cayoun et al. (2020)	-	-	Non-significant, d = 0.28, small	
	Flink et al. (2009)	Slight decrease	-	Slight decrease	
	Linton (2010)	Dramatic decrease	-	Maintained	
	Dobe et al. (2009)	Significant decrease	-	No pain experience	
	Wald et al. (2010)	Slightly lessen	-	Back to pretreatment level	
Disability	Andersen et al. (2017)	-	Non-significant, η^2p = .00	Significant, η^2p = .19, medium	14 – 27
	Wicksell et al. (2008)	-	Significant, $\eta 2p$ = .44, large	Non-significant, η^2p = .28, large	
	Nicholas et al. (2014)	-	Non-significant	Significant, d = −0.64, medium	
	Flack et al. (2018)	Significant, η^2p = .23, large	Non-significant	Significant, η^2p = .41, large	
	Wicksell et al. (2009)	-	Non-significant, η^2p = .00	Significant, η^2p = .38, large	
	Simshäuser et al. (2020)	Non-significant, d = 0.66, medium	Non-significant, η^2p = .00	-	
	Hechler et al. (2010)	-	Non-significant	Significant	
	Flink et al. (2009)	Relatively large improvement	-	Maintained	
	Linton (2010)	-	-	-	
	Dobe et al. (2009)	Decreased	-	-	

Pain interference	Wicksell et al. (2008)	-	Non-significant, η^2p = .31, large	Significant, η^2p = .36, large	14 – 26
	Craske et al. (2011)	*d* = 0.73, medium	Non-significant, *d* = 0.46, small	Significant, *d* = 0.78, medium	
	Wicksell et al. (2009)	-	Non-significant, η^2p = .16, medium	Non-significant, η^2p = .28, large	
	Zucker et al. (2017)	Significant, *d* = 0.63, medium	-	-	
	Wald et al. (2010)	Slightly decrease	-	Back to pretreatment level	
Medication use	Nicholas et al. (2014)	-	Non-significant	Significant, *d* = 1.01, large	23 – 27
	Simshäuser et al. (2020)	Significant, *d* = 0.60, medium	Non-significant, η^2p = .05, small	-	
School absence	Flack et al. (2018)	-	Non-significant	Significant, η^2p = .24, large	14 – 27
	Hechler et al. (2010)	-	Non-significant	Significant	
	Dobe et al. (2009)	Attend school regularly	-	-	
Quality of life	Craske et al. (2011) (FA)	*d* = 0.60, medium	Non-significant, *d* = 0.25	Significant, *d* = 0.91, large	14 – 26
	Wicksell et al. (2008) (LS)	Significant	Significant, η^2p = .40, large	Significant, η^2p = .53, large	
	Wicksell et al. (2009) (LS)	-	Non-significant, η^2p = .15, medium	Non-significant, η^2p = .22, medium	
	Simshäuser et al. (2020) (LS)	Significant, *d* = 0.47, small	Non-significant, η^2p = .04, small	-	
	Linton (2010) (SQ)	-	-	Significant increase	

Abbreviations: -, not reported; SM, stress management; FA, food avoidance; LS, life satisfaction; SQ, sleep quality.

3.5 Emotion-related outcomes

Emotion-related outcome measures including depression, anxiety, anxiety sensitivity, distress, and post-traumatic stress disorder (PTSD) are presented in Table 4.

One excellent quality study (Andersen et al., 2017), one good quality study (Wicksell et al., 2008), and one poor quality study (Wald et al., 2010) assessed the effect of IE interventions on PTSD symptoms for patients with chronic pain and comorbid PTSD. Significant improvement from baseline to 7 – 12 months follow-up assessments were found in two RCTs, with effect sizes ranging from small to large (η^2p = .37, d = 0.46) (Andersen et al., 2017; Wicksell et al., 2008). However, in both studies, differences between IE treatment groups and TAU groups on the reduction of PTSD symptoms failed to reach significance (Andersen et al., 2017; Wicksell et al., 2008). As Andersen et al. (2017) specified, significant improvement from baseline to 12 months follow-up was only found in the IE group, but not in the TAU group. In addition, Wald et al. (2010) indicated that a slight reduction in the scores of Clinician-Administered PTSD Scale (CAPS) was found after IE exercises, with mean score reduced from 83 (*SD* = 8.43) to 71.8 (*SD* = 11.01). Additionally, after completing four sessions of IE and an additional eight sessions of trauma-related exposure treatment, three out of five participants in their study no longer met diagnostic criteria for PTSD, with mean CAPS score of 55.2 (*SD* = 10.62).

Nine studies evaluated changes of depressive symptoms following treatments, including two excellent quality studies (Nicholas et al., 2014; Wicksell et al., 2009), three good quality studies (Hechler et al., 2010; Simshäuser et al., 2020; Wicksell et al., 2008), one fair quality study (Cayoun et al., 2020), and three poor quality studies (Dobe et al., 2009; Linton, 2010; Wald et al., 2010). Seven of them found optimistic results (Cayoun et al., 2020; Dobe et al., 2009; Hechler et al., 2010; Linton, 2010; Nicholas et al., 2014;

Simshäuser et al., 2020; Wicksell et al., 2008). One excellent quality study and one good quality study reported significant decreases both in the IE groups and the control groups (i.e., distraction and standard multi-model inpatient treatment, respectively) on depression score with a small effect size (range d = 0.42 – 0.50) at 3 – 12 months follow-up assessment (Hechler et al., 2010; Nicholas et al., 2014). Two studies with good quality reported significantly decreased depression in the IE group post-treatment (d = 0.50) or at 7 months follow-up assessment (η^2p = .44), but not in the TAU groups (Simshäuser et al., 2020; Wicksell et al., 2008). Among these, only one study reported a significant difference between the IE group and TAU control group in favour of IE on the treatment efficacy in decreasing depression, with a large effect size (η^2p = .60) (Wicksell et al., 2008). Cayoun et al. (2020) indicated that the decrease of depression did not reach significance after treatment, but reached significance at two-month follow-up assessment, with a medium effect size (d = 0.65). Finally, the two case studies both indicated that the patients' depression scores decreased to normal level after treatments (Dobe et al., 2009; Linton, 2010).

Eight studies assessed changes in general anxiety and pain-related anxiety, including two excellent quality studies (Craske et al., 2011; Flack et al., 2018), three good quality studies (Hechler et al., 2010; Simshäuser et al., 2020; Wicksell et al., 2008), one fair quality study (Cayoun et al., 2020), and two poor quality studies (Dobe et al., 2009; Wald et al., 2010). Of these, two RCTs, one case control study, and one cohort study found that both in the IE groups and the control groups (i.e., stress management, attention control, and standard multi-model inpatient treatment), significant decreases in anxiety were observed after treatments and at three-month follow-up assessments, with medium to large effect sizes (range d = 0.54 – 1.36) (Cayoun et al., 2020; Craske et al., 2011; Hechler et al., 2010; Simshäuser et al., 2020). Two studies with poor quality also found some level of decrease in anxiety after treatment and maintained effects at the

follow-up assessments (Dobe et al., 2009; Wald et al., 2010). For example, the mean Beck Anxiety Inventory (BAI) score reported by Wald et al. (2010) changed from 34.50 (*SD* = 9.36) at pre-treatment to 28.60 (*SD* = 3.65) post-treatment, and further decreased to 21.77 (*SD* = 9.29) at three-month follow-up. Only one RCT study reported significantly greater improvement of anxiety in the IE group when compared to the TAU control group, in which the decrease of anxiety did not reach significance, with a large effect size (η^2p = .20) (Simshäuser et al., 2020). Whereas four studies found no difference between IE and TAU, CBT based stress management, relaxation therapy, and standard multimodal inpatient treatment (Craske et al., 2011; Flack et al., 2018; Hechler et al., 2010; Wicksell et al., 2008). Two RCT studies found a decreasing trend in anxiety from pre-treatment to three months after IE interventions but the improvements did not reach significance (Flack et al., 2018; Wicksell et al., 2008).

Two studies (Flack et al., 2018; Wald et al., 2010) assessed IE interventions for decreasing anxiety sensitivity. In an excellent-quality study, Flack et al. (2018) observed a significant moderate increase in anxiety sensitivity from the pre-post IE treatment comparison (η^2p = .08), but the increasing effect was not maintained at three-month follow-up. Significant increase in anxiety sensitivity was also found in the relaxation therapy group, and no difference in the changes of anxiety sensitivity was found between the IE group and relaxation therapy group. On the other hand, in the poor-quality case study, Wald et al. (2010) reported that there was a substantial decrease in anxiety sensitivity after IE exercises, and a further slight reduction in the anxiety sensitivity scales after the following trauma-related exposure therapy. IE was associated with larger reductions in anxiety sensitivity than trauma-related exposure therapy for four out of five participants. The fifth participants who had the lowest pre-treatment anxiety sensitivity had little change after completing IE. For the three participants who

completed three-month follow-up assessment, anxiety sensitivity scores were slightly worse than post-treatment assessment, but remained lower than pre-treatment scores.

Three studies (Cayoun et al., 2020; Simshäuser et al., 2020; Zucker et al., 2017) evaluated IE for decreasing pain-related distress. In one good-quality study, Simshäuser et al. (2020) found that a significant decrease of distress from pre to post-treatment was observed in the IE group with a small effect size (d = 0.47), but not in the TAU group. They also reported a significant difference between treatment groups and the TAU group in favour of the IE group, with a large effect size (η^2p = .16). Similarly, in the two fair-quality studies, Zucker et al. (2017) and Cayoun et al. (2020) studies both found significant moderate decreases of distress after IE treatment (range d = 0.61 – 0.71), and a significant large decrease was found at two-month follow-up assessment (d = 0.81) (Cayoun et al., 2020).

Eight studies evaluated IE for decreasing fear of pain (Andersen et al., 2017; Flack et al., 2018; Flink et al., 2009; Linton, 2010; Nicholas et al., 2014; Wald et al., 2010; Wicksell et al., 2008; Wicksell et al., 2009). In four excellent-quality studies significantly decreased fear of pain in the IE group was observed at follow-up assessments, with effect sizes ranging from small to large (range η^2p = .07 – .56, range d = 0.45 – 0.67) (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009). Similarly, decreased fear was also observed in one fair-quality study (Flink et al., 2009) and two poor-quality studies (Linton, 2010; Wald et al., 2010). In a case study, the patient reported increased numbers of activities after treatment which she attributed to the reduction of her fear (Linton, 2010). In addition, one RCT study found a non-significant large decrease of fear at seven-month follow-up assessment, but revealed a significant difference between the IE group and TAU group in favour of IE in reducing fear of pain, with a large effect size (η^2p = .40) (Wicksell et al., 2008).

Specifically, Flack et al. (2018) indicated that patients with a higher fear of pain before treatment were more likely to benefit from IE intervention.

Table 4. Emotional-related outcome measures

Outcomes	Studies	Improvement post-intervention	Improvement compared to control	Maintained at follow-up	Quality
Depression	Wicksell et al. (2008)	-	Significant, η^2p = .60, large	Significant, η^2p = .44, large	14 – 27
	Nicholas et al. (2014)	-	Non-significant,	Significant, d = −0.50, small	
	Wicksell et al. (2009)	-	Non-significant, η^2p = .12, medium	Non-significant, η^2p = .18, medium	
	Simshäuser et al. (2020)	Significant, d = 0.50, medium	Non-significant, η^2p = .06, small	-	
	Hechler et al. (2010)	-	Non-significant	Significant	
	Cayoun et al. (2020)	Non-significant, d = 0.23, small	-	Significant, d = 0.65, medium	
	Linton (2010)	Decreased substantially	-	Maintained	
	Dobe et al. (2009)	Back to normal level	-	-	
	Wald et al. (2010)	unchanged	-	Maintained	
Anxiety	Wicksell et al. (2008)	-	Non-significant, η^2p = .16, medium	Non-significant, η^2p = .29, large	14 – 27
	Craske et al. (2011)	d = 0.58, medium	Non-significant, d = 0.32, small	Significant, d = 0.94, large	
	Flack et al. (2018)	Non-significant	Non-significant	Non-significant	
	Simshäuser et al. (2020)	Significant, d = 0.54, medium	Significant, η^2p = .20, large	-	
	Hechler et al. (2010)	-	Non-significant	Significant	
	Cayoun et al. (2020)	Significant, d = 0.96, large	-	Significant, d = 1.36, large	
	Dobe et al. (2009)	Decrease	-	-	
	Wald et al. (2010)	Lessen	-	Maintained	
Anxiety sensitivity	Flack et al. (2018)	Significant increase, η^2p = .08, medium	Non-significant	Non-significant	14 – 27
	Wald et al. (2010)	Substantial decrease	-	Maintained	
PTSD	Andersen et al. (2017)	-	Non-significant, η^2p = .01	Significant, d = 0.46, small	14 – 26
	Wicksell et al. (2008)	-	Non-significant, η^2p = .31, large	Significant, η^2p = .37, large	
	Wald et al. (2010)	No longer met diagnosis	-	Maintained	

Distress	Simshäuser et al. (2020)	Significant, d = 0.47, small	Significant, η^2p = .16, large	-	17 – 23
	Zucker et al. (2017)	Significant, d = 0.61, medium	-	-	
	Cayoun et al. (2020)	Significant, d = 0.71, medium	-	Significant, d = 0.81, large	
Fear of injury	Andersen et al. (2017)	-	Non-significant, η^2p = .03	Significant, η^2p = .07 d = 0.45 small	14 – 27
	Wicksell et al. (2008)	-	Significant, η^2p = .40, large	Non-significant, η^2p = .27, large	
	Nicholas et al. (2014)	-	Non-significant, d = −0.25	Significant, d = -0.67, medium	
	Flack et al. (2018)	Significant, η^2p = .27, large	Non-significant	Significant, η^2p = .40, large	
	Wicksell et al. (2009)	-	Non-significant, η^2p = .21, medium	Significant, η^2p = .56, large	
	Flink et al. (2009)	Relatively large improvement	-	Maintained	
	Linton (2010)	Significant decrease	-	-	
	Wald et al. (2010)	Decrease	-	Maintained	

Abbreviations: -, not reported.

3.6 Cognitive process outcomes

Cognitive process variables including acceptance, catastrophizing, self-efficacy, psychological flexibility, attention to pain and perception, and pain impairment beliefs are presented in Table 5.

There were four studies with quality ranging from excellent to poor evaluated acceptance of chronic pain. One fair quality study and one poor quality both reported increasing trends of acceptance after IE treatment, which were maintained at three-month follow up (Flink et al., 2009; Linton, 2010). Similarly, two RCTs both found significant increases of acceptance post IE treatments or at twelve months follow-up assessments, with effect sizes ranged from medium to large (range d = 0.50 – 1.22) (Nicholas et al., 2014; Simshäuser et al., 2020). Meanwhile, these two studies also observed significant increases of acceptance from control groups (the distraction group and TAU). Yet, compared to either the distraction group or the TAU group, no significant advantage in the improvement of pain acceptance was apparent in the IE groups (Nicholas et al., 2014; Simshäuser et al., 2020).

Four excellent-quality RCTs evaluated catastrophic thinking related to pain (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009). With one exception (Wicksell et al., 2009), all found a significant decreasing effect of IE in reducing pain catastrophizing levels from baseline to three- or twelve-months follow-up assessments, with effect sizes ranging from small to large (range η^2p = .06 – .35, d = 0.98). Meanwhile, Flack et al. (2018) and Nicholas et al. (2014) also reported a significant decrease of pain catastrophising after relaxation therapy and distraction strategy. Respectively. There was one fair-quality study and one poor-quality study that assessed pain catastrophizing levels as well, and significant decreases were observed post-treatment (Flink et al., 2009; Linton, 2010). In terms of between-group

comparison, IE interventions did not perform stronger effects than relaxation, distraction, TAU and MDT in reducing pain catastrophic thinking (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009).

Three studies evaluated patients' subjective perception of pain (Cayoun et al., 2020; Simshäuser et al., 2020) and attention to pain (Craske et al., 2011). The quality of the studies ranges from excellent to fair. There were significant decreases in pain vigilance and awareness in the IE group and stress management group from baseline to post-treatment and to three-month follow-up, with effect sizes *d* ranging from 0.46 to 0.86, but not in the attention control group (Craske et al., 2011). Also, Craske et al. (2011) revealed significantly lower pain awareness scores for the IE group than the attention control group at post-treatment and three-month follow-up assessment, with a medium effect size ($d = 0.64$). Cayoun et al. (2020) found a significant improvement of pain perception from baseline to post-treatment with a large effect size ($d = 0.86$), which was largely maintained at two-month follow-up ($d = 1.22$). In a good-quality study, Simshäuser et al. (2020) revealed that both the IE group and the TAU group showed significant improvements in the affective components of pain perception over time, with medium to large effect sizes *d* ranging from 0.72 to 0.81. The sensory component of pain perception was significantly improved in the IE group but not in the TAU group. Additionally, the IE group showed a significantly greater reduction in their sensory component of pain perception than the TAU group, with a large effect size ($\eta^2 p = .18$).

One excellent quality study and one good quality study assessed IE for improving pain-related self-efficacy (Nicholas et al., 2014; Simshäuser et al., 2020). Nicholas et al. (2014) revealed that both in the IE group and the distraction group significant improvements were found from pre-treatment to twelve-month follow-up assessments, with large effect sizes (range $d = 0.90 – 1.00$). Simshäuser et al. (2020) found significant

improvement in self-efficacy only from the IE group, but not from the TAU group. In addition, the increasing effect of IE was significantly greater than TAU (medium effect size, η^2p = .11) (Simshäuser et al., 2020), but not greater than distraction (Nicholas et al., 2014).

In addition, in one excellent quality study, Wicksell et al. (2009) assessed patients' beliefs, and attitudes regarding pain, pain-related discomfort thinking, and ability to function despite discomfort. Both in the IE group and the MDT group, significant reductions were seen in pain impairment beliefs from pre-treatment to six-month follow-up assessment, with large effect sizes (range η^2p = .33 – .47). Pain-related discomfort decreased significantly in the IE group but not in the MDT group. Meanwhile, the reducing effects of IE on both pain impairment beliefs and pain-related discomfort thinking were significantly stronger than the effects of MDT treatment, with large effect sizes (range η^2p = .29 – .34).

Finally, one good quality study assessed psychological inflexibility in the aspects of avoidance of pain and fusion with pain (Wicksell et al., 2008). Results on both subscales showed significant improvements for the IE condition from pre-treatment to seven-month follow-up assessment, with large effect sizes η^2p ranging from .42 to .73. Similarly, significant differences between the IE group and the TAU group in favour of the IE condition were found in both subscales, with large effect sizes η^2p ranging from .34 to .61.

Table 5. Cognitive process outcome measures

Outcomes	Studies	Improvement post-intervention	Improvement compared to control	Maintained at follow-up	Quality
Psychological flexibility	Wicksell et al. (2008)	-	Significant, η^2p = .34 – .61, large	Significant, η^2p = .42 – .73, large	25
Pain impairment beliefs	Wicksell et al. (2009)	-	Significant, η^2p = .29, large	Significant, η^2p = .47, large	26
Pain-related discomfort	Wicksell et al. (2009)	-	Significant, η^2p = .34, large	Significant, η^2p = .42, large	26
Self-efficacy	Nicholas et al. (2014)	-	Non-significant, d = 1.09	Significant, d = 1.00, large	23 – 27
	Simshäuser et al. (2020)	Significant, d = −0.68, medium	Significant, η^2p = .11, medium	-	
Catastrophizing	Andersen et al. (2017)	-	Non-significant, η^2p = .00	Significant, η^2p = .06, small	14 – 27
	Nicholas et al. (2014)	-	Non-significant, d = 0.02	Significant, d = −0.98, large	
	Flack et al. (2018)	Significant, η^2p = .17, large	Non-significant	Significant, η^2p = .35, large	
	Wicksell et al. (2009)	-	Non-significant, η^2p = .01, small	Non-significant, η^2p = .19, medium	
	Flink et al. (2009)	Relatively large improvement	-	Maintained	
	Linton (2010)	Significant decrease	-	-	
Pain perception	Simshäuser et al. (2020)	Significant, d = −0.79 – 0.81, medium	Significant, η^2p = .18, large	-	18 – 23
	Cayoun et al. (2020)	Significant, d = 0.86, large	-	Significant, d = 1.22, large	
Attention to pain	Craske et al. (2011)	d = −0.46, small	Significant (IE vs. AC) d = −0.64, medium	Significant, d = −0.86, large	26
Acceptance	Nicholas et al. (2014)	-	Non-significant, d = 0.48	Significant, d = 1.10, large	14 – 27
	Simshäuser et al. (2020)	Significant, d = −0.50 – 0.54, medium	Non-significant, η^2p = .00	-	
	Flink et al. (2009)	Increase trend	-	-	
	Linton (2010)	Increased	-	-	

Abbreviations: -, not reported.

3.7 Treatment evaluation

Five studies assessed adherence, treatment credibility, and satisfaction (Cayoun et al., 2020; Craske et al., 2011; Flack et al., 2018; Nicholas et al., 2014; Simshäuser et al., 2020). Adherence was assessed through interviews, questionnaire, and homework compliance. Overall, all the interventions applied in the studies were judged by the participants as acceptable and helpful, with participants reporting that they were satisfied by the treatment and would recommend it to others. Simshäuser et al. (2020) indicated that participants in the IE group reported higher rates of satisfaction, attendance, compliance with homework, and there were significantly lower drop-out rates than the TAU group. Other RCTs, however, reported no differences in the treatment credibility and satisfaction between treatment conditions.

Chapter 4 Discussion

The aims of the present review were to investigate whether IE interventions are effective in treating chronic pain outcomes, and to examine the populations for which these interventions are particularly effective. This systematic review provided evidence for positive treatment effects of IE interventions in pain-related outcomes and functions. This review highlighted a small but varied corpus of research regarding the utilisation of IE interventions in chronic pain treatment, though with a lack of excellent quality of evidence. Specifically, of the 14 studies identified, only seven employed RCT designs, where control groups were available.

The findings of this review showed that IE was associated with decreased pain intensity, disability, and pain interference, as well as increased quality of life. Furthermore, this review showed that IE was effective in improving pain-related cognitive processes. There was a consistent finding that IE was effective in reducing pain catastrophising and pain attention. Meanwhile, there was evidence of beneficial effects of IE on increasing self-efficacy, acceptance, and flexibility. Finally, this review showed encouraging results for the potential positive effects of IE interventions in improving emotional states, including fear of pain, PTSD, depression, and distress, though there were inconsistent findings in terms of the effects of IE interventions in reducing anxiety and anxiety sensitivity.

The findings of this study showed that in the context of chronic pain management, the effects of IE were comparable to other types of interventions such as relaxation and distraction strategies. For example, Nicholas et al. (2014) found that the combination of CBT and IE was as efficient as CBT plus distraction in decreasing pain intensity, disability, depression, fear of pain, and catastrophising, or increasing acceptance and self-efficacy. Similarly, Flack et al. (2018) reported that for patients with chronic pain

who were under the intensive interdisciplinary pain treatment, additional PPT was equivalent to relaxation therapy in reducing pain intensity, disability, anxiety, and anxiety sensitivity. When compared to standard treatment methods such as treatment as usual, only a few studies reported significant effects of IE in treating chronic pain beyond TAU. For instance, Wicksell et al. (2008) found that the combination of IE and TAU is more effective than TAU alone in reducing disability, depression, fear, and inflexibility. Simshäuser et al. (2020) found the advanced effects of IE in reducing anxiety, distress, and pain perception, as well as increasing self-efficacy. In addition, Wicksell et al. (2009) reported that IE was more helpful than TAU in reducing fear of pain, pain-related discomfort and impaired beliefs.

4.1 Pain and function outcomes

All the included studies showed a decreased trend of pain intensity after IE interventions. Five RCTs out of seven reported significant decreases of pain intensity, and yielded medium to large treatment effects. Studies suggested promising effects not only immediately after treatments, but also at three to twelve months follow-up (Andersen et al., 2017; Craske et al., 2011; Flack et al., 2018; Wicksell et al., 2009). Specifically, Cayoun et al. (2020) assessed the immediate effect of a 30-second mindfulness-based interoceptive exposure task (MIET) to pain intensity after each 30-second exposure, and its effects in daily life of chronic pain patients following a 10-week period of self-implementation. At pre-treatment (during the first session), post-treatment (following two weeks of self-implementation), and two months follow-up, pain intensity decreased significantly from pre-exposure to post-exposure with large effect sizes, which suggested a promising immediate effect of the 30-second MIET on pain intensity. Meanwhile, there was a trending increase in changes in pain intensity from post-treatment to follow-up, demonstrating maintained benefits from the self-implementation of MIET.

This review showed a consistent finding that IE was effective in improving pain-related functions. There were both RCTs and non-RCTs that suggested beneficial effects of IE on disability reduction posttreatment and at follow-up. Three studies with excellent quality found significant moderate to large treatment effects after IE interventions (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014). The two case studies both indicated that the clients began to participate in a variety of goal activities during therapy, and reported continuous gains in physical and social functioning. They attributed these improvements to a reduction of fear and to the disturbing memories of pain (Dobe et al., 2009; Linton, 2010).

Further, evidence suggested beneficial effects of IE on improving quality of life and reducing pain interference. For example, Craske et al. (2011) indicated that IE led to significant reductions in life interference and food avoidance resulting from IBS symptoms. Wicksell et al. (2008) yielded significant treatment effects of IE with large effect sizes in reducing pain interference and increasing quality of life. Nicholas et al. (2014) and Simshäuser et al. (2020) revealed significant and sustained improvements in medication use from post-treatment and one-year follow-up, with medium to large effect sizes. Lastly, children and adolescents with chronic pain reported a significant decrease of school absence after IE intervention. As Flack et al. (2018) indicated, the average days of school absence was reduced from 3.9 days during the four weeks before treatment to 0.3 days at three months follow-up.

The results that IE led to significant improvements in pain intensity, disability and quality of life support previous findings indicating that psychological interventions have a potential benefit on the treatment of chronic pain. For example, Gardner-Nix, Backman, Barbati, and Grummitt (2008) reported that mindfulness-based intervention significantly improved the levels of pain, as well as both physical and mental aspects in

the quality of life. Söderlund and Lindberg (2001) suggested the cognitive behavioural components as an effective approach in physiotherapy management for patients with chronic whiplash associated disorders. Previous research has suggested that quality of life in patients with chronic pain is more associated with beliefs about pain, such as catastrophising thoughts and self-efficacy, than with pain intensity (Lamé, Peters, Vlaeyen, Kleef, & Patijn, 2005). Therefore, in CBT interventions, positive treatment outcomes could be enhanced by increasing patients' self-efficacy and by changing their negative thoughts about pain. Similarly, IE interventions may effect change in pain and function outcomes through reduction in maladaptive pain cognitions, though further research is needed to test this hypothesis.

4.2 Emotion-related outcomes

In addition, this review found promising treatment effects of IE in improving emotional states. For example, in the four RCTs where depression was assessed, three studies reported significant improvements after IE interventions, yielding small to large treatment effects (Nicholas et al., 2014; Simshäuser et al., 2020; Wicksell et al., 2008). Four non-RCTs also revealed a decreasing trend of depression from pre-treatments to follow-ups (Cayoun et al., 2020; Dobe et al., 2009; Hechler et al., 2010; Linton, 2010). In line with treatment effects of IE for anxiety, two RCTs found significant improvement after treatment, yielding medium to large treatment effects (Craske et al., 2011; Simshäuser et al., 2020). A decreasing trend of anxiety was also reported in four non-RCTs (Cayoun et al., 2020; Dobe et al., 2009; Hechler et al., 2010; Wald et al., 2010). Additionally, Flack et al. (2018) indicated that the patients who scored high levels of fear at baseline were more likely to report a decrease in general anxiety after IE intervention, whereas the patients who scored low levels of fear before treatment were more likely to report an increase in general anxiety after IE intervention. There was not enough research on the effects of IE in reducing pain-related distress. One RCT

and two non-RCTs assessed the level of distress, yielding small to medium treatment effects post-treatment (Cayoun et al., 2020; Simshäuser et al., 2020; Zucker et al., 2017). The findings suggested that IE may elicit short-term improvement for chronic pain patients suffering from distress.

These findings support previous research, where IE showed promising effects in treating depression, anxiety disorders, and emotional distress (e.g., Boswell, Anderson, & Barlow, 2014; Collimore & Asmundson, 2014; Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010). For example, Lumley et al. (2008) indicated that emotional exposure treatment was significantly effective in reducing emotional distress and stress symptoms such as hyperarousal for people with fibromyalgia syndrome. Likewise, Ellard et al. (2010) and (Boswell et al., 2014) examined the effectiveness of a transdiagnostic Unified Protocol treatment with an emphasis on emotion exposure through interoceptive and situational cues in treatment of mood disorders, and found clinically significant decreases in depression, anxiety, and panic disorders.

There was also a lack of relevant research that assessed the effect of IE on anxiety sensitivity within the chronic pain treatment, and inconsistent findings were found. A decreasing trend of anxiety sensitivity was reported by a non-RCT (Wald et al., 2010). However, Flack et al. (2018) assessed the changes of anxiety sensitivity for all the patients that received IE or relaxation therapy in the context of intensive interdisciplinary pain treatment (IIPT), and found a significant increase between admission and discharge. This result contradicted previous research that has shown the beneficial effect of IE in reducing anxiety sensitivity across a range of disorders (Boswell et al., 2013). However, Boettcher and Barlow (2019) conducted a study where utilising IE in the treatment of panic disorder and claustrophobia and found that, IE does

not necessarily lead to decrease in AS, which was consistent with the finding of this review.

Fear of pain was assessed by eight studies and a general decreased trend was reported. Four RCTs found that IE was significantly effective in reducing fear of pain, yielding small to large treatment effects (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014; Wicksell et al., 2009). Flack et al. (2018) investigated which subgroup of patients benefited the most from IE in the decrease of fear of pain, and found that IE was more effective than RT in reducing fear of pain for the patients with higher fear of pain before treatment, whereas the effectiveness of IE and RT were equivalent for the patients with lower fear of pain. Linton (2010) indicated in the case study that at the end of the therapy, the client reported a decrease in fear of pain. More than that, she was more willing to participate in activities and was able to function at a much more satisfying level, which she attributed to the reduction of fear. As demonstrated in previous research on IE interventions for panic disorders, IE may lead to fear extinction, thereby decreasing distress, expectancies of feared outcomes, and increasing subjective fear tolerance (Boettcher et al., 2016). Boettcher and Barlow (2019) emphasised that IE is most beneficial to people whose fears are associated with physical arousal such as heart attack, rather than extrinsic components such as humiliation.

Finally, this study showed that there was insufficient research on the application of IE in treating people with chronic pain and comorbid PTSD. Two RCTs revealed significant effects of IE in reducing PTSD, yielding small to large treatment effects (Andersen et al., 2017; Wicksell et al., 2008). Additionally, Wald et al. (2010) suggested the combination of IE and trauma-related exposure therapy as a potentially effective intervention for treating PTSD in individuals who also have chronic pain. This finding also corroborates previous research, in which IE improved PTSD symptoms in a range

of populations such as refugees, combat victims, and vehicle accident survivors (Wald & Taylor, 2010; Wald et al., 2010). In addition, Lumley et al. (2008) also found that an emotional exposure treatment was effective for patients with fibromyalgia syndrome in improving traumatic stress symptoms and reducing the impact of chronic pain. Further research on treatment efficacy for chronic pain patients with particular comorbid psychiatric conditions is therefore warranted.

4.3 Cognitive process outcomes

Promising evidence was exhibited on the effects of IE in improving cognitive processes related to pain, such as pain catastrophising, pain self-efficacy, attention to pain, and acceptance. In a case study, Linton (2010) reported that IE led to a decrease of pain catastrophising. This finding was in accordance with the three RCTs, which reported a significant effect of IE in reducing catastrophising, yielding small to large treatment effects (Andersen et al., 2017; Flack et al., 2018; Nicholas et al., 2014). There was a lack of relevant research that assessed the effect of IE in improving self-efficacy, with only two RCTs finding significant improvements after treatment with medium to large treatment effects (Nicholas et al., 2014; Simshäuser et al., 2020). Further, only one study assessed the changes of attention to pain, and found that the utility of IE for patients with IBS led to significant reduction in pain awareness with large effect, suggesting less attention was paid to gastrointestinal symptoms after treatment (Craske et al., 2011).

Previous research has suggested that the effectiveness of IE on chronic pain and other disorders are mediated by cognitive restructuring and enhancing self-efficacy (Beck, Shipherd, & Zebb, 1997). As indicated by Barrera et al. (2014), repeated exposure to interoceptive cues enables an individual to disconfirm the catastrophic consequences of internal sensations. For example, Garland et al. (2012) indicated that an MBSR

programme for people with IBS may promote a nonreactive mindset, which in turns lead to decreased pain catastrophising, less IBS severity, and improved quality of life. Additionally, IE may increase self-efficacy by providing individuals an opportunity to experience the success of coping with pain-related sensations (Stewart & Watt, 2008). Meanwhile, individuals may learn from repeated exposure that they can exert some degree of control over the aversive sensations, which contribute to a decrease in pain-related fear.

Finally, six studies evaluated the effects of IE from the acceptance-based perspective. Two RCTs and two non-RCTs evaluated the change of pain acceptance before and after IE interventions, and revealed an increased trending, with medium to large treatment effects (Flink et al., 2009; Linton, 2010; Nicholas et al., 2014; Simshäuser et al., 2020). Linton (2010) indicated that the client was not bothered by the ups and downs of the pain any more as she reported being able to accept the pain after treatment. One study investigated the effect of IE in improving psychological flexibility, the ability to function effectively in accordance with personal values despite the presence of pain, pain-related disturbing thoughts and emotions. This study found significant improvements from pre- to post-treatment, which corresponded with improvements in life quality and functioning (Wicksell et al., 2008). In addition, Wicksell et al. (2009) suggested that the treatment based on exposure and acceptance showed substantial and sustained improvements in pain-related discomfort, pain impairment beliefs, with large effect sizes. These findings provide evidence for previous research indicating that IE allows a challenging of negative evaluations of normal sensations, facilitates a more realistic appraisal of the threat of pain, and enables an individual to engage in valued activities with an attitude of acceptance (Stewart & Watt, 2008). Further research with a focus on cognitive process outcomes may yield more understanding of potential mechanisms of IE interventions.

4.4 Comparison with other treatments

There was a lack of relevant research that compares IE interventions to other types of interventions for chronic pain. One study compared treatment outcomes from a CBT pain management programme incorporating either IE or distraction from pain and found significant improvements in both treatment conditions. The addition of IE to behavioural exposure was comparable to an additional distraction strategy in improving outcomes (Nicholas et al., 2014). Flack et al. (2018) found that both IE and relaxation therapy were effective in improving the treatment outcomes of IIPT in reducing pain intensity, disability, school absence, anxiety, fear of pain and catastrophising in the context of IIPT for paediatric chronic pain patients, and the improvements led by IE and relaxation therapy were similar. However, they found that patients with higher scores in fear of pain before treatment showed greater decreases in their fear of pain and general anxiety when they received IE instead of relaxation therapy. This study suggested that IE may be particularly effective for the patients with a higher fear of pain before treatment. Further, Craske et al. (2011) found that participants with IBS who received CBT focused on IE showed significantly greater reduction in bowel symptom severity compared to CBT focused on stress management, and showed significantly greater reduction in attention to pain compared to the attention control group. This study suggested that IE added some potential benefits for CBT in IBS treatment as it directly targets fear and avoidance of visceral sensations.

Three studies investigated the effectiveness of IE in comparison to TAU in the context of chronic pain treatment, and inconsistent findings were reported. Overall, the findings suggested some advantages for IE to all the outcomes compared to TAU, but only a few of the between-group differences reached statistical significance. For example, one study by Wicksell et al. (2008) found significantly greater reductions of disability in the IE group compared to TAU, but this finding was not observed in the other two studies

(Andersen et al., 2017; Simshäuser et al., 2020). Two studies compared the effectiveness of IE and TAU in increasing quality of life (Simshäuser et al., 2020; Wicksell et al., 2008), but only Wicksell et al. (2008) reported significant differences in favour of IE. Both studies compared the effects of IE and TAU in reducing depression and anxiety. Wicksell et al. (2008) suggested that IE was more effective than TAU in reducing depression, with little difference in reducing anxiety. However, Simshäuser et al. (2020) reported an opposite finding, indicating a greater effect of IE than TAU in reducing anxiety, but not in depression.

4.5 The research quality

The quality of the included studies was assessed using the modified Downs and Black checklist (Downs & Black, 1998), with the cut-offs ranging from 26 – 29 points as excellent, 20 – 25 points as good, 15 – 19 points as fair, and 14 points or less as poor quality (Hooper et al., 2008). This review identified five excellent quality, three good quality, three fair quality, and three poor quality studies. Particularly, ten studies had small sample sizes ranging from 1 to 62, which meant the results of the studies may be less powerful to detect clinically important effects. Furthermore, this review revealed the large variances between studies in the utilisation of outcome measures, thus any potential meta-analyses may be some time away.

4.6 Clinical implications

The existing evidence suggests several implications that could affect clinical practice. First, this review highlighted the promising effects of IE in reducing pain, improving pain-related function, emotional states, and cognitive processes, that are supported by existing research. The positive effect of IE was found when the patients did not receive general pain treatment (Craske et al., 2011), or only received TAU (Simshäuser et al., 2020; Wicksell et al., 2008). However, there was no superiority of IE over relaxation

therapy and distraction (Flack et al., 2018; Nicholas et al., 2014). Thus, IE may be effective in health-care settings as a component of pain management and as part of a multidisciplinary approach to treating chronic pain, providing an additional option for clinicians and patients. Further research is needed, however, particularly using research designs incorporating active control groups to further explore this potential and strengthen recommendations.

Although IE did not show a general incremental benefit when added in a comprehensive pain treatment program, it may particularly benefit specific subsamples of patients. Flack et al. (2018) indicated that IE seems especially effective for people with higher pain-related fear before treatment. Many studies have highlighted the association between higher fear of pain and poorer treatment outcome. Thus, if treatment with relaxation or distraction strategies cannot bring optimal treatment outcomes for patients with a high fear of pain, IE would be an alternative option that may lead to benefits. In addition, Craske et al. (2011) revealed significant effectiveness of IE in reducing IBS symptoms. This study indicated that the potential mechanism of IE that focuses on fear and avoidance of visceral sensations was more effective for patients with IBS. Similarly, Flack et al. (2018) also found the promising effect of IE for patients with abdominal pain. Further, IE has the potential to be applied as an adjunct to in the treatment of chronic pain and comorbid PTSD. As Andersen et al. (2017) indicated, an additional IE in combination to TAU may lead to more desirable outcomes than TAU alone in treating PTSD and fear of movement. Wald et al. (2010) also suggested that a brief IE intervention before trauma-related exposure therapy can enhance the effect of trauma-related exposure in reducing PTSD symptoms.

4.7 Recommendations for future research

The analysis of the studies identified in this research revealed a lack of high quality evidence regarding the utilisation of IE in the context of chronic pain treatment, though indications so far are encouraging and suggest the need for more thorough investigation. More RCTs will be valuable in future research, particularly designs with a clear description of active control groups which are matched for length, symptom intensity, sample characteristics, and clinician allegiance. In addition, future research should recruit larger sample sizes, with a priori power calculations, so that clinically relevant effects can be detected. Further, among the existing RCTs, only two studies provided data from both post-treatment and follow-up assessment. To allow accurate calculation of effect sizes and comparison, future studies should report data more efficiently by providing means and standard deviations or standard errors for pre-treatment, post-treatment, and follow-up assessments. The design of non-RCTs could also be improved by reporting reliable changes in outcomes and adding relevant comparison groups.

Further, due to the low number of studies and diverse outcomes that have been reported, meta-analysis is currently not feasible or sufficient for answering the research question this thesis poses. Therefore, a recommendation is that future studies could adopt a standard set of outcome measures when designing chronic pain clinical trials. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommend six core outcome domains that should be considered in clinical research, including pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition (Dworkin et al., 2005). Adopting of these core outcome measures could allow future research to develop research protocols more easily and may enable future systematic reviews to pool data from different studies, and draw meaningful comparisons among treatments of the clinical importance of their

outcomes. As further evidence builds, stronger conclusions could be drawn from more robust methods, including RCTs with active controls and, thereafter, the use of meta-analysis with more unified outcome measures.

There was only a small number of studies that assessed changes of fear of pain, catastrophising, self-efficacy, and acceptance in chronic pain treatment; however, promising effects have been shown. Therefore, this thesis indicated that further studies in the improvements of these cognitive processes are worth conducting. Previous studies consistently associate high levels of fear and catastrophizing along with low self-efficacy with more severe pain and disability. There is a need to investigate how these factors influence the treatment outcomes, and which type of pain-related cognitions elicit the most promising improvement in pain and function. In addition, an understanding of the working mechanisms of effective IE may increase through further exploration in the changes of these cognitive processes.

4.8 Limitations

Several limitations should be considered in this study. First, the data collection and selection process used may restrict the studies that were included. Since the search terms were identified through an initial review of a limited literature, some extraneous terms may have been included. For example, the term “desensitis*” was included because the process of systematic desensitisation was indicated in several studies as a type of interoceptive exposure (e.g., Boettcher, Brake, & Barlow, 2016). However, by screening all the identified studies, it was found that the term “desensitis*” led to zero relevant articles. On the other hand, the review of the reference lists from the selected articles identified several relevant studies that were not identified by the database search, in which the effectiveness of IE intervention in treating chronic pain was evaluated in patients with IBS. It is possible, therefore, that some adequate search terms

could have been missed. Further, the identified data was manually filtered. The initial selection process was conducted by screening the title, abstract, and keywords. Thus, it is possible that some relevant material could have been excluded. However, using multiple databases as part of the search strategy may have gone some way to counter this potential limitation.

Second, as there were only few studies that recruited children or used an adolescent sample, this review did not differentiate these studies from the studies with adult samples. It could be argued that grouping the findings by age may be more informative; however, at present the paucity of research in this regard prevented the possibility of conducting any meaningful comparisons.

Third, because of the existence of limited studies and the large variances between studies in outcome measures, meta-analyses could not be conducted. As relevant research has increased rapidly in recent years, standardised assessments may be recommended in future research to provide sufficient data for future meta-analyses.

Conclusion

This study is the first systematic review that explored the existing research in the application of interoceptive exposure in chronic pain treatment. It suggested the potential benefits of IE in chronic pain treatment, highlighted the shortage of relevant research along with limitations, and recommended future research in this area. Overall, IE interventions show potential effectiveness in reducing pain and disability, meanwhile improving daily functioning. These changes are corresponding with the improvements of cognitive processes such as catastrophising, self-efficacy, and acceptance. In addition, significant improvements in emotional distress, PTSD, and fear related to pain were observed after IE intervention, although the findings with regard to anxiety and anxiety sensitivity showed some inconsistency. The rapidly increasing research shows

the promising effects of IE in improving function, emotion, and cognition for people with chronic pain, which were comparable to relaxation and distraction strategies. This review especially suggests that IE is more effective than other types of psychological interventions for people with a high fear of pain. More RCTs with active controls and, for that matter, other study designs of a higher quality that incorporate more unified outcome measures are needed in the future in order to provide robust and strong clinical evidence, to further investigate potential mechanisms, and to explore the specific circumstances where IE can exert its most effectiveness in the treatment of chronic pain.

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Appendices

Appendix A – Modified Downs and Black checklist for quality assessment

Reporting

1. *Is the hypothesis/aim/objective of the study clearly described?*

Yes	1
No	0

2. *Are the main outcomes to be measured clearly described in the Introduction or Methods sections?*

   If the main outcomes are first mentioned in the Results section, the question should be answered no.

Yes	1
No	0

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.

Yes	1
No	0

4. *Are the interventions of interest clearly described?*

   Treatments and placebo (where relevant) that are to be compared should be clearly described.

Yes	1
No	0

5. *Are the distributions of principal confounders in each group of subjects to be compared clearly described?*

   A list of principal confounders is provided.

Yes	2
Partially	1
No	0

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).

Yes	1
No	0

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.

Yes	1
No	0

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).

Yes	1
No	0

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 affected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.

Yes	1
No	0

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?*

Yes	1
No	0

External validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11. *Were the subjects asked to participate in the study representative of the entire population form 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.

Yes	1
No	0
Unable to determine	0

12. *Were those subjects who were prepared to participate representative of he 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.

Yes	1
No	0
Unable to determine	0

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.

Yes	1
No	0
Unable to determine	0

Internal validity – bias

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.

Yes	1
No	0
Unable to determine	0

15. *Was attempt made to blind those measuring the main outcomes of the intervention?*

Yes	1
No	0
Unable to determine	0

16. *If any of the results of the study were base 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.

Yes	1
No	0
Unable to determine	0

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 were differences in follow-up are ignored should be answered no.

Yes	1
No	0
Unable to determine	0

18. *Were the statistical tests used to assess the main outcomes appropriate?*

    The statistical techniques used must be appropriate to the data. For example non-parametric 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.

Yes	1
No	0
Unable to determine	0

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.

Yes	1
No	0
Unable to determine	0

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.

Yes	1
No	0
Unable to determine	0

Internal validity – confounding (selection bias)

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 cases-control studies where there is no information concerning the source of patients included in the study.

Yes	1
No	0
Unable to determine	0

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.

Yes	1
No	0
Unable to determine	0

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 mot ensure random allocation. For example alternate allocation would score no because it is predictable.

Yes	1
No	0
Unable to determine	0

24. *Was the randomised intervention assignment concealed from both patients and health care staff until recruitment as 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.

Yes	1
No	0
Unable to determine	0

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 non-randomised 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.

Yes	1
No	0
Unable to determine	0

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.

Yes	1
No	0
Unable to determine	0

Power

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%?

A study would be scored 2 points if it mentioned having conducted a power analysis to determine the sample size needed to detect a significant difference in effect size, and sufficient power was emphasised. If a power analysis was conducted, but not sufficient enough to detect a clinically important effect, the study would be scored 1 point. 0 points would be given if the study did not mention having conducted a power analysis.

Sufficient	2
Not sufficient	1
No power analysis	0