'Are all treatment components created equal?'

A Systematic Review and Meta-analysis of Treatment Components in Psychological Interventions for Chronic Pain

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Submitted in accordance with the requirements for the degree of
Doctor of Clinical Psychology (D. Clin. Psychol.)

The University of Leeds

School of Medicine

Academic Unit of Psychiatry and Behavioural Sciences

June, 2017

The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

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Acknowledgements

To my partner, family, friends, and colleagues who have supported, inspired and motivated me through the process of completing this thesis; thank you.

I am also grateful to Ms. Jade Martin for her diligence, Dr. Rebecca Walwyn for her support and statistical counsel, and the authors who willingly shared their raw data with me.

I am indebted to Dr. Gary Latchford, who stepped in to help and encourage me in difficult and challenging times.

Finally, I am proud and grateful to have started this thesis under the knowledgeable, warm and thoughtful guidance of Professor Stephen Morley. It was an honour to have worked with him, a privilege to have known him, and a great sadness to have lost him.

Abstract

Background: Though we know that psychological interventions for adults with chronic pain are effective, many unanswered questions remain. In particular, we have a poor understanding of how some aspects of treatment, such as treatment 'dose', relate to outcome. We also know little about the contribution of specific components included in broad treatment packages, such as CBT.

Objectives: I replicated Williams, Eccleston and Morley's (2012) Cochrane review of psychological interventions for adults with non-cancer chronic pain (excluding headache) but extended this in two ways: I investigated the relationship between dose and outcome, and developed a system of categorising treatment content across trials.

Results: 64 randomised controlled trials (N = 7,840 participants) were included. Effect sizes (standardised mean differences) were calculated and used in meta-analysis to explore five outcome domains: pain experience, pain behaviour, emotional functioning, and coping and cognitive appraisal. My findings converge with previous reviews; psychological interventions were effective, but effect sizes were relatively small.

Meta-regression analyses found limited evidence for the moderating role of treatment 'dose' on outcome. There was some evidence that the period over which treatment was delivered (i.e. 'dose in weeks'), may be related to outcome for two out of five outcome domains.

In terms of treatment content, trials that appeared to utilise the same broad treatment package (e.g. CBT), often appeared to feature different treatment components. Moreover, treatments described as being distinct (e.g. ACT and CBT) often used similar treatment components.

Conclusions: The relationship between treatment dose and outcome is complex and dependent on the outcome being assessed. Broad labels of treatment types, such as CBT, are vague and do not represent homogenous groups.

This suggests that all treatment components are not created equal. I propose single-case design and patient-level data analysis as tools to help further explore treatment components, including treatment dose, and outcome.

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1 Introduction

1.1 Overview

Chronic pain is one of the leading causes of disability worldwide. Psychological interventions are a well-established, and nationally recommended, element of treatments for chronic pain. Researchers have typically focused on whether psychological interventions are effective in their aims of improving functioning and reducing distress. We now have a diverse body of literature that has investigated the effectiveness of these interventions, the findings of which converge to suggest that psychological interventions do indeed improve functioning and reduce distress. However, many unanswered questions remain. For instance, we still know little about whether some components of treatment are more important than others in their ability to bring about a greater magnitude of change. One such component that may be important is the amount of treatment delivered, or treatment 'dose'. My thesis aims to fill this gap by exploring the relationship between key treatment components such as dose of therapy, and the extent of improvement for a variety of outcomes.

1.2 Background

In this section, I will define chronic pain and present a brief history of our theoretical understanding of chronic pain before discussing psychological treatments for chronic pain in practice.

1.2.1 Defining chronic pain

Pain can be understood as a vital warning to potential harm, ultimately promoting survival. Despite the utility of short-term pain for safety, many individuals experience pain that is chronic. Chronic pain persists longer than the typical healing process, which is commonly defined as longer than three months. Such pain is increasingly called 'persistent pain' in clinical practice. To be consistent with the terminology used in research literature, I will use the term 'chronic pain'. Chronic pain often causes high levels of distress and disability, while offering little or no protective function (Kerns, Sellinger, & Goodin, 2011). Those living with chronic pain must negotiate significant declines in physical, social and emotional functioning. Living with pain not only interferes with one's ability to complete tasks effectively, but is also a threat to one's self identity as one must adjust to increasing limitations in functioning (Morley, 2008). Recent definitions of chronic pain are increasingly recognising the complex and debilitating nature of pain. For example, Williams

and Craig (2016) proposed a definition of chronic pain as "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive and social components" (p. 2).

The importance of chronic pain as a health condition is well-established. Indeed, chronic pain has been identified as one of the leading causes of disability across the world, and a global health priority (Goldberg & McGee, 2011). Although prevalence estimates of chronic pain vary between studies, it is widely recognised that chronic pain is a problem for many individuals worldwide. For example, a review of 19 studies and 65 surveys across 34 countries found that the global prevalence of chronic pain was 30.3% (SD = 11.7%; Elzahaf, Tashani, Unsworth, & Johnson, 2012). Moreover, this number is only set to rise; with an ageing population and older people being more likely to experience chronic pain (Molton & Terrill, 2014), effective treatments for chronic pain remain high on the research and clinical agenda.

1.2.2 Toward a biopsychosocial understanding of chronic pain

Historically, chronic pain researchers held a unidimensional conceptualisation of pain, with treatment based upon the traditional biomedical approach (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). The Gate Control Theory of Pain (Melzack & Wall, 1965) was a multidimensional attempt to understand complex aspects of chronic pain, such as the fact that pain can persist long after damaged tissue has healed and that the location of pain can change over time. The Gate Control Theory of Pain understands the experience of pain as the end result of a combination of cognitive-evaluative, motivational and sensory features. This theory prompted a surge in research into chronic pain as researchers sought to better understand pain mechanisms.

Continued research, coupled with advances in neuroscientific methodology, has meant that a biopsychosocial model of chronic pain is now widely accepted as a way to understand and treat chronic pain (Gatchel et al., 2007). This model places pain as the outcome of a dynamic and complex interaction between physiological, psychological and social factors. In line with our increasingly holistic theoretical conceptualisation of chronic pain, clinical management of chronic pain has evolved to be multi-modal. In recognising that an individual's experience of pain brings together biological, social and psychological factors, a biomedical treatment approach is insufficient. Rather, an interdisciplinary pain management approach has been recommended, and almost universally adopted (Gatchel, McGeary, McGeary, & Lippe, 2014).

1.2.3 Psychological treatments for chronic pain

Psychological treatments have been part of an inter-disciplinary framework since the 1970s, with an initial focus on behavioural pain management strategies (Fordyce, 1976).

Since then, cognitive interventions have been added to treatment protocols. The popularity of such interventions has meant that the most comprehensively evaluated treatment for chronic pain is Cognitive Behavioural Therapy (CBT). The aim of CBT for chronic pain is to help patients replace maladaptive cognitions and behaviours with more adaptive ones. Over the past 20 years a range of other psychological treatments have grown in popularity and become more frequently used. For example, the development of 'third wave' CBT techniques have added even greater diversity to the study of psychological interventions for chronic pain. Acceptance and Commitment Therapy (ACT) is an example of a third wave intervention that has grown in popularity within research trials for chronic pain (Veehof, Oskam, Schreurs, & Bohlmeijer, 2011). The aim of ACT is to help the patient to accept difficult thoughts and feelings, and rather than trying to replace them, making 'committed action' to do things that are personally important or meaningful. Although ACT and CBT are the most commonly used treatments by psychologists in clinical practice (Fenton, 2010), a number of alternative treatments are also used by clinicians and researchers, including biofeedback, relaxation, mindfulness, and coping skills training. Kerns et al. (2011) reviewed these interventions, highlighting that the field of psychology has been "at the forefront of scientific investigations of pain" (p. 428), and that we have a wide range of psychological interventions.

With such a broad range of psychological interventions being studied through scientific investigation, we now have a wealth of research investigating treatment efficacy. That is, whether the treatment has an impact on outcome (Nathan, Stuart, & Dolan, 2000). This research has provided an opportunity to look across trials and test whether particular interventions continue to have efficacy when their results are combined with those from different studies. One approach to evaluating whether treatments are broadly efficacious is to synthesise outcome data from multiple trials using meta-analytic techniques.

1.3 Evidence-Based Psychological Interventions for Chronic Pain

Meta-analysis is the process of using statistical methods to summarise and combine the results of independent studies (Liberati et al., 2009). Throughout this thesis I will refer to meta-analytic studies as 'secondary studies' and the individual studies that are included in meta-analyses as 'primary studies'. Meta-analysis allows researchers to combine outcomes from different measures by calculating an effect size for each outcome. In clinical trials, we can think of an effect size as an attempt to quantify the magnitude of change that is brought about by the intervention. In this section, I provide a brief overview of the meta-analyses that have investigated the evidence-base for psychological interventions for chronic pain. As meta-analytic techniques are only as good as the reporting of interventions in primary

studies, I will then discuss what the findings can tell us about the content of psychological interventions.

1.3.1 Building an evidence base through meta-analyses

Table 1.1 summarises key characteristics of the meta-analyses that have been completed in the field of psychological interventions for chronic pain in adults. To my knowledge, there have been 21 meta-analyses in total. The mean number of studies included across the meta-analyses is relatively small (n = 24), but the range is large (Range = 2 – 65). Most meta-analyses have focused on a particular type of chronic pain. The most frequently studied is back pain (n = 6), followed by fibromyalgia (n = 4). There have been six meta-analyses that have not been restricted to a particular type of chronic pain, three of which were Cochrane reviews. In addition to focusing on a particular type of pain, most also focus on reviewing a particular type of intervention. Multidisciplinary rehabilitation was the most commonly studied type of intervention (n = 4). Three meta-analyses considered psychological interventions alongside other non-medical interventions, such as physiotherapy. Seven meta-analyses investigated any type of psychological intervention. Looking across all meta-analyses, then, we can see that there is striking variability in the specificity of meta-analyses; some exploring a particular type of intervention for a particular type of chronic pain (i.e. chronic pain diagnoses), while others are more comprehensive, exploring any type of treatment for any type of chronic pain. The three most comprehensive meta-analyses are Cochrane reviews.

On the whole, the meta-analyses support the beneficial effect of psychological interventions. This is especially true when they are compared to wait list or treatment as usual control groups. The exception to this was Karjalainen et al. (2000), who found no quantifiable benefits for multidisciplinary rehabilitation in their analyses of seven low quality trials. Typically reported effect sizes were generally small to moderate, and were smaller when comparing two active interventions. This pattern is similar to those observed across psychotherapeutic interventions more generally (Luborsky et al., 2006; Luborsky, Singer, & Luborsky, 1975). Effect sizes also got smaller over time; with the strongest effect being noted immediately following treatment, and smaller effects, although often not completely diminished effects, observed at follow-up.

Table 1.1. Overview of meta-analyses exploring psychological interventions for chronic pain.

First Author*	Year	No. Studies Included	Chronic Pain Diagnosis	Type of Psychological Intervention
Malone	1988	48	Chronic pain	Non-medical treatments for chronic pain
Flor	1992	65	Back pain	Multidisciplinary treatments
Morley (CR)	1999	25	Chronic pain	Psychological interventions
Karjalainen (CR)	2000	7	Fibromyalgia and musculoskeletal pain	Multidisciplinary rehabilitation
Karjalainen (CR)	2003a	2	Neck and shoulder pain	Multidisciplinary rehabilitation
Karjalainen (CR)	2003b	2	Low back pain	Multidisciplinary rehabilitation
Hoffman	2007	22	Low back pain	Psychological interventions
Dixon	2007	27	Arthritis	Psychological interventions
Eccleston (CR)	2009	40	Chronic pain	Psychological interventions
Hauser	2009	9	Fibromyalgia	Multicomponent treatment
Glombiewski	2010	23	Fibromyalgia	Psychological interventions
Henschke	2010	30	Low back pain	Behavioural interventions
Bernardy	2010	14	Fibromyalgia	CBT
Williams (CR)	2012	35	Chronic pain	Psychological interventions
Cheong (CR)	2014	21	Pelvic pain	Non-surgical interventions
Kamper (CR)	2014	41	Low back pain	Multidisciplinary rehabilitation
van Dessel (CR)	2014	21	Medically unexplained pain	Non-pharmacological interventions
Monticone (CR)	2015	10	Neck pain	CBT
Pike	2016	14	Chronic pain	Psychological interventions
Veehof	2016	25	Chronic pain	Acceptance & mindfulness-based interventions
Sielski	2017	21	Back pain	Biofeedback

CR = Cochrane Review

* Studies were identified through online searches of databases including MEDLINE, PsychINFO, and Google Scholar, as well as searching citing articles for each meta-analysis.

In terms of outcome measures, while there was variation between meta-analyses in the outcomes that improved following psychological interventions, positive effects for reported pain, mood, quality of life, anxiety, depression and catastrophising have been reported with some consistency.

The absence of large effects that are stable over time may be interpreted as a failing of psychological interventions to bring about considerable change for patients living with chronic pain. However, as Morley and Williams (2015) have cautioned, we must be careful not to hold overly optimistic expectations of psychological interventions for chronic pain. It is important to remember that those living with chronic pain have often been in pain for several years before seeking psychological support. Managing the distress that comes as a result of living in pain is inevitably difficult and complicated work. Representing the outcome of this complex work is, perhaps, oversimplified by the presentation of summary effect sizes.

In summary, findings from the meta-analyses available converge to suggest that psychological interventions for a range of chronic pain diagnoses are effective. Effect sizes are small, but appear to be consistent across a range of outcome measures. However, despite certainty within the field that psychological treatments for chronic pain are effective (Eccleston, Morley, & Williams, 2013), many unanswered questions remain. For instance, while we can broadly say that psychological interventions are effective, we do not know whether there are particular treatment components that are important for outcome. It may be that all treatment components within each intervention are equally important in contributing to change. I will now discuss what we know about the content of the psychological interventions that are investigated in primary studies of chronic pain.

1.3.2 Content of psychological interventions

In this section, I will discuss the possibility that there is overlap in the treatment components used across psychological interventions that are assumed to be independent. I will propose that it is time for a detailed description of the content that makes up the psychological interventions that have investigated by primary studies of chronic pain.

As described earlier, the meta-analyses conducted thus far usually focus on evaluating primary trials comparing a particular type of treatment package, such as ACT, and excluding trials that use alternative treatments. For example, Veehof et al. (2016) completed a meta-analysis comparing trials of ACT and mindfulness based stress reduction (MBSR). The implicit assumption here is that ACT and MBSR are sufficiently different to be considered independent of each other. However, this assumption may be flawed. To continue with the meta-analysis completed by Veehof et al. as an example, while there are

likely to be differences between ACT and MBSR, there will also be treatment components that overlap between them, such as bringing a non-judgemental approach to one's thoughts. Although randomised controlled trials (RCTs) are designed to control for as much variability as possible, in-depth descriptions of treatment protocols are not always provided in publications. A potential implication of this is that even if two treatments in the same trial are sufficiently different, the same treatment packages in a different trial may be delivered according to different protocols. Adding strength to this argument, Morley and Williams (2015) highlighted that a definitive CBT protocol does not exist, and treatment programmes usually comprise of multiple components. Indeed, studies might state that they are investigating CBT but the intervention used may actually include multiple components that are not unique to this therapy, such as relaxation. This is important when synthesising data across trials because interventions may be given the same name but operationalised differently, or alternatively, may be given different names but operationalised similarly (Coe, 2002).

To add to this complexity, there is reason to believe that interventions being used by clinicians are more heterogeneous than those being studied at a primary level through RCTs. For example, Fenton and Morley (2013) found that more pain management programmes (PMPs) completed as part of RCTs were classified as 'CBT' or 'CBT in addition to other components' than were PMPs completed by clinicians in routine clinical practice. PMPs were nearly twice as likely to be described as 'mixed' interventions by clinicians delivering interventions routinely. On the one hand, the use of a variety of psychological interventions for chronic pain may be advantageous. If we subscribe to a biopsychosocial model of chronic pain, then an intervention that includes several different components targeting different aspects of the model may well be beneficial. On the other hand, for this to be the case, we must be confident that all components of treatment are effective. Our approach to developing interventions for people with chronic pain cannot be an unconsidered 'bolting on' strategy, where the latest treatment is added to an existing protocol without an evaluation of the value it adds in relation to outcome. This potential for confounding of treatment effects due to their shared components, coupled with the finding that few meta-analyses have established superiority of one active psychological intervention over another, suggests that we need to better describe the various components that comprise broad intervention labels. Developing more detailed knowledge about what components comprise each broad intervention may help us to understand the extent to which there is overlap in the treatments being delivered.

When conceptualising treatment components, it is helpful to divide them into two groups: *treatment content* and *treatment context*. Treatment content refers to aspects of the treatment itself, for example, whether specific components of treatment such as behavioural

activation or mindfulness were included. Treatment context refers to the way in which the treatment components were delivered. For example, how much treatment was delivered, or how experienced the therapist was. In addition to treatment components, it may be prudent to also consider how aspects of *participant characteristics* could relate to magnitude of change. As an example of this, it may be that those who have lived with pain for more years are less likely to change because their difficulties are more established. Or perhaps those who are younger can more readily make use of the psychological interventions on offer? Although such participant characteristics are different to components relating to treatment content and context, it is important to consider that outcome may be influenced by factors other than those that the researcher can control.

1.4 Understanding Treatment Components: Meta-Regression

The need to better understand whether certain treatment components are more important than others in psychological interventions for chronic pain has been identified for some time (Morley & Williams, 2002). The same authors have more recently asserted that the challenge for the field is to discover ways of enhancing the overall magnitude of effects (Morley & Williams, 2015). It is possible that a better understanding of the treatment components included in broad treatment packages could enable clinicians to deliver greater improvement for patients. Meta-regression is one statistical approach that can be used to explore the relationship between components of treatment and outcome. In this section, I will describe how meta-regression analyses have been used in attempts to better understand treatment components.

Meta-regression can be thought of as similar to simple regression. Simple regression enables us to fit a model to our data and use the model to predict outcome values from a predictor variable. In essence, regression enables us to predict an outcome variable from a predictor variable (Field, 2009). As an illustrative example, we might use regression to predict a depression score (an outcome value) from the number of social networks a person has (a predictor variable). Whereas simple regression deals with data from within a trial, meta-regression deals with data across multiple trials (Borenstein, Hedges, Higgins, & Rothstein, 2009). Despite the potential of meta-regression to aid our understanding of how interventions bring about change, it has rarely been used by clinical psychologists. For example, since its inception in 1981, the journal 'Clinical Psychology Review' has published just 26 reviews that use meta-regression to explore treatment effectiveness for adults with different types of mental health difficulties. In the field of psychological interventions for chronic pain, meta-regressions have been used with even less frequency. To my knowledge, there have been just two studies that have used meta-regression. The first, Hoffman et al. (2007), explored the impact of psychological interventions for chronic

low back pain. Their analyses considered the following predictors and their influence on effect size across 22 trials: percentage of males, sample size, study methodology elements (e.g. treatment credibility), and age. Interestingly, the authors also noted that there were three other predictors that they could not include due to insufficient data: duration of pain, ethnicity, and education. Hoffman and colleagues found that only the percentage of males and study methodology predicted outcome, in the direction of smaller effect sizes. The lack of substantive findings for moderator effects led the authors to conclude that treatment effects do not vary by patient and study. The second meta-regression was published by Glombiewski et al. (2010), and explored 23 studies of psychological interventions for fibromyalgia. Glombiewski and colleagues found moderating effects for all three moderators that they tested: study quality, treatment dose (total number of hours spent in psychological interventions), and treatment type (e.g. CBT, relaxation etc.). Reductions in pain intensity and depression were moderated by both treatment dose and study quality, with higher doses and lower quality being associated with larger effect sizes. The finding that lower quality is associated with larger effects may be surprising, but is perhaps explained by the possibility that studies with lower quality account for less error and might include more bias, which inflates estimates of effect. Functional status was moderated only by the quality of studies, and not by treatment dose. There were no significant moderators of catastrophising. 'Type of treatment' analyses revealed that CBT reduced scores of pain intensity significantly more than other psychological interventions. On the basis of their findings, the authors recommended that patients with fibromyalgia be offered high-dose CBT.

Taken together, these two meta-regressions present discrepant findings. There are differential findings between Hoffman et al. and Glombiewski et al. in terms of how treatment content (e.g. dose), treatment context (e.g. study methodology) and participant characteristics (e.g. age, and gender) are related to outcome. It is surprising that there have not been further attempts to replicate this methodology to help clarify this incongruity. This is especially surprising given that potentially important factors, such as duration of pain, have not been investigated because of insufficient data. Indeed, it has long been recommended that meta-analysts attend more to between-study differences when using meta-analytic approaches (Wilson & Lipsey, 2001). One reason for the paucity of meta-regressions in the field may be the lack of primary studies needed to run such analyses well. This was the case for both Eccleston et al. (2009) and Williams et al. (2012), who reported that they had planned to run moderator analyses but were unable to because of small sample sizes.

Despite the continuing surge in the number of RCTs of psychological interventions for chronic pain, the most recent comprehensive meta-analysis (exploring all psychological

interventions for all types of chronic pain) was conducted in 2012 (Williams et al.). This suggests there is a need to update this search, and capitalise on the increased number of RCTs by using meta-regression analyses to further delineate the effect of treatment components to help understand the discrepancy between the two meta-regressions described above.

1.5 The Dose-Response Question

Although there are many treatment components that would be interesting to investigate, in this section I will introduce 'treatment dose' as a component that merits more attention. Lending a concept from the field of pharmacology, one can think about this as the 'dose-response' question (Howard, Kopta, Krause, & Orlinsky, 1986). I will analyse previous attempts to answer the dose-response question in the field of psychological interventions for chronic pain, and highlight why further investigation of the dose-response question is necessary.

The dose of treatment is important for three reasons. Firstly, high dose interventions are more intensive for patients. With this comes an ethical imperative to ensure that high-dose interventions are effective and that we are not 'wasting time' for patients. Secondly, high dose interventions are time consuming for clinicians. The longer a treatment takes for an individual patient – or group of patients – the fewer patients can be seen by the clinician. This means that the issue of dose is inter-related with the dilemma of seeing more patients for less time or fewer patients for longer. Finally, high dose interventions are financially costly. This is especially important at the moment; with more financial pressure on healthcare services around the world than ever before (Deloitte, 2017), there is an economic imperative to ensure that greater returns are seen in exchange for higher doses.

In addition to the conclusion drawn by Glombiewski et al. (2010) that patients with fibromyalgia ought to be offered high dose CBT, other investigations of how much treatment might be needed for significant improvements in functioning have focused on low back pain. An early attempt to answer this question concluded that more than 100 hours of multi-disciplinary rehabilitation was required for significant improvements to be seen (Guzmán et al., 2001). However, there were significant limitations to this research. Only ten trials were included in the analysis, which focused only on selected outcome measures (excluding psychological and physical measures). Moreover, only trials of multi-disciplinary treatments were included. Perhaps most crucially, Guzmán and colleagues compared studies based on a dichotomy between those where dose was less than 30 hours, and those where dose was more than 100 hours. At best, we can say that this was a limited attempt to explore the dose-response question. Despite these shortcomings, the authors'

conclusion that more than 100 hours of rehabilitation are required was incorporated into National Institute of Clinical and Health Excellence guidance (NICE, 2009). References to a minimum number of hours has been removed in the latest guidelines, with no updated recommendations about duration of treatment (NICE, 2016).

More recently, Waterschoot et al. (2014) have attempted to account for some of these methodological issues. They conducted more complex and sophisticated analyses using a statistical approach called multilevel modelling to analyse outcomes from pain rehabilitation programmes for adults with low back pain. Based on this, they emphasized the complexity of the dose-response question and concluded that a wide range of contact hours (from 6.4 to 196.8 hours) could lead to greater effect sizes than control interventions. Key findings from the paper were that evaluation moment (i.e. immediately post-intervention, 6-month follow-up etc.), number of disciplines, type of intervention, duration of intervention in weeks, percentage of women and age influenced the outcomes of pain rehabilitation programmes. It is interesting that duration of intervention in weeks and not dose of intervention in hours influenced outcome. Waterschoot and her colleagues concluded that the independent effect of dose variables could not be distinguished from content because these variables were strongly associated. Although this analysis of the dose-response question is laudable, it was limited in that it only included 18 studies, and was restricted to patients with low back pain. With this in mind, Waterschoot's paper presents an interesting methodology, and a potential to apply this to a broader set of trials and outcome data.

In summary, attempts to explore the dose-response question have been limited and have highlighted the complexity of trying to tease apart other interrelated and important aspects of treatment that may also be important. Rather than such complexity preventing further analysis, I argue that we must further explore the issue of dose *because* of this complexity. As Williams (2014) points out, Waterschoot et al. have "laid some ground for larger and more incisive attempts to disentangle some of the factors in pain management that we can manipulate to improve treatment provision" (p. 9). The increased number of trials, and inclusion criteria that are broader than those used by Waterschoot et al. may mean that the relationship between treatment dose and outcome can be better explored.

1.6 Present Thesis

In sum, we know that psychological treatments for chronic pain are effective. However, there may be overlap in the treatment content of interventions that have been delivered. This overlap has not been reviewed, but is important for the conclusions that we can draw from attempts to synthesise outcomes across different interventions. Furthermore, to continue to develop our interventions, a better understanding of treatment components is

required. One important component is ‘dose’ of treatment. Meta-regression presents a sophisticated approach to exploring relationships between potential moderators, such as dose, and magnitude of change following a treatment.

The primary purpose of the present thesis is to further explore the dose-response question. I will replicate the most recent comprehensive meta-analysis that included all types of non-cancer chronic pain, excluding headache, and all types of psychological interventions (Williams et al., 2012). The rationale for excluding chronic headaches is that the psychological interventions aim to reduce the frequency, intensity and duration of the headache. This is different to the aim of interventions for other types of chronic pain; to rehabilitate individuals in-spite of ongoing chronic pain. Similarly, psychological interventions for individuals with pain from life-threatening diseases such as cancer are not focused on rehabilitation in the same way that chronic pain interventions are. For these reasons, the present study focuses on interventions for non-cancer chronic pain excluding headaches. I will, however, also extend this review by using meta-regression to analyse dose as a potential moderator of change. Given the paucity of meta-regressions analysing psychological interventions for chronic pain, this will enable me to generate hypotheses about the relationship between dose and effect. The secondary purpose of this thesis is to explore specific descriptions of treatments delivered in trials to facilitate an improved understanding of what components of psychological treatments are delivered; moving away from broad labels of treatment packages. Due to the lack of consistent and convergent findings in this area it is difficult to sensibly hypothesise about the relationship that will be found. As such, this thesis ought to be considered hypothesis generating in nature.

To conclude, I will explore whether ‘all treatment components are created equal’ by asking two broad questions:

1. Is dose related to outcome in psychological interventions for adults with chronic pain?
2. What are the core components of treatment being delivered in psychological interventions for chronic pain, and how do they differ between types of intervention?

2 Method

In this section, I will outline my approach to identifying appropriate trials, data extraction, and data analysis in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA; Liberati et al., 2009). I will present summary data alongside descriptions of method to allow for ease of reading. For example, the number of studies selected is presented alongside the description of study search strategies.

2.1 Ethical Considerations

This thesis analysed data that is publically available in published journal articles. As such, it did not require the approval of an ethics committee.

2.2 Search Methods

2.2.1 Criteria for considering studies for analysis

The criteria used by the most recent Cochrane review of psychological interventions for chronic pain was replicated (Williams, Eccleston, & Morley, 2012). For studies to be included, they had to be randomised controlled trials of credible psychological interventions for chronic pain in adults (> 18 years and older). Chronic pain was defined as pain lasting longer than three months, and excluded headache or pain associated with a malignant cause such as cancer. Psychological interventions were deemed to be credible if they had definable psychotherapeutic content, based on an existing psychological model or framework, and delivered, trained or supervised by a psychologist. Trials where the primary aim was not the alleviation of chronic pain were excluded. For example, trials treating insomnia in participants with chronic pain. Trials that were delivered online were also excluded, on the basis that the treatment characteristics were different to interventions delivered in-person (see Buhrman et al., 2015 for a review of internet interventions for chronic pain). Any trial that had an arm where the sample size was less than 20 was excluded. No restrictions were placed around type of outcome measure. Only primary publications of studies were included; publications reporting secondary analyses were excluded.

2.2.2 Search strategy

In line with Williams et al. (2012), electronic searches were completed of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and PsychINFO. The searches included studies published between 2012 and January 2016. Filters were used to

include only studies of humans, and adults (18 years and older). Searches were completed twice. The first was completed in August 2016, and the second was in January 2017 to ensure that any studies published in the previous five months were included. No additional papers that met the inclusion criteria were found during the second search. Full details of the search strategy, including MeSH terms are provided in **Appendix A**.

2.2.3 Selection of studies

Trials included in the Williams et al. (2012) review were automatically selected. In addition, the initial search of literature published since 2012 yielded a total of 1452 studies. I evaluated whether each study met the inclusion criteria by following three steps; firstly, reviewing all titles, secondly, reviewing abstracts, and finally reviewing full texts. To compensate for the possibility of human error in evaluating such a large data set, a final year undergraduate psychology student was trained in evaluating whether studies met inclusion criteria. The student independently completed a review of all titles, and a sample of 50 abstracts (17% of total abstracts reviewed). This process revealed that no relevant papers were missed, and exclusion and inclusion rates were similar between evaluators. The student excluded more studies earlier than I did, suggesting that my approach was more conservative. I completed a review of all full texts. Any queries regarding whether a paper ought to be included were discussed in supervision. **Figure 2.1** shows the flow of studies through the search process, which resulted in 65 trials being included. One study was a long-term follow-up of an existing study (Tavafian, Jamshidi, & Mohammad, 2014). New data were extracted from this paper, but all other study data were only extracted from the original paper (Tavafian, Jamshidi, & Mohammad, 2011) to ensure that data such as participant demographics were not accounted for twice.

2.3 Assessing Quality and Risk of Bias

The Yates Quality Rating Scale (Yates, Morley, Eccleston, & Williams, 2005) and the Cochrane Risk of Bias Tool (Higgins et al., 2011) were used to assess quality and risk of bias. **Table 2.1** lists the items included in both measures. To ensure that I could use these tools accurately, I trained myself by independently assessing the quality and bias of nearly half (48%) of trials included in Williams et al. (2012). Intra class correlation (ICC) coefficients were .81 and .84 for quality and bias ratings respectively. Yates et al. (2005) reported a median ICC of .81, suggesting that this calibration exercise was successful.

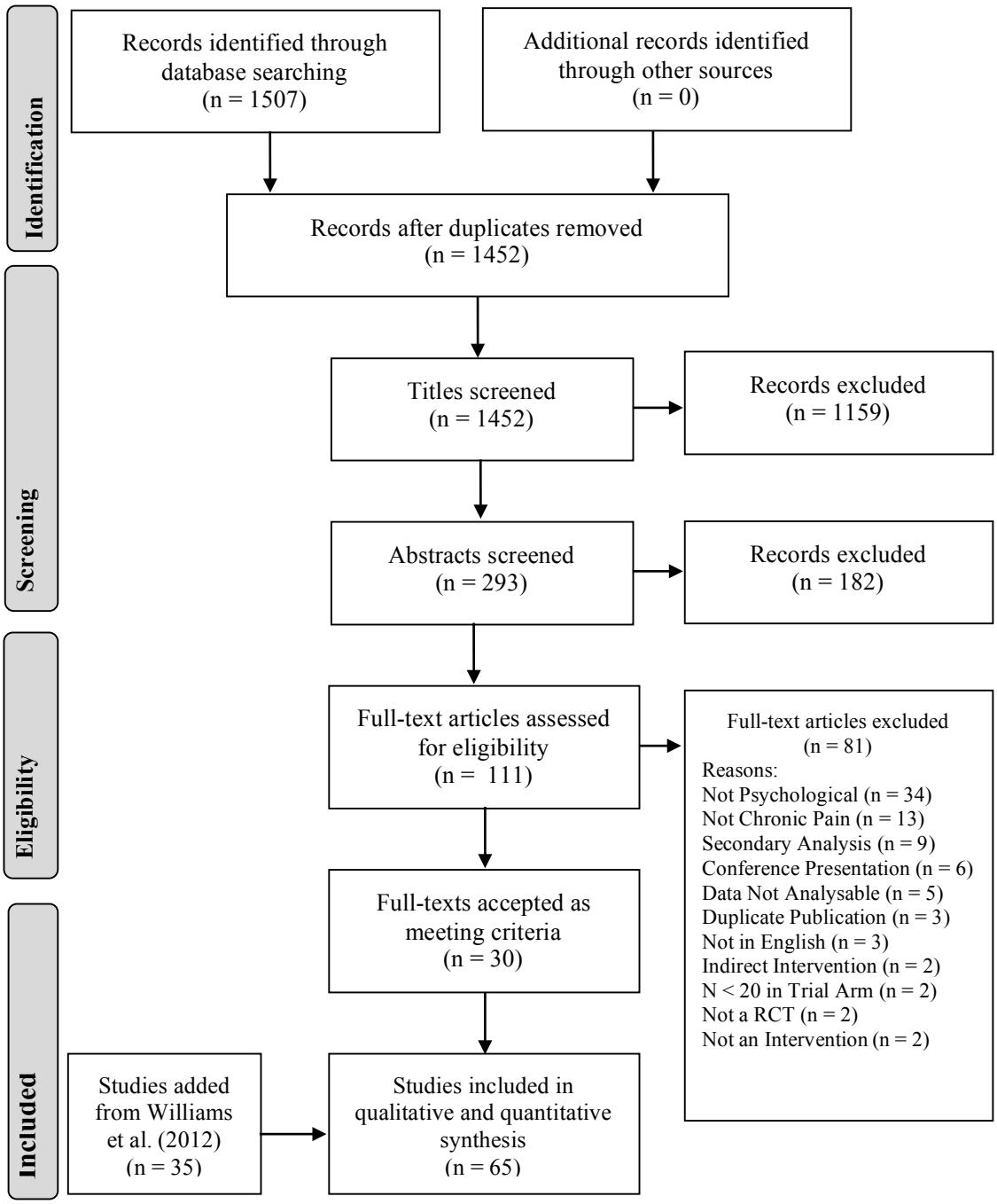

Figure 2.1. PRISMA flow diagram of studies through search process.

2.3.1 Yates Quality Rating Scale

The Yates Quality Rating Scale (Yates et al., 2005) is a tool to assess the quality of treatment and study design. It was developed specifically to evaluate quality in psychological treatment studies of chronic pain. As this thesis explored in-depth descriptions of the treatments delivered, only the study design items of the measure were used.

There are 20 items evaluating study design quality, for example, whether the intervention was manualised, whether inclusion criteria were met, and whether there was a

six-month follow-up. A total score of 26 is possible, with higher scores indicating better quality. It has been noted that use of quality rating scales to assess risk of bias is limited because they often assign weights in ways that are difficult to justify (Higgins et al., 2011). As such, the Cochrane Risk of Bias Tool was also used.

2.3.2 Cochrane risk of bias tool

In line with Cochrane recommendations, I used the 'Cochrane Risk of Bias Tool' (Higgins et al., 2011) to assess four types of bias in included studies: selection bias, detection bias, attrition bias, and reporting bias. Five items assess these four types of bias, and responses are presented as 'high risk of bias', 'low risk of bias', or 'unclear'. Justification of rating is also noted.

Table 2.1. Items from Yates Quality Rating Scale and Cochrane Risk of Bias Tool.

Yates Quality Rating Scale Items
1. Are the inclusion and exclusion criteria specified?
2. Is there evidence that CONSORT guidelines for reporting attrition have been followed?
3. Is there a good description of the sample in the trial? [Sub items: sample characteristics; group equivalence]
4. Have adequate steps been taken to minimise biases? [Sub items: randomisation; allocation bias; measurement bias; treatment expectations]
5. Are the outcomes that have been chosen justified, valid and reliable?
6. Has there been a measure of any sustainable change between the treatment and control groups (i.e. follow-up of six months or longer)?
7. Are the statistical analyses adequate for the trial? [Sub items: Power calculation; Sufficient sample size, Planned data analysis; Statistics reporting; Intention to treat analysis]
8. Has a good, well-matched alternative treatment group been used?
Cochrane Risk of Bias Tool Items
1. Was the allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Was knowledge of the allocated interventions adequately prevented during the study?
4. Were incomplete outcome data adequately addressed?
5. Are reports of the study free of suggestion of selective outcome reporting?

2.3.3 Overview of bias and quality scores

As recommended by Liberati et al. (2009), **Table 2.2** displays all studies that were included in this thesis, along with data about trial design quality and risk of bias within each

study. **Figure 2.2** presents the risk of bias data across all trials, showing the percentage of studies with low, high and unclear risk of bias in relation to each of the five items measured by the 'Cochrane Risk of Bias Tool'. **Figure 2.2** shows that there was a relatively low or unclear risk of bias when viewed across all studies. The exception to this was that the risk of detection bias was relatively high because outcome assessments were not typically blinded. Although one might minimise the potential impact of not blinding assessors when most measures are self-report, it is plausible that assessors who are aware of the condition that participants were randomised to may consciously or unconsciously influence outcome. For example, if an assessor expects greater improvement because they know that a participant has received the active treatment, they may be more encouraging and positively reinforcing in their interactions than if they do not expect that a participant will have changed because they have been on a waiting list. Only four studies were without any risk of bias (Leeuw et al., 2008; Monticone et al., 2013; Sharpe & Schrieber, 2012; Somers et al., 2012). One study scored high across all risk of bias items (Mishra, Gatchel, & Gardea, 2000). Scores of trial design quality have increased slightly since the 2012 Cochrane review from 15.8/26 to 17.59/26. This means that the trend for increased trial quality with year of publication continues to be statistically significant (Spearman's rho = 0.46, $p < .01$).

2.3.4 Publication bias

Publication bias describes the tendency for journals to publish statistically significant results (Rothstein, Sutton, & Borenstein, 2006). This has the potential to skew the results of meta-analysis because effect sizes would be larger than if non-significant trials had been published. I assessed publication bias by calculating fail-safe *N* in accordance with methods outlined by Rosenthal (1979). Fail-safe *N* is a frequently used computation that estimates how many additional non-significant studies would be needed to reduce the treatment effect found in meta-analysis to zero. If the number of additional studies required is large (e.g. more than 5,000) then we can be more confident that the effect size found in the meta-analysis is robust (Rosenthal, 1991).

Table 2.2. Quality and risk of bias summary for each included study.

Trial ID	Design Quality	Random Sequence Generation	Allocation Concealment	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Altmaier 1992	11	-	-	-	-	+
Amris 2014	19	+	+	?	?	+
Basler 1997	12	-	-	-	+	+
Bennell 2016	22	+	+	+	?	+
Bliokas 2007	15	+	-	-	+	+
Broderick 2014	17	+	?	+	+	+
Cash 2015	16	+	+	-	+	-
Castel 2013	18	+	-	+	-	-
Castro 2012	13	-	+	-	-	+
Chavooshi 2016	15	-	-	?	-	+
Cherkin 2016	23	+	+	+	?	+
Ehrenborg 2010	17	?	-	-	+	+
Ersek 2008	21	+	+	+	+	-
Evers 2002	18	?	+	-	+	+
Falcao 2008	14	?	-	+	?	+
Geraets 2005	20	+	+	+	+	+
Glombiewski 2010b	17	+	?	-	?	+
Greco 2004	20	+	-	+	?	+
Haldorsen 1998	10	+	+	?	-	-
Hammond 2001	15	-	+	+	-	+
Heutink 2012	17	-	-	-	-	+
Jensen 2001	20	?	+	?	-	+
Jensen 1997	13	?	-	+	-	-
Kääpä 2006	20	+	+	-	?	+
Khan 2014	15	+	-	-	+	+
Karlsson 2015	19	+	+	-	+	+
Keefe 1990	18	?	-	-	+	+
Keefe 1996	17	-	-	-	?	+
Kemani 2015	22	+	-	-	?	-
Kerns 2014	23	+	+	+	+	-
Kraaimaat 1995	14	-	-	-	?	+
Leeuw 2008	24	+	+	+	+	+
Litt 2009	11	+	-	-	-	+
Luciano 2014	22	+	+	+	?	+
Martín 2012	19	+	-	?	+	+
McCarberg 1999	9	?	-	-	?	+
McCracken 2013	16	+	-	+	+	+
Mishra 2000	12	-	-	-	-	-
Monticone 2012	20	+	+	+	-	+

Trial ID	Design Quality	Random Sequence Generation	Allocation Concealment	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Monticone 2013	22	+	+	+	+	+
Nicassio 1997	15	?	-	-	+	+
Nicholas 2013	20	+	+	+	-	+
Nicholas 2014	20	+	+	-	-	+
Poleshuck 2014	19	+	?	-	-	+
Puder 1988	10	-	-	-	?	-
Scheidt 2013	21	?	+	-	-	+
Schmidt 2011	23	+	+	+	?	+
Sharpe 2012	24	+	+	+	+	+
Siemonsma 2013	19	+	+	-	-	+
Sleptsova 2013	18	+	+	-	-	+
Smeets 2008	23	+	+	+	?	+
Somers 2012	22	+	+	+	+	+
Tavafian 2011	19	-	+	-	-	+
Thieme 2003	11	-	-	-	?	+
Thorsell 2011	13	?	-	-	?	+
Turner 2006	22	+	+	+	?	+
Turner 1988	15	-	-	-	?	+
Van Koulil 2010	15	-	-	-	?	+
Van Der Maas 2015	18	+	+	-	-	+
Vlaeyen 1996	16	-	-	-	+	+
Wetherell 2011	24	+	+	+	?	+
Williams 1996	15	?	-	+	+	-
Zangi 2012	19	+	+	+	-	+
Zautra 2008	19	+	-	+	?	+

+ = low risk of bias; - = high risk of bias; **?** = unknown risk of bias.

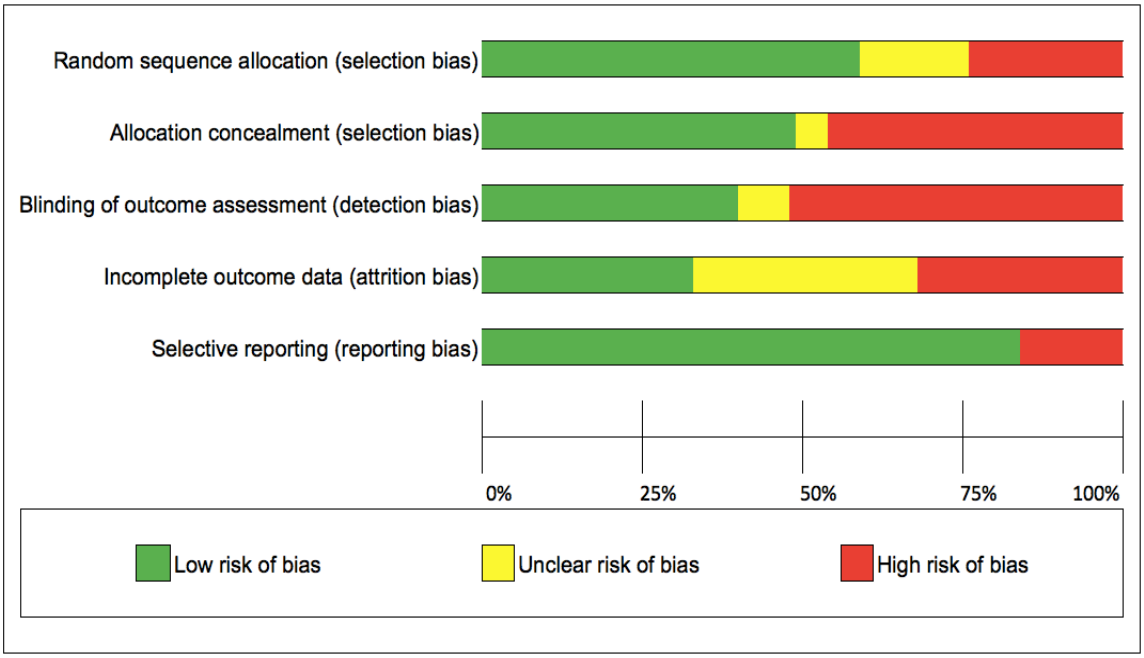

Figure 2.2. Risk of bias graph presented as percentages across all included studies.

2.4 Data Extraction

I extracted four types of data from each trial; participant demographics, treatment context, treatment content and treatment outcomes. In this section, I provide an overview of the types of data extracted. I used Microsoft Excel (version 15.33) to extract the data from each study, adapting a data extraction book created for previous reviews (Eccleston, Palermo, Williams, Lewandowski, & Morley, 2009; Williams et al., 2012). If data were missing, it was scored as 'not reported', meaning that I did not estimate or assume any data.

2.4.1 Trial conditions

All data were extracted at the level of the trial condition (sometimes referred to as the 'trial arm'). I classified trial conditions as 'active treatment' to identify the intervention of primary interest in each trial. I classified conditions as 'active control' when control participants were offered a treatment of any kind that was not the same as the target active treatment. Some trials had more than one active control condition, these were recorded in order as; 'active control 1, active control 2', and so forth. I will use the term 'active conditions' throughout this thesis, to refer to active treatment and active control conditions. I also extracted data about wait list control (WLC) and treatments as usual (TAU) conditions. TAU conditions differ from active control conditions because they do not usually receive a consistent, structured intervention and support can vary from regular consultations to access to care, if needed.

2.4.2 Participant demographics

I extracted information about the participant characteristics that were most frequently reported in trials. I decided which characteristics were frequently reported by extracting all information from the first five trials and looking at the data that were commonly reported across all. While this meant that the data extracted was determined by the trial data that was available, it also meant that some important information, such as number of previous treatments for chronic pain, was not frequently reported and therefore not extracted. Participant demographics were extracted for each arm of the trial. For example, the average age of the control group was extracted as well as the average age of the intervention group (rather than extracting the average of the whole sample). I extracted information about the following aspects of participants:

- Age.
- Gender – percentage female.
- Marital status – percentage married, single, widowed, or separated.
- Ethnicity – percentage White, Black, Asian, or 'other ethnicity'.
- Education – percentage who completed some level of high school education, graduated from university, or completed a post graduate qualification.
- Employment status – percentage employed, unemployed, receiving social benefits, or receiving disability pensions. Students were rarely reported as being included in trials, as such information on whether participants were currently studying was not included.
- Primary chronic pain diagnosis, secondary chronic pain diagnosis and the percentage of participants with these diagnoses.
- Pain duration – the mean length of time that someone had been living with pain, measured in years. Where this was reported in months, I divided by 12 to get an estimate in years.
- Medication – percentage on any medication, opioids, Nonsteroidal Anti-inflammatories (NSAIDs), antidepressants and anticonvulsants.

2.4.3 Treatment context

Data about treatment context includes information about the design of the trial. I extracted information about key characteristics, including:

- Type of service – categorised as hospital, community, or university.
- Treatment setting – categorised as either residential or outpatient.
- Country – categorised as the name of the country where the trial was completed.
- Manualisation – categorised as whether use of a treatment manual was reported.

- Adherence to manualisation – verbatim description of manualisation adherence extracted, these descriptions were subsequently coded categorically as 'yes' or 'no'.
- Therapist training – categorised as Not Reported, Inexperienced, Experienced, or Advanced.
- Number of multi-disciplinary team (MDT) members – count of MDT members described.
- Professions included in the MDT – list of all MDT members described.
- Treatment dose (hours) – total hours of treatment.
- Treatment duration (weeks) – total number of weeks over which treatment was delivered.
- Treatment format – categorised as group or individual.
- Mean group size.
- Group size range.

2.4.4 Treatment content

Analysing data from trials on the basis of broad intervention names like 'CBT' or 'ACT' poses a problem because interventions may be given the same name but operationalised differently, or alternatively, may be given different names but operationalised similarly (Coe, 2002). To enable a better understanding of the interventions that were delivered, specific data about treatment content were extracted. 'Treatment content' refers to specific information about what was delivered in each intervention. Descriptions of interventions were extracted verbatim from the text, and varied in specificity. A total of 475 unique descriptions of treatment content were found from the first extraction of information. To enable meaningful analysis of this data, broader treatment categories were created. This process involved 'coding' the treatment content descriptions until broad categories were established that best represented the content descriptions. **Figure 2.3** demonstrates this process with the example of how the final code of 'Behaviour Strategies' was established. Treatment content that was uncommon was excluded. For example, biofeedback occurred fewer than 25 times across all trial arms and so was excluded. Thirteen treatment categories were found to best represent the treatment content (see below). All treatment categories, along with their definitions, were reviewed and agreed in supervision. Each arm of every study was then examined to assess whether it included any of the 13 treatment categories. Only components that were specifically described were rated as being included. This meant that I made no assumptions about what components may have been included in an intervention. For example, if an intervention was called 'cognitive behaviour therapy' one could assume that cognitive strategies (such as cognitive restructuring) would have been used, but unless the study specifically reported that this was the case, I recorded the

component as ‘not included’. This means that the treatment categories used are only as good as the descriptions in the trial, but this was necessary to ensure the replicability of my method.

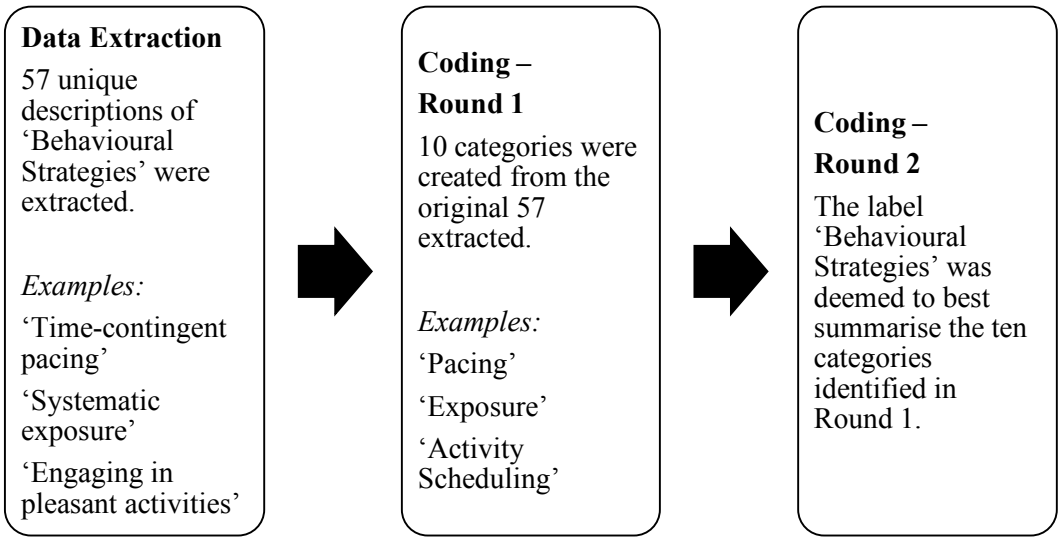

Figure 2.3. Example of coding process to identify treatment category labels.

1. *Attention management* - Includes distraction techniques used to help patients manage their pain. For example - external focusing, counting backwards and guided imagery.

2. *Behaviour Strategies* - Describes techniques used to increase physical functioning, by helping patients to reduce psychological barriers to completing day-to-day activities. For example - exposure, pacing and activity scheduling.

3. *Cognitive Strategies* - Includes any technique that aims to change maladaptive thoughts or the impact of thoughts on patients’ lives, such as thought challenging, cognitive restructuring, and cognitive defusion. While the theory and application of these strategies differ, it was deemed appropriate to group them because they all aim to work at a cognitive level.

4. *Communication* - Includes techniques that aim to improve interpersonal relationships. Such as; assertiveness training, effective communication, and relationship issues. It could be argued that relationship issues ought to be considered separately to general issues of communication. However, they were grouped together because both serve the aim of improving interpersonal relationships.

5. *Psychoeducation* - Describes education that had a psychological component, such as education about mindfulness, stress or relaxation. There were ten occurrences of education being mentioned without further information about the content of the education. These occurrences were classed as psychoeducation because this was the most common category of education and all studies were of psychological interventions and so it seemed sensible that it was likely to be psychoeducation.

6. *Non-Psychological Education* - Describes education that did not have a psychological component, such as education about medication, assistive devices or exercise.

7. *Exercise* - Includes any physical activity where the aim is to improve physical fitness. There were three main types of exercises: strengthening, stretching and aerobic exercise. It was common for trials to not report exactly which types of exercises were included. It is worth noting that although 'Exercise' and 'Behaviour Strategies' categories may both result in more day-to-day activities and increased fitness, their aims are rather different. The conceptualisation here is that exercise aims to improve fitness, and behaviour strategies aim to reduce psychological barriers to engaging in activity.

8. *Goal Setting* - Captures the inclusion of a goal setting in the trials.

9. *Homework* - Captures the inclusion of homework as part of the therapeutic tasks. Details of the homework tasks were frequently unreported.

10. *Mindfulness* - Captures any treatment component that aimed to bring purposeful attention to the present moment or to one's body, such as mindfulness, body awareness training, and proprioceptive exercises. Relaxation was not included here (see 'Relaxation' category below). It may be argued that mindfulness is a sub-component of attention diversion. However, mindfulness has a focus on attention toward the 'self', which is perhaps the opposite of what one might try to achieve through attention diversion. As such, I defined it to be sufficiently different to be worth a separate category.

11. *Problem Solving* - Captures the inclusion of problem solving. Details of the strategies used as part of the problem solving component were seldom reported.

12. *Relapse Prevention* - Reflects the planning at the end of treatment that aims to maintain positive change.

13. *Relaxation* - Describes strategies that aim to help patients relax. Such as; applied relaxation, breathing exercises, and progressive muscle relaxation. It may be argued that there is overlap between relaxation and mindfulness as categories (e.g. both often facilitate a focus on one's breathing). However, the essence of mindfulness is to notice rather than to change, whereas relaxation exercises often encourage patients to change their breathing or muscle tension. Thus, differentiating mindfulness and relaxation was appropriate.

2.4.5 Outcome measures and outcome domains

The wide range of the measures used to evaluate trials has been well noted in the field of psychological interventions for chronic pain (Deckert et al., 2016; Fenton & Morley, 2013; Turk et al., 2003), and was a further challenge to data extraction. In total, data were available from 348 different measures. One way to manage this diversity is to use broader outcome domains that aggregate scores across different measures of the same construct. In accordance with Fenton and Morley's (2013) Delphi study, which established outcome domains in chronic pain trials, five outcome domains were used: pain experience, pain behaviour, emotional functioning, physical functioning and coping and cognitive appraisal. Importantly, this approach to analysis was different to the approach used in the Williams et al. (2012) Cochrane review, where a primary outcome measure was selected and used in the analysis across four domains (disability, pain, mood, and catastrophising). While there was an argument to be made for keeping analysis in line with Williams et al. (2012), namely that a more direct comparison between findings could be made, aggregating across multiple measures provided a more sophisticated approach to analysis because it enabled more data to be used. For example, while not all studies used a measure of catastrophising, many did use some measure of coping and cognitive appraisal (which includes measures of catastrophising). This meant that more data included in the primary trials could be included in my analyses.

Table 2.3 provides a brief description of each domain, along with examples of questionnaires, and the number of studies included in this thesis that measured each domain. Pain experience and physical functioning were used in almost all studies (61 and 60 respectively). Measures of pain behaviour were the least frequently used, with only 15 studies reporting data on pain behaviour. Purely biological measures were excluded, for example, blood samples to measure osteoarthritis.

Table 2.3. Overview and example measures of outcome domains.

Outcome Domain Name	Number of studies measuring domain	Definition	Example Measures
Coping and Cognitive Appraisal	39	Measures that aim to explore the degree to which participants are able to cope with aspects of living with chronic pain. It also includes measures that explore helpful and maladaptive cognitions related to chronic pain.	*Chronic Pain Acceptance Questionnaire* (McCracken, Vowles, & Eccleston, 2004) *Coping Strategies Questionnaire* (Gil, Williams, Thompson, & Kinney, 1991)
Emotional Functioning	54	Measures participants' mood, emotions, or anxiety.	*Beck Depression Inventory* (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) *Hospital Anxiety and Depression Scale* (Zigmond & Snaith, 1983)
Pain Behaviour	15	Measures that capture overt expressions of pain, and behaviours that indirectly indicate expressions of pain such as visits to one's General Practitioner, or taking pain medications.	*Pain Behaviour Checklist* (Philips & Hunter, 1981) *Number of Days in Hospital*
Pain Experience	61	Measures that assess the aspects of pain itself, such as intensity or pain severity.	*Graded Chronic Pain Scale* (Von Korff, Ormel, Keefe, & Dworkin, 1992) *Visual Analogue Scale of Pain Intensity*
Physical Functioning	60	Measures day-to-day disability caused by pain, such as quality of life, sleep and activities of daily living.	*Fibromyalgia Impact Questionnaire* (Burckhardt, Clark, & Bennett, 1991) *The West Haven-Yale Multidimensional Pain Inventory* (Kerns, Turk, & Rudy, 1985)

2.4.6 Outcome data

Studies usually included continuous outcome data. Dichotomous outcome data were uncommon and were not extracted. A small number of trials reported percentages as outcome data. For example, the percentage of participants scoring within the clinical range for depression, however; such data were excluded because they were uncommon. Means and standard deviations (SDs) were extracted for all questionnaires presented in the trials. If means and SDs were not available, authors were contacted to request these data. Five authors

responded to my request and sent relevant data. If authors did not reply to my initial request one further prompt message was sent, thereafter the paper was excluded if no response was provided. This was the case for three studies. One author did reply to my request, but stated that the data requested (number of participants in each arm of the RCT) were not available and this paper was excluded.

Five studies reported confidence intervals (CIs) instead of SDs. **Equation 1** and **Equation 2** were used to calculated SDs, where SEM is the standard error of the mean, HiCI and LoCI refer to the upper and lower confidence intervals respectively:

Equation 1 $$\boldsymbol{SEM = \frac{HiCI - LoCI}{3.92}}$$

Equation 2 $$\boldsymbol{SD = SEM(\sqrt{n})}$$

Raw means and SDs were pooled together in three studies; (1) Jensen, Bergström, Ljungquist, Bodin, and Nygren (2001) reported data by gender, (2) Zautra et al. (2008) reported data by whether patients had a history of depression, (3) van Koulil et al. (2010), reported two active treatment conditions of primary interest. In all three cases, one group was created by using **Equation 3** to calculate a pooled mean estimate ($Pooled_M$) and **Equation 4** to calculate a pooled SD estimate ($Pooled_{SD}$).

Equation 3 $$\boldsymbol{Pooled_M = \frac{(M_1\, n_1)+(M_2\, n_2)}{n_1 + n_2}}$$

Equation 4 $$\boldsymbol{Pooled_{SD} = \sqrt{\frac{(SD_1^2(n_1-1))+(SD_2^2(n_2-1))}{(n_1+n_2)-2}}}$$

2.4.7 Follow-up data

One challenge to extracting data was the variability of follow-up times used within trials. While most follow-up times were 6 or 12 months, there were occasions where follow-up times were atypical, such as two months post-intervention. If a trial had a follow-up time point that was atypical it was rounded to one of the following time-points: post intervention, 3, 6, 9, 12, 18, and 24 months. **Table 2.4** shows the number of trials included in this thesis that collected data at each time point. Nearly all trials collected data immediately following the intervention (n = 57). The next most frequently used follow-up time points were at 6 and 12 months (included in 36 and 24 studies respectively).

Table 2.4. Number of studies collecting data at each time point.

Follow-up time point	Number of studies
Post	57
3	14
6	36
9	2
12	24
18	3
24	1

2.5 Data Analysis

Data were analysed in two ways. Firstly, data regarding treatment content, context and participant characteristics were analysed using descriptive statistics. Next, meta-regression analyses were conducted to explore the quantitative outcome data. In this section, I outline the steps taken to complete the meta-regression analyses.

A weighted meta-regression was used to examine the impact of predictors, such as dose, on outcome which was effect size between the active treatment condition and control conditions. This statistical approach has been recommended by The Cochrane Collaboration when looking at the relationship between clinical characteristics, such as dose of treatment, and intervention effect (Higgins & Green, 2011; p. 277). Analyses were conducted with data immediately following the intervention, when most trials reported data. In an attempt to deal with heterogeneity, a random-effects model was used as opposed to a fixed-effect model. The fixed-effect model accounts for only within study variance, whereas the random-effects model is more conservative as it accounts for both within study variance and between study variance. This was important because the inclusion criteria were broad, and so it was probable that there would be significant heterogeneity between trials. A random-effects model has been recommended when this is believed to be the case (Thompson & Higgins, 2002). Moreover, a restricted maximum likelihood (REML) estimate was used because this accounts for the degrees of freedom employed in the model and so minimises the risk that the variances will be underestimated (Thompson & Higgins, 2002; Thompson & Sharp, 1999).

There are no definitive standards for what the minimal number of studies needed to complete a meta-regression should be. However, ten has been recommended (Borenstein et al., 2009). This suggests that the 64 trials included in this thesis justifies the use of a meta-regression to explore relationships between treatment characteristics and outcome. As I aimed to generate hypotheses, the statistical convention of using a 0.05 level of significance was relaxed to 0.2. Such an adjustment is sensible when making multiple comparisons between explanatory

variables and outcome. Once all data were extracted into the Excel file, it was exported to SPSS (Version 22.0) for descriptive analysis. Meta-regression was conducted in Stata (Version 13.1), using the 'metareg' command (Harbord & Higgins, 2008).

2.5.1 Calculating effect sizes

As with meta-analysis, meta-regression involves the comparison of effect sizes. For the purposes of this thesis, I generated an effect size (ES) for the difference between the treatment condition and the active control condition, as well as the difference between the treatment and the TAU / WLC condition depending on which type of control group was used in the study. Grouping TAU and WLC conditions is not optimal because participants allocated to TAU do receive some treatment. However, the unstructured (and often unreported) nature of TAU conditions meant that the most conservative approach was to group it with WLC and compare both with the active treatment. This approach is in line with the Williams et al. (2012) review.

A standardised mean difference (SMD) effect size was chosen (Hedges' *g*) because the trials included here measure the same outcome domains (e.g. pain experience) but do so on different scales. The standardised mean difference (that is, standardised difference between means), allows us to standardise the results of studies into a uniform scale so that they can be meaningfully combined (Higgins & Green, 2011, p. 256). In calculating the SMD, a study's effect size is calculated relative to the inverse variability observed in the study and between studies. To do this, an uncorrected effect size (Cohen's *d*) was calculated for each outcome measure (Cohen, 1988). **Equation 5** shows this formula, where M_T refers to the mean of the active treatment, M_C refers to the mean of the control condition, and SD_{Pooled} refers to the pooled standard deviation for both treatment and control conditions, which is a commonly used denominator when calculating *d* (Rosnow & Rosenthal, 1996).

Equation 5 $$\boldsymbol{d = \frac{(M_T - M_C)}{SD_{Pooled}}}$$

SD_{Pooled} was calculated using **Equation 6.** Here, N_T refers to the sample size of the treatment group, N_C refers to the sample size of the control group, SD_T refers to the SD of the treatment group, and SD_C refers to the SD of the control group. These were all taken at the post treatment time point.

Equation 6 $$\boldsymbol{SD_{Pooled} = \sqrt{\frac{((N_T - 1)SD_T^2) + ((N_C - 1)SD_C^2)}{(N_T + N_C) - 2}}}$$

The Hedges correction for small sample bias was then added to account for the tendency of Cohen's *d* to be upwardly biased when based on small samples (Hedges, 1981). Three steps were taken to achieve this:

1. Degrees of freedom (*df*) were calculated using **Equation 7.**
2. The size corrected ES (d_i) was then calculated using **Equation 8.**
3. Hedges'g was then calculated by multiplying the Cohen's d by the sample size adjusted Cohen's d_i, as shown in **Equation 9.**

Equation 7 $$\boldsymbol{df = (N_T + N_C) - 2}$$

Equation 8 $$\boldsymbol{d_i = 1 - \frac{3}{4(df)-1}}$$

Equation 9 $$\boldsymbol{Hedges'g = (d)(d_i)}$$

The final correction made to the ES was to correct for direction of change such that a positive g indicated improvement, and a negative g indicated deterioration. This was achieved by multiplying the g by -1 or 1 depending on the direction of pre-post change needed for improvement and whether the Hedges' g was negative of positive before sign correction. The standard error of Hedges' g was calculated using **Equation 10.**

Equation 10 $$\boldsymbol{se = \left(\frac{1}{N_T} + \frac{1}{N_C}\right) + \left(\frac{g(1-(df-2))}{d_i^2\,(df)}\right)}$$

Next, it was necessary to weight the effect sizes. This is important because studies vary in size, and those with a larger sample size often have a more precise estimate of the population effect size. As such, studies with larger sample sizes should carry greater weight than those with smaller samples. The recommended approach to weighting studies is by the inverse of their variance. This approach was used in line with Wilson and Lipsey's (2001) recommendations. As a random effects model was being used, the weights applied to each effect size needed to account for both within trial variance, and between trial variance. **Equation 11** calculated weighted effect sizes accounting for both variances. Where $\boldsymbol{w_i}$ refers to the weight of the effect size, $\boldsymbol{se_i^2}$ refers to the square of the standard error of the effect size and $\boldsymbol{\hat{V}_\theta}$ refers to the between trial variance.

Equation 11 $$\boldsymbol{w_i = \frac{1}{se_i^2 + \hat{V}_\theta}}$$

Five trials compared an active treatment condition with two active control groups. For the purposes of these analyses only one active control arm was used for these trials. Moreover, meta-regression analyses were only conducted on data immediately following the intervention ('post intervention').

2.5.2 Assessing heterogeneity

Heterogeneity was assessed using the two common statistics; $\tau^2$and I^2. The first, τ^2, is an estimate of the variance among true effect sizes. The second, I^2, can be thought of as the percentage of overall heterogeneity that is due to variation of the true effects rather than chance (Higgins, Thompson, Deeks, & Altman, 2003). Higgins and his colleagues suggested that I^2 values of 25%, 50%, and 75% should be regarded as low, moderate and high heterogeneity, respectively (2003).

2.5.3 Data cleaning

All data were examined in the process of sign correction, which provided an opportunity to second check all data entry for human error. Data were also checked by highlighting all ESs above 1.5, to ensure that such a large score was not due to error in the data extraction process such as a decimal point in the wrong place. Finally, I compared the effect sizes calculated in this thesis with those presented in the appendices of Williams et al. (2012). This allowed me to explore whether my calculations were likely to be correct, and whether my adjustments for direction of change had been effective (i.e. that a positive effect size reflected a more effective active treatment condition). I did not find any exceptions that led me to believe that there had been any errors in my calculations. This process was particularly useful for confirming that large effect sizes were not due to error in the statistical method employed here. For example, I calculated the effect size for pain experience from Thieme et al. (2003) to be 1.56. This is similar to the calculation of 1.64 by Williams et al. (2012). It is important to note that we would not expect this number to be identical because I aggregated across multiple measures to calculate effect sizes, whereas Williams and colleagues identified the primary outcome measure to calculate effect sizes.

3 Results

My results are presented in three sections. Firstly, a detailed analysis of the included studies, their participants and the treatments delivered. Secondly, a description of the meta-analytic results without accounting for predictors. Finally, I will present the results of my meta-regression analyses.

3.1 Characteristics of Included Studies

3.1.1 Overview

Key study characteristics are presented in **Table 3.1**. The 64 included studies were published between 1988 and 2016. Studies were conducted across 15 different countries, but most were conducted in the United States (n = 20), the Netherlands (n = 11), or Sweden (n = 6). The type of service where the treatment was delivered was reported in 51 studies. Of these, 24 were conducted in hospitals, 14 were community based, and 13 were in a university setting. Residential interventions were uncommon; with only four trials (Altmaier et al., 1992; Jensen et al., 1997; Thieme et al., 2003; Williams et al., 1996), the remainder investigated outpatient interventions.

3.1.2 Therapist characteristics

I recorded therapist experience as either (i) 'inexperienced', defined as minimal training and experience, (ii) 'experienced', defined as between 1-5 years of experience or a description of comprehensive training provided, and (iii) 'advanced', defined as more than five years of experience, and extensive training. A total of 29% of conditions had no description of therapist experience and could not be classified. Of those that did describe therapist experience, 43% were delivered by experienced therapists, 15% were delivered by inexperienced therapists, and only 12% delivered by therapists with advanced experience. I recognise that these classifications are a crude measure of therapist experience, however, detailed descriptions of therapist experience were rarely reported. These broad classifications enabled me to gain at least a general sense of therapist experience.

Multidisciplinary team (MDT) interventions were relatively common, accounting for nearly half of active treatment and control conditions (48%), the remaining conditions were delivered by one professional (52%). Of the interventions delivered by a MDT, the mean number of professionals in each team was 3 (SD = 1, Range = 2-6). Psychologists delivered most active treatment and control interventions (74%). Although this number may seem high, it

means that a quarter of interventions were delivered by non-psychologists. Physiotherapists frequently delivered interventions (47%), with medical physicians, nurses and occupational therapists delivering 31%, 22%, and 16% of interventions respectively.

3.2 Participant Characteristics

3.2.1 Number of participants

A total of 7,840 participants were included at baseline, with data provided from 6,433 immediately post-treatment. A total number of 3,557 participants were randomised to receive the active treatment. The mean number of participants per trial had reduced from 114 in Williams et al. (2012), to 99 here. Although this is still an increase from the review by Eccleston et al. (2009), which reported a mean of 91 participants per trial.

3.2.2 Attrition

Average attrition rates were relatively low between baseline and immediately following intervention. Across all participants and study conditions the attrition rate was 16%. This was slightly higher for active control conditions than active treatment conditions (21% compared with 19%). The lowest attrition rate was for TAU / WLC conditions (7%). These attrition rates are comparable to other meta-analysis of chronic pain, such as Glombiewski et al., (2010) who reported 21% and 20% for treatment and control group, respectively. More recently, Sielski, Rief, and Glombiewski (2017) reported 17% for both treatment and control groups.

3.2.3 Participant demographics

Demographic data were similar to those presented in the 2012 review. Women usually outnumbered men, with the mean percentage of women per trial being 74% (*SD* = 21, Range = 6-100%). Twelve studies included only women. The mean age of participants was 50 (*SD* = 9). The range of mean ages varied widely between studies (Range = 34-82). Most participants were educated to high school level (including college diplomas; 67%), over a quarter had an undergraduate degree (26%), and few held post graduate qualifications (14%). It is not possible to describe participants' ethnicity as only seven trials reported data on ethnicity.

3.2.4 Pain characteristics

Participants had been living with pain for a median of 9 years (Range = 1-35, based on 34 studies providing data). Most studies investigated specific types of pain (47 out of 64 trials), for example; only recruiting participants with a diagnosis of fibromyalgia or chronic low back

pain. As such, 100% of participants in those studies had the same type of chronic pain diagnosis. The most frequently reported type of pain was fibromyalgia (24% of participants), followed by arthritis and low back pain (24% and 21% respectively). The remaining participants had a variety of less commonly investigated chronic pain diagnoses, such as pain of the legs and feet, lupus, and temporomandibular joint disorder. **Table 3.2** summarises key participant demographic information.

Table 3.1. Study characteristics of included trials.

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Altmaier 1992	United States	Low Back Pain	Active Treatment	Multidisciplinary Group	Group	NR	3
			Treatment as Usual	Multidisciplinary Group	Group	NR	3
Amris 2014	Denmark	Fibromyalgia	Active Treatment	Multidisciplinary Group	Group	35	2
			Waiting List	No Treatment - Control Group	N/A - Control	0	2
Basler 1997	Germany	Low Back Pain	Active Treatment	Cognitive Behavioural Therapy	Group	24	12
			Control Treatment 1	Medication / Medical Visits	Individual	NR	NR
Bennell 2016	Australia	Knee Osteoarthritis	Active Treatment	Coping Skills	Individual	11.66	12
			Control Treatment 1	Coping Skills	Individual	7.5	12
			Control Treatment 2	Physiotherapy / Exercise	Individual	4.1	12
Bliokas 2007	Australia	Low Back Pain	Active Treatment	Multidisciplinary Group	Group	66.5	8
			Control Treatment 1	Multidisciplinary Group	Group	66.5	8
			Waiting List	No Treatment - Control Group	N/A - Control	NR	NR
Broderick 2014	United States	Osteoarthritis	Active Treatment	Coping Skills	Individual	6.25	0
			Treatment as Usual	Unknown – TAU	NR	0	10
Cash 2015	United States	Fibromyalgia	Active Treatment	Mindfulness Programme	Group	20	8
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Castel 2013	Spain	Fibromyalgia	Active Treatment	Multidisciplinary Group	Group	48	12
			Treatment as Usual	Medication / Medical Visits	Individual	0	12
Castro 2012	Brazil	Musculoskeletal Pain	Active Treatment	Cognitive Behavioural Therapy	Group	20	10
			Treatment as Usual	Unknown – TAU	NR	NR	NR
Chavooshi 2016	Iran	Medically Unexplained Pain	Active Treatment	Other	Individual	20	20
			Control Treatment 1	Mindfulness Programme	Group	12	8
			Treatment as Usual	Unknown – TAU	NR	0	0

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Cherkin 2016	United States	Low Back Pain	Active Treatment	Mindfulness Programme	Group	22	8
			Control Treatment 1	Cognitive Behavioural Therapy	Group	16	8
			Treatment as Usual	Unknown – TAU	NR	0	0
Ehrenborg 2010	Sweden	Neck and Shoulder Pain	Active Treatment	Multidisciplinary Group	Group	150	6
			Control Treatment 1	Multidisciplinary Group	Group	150	6
Ersek 2008	United States	Legs / Feet	Active Treatment	Other	Group	10.5	7
			Control Treatment 1	Education	Individual	0	7
Evers 2002	Netherlands	Rheumatoid Arthritis	Active Treatment	Cognitive Behavioural Therapy	Individual	11	24
			Treatment as Usual	Unknown – TAU	NR	NR	NR
Falcao 2008	Brazil	Fibromyalgia	Active Treatment	Cognitive Behavioural Therapy	Group	30	10
			Control Treatment 1	Medication / Medical Visits	Individual	NR	10
Geraets 2005	Netherlands	Shoulder Pain	Active Treatment	Behavioural Intervention	Group	18	12
			Treatment as Usual	Unknown – TAU	NR	NR	NR
Glombiewski 2010b	Germany	Back Pain	Active Treatment	Cognitive Behavioural Therapy	Individual	25	25
			Control Treatment 1	Cognitive Behavioural Therapy	Individual	25	25
			Waiting List	No Treatment - Control Group	N/A - Control	0	NR
Greco 2005	United States	Lupus	Active Treatment	Cognitive Behavioural Therapy	Individual	6	6
			Control Treatment 1	Other	Individual	6	6
			Treatment as Usual	Medication / Medical Visits	Individual	0	0
Haldorsen 1998	Norway	Back Pain	Active Treatment	Cognitive Behavioural Therapy	Group	120	4
			Treatment as Usual	Unknown – TAU	NR	0	0
Hammond 2001	United Kingdom	Rheumatoid Arthritis	Active Treatment	Cognitive Behavioural Therapy	Group	8	4
			Control Treatment 1	Education	Group	8	4

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Heutink 2012	Netherlands	Spinal Cord Injury	Active Treatment	Multidisciplinary Group	Group	30	10
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Jensen 2001	Sweden	Back Pain	Active Treatment	Multidisciplinary Group	Group	136	4
			Control Treatment 1	Cognitive Behavioural Therapy	Group	56	4
			Control Treatment 2	Physiotherapy / Exercise	Group	80	4
			Control Treatment 3	Unknown – TAU	NR	0	0
Jensen 1997	Sweden	Back Pain	Active Treatment	Multidisciplinary Group	Group	200	5
			Control Treatment 1	Multidisciplinary Group	Group	200	5
Kaapa 2006	Finland	Low Back Pain	Active Treatment	Multidisciplinary Group	Group	70	8
			Control Treatment 1	Physiotherapy / Exercise	Individual	10	8
Khan 2014	Pakistan	Low Back Pain	Active Treatment	Multidisciplinary Group	Group	36	12
			Control Treatment 1	Physiotherapy / Exercise	Group	36	12
Karlsson 2015	Sweden	Fibromyalgia	Active Treatment	Cognitive Behavioural Therapy	Group	69	24
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Keefe 1990	United States	Knee Osteoarthritis	Active Treatment	Coping Skills	Group	15	10
			Control Treatment 1	Education	Group	15	10
			Treatment as Usual	Unknown – TAU	NR	0	0
Keefe 1996	United States	Knee Osteoarthritis	Active Treatment	Coping Skills	Group	20	10
			Control Treatment 1	Coping Skills	Group	20	10
			Control Treatment 2	Education	Group	20	10
Kemani 2015	Sweden	Idiopathic Pain	Active Treatment	Acceptance and Commitment Therapy	Group	18	12
			Control Treatment 1	Relaxation	Group	18	12
Kerns 2014	United States	Low Back Pain	Active Treatment	Cognitive Behavioural Therapy	Individual	10	10
			Control Treatment 1	Cognitive Behavioural Therapy	Individual	10	10

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Kraaimaat 1996	Netherlands	Rheumatoid Arthritis	Active Treatment	Cognitive Behavioural Therapy	Group	20	10
			Control Treatment 1	Other	Group	20	10
Leeuw 2008	Netherlands	Low Back Pain	Active Treatment	Behavioural Intervention	Group	16	8
			Control Treatment 1	Behavioural Intervention	Group	26	13
Litt 2009	United States	Temporomandibular Joint Disorder	Active Treatment	Cognitive Behavioural Therapy	Group	NR	6
			Treatment as Usual	Other	Group	NR	6
Luciano 2014	Spain	Fibromyalgia	Active Treatment	Acceptance and Commitment Therapy	Group	20	NR
			Control Treatment 1	Medication / Medical Visits	Individual	0	0
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Martin 2012	Spain	Fibromyalgia	Active Treatment	Multidisciplinary Group	Group	21	6
			Control Treatment 1	Medication / Medical Visits	Individual	0	0
McCarberg 1999	United States	Low Back Pain	Active Treatment	Cognitive Behavioural Therapy	Group	16	8
			Control Treatment 1	Other	NR	0	0
McCracken 2013	United Kingdom	Fibromyalgia	Active Treatment	Acceptance and Commitment Therapy	Group	16	2
			Treatment as Usual	Unknown – TAU	NR	0	0
Mishra 2000	United States	Temporomandibular Joint Disorder	Active Treatment	Cognitive Behavioural Therapy	Group	24	8
			Control Treatment 1	Cognitive Behavioural Therapy	Group	18	8
			Control Treatment 2	Other	Group	18	8
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Monticone 2012	Italy	Neck Pain	Active Treatment	Multidisciplinary Group	Individual	10	12
			Control Treatment 1	Physiotherapy / Exercise	Individual	10	12
Monticone 2013	Italy	Low Back Pain	Active Treatment	Multidisciplinary Group	Individual	17	57
			Control Treatment 1	Physiotherapy / Exercise	Individual	10	57

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Nicassio 1997	United States	Fibromyalgia	Active Treatment	Behavioural Intervention	Group	15	10
			Control Treatment 1	Education	Group	15	10
Nicholas 2013	Australia	Multiple Sites	Active Treatment	Multidisciplinary Group	Group	16	4
			Control Treatment 1	Other	Group	16	4
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Nicholas 2014	Australia	Multiple Sites	Active Treatment	Cognitive Behavioural Therapy	Group	120	5
			Control Treatment 1	Cognitive Behavioural Therapy	Group	120	5
Poleshuck 2014	United States	Pelvic Pain	Active Treatment	Other	Individual	8	36
			Control Treatment 1	Other	Individual	0	36
Puder 1988	United States	Musculoskeletal Pain	Active Treatment	Cognitive Behavioural Therapy	Group	20	10
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Scheidt 2013	Germany	Fibromyalgia	Active Treatment	Other	Individual	25	25
			Treatment as Usual	Unknown – TAU	Individual	1	24
Schmidt 2011	Netherlands	Fibromyalgia	Active Treatment	Mindfulness Programme	Group	27	8
			Control Treatment 1	Other	Group	20	8
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Sharpe 2012	Australia	Rheumatoid Arthritis	Active Treatment	Cognitive Behavioural Therapy	Individual	8	8
			Control Treatment 1	Other	Individual	8	8
			Control Treatment 2	Behavioural Intervention	Individual	8	8
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Siemonsma 2013	Netherlands	Low Back Pain	Active Treatment	Cognitive Behavioural Therapy	Group	14	14
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Sleptsova 2013	Switzerland	Medically Unexplained Pain	Active Treatment	Cognitive Behavioural Therapy	Group	37.5	24
			Control Treatment 1	Physiotherapy / Exercise	Group	37.5	24

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Smeets 2006	Netherlands	Low Back Pain	Active Treatment	Multidisciplinary Group	Group	78	10
			Control Treatment 2	Physiotherapy / Exercise	Group	52.5	10
			Control Treatment 1	Behavioural Intervention	Group	23.5	10
Somers 2012	United States	Osteoarthritis	Active Treatment	Coping Skills	Group	40.5	24
			Control Treatment 1	Coping Skills	Group	18	24
			Control Treatment 2	Other	Group	22.5	24
			Treatment as Usual	Unknown – TAU	NR	NR	NR
Tavafian 2011	Iran	Low Back Pain	Active Treatment	Multidisciplinary Group	Group	10	24
			Control Treatment 1	Medication / Medical Visits	Individual	NR	NR
Thieme 2003	Germany	Fibromyalgia	Active Treatment	Behavioural Intervention	Group	75	5
			Control Treatment 1	Physiotherapy / Exercise	Group	75	5
Thorsell 2011	Sweden	NR	Active Treatment	Acceptance and Commitment Therapy	Individual	6.5	7
			Control Treatment 1	Relaxation	Individual	6.5	7
Turner 2006	United States	Temporomandibular Joint Disorder	Active Treatment	Cognitive Behavioural Therapy	Individual	NR	8
			Control Treatment 1	Other	Individual	NR	8
Turner 1988	United States	Low Back Pain	Active Treatment	Cognitive Behavioural Therapy	Group	16	8
			Control Treatment 1	Behavioural Intervention	Group	16	8
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Van Koulil 2010	Netherlands	Fibromyalgia	Active Treatment	Cognitive Behavioural Therapy	Group	64	10
			Active Treatment	Cognitive Behavioural Therapy	Group	64	10
			Waiting List	Other	N/A - Control	0	0
			Waiting List	Other	N/A - Control	0	0
Van Der Maas 2015	Netherlands	Neck Pain	Active Treatment	Multidisciplinary Group	Group	112	24
			Control Treatment 1	Multidisciplinary Group	Group	97	24

First Author & Date	Country	Primary Type of Pain	Trial Arm	Type of Treatment	Intervention Format	Dose (hours)	Duration (weeks)
Vlaeyen 1996	Netherlands	Fibromyalgia	Active Treatment	Cognitive Behavioural Therapy	Group	42	6
			Control Treatment 1	Education	Group	24	6
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Wetherell 2011	United States	Osteoarthritis	Active Treatment	Acceptance and Commitment Therapy	Group	12	8
			Control Treatment 1	Cognitive Behavioural Therapy	Group	12	8
Williams 1996	United Kingdom	Multiple Sites	Active Treatment	Cognitive Behavioural Therapy	Group	148	4
			Control Treatment 1	Cognitive Behavioural Therapy	Group	28	8
			Waiting List	No Treatment - Control Group	N/A - Control	0	0
Zangi 2012	Norway	Rheumatoid Arthritis	Active Treatment	Mindfulness Programme	Group	45	24
			Treatment as Usual	Other	N/A - Control	NR	NR
Zautra 2008	United States	Rheumatoid Arthritis	Active Treatment	Cognitive Behavioural Therapy	Group	16	8
			Control Treatment 1	Mindfulness Programme	Group	16	8
			Control Treatment 2	Education	Group	16	8

N/A = Not applicable; NR = Not reported; TAU = Treatment as usual.

Table 3.2. Participant characteristics summarised by treatment condition.

	No. of Studies Providing Data*	Active Treatment			Active Control			TAU / WLC		
		Mean	Range	SD	Mean	Range	SD	Mean	Range	SD
Age	51	49.9	34.2-81.9	8.8	50.7	35.6-81.8	9.0	51.1	35.2-75.0	8.3
Female (%)	53	77.0	12.0-100	20.6	72.1	5.5-100	19.4	77.3	29.0-100	18.6
Married (%)	32	69.7	17.3-100	19.3	68.6	8.0-100	20.2	68.2	11.5-91.7	17.6
High School Educated (%)	35	67.3	18.0-100	23.3	64.1	7.0-100	26.5	69.9	12.0-100	28.6
Employed (%)	34	48.6	9.1-100	28.0	53.3	5.0-100	31.0	41.4	3.0-100	26.2
Unemployed (%)	18	26.9	0-90.9	30.2	22.8	0-94.10	27.7	29.5	0-93.4	35.1
Social Benefits (%)**	26	18.3	0-98.0	20.7	13.2	0-65	15.9	25.7	0-79.0	19.4
Pain Duration (Years)	34	9.8	1.3-34.5	7.1	8.6	1.1-33.9	6.4	12.4	3.5-32.8	7.0

*Number of studies providing data for each arm of the trial out of 64.

**Percentage of participants on social benefits or a disability pension.

TAU = Treatment as Usual; WLC = Wait List Control.

3.3 Treatment Characteristics

3.3.1 Overview of treatment and control conditions

Of the 64 included studies, 43 had two conditions, 16 had three conditions, and five had four conditions. Most studies had at least one active control condition (n = 46). TAU and/or WLC conditions were used in 34 trials. In total, there were 152 arms across the 64 trials.

Manualisation

Active treatment and active control conditions were reported as being manualised in 62% of conditions. However, less than half of these reported measuring treatment fidelity in relation to the manual, such as listening to recordings of treatment sessions (42%).

Treatment format (group vs. individual)

Nearly two thirds of active conditions were group interventions (64%). Individual interventions were reported in 27% of active conditions. Treatment delivery was not specified for 9% conditions. These were typically 'treatment as usual' conditions, so a reasonable assumption is that they were individual interventions. Mean group size was only reported for 30% of group interventions. The mean number of participants per group for those reporting data was 10 (SD = 5, Range = 5-19). The mean range of group sizes was reported more frequently (55% of arms), the mean range was 5 – 9 participants per group.

3.3.2 Types of treatment delivered

A wide range of treatments were delivered across the active conditions. I initially extracted treatment names verbatim. This resulted in 106 different treatment types. This number was high because there were often slight variations in descriptions of what appeared to be similar interventions. For example, CBT was labelled in 10 different ways across 20 studies, such as: CBT + Pain Avoidance, CBT + Distraction, CBT + Treatment as Usual. To enable a useful exploration of these data, I categorised these treatments into one of 13 treatment types. To continue with the example of CBT above, I categorised each of those labels as 'CBT'. **Figure 3.1** shows the frequency of each treatment type across active conditions. The most commonly used treatment was described as CBT (27%), followed by multidisciplinary groups (17%), and physiotherapy / exercise based interventions (8%) that were used as active control interventions. A total of 14% of trial arms were classified as 'other' because they were reported infrequently and could not be classified into a broader category, such as Intensive Short-Term

Dynamic Psychotherapy (ISTDP), which was present in one study (Chavooshi et al., 2016). The 'other' category also includes treatment as usual conditions that could not be classified into a particular treatment type due to lack of specific reporting.

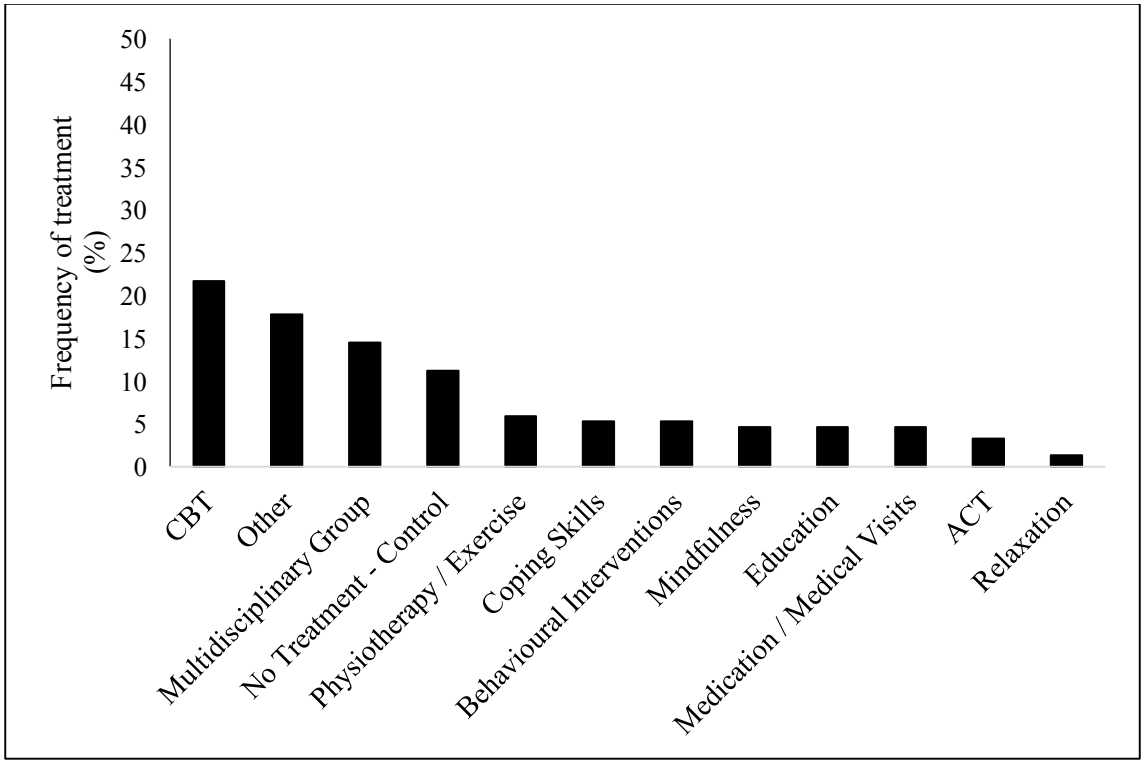

Figure 3.1. Frequency of each treatment type across active conditions.

3.4 Treatment Components

3.4.1 Overview of treatment components used

Figure 3.2 shows the total frequency with which each treatment component was used. Homework and psychoeducation were the most frequently used components, both being described in 45% of conditions. Relapse prevention and mindfulness were the least frequently used interventions (16% and 12% of conditions, respectively).

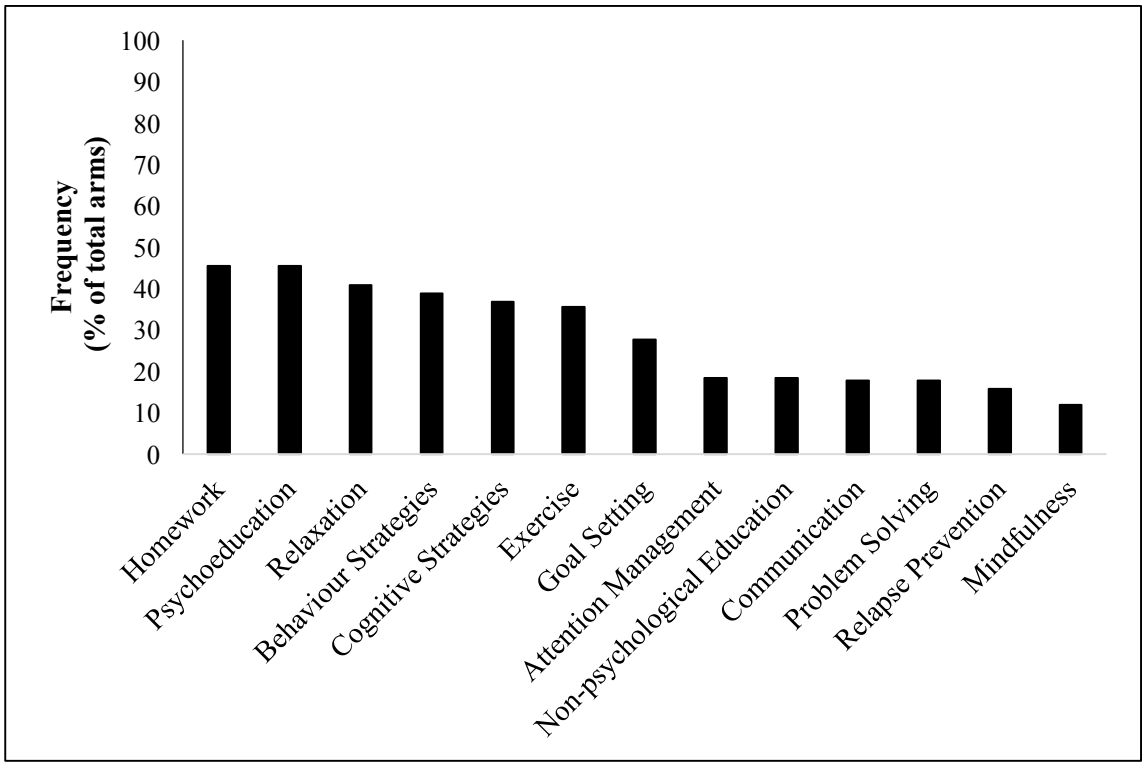

Figure 3.2. Frequency of each treatment component across all active conditions.

3.4.2 Breakdown of components by treatment and control conditions

When looking at the treatment components delivered across different conditions, more components were delivered in active treatment conditions (M = 6, SD = 2, Range = 0-11) than active control conditions (M = 3, SD = 2, Range = 1-6). This difference is interesting because one might expect that active control conditions would have been comparable to active treatment conditions.

Treatment as usual conditions rarely reported what treatment was delivered. When treatment was described, only four treatment components (out of the total of 13 components) were described at all. They were: homework, psychoeducation, exercise and non-psychological education. As expected, no treatment components were described for those allocated to the wait list control trial condition.

3.4.3 Breakdown of components used by 'treatment type'

When exploring treatment components as a factor of different treatment types, two findings emerged that illustrate the complexity of the interventions and the degree of individual variation between trials: (1) different interventions often used similar treatment components, and (2) similar treatments used different components. I have attempted to demonstrate both findings below. Firstly, **Figure 3.3** displays how often homework (the most frequently reported component) was used by different treatments. It highlights that only two treatments were consistent in the way that they described using homework; relaxation and medication / medical

visits. There was no such consistency across other treatments. For example, while two thirds of the active conditions that stated they were using CBT included homework (67%), this means a third of trials using CBT did *not* include homework (or, importantly, failed to report that they included it). A further observation to make of **Figure 3.3** is that there are striking similarities between different treatments in the proportions of trials using homework. As an example, 71% of mindfulness programmes reported including homework, which is similar to the 67% of CBT trials. Furthermore, we might expect homework to be included in 100% of both mindfulness and CBT trials.

Secondly, **Table 3.3** presents a checklist of whether each treatment component was present across all active treatments. This table highlights that while there are some components that are consistently used in treatments, such as the use of cognitive strategies in all ACT trials, there is notable variation in others, for example, not all ACT trials included a relapse prevention component.

Taken together, this suggests that broad treatment type labels may be of little utility in attempting to understand what treatment components were included in the treatment protocol.

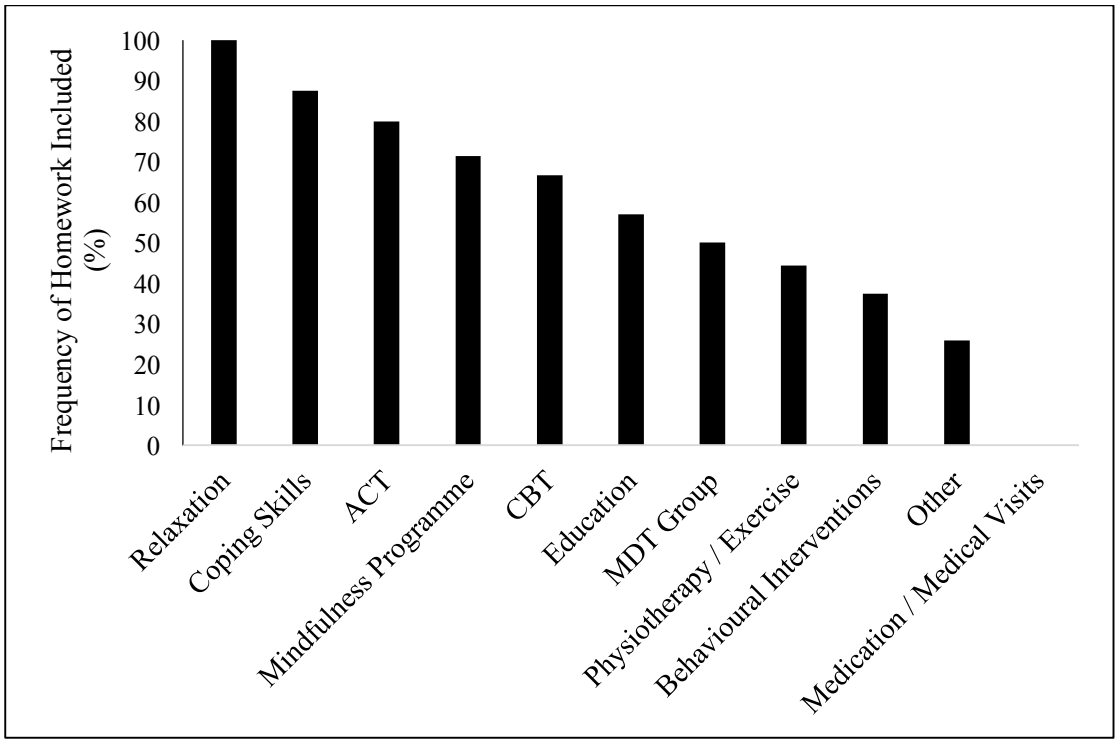

Figure 3.3. Frequency of homework used as a component of each treatment type.

Table 3.3. Checklist of included components for each active treatment across all included trials.

First Author	Treatment Type	Attention Management	Behaviour Strategies	Cognitive Strategies	Communication	Psychoeducation	Non-Psychological Education	Exercise	Goal Setting	Homework	Mindfulness	Problem Solving	Relapse Prevent	Relaxation
Kemani	ACT	✗	✓	✓	✗	✓	✗	✗	✗	✓	✗	✗	✓	✗
Luciano	ACT	✗	✓	✓	✗	✓	✗	✗	✗	✓	✓	✗	✗	✓
McCracken	ACT	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Thorsell	ACT	✗	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗
Geraets	Behavioural	✗	✓	✗	✗	✗	✗	✓	✓	✗	✗	✗	✗	✗
Leeuw	Behavioural	✗	✓	✗	✗	✓	✗	✗	✓	✗	✗	✗	✗	✗
Nicassio	Behavioural	✗	✓	✗	✗	✓	✗	✗	✓	✗	✗	✗	✗	✓
Thieme	Behavioural	✗	✓	✗	✗	✓	✗	✗	✗	✓	✗	✗	✗	✗
Basler	CBT	✓	✓	✓	✓	✗	✓	✗	✓	✗	✓	✗	✗	✗
Castro	CBT	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✗	✓
Evers	CBT	✗	✓	✓	✗	✗	✗	✗	✓	✓	✗	✓	✓	✗
Falcao	CBT	✗	✗	✓	✗	✓	✗	✗	✗	✓	✗	✗	✗	✓
Glombiewski	CBT	✓	✓	✓	✗	✓	✗	✗	✓	✓	✗	✗	✓	✓
Greco	CBT	✗	✗	✓	✓	✗	✗	✗	✗	✓	✗	✓	✗	✓
Haldorsen	CBT	✗	✗	✗	✗	✓	✗	✓	✗	✗	✓	✗	✗	✓
Hammond	CBT	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	✓	✗	✗
Karlsson	CBT	✗	✓	✓	✓	✓	✗	✗	✗	✓	✓	✓	✗	✓
Kerns	CBT	✗	✓	✓	✓	✓	✗	✓	✗	✗	✗	✗	✓	✓
Kraaimaat	CBT	✓	✓	✓	✗	✗	✓	✗	✓	✓	✗	✗	✗	✓
Litt	CBT	✗	✗	✓	✗	✓	✗	✗	✗	✓	✗	✗	✗	✓
McCarberg	CBT	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✗
Mishra	CBT	✓	✓	✓	✓	✓	✗	✗	✗	✓	✗	✗	✓	✓

First Author	Treatment Type	Attention Management	Behaviour Strategies	Cognitive Strategies	Communication	Psychoeducation	Non-Psychological Education	Exercise	Goal Setting	Homework	Mindfulness	Problem Solving	Relapse Prevent	Relaxation
Nicholas 2014	CBT	✗	✓	✓	✗	✓	✗	✗	✓	✓	✗	✗	✗	✗
Puder	CBT	✓	✗	✓	✗	✓	✗	✗	✗	✓	✗	✗	✗	✓
Sharpe	CBT	✓	✗	✓	✓	✓	✗	✗	✓	✗	✗	✓	✗	✓
Siemonsma	CBT	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Sleptsova	CBT	✗	✗	✗	✗	✓	✗	✓	✗	✗	✗	✗	✗	✗
Turner	CBT	✗	✗	✓	✗	✓	✗	✓	✓	✓	✗	✗	✓	✓
Van Koulil	CBT	✗	✓	✗	✗	✗	✗	✓	✓	✓	✗	✗	✓	✓
Vlaeyen	CBT	✓	✓	✗	✗	✓	✓	✓	✓	✓	✗	✗	✗	✗
Wetherell	CBT	✗	✓	✓	✗	✗	✗	✗	✓	✓	✓	✗	✗	✗
Williams	CBT	✗	✓	✓	✗	✓	✓	✓	✓	✗	✗	✓	✓	✓
Zautra	CBT	✗	✓	✓	✗	✓	✗	✗	✗	✓	✗	✓	✓	✓
Bennell	Coping Skills	✓	✓	✓	✗	✓	✗	✓	✗	✓	✗	✓	✗	✗
Broderick	Coping Skills	✓	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✓
Keefe 1990	Coping Skills	✓	✓	✓	✗	✓	✗	✗	✗	✓	✗	✗	✗	✓
Keefe 1996	Coping Skills	✓	✓	✓	✓	✗	✓	✗	✓	✓	✗	✗	✗	✓
Somers	Coping Skills	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗	✗	✓	✓
Altmaier	MDT Group	✗	✓	✓	✗	✓	✗	✓	✗	✓	✗	✗	✗	✓
Amris	MDT Group	✗	✓	✗	✓	✓	✗	✓	✗	✗	✗	✗	✗	✓
Bliokas	MDT Group	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✓
Castel	MDT Group	✗	✓	✓	✓	✓	✗	✓	✓	✓	✗	✗	✓	✓
Ehrenborg	MDT Group	✗	✗	✗	✗	✓	✗	✓	✗	✗	✓	✗	✗	✓
Heutink	MDT Group	✗	✗	✗	✓	✓	✗	✗	✓	✗	✗	✗	✗	✓
Jensen 2001	MDT Group	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓
Jensen 1997	MDT Group	✗	✗	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗	✓

First Author	Treatment Type	Attention Management	Behaviour Strategies	Cognitive Strategies	Communication	Psychoeducation	Non-Psychological Education	Exercise	Goal Setting	Homework	Mindfulness	Problem Solving	Relapse Prevent	Relaxation
Khan	MDT Group	✗	✓	✓	✗	✗	✗	✓	✗	✓	✗	✓	✗	✗
Martin	MDT Group	✗	✓	✓	✓	✓	✗	✓	✗	✓	✗	✗	✗	✓
Monticone	MDT Group	✓	✓	✓	✗	✓	✗	✓	✗	✓	✗	✗	✗	✗
Monticone	MDT Group	✓	✓	✓	✗	✓	✗	✓	✗	✗	✗	✗	✗	✗
Nicholas 2013	MDT Group	✗	✓	✓	✓	✓	✗	✓	✓	✓	✗	✓	✓	✗
Smeets	MDT Group	✗	✓	✗	✗	✓	✗	✓	✓	✓	✗	✓	✗	✗
Tavafian	MDT Group	✗	✓	✓	✗	✓	✓	✓	✗	✗	✗	✗	✗	✓
VanDerMaas	MDT Group	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✗	✓
Cash	Mindfulness	✓	✗	✗	✗	✗	✗	✓	✗	✓	✓	✗	✗	✗
Chavooshi	Mindfulness	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Cherkin	Mindfulness	✗	✗	✗	✗	✗	✗	✓	✗	✓	✓	✗	✗	✗
Schmidt	Mindfulness	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	✗
Zangi	Mindfulness	✓	✗	✓	✗	✗	✗	✗	✗	✓	✓	✗	✗	✓
Ersek	Other	✗	✓	✓	✗	✓	✓	✓	✓	✓	✗	✗	✓	✓
Poleshuck	Other	✗	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✓
Scheidt	Other	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Turner	Other	✗	✗	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✓

3.5 Overview of Treatment Dose

There was considerable variability in the number of hours delivered. Of a total of 152 treatment and control conditions, 139 provided information on dose measured in hours. The median number of hours was 16 (Range = 0-200). The lower range of 0 is explained by some control conditions being interventions such as 'standard pharmacologic treatments'.. In total, 29% of conditions were 25 hours or longer. The longest interventions on average were active treatments, with a median of 20 hours (Range 6-200). Active control conditions were shorter than treatment conditions (*Median* = 18, Range = 0-200). With the exception of one trial, data about dose was not reported for TAU conditions. Scheidt et al. (2013) reported that TAU was approximately one hour of consultation with participants' primary physician (spread over four consultations).

Variability was also substantial in terms of the number of weeks over which treatment was delivered. In total, 144 conditions reported their duration in weeks (out of a possible 152). The median number of weeks was 8 (Range = 0-36). Again, active treatments were the longest (*Median* = 8, Range = 2-36), but active control conditions were comparable in terms of length (*Median* = 8, Range = 0-36). TAU conditions were shorter (*Median* = 0, Range = 0-24).

The large range of treatment dose variation in both hours and timescale for delivery lends further support for the use of meta-regression as a tool to investigate dose as a predictor of change.

3.6 Meta-Analyses

I completed two meta-analyses; comparing active treatment with active control, and comparing active treatment with TAU / WLC. Neither analyses included any additional moderators. This section will provide an overview of the findings from this analysis, broken down by outcome domain. **Table 3.4** shows the number of studies and number of participants included in analyses for each outcome domain. See **Appendix B** and **Appendix C** for comprehensive results tables of meta-analysis results by outcome domain.

Table 3.4. Number of studies and participants included in each comparison for each outcome domain.

	Active treatment vs. active control		Active treatment vs. TAU / WLC	
Outcome Domain	**Number of Studies**	**Number of Participants**	**Number of Studies**	**Number of Participants**
Pain Experience	38	1712	28	1398
Pain Behaviour	12	608	5	197
Emotional Functioning	35	1611	25	1234
Physical Functioning	38	1701	28	1402
Coping & Cognitive Appraisal	24	1073	17	127

3.6.1 Active treatment compared with active control

The forest plot shown in **Figure 3.4** summarises the effect sizes (Hedges' *g*) for the difference between active treatment and active control conditions, along with 95% CIs. Outcomes favoured the active treatment condition, with small to moderate effects. The largest effect was for the coping and cognitive appraisal outcome domain, however; large confidence intervals suggest caution is needed in interpreting this result.

The difference between the active treatment and active control conditions was not statistically significant for pain experience (Hedges' $g = 0.31$, $p = 0.057$, *ns*) nor coping and cognitive appraisal (Hedges' $g = 0.58$, $p = 0.11$, *ns*). Effect sizes were statistically significant for pain behaviour (Hedges' $g = 0.28$, $p < 0.05$), emotional functioning (Hedges' $g = 0.27$, $p < 0.05$), and physical functioning (Hedges' $g = 0.31$, $p < 0.05$). Heterogeneity was high for analyses across all outcome domains (Mean $I^2 = 99.36\%$, Range = 98.04 – 100%).

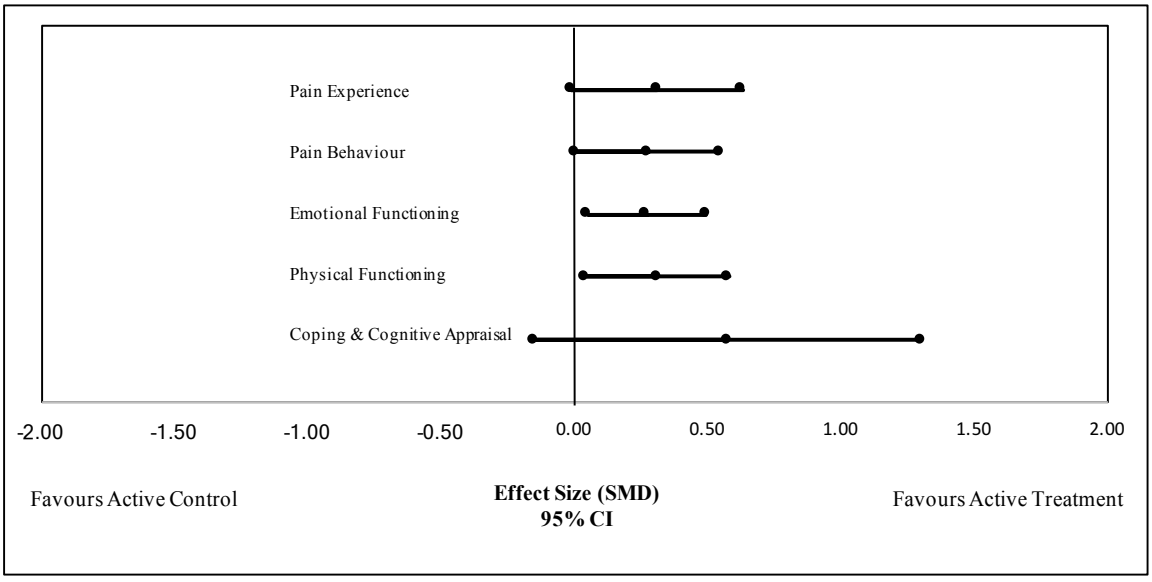

Figure 3.4. Forest plot of effect sizes (Hedges' *g*) for active treatment vs. active control conditions.

3.6.2 Active treatment compared with TAU / WLC

The forest plot shown in **Figure 3.5** summarises Hedges' *g* effect sizes for the difference between active treatment and TAU / WLC conditions, along with 95% CIs. Outcomes were again more favourable for the active treatment condition than the control condition, with similar effect sizes as when active treatment was compared with active control: small to moderate.

The difference between active treatment and TAU / WLC conditions was not statistically significant for pain experience (Hedges' $g = 0.39$, $p = 0.062$, *ns*). However, effect sizes were statistically significant for pain behaviour (Hedges' $g = 0.36$, $p < 0.05$), emotional functioning (Hedges' $g = 0.24$, $p < 0.01$), physical functioning (Hedges' $g = 0.12$, $p < 0.05$), and coping and cognitive appraisal (Hedges' $g = 0.38$, $p < 0.001$). Heterogeneity was high again for all analyses across all outcome domains (Mean $I^2 = 98.55\%$, Range 96.57% - 99.94%).

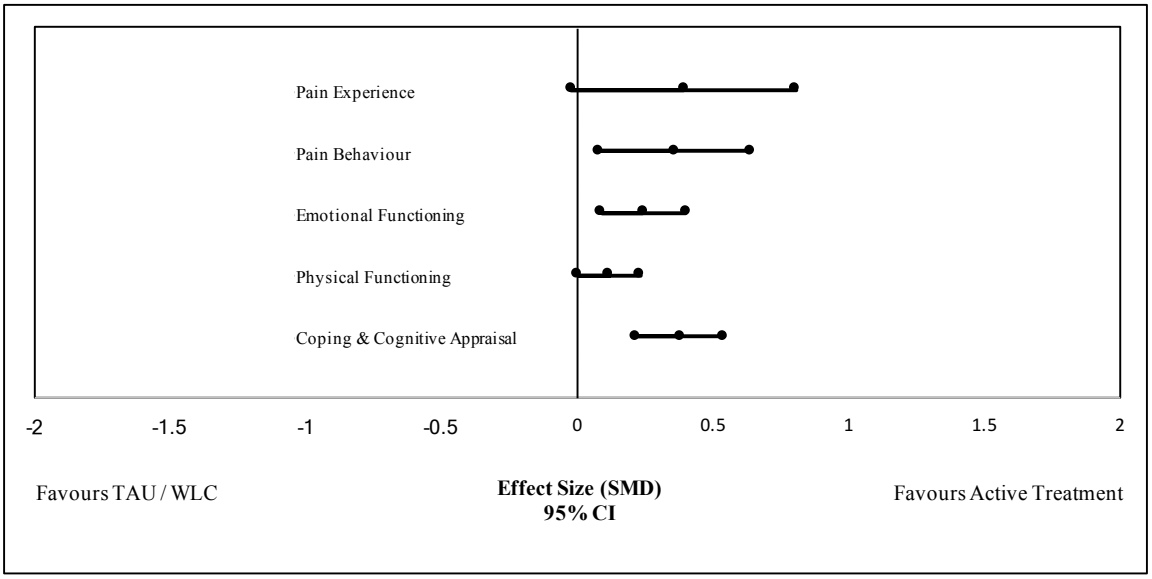

Figure 3.5. Forest plot of effect sizes (Hedges' *g*) for active treatment vs. TAU / WLC control conditions.

3.6.3 Publication bias

The fail-safe *N* was 9,637 for active treatment compared with active controls, and 9,197 for active treatment compared with TAU/WLC. These fail-safe *N* values are high, and suggest that the potential impact of publication bias is likely to be minimal on the results presented here.

3.7 Meta-regression Analyses: The 'Dose-Response' Question

In this section I will describe the findings of meta-regression analyses using dose in hours, followed by dose in weeks as predictors. I present summary data in tables, and graphical displays for statistically significant relationships.

3.7.1 Dose in hours and response

Active treatment compared with active control

When comparing active treatment with active control conditions, magnitude of change did not vary significantly by dose in hours across any outcome domain. **Table 3.5** presents the regression coefficients across all outcome domains for dose in hours as a predictor. Thus, the coefficient represents the interaction between the effect and dose in hours. A negative coefficient indicates that treatment is less effective as the level of the predictor decreases. Recall that the conventional 0.05 level of significance can be relaxed to 0.2 for the purposes of generating hypotheses. Despite this adjustment, there were no statistically significant relationships.

Active treatment compared with TAU / WLC

Similarly, when comparing active treatment with TAU / WLC, magnitude of change did not vary significantly by dose in hours across any outcome domain. **Table 3.6** presents the regression coefficients across all outcome domains for dose in hours as a predictor.

3.7.2 Timescale of intervention (dose in weeks) and response

Active treatment compared with active control

When comparing active treatment with active control conditions, magnitude of change did not vary significantly by dose in weeks across any outcome domain. **Table 3.7** presents the regression coefficients across all outcome domains for dose in weeks as a predictor.

Active treatment compared with TAU / WLC

In contrast, dose in weeks was significantly associated with increased effect sizes (Hedges' g) for pain experience ($\beta = 0.04$, $p < 0.2$), and coping and cognitive appraisal ($\beta = 0.01$, $p < 0.2$) when active treatments were compared with TAU / WLC. This means that for every additional week over which treatment was delivered, there was an estimated increase in effect size of 0.04 and 0.01 for pain experience and coping and cognitive appraisal, respectively. **Figure 3.6** and **Figure 3.7** display this finding, where each circle represents a trial and the area of each circle is the weight given to that trial (based on the inverse of its variance). The close clustering of trials around the line for pain experience suggests that we can be confident in the assertion that pain dose in weeks is associated with pain experience. In contrast, the dispersion of trials away from the line for coping and cognitive appraisal suggests that more caution is required when interpreting the association between dose in weeks and effect size for this domain. For other outcome domains, effect size did not vary significantly by dose in weeks. **Table 3.8** presents the regression coefficients across all outcome domains for dose in weeks as a predictor.

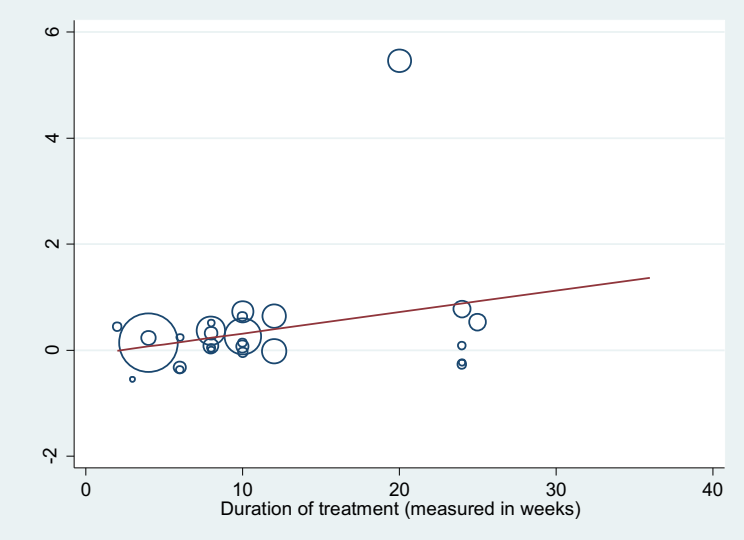

Figure 3.6. Dose in weeks and Hedges' *g* for pain experience – Active treatment vs. TAU / WLC.

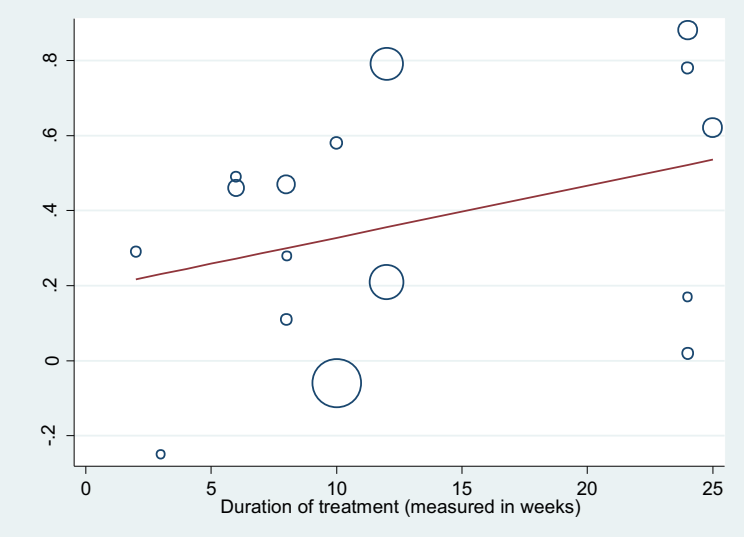

Figure 3.7. Dose in weeks and Hedges' *g* for coping and cognitive appraisal – Active treatment vs. TAU / WLC.

3.7.3 Interim comment on the 'dose-response' question

In sum, there is limited evidence of a clear linear relationship between dose and magnitude of change. Dose in hours was not significantly associated with increasing effect sizes for any outcome domains. This was true when active treatments were compared with active controls, and when they were compared with TAU / WLC control groups. The only significant association found was for coping and cognitive appraisal, and pain experience when active treatment was compared with TAU / WLC. For these two outcome domains, treatments lasting for more weeks were related to greater change.

Heterogeneity was high across all analyses, suggesting that there is variability between studies that is not related to chance. I completed meta-regression analyses for three participant

demographic predictors to explore whether they were associated with magnitude of change. The three predictors chosen were: percentage of females, age of participants, and duration of pain (in years). I chose these because they have all been subject to analyses in previous analyses of psychological interventions for chronic pain. Although there were a number of further participant demographic predictors that I could have used as well, I restricted my analyses to these three predictors to avoid data mining.

Table 3.5. Dose in hours: regression coefficients by outcome domain – active treatment compared with active control.

Active treatment vs. active control									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	37	1636	-0.002	0.004	0.56	-0.011	0.006	99.83%	0.991
Pain Behaviour	12	608	0.004	0.004	0.27	-0.004	0.013	98.20%	0.170
Emotional Functioning	34	1535	-0.002	0.003	0.47	-0.007	0.003	99.39%	0.430
Physical Functioning	37	1625	-0.003	0.003	0.39	-0.009	0.003	99.58%	0.688
Coping & Cognitive Appraisal	23	997	-0.003	0.009	0.69	-0.021	0.014	99.99%	3.181

β = regression coefficient

Table 3.6. Dose in hours: regression coefficients by outcome domain – active treatment compared with TAU / WLC.

Active treatment vs. TAU / WLC									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	26	1355	-0.004	0.007	0.56	-0.018	0.010	99.94%	1.222
Pain Behaviour	5	197	0.010	0.008	0.29	-0.015	0.036	96.14%	0.040
Emotional Functioning	23	1191	-0.001	0.002	0.79	-0.006	0.004	99.26%	0.151
Physical Functioning	26	1359	0.000	0.002	0.87	-0.004	0.003	98.19%	0.077
Coping & Cognitive Appraisal	16	753	0.003	0.004	0.47	-0.005	0.011	97.64%	0.080

β = regression coefficient

Table 3.7. Dose in weeks: regression coefficients by outcome domain – active treatment compared with active control.

Active treatment vs. active control									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	37	1660	0.019	0.025	0.44	-0.031	0.069	99.82%	0.979
Pain Behaviour	12	608	-0.001	0.019	0.96	-0.044	0.042	98.21%	0.194
Emotional Functioning	34	1559	-0.004	0.016	0.79	-0.036	0.028	99.37%	0.433
Physical Functioning	37	1649	-0.002	0.020	0.94	-0.042	0.039	99.58%	0.702
Coping & Cognitive Appraisal	23	1021	0.018	0.064	0.79	-0.115	0.150	100.00%	3.206

β = regression coefficient

Table 3.8. Dose in weeks: regression coefficients by outcome domain – active treatment compared with TAU / WLC.

Active treatment vs. TAU / WLC									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	27	1345	0.041	0.029	0.17	-0.019	0.100	99.93%	1.115
Pain Behaviour	5	197	-0.014	0.012	0.32	-0.050	0.023	93.68%	0.042
Emotional Functioning	24	1181	0.001	0.008	0.93	-0.016	0.018	98.62%	0.095
Physical Functioning	27	1349	0.006	0.008	0.45	-0.010	0.023	97.78%	0.088
Coping & Cognitive Appraisal	16	721	0.014	0.010	0.18	-0.007	0.035	98.81%	0.095

β = regression coefficient

3.8 Meta-regression Analyses: Patient Characteristics

In this section I will describe the findings of meta-regression analyses using participant characteristics as predictors. As discussed in my introduction, there are a number of characteristics that could have been explored. I chose to analyse three characteristics to limit the possibility of spurious results due to multiple analyses. Age and gender were chosen because they have been analysed in previous trials with mixed results (Waterschoot et al., 2014; Hoffman et al., 2007; Glombiewski et al., 2010). I chose pain duration because it has been highlighted as a characteristic that merits investigation but there has been insufficient data to enable this until now (Waterschoot et al., 2014; Hoffman et al., 2007). Again, I present all summary data in tables, and graphical displays for statistically significant relationships.

3.8.1 Percentage of females

Active treatment compared with active control

When comparing active treatment with active control conditions, magnitude of change did not vary significantly by percentage of females across any outcome domain. It appears that percentage of females was approaching significance for pain behaviour ($\beta = 0.006$, $p = 0.2$, *ns*). This relationship is displayed in **Figure 3.8**. The relatively small number of studies included in this analyses may be a reason why this did not reach statistical significance. **Table 3.9** presents the regression coefficients across all outcome domains for percentage of females as a predictor.

Active treatment compared with TAU / WLC

Interestingly, the percentage of females was less associated with magnitude of change for pain behaviour when active treatment was compared with TAU / WLC ($\beta = 0.01$, $p = 0.43$, *ns*), although it may be important to note that only four studies provided data that were analysable here, in contrast to 10 studies that provided data on active treatment and active control for pain behaviour. There were also no significant associations between percentage of females and outcome for emotional functioning or physical functioning. However, magnitude of change was significantly associated with percentage of females for pain experience ($\beta = 0.005$, $p < 0.2$) and coping and cognitive appraisal ($\beta = 0.01$, $p < 0.05$). This indicates that for every additional 10% of females included, effect sizes increase by an estimated 0.05 for pain experience and 0.1 for coping and cognitive appraisal. **Figure 3.9** and **Figure 3.10** visually present this association. **Table 3.10** presents the regression coefficients across all outcome domains for percentage of females as a predictor.

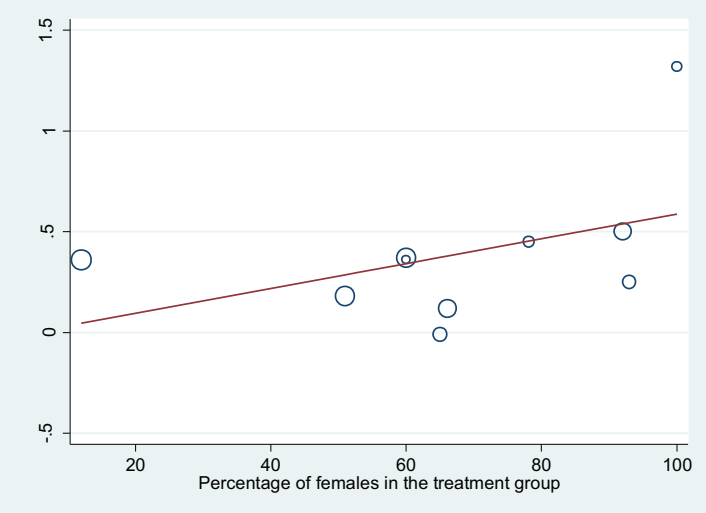

Figure 3.8. Percentage of females and Hedges' *g* for pain behaviour – Active treatment vs. active control.

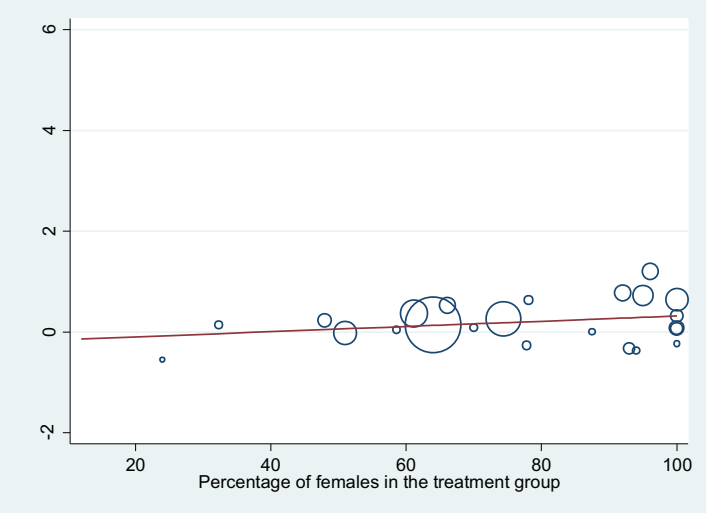

Figure 3.9. Percentage of females and Hedges' *g* for pain experience – Active treatment vs. TAU/WLC.

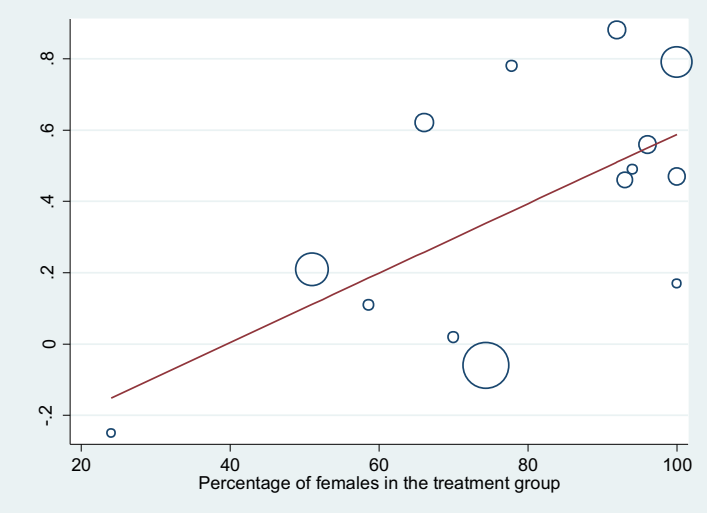

Figure 3.10. Percentage of females and Hedges' *g* for coping and cognitive appraisal – Active treatment vs. TAU/WLC.

Table 3.9. Percentage of females: regression coefficients by outcome domain – active treatment compared with active control.

Active treatment vs. active control									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	30	1439	0.004	0.005	0.51	-0.007	0.014	99.32%	0.404
Pain Behaviour	10	544	0.006	0.004	0.20	-0.004	0.016	97.92%	0.115
Emotional Functioning	30	1434	0.001	0.005	0.93	-0.011	0.012	99.39%	0.427
Physical Functioning	30	1420	-0.001	0.003	0.70	-0.008	0.005	98.32%	0.148
Coping & Cognitive Appraisal	19	874	-0.013	0.024	0.59	-0.064	0.037	99.99%	3.197

β = regression coefficient

Table 3.10. Percentage of females: regression coefficients by outcome domain – active treatment compared with TAU / WLC.

Active treatment vs. TAU / WLC									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	23	1270	0.005	0.004	0.19	-0.003	0.013	98.92%	0.167
Pain Behaviour	4	176	0.011	0.012	0.43	-0.038	0.061	97.55%	0.063
Emotional Functioning	22	1165	0.005	0.004	0.21	-0.003	0.013	98.92%	0.147
Physical Functioning	24	1294	0.001	0.003	0.68	-0.004	0.006	98.32%	0.148
Coping & Cognitive Appraisal	14	688	0.010	0.003	0.02	0.002	0.017	98.76%	0.074

β = regression coefficient

3.8.2 Age

Active treatment compared with active control

When comparing active treatment with active control conditions, magnitude of change did not vary significantly by mean age of participants across any outcome domain. **Table 3.11** presents the regression coefficients across all outcome domains for age as a predictor.

Active treatment compared with TAU / WLC

Similarly, when comparing active treatment with active control conditions, magnitude of change did not vary significantly by mean age of participants across any outcome domain. It appears that age was approaching significance for pain experience (β = 0.015, p = 0.25, *ns*) and pain behaviour (β = -0.024, p = 0.24, *ns*). Although this result was non-significant, the trend is interesting as a pair of results because it suggests that the older the participants, they are simultaneously more likely to improve in terms of pain experience and less likely to improve in pain behaviour. These trends are displayed in **Figure 3.11** and **Figure 3.12**.

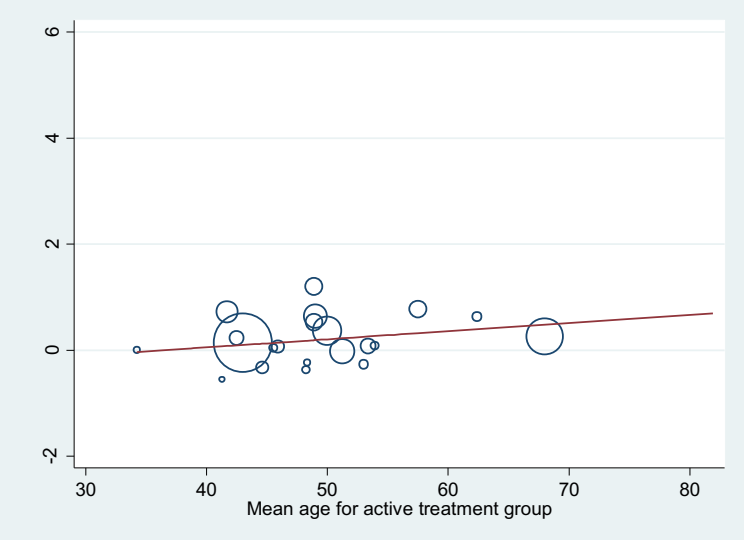

Figure 3.11. Age and Hedges' *g* for pain experience – Active treatment vs. TAU/WLC.

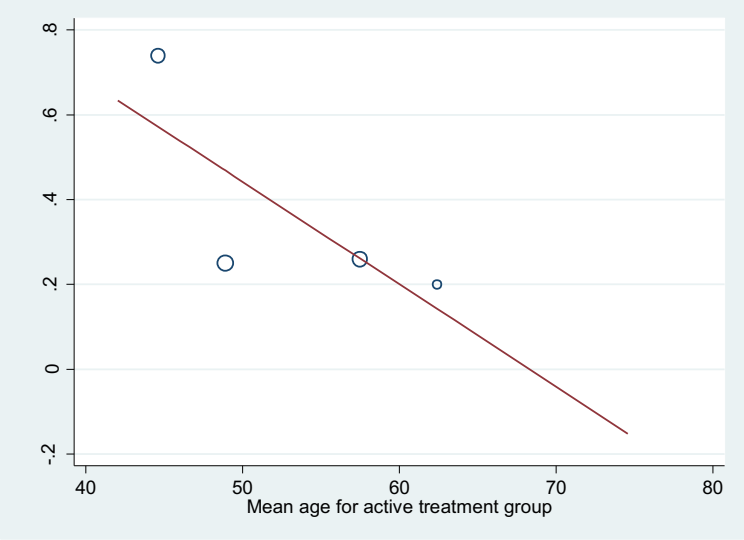

Figure 3.12. Age and Hedges' *g* for pain behaviour – Active treatment vs. TAU/WLC.

Table 3.11. Age: regression coefficients by outcome domain – active treatment compared with active control.

Active treatment vs. active control									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	30	1439	0.008	0.011	0.49	-0.015	0.030	99.33%	0.403
Pain Behaviour	10	544	-0.010	0.012	0.44	-0.037	0.017	98.08%	0.132
Emotional Functioning	30	1434	-0.002	0.011	0.89	-0.025	0.022	99.38%	0.427
Physical Functioning	30	1420	0.004	0.007	0.58	-0.010	0.018	98.31%	0.147
Coping & Cognitive Appraisal	14	874	-0.018	0.035	0.61	-0.093	0.056	100%	3.205

β = regression coefficient

Table 3.12. Age: regression coefficients by outcome domain – active treatment compared with TAU / WLC.

Active treatment vs. TAU / WLC									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	21	1200	0.015	0.013	0.25	-0.012	0.042	99.26%	0.186
Pain Behaviour	4	176	-0.024	0.014	0.24	-0.086	0.038	96.51%	0.038
Emotional Functioning	21	1135	-0.001	0.013	0.97	-0.028	0.027	99.34%	0.166
Physical Functioning	22	1224	0.005	0.009	0.57	-0.014	0.025	98.42%	0.079
Coping & Cognitive Appraisal	13	648	0.001	0.016	0.93	-0.034	0.037	98.59%	0.137

β = regression coefficient

3.8.3 Duration of pain

Active treatment compared with active control

When comparing active treatment with active control conditions, magnitude of change was significantly associated with duration of pain (measured in years) for physical functioning (β = -0.017, $p < 0.2$), and coping and cognitive appraisal (β = -0.125, $p < 0.2$). This indicates that for every additional year in pain, effect sizes reduce by approximately 0.02 for physical functioning, and by 0.13 for coping and cognitive appraisal. Although this may seem like rather a small change, considering effect sizes were small to moderate (Hedges' *g* typically ranging between 0.2 – 0.3), a 0.1 change is a proportionally large statistical change; at least a 33% improvement. **Figure 3.13** and **Figure 3.14** present these associations. There were no other significant associations between duration of pain and magnitude of change. **Table 3.13** presents the regression coefficients across all outcome domains for duration of pain as a predictor.

Active treatment compared with TAU / WLC

In contrast, there were no significant associations between magnitude of change and duration of pain when active treatment was compared with TAU / WLC. **Table 3.14** presents the regression coefficients across all outcome domains for age as a predictor.

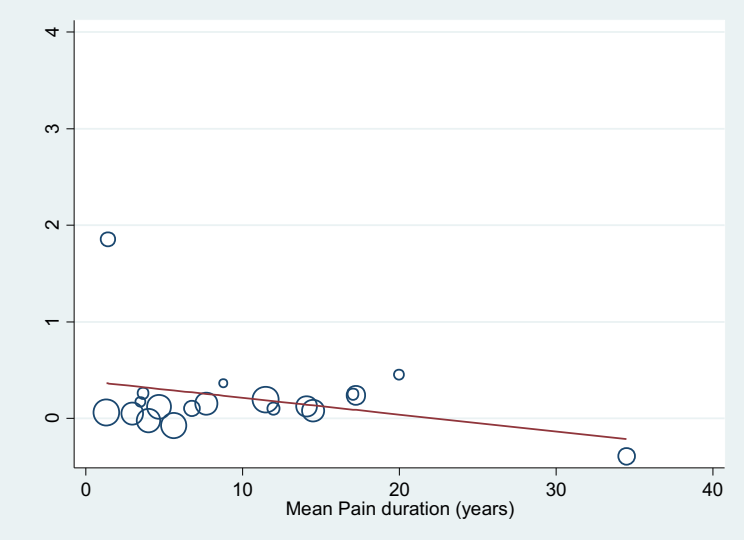

Figure 3.13. Duration of pain and Hedges' *g* for physical functioning – Active treatment vs. active control.

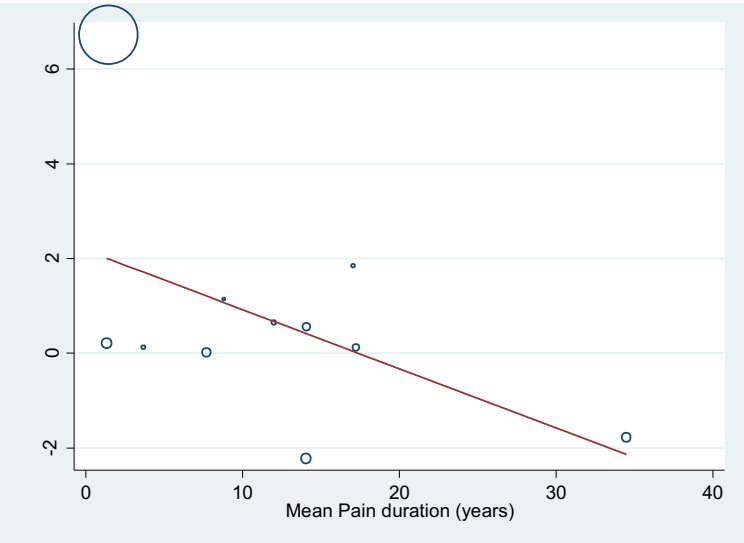

Figure 3.14. Duration of pain and Hedges' *g* for coping and cognitive appraisal – Active treatment vs. active control.

Table 3.13. Pain duration: regression coefficients by outcome domain – active treatment compared with active control.

Active treatment vs. active control									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	20	881	-0.008	0.022	0.71	-0.054	0.038	99.50%	0.550
Pain Behaviour	6	356	0.004	0.023	0.86	-0.059	0.068	98.91%	0.283
Emotional Functioning	20	883	0.003	0.022	0.89	-0.043	0.049	99.48%	0.584
Physical Functioning	19	837	-0.017	0.012	0.17	-0.043	0.008	98.48%	0.174
Coping & Cognitive Appraisal	11	444	-0.125	0.071	0.11	-0.285	0.035	99.99%	4.447

β = regression coefficient

Table 3.14. Pain duration: regression coefficients by outcome domain – active treatment compared with TAU / WLC.

Active treatment vs. TAU / WLC									
Outcome Domain	No. of Studies	No. of Participants	β Coefficient	Standard Error	P	Lower CI	Upper CI	I^2	τ^2
Pain Experience	12	594	-0.015	0.017	0.40	-0.052	0.023	99.26%	0.217
Pain Behaviour	$	$	$	$	$	$	$	$	$
Emotional Functioning	13	617	0.004	0.017	0.83	-0.034	0.042	99.46%	0.235
Physical Functioning	13	617	0.004	0.009	0.68	-0.016	0.024	95.44%	0.064
Coping & Cognitive Appraisal	9	462	0.009	0.014	0.52	-0.023	0.041	99.41%	0.112

β = regression coefficient; $ = not enough studies for analysis

4 Discussion

This thesis replicated and extended the most recent comprehensive Cochrane review of psychological interventions for chronic pain (Williams et al., 2012). I extended the previous review in three ways: (1) I investigated treatment content within each intervention and created a list of treatment components, (2) I included all outcome measures by aggregating data into five outcome domains, and (3) I applied sophisticated meta-regression analyses to explore the impact of dose on improvement.

I conducted a total of 60 analyses of data from a total of 7,840 participants across 64 randomised controlled trials. Active treatments were compared with both active control and TAU / WLC control conditions across the five outcome domains. In addition to dose in hours and duration of intervention in weeks, I accounted for three participant characteristics as potential predictors; percentage of females, age, and duration of pain. To date, this is the largest meta-analysis of findings from studies of non-cancer chronic pain (excluding headache).

The included trials varied in terms of participant characteristics, but on average they included more females than men, were middle aged, and were mostly educated to high school level. Ethnicity was rarely reported. Trials included a variety of chronic pain diagnoses, such as temporomandibular joint disorder, fibromyalgia, chronic low back pain, and arthritis. Although it is possible that different types of pain have different treatment trajectories, I did not differentiate between different pain types in any of my analyses. The treatments delivered were mostly group interventions, and mostly called CBT.

Risk of bias was relatively low or unclear across all aspects of the Cochrane Risk of Bias tool, suggesting that plausible bias is unlikely to seriously alter the results. The highest risk of bias was for detection bias, where outcome assessment was not blinded. Although a high risk of bias would usually be interpreted as potentially weakening the confidence that one could place in the results, it should be noted that as most measures used were self-reported, the impact of this bias may be minimal.

4.1 Meta-analytic Results

Effect sizes (Hedges' g) were similar both when comparing active treatments with active controls (Mean Hedges' $g = 0.35$) and when comparing active treatments with TAU / WLC control (Mean Hedges' $g = 0.3$) conditions. In both cases, effects were small to moderate across all outcome domains. Although the effects were broadly consistent, albeit slightly higher, here than in the Williams et al. (2012) review when comparing active treatment with active

control. Small differences were expected given the different approaches to including and analysing outcome measures.

One might argue that such modest effect sizes are unimportant. However, as Lipsey and Wilson (2001) explain, a small effect size may have significant implications for clinical practice because meta-analysis does not take account of the context of the intervention. An intervention that has few resources and requires little of participants but brings about a change may be clinically meaningful. Baguley (2009) takes this one step further and proposes that verbal categorisations of effect sizes (such as 'small') are not used because of the critical roles that context of treatment and setting play in interpreting change. Indeed, Lepper, Henderlong, and Gingras (1999) remind us that "although it may be tempting to succumb to the facile assumption that meta-analysis provides clear-cut, objective answers to complex questions, we must resist this oversimplification" (p. 675). The exploration of potential moderators may help us to resist such oversimplification.

4.2 Treatment Components

Two key findings emerged from my investigation of treatment content. First, there was disparity between trials in the treatment components used even when the trials appeared to be delivering the same type of treatment. Second, treatments that were described as being distinct, actually used treatment content that was often similar. For example, homework is considered a core part of CBT, and is included in the Cognitive Therapy Rating Scale that is used by clinicians and researchers to check adherence to a CBT protocol (Young & Beck, 1980). However, my findings suggest that 33.3% of CBT trials do not include homework (or do not report that they use homework). Clinical wisdom suggests that this is accurate. Clinicians might add a component, say mindfulness, to CBT if they believe it is clinically appropriate. Indeed, a recent survey of over 1,000 therapists found that the majority prefer an eclectic approach to therapy – only 15% indicated that they use one theoretical orientation (Tasca et al., 2015). However, this should not be the case in RCTs, which are highly thought of because they limit variation. On the one hand, this may add external validity of the trial's findings to clinical practice, but such variation makes it difficult to be confident in the conclusions about the treatment effects. The limitations of RCT methodology to evaluate clinical effectiveness in psychological interventions are acknowledged academically. Westen, Novotny and Thompson-Brenner (2004) highlight that although RCTs may profess to analyse a particular therapy, they are actually testing a treatment package and are not testing the specific interventions that make up that treatment package. Westen et al. (2004) go on to argue that investigators should move away from investigating commonly accepted complete treatment packages (such as CBT) and

focus on testing specific interventions; a proposition that goes hand-in-hand with the findings that emerged here.

To my knowledge, this is the first systematic attempt to establish the variability in the components used by psychological treatments for chronic pain. There are two conclusions that can be drawn from the findings about treatment components presented here. The first is to be cautious when exploring and interpreting any apparent statistical differences between different treatment types, for example, whether ACT facilitates more change than CBT. This conclusion may reflect limitations of how psychological interventions are evaluated more broadly. Linden (2013) describes similar difficulties in the field of psychological interventions in Cardiology, such as cardiac rehabilitation following a heart attack. Linden warns that any research concluding that differential treatment outcomes were found as a function of treatment type "should be approached with considerable mistrust" (p. 333). He also notes that if we are to use broad classifications of treatment type (such as 'CBT'), then we must only do so when we can demonstrate reliable, blind classifications with non-overlapping categories. It is clear from the findings of this thesis that we are currently a long way from this goal in chronic pain.

One potential reason for the use of broad treatment type classifications as the research strategy of choice is that it simplifies the complexities of delivering multiple components. In their paper on contemporary issues in pain, O'Connell, Moseley, McAuley, Wand, and Herbert (2015) remind us of the words of physicist, Richard Feynman: "For a successful technology, reality must take precedence over public relations, for Nature cannot be fooled" (p. 1092). This resonates with research into psychological treatments, where we have a number of treatment types that may be competing, even if not explicitly, to be the 'lead' model (McCracken & Marin, 2014). We must not succumb to a simple narrative of psychological treatment as neatly and consistently packaged in one particular 'type', such as CBT. To do so may prevent us from developing a more refined understanding of treatment content and outcome.

4.3 The 'Dose-Response' Question

4.3.1 Summary of findings

Overall, there was limited evidence for the association between dose and outcome. This was especially true when measured in hours, suggesting that the patient's improvement following psychological intervention is not necessarily dependent on the total amount of treatment delivered. When dose was measured in weeks, i.e. the period over which treatment was delivered, there was a significant association with outcome for two out of five outcome domains; coping and cognitive appraisal, and pain experience. This association was only found when the active treatment was compared with TAU / WLC, not when active treatment was

compared with active control. There were studies that brought about improvement with relatively few weeks and hours of treatment and others that facilitated relatively little change despite many weeks of treatment. As an example, Nicassio et al. (1997) delivered 15 hours of treatment over 10 weeks and participants improved in emotional functioning (Hedges' $g = 0.47$). In contrast, Sleptsova, Woessmer, Grossman, and Langewitz (2013) found much smaller effects (Hedges' $g = 0.02$) despite 37.5 hours of treatment over 24 weeks. These findings are broadly similar to those presented by Waterschoot et al. (2014), who also reported differential associations between dose and response as a factor of type of outcome (disability, work participation and quality of life). In contrast, my findings contradict those by Glombiewski et al. (2010) where dose in hours was found to be related to reductions in pain intensity and depression. The authors concluded that patients with fibromyalgia should be offered high doses of CBT, a conclusion that cannot be supported based on findings here.

There may be statistical reasons for the lack of support for a relationship between dose and outcome. One reason may be the 'range restriction problem'. This is caused by the limited range of small effect sizes resulting in little opportunity to detect true effects (Linden, 2013). Moreover, the Cochrane Handbook for Systematic Reviews also explains that stating that a dose-response relationship does not exist should be done only with caution because of the potential for underpowered results (Higgins & Green, 2011). Taken together, the findings from this thesis do not seem to support the notion that treatment outcomes improve as the amount of treatment increases. This is contrary to what would be predicted in line with the traditional dose-response concept. Nevertheless, further statistical analyses using different research methods are required before we should firmly conclude that a dose-response relationship does not exist.

4.3.2 Alternatives to the dose-response concept

To fully critique the dose-response concept, we must explore its underlying assumptions. Arguably, the two most important assumptions made by the concept of dose-response are inter-related; that the more treatment is given, the bigger effects one ought to see and that this pattern will be consistent across patients. However, such assumptions cannot be fully supported by the evidence presented here. On the whole, treatment effects did not get bigger the more treatment was given. Moreover, as I will discuss shortly, it is unlikely that the relationship between dose and outcome will be the same across patients because some patient characteristics were related to differential amounts of change.

There are a number of reasons why the relationship between dose and outcome is not as simple as 'the more the better'. One might hypothesise, for example, that longer interventions are more intensive and thus lead to less adherence, or that participants who are more anxious will require longer therapy whereas those who are less anxious may respond more quickly. In

the broader field of psychotherapy, research has attempted to shed light on whether there is a non-linear relationship between dose and outcome. Particularly interesting is an alternative to the 'dose-response' concept of change proposed by Barkham and colleagues (2006). The 'Good Enough Level' model of change (GEL) places less importance on the total number of sessions, and posits instead that clients are generally inclined to stay in therapy until they have benefited from it, that is, until they feel 'good enough'. This implies that rather than there being one pattern of change in response to dose, there are several patterns of change and patients are active agents in this. This notion certainly has face validity. We know that the right amount of medication for one person may be an overdose or an underdose for another person (Kazdin, 2007). In addition to face validity, there is empirical support for the idea of patient specific patterns of change.

Owen et al. (2015) found three patterns of change when they investigated the GEL model in relation to psychological functioning following short-term (up to 14 sessions) psychotherapy. The first pattern was early change followed by a plateau, the second was initial decrease followed by a rapid increase and the third was a linear and steady increase over sessions. What differentiates the participants who might follow each pattern requires further exploration. Owen and colleagues found that those following the initial decrease then rapid increase in functioning pattern were more distressed on entry. Furthermore, Reese, Norsworthy, and Rowlands (2009) found that frequency of sessions was related to change; such that students who attended a university counselling service for more sessions per week demonstrated more rapid improvement than those who attended for the same number of sessions over a longer period of time. In sum, the GEL presents an alternative way of thinking about the relationship between dose and response. The GEL model is more comprehensive in that it would enable testing of patient characteristics, frequency of treatment delivery as well as 'amount' of treatment. Having said that, a significant shift in current research paradigms is needed before we can robustly investigate how the GEL model relates to change following psychological interventions for chronic pain. As it stands, trials rigidly apply a dose that all participants receive. This means that participants cannot simply attend until they feel as though they have benefited enough. Or, indeed, cannot continue in therapy if they still need further support past the allocated 'dose' of therapy. One approach to overcoming this would be to use different research methods. One promising method is the single case design, which I will describe shortly.

4.3.3 Patient characteristics and outcome

I found that some characteristics may be related to magnitude of change. Percentage of females was related to change in outcomes for pain experience and coping and cognitive appraisal. This finding complements those of Hoffman et al. (2007), where the percentage of

males in trials was associated with smaller effects. I also found that the length of time that participants had been living with pain (i.e. pain duration) was associated with improvement in physical functioning and coping and cognitive appraisal. This suggests that these characteristics are important for further research. Age seemed unrelated to outcome but there are several reasons why this may be the case. It is important to consider these reasons because they also have relevance to our interpretation of the lack of evidence for the dose-response question.

To account for these three patient characteristics in my analyses, I extracted mean data from each trial. However, it is possible that this overlooks within-trial effects. Thompson and Higgins (p. 1564; 2002) describe and illustrate this well; "the relationship with patient averages [and treatment effect] across trials may not be the same as the relationship for patients within trials". **Figure 4.1** replicates a figure from their paper (p. 1564). The lines show within-trial treatment effects, and circles represent the relationship between trials. The top graph demonstrates that *within* each trial there is a relationship between age and treatment effect, but this would not be identified if you were to look for a relationship in the mean scores *across* trials. In contrast, the bottom graph shows that there is no relationship between age and effect *within* each trial, but there would appear to be a relationship looking *across* trials. This phenomenon can be thought of as the 'aggregation bias' (Morgenstern, 1982), and cannot be explored without data at the patient level, rather than the trial level (Thompson & Higgins, 2002).

A further challenge of exploring the relationship between patient characteristics and outcome is that research trials do not always publish comprehensive accounts of participant characteristics. For example, despite the potentially important influence of taking medication while receiving psychological interventions authors rarely reported on medication use. This means that we might be reporting participant characteristics (such as age) that bear little weighting on outcome while missing other relevant characteristics altogether. A further example is that there may be a meaningful psychological (as well as functional) difference between someone living with chronic pain who is 'employed' and working full time, and someone who is 'employed' but working one day per week. At best, trials currently report the percentage of participants 'employed', with only a select few specifying 'full time' or 'part time'. To advance the study of psychological interventions for chronic pain and allow greater specificity of analyses, more detailed reporting of participant characteristics is required. This ought to include the number and type of previous treatments for chronic pain (such as use of spinal cord stimulator, physiotherapy etc.), ethnicity, medication use. Reporting such nuances is not common practice, but would facilitate better analyses and aid our understanding of mechanisms of change in psychological interventions for chronic pain.

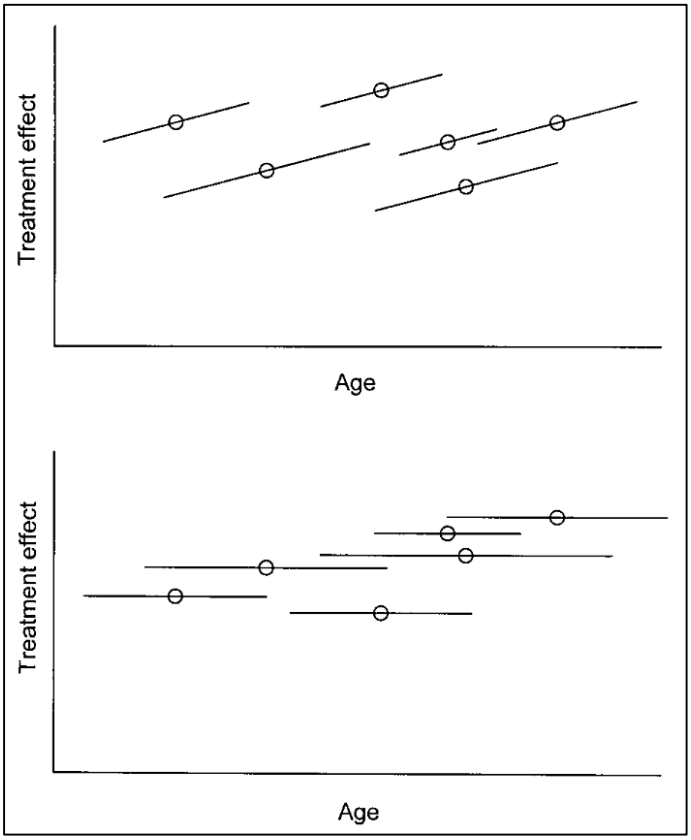

Figure 4.1. Hypothetical relationship between age and treatment effect both within trials (represented by the lines) and between trials represented by the dots (taken from Thompson & Higgins, 2002; p. 1564).

4.4 Implications for Research

4.4.1 Implications for dose-response

There are two potential hypotheses that may be generated from my findings:

1. The longer the intervention (in weeks), the greater the improvement in pain experience, and coping and cognitive appraisal outcomes.
2. There is a non-linear relationship between dose (in hours) and outcome.

To test these hypotheses in a robust manner, it is crucial that we do not overly rely on the RCT as a research design. Moving away from RCTs has long been advocated as a strategy for the field of psychological interventions for chronic pain. Perhaps the strongest campaign for change was Morley, Williams, and Eccleston's (2013) call for a paradigm shift. Among several suggestions for innovation in the field, they proposed that single case study designs and analysis of patient level data may be prudent approaches to enhance our knowledge. I will now outline how these two methodologies may help better understand and potentially resolve the issues

raised in this thesis. I will also describe recommendations for the continued study of treatment components as well as treatment types.

Single-case studies

Single case studies, or single case series, are characterised by the repeated measurement of individual patients over time; often before, during and after an intervention (McMillan & Morley, 2010). For some time, they have been considered the 'poor cousin' of the RCT (Morley, in press), however, the findings of this thesis add to the argument that they should have a high place on the research agenda. Synthesising data about how treatment dose relates to outcome in primary studies has yielded little in the way of clear evidence. Single-case studies would allow us to explore potential relevance of the 'good enough level' models of dose. The frequent assessments of change over time would enable us to explore whether there are 'rapid responders' to psychological interventions. Over time, this would allow us to profile participants and perhaps offer particular components of treatments based on psychological profiles rather than chronic pain diagnoses, which may be unrelated to the extent to which a patient is struggling or in distress (Williams et al., 2012). This suggests that single-case studies would help us to learn more about dose-effect relationships and build on the tentative hypotheses generated here.

Patient-level data

Patient-level data may help us to overcome the aggregation bias mentioned earlier, where important variation within trials is not represented by mean variation across trials. Berlin, Santanna, Schmid, Szczech, and Feldman (2002) take this one step further by highlighting that the group-level (also called 'ecological') analysis that is achievable through meta-regressions may fail to identify important differences in the effect of treatment between two sub-groups. In all, the challenges of exclusively using primary study-level data in meta-analysis cannot be ignored. To account for these differences, a real change is needed in publishing practices. If researchers were to make patient-level data publicly available, we could account for the limitations described by Berlin et al. (2002), and better understand sub-groups that may be missed by broad aggregation at a primary study level. Moreover, we could develop more sophisticated models that account for patient demographics in relation to change. This would enable us to move away from the mean and potentially offer patients more than just an 'average' treatment. Such a shift in publishing practice will not happen overnight, but there has been some progress in making patient data more available. Perhaps the best example of this is the OpenTrials initiative (www.opentrials.net), led by Ben Goldacre. OpenTrials is a collaborative and open online database of information about clinical research trials around the world

(Goldacre & Gray, 2016). Such initiatives are in their infancy, but hold promise in easily enabling meta-analysis of patient level data.

Until collaborations like OpenTrials are well established, the responsibility for gathering patient-level data might lie with the meta-analyst, who could contact authors of primary studies requesting patient-level data. Initial skepticism about potential response rates is understandable, and the consequent bias of only being able to analyse data from the self-selecting sample of authors who share their data should not be overlooked. Indeed, there are infamous examples of trial teams being reluctant to share data. A recent example is the PACE-trial, which investigated psychotherapy for chronic fatigue syndrome (White et al., 2011). Patient groups and academics had to spend considerable time and money requesting patient data through freedom of information requests before it was released. After secondary analysis, it became clear that the authors had deviated from their pre-stated protocol, which had led to inflated treatment effects (Geraghty, 2016). However, we must not let such examples deter us from attempting to synthesise patient-level information across trials. Indeed, there have been examples of such approaches being used with some success. For example, Vickers et al. (2012) were able to obtain patient data for 29 out of 31 relevant studies when they used meta-analysis of patient level data to explore the effects of acupuncture for chronic pain. While this movement is currently emerging as a trend, enabling wider access to patient-level data sets would allow even greater precision when inferring relationships between predictors such as dose of treatment and patient outcome.

4.4.2 Implications for treatments

The lack of adequate treatment descriptions makes it difficult to identify active ingredients in treatments. To continue to better understand the relationship between different treatment components and outcome, reporting of the specific treatment content must improve. It is insufficient to describe in a sentence or two what 'CBT' meant in the trial because such descriptions would not enable replications of treatment protocol. Studies that do not report treatment in such a way ought to be deemed low quality. It is also time to pause 'bolting on' additional treatment components, such as mindfulness, to existing treatment protocols. The research priority should be establishing the effectiveness of the components frequently used at the moment before adding further variations.

One natural extension of this thesis would be to move toward a better understanding of the dose of each component. This was rarely reported in the primary studies included here, and when it was reported, it was usually for the exercise components only. Again, specific reporting about the amounts of each component may help us to understand whether there are specific components of treatment that help to bring about change more quickly. For example, one might

hypothesise that including lots of 'problem solving' toward the beginning of therapy might improve outcomes by equipping patients with the skills to resolve potential barriers that might otherwise have prevented them from continuing in therapy. There is, I acknowledge, an inherent difficulty here in that the underlying assumption of this point rests on the idea that one hour of treatment component A is equal to one hour of treatment component B. This is unlikely to be the case, but until we are able to breakdown the specific details of interventions that are delivered, our conclusions about whether all treatment components are created equal will be relegated to the realm of the vague and general.

4.5 Implications for Clinical Practice

The issue of dose is important for designing and managing clinical services. This thesis found that there was an association between the number of weeks over which the treatment was delivered and outcome, such that longer treatments resulted in larger improvements, at least for some outcomes. This suggests that although clinical services are under increasing pressure to see more clients in less time, clinicians need to be mindful that large change may take time. Having said this, there were examples where improvement was seen for relatively short psychological interventions. The implication here is a political one. In light of the evidence that has accumulated through this review and others (e.g. Waterschoot et al., 2014), NICE guidelines must go further than excluding any reference to minimum number of hours, and ought to clarify that a range of treatment hours are able to bring about a change – more than 100 hours are not necessarily needed to facilitate improvement.

Early intervention may be important to consider. The average person included in the primary studies here had been living with pain for nearly ten years. I found some evidence that treatment effects were smaller the longer that participants had been living with pain. This suggests that if we can intervene earlier, we may be able to help people see greater benefits from psychological interventions. This is meaningful for clinical practice where psychological interventions are usually referred to as a last resort if a person continues to be in pain despite many years of searching for a medical 'cure'. Perhaps if psychological interventions were brought earlier into the chronic pain treatment pathway, we might see larger effects.

Finally, clinicians may be interested in the similarities between treatment components across different treatment types. For some clinicians this may fit with their experience of delivering psychological interventions for chronic pain. They might create their own 'blend' of psychological treatments by using the components that fit well for them, or that they think might be helpful to the client in front of them. Clinicians can play a key role in piecing together the fragmented approach to treatment components by building a body of practice-based evidence

(Margison et al., 2000). The single-case study design described earlier can be readily applied in routine clinical settings and could help learn more about the relevance of specific treatment components for outcome.

4.6 Strengths of this Thesis

A key strength of this thesis is that it is one of the largest reviews about the impact of psychological interventions for chronic pain to date. Indeed, I included nearly three times as many studies as previous meta-regressions in the field (Glombiewski et al., 2010; Hoffman et al., 2007). The breadth of studies included has meant that findings included a range of types of chronic pain and a range of treatment types. This is reflective of real-world clinical practice, and adds to the generalisability of my findings. For example, the inclusion of studies that had an active psychological intervention but were not facilitated by a psychologist (i.e. they were supervised or trained by a psychologist), adds to the generalisability of these findings with increasingly more psychological interventions being delivered by non-psychologists.

Attrition rates were relatively low, suggesting that the findings here are generalisable beyond the 'treatment completers'. Analysis of the quality of trials, as measured by the Yates Quality Rating Scale showed that quality of trials has improved over time, and risk of bias was moderately low. This adds credibility to the findings here.

The main pitfall of meta-regression analyses has been described as 'data-dredging' (Thompson & Higgins, 2002), where so many analyses are run that spurious findings are generated. While it would be possible that some of the findings presented here are spurious, there are two reasons to believe that they are not. The first is that they are broadly comparable with previous research, such as the reviews by Williams et al. (2012) and Waterschoot et al. (2014). The second is that I limited the number of analyses that I conducted, analysing only three out of nine participant characteristics that I extracted data about. This suggests the number of false positive results should be limited.

4.7 Limitations of this Thesis

I have already discussed several limitations and challenges of this thesis. In this section, I focus on the limitations of developing treatment components, aggregating across outcome measures and teasing apart efficacy and effectiveness.

4.7.1 Developing treatment components

A challenge to creating the treatment component categories was that the information was extracted from the published research papers. Descriptions of the specific content of treatments may not be well represented in trial write-ups. Although this is a problem is not limited to the field of psychological interventions for chronic pain, it does present a problem for

meta-analytic exploration of treatment components. It may well be that components were included in treatments but were not reported. This means that the treatment categories are only as precise as the descriptions of treatment content in trials. A more robust approach to extracting information about treatment components would have been to request a copy of the treatment protocol from authors. This was beyond the scope of this thesis, but may be a helpful strategy for future research and would help to further shine light on the discrepancies between what might be delivered and what is reported. It also reinforces the importance of comprehensively reporting treatment protocols. In theory, one's treatment protocol should be descriptive enough that it could be replicated by others, but this was rarely the case. Exceptions to this were where authors included a table of components and how they were defined. Kerns et al. (2014) reported something similar in their trial, which was a list of treatment 'modules' such as relaxation or pacing, and provided a brief description about what this meant. Such a detailed approach to reporting treatments might be considered as best practice.

A second criticism of my analysis lies with the 'bottom up' approach to exploring treatment components. This approach meant that trials that were more commonly included may have skewed the final list of treatment components. One might argue that because of the dominance of CBT in trials of psychological interventions for chronic pain, that the treatment components that I have created are overly CBT focused. I would argue that the fact that a high proportion of non-CBT trials included these components confirms that the final list of treatment components did not overly represent components used in CBT. For example, problem solving could be used in ACT or a multidisciplinary group, as well as CBT. This suggests that the 'bottom-up' approach, while not perfect, was a reasonable approach to categorising treatment content. An alternative approach would be a Delphi study to explore categorise content in a 'top-down' manner (Cantrill, Sibbald, & Buetow, 1996). This would involve surveying a panel of experts in the field and gathering their thoughts on what a potential list of treatment components may be comprised of. This would be a valuable avenue for further research, and the list generated here might present a helpful starting block.

4.7.2 Outcome measures

The variety of outcome measures used across trials of psychological interventions for chronic pain has been well documented, and has led to recommendations regarding which outcome measures should be included in trials (Turk et al., 2003). Rather than selecting only one outcome measure per study, I created aggregated outcome domains by combining results across different measures of the same construct. However, this is not a perfect solution to the challenge of outcome heterogeneity. One problem that this may cause is that outcome domains may not be truly independent of each other. For example, I categorised quality of life measures as assessing 'physical functioning'. Although this is in line with previous attempts to group

measures into outcome domains (Fenton & Morley, 2013), it is an over-simplistic representation of what a quality of life measure actually assesses. One might be functioning relatively well physically, but have a low score on a quality of life measure because of difficulties with low mood and anxiety. This means that the low quality of life score actually reflects difficulties with emotional functioning, rather than physical functioning. It may be important to remember, therefore, that while outcome domains are a helpful way of including more data from included studies, they represent a broad range of outcome measures and are unlikely to be totally independent of each other.

Furthermore, almost all outcome measures used in primary studies were self-report. This may have introduced bias in several ways. Patients may perceive themselves as changing more or less than they have actually changed. Alternatively, they may wish to present themselves as having changed because of social desirability bias; a tendency to choose responses that others are most likely to approve of (van de Mortel, 2008). Having said this, it is possible that self-report measures should not cause too much concern. In a meta-regression of psychotherapy for depression, Cuijpers, Li, Hofmann, and Andersson (2010) compared self-reported and clinician-reported change. They found that clinicians reported greater improvements than patients (i.e. the clinicians' effect sizes were inflated). This suggests that the results from self-report may be a conservative estimate of improvement. In addition, I would argue that it is the patient's perception of whether they have changed that is most important, rather than attempting to identify some measure of 'true' change.

4.7.3 Efficacy, but not necessarily effectiveness

An important distinction should be made between efficacy and effectiveness. Nathan, Stuart, and Dolan (2000) describe efficacy as the evaluation of treatment effects under conditions of high *internal* validity (i.e. highly controlled studies). Whereas effectiveness is the evaluation of treatment effects under conditions of high *external* validity (i.e. less controlled and more similar to routine clinical practice). I only included RCTs in this review. RCTs are the 'gold standard' approach to test efficacy. Although my findings point to the need for further evaluation of treatment fidelity, and perhaps more scrutiny of treatment manuals, there is a wealth of RCTs that have consistently demonstrated positive (albeit modest) effects for psychological interventions for chronic pain. This means that we can be confident psychological treatments are efficacious as treatment approaches. However, the exclusion of trials that were not RCTs means that we may be less confident in our ability to comment on the effectiveness of the trials. Coupled with this is the issue that the measure of magnitude of change that is used in meta-analysis, the effect size, relates only to statistical change. We can say little (if anything) about how this might relate to clinically significant change.

A separate but related point is that I only included trials that had been published in peer reviewed journals. There are several ways in which excluding unpublished studies limits this thesis. First, it may be that there is an over-representation of certain types of chronic pain, and / or certain types of treatment. Perhaps most notably, the frequency of CBT may not be purely attributable to its popularity, rather it may be that CBT trials were more likely to receive funding and be published. Consequently, other therapeutic modalities may be poorly represented in the trials included here, or not represented at all. For example, anecdotally, clinicians might talk about using models such as Cognitive Analytic Therapy (Ryle, Poynton, & Brockman, 1990) or Compassion Focused Therapy (Gilbert, 2009), but these modalities do not seem to have appeared in peer-reviewed publications. Secondly, we must be careful not to consider the peer-review process a panacea to issues of bias, quality and availability of evidence. As Glass, the founder of meta-analysis, explained at a conference; "It is one thing to believe that peer review guarantees truth; it is quite another to believe that all truth appears in peer reviewed journals" (Glass, 2000). Having said that, Veehof et al. (2011) included both published and unpublished trials in their meta-analysis of psychological interventions for chronic pain and found inflated effect sizes for unpublished studies in comparison with published studies. Although Veehof et al. is just one review, it suggests that restricting the inclusion criteria to only include published studies may have resulted in a conservative estimate of effect. Nonetheless, we must not negate the potential for unpublished studies to have an important contribution to understanding whether all treatment components are created equal. In sum, this means that the findings should be cautiously generalised to 'real-world' clinical settings.

4.8 Conclusion

The aim of this thesis was to explore two questions:

1. Is dose related to outcome in psychological interventions for adults with chronic pain?
2. What are the core components of treatment being delivered in psychological interventions for chronic pain, and how do they differ between types of intervention?

This thesis goes some way to establishing that there does not seem to be a linear relationship between dose and outcome. It seems as though there are differential relationships between dose (measured in weeks) and certain outcome measures. These findings reinforce the complex process of helping patients who have been living with chronic pain. One striking finding from this thesis is the lack of consistency in the components of treatment delivered by the 'same' psychological intervention used across trials, coupled with considerable overlap in the components used by 'different' interventions.

I have pointed to several potential implications of this work. Perhaps the most important will be the further investigation of dose-response relationships through the use of single-case designs and analysis of patient level data to test the hypotheses generated here. Another important implication is that we ought to clarify current NICE guidelines, which have currently removed any reference to the important issue of treatment dose. I suggest that it should be clarified that there is no evidence to support a minimum number of hours required for psychological interventions to be effective.

So, are all treatment components created equal? In short, no. No relationship was established between dose in hours and outcome, but some relationships were found for dose in weeks and outcome. Even then, dose in weeks was not equally able to bring about improvement across all outcome domains. Coupled with this, it seems as though there are patient characteristics, such as pain duration, that may affect the extent to which treatment can bring about change. Taken together, it would appear unlikely that there is one 'optimal' treatment for everyone living with chronic pain. Alternative and more flexible research designs are needed to enable a better understanding of how participant characteristics and treatment components interact. Until then, we will be limited in our ability to consider 'optimal' approaches to personalising treatments.

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List of Abbreviations

ACT – acceptance and commitment therapy

CBT – cognitive behavioural therapy

CR – Cochrane review

ES – effect size

GEL – good enough level

ISTDP – intensive short term dynamic psychotherapy

MBSR – mindfulness-based stress reduction

MDT – multi-disciplinary team

MeSH – medical subject headings

NICE – National Institute of Clinical and Health Excellence

NR – not reported

NS – non-significant

NSAIDS – non-steroidal anti-inflammatory drugs

PMP – pain management programme

PRISMA - preferred reporting items for systematic reviews and meta-analyses

RCTs – randomised controlled trials

SD – standard deviation

SE – standard error

SEM – standard error of the mean

SMD – standardised mean difference

TAU – treatment as usual

WLC – wait list control

Appendices

Appendix A. MeSH Terms Search Strategy

MEDLINE search strategy (via OVID)

1. PAIN explode all trees (MeSH)

2. (chronic* near pain*)

3. (#1 and (chronic* near pain*))

4. (chronic* near discomfort)

5. (chronic* near ache*)

6. (chronic* near fibromyalgia:ab)

7. (chronic* near fibromyalgia:ti)

8. (chronic* near neuralgi*:ab)

9. (chronic* near neuralgi*:ti)

10. (chronic* near dysmenorrhea:ti)

11. (chronic* near dysmenorrhea:ab)

12. (chronic* near dysmenorrhoea:ti)

13. (chronic* near dysmenorrhoea:ab)

14. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)

15. PSYCHOTHERAPY explode tree 1 (MeSH)

16. COGNITIVE THERAPY single term (MeSH)

17. BEHAVIOR THERAPY explode tree 1 (MeSH)

18. BIOFEEDBACK (PSYCHOLOGY) single term (MeSH)

19. ((behaviour* next therapy) or (behaviour* next therapies))

20. ((cognitive next therapy) or (cognitive next therapies))

21. (relax* near technique*)

22. ((relax* near therapy) or (relax* near therapies))

23. meditat*

24. psychotherap*

25. (psychological next treatment)

26. ((psychological next therapy) or (psychological next therapies))

27. (group next therapy)

28. (self-regulation next training)

29. (coping next skill*)

30. (pain-related next thought*)

31. (behaviour* near rehabilitat*)

32. (psychoeducation* next group)

33. (psychoeducation* next groups)

34. (psycho-education* next groups)

35. (psycho-education* next group)

36. (mind and (body next relaxation next technique*))

37. MIND-BODY AND RELAXATION TECHNIQUES explode tree 1 (MeSH)

38. (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37)

39. (#14 and #38)

Appendix B. Comprehensive Meta-analysis Results Table for Active Treatment Compared with Active Control.

Active treatment vs. active control										
Outcome Domain	No. of Studies	No. of Participants	Effect Size (Hedges' *g*)	Standard Error	t	Sig	Lower CI	Upper CI	I^2	τ^2
Pain Experience	38	1712	0.31	0.16	1.97	0.057	-0.01	0.63	99.83%	0.949
Pain Behaviour	12	608	0.28	0.12	2.27	0.044	0.01	0.55	98.04	0.176
Emotional Functioning	35	1611	0.27	0.11	2.51	0.017	0.05	0.50	99.36	0.412
Physical Functioning	38	1701	0.31	0.13	2.35	0.024	0.04	0.58	99.56	0.665
Coping & Cognitive Appraisal	24	1073	0.58	0.35	1.65	0.112	-0.15	1.30	100	2.938

Appendix C. Comprehensive Meta-analysis Results Table for Active Treatment Compared with TAU / WLC

Active treatment vs. TAU / WLC										
Outcome Domain	No. of Studies	No. of Participants	Effect Size (Hedges' *g*)	Standard Error	t	Sig	Lower CI	Upper CI	I^2	τ^2
Pain Experience	28	1398	0.39	0.20	1.95	0.062	-0.02	0.81	99.94	1.139
Pain Behaviour	5	197	0.36	0.10	3.56	0.024	0.08	0.64	96.57	0.475
Emotional Functioning	25	1234	0.24	0.08	3.24	0.003	0.09	0.40	99.18	0.139
Physical Functioning	28	1402	0.12	0.06	2.11	0.044	0.00	0.23	98.12	0.084
Coping & Cognitive Appraisal	17	127	0.38	0.08	4.92	0.000	0.22	0.54	98.93	0.098